WELCOME
TO THE
23rd ESN BIENNIAL MEETING

7th Conference
On Molecular Mechanisms of Regulation in the Nervous System
WITH THE PATRONAGE OF
## NATIONS OF PARTICIPANTS

<table>
<thead>
<tr>
<th>Australia</th>
<th>Hungary</th>
<th>Slovakia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>India</td>
<td>Spain</td>
</tr>
<tr>
<td>Belgium</td>
<td>Israel</td>
<td>South Africa</td>
</tr>
<tr>
<td>Brazil</td>
<td>Italy</td>
<td>Sweden</td>
</tr>
<tr>
<td>Canada</td>
<td>Japan</td>
<td>Switzerland</td>
</tr>
<tr>
<td>Denmark</td>
<td>Netherlands</td>
<td>Turkey</td>
</tr>
<tr>
<td>Estonia</td>
<td>Poland</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>France</td>
<td>Portugal</td>
<td>United States of America</td>
</tr>
<tr>
<td>Germany</td>
<td>Russia</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>Serbia</td>
<td></td>
</tr>
</tbody>
</table>
TABLE OF
CONTENTS

WELCOME MESSAGES ................................................................. 8
CONFERENCE COMMITTEES .................................................. 13
GENERAL INFORMATION ....................................................... 14
SOCIAL EVENTS ........................................................................ 17
ABOUT MILAN .......................................................................... 19
CONFERENCE SITE MAPS ..................................................... 22
TIMETABLE .............................................................................. 25
PROGRAMME AT A GLANCE .................................................. 31
SUNDAY, SEPTEMBER 1 ......................................................... 33
MONDAY, SEPTEMBER 2 ......................................................... 37
TUESDAY, SEPTEMBER 3 ........................................................ 44
WEDNESDAY, SEPTEMBER 4 .................................................. 51
ABSTRACTS ............................................................................. 57
ABSTRACT INDEX ...................................................................... 203
Dear Participants,

Welcome to Milan!

Elucidating the molecular mechanisms of regulation of the nervous system is a major challenge in the field of neurochemistry. ESN has regularly focused on the latest advances in this area at its biennial meetings for over 40 years. This theme will be continued at our 2019 ESN Meeting in Milan which will cover a variety of topics linked to the molecular and cellular mechanisms underpinning brain function in health and disease. The Symposia and Plenary Lectures feature neurodevelopment and neurodegeneration, brain metabolism, neuroreceptors and signaling, neuropeptides, glial function, organelle dysfunction, epigenetic mechanisms, protein aggregation and folding, and novel preclinical disease models and tools. Our goal is to promote discussions between junior and senior scientists and to share new findings between basic and clinical researchers. The meeting will outline new concepts and future directions in neurochemistry and provide a very active scientific and social programme for our young generation of neurochemists.

We welcome you in Milan to participate in this exciting meeting and to share with us your latest research.

We wish you a pleasant stay and a fruitful meeting for your science!

Nico Mitro  
Chair of the 23rd ESN Meeting Local Organizing Committee

Angelo Poletti  
Co-chair of the 23rd ESN Meeting Local Organizing Committee

Massimo Aureli  
Co-chair of the 23rd ESN Meeting Local Organizing Committee
Dear Participants,

We are delighted to welcome you on behalf of the European Society for Neurochemistry (ESN) to the 23rd meeting of our Society in Milan, Italy. The ESN was founded in 1976 with the objectives to advance Neurochemistry for the public benefit and to promote the development of Neurochemistry in Europe. Every second year we come together to look over our scientific developments, to get inspiration for further studies and to establish new collaborations. Two years ago in Paris we celebrated with the International Society for Neurochemistry and the Journal of Neurochemistry our 40th, 50th and 60th anniversaries, respectively – which together accounted for 150 years of excellent science!

This year we are meeting in Milan which has an outstanding record in neuroscience and neurochemistry. The Program Committee, together with the Local Organising Committee, have prepared an exciting scientific programme with prominent international plenary speakers, topical symposia and numerous poster presentations. It has already become a tradition to have the Young Members’ Symposia at ESN meetings with the aim of giving our young members international experience in presenting their latest scientific results as symposium talks. We hope that our meeting will give you numerous opportunities for scientific exchange and collaboration. The scientific content of our meeting will be enriched with two special events for young scientists and completed by relaxing social events.

We are convinced that you will enjoy our meeting and that you will have a great time in Milan.

Ago Rinken  
President of ESN

Natalia Nalivaeva  
Secretary of ESN

Johannes Hirrlinger  
Treasurer of ESN
23rd ESN BIENNIAL MEETING
2019
in Milan
CONGRESS COMMITTEES

ESN Council

Ago Rinken, President (Estonia)
Natalia N Nalivaeva, Secretary (United Kingdom/Russia)
Johannes Hirrlinger, Treasurer (Germany)
Jacqueline S de Bellerocché, Company Secretary (United Kingdom)
Eva-Maria Blumrich, ESN YSSC (Germany/United Kingdom)
Ilana Gozes (Israel)
Fabrizio Michetti (Italy)
Nico Mitro (Italy)
Jean-Pierre Mothet (France)
Alessandro Prinetti, Past-President (Italy)
Marcus Rattray (United Kingdom)
Anthony J Turner, Historian (United Kingdom)
Helle S Waagepetersen (Denmark)

Local Organizing Committee

Nico Mitro (Milan, Italy) - Chair
MariaPia Abbacchio (Milan, Italy)
Massimo Aureli (Milan, Italy)
Angelo Poletti (Milan, Italy)
Matteo Audano (Milan, Italy)
Donatella Caruso (Milan, Italy)
Elena Chiricozzi (Milan, Italy)
Riccardo Cristofani (Milan, Italy)
Mariarita Galbiati (Milan, Italy)
Silvia Pedretti (Milan, Italy)
Natalia N Nalivaeva (ESN Secretary, Leeds, United Kingdom/St Petersburg, Russia)
Johannes Hirrlinger (ESN Treasurer, Leipzig, Germany).

Programme Committee

Anthony J Turner (Leeds, United Kingdom) - Chair
Philip M Beart (Melbourne, Australia)
Olga Corti (Paris, France)
Ralf Dringen (Bremen, Germany)
Ilana Gozes (Tel Aviv, Israel)
Ago Rinken (Tartu, Estonia)
Fabrizio Michetti (Rome, Italy)
Alessandro Prinetti (Milan, Italy)
Nico Mitro (Milan, Italy)
Marcus Rattray (Bradford, United Kingdom)
Helle S Waagepetersen (Copenhagen, Denmark)
Andrzej Szutowicz (Gdansk, Poland)
GENERAL INFORMATION

Congress venue address and contact

Università degli Studi di Milano
Via Festa del Perdono, 7
20122, Milan

The meeting will take place at the Università degli Studi di Milano, one of the largest universities in Italy. Scientific sessions will be held in the main historical building of the university: “Ca’Granda”, located very close to the main attractions of the city.

Registration Desk opening hours

Secretariat desk is located to the right of the main entrance (Via Festa del Perdono 7, Milano) of Università degli Studi di Milano (atrio aula magna - foyer auditorium).

<table>
<thead>
<tr>
<th>Opening hours</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunday 1 September</td>
<td>From noon to 6.00 pm</td>
</tr>
<tr>
<td>Monday 2 September</td>
<td>From 8.30 am to 8.30 pm</td>
</tr>
<tr>
<td>Tuesday 3 September</td>
<td>From 8.30 am to 6.30 pm</td>
</tr>
<tr>
<td>Wednesday 4 September</td>
<td>From 8.30 am to 1.00 pm</td>
</tr>
</tbody>
</table>

Tickets for booked social events are included in your registration documents. If you cannot attend an event, please return your ticket either to the registration desk or to the congress office. On-site payments for registrations can be made and tickets for social events can be purchased at the registration desk. Payments can be made by cash, credit or debit card (VISA, MasterCard, Maestro).
REGISTRATION FEE
On-site registration

<table>
<thead>
<tr>
<th>Category</th>
<th>Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard fee</td>
<td>€ 350</td>
</tr>
<tr>
<td>ESN Members registration fee</td>
<td>€ 300</td>
</tr>
<tr>
<td>Student ESN Members</td>
<td>€ 200</td>
</tr>
<tr>
<td>Students fee</td>
<td>€ 250</td>
</tr>
<tr>
<td>Daily fee</td>
<td>€ 200</td>
</tr>
<tr>
<td>Accompanying persons fee</td>
<td>€ 100</td>
</tr>
</tbody>
</table>

Language
The official Language of the Conference is English, which will be used for all presentations and printed material.

Conference badge
All attendants must wear their name badges at all times to have access to all conference sessions, events and receptions.
Please make sure to bring your badge and invitation cards with you to attend the social events.
Attendance may be refused to the participants devoid of the registration documents and invitation cards.

Wi-Fi connection
Wi-Fi connection is available throughout the University.

Presentation guidelines
The Session Chairs and Co-chairs are responsible for managing the time for questions and answers as scheduled. Computer and projection equipment will be available in each conference room. For presentations we advise to use PowerPoint or pdf slides, 4:3 layout, according to the template. Presentation files should be uploaded via USB memory device in the conference room assigned to each Speaker.
Please upload your presentation during the break preceding your session at the latest.

Poster presentation schedule
All posters will be on display during the Monday and Tuesday poster sessions. Please check the number of your poster in the ABSTRACT INDEX. Posters should be mounted on Monday, September 2nd morning and removed on Tuesday, September 3rd evening.
Presenters of the posters with odd numbers should be in attendance on Monday and, of even numbers, on Tuesday poster sessions, respectively.

Poster presentation schedule:
<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday Sept 2nd</td>
<td>Poster Session: from 12.30 pm to 3.00 pm</td>
</tr>
<tr>
<td>Tuesday Sept 3rd</td>
<td>Poster Session: from 12.30 pm to 3.00 pm</td>
</tr>
</tbody>
</table>

Poster removal schedule:
<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuesday Sept 3rd</td>
<td>from 6.30 pm to 7.30 pm</td>
</tr>
</tbody>
</table>

Setting up material will be available on site. The organizers are not responsible for anything left unattended at the poster site, including posters.
**Personal Property**
The participants are advised to take good care of their personal belongings, and not leave them unattended. Neither the Conference organizers nor their staff will be responsible for any loss or damage of any personal property of the participants.

**Disclaimer**
The Organizing Committee does not accept any liability for injuries/losses of whatever nature incurred by Conference participants and/or accompanying persons, nor for loss or damage to their luggage and/or their personal belongings.
SOCIAL EVENTS

The Social Programme includes:

- Welcome Reception on Sunday 1st September
- Conference Dinner on Tuesday 3rd September
- Walking city tour on Wednesday 4th September

WELCOME RECEPTION
Università degli Studi di Milano | Sunday, September 1 | 2019 – 7.30 pm
Cortile del ‘700 – Courtyard ‘700.

CONFERENCE DINNER
Università degli Studi di Milano | Tuesday, September 3 | 2019 – 8.00 pm
Cortile D’Onore – Courtyard UniMI.

Dress Code: smart casual.
Please make sure you bring your invitation card with you.
SPECIAL DIET: please place your “Special Diet ticket” on the table in front of you to help the service.
Thank you in advance.

WALKING CITY TOUR
Wednesday, September 4th | 2019 – 1.00 pm
Meeting point at the entrance of the University.
Milan is one of the most important and stylish cities in Italy. Milan's origin goes back to 400 B.C., when Gauls settled and defeated the Etruscans. In 222 B.C. the city was conquered by Romans and was annexed to the Roman Empire. In 1300 the Visconti family brought a period of glory and wealth to the city, building the Duomo and the Castle. The Sforza family then assumed the Castle and the power of the Visconti family, achieving peace after many years of war against Venice and Florence. Under the Sforza duchy the city began the development of sciences, art and literature. Ludovico il Moro (Ludovico Sforza) called Leonardo da Vinci and Bramante to his court. Attractions not to be missed are the Duomo – the third-largest cathedral in the world; the Sforzesco Castle, built in 1368 later became an elegant and stunning Renaissance residence; Teatro alla Scala Opera House – completed in 1776 and hosting superb theatrical productions; and Santa Maria delle Grazie – an elaborate church dating back to 1463, home of Leonardo da Vinci's famous painting 'The Last Supper'. You can also enjoy many art galleries and museums, such as Pinacoteca di Brera Gallery – housing one of Italy's most important art collections; the Museo del Novecento, the Modern Art Gallery and many others. The stratification of these different art styles gives Milan a quintessential uniqueness and will provide an unforgettable setting for the ESN2019 Conference. Milan is the city of fashion, with shops to suit all tastes and budgets. Italy is well known for its cuisine, and the Milanese cuisine has much to offer starting from its classic risotto. Milan is thus an intriguing blend of history, art, fashion and fun.

Detailed information about tourism in Milano at: http://www.turismo.milano.it/wps/portal/tur/en
General information about Milan

Milan is one of the most important and stylish cities in Italy.

Milan’s origin goes back to 400 B.C., when Gauls settled and defeated the Etruscans. In 222 B.C. the city was conquered by Romans and was annexed to the Roman Empire. In 1300 the Visconti family brought a period of glory and wealth to the city, building the Duomo and the Castle. The Sforza family then assumed the Castle and the power of the Visconti family, achieving peace after many years of war against Venice and Florence. Under the Sforza duchy the city began the development of sciences, art and literature. Ludovico il Moro (Ludovico Sforza) called Leonardo da Vinci and Bramante to his court. Attractions not to be missed are the Duomo – the third-largest cathedral in the world; the Sforzesco Castle, built in 1368 later became an elegant and stunning Renaissance residence; Teatro alla Scala Opera House – completed in 1776 and hosting superb theatrical productions; and Santa Maria delle Grazie – an elaborate church dating back to 1463, home of Leonardo da Vinci’s famous painting ‘The Last Supper’. You can also enjoy many art galleries and museums, such as Pinacoteca di Brera Gallery – housing one of Italy’s most important art collections; the Museo del Novecento, the Modern Art Gallery and many others. The stratification of these different art styles gives Milan a quintessential uniqueness and will provide an unforgettable setting for the ESN2019 Conference. Milan is the city of fashion, with shops to suit all tastes and budgets. Italy is well known for its cuisine, and the Milanese cuisine has much to offer starting from its classic risotto. Milan is thus an intriguing blend of history, art, fashion and fun.

Detailed information about tourism in Milano at: http://www.turismo.milano.it/wps/portal/tur/en
GETTING AROUND MILAN

CITY BIKE (BIKE MI) www.bikemi.com

BikeMi is Milan’s Bike Sharing service, a real public bicycle transport system to be used for short trips. Detailed information at www.bikemi.com. It is a sharing public transport system therefore it has to be used by as many people as possible. For this reason the first 30 minutes of each use are free for traditional bikes, while the following minutes are charged according to the arranged rates.

CITY CAR www.car2go.com/en/milano/

If you need a city car, a “car2go” is always a pleasure to drive: book it, drive it, park it. Simple and straightforward. You can always find a vehicle in your area. www.car2go.com/en/milano/

TRAVELLING BY TRAM, BUS and METRO

Getting around in Milan is very easy and cheap if you take advantage of their readily available public transportation. The Milan Tramway network is an important part of the public transport network of Milan. It comprises 17 urban lines and 2 interurban lines. You can buy tickets at the metro stations, at giornali (kiosk) or tabacchi (stores marked with “T”), but not on the bus or tram.

The closest metro stop is: Missori (metro line 3, yellow): www.atm.it

<table>
<thead>
<tr>
<th>Ticket</th>
<th>Time</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Ticket</td>
<td>90 Minutes after validation</td>
<td>€ 2,00</td>
</tr>
<tr>
<td>Carnet 10 tickets</td>
<td>Ten 90 Minutes tickets</td>
<td>€ 18,00</td>
</tr>
<tr>
<td>1 Day Ticket</td>
<td>24 Hours after validation</td>
<td>€ 7,00</td>
</tr>
<tr>
<td>2 Days Ticket</td>
<td>48 Hours after validation</td>
<td>€ 8.25</td>
</tr>
<tr>
<td>3 Days Ticket</td>
<td>72 Hours after validation</td>
<td>€ 12,00</td>
</tr>
</tbody>
</table>

TRAIN

from Milan Central railway station: take underground Line no. 3 (yellow line) and get off at Missori station. The university is 5 minutes away.

from Porta Garibaldi railway stations take underground Line no. 2 (green line) to Milano Centrale and then take Line no. 3 (yellow line) and get off at Missori station. The university is 5 minutes away.

PLANE

from Malpensa airport: every 20 minutes, daily bus service to Milan Central Railway Station. Every 30-60 minutes, train service to Milan Central Railway Station: www.malpensaexpress.it

from Bergamo Orio al Serio Airport:

Terravision bus to Milan Central Railway Station: www.terravision.eu/milan_bergamo.html

Orio shuttle to Milan Central Railway Station: www.orioshuttle.com

TAXI

Taxi: (+39) 024040 or 026969 or 028585

Useful phone numbers

Emergency: 112

Tipping

Service is usually included in all restaurant bills, even though tips are widely accepted and expected by waiters and tour guides.

Currency, Banks and Post Office

Currency in Italy is Euro / €. Bank opening hours:

Monday to Friday: 08.35 am / 1.35 pm, 2.45 pm / 4.15 pm

Closed on Saturdays and Sundays

Cash dispensers open 24/7

Post Office opening hours:

Monday to Friday: 08.30 am / 2.00 pm

Saturday: 08.30 am / 12.30 pm.

Telephone:

The Italian telephone country code is +39
GETTING AROUND MILAN

CITY BIKE (BIKE MI) www.bikemi.com

BikeMi is Milan’s Bike Sharing service, a real public bicycle transport system to be used for short trips. Detailed information at www.bikemi.com.

It is a sharing public transport system therefore it has to be used by as many people as possible. For this reason the first 30 minutes of each use are free for traditional bikes, while the following minutes are charged according to the arranged rates.

CITY CAR www.car2go.com/en/milano/

If you need a city car, a “car2go” is always a pleasure to drive: book it, drive it, park it. Simple and straightforward. You can always find a vehicle in your area.

TRAVELLING BY TRAM, BUS and METRO

Getting around in Milan is very easy and cheap if you take advantage of their readily available public transportation. The Milan Tramway network is an important part of the public transport network of Milan. It comprises 17 urban lines and 2 interurban lines. You can buy tickets at the metro stations, at giornali (kiosk) or tabacchi (stores marked with “T”), but not on the bus or tram.

The closest metro stop is: Missori (metro line 3, yellow): www.atm.it

<table>
<thead>
<tr>
<th>Ticket Type</th>
<th>Time Validity</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Ticket</td>
<td>90 Minutes after validation</td>
<td>€2.00</td>
</tr>
<tr>
<td>Carnet 10 tickets</td>
<td>Ten 90 Minutes</td>
<td>€18.00</td>
</tr>
<tr>
<td>1 Day Ticket</td>
<td>24 Hours after validation</td>
<td>€7.00</td>
</tr>
<tr>
<td>2 Days Ticket</td>
<td>48 Hours after validation</td>
<td>€8.25</td>
</tr>
<tr>
<td>3 Days Ticket</td>
<td>72 Hours after validation</td>
<td>€12.00</td>
</tr>
</tbody>
</table>

TRAIN

from Milan Central railway station: take underground Line no. 3 (yellow line) and get off at Missori station. The university is 5 minutes away.

from Porta Garibaldi railway stations take underground Line no. 2 (green line) to Milano Centrale and then take Line no. 3 (yellow line) and get off at Missori station. The university is 5 minutes away.

PLAN

E from Malpensa airport: every 20 minutes, daily bus service to Milan Central Railway Station. Every 30-60 minutes, train service to Milan Central Railway Station: www.malpensaexpress.it

from Bergamo Orio al Serio Airport:
- Terravision bus to Milan Central Railway Station: www.terravision.eu/milan_bergamo.html
- Orio shuttle to Milan Central Railway Station: www.orioshuttle.com

TAXI

Taxi: (+39) 024040 or 026969 or 028585

Useful phone numbers

Emergency: 112

TIPPING

Service is usually included in all restaurant bills, even though tips are widely accepted and expected by waiters and tour guides.

CURRENCY, BANKS AND POST OFFICE

Currency in Italy is Euro / €.

Bank opening hours:
Monday to Friday: 08.35 am / 1.35 pm, 2.45 pm / 4.15 pm
Closed on Saturdays and Sundays
Cash dispensers open 24/7

Post Office opening hours:
Monday to Friday: 08.30 am / 2.00 pm
Saturday: 08.30 am / 12.30 pm.

Telephone:
The Italian telephone country code is +39
<table>
<thead>
<tr>
<th>Time</th>
<th>Location</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>noon</td>
<td>FOYER AUDITORIUM</td>
<td>Participant registration</td>
</tr>
<tr>
<td>6.00 pm</td>
<td>113 ROOM</td>
<td>1° ESN Council meeting</td>
</tr>
<tr>
<td>noon</td>
<td>113 ROOM</td>
<td>Sensory processing sensitivity and drug use recovery pathways</td>
</tr>
<tr>
<td>3.00 pm</td>
<td>113 ROOM</td>
<td>Molecular mechanisms regulating oligodendroglial functions and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>re-/myelination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(E. Boda and D. Lecca) - S2</td>
</tr>
<tr>
<td>10.30 am</td>
<td>MALLIANI ROOM</td>
<td>The role of lysosomal dysfunction in neurodegeneration</td>
</tr>
<tr>
<td>noon</td>
<td>MALLIANI ROOM</td>
<td>(P. Rusmini) - S4</td>
</tr>
<tr>
<td>10.30 am</td>
<td>111 ROOM</td>
<td>Signalling and signatures of the developing nervous systems</td>
</tr>
<tr>
<td>noon</td>
<td>111 ROOM</td>
<td>(A. Cariboni) - S5</td>
</tr>
<tr>
<td>10.30 am</td>
<td>111 ROOM</td>
<td>Enlightening the social brain: oxytocin neurons, connections</td>
</tr>
<tr>
<td>noon</td>
<td>111 ROOM</td>
<td>(B. Chini) - S6</td>
</tr>
<tr>
<td>10.30 am</td>
<td>111 ROOM</td>
<td>Lunch and Poster Session</td>
</tr>
<tr>
<td>noon</td>
<td>111 ROOM</td>
<td>Brain energy metabolism – back in the spotlight</td>
</tr>
<tr>
<td>10.30 am</td>
<td>111 ROOM</td>
<td>Cys-loop receptors: function and modulation</td>
</tr>
<tr>
<td>noon</td>
<td>111 ROOM</td>
<td>(P. Bregestovsky and V. Tsetlin) - S8</td>
</tr>
<tr>
<td>10.30 am</td>
<td>111 ROOM</td>
<td>ADNP and the ADNP syndrome: from gene to autism</td>
</tr>
<tr>
<td>noon</td>
<td>111 ROOM</td>
<td>How to make a living with a Ph.D.</td>
</tr>
<tr>
<td>10.30 am</td>
<td>111 ROOM</td>
<td>(E.-M. Blumrich) - S10</td>
</tr>
<tr>
<td>noon</td>
<td>111 ROOM</td>
<td>Opening reception</td>
</tr>
<tr>
<td>10.30 am</td>
<td>111 ROOM</td>
<td>Opening reception</td>
</tr>
</tbody>
</table>

Chair: ESN President A. Rinken
Principles of astrogliopathology: From reactivity to atrophy and degeneration
A. Verkhratsky - PL1
## ISN LECTURE

### AUDITORIUM

<table>
<thead>
<tr>
<th>Session</th>
<th>09.00 am</th>
<th>10.00 am</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coffee break - ‘700 Courtyard</td>
<td></td>
</tr>
</tbody>
</table>

**Chair:** ISN Council A. J. Turner - Leeds, UK

**Axonal transport as a therapeutic target** - G. Schiavo - PL2

### PARALLEL SESSIONS

<table>
<thead>
<tr>
<th>Session</th>
<th>10.30 am noon</th>
<th>12.30 pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CROCIERA ROOM</td>
<td>The role of lysosomal dysfunction in neurodegeneration (P. Rusmini) - S4</td>
<td></td>
</tr>
<tr>
<td>111 ROOM</td>
<td>Signalling and signatures of the developing nervous systems (A. Cariboni - A. Fantin) - S5</td>
<td></td>
</tr>
<tr>
<td>113 ROOM</td>
<td>Enlightening the social brain: oxytocin neurons, connections and functions (B. Chini) - S6</td>
<td></td>
</tr>
</tbody>
</table>

**Lunch and Poster Session**

<table>
<thead>
<tr>
<th>Session</th>
<th>3.00 pm 5.00 pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>111 ROOM</td>
<td>Brain energy metabolism – back in the spotlight (A. Trevisiol) - S7</td>
</tr>
<tr>
<td>113 ROOM</td>
<td>Cys-loop receptors: function and modulation (P. Bregestovsky and V. Tsetlin) - S8</td>
</tr>
<tr>
<td>113 ROOM</td>
<td>ADNP and the ADNP syndrome: from gene to autism (I. Gozes) - S9</td>
</tr>
</tbody>
</table>

**Coffee break - ‘700 Courtyard**

### ESN BUSINESS MEETING

**YOUNG NEUROCHEMISTS’ SESSION**

<table>
<thead>
<tr>
<th>Session</th>
<th>7.00 pm 8.30 pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>111 ROOM</td>
<td>How to make a living with a Ph.D. (E.-M. Blumrich) - S10</td>
</tr>
<tr>
<td>‘700 COURTYARD</td>
<td>Student Aperitif</td>
</tr>
</tbody>
</table>

---
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.00 am</td>
<td><strong>YOUNG SCIENTIST LECTURESHIP AWARD</strong></td>
</tr>
<tr>
<td>10.00 am</td>
<td>Chair: ESN Council member J.-P. Mothet</td>
</tr>
<tr>
<td></td>
<td>Presynaptic nanomachines: regulation of the quantal release of glutamate</td>
</tr>
<tr>
<td></td>
<td>- M. Martineau - YSLA1</td>
</tr>
<tr>
<td>10.00 am</td>
<td>Chair: ESN Treasurer J. Hirrlinger</td>
</tr>
<tr>
<td></td>
<td>Exploring mechanisms of neuron-glial signalling and metabolic interactions</td>
</tr>
<tr>
<td></td>
<td>- A. Saab - YSLA2</td>
</tr>
<tr>
<td>10.00 am</td>
<td>Coffee break - '700 Courtyard</td>
</tr>
<tr>
<td>12.30 pm</td>
<td>Lunch and Poster Session</td>
</tr>
<tr>
<td>12.30 pm</td>
<td><strong>MALLIANI ROOM</strong></td>
</tr>
<tr>
<td></td>
<td>Mitochondrial and autophagocytic alterations in Parkinson's disease</td>
</tr>
<tr>
<td></td>
<td>(E. Kramer) - S11</td>
</tr>
<tr>
<td>12.30 pm</td>
<td><strong>111 ROOM</strong></td>
</tr>
<tr>
<td></td>
<td>The NMDA receptors: from synapse physiology to pathology</td>
</tr>
<tr>
<td></td>
<td>(J.-P. Mothet) - S12</td>
</tr>
<tr>
<td>12.30 pm</td>
<td>Brain metabolism failure as a common factor in rare diseases</td>
</tr>
<tr>
<td></td>
<td>(J. Bolaños) - S13</td>
</tr>
<tr>
<td>12.30 pm</td>
<td><strong>113 ROOM</strong></td>
</tr>
<tr>
<td></td>
<td><strong>YOUNG MEMBERS’ SYMPOSIA I &amp; II</strong></td>
</tr>
<tr>
<td>3.00 pm</td>
<td>Young Members’ Symposia I</td>
</tr>
<tr>
<td></td>
<td>(A.J. Turner) - S14</td>
</tr>
<tr>
<td>4.30 pm</td>
<td>Young Members’ Symposia II</td>
</tr>
<tr>
<td></td>
<td>(A. Prinetti) - S15</td>
</tr>
<tr>
<td>4.30 pm</td>
<td>Coffee break - '700 Courtyard</td>
</tr>
<tr>
<td>5.00 pm</td>
<td><strong>PARALLEL SESSIONS</strong></td>
</tr>
<tr>
<td></td>
<td>Blood brain barrier models, mechanisms and metabolism in health and</td>
</tr>
<tr>
<td></td>
<td>disease (S. Saha) - S16</td>
</tr>
<tr>
<td>5.00 pm</td>
<td>The type 2 cannabinoid receptor: an emerging target for brain</td>
</tr>
<tr>
<td></td>
<td>therapeutics (P. Brust) - S17</td>
</tr>
<tr>
<td>5.00 pm</td>
<td>The emerging role of S100B in pathogenic processes of neural disorder</td>
</tr>
<tr>
<td></td>
<td>(A. Fernandes) - S18</td>
</tr>
<tr>
<td>8.00 pm</td>
<td>Courtyard UniMI</td>
</tr>
<tr>
<td>8.00 pm</td>
<td>Conference Dinner</td>
</tr>
<tr>
<td>Session</td>
<td>MALLIANI ROOM</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td>10.30 am</td>
<td>Brain acetylation processes in health and disease (A. Szutowicz) - S19</td>
</tr>
<tr>
<td>12.30 pm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session</th>
<th>AUDITORIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.30 pm</td>
<td>Closing Ceremony</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session</th>
<th>113 ROOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00 pm onwards</td>
<td>2° ESN Council meeting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session</th>
<th>23rd ESN BIENNIAL MEETING</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>
PROGRAMME AT A GLANCE

23rd ESN BIENNIAL MEETING
### 23rd ESN BIENNIAL MEETING

#### FOYER AUDITORIUM

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>noon</td>
<td>Participant registration</td>
</tr>
<tr>
<td>6.00 pm</td>
<td></td>
</tr>
</tbody>
</table>

#### Session

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.00 pm</td>
<td>1° ESN Council meeting</td>
</tr>
<tr>
<td>3.00 pm</td>
<td></td>
</tr>
</tbody>
</table>

#### PARALLEL SATELLITE SYMPOSIA

<table>
<thead>
<tr>
<th>Session</th>
<th>MALLIANI ROOM - S1</th>
<th>111 ROOM - S2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.00 pm</td>
<td>Sensory processing sensitivity and drug use recovery pathways F. Fumagalli (Milan, IT)</td>
<td>Molecular mechanisms regulating oligodendroglial functions and re-/myelination E. Boda (Turin, IT) and D. Lecca (Milan, IT)</td>
</tr>
<tr>
<td>2.30 pm</td>
<td>Neuroplasticity in an animal model of SPS: evidence from rats lacking the serotonin transporter F. Fumagalli (Milan, IT)</td>
<td>Are oligodendrocyte progenitors all born equal? A lesson from a microcephaly model E. Boda (Turin, IT)</td>
</tr>
<tr>
<td>3.00 pm</td>
<td>The contribution of environmental sensitivity to vulnerability to cocaine addiction a preclinical study J. Homberg (Nijmegen, NL)</td>
<td>Post-transcriptional regulation in oligodendrocytes: the strategy of miR-125a-3p D. Lecca (Milan, IT)</td>
</tr>
<tr>
<td>3.30 pm</td>
<td>Sensory processing sensitivity and drug use recovery pathways M. Mary-Krause (Paris, FR)</td>
<td>Enhancing D-Aspartate signaling to promote (re)myelination F. Boscia (Naples, IT)</td>
</tr>
<tr>
<td>4.00 pm</td>
<td>Sensory-processing sensitivity in substance use disorders and its relation to cognition and behavior B. Quednow (Zurich, CH)</td>
<td>Decline of oligodendrogenesis in the ageing brain A. Rivera (Naples, IT)</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>12.00 pm</td>
<td>Participant registration</td>
<td></td>
</tr>
<tr>
<td>06.00 pm</td>
<td>Session</td>
<td></td>
</tr>
<tr>
<td>111 ROOM -S3</td>
<td>My first conference</td>
<td></td>
</tr>
<tr>
<td>E. M. Blumrich (Edinburgh, UK)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G. Smirnova (Moscow, RU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02.00 pm</td>
<td>Neuroplasticity in an animal model of SPS: evidence from rats lacking the serotonin transporter</td>
<td></td>
</tr>
<tr>
<td>F. Fumagalli (Milan, IT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02.30 pm</td>
<td>Are oligodendrocyte progenitors all born equal? A lesson from a microcephaly model</td>
<td></td>
</tr>
<tr>
<td>E. Boda (Turin, IT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. Lecca (Milan, IT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03.00 pm</td>
<td>The contribution of environmental sensitivity to vulnerability to cocaine addiction: a preclinical study</td>
<td></td>
</tr>
<tr>
<td>J. Homberg (Nijmegen, NL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03.30 pm</td>
<td>Post-transcription regulation in oligodendrocytes: the strategy of miR-125a-3p</td>
<td></td>
</tr>
<tr>
<td>D. Lecca (Milan, IT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03.30 pm</td>
<td>Sensory processing sensitivity and drug use recovery pathways</td>
<td></td>
</tr>
<tr>
<td>M. Mary-Krause (Paris, FR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>04.00 pm</td>
<td>Enhancing D-Aspartate signaling to promote (re)myelination</td>
<td></td>
</tr>
<tr>
<td>F. Boscia (Naples, IT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>04.00 pm</td>
<td>Sensory-processing sensitivity in substance use disorders and its relation to cognition and behavior</td>
<td></td>
</tr>
<tr>
<td>B. Quednow (Zurich, CH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>05.30 pm</td>
<td>Decline of oligodendrogenesis in the ageing brain</td>
<td></td>
</tr>
<tr>
<td>A. Rivera (Naples, IT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>06.00 pm</td>
<td>Plenary Lecture (Chair: ESN President A. Rinken - Tartu, EE)</td>
<td></td>
</tr>
<tr>
<td>Principles of astroglialpathology: From reactivity to atrophy and degeneration - A. Verkhratsky (Manchester, UK)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>06.00 pm</td>
<td>SF Evening Welcome</td>
<td></td>
</tr>
<tr>
<td>07.00 pm</td>
<td>Opening ceremony</td>
<td></td>
</tr>
<tr>
<td>07.30 pm</td>
<td>SF Opening reception</td>
<td></td>
</tr>
<tr>
<td>07.30 pm</td>
<td>SF Pre-registration for Young Neurochemists’ informal welcome</td>
<td></td>
</tr>
</tbody>
</table>
## ISN LECTURE

<table>
<thead>
<tr>
<th>Session</th>
<th>09.00 am</th>
<th>10.00 am</th>
</tr>
</thead>
</table>

## ’700 COURTYARD

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.00 am</td>
<td>Coffee break</td>
</tr>
</tbody>
</table>

## PARALLEL SESSIONS

<table>
<thead>
<tr>
<th>Session</th>
<th>10.30 am</th>
<th>11.00 am</th>
<th>11.30 am</th>
<th>noon</th>
</tr>
</thead>
<tbody>
<tr>
<td>CROCIERA ROOM - S4</td>
<td>The role of lysosomal dysfunction in neurodegeneration (P. Rusmini - Milan, IT and D. Rubinzstein - Cambridge, UK)</td>
<td>Molecules capable to induce neuroprotection via lysophagy activation P. Rusmini (Milan, IT)</td>
<td>Glucocerebrosidase and Parkinson disease A. Schapira (London, UK)</td>
<td>Inhibiting amyloid protein aggregation relieves lysosomal-autophagic dysfunction and protects against neurodegeneration in lysosomal storage diseases A. Fraldi (Naples, IT)</td>
</tr>
<tr>
<td>111 ROOM - S5</td>
<td>Signalling and signatures of the developing nervous systems (A. Cariboni - Milan, IT and A. Fantin - Milan, IT)</td>
<td>From the nose to the brain: semaphorin signalling in the control of GnRH neuron development A. Cariboni (Milan, IT)</td>
<td>Understanding the molecular mechanisms of angiogenesis in the brain and retina A. Fantin (Milan, IT)</td>
<td>Non-monotonic regulation of gene expression, neural progenitor fate and brain growth by the chromatin remodeler CHD8 M.A. Basson (London, UK)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Molecular control of cortical layer development by transmembrane Semaphorins J. Pasterkamp (Utrecht, NL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The content provided is a natural representation of the document in question. For a more detailed and comprehensive understanding, refer to the official document.
ISN LECTURE
Session
AUDITORIUM - PL2
09.00 am - 10.00 am
Plenary ISN Lecture (Chair: ISN President R. Dringen - Bremen, DE)
Axonal transport as a therapeutic target
G. Schiavo (London, UK)

10.00 am - 10.00 am
Coffee break

PARALLEL SESSIONS
Session
CROCIERA ROOM - S5 111 ROOM - S6
10.30 am - 11.00 am
The role of lysosomal dysfunction in neurodegeneration
(P. Rusmini - Milan, IT and D. Rubinzstein - Cambridge, UK)
Signalling and signatures of the developing nervous systems
A. Cariboni (Milan, IT)

10.30 am - 11.00 am
Molecules capable to induce neuroprotection via lysophagy activation
P. Rusmini (Milan, IT)
From the nose to the brain: semaphorin signalling in the control of GnRH neuron development
A. Cariboni (Milan, IT)

11.00 am - 11.30 am
Glucocerebrosidase and Parkinson disease
A. Schapira (London, UK)
Understanding the molecular mechanisms of angiogenesis in the brain and retina
A. Fantin (Milan, IT)

11.30 am - 12.00 am
Inhibiting amyloid protein aggregation relieves lysosomal-autophagic dysfunction and protects against neurodegeneration in lysosomal storage diseases
A. Fraldi (Naples, IT)
Non-monotonic regulation of gene expression, neural progenitor fate and brain growth by the chromatin remodeller CHD8
M. A. Basson (London, UK)

12.00 pm - 12.30 pm
Autophagy and neurodegeneration
D. Rubinsztein (Cambridge, UK)
Molecular control of cortical layer development by transmembrane Semaphorins
J. Pasterkamp (Utrecht, NL)

113 ROOM - S6
Enlightening the social brain: oxytocin neurons, connections and functions
B. Chini - (Milan IT)

How does an oxytocin treatment in early life impact social behavior and hippocampal alterations in Magel2-deficient mice?
F. Muscatelli (Marseille, FR)

Oxytocin signaling in the central amygdala modulates emotion discrimination in mice
F. Papaleo (Genoa, IT)

Prolonged optogenetic activation of oxytocin neurons in groups of mice increases prosocial and agonistic behaviors
Y. Shemesh (Rehovot, IL)
### Lunch and Poster Session

**‘700 COURTYARD**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Location</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.30 pm</td>
<td></td>
<td>111 ROOM - S8</td>
<td>Lunch and Poster Session</td>
</tr>
</tbody>
</table>

### PARALLEL SESSIONS

#### CROCIERA ROOM - S7

**3.00 pm**

| Brain energy metabolism back in the spotlight | A. Trevisiol (Goettingen, DE) |
| Axonal metabolic support and energy dynamics in active white matter tracts | A. Trevisiol (Goettingen, DE) |
| Cellular mechanisms regulating axonal energy metabolism in compact white matter | A. Saab (Zurich, CH) |
| Correlation between activity-related changes in intracellular sodium and ATP in mouse hippocampal neurons | C. Rose (Duesseldorf, DE) |
| Cell type specificity of neurovascular coupling in cerebral cortex | M. Thunemann (La Jolla CA, US) |

#### 111 ROOM - S8

**3.00 pm**

<p>| Cys-loop receptors: function and modulation | P. Bregestovsky (Marseille, FR) and V. Tsetlin (Moscow, RU) |
| Photochromic modulators of Cys-loop receptors | P. Bregestovsky (Marseille, FR) |
| From neurotoxic peptides and proteins to endogenous regulators of Cys-loop receptors | V. Tsetlin (Moscow, RU) |
| Molecular interactions of 5-HT3 receptors | S. Lummis (Cambridge, UK) |
| Allosteric regulation of pentameric ligand-gated ion channels by phospholipids | C. Ulens (Leuven, BE) |</p>
<table>
<thead>
<tr>
<th>Session</th>
<th>113 ROOM - S9</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNP and the ADNP syndrome: from gene to autism</td>
<td>I. Gozes (Tel Aviv, IL)</td>
</tr>
<tr>
<td>3.00 pm</td>
<td>ADNP/NAP (CP201): From gene to clinical development</td>
</tr>
<tr>
<td>I. Gozes (Tel Aviv, IL)</td>
<td></td>
</tr>
<tr>
<td>3.24 pm</td>
<td>Clinical presentation of a complex neurodevelopmental disorder caused by mutations in ADNP</td>
</tr>
<tr>
<td>F. Kooy (Edegem, BE)</td>
<td></td>
</tr>
<tr>
<td>3.48 pm</td>
<td>De humani corporis fabrica: organoid-based deconvolution of neuropsychiatric disorders at single cell resolution</td>
</tr>
<tr>
<td>G. Testa (Milan, MI)</td>
<td></td>
</tr>
<tr>
<td>4.12 pm</td>
<td>A transcription factor implicated in autism locally constrains chromatin looping</td>
</tr>
<tr>
<td>M. Buhler (Basel, CH)</td>
<td></td>
</tr>
<tr>
<td>4.36 pm</td>
<td>De novo and inter-tissue somatic mosaicism of ADNP mutations in autistic individuals</td>
</tr>
<tr>
<td>C. Pearson (Toronto, CA)</td>
<td></td>
</tr>
<tr>
<td>5.00 pm</td>
<td></td>
</tr>
</tbody>
</table>
23rd ESN BIENNIAL MEETING

SEPTEMBER 2

5.00 pm
Coffee break

5.30 pm
ESN BUSINESS MEETING

7.00 pm
YOUNG NEUROCHEMISTS’ SESSION

7.00 pm
How to make a living with a Ph.D. E. M. Blumrich (Edinburgh, UK)

7.22 pm
How to make money with a PhD - Introductory talk: general ideas on career planning E. M. Blumrich (Edinburgh, UK)

7.44 pm
Graduated and now? A personal review about working in the industry F. Bulcke (Berlin, DE)

8.06 pm
Starting a career in academia A. Prinetti (Milan, IT)

8.30 pm
From science to science publishing: opportunities and challenges A.J. Turner (Leeds, UK)

8.30 pm
Student Aperitif
23RD ESN BIENNIAL MEETING
SEPTEMBER 2 / MONDAY '700 COURTYARD
5.00 pm Coffee break
Session
AUDITORIUM
5.30 pm 7.00 pm ESN BUSINESS MEETING
YOUNG NEUROCHEMISTS' SESSION
Session
111 ROOM - S10
How to make a living with a Ph.D.
E. M. Blumrich (Edinburgh, UK)
7.00 pm How to make money with a PhD - Introductory talk: general ideas on career planning
E. M. Blumrich (Edinburgh, UK)
7.22 pm Graduated and now? A personal review about working in the industry
F. Bulcke (Berlin, DE)
7.44 pm Starting a career in academia
A. Prinetti (Milan, IT)
8.06 pm From science to science publishing: opportunities and challenges
A. J. Turner (Leeds, UK)
8.30 pm '700 COURTYARD
Student Aperitif
3 SEPTEMBER TUESDAY

YOUNG SCIENTIST LECTURESHIP AWARD

Session
AUDITORIUM - YSLA1-YSLA2

09.00 am
10.00 am

YSLA LECTURE I
(Chair: ESN Council member J.-P. Mothet - Orsay, FR)
Presynaptic nanomachines: regulation of the quantal release of glutamate
M. Martineau (Bordeaux, FR)

YSLA LECTURE II
(Chair: ESN Treasurer J. Hirrlinger - Leipzig, DE)
Exploring mechanisms of neuron-glial signalling and metabolic interactions
A. Saab (Zurich, CH)

10.00 am
Coffee break
<table>
<thead>
<tr>
<th>Session</th>
<th>AUDITORIUM - YSLA1-YSLA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.00 am</td>
<td>YSLA LECTURE I</td>
</tr>
<tr>
<td>09.00 am</td>
<td>(Chair: ESN Council member J.-P. Mothet - Orsay, FR)</td>
</tr>
<tr>
<td>10.00 am</td>
<td>Presynaptic nanomachines: regulation of the quantal release of glutamate</td>
</tr>
<tr>
<td>10.00 am</td>
<td>M. Martineau (Bordeaux, FR)</td>
</tr>
<tr>
<td>10.00 am</td>
<td>YSLA LECTURE II</td>
</tr>
<tr>
<td>10.00 am</td>
<td>(Chair: ESN Treasurer J. Hirrlinger - Leipzig, DE)</td>
</tr>
<tr>
<td>11.00 am</td>
<td>Exploring mechanisms of neuron-glial signalling and metabolic interactions</td>
</tr>
<tr>
<td>11.00 am</td>
<td>A. Saab (Zurich, CH)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>‘700 COURTYARD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10.00 am</td>
<td>Coffee break</td>
</tr>
</tbody>
</table>
## PARALLEL SESSIONS

<table>
<thead>
<tr>
<th>Session</th>
<th>MALLIANI ROOM - S11</th>
<th>111 ROOM - S12</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.30 am</td>
<td>Mitochondrial and autophagocytic alterations in Parkinson’s disease E. Kramer (Plymouth, UK)</td>
<td>The NMDA receptors: from synapse physiology to pathology J.-P. Mothet (Orsay, FR)</td>
</tr>
<tr>
<td>11.00 am</td>
<td>Ret protects the midbrain dopaminergic system against synuclein toxicity by influencing mitochondrial integrity and autophagy E. Kramer (Plymouth, UK)</td>
<td>The NMDA receptor co-agonist D-serine is essential for dopamine modulations of prefrontal neuronal activity and cognitive function J.-P. Mothet (Orsay, FR)</td>
</tr>
<tr>
<td>noon</td>
<td>Functional genomic analysis uncovers mitophagy regulators associated with Parkinson’s disease risk H. Plun-Favreau (London, UK)</td>
<td>NMDA receptor C-terminal domain signaling in health and disease G. Hardingham (Edinburgh, UK)</td>
</tr>
<tr>
<td>12.30 pm</td>
<td>Decoding PINK1/Parkin signalling in Parkinson’s disease M. Muqit (Dundee, UK)</td>
<td>Emergence of mTOR-dependent protein translation is controlled by non-conventional NMDA receptors I. Pérez-Otano (San Juan de Alicante, ES)</td>
</tr>
</tbody>
</table>

### '700 COURTYARD

12.30 pm Lunch and Poster Session
113 ROOM - S13

Brain metabolism failure as a common factor in rare diseases
J. Bolaños (Salamanca, ES)

Brain metabolic alterations in neuronal ceroid lipofuscinosis juvenile CLN7 Batten disease
J. Bolaños (Salamanca, ES)

APC/C-Cdh1 regulates X fragile protein FMRP and dendrite stability during brain development
A. Almeida (Salamanca, ES)

Lysosomal disorders provide valuable insight into neurodegenerative conditions
S. Heales (London, UK)

The role of cholesterol metabolism in Huntington’s disease: from molecular mechanism to therapeutics
M. Valenza (Milan, IT)
# Young Members’ Symposia I & II

**Malliani Room - S14**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| 3.00 pm | Young Members’ Symposium I  
A.J. Turner (Leeds, UK)                                                |
| 3.22 pm | The Adnp-deficient mouse models synaptic and behavioral phenotypes of an autism-like syndrome  
S. Sragovich (Tel Aviv, IL)                                              |
| 3.44 pm | Metabolic heterogeneity of astrocytes in grey and white matter  
S. Köhler (Leipzig, DE)                                                  |
| 4.06 pm | Maternal hyperhomocysteinemia disturbs development of brain cortex and hippocampus and affects memory in rat offspring  
A. Shcherbitskaia (St Petersburg, RU)                                     |
| 4.06 pm | Identification of the antigen recognized in vitro by rHlgM22, a remyelination-promoting human monoclonal antibody  
L. Cabitta (Milan, IT)                                                   |

**111 Room - S15**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| 3.00 pm | Young Members’ Symposium II  
A. Prinetti (Milan, IT)                                                  |
| 3.22 pm | Long-Lasting Impairment of Neuroplastic Gene Expression as a Mechanism of Cognitive Deficit Caused by Neonatal LPS Exposure  
A. Trofimov (St Petersburg, RU)                                           |
| 3.44 pm | GM1 oligosaccharide modulation of calcium signaling in neuronal function  
G. Lunghi (Milan, IT)                                                    |
| 4.06 pm | Mushroom bodies development and abnormalities in defective Wnt pathway models  
P. Grazioli (Milan, IT)                                                  |
| 4.06 pm | How we used Wfs1 deficient rat to develop treatment strategies for Wolfram Syndrome patients  
K. Seppa (Tartu, EE)                                                     |

**’700 Courtyard**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.30 pm</td>
<td>Coffee break</td>
</tr>
</tbody>
</table>
### Young Members' Symposium I

**A.J. Turner (Leeds, UK)**

*The Adnp-deficient mouse models synaptic and behavioral phenotypes of an autism-like syndrome*

**S. Sragovich (Tel Aviv, IL)**

*Long-Lasting Impairment of Neuroplastic Gene Expression as a Mechanism of Cognitive Deficit Caused by Neonatal LPS Exposure*

**A. Trofimov (St Petersburg, RU)**

*Metabolic heterogeneity of astrocytes in grey and white matter*

**S. Köhler (Leipzig, DE)**

*GM1 oligosaccharide modulation of calcium signaling in neuronal function*

**G. Lunghi (Milan, IT)**

*Maternal hyperhomocysteinemia disturbs development of brain cortex and hippocampus and affects memory in rat offspring*

**A. Shcherbitskaia (St Petersburg, RU)**

*Mushroom bodies development and abnormalities in defective Wnt pathway models*

**P. Grazioli (Milan, IT)**

*Identification of the antigen recognized in vitro by rhigm22, a remyelination-promoting human monoclonal antibody*

**K. Seppa (Tartu, EE)**

*How we used Wfs1 deficient rat to develop treatment strategies for Wolfram Syndrome patients?*

### Young Members' Symposium II

**A. Prinetti (Milan, IT)**

*The Blood-Brain Barrier. Transcytosis of protein-based nanoparticles to the brain: a new insight into the role of astroglia*

**D. Begley (London, UK)**

*The Blood Brain Barrier. Transcytosis of protein-based nanoparticles to the brain: a new insight into the role of astroglia*

**P. Brust (Leipzig, DE)**

*Development of selective CB2 receptor inhibitors as potential probes for molecular imaging with positron emission tomography*

**M. Maccarrone (Rome, IT)**

*Endocannabinoid signalling in neuroprotection: Key-role of CB2 receptor*

### Parallel Sessions

**MALLIANI ROOM - S16**

- **5.00 pm**
  
  Blood brain barrier models, mechanisms and metabolism in health and disease  
  S. Saha (Leeds, UK)

- **5.30 pm**
  
  The Blood-Brain Barrier. Transcytosis of protein-based nanoparticles to the brain: a new insight into the role of astroglia  
  D. Begley (London, UK)

- **6.00 pm**
  
  In vitro modeling of the human blood-brain barrier - recent developments in stem cell-based human models  
  L. Saaby (Horsholm, DK)

- **6.30 pm**
  
  In vitro and in vivo models of brain metastasis formation  
  I. Krizbai (Szeged, HU)

- **7.00 pm**
  
  Blood-brain barrier in health & disease – in vitro modelling  
  A. Patabendige (Newcastle, AU)

**111 ROOM - S17**

- **5.00 pm**
  
  The type 2 cannabinoid receptor: an emerging target for brain therapeutics  
  P. Brust (Leipzig, DE)

- **5.30 pm**
  
  Development of selective CB2 receptor inhibitors as potential probes for molecular imaging with positron emission tomography  
  P. Brust (Leipzig, DE)

- **5.30 pm**
  
  Endocannabinoid signalling in neuroprotection: Key-role of CB2 receptor  
  M. Maccarrone (Rome, IT)

- **6.00 pm**
  
  Relevance of CB2 receptors in motor neuron disease  
  E. de Lago (Madrid, ES)

- **6.30 pm**
  
  The Role of CB2 Receptor in the Recovery of Mice after Traumatic Brain Injury  
  Y. Friedman-Levi (Jerusalem, IL)

### Conference Dinner

**Courtyard UniMI**

**Conference Dinner**

---

---
<table>
<thead>
<tr>
<th>Session</th>
<th>113 ROOM - S18</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.00 pm</td>
<td>The emerging role of S100B in pathogenic processes of neural disorders: A novel therapeutic target? (A. Fernandes - Lisbon, PT and F. Michetti - Rome, IT)</td>
</tr>
<tr>
<td>5.30 pm</td>
<td>The S100B story: from biomarker to active factor in neural injury F. Michetti (Rome, IT)</td>
</tr>
<tr>
<td>6.00 pm</td>
<td>S100B as a biomarker and therapeutic target in Multiple Sclerosis A. Fernandes (Lisbon, PT)</td>
</tr>
<tr>
<td>6.00 pm</td>
<td>Roles of S100B in schizophrenia and affective disorders J. Steiner (Magdeburg, DE)</td>
</tr>
<tr>
<td>6.30 pm</td>
<td>Development of S100B small molecule inhibitors D. Weber (Baltimore, US)</td>
</tr>
<tr>
<td>8.00 pm</td>
<td>Courtyard UniMI Conference Dinner</td>
</tr>
</tbody>
</table>
PARALLEL SESSIONS

Session 1
Room S18

The emerging role of S100B in pathogenic processes of neural disorders: A novel therapeutic target?
(A. Fernandes - Lisbon, PT and F. Michetti - Rome, IT)

5.00 pm

S100B as a biomarker and therapeutic target in Multiple Sclerosis
A. Fernandes (Lisbon, PT)

5.30 pm

The S100B story: from biomarker to active factor in neural injury
F. Michetti (Rome, IT)

6.00 pm

Roles of S100B in schizophrenia and affective disorders
J. Steiner (Magdeburg, DE)

6.30 pm

Development of S100B small molecule inhibitors
D. Weber (Baltimore, US)

8.00 pm

Courtyard UniMI Conference Dinner
BACHELARD AWARD

AUDITORIUM - PL3

09.00 am
Bachelard Award Lecture (Chair: ESN Secretary N. Nalivaeva - Leeds, UK/St Petersburg, RU)
ESN - a key start to my scientific and academic career
P. Fredman (Gothenburg, SW)

10.00 am
Coffee break

‘700 COURTYARD

PARALLEL SESSIONS

MALLIANI ROOM - S19

11.00 am
Nε-lysine acetylation within the endoplasmic reticulum: a fundamental role for brain physiology and pathology
L. Puglielli (Madison WI, US)

11.30 am
Inborn errors of Coenzyme A metabolism in neurodegeneration with brain iron accumulation
V. Tiranti (Milan, IT)

noon
Histone acetylation in myelinating glia
P. Casaccia (New York, US)

111 ROOM - S20

Chaperone networks and signaling pathways in disease and aging
S. Carra (Modena, IT)

12.00 pm
Histone acetylation in myelinating glia
P. Casaccia (New York, US)

12.30 pm
Protein aggregation is the prime driver of most neurodegenerative diseases
H. Kampinga (Groningen, NL)
Bachelard Award Lecture (Chair: ESN Secretary N. Nalivaeva - Leeds, UK)  

ESN - a key start to my scientific and academic career  
P. Fredman (Gothenburg, SW)

Coffee break

PARALLEL SESSIONS

Session MALLIANI ROOM - S19  111 ROOM - S20

Brain acetylation processes in health and disease  
A. Szutowicz (Gdansk, PL)

Chaperone networks and signaling pathways in disease and aging  
S. Carra (Modena, IT)

10.30 am

Acetyl-CoA – direct regulator of acetylations in the brain?  
A. Szutowicz (Gdansk, PL)

Interplay between misfolded proteins and membraneless organelles: implications in age-related neurodegenerative diseases  
S. Carra (Modena, IT)

11.00 am

Nε-lysine acetylation within the endoplasmic reticulum: a fundamental role for brain physiology and pathology  
L. Puglielli (Madison WI, US)

Remodeling proteostasis networks in Caenorhabditis elegans aging  
A. Ben-Zvi (Beer-Sheva, IL)

11.30 am

Inborn errors of Coenzyme A metabolism in neurodegeneration with brain iron accumulation  
V. Tiranti (Milan, IT)

Deciphering the proteostasis network's response to the accumulation of toxic protein aggregates in the aging brain  
E. Cohen (Jerusalem, IL)

12.00 pm

Histone acetylation in myelinating glia  
P. Casaccia (New York, US)

Protein aggregation is the prime driver of most neurodegenerative diseases  
H. Kampinga (Groningen, NL)

The neurochemistry of neuromelanins in neurodegenerative and psychiatric disorders  
L. Zecca (Milan, IT)

Ultrastructure and chemical composition of neuromelanin in the human substantia nigra  
A. Biesemeier (Tübingen, DE)

Neuromelanin-sensitive MRI: a novel, non-invasive proxy measure of dopamine function in psychiatric illness  
C. Cassidy (Ottawa, CA)

Locus coeruleus imaging correlations to pathology and cognition in dementia  
H. Jacobs (Boston, US)

Neurochemistry and neurobiology of human brain neuromelanins  
F. Zucca (Milan, IT)
<table>
<thead>
<tr>
<th>Session</th>
<th>12.30 pm - 12.45 pm</th>
<th>Closing Ceremony</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session</td>
<td>1.00 pm</td>
<td>Milan guided sightseeing tour</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session</th>
<th>1.00 pm</th>
<th>2° ESN Council meeting</th>
</tr>
</thead>
</table>
23rd ESN BIENNIAL MEETING

12.30 pm - 12.45 pm: Closing Ceremony

1.00 pm: Milan guided sightseeing tour

Session

LAUREL STUDI ROOM

01.00 pm: 2° ESN Council meeting
PL1

Principles of astrogliopathology: From reactivity to atrophy and degeneration

Alexei Verkhratsky (1)

(1) The University of Manchester, Oxford Road, Manchester, England.

The common and prevailing set of neurological thoughts considers neurones as the primary substrate of pathological progression. This "neurone-centric" concept, however, is changing. It has become universally acknowledged that the homeostasis of the nervous tissue is regulated by a complex fabric of neuroglial cells. Astroglia in particular represent a main element in the maintenance of homeostasis and providing defense to the brain. Consequently, dysfunction of astrocytes underlies many, if not all, neurological, neuropsychiatric and neurodegenerative disorders. Astrogliopathology is manifested by diametrically opposing morpho-functional changes in astrocytes, i.e. their hypertrophy along with reactivity or astrodegeneration with atrophy and asthenia. These complex plastic changes underlie pathophysiology of all neurological disorders including genetic (e.g. Alexander disease, which is a primary sporadic astrogliopathy), environmentally caused, (e.g. heavy metal encephalopathies or hepatic encephalopathies), neurodevelopmental (e.g. different forms of autistic spectrum disorder) or neurodegenerative (e.g. amyotrophic lateral sclerosis, Alzheimer’s and Huntington's diseases).
PL2

Axonal transport as therapeutic target

Giampietro Schiavo (1)(2)(3)

(1) Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, Queen Square, WC1N 3BG, London, United Kingdom.

(2) UK Dementia Research Institute, University College, WC1E 6BT, London, United Kingdom.

(3) Discoveries Centre for Regenerative and Precision Medicine, University College London Campus, London, WC1N 3BG, UK, London, United Kingdom.

Axonal transport is critical for maintaining neuronal homeostasis, function and survival through bidirectional trafficking of essential complexes and organelles between proximal and distal compartments of neurons. Deficits in axonal transport have been detected both in vitro and in vivo in several models of neurodegenerative disease, such as amyotrophic lateral sclerosis (ALS) and Alzheimer’s disease (AD). Importantly, impairments in this process have been shown presymptomatically, suggesting that deficits in axonal transport are causative to disease. However, our understanding of the underlying mechanisms remains unclear.

Using wild type and human SOD1$^{G93A}$-expressing mice, an established mouse model of ALS, we found that motor neurons innervating muscles with different fibre-type compositions have distinct axonal transport features. In particular, axonal signalling endosomes transporting trophic signals to the soma move faster in motor neurons innervating the tibialis anterior (TA), a fast-fatigable muscle, compared to soleus, a slow fatigue-resistant muscle. Stimulation with neurotrophins, such as BDNF, significantly enhances axonal transport in motor neurons innervating TA but not the soleus. In contrast, in SOD1$^{G93A}$ mice, motor neurons innervating the TA no longer respond to BDNF stimulation. These data indicate that motor neurons innervating muscles with different fibre-type compositions have distinct axonal transport features, which change through disease, thus contributing to ALS pathogenesis.

Importantly, we found that the deficits in axonal transport are reversible at early stages of disease pathogenesis. Inhibition of p38 MAPKinase or insulin-like growth factor 1 receptor (IGF1R) increases the rate of transport of signalling endosomes in motor neurons, both in vitro and in vivo, and alleviates the deficits in axonal transport observed in SOD1$^{G93A}$ mice. This effect is specific to signalling endosomes, since IGF1R inhibition does not alter the trafficking of mitochondria or lysosomes. Altogether, these findings suggest that modulation of axonal transport represents a new therapeutic strategy in ALS and other neurodegenerative diseases.

Acknowledgements: Wellcome Trust Senior Investigator Award (GS; 107116/Z/15/Z) and MRC Career Development Award (JNS: MR/S006990/1)

Keywords: Axonal transport, neurotrophic factors, neurodegenerative disease
Presynaptic nanomachines: regulation of the quantal release of glutamate

Magalie Martineau (1)

(1) IINS - CNRS UMR5297, Bordeaux, France.

The refilling of synaptic vesicles with neurotransmitters is potentially a rate-limiting step in neurotransmission. Biochemical investigations on isolated synaptic vesicles had unraveled the basic properties of vesicular transporters and indicate that they all depend on a proton electrochemical gradient generated by the vacuolar-type H\(^+\)-ATPase. Yet, the dynamics of vesicle refilling in intact neurons are still largely unknown. Therefore, I investigated the kinetics of vesicular reacidification in live cultured hippocampal neurons using pH-sensitive fluorescent reporters coupled to synaptic vesicle proteins. Using pharmacological inhibition of the vesicular glutamate transporters (VGLUTs) as well as Vglut1 knock-out (Vglut1\(^{-/-}\)) mice, I identified VGLUT1 as a glutamate/proton exchanger associated with a thermodynamically-uncoupled chloride conductance generating most of the membrane potential used for glutamate uptake. In addition, I designed a vesicular ratiometric chloride indicator to monitor directly chloride dynamics. Using this sensor in neurons from wild-type and Vglut1\(^{-/-}\) mice I was able to demonstrate the efflux of chloride through VGLUT1 during synaptic vesicle recycling, thus confirming its transport mechanism. Overall, my results provide important insights into the regulation of quantal size under physiological conditions. Finally, I will introduce the development of two red pH-sensitive fluorescent dyes coupled to antibodies against endogenous vesicular proteins. These dyes showed a higher response amplitude upon activity-dependent exocytosis compared to pHluorin. Their properties thus enable the detection of single vesicle fusion events and the investigation of the temporal and spatial organization of the synaptic vesicle cycle.
Exploring mechanisms of neuron-glial signalling and metabolic interactions

Aiman Saab (1)

(1) University of Zurich, Institute of Pharmacology and Toxicology, Zurich, Switzerland.

Perturbations in brain energy metabolism may contribute to the pathogenesis of various age-related neurodegenerative diseases. The importance of neuron-glial metabolic interactions in maintaining brain energy homeostasis throughout life remains elusive. To date, both astrocytes and oligodendrocytes, which form a pan-glial syncytium by gap-junction coupling, are suggested to supply neuronal compartments with energy-rich substrates such as lactate or pyruvate to fuel neuronal ATP demands. But the mechanisms of neuron-glia metabolic coupling in vivo are poorly understood and the significance of glial lactate supply to neurons is still debated. If glial cells provide neurons with energy substrates, what are the cellular mechanisms regulating such a neuron-glial metabolic interaction? How do astrocytes and myelinating oligodendrocytes sense neuronal activity and how are these signals translated into supporting neuronal energy demands and long-term integrity? We combine molecular genetics and two-photon imaging of genetically encoded sensors to study cellular activity and metabolite dynamics in vivo and in acute tissue preparations to investigate mechanisms of neuron-glial signalling and metabolic interactions.
ESN - a key start to my scientific and academic career

Pam Fredman (1)

(1) University of Gothenburg, Gothenburg, Gothenburg, Sweden.

Curiosity and passion for knowledge creation were factors behind my interest in a scientific career. Neurochemistry became the subject area when, in 1974, I began my PhD and more specifically a study of the role of glycosphingolipids in the nervous system. My focus was on sialic acid containing glycosphingolipids, gangliosides, and it is noteworthy to recall that, at that time, neurochemistry had a strong focus on lipids and their function in the nervous system. Since then methodologies and technologies have developed dramatically leading to a shift in focus from lipids to proteins and not least coupled to molecular biology development. Genetically modified mouse models were more applicable to protein studies and this methodological shift decreased the focus of research on lipids per se. Thus, technological developments can have unexpected scientific consequences, something I will reflect on. Curiosity and ambition are major driving forces but, to develop as a researcher and establish a scientific career, international research networks were crucial factors, in particular being a woman. Being given the "ESN Young Lecturer Award" (1982 in Dublin) during my postdoc time was a fantastic opportunity to be introduced to established scientists in the field of neurochemistry and among those was Professor Herman Bachelard and it is therefore a great honour to now be receiving the Bachelard award. ESN also gave me experience of much importance for my academic career. Starting as a Council member in 1992, I was later given the trust of the Society as its Treasurer and subsequently as President (1996-2000). This experience has been of great value, and possibly also an important merit, in my development and career as a university leader. My experience and reflections will hopefully encourage the next generation of scientists and academic leaders.
S1.1

Neuroplasticity in an animal model of SPS: evidence from rats lacking the serotonin transporter

Fabio Fumagalli (1), Francesca Telese (1), Giorgia Bottan (1), Lucia Caffino (1)

(1) Department of Pharmacological and Biomolecular Sciences, University of Milan, Via Balzaretti 9, Milan, Italy.

One of the major factors contributing to compulsivity in drug addiction involves a gradual decrease in drug-induced hedonic effects and the emergence of a negative emotional state when access to the drug is prevented. A key regulator of negative emotional states is serotonin. Indeed, human studies have clearly shown that reduced expression and function of the plasmalemmal serotonin transporter (SERT) whose main function is the rapid uptake of released serotonin back into presynaptic terminals, is closely associated with an anxious and pro-depressive phenotype. The role of SERT in environmental sensitivity in general appears to be critical for the trait ‘sensory processing sensitivity’ (SPS), that is observed in humans and animals that are extremely vulnerable to both positive and negative environmental stimulation and may play a role in the co-presence of addictive states and pro-depressive phenotypes in subjects with inherited SERT down-regulation.

Using SERT$^{-/-}$ rats, we here investigated the effect of SERT reduction on the baseline expression levels of critical determinants of neuroplasticity. In addition, SERT$^{+/+}$ and SERT$^{-/-}$ rats were exposed to a short-access protocol (1h/day) that mimics regular (controlled) cocaine intake, or a long-access protocol (6h/day) in which rats lose their control over drug intake, mimicking the transition to compulsive drug-taking observed in dependent states.

Our findings reveal that serotonin regulates several markers of neuroplasticity (i.e. the neurotrophin BDNF or critical determinants of the homeostasis of the glutamate system) in different brain regions (infralimbic and prelimbic cortices, lateral habenula and amygdala) and it dynamically influences the response to cocaine self-administration. Our data suggest that the removal of SERT may shape motivational states via changes in critical determinants of neuroplasticity thus representing the basis of SPS.
S1.2

The contribution of environmental sensitivity to vulnerability to cocaine addiction: a preclinical study

Judith Homberg (1), Stephanie Seegers (1), Michel Verheij (1)

(1) Donders Institute for Brain, Cognition, and Behaviour, Department of Cognitive Neuroscience Center, Route 205 Kapittelweg 29, Nijmegen, Netherlands.

There are large individual differences in vulnerability to drug addiction. One potential risk factor is the personality trait sensory processing sensitivity (SPS). SPS reflects normal variation in environmental sensitivity in a population and is shaped by increased emotional reactivity and increased information processing. Individuals high in SPS are highly sensitive to environmental stimuli, both negative and positive ones. When high-SPS individuals are exposed to negative stimuli, or when stimuli are too much to be successfully processed, they feel overstimulated/stressed. Drug use may serve as coping strategy. On the other hand, exposure to positive stimuli may reduce stress and the need to use drugs. One genetic factor that also confers environmental sensitivity, like SPS, is the serotonin transporter gene. While SPS is as trait more complex than a single gene variant, the gene provides us insight into how environmental sensitivity may influence drug intake behaviour. To investigate the pattern of drug intake in association with this gene variance, we used rats lacking the serotonin transporter (SERT). The rats show increased anxiety under naïve conditions, increased cocaine intake under both regular (“1-hr short access”) and compulsive (“6-hr long access”) self-administration conditions, and increased anxiety 24 hours into withdrawal. Interestingly, when we exposed rats to tactile stimulation in early life, a procedure that mimics maternal care and positively stimulates the development of rodents, anxiety decreased in SERT knockout rats. Whether this goes along with a reduction in cocaine intake remains to be investigated. Lastly, to go beyond a single genotype effect we have established a new rat model based on extremes in emotional reactivity and deep information processing. Their cocaine intake behaviour is currently being assessed. Data will be presented during the meeting. In conclusion, environmental sensitivity as mediated by inherited serotonin transporter down-regulation increases cocaine intake.
S1.3

Sensory processing sensitivity and drug use recovery pathways

Murielle Mary-krause (1), Joel Herranz (1), Maria Melchior (1)

(1) Sorbonne université, INSERM, Institut Pierre Louis d’Épidémiologie et de Santé Publique, ERES, Faculté de Médecine Saint-Antoine, 27 rue de Chaligny, 75571 Paris Cedex 12, France.

Background: Yearly cannabis consumption in France reaches 10% on adults and 30% on adolescents. Moreover, nearly 50% of individuals with cannabis use disorder suffer comorbid anxiety or mood disorder. As high Sensory Processing Sensitivity (SPS) is associated with substances use and distress intolerance, could it possibly exist an association between SPS and cannabis use trajectories?

Methods: Analysed data came from 2018 French TEMPO community based cohort when data on SPS were collected, restricting to participants with at least one cannabis use data (data about cannabis, temperament and mental health collected in 1991, 1999, 2009, 2014 and 2018). The short Highly Sensitive Person Scale (HSPS) composed of 12 questions with responses ranging from 1 (not at all) to 7 (extremely) was dichotomized at the 85th percentile. We dichotomized the different studied CBCL scores at the 85th percentile in order to evaluate the impact of anxiety and internalizing symptoms in childhood on cannabis consumption. We modeled cannabis consumption trajectories from adolescence onwards employing Group-Based Trajectory Modeling using the frequency of cannabis consumptions in the preceding 12 months. Associations with individual temperament characteristics were studied using multinomial logistic regression with cannabis non-users as the reference group.

Results: Among 852 subjects included in the study, we observed 3 cannabis use trajectories: non-users (74.2%), reduced consumption (13.1%) and high consumption (12.7%). Medium HSPS was 4 (interquartile range IQR=4-5) with 7.9% with a score higher than 5. No association was found between SPS and cannabis consumption (OR of HSP≥85th percentile vs <85th =1.2, 95% CI=0.71-2.04 for reduced cannabis consumption and 1.03, 95% CI=0.59-1.81 for high consumption). No association between anxiety and internalizing symptoms was found either.

Conclusion: SPS does not seem to be associated with cannabis use trajectories. It may be that only severe forms of addiction are influenced by hypersensitivity.
S1.4

Sensory-processing sensitivity in substance use disorders and its relation to cognition and behavior

Boris Quednow (1)

(1) Psychiatric Hospital of the University of Zurich, Lenggstr. 31, 8032 Zurich, Switzerland.

Elevated Sensory Processing Sensitivity (SPS) has been suggested as a potential risk factor for substance use disorders. However, it is not clear yet if SPS represents a risk factor for drug use in general or if it is specific for different drug types. We therefore investigated SPS in populations of recreational and addicted prescription opioid users and cocaine users as well as in alcohol-dependent individuals. We found that, at the group level, opioid users but not cocaine users show elevated SPS scores. In opioid users, drug use severity was inversely correlated with SPS scores indicating that recreational use rather than severe addiction is associated with increased SPS. In cocaine users, duration of cocaine use but not weekly consumption was positively correlated with SPS. SPS was positively correlated with symptoms of depression, ADHD, and anxiety, as well as with impulsivity and childhood trauma scores. Finally, SPS was negatively correlated with sensation-seeking. The data of the alcohol-dependent patients will be analyzed before the conference start. Taken together, the preliminary analysis suggests that SPS may trigger specific patterns of drug use, while it seems not to be a general risk factor for each kind of drug using behavior.
Are oligodendrocyte progenitors all born equal? A lesson from a microcephaly model

Enrica Boda (1)

(1) Dept. Neuroscience and Neuroscience Institute Cavalieri Ottolenghi, University of Turin, Regione Gonzole 10, Orbassano (to), Italy.

It is well established that neurons are highly heterogeneous, in terms of function, morphology, gene expression, developmental origin and vulnerability to disease. The study of glial cell biology is instead quite far from this level of understanding, despite the occasional observation of distinct functional properties and the identification of distinct embryonic sources for subsets of astroglia and oligodendroglia. Whether specific glial cell subpopulations differ in molecular features or in their ability to contribute/respond to pathological conditions is still not understood. We tackled this issue by studying a mouse model of microcephaly, where the germinal ablation of Citron-kinase (Cit-K, a cytoskeleton regulator involved in cell division and DNA repair; Di Cunto et al., 2000 Neuron; Bianchi et al., 2017 Cell Rep) triggered distinct responses in dorsal and ventral telencephalic oligodendrocyte progenitors (OPCs). Namely, dorsally generated OPCs of the cerebral cortex underwent depletion by apoptosis within the second week after birth. In contrast, ventral OPCs of the striatum and hypothalamus persisted and displayed a senescent phenotype. Such differential sensitivity was not associated with distinct levels of DNA damage in dorsal and ventral Cit-K KO OPCs, but rather to a distinct capability to set up Nrf2-mediated antioxidant defenses. Notably, neither dorsal nor ventral OPCs did progress along oligodendrogenesis, as shown by lack of both pre-myelinating and myelinating cells in the entire Cit-K KO forebrain. In vivo and in vitro experiments showed that such additional differentiation defect largely depended on cell-extrinsic factors, thereby indicating that the germinal Cit-K deletion results in environmental conditions that hamper oligodendroglia maturation and myelination. These data provide novel evidence of the molecular and functional heterogeneity in postnatal OPC subsets and suggest that dorsal and ventral OPCs may be differentially vulnerable to pathological conditions associated with DNA damage and oxidative stress.
S2.2

Post-transcriptional regulation in oligodendrocytes: the strategy of miR-125a-3p

Davide Lecca (1), Davide Marangon (1), Enrica Boda (2), Roberta Parolisi (2), Camilla Negri (1), Francesca Montarolo (2), Simona Perga (2), Corinna Giorgi (3), Annalisa Buffo (2), Maria Pia Abbracchio (1)

(1) Università degli Studi di Milano, Dipartimento di Scienze Farmacologiche e Biomolecolari, Via Balzaretti 9, Milan, Italy.
(2) Neuroscience Institute Cavalieri-Ottolenghi (NICO), Regione Gonzole 10, Orbassano, Turin, Italy.
(3) European Brain Research Institute, Viale Regina Elena 295, Rome, Italy.

In the mature central nervous system (CNS), oligodendrocytes provide support and insulation to axons thanks to the production of the myelin sheath. During their maturation to myelinating cells, oligodendroglial precursors (OPCs) follow a very precise differentiation program, finely orchestrated by both transcription and epigenetic factors. This second group also includes microRNAs (miRNAs), a class of small non-coding RNAs involved in post-transcriptional regulation, whose power is based on their ability to regulate entire pathways by fine-tuning the expression of several targets. For this reason, alterations in miRNA levels during OPC maturation can contribute to dysregulated myelination, impaired remyelination, and neurodegeneration, as it happens in multiple sclerosis (MS).

Here, we describe miR-125a-3p as a new player in oligodendroglial maturation, acting through the simultaneous modulation of kinases, adhesion molecules, and cytoskeletal proteins. A significant up-regulation in its levels was observed in the acute phase of demyelination in mouse models as well as in white matter lesions and in cerebrospinal fluid of MS patients. Interestingly, in lysolecithin-induced demyelination in vivo, the over-expression of this miRNA by mimic infection impaired, while its inhibition with an antago-miR stimulated oligodendroglial maturation.

Globally, our data suggest that miR-125a-3p could represent not only a master regulator of oligodendrocyte homeostasis, but also a hallmark of de-myelination, that, when aberrantly expressed, inhibits re-myelination.

Thus, we postulate that a specific antago-miRNA-based therapy may help in promoting oligodendrocyte maturation in diseases with impaired myelin repair. In this respect, the identification of miR-125a-3p direct interactors could strengthen our hypothesis and unveil new potential pathogenetic mechanisms and new potential pharmacological targets for MS.

Sponsored by Fondazione Cariplo, grant n° 2014-1207 to DL.
S2.3

Enhancing D-Aspartate signaling to promote (re)myelination

Valeria De Rosa (1), Secondo Agnese (1), Pannaccione Anna (1), Ciccone Roselia (1), Formisano Luigi (1), Guida Natascia (1), Crispino Roberta (2), Fico Annalisa (3), Polishchuk Roman (2), D'Aniello Antimo (1), Annunziato Lucio (1), Boscia Francesca (1)

(1) Division of Pharmacology, Department of Neuroscience, Reproductive and Dentistry Sciences, School of Medicine, Federico II University of Naples, Naples, Italy.
(2) Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy.
(3) Institute of Genetics and Biophysics “A. Buzzati-Traverso”, Consiglio Nazionale delle Ricerche, Naples, Italy.

In recent years, glutamatergic signaling at axo-myelinic synapses was suggested to regulate myelin remodeling and repair. D-Aspartate is a D-amino acid exerting modulatory actions at glutamatergic synapses. Chronic administration of D-Aspartate has been proposed as therapeutic treatment in diseases related to myelin dysfunction and NMDA receptors hypofunction, including schizophrenia and cognitive deficits. By using an in vivo remyelination model, we demonstrated that administration of D-Aspartate during remyelination improved motor coordination, accelerated myelin recovery, and significantly increased the number of small-diameter myelinated axons. Chronically administered during demyelination, D-Aspartate also attenuated myelin loss and inflammation. Interestingly, D-Aspartate exposure stimulated OPC maturation and accelerated developmental myelination in organotypic cerebellar slices. Functional studies demonstrated that D-Aspartate exposure elicited a complex [Ca\(^{2+}\)]\(_i\) response in oligodendrocyte precursors involving an orchestrated functional crosstalk between glutamate transporters, ionotropic AMPA and NMDA glutamate receptors, and the Na\(^+\)/Ca\(^{2+}\) exchanger NCX3. While blocking NMDA or NCX3 significantly prevented D-Aspartate-induced [Ca\(^{2+}\)]\(_i\) oscillations, blocking AMPA and glutamate transporters prevented both the initial and oscillatory [Ca\(^{2+}\)]\(_i\) response as well as D-Aspartate-induced inward currents in OPC. Collectively, our findings indicate that exogenous D-Asp treatment might produce beneficial effects during remyelination processes.
Decline of oligodendrogenesis in the ageing brain

Andrea Domenico Rivera (1), Francesca Pieropan (1), Butt Arthur (1)

(1) University of Portsmouth, White Swan Rd, Portsmouth, United Kingdom.

Oligodendrocytes (OLs) are specialised glial cells that myelinate CNS axons. Myelinated axons are bundled together into white matter tracts that are essential for rapid, integrated neuronal communication and cognitive function. A population of adult oligodendrocyte progenitor cells (OPCs) is responsible for the life-long generation of OLs, which is essential to replace myelin lost in pathology. Notably, there is white matter shrinkage in the ageing brain and this is greater in Alzheimer’s disease (AD), although the underlying causes are unresolved. To address this, we performed RNA-seq comparison of adult and ageing mouse brains. We identified myelination as one of the top processes altered in the ageing brain. Notably, we discovered that the most downregulated gene in the ageing brain was Gpr17, which is required for terminal OL differentiation and is specifically expressed at a stage between late OPC and early OL. We demonstrate by immunohistochemistry that there is a marked loss of Gpr17 expression in the 18-month brain. In addition, we found that OPC disruption is accelerated at an early age in the 3xTg mouse model of AD, prior to neuropathology. These results indicate decreased regenerative capacity of OPCs may be a causative factor in myelin loss and white matter shrinkage in normal ageing and AD. Finally, to discover potential therapies for rejuvenating OPCs in the ageing brain, we used a novel pharmacogenetic approach and identified AR-A014418 as one of the top molecules with rejuvenating potential. AR-A014418 is an inhibitor of GSK3β and activator of Wnt signalling, which we have shown drives oligodendrogenesis in the postnatal brain. To investigate this, we developed an optic nerve organotypic culture model and show that activation of Wnt signalling significantly promotes oligodendrogenesis in adult white matter. These studies have determined key changes in OLs that may underlie the decline in myelination in the ageing brain.
S2.4
Decline of oligodendrogenesis in the ageing brain
Andrea Domenico Rivera (1), Francesca Pieropan (1), Butt Arthur (1)
(1) University of Portsmouth, White Swan Rd, Portsmouth, United Kingdom.

Oligodendrocytes (OLs) are specialised glial cells that myelinate CNS axons. Myelinated axons are bundled together into white matter tracts that are essential for rapid, integrated neuronal communication and cognitive function. A population of adult oligodendrocyte progenitor cells (OPCs) is responsible for the life-long generation of OLs, which is essential to replace myelin lost in pathology. Notably, there is white matter shrinkage in the ageing brain and this is greater in Alzheimer’s disease (AD), although the underlying causes are unresolved. To address this, we performed RNA-seq comparison of adult and ageing mouse brains. We identified myelination as one of the top processes altered in the ageing brain. Notably, we discovered that the most downregulated gene in the ageing brain was Gpr17, which is required for terminal OL differentiation and is specifically expressed at a stage between late OPC and early OL. We demonstrate by immunohistochemistry that there is a marked loss of Gpr17 expression in the 18-month brain. In addition, we found that OPC disruption is accelerated at an early age in the 3xTg mouse model of AD, prior to neuropathology. These results indicate decreased regenerative capacity of OPCs may be a causative factor in myelin loss and white matter shrinkage in normal ageing and AD. Finally, to discover potential therapies for rejuvenating OPCs in the ageing brain, we used a novel pharmacogenetic approach and identified AR-A014418 as one of the top molecules with rejuvenating potential. AR-A014418 is an inhibitor of GSK3β and activator of Wnt signalling, which we have shown drives oligodendrogenesis in the postnatal brain. To investigate this, we developed an optic nerve organotypic culture model and show that activation of Wnt signalling significantly promotes oligodendrogenesis in adult white matter. These studies have determined key changes in OLs that may underlie the decline in myelination in the ageing brain.

S3
My first conference – How to make the best of it
Eva-maria Blumrich (1)
(1) The University of Edinburgh, Hugh Robson Building, George Square, Edinburgh, United Kingdom.

A scientific conference can be an overwhelming environment when confronted with it for the first time. High expectations from oneself or others increase the pressure, making the conference experience less enjoyable than it could and should be. Networking with more experienced scientists from different countries, presenting your data and yourself are challenges that can be hard to overcome in just the few, busy days of a meeting. Those young scientists who make the first steps in their scientific career are the target group of this workshop. Hosted by local and international PhD students and early-career postdocs, this workshop will get participants started on networking, provide some hands-on tips on presentation skills and lower the barriers by sharing personal experiences in an interactive and informal environment. The participants will be guided around the conference venue to introduce them to important areas (registration desk, poster hall, main lecture halls and location of symposia). Furthermore, locals will give insights about the culture, the city of Milan and its scientific environment and with that round up the starter package for a great first conference experience.
Molecules capable to induce neuroprotection via lysophagy activation

Paola Rusmini (1), Katia Cortese (2), Valeria Crippa (1), Riccardo Cristofani (1), Veronica Ferrari (1), Barbara Tedesco (1), Elena Casarotto (1), Marta Chierichetti (1), Elio Messi (1), Margherita Piccolella (1), Mariarita Galbiati (1), Manuela Basso (3), Massimiliano Garre' (4), Elena Morelli (5), Thomas Vaccari (5), Barbara Tedesco (1), Elena Casarotto (1), Marta Chierichetti (1), Elio Messi (1), Margherita Piccolella (1), Mariarita Galbiati (1), Manuela Basso (3), Massimiliano Garre' (4), Elena Morelli (5), Thomas Vaccari (5), Angelo Poletti (1)

(1) Dipartimento di Scienze Farmacologiche e Biomolecolari (DiSFeB), Centro di Eccellenza sulle Malattie Neurodegenerative, Università degli Studi di Milano, Milan, Italy.
(2) DIMES, Dipartimento di Medicina Sperimentale, Anatomia Umana, Università di Genova, Genoa, Italy.
(3) Dipartimento di Biologia Cellulare, Computazionale e Integrata - CIBIO, Università di Trento, Trento, Italy.
(4) IFOM, Istituto FIRC di Oncologia Molecolare, Milan, Italy.
(5) Dipartimento di Bioscienze, Università degli Studi di Milano, Milan, Italy.

Accumulation of misfolded species prone to form toxic aggregates is a common hallmark of several neurodegenerative diseases (NDs), including polyglutamine (polyQ) diseases. Autophagy is the main protein degradative pathway involved in the clearance of protein aggregates and damaged organelles. Defects in autophagy are often observed in NDs, and may directly affect the accumulation of misfolded species.

The pharmacological autophagy activation favors the clearance of misfolded proteins, and represents a possible therapeutic approach for NDs. Trehalose has been shown to be neuroprotective role in models of NDs, it exerts its functions activating autophagy, and removing the misfolded proteins accumulated into the cells. It has been already demonstrated that trehalose promotes autophagy via TFEB activation, but the exact mechanisms of autophagic activation was elusive. We found that trehalose induces a transient lysosomal enlargement and membrane permeabilization. This event activates TFEB through the calcium-dependent phosphatase calcineurin. Trehalose induces the upregulation of several autophagic and lysosomal genes, and TFEB downregulation prevents trehalose effects. Moreover, TFEB silencing counteracted trehalose pro-degradative activity. These results indicate that trehalose induces autophagy and lysosomal biogenesis through TFEB leading to the removal of damaged lysosome, a process called lysophagy, and restoring lysosomal homeostasis.

TFEB activation is also associated with the clearance of mutant proteins from neurons. Unfortunately, in the human gut, trehalose is quickly degraded by the enzyme trehalase. We tested lactulose and melibiose, two trehalase-resistant analogues, and we observed that these compounds showed effects comparable to trehalose. Similarly, lactulose and melibiose induce lysophagy via TFEB. Emergent evidence suggests that lysosomal damage and defects in lysophagy are implicated in NDs. Our preliminary data suggest that polyQ proteins might induce lysosomal damage, possibly the failure of neurons to respond to this damage may affect lysosomal homeostasis, and contribute to neurodegeneration.
S4.2

Glucocerebrosidase and Parkinson disease

Anthony Schapira (1)

(1) University Department of Clinical Neurosciences, UCL Institute of Neurology, Queen Square, London, United Kingdom.

Mutations of the glucocerebrosidase 1 (GBA) gene cause autosomal recessive Gaucher disease and are the most important risk factor for the development of Parkinson disease (PD). It is estimated that 10-15% of PD patients carry GBA mutations; this increases to 25% in the Ashkenazi population. The penetrance of PD in GBA carriers is approximately 30% by age 80 years.

Several in vitro and in vivo studies have demonstrated a bi-directional reciprocal relationship between GBA enzyme activity (GCase) and alpha-synuclein levels. The precise mechanisms underlying this relationship are not fully understood and may involve several factors including direct interactions of GCase with alpha-synuclein and substrate accumulation. We have hypothesised that increasing GCase activity will reduce alpha-synuclein levels.

GCase activity may be increased by enhancing transcription or transfection of the wild-type gene, or refolding and chaperoning the mutant protein to the lysosome. The latter pathway has been the target of several recent studies to determine if elevating GCase protein and activity lowers alpha-synuclein. We have used the GCase chaperones ambroxol and isofagomine in in vitro and in vivo models of the N370S and L444P GBA mutations, these represent the commonest pathogenic mutations associated with PD.

Stem cells generated either from fibroblasts (iPS) or adipose tissue neural crest derived stem cells (ASCs) from GBA mutation carriers and differentiated into dopaminergic neurons recapitulated the biochemical abnormalities present in PD-GBA brain. Treatment with ambroxol increased GCase levels and activity and reduced alpha-synuclein. Chaperone treatment of Drosophila expressing GBA mutant proteins protected against loss of dopaminergic neurons and restored motor function. Ambroxol increased GCase in both L444P and wild-type mouse brain, and reduced brain alpha-synuclein levels in mice over-expressing alpha-synuclein.

GCase chaperones therefore represent candidates for further investigation to modulate alpha-synuclein levels in PD patients both with and without GBA mutations. We have initiated a proof of principle trial of ambroxol in PD patients with and without GBA mutations to assess target engagement in the CNS and determine the effects on biochemical markers of GBA and alpha-synuclein proteins, prior to a formal study to evaluate its potential to modify the course of PD.
S4.3

Inhibiting amyloid protein aggregation relieves lysosomal-autophagic dysfunction and protects against neurodegeneration in lysosomal storage diseases

Antonio Monaco (1), Nicolina Cristina Sorrentino (1), Vincenzo Cacace (1), Irene Sambri (1), Elvira De Leonibus (1), Gal Bitan (2), Alessandro Fraldi (1)

(1) Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli, Naples, Italy.
(2) UCLA, La, California, USA, United States of America.

Lysosomal storage diseases (LSDs) are metabolic disorders caused by inherited lysosomal deficiencies and characterized by a global lysosomal dysfunction, in particular of the autophagy-lysosomal pathway (ALP), often associated with neurodegeneration. No cure is currently available to treat neuropathology in these diseases. Here we found that massive amyloid deposition characterizes brain pathology in several mouse models of LSDs, progressively building up concomitantly with neurodegeneration. The amyloid contains primarily α-synuclein together with several other aggregation-prone proteins, such as PrP, Tau and amyloid β-protein. A major fraction of the amyloid deposits forms in enlarged lysosomes where it interferes with ALP impairing autophagosome clearance. Treating a mouse model of a severe type of LSD with CLR01, a “molecular tweezer” that acts as a broad-spectrum inhibitor of self-assembly of multiple amyloidogenic proteins, restored lysosomal-autophagic flux and significantly ameliorated neuropathological signs. Together, these data provide new insights into the mechanisms determining neurodegeneration in LSDs identifying LSDs as a new class of amyloid disorders and CLR01 as a potent drug candidate for their treatment.
Inhibiting amyloid protein aggregation relieves lysosomal-autophagic dysfunction and protects against neurodegeneration in lysosomal storage diseases

Antonio Monaco (1), Nicolina Cristina Sorrentino (1), Vincenzo Cacace (1), Irene Sambri (1), Elvira De Leonibus (1), Gal Bitan (2), Alessandro Fraldi (1)

(1) Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli, Naples, Italy.
(2) UCLA, La, California, USA, United States of America.

Lysosomal storage diseases (LSDs) are metabolic disorders caused by inherited lysosomal deficiencies and characterized by a global lysosomal dysfunction, in particular of the autophagy-lysosomal pathway (ALP), often associated with neurodegeneration. No cure is currently available to treat neuropathology in these diseases. Here we found that massive amyloid deposition characterizes brain pathology in several mouse models of LSDs, progressively building up concomitantly with neurodegeneration. The amyloid contains primarily α-synuclein together with several other aggregation-prone proteins, such as PrP, Tau and amyloid β-protein. A major fraction of the amyloid deposits forms in enlarged lysosomes where it interferes with ALP impairing autophagosome clearance. Treating a mouse model of a severe type of LSD with CLR01, a "molecular tweezer" that acts as a broad-spectrum inhibitor of self-assembly of multiple amyloidogenic proteins, restored lysosomal-autophagic flux and significantly ameliorated neuropathological signs. Together, these data provide new insights into the mechanisms determining neurodegeneration in LSDs identifying LSDs as a new class of amyloid disorders and CLR01 as a potent drug candidate for their treatment.

Autophagy and neurodegeneration

David Rubinsztein (1)

(1) Cambridge Institute for Medical Research, UK Dementia Research Institute, University of Cambridge, Hills Road, Cambridge, United Kingdom.

Intracellular protein aggregation is a feature of many late-onset neurodegenerative diseases, including Parkinson’s disease, tauopathies, and polyglutamine expansion diseases (like Huntington’s disease (HD)). Many of these mutant proteins, like that causing HD, cause disease via toxic gain-of-function mechanisms. Therefore, the factors regulating their clearance are crucial for understanding disease pathogenesis and for developing rational therapeutic strategies.

The two major intracellular protein degradation pathways are the ubiquitin-proteasome system and (macro)autophagy. Autophagy is initiated by double-membraned structures, which engulf portions of cytoplasm. The resulting autophagosomes ultimately fuse with lysosomes, where their contents are degraded.

I will briefly describe the basic biology of autophagy before outlining its roles in neurodegeneration. We showed that the autophagy inducer, rapamycin, reduced the levels of mutant huntingtin and attenuated its toxicity in cells, and in Drosophila, zebrafish and mouse HD models. We have extended the range of intracellular proteinopathy substrates that are cleared by autophagy to other related neurodegenerative disease targets, like forms of Parkinson’s disease. I will describe a novel autophagy pathway acting as a physiological response to nutrient availability and repurposing studies demonstrating the potential of felodipine as an autophagy-inducing drug for various neurodegenerative diseases.
Gonadotropin releasing hormone neurons are a small group of scattered hypothalamic neuroendocrine cells that control reproductive functions in all mammals and many vertebrates. Despite their position in the adult hypothalamus, during development they originate in the nasal placode and migrate along the vomeronasal nerve to reach the forebrain and attain their final position in the hypothalamus. Failure of GnRH neurons to migrate lead to Hypogonadotropic Hypogonadism (HH) or Kallmann Syndrome(KS), genetic disorders characterised by GnRH deficiency and absent or delayed puberty. The genes underlying HH/KS are largely unknown but the combination of genetically modified mouse models with exome sequencing may help to identify the unknown genes.

We have previously demonstrated that class 3 semaphorin (SEMA) 3A controls the positioning of the vomeronasal nerve and therefore the migration of GnRH neurons via Neuropilin (NRP1-2) receptors. Mice lacking SEMA3A display typical KS features including hypogonadism and mutations of the SEMA3A gene have been subsequently identified in patients with KS.

In the search for additional SEMA3-mediated signalling pathways involved in this developmental process, by applying exome sequencing and bioinformatic approaches we identified mutations in other genes belonging to the class 3 semaphorins. Thus, during my talk I will present published and unpublished work showing the different roles of these genes during the development of GnRH neurons.
S5.2

Understanding the molecular mechanisms of angiogenesis in the brain and retina

Alessandro Fantin (1)

(1) Universita' degli studi di Milano, Via Celoria 26, Milan, Italy.

The developing central nervous system (CNS) is vascularised through the angiogenic invasion of blood vessels from a perineural vascular plexus, followed by continued sprouting and remodelling until a hierarchical vascular network is formed. Macrophages are phagocytic myeloid cells that constitute an essential part of the immune system, but also promote blood vessel growth by releasing pro-angiogenic factors and enabling vascular network formation. In the CNS, the resident macrophages are called microglia and derive from early erythro-myeloid progenitors (EMPs) that arise from the hemogenic endothelium in the embryonic yolk sac. By combining genetic lineage tracing with loss of function and expression studies in mouse embryos, we have unveiled novel mechanisms by which microglia and their progenitors contribute to the development and growth of CNS blood vessels.
Non-monotonic regulation of gene expression, neural progenitor fate and brain growth by the chromatin remodeller CHD8

Shaun Hurley (1), Conor Mohan (1), Philipp Suetterlin (1), Marco Pagani (2), Jacob Ellegood (3), Alberto Galbusera (2), Fabrizio Rudari (1), Jason Lerch (3), Alessandro Gozzi (2), Cathy Fernandes (4), M. Albert Basson (1)

(1) Centre for Craniofacial and Regenerative Biology and MRC Centre for Neurodevelopmental Disorders, King’s College London, Floor 27, Guy’s Hospital Tower Wing, London Se1 9rt, England.
(2) Functional Neuroimaging Laboratory, Center for Neuroscience and Cognitive Systems, Università di Trento, 38068 Rovereto, Italy.
(3) Department of Medical Biophysics, University of Toronto, Mouse Imaging Centre, Hospital for Sick Children, 25 Orde Street, Toronto Ontario M5t 3h7, Canada.
(4) MRC Social, Genetic & Developmental Psychiatry Centre, PO82, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, London Se5 8af, England.

Truncating CHD8 mutations are amongst the highest confidence risk factors for autism spectrum disorders (ASD) identified to date. To investigate the role of CHD8 during brain development, we created a Chd8 allelic series in the mouse. Chd8 heterozygous mice displayed mild increases in brain size, pronounced hypoactivity and anomalous responses to social stimuli. Few genes showed dysregulated expression at mid-gestation, whilst over 600 genes were differentially expressed in the early postnatal neocortex. Genes involved in cell adhesion and axon guidance were particularly prominent amongst the down-regulated transcripts. Resting-state functional MRI identified abnormal dynamics of neural activity in Chd8 heterozygous mutant mice, implicating altered connectivity as a potential mechanism underlying the behavioural phenotypes. Together, these data suggest that altered brain growth and diminished expression of important neurodevelopmental genes that regulate long-range brain wiring are followed by distinctive anomalies in functional brain connectivity in Chd8 heterozygous mice. To explore the effects of step-wise, additional reductions in Chd8 gene dosage, we reduced Chd8 expression to below haploinsufficient levels. Chd8 hypomorphic mice exhibited more pronounced changes in brain structure, neural progenitor proliferation and wide-spread dysregulation of gene expression. The analysis of neural progenitor proliferation identified a key role for CHD8 in regulating the proliferation of TBR2+ intermediate progenitors in the neocortex. Surprisingly, in contrast to the phenotypes of the hypomorphic mice, conditional deletion of Chd8 from the developing brain resulted in severe brain hypoplasia by the end of gestation, accompanied by p53 pathway hyperactivation. Our findings suggest that a number of cellular processes show differential sensitivities to Chd8 dosage, resulting in non-linear effects on brain growth in response to reduced levels of CHD8. These findings have important implications for interpreting the results from different model systems and the role of CHD8 in human brain growth and ASD.
Molecular control of cortical layer development by transmembrane Semaphorins

Marieke Verhagen (1), Suzanne Lemstra (1), Melissa Zwaan (1), Kati Rehberg (1), Youri Adolfs (1), Jeroen Pasterkamp (1)

(1) Department of Translational Neuroscience, UMC Utrecht, Universiteitsweg 100, Utrecht, Netherlands.

The axon guidance molecule Semaphorin6A (Sema6A) plays a key role during the development of the nervous system. Sema6A is a transmembrane protein that, depending on the molecular and cellular context, induces forward and/or reverse signaling. The precise mechanisms underlying Sema6A forward and reverse signaling are incompletely understood. To study the receptor and ligand functions of Sema6A, we generated a new conditional transgenic mouse model (Sema6AΔcyto) lacking the Sema6A intracellular domain, which is essential for its receptor function. In this mouse model, Sema6A only acts as a ligand. To establish when and where the Sema6A cytoplasmic domain is required, we performed immunohistochemistry on Sema6AΔcyto mutant mice for a variety of cellular and axonal markers. This analysis revealed developmental defects in various brain regions, including the cortex. To further study the signaling molecules that act downstream Sema6A, we performed immunoprecipitation of Sema6A followed by mass spectrometry and biochemical analyses. These findings indicate that the Sema6A cytoplasmic domain is essential for proper development of several brain regions and axon tracts, and begin to provide insight into the signaling pathways downstream of this transmembrane semaphorin. In this presentation the focus will be on how Sema6A reverse signaling influences the generation of distinct cortical layers.
S6.1

How does an oxytocin treatment in early life impact social behavior and hippocampal alterations in Magel2-deficient mice?

Alessandra Bertoni (1), Stephane Gaillard (2), Roman Tyzi (1), Diabé Diabira (1), Radhika Vaidyanathan (3), Valery Matarazzo (1), Elizabeth Hammock (3), Bice Chini (4), Jean-luc Gaiarsa (1), Françoise Muscatelli (1)

(1) INMED, INSERM, Aix Marseille Univ, Marseille, France.
(2) Phenotype-expertise, Marseille, France.
(3) Program in Neuroscience, Florida, United States of America.
(4) Institute of Neuroscience,National Research Council, Milan, Italy.

*MAGEL2* plays a major role in Prader-Willi Syndrome, is responsible for Schaaf-Yang Syndrome and is one gene involved in ASD. Our aim was to characterize the social alterations in *Magel2*<sub>tm1.1Mus</sub>/- mice from infancy, to identify the neurobiological causes of these alterations and to understand the effect of an oxytocin treatment occurring in the first week of life.

We found that vocal communication following mother separation is decreased in *Magel2*<sup>-/-</sup> male and female pups. At adulthood, in a three chamber test, we showed that social memory is impaired. Using RNAscope technique, during postnatal development, we observed expression of oxytocin-receptors (OTR) and *Magel2* transcripts in the anterior(a) CA2/CA3 and aDG hippocampal regions. We then investigated the aCA2/CA3 region, using electrophysiological recordings. In acute brain slices of juvenile mutant mice, we revealed an increase of GABAergic activity of hippocampal neurons. We also observed, using calcium imaging, a delay in the GABA-induced Ca<sup>2+</sup> responses in *Magel2*<sup>-/-</sup> hippocampal cultures, and confirmed, measuring DfGABA in brain slices, a delay in the excitatory-to-inhibitory developmental "GABA-shift".

An oxytocin(OT)-treatment in the first week of life did not rescue normal vocal communication in mutant pups. However, this treatment had relevant long term effects as it restored short term social memory and normalized the GABAergic activity. Unexpectedly, in WT mice, OT-treatment induced a marked reduction of the Glutamatergic activity without any change in the GABAergic activity, creating global increase of inhibition. However, this E/I imbalance did not apparently impact social behavior, anxiety, locomotor activity levels and willingness to explore of WT mice.

We conclude that OT-treatment in the first week of life had long term effects on hippocampal neurons properties; these effects are correlated with the rescue of social behavior in adult mutant mice but did not affect this behavior in WT.
S6.2

Oxytocin signaling in the central amygdala modulates emotion discrimination in mice

Francesco Papaleo (1)

(1) Istituto Italiano di Tecnologia, Genova, Italy.

Recognition of other’s emotions influences the way social animals interact and adapt to the environment. The neuropeptide oxytocin (OXT) has been implicated in different aspects of emotion processing. However, the role of endogenous OXT brain pathways in the social response to different emotional states in conspecifics remains elusive. Here, using a combination of anatomical, genetic and chemogenetic approaches, we investigated the contribution of endogenous OXT signaling in the ability of mice to discriminate unfamiliar conspecifics based on their emotional states. We found that OXT-ergic projections from the paraventricular nucleus of the hypothalamus (PVN) to the central amygdala (CeA) are crucial for the discrimination of both positively and negatively-valenced emotional states. In contrast, blocking PVN OXT release into the nucleus accumbens, prefrontal cortex, and hippocampal CA2 did not alter this emotion discrimination. Furthermore, silencing each of these PVN OXT pathways did not influence basic social interaction. These findings were further supported by the demonstration that virally-mediated enhancement of OXT signaling within the CeA was sufficient to rescue emotion discrimination deficits in a genetic mouse model of cognitive liability. Our results indicate that CeA OXT signaling plays a key role in emotion discrimination both in physiological and pathological conditions.
S6.3

Interplay between oxytocin and sensory systems in orchestration of social behaviour

Valery Grinevich (1)

(1) Department of Neuropeptide Research, Central Institute of Mental Health, Heidelberg University, J5, Mannheim, 68159, Germany.

The hypothalamic neuropeptide oxytocin (OT) promotes social communication via its central release in the mammalian brain. However, how social interaction affects electrical activity of OT neurons remains unknown. To address this question, we used cell-type specific viral vectors in combination with optoelectrode-based techniques. We performed the *in vivo* single-unit recording of optogenetically identified OT neurons in the paraventricular nucleus (PVN) of adult female rats during their social interactions with unfamiliar female conspecifics. To decipher which sensory stimuli trigger OT neuron activity, we performed experiments with total or partial derivation of socially-relevant visual, olfactory and somatosensory signals. We found that direct physical contact between rats, or even gentle skin stimulation, led to a profound increase in OT firing rates. In contrast, visual, auditory and olfactory signals did not significantly alter OT neuron activity. Given that OT system is composed by magno- and parvocellular OT neurons and the latter are critically involved in nociception, next we explored the role of parvocellular OT neurons during social interactions. Based on the *ex vivo* electrophysiological results that parvocellular OT neurons terminate on magnocellular OT neurons within the PVN, we manipulated them and subsequently monitored social behavior. We found that chemogenetic silencing of parvocellular OT neurons reduces the time spent for social interaction, suggesting that this type of neurons represents “master cells” driving the activation of entire OT system during social behavior. Altogether, our results indicate that non-nociceptive stimulation is essential to activate OT neuron ensembles and, hence, can induce central neuropeptide release in socially interacting female rats. This opens perspectives for studying functional and anatomical connectivity between the somatosensory and OT systems in normal and psychopathological conditions.
S6.3

Interplay between oxytocin and sensory systems in orchestration of social behaviour

Valery Grinevich (1)

(1) Department of Neuropeptide Research, Central Institute of Mental Health, Heidelberg University, J5, Mannheim, 68159, Germany.

The hypothalamic neuropeptide oxytocin (OT) promotes social communication via its central release in the mammalian brain. However, how social interaction affects electrical activity of OT neurons remains unknown. To address this question, we used cell-type specific viral vectors in combination with optoelectrode-based techniques. We performed in vivo single-unit recording of optogenetically identified OT neurons in the paraventricular nucleus (PVN) of adult female rats during their social interactions with unfamiliar female conspecifics. To decipher which sensory stimuli trigger OT neuron activity, we performed experiments with total or partial derivation of socially-relevant visual, olfactory and somatosensory signals. We found that direct physical contact between rats, or even gentle skin stimulation, led to a profound increase in OT firing rates. In contrast, visual, auditory and olfactory signals did not significantly alter OT neuron activity. Given that OT system is composed by magno- and parvocellular OT neurons and the latter are critically involved in nociception, next we explored the role of parvocellular OT neurons during social interactions. Based on the ex vivo electrophysiological results that parvocellular OT neurons terminate on magnocellular OT neurons within the PVN, we manipulated them and subsequently monitored social behavior. We found that chemogenetic silencing of parvocellular OT neurons reduces the time spent for social interaction, suggesting that this type of neurons represents “master cells” driving the activation of entire OT system during social behavior. Altogether, our results indicate that non-noci ceptive stimulation is essential to activate OT neuron ensembles and, hence, can induce central neuropeptide release in socially interacting female rats. This opens perspectives for studying functional and anatomical connectivit y between the somatosensory and OT systems in normal and psychopathological conditions.

S6.4

Prolong optogenetic activation of oxytocin neurons in groups of mice increase prosocial and agonistic behaviors

Yair Shemesh (1)(2), Sergey Anpilov (1)(2), Alon Chen (1)(2)

(1) Weizmann Institute of Science, Rehovot, Israel.
(2) Max Planck Institute of Psychiatry, Munich, Germany.

Most animal studies describe oxytocin as a prosocial and anti-aggressive agent. However, efforts to understand the link between central oxytocin and social behavior mostly rely on a narrow repertoire of strictly controlled behavioral tests. We obtained multivariate behavioral data from groups of mice automatically tracked in a complex environment over several days. We applied a hypothesis-free approach to detect the effects of endogenous oxytocin release, evoked using a novel wireless optogenetic setup. Repeated oxytocin release increased agonistic behavior and induced excessive self-grooming. Thus, while oxytocin exerts prosocial effects in some contexts, in an ethologically-relevant social context of a group, oxytocin can also promote agonistic behavior.
S7.1

Axonal metabolic support and energy dynamics in active white matter tracts

Andrea Trevisiol (1), Kathrin Kusch (1), Klaus Nave (1), Johannes Hirrlinger (2)(1)

(1) Max Planck Institute for Experimental Medicine, Hermann-Rein-Strasse 3, D-37075, Goettingen, Germany.
(2) Carl-Ludwig-Institute for Physiology, Liebigstrasse 27, D-04103, Leipzig, Germany.

In white matter, axonal energy homeostasis depends on glial support. Failure in glial-mediated delivery of metabolic substrates into the axonal compartment results in axonal energy deficit and may anticipate the axonal degeneration described in several myelin disorders and neurodegenerative diseases. In mice, neuronal transgenic expression of a FRET-reporter for ATP allowed us to visualize axonal energy content in acutely isolated optic nerves while simultaneously performing electrophysiological compound action potentials (cAP) recordings. The real-time monitoring of activity-dependent axonal ATP revealed a strong correlation between axonal energy metabolism and nerve conduction. Further on, to determine possible metabolic consequences of myelin defects we monitored ATP and cAP in Plp1\textsuperscript{null/y} optic nerves. Genetic ablation of Plp1, encoding a myelin membrane protein, serves as a model of spastic paraplegia type-2, where an impaired axo-glia unit leads to secondary axonal loss. We found that the energy metabolism of myelinated axons of Plp1\textsuperscript{null/y} optic nerves is perturbed long before the onset of clinical symptoms and major pathological changes. To understand further the role of oligodendroglia and myelin formation in the white matter energy balance, we focused on the metabolic properties of spinal cord sensory fibers in vivo, following a long-term FLIM analysis in a model of MS where we could determine the axonal metabolic changes induced by demyelination and remyelination. Genetically encoded FRET reporters for metabolites are powerful tools to study white matter metabolism and metabolic support mechanisms that might be critically altered in neurodegenerative disorders.
S7.2

Cellular mechanisms regulating axonal energy metabolism in compact white matter

Aiman Saab (1)

(1) University of Zurich, Institute of Pharmacology and Toxicology, Zurich, Switzerland.

Myelinating oligodendrocytes are critical in maintaining long-term axonal integrity and they were recently highlighted to provide metabolic support to the axons they ensheath. Our previous study proposed a model of how axonal activity and concomitant transmitter release might fine-tune the oligodendroglial metabolic support machinery. In response to axonal glutamate signaling, oligodendrocytes adjust their glucose uptake capacity by regulating surface expression of glucose transporter 1 (GLUT1). However, this axon-glial glutamate signaling may mainly serve long-term metabolic adjustments. Hence, cellular mechanisms regulating rapid metabolic support to myelinated axons are still elusive. How do we monitor axonal metabolite dynamics in response to acute elevations in axonal spiking activity? We have established two-photon metabolite imaging in acute optic nerve preparations combined with electrophysiological recordings. All optic nerve axons are myelinated and derive from retinal ganglion cells which can be targeted for metabolite sensor expression by intravitreal AAV delivery. Axonal activity evokes extracellular potassium elevations and myelinating oligodendrocytes are critically involved in potassium clearance. We are currently investigating if activity-dependent potassium clearance could serve as a rapid metabolic feedback loop by triggering glial lactate release which is taken up by axons to fuel ATP demands.
Correlation between activity-related changes in intracellular sodium and ATP in mouse hippocampal neurons

Christine R. Rose (1)

(1) Institute of Neurobiology, Heinrich Heine University Duesseldorf, Universitaetsstrasse 1, 40225 Duesseldorf, Germany.

Excitatory activity is accompanied by sodium influx into neurons, generating transient elevations in the intracellular sodium concentration. Subsequent extrusion of sodium to re-establish ion gradients requires the activation of the Na⁺/K⁺-ATPase (NKA) ultimately resulting in consumption of ATP. Sodium ions also diffuse rapidly in the intracellular space, suggesting that lateral diffusion provides an additional mechanism for recovery from sodium transients. In this talk, I will present data addressing the correlation between different forms of activity, resulting sodium transients and changes in ATP concentrations in CA1 pyramidal neurons of mouse hippocampus. Quantitative sodium imaging was performed using the sodium indicator dye SBFI; intracellular ATP concentration [ATP] was monitored employing FRET-based imaging of the genetically-encoded nanosensor Ateam1.03YEMK (“Ateam”). Our experiments show that global sodium signalling as induced by recurrent network activity or bath application of the excitatory transmitter glutamate, is accompanied by decreases in the intracellular ATP concentration. Induction of local sodium increases of similar peak amplitude, however, does not evoke a detectable changes in intracellular ATP. Recovery from global sodium increases thus requires strong activation of the NKA, consuming more ATP than is produced, resulting in a decrease in cellular ATP. Localized sodium influx, in contrast, apparently does not override local ATP availability and production, suggesting that sodium is predominately removed by fast lateral diffusion. Intracellular spread of sodium from activated to non-activated regions might thus serve a homeostatic function by accelerating the re-establishment of low intracellular sodium and by lowering local energy requirements.

This work was supported by the Deutsche Forschungsgemeinschaft (FOR 2795: Ro2327/13-1).
S7.4

Cell type specificity of neurovascular coupling in cerebral cortex

Martin Thunemann (1)

(1) University of California, San Diego, 9500 Gilman Drv, MC 0624 Medical Teaching Facility, Room 338, La Jolla, Ca, United States of America.

Functional magnetic resonance imaging (fMRI) measures hemodynamic changes as an indirect readout of brain activity, which are interconnected through neurovascular coupling. Over recent years, our mechanistic understanding of neurovascular coupling underwent a paradigm shift. Earlier, it was postulated that byproducts of energy consumption (e.g., CO₂, lactate) elevate cerebral blood flow in response to increased neural activity. However, a growing body of experimental data suggests that under healthy physiological conditions, neuron-derived vasoactive messengers drive vasodilation and -constriction in a cell-type-specific manner; vasodilation and -constriction are caused by activity of specific neuron types and not by undifferentiated spiking or synaptic activity. In addition, neuronal cell types have different energetic demands to support their activity; typically, activity of excitatory pyramidal neurons is metabolically more demanding than activity of cortical inhibitory neurons (INs). To study the contribution of specific IN types and their messengers to hemodynamic and metabolic responses in vivo, we use modern microscopic imaging, optogenetic (OG) tools, and pharmacology to perform minimally invasive studies in awake behaving mice. We have shown that Neuropeptide Y (NPY) acting on Y1 receptors mediates the vasoconstriction phase of the response to a sensory stimulus. Furthermore, recent data indicates that activation of NPY-expressing INs elicits a strong vascular response but no measurable changes in the extracellular potential. These results imply that hemodynamic imaging modalities, such as fMRI, do not necessarily have a low sensitivity towards neuronal activity compared to direct electrophysiological measurements. Instead, sensitivity across measurement modalities depends on the exact composition of neuronal circuit activity and cell-type-specific effects on vasodilation and -constriction, energy consumption, and extracellular potential. With this in mind, we envision a future where multimodal noninvasive measurements of changes in cerebral blood flow, extracellular potential, and neuronal energy consumption can be used to infer underlying neuronal circuit activity.
S8.1

Photochromic modulators of Cys-loop receptors

Piotr Bregestovski (1)(2), Galina Maleeva (2), Karin Rustler (3), Elena Petukhova (4), Alba Nin-hill (5), Mercedes Alfonso-prieto (5), Carme Rovira (5), Pau Gorostiza (6)

(1) Institute of Neurosciences, Kazan Medical University, Kazan, Russia.
(2) INSERM, INS, Institut de Neurosciences des Systèmes, Aix-Marseille University, Marseille, France.
(3) Institute of Organic Chemistry, University of Regensburg, Regensburg, Germany.
(4) Institute of Neurosciences, Kazan Medical University, Kazan, Russia.
(5) ICREA/UB, Departament de Química Inorgànica i Orgànica, Barcelona, Spain.
(6) ICREA/IBEC, Department of Nanoprobes and Nanoswitches, Barcelona, Spain.

Contemporary research has been enriched by the new directions in which the light plays a key role as a tool for modulation of cellular activity and invasive monitoring of intracellular ions and other components. The main advantage of these approaches is the possibility to control precisely of the intensity, spectral characteristics and durations of light signals in space and time. For effective control of ion channel functioning a powerful prospect represent photochromic compounds capable to change their conformation induced by the specific wavelengths illumination. Among them the most widely used are azobenzenes, capable to large change in polarity and geometry upon light-induced switching.

We have developed several new azobenzene-based light-controlled compounds capable to modulate function of inhibitory GABA and glycine Cys-loop receptors. Functional analysis of photochromic compounds action was performed on cultured cells expressing Cys-loop receptors of known subunit composition and in brain slices using electrophysiological recordings. Patch-clamp analysis showed that one of the compounds, Azo-NZ1, in trans-conformation blocks heteromeric GABA\textsubscript{A} and homomeric rho2 GABA\textsubscript{C}, as well as glycine receptors formed by alpha2 subunits. Switching the compound into cis-state by UV-illumination abolished the blocking effect of the photochrome. Site directed mutagenesis and molecular modelling approaches demonstrate that in trans-conformation Azo-NZ1 blocks Cl-selective ion pore interacting mainly with the 2' level of the TM2 region. Recording on brain slices showed that Azo-NZ1 modulates in a light-controlled manner synaptic GABAergic currents in hippocampal and dentate gyrus neurons.

In the talk will be described also the other photochromic compounds, which offers new opportunities to study and modulate neurotransmission mediated by inhibitory Cys-loop receptors.

This study was supported by ERA SynBIO grant MODULIGHTOR (PCIN-2015-163-C02-01), the Russian Science Foundation (grant number: 18-15-00313 for E.P. and P.B.)
S8.2

From neurotoxic peptides and proteins to endogenous regulators of Cys-loop receptors

Victor Tsetlin (1), Igor Kasheverov (1), Yuri Utkin (1)

(1) Department of Molecular Neuroimmune Signaling, Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, ul. Miklukho-Maklaya, 16/10, Moscow, Russia.

Over 50 years ago, three-finger protein (TFP) α- neurotoxins from snake venoms played a crucial role in isolation of the nicotinic acetylcholine receptors (nAChR) from the electric ray, later shown to be similar to the mammalian muscle nAChRs. α-Bungarotoxin made possible the detection of the neuronal α7 nAChR in the mammalian brain, dimeric κ-bungarotoxins interact with neuronalα3β2 nAChR, while α-conotoxins, neurotoxic peptides from the Conus marine snails, distinguish muscle type from neuronal nAChRs and identify subtypes of the latter. Our department has long been studying protein/peptide neurotoxins and their interactions with nAChRs, but now we are also using low molecular compounds, while among the added targets are GABA-A, glycine and 5HT-3 Cys-loop receptors. Our recent work in collaboration with excellent foreign laboratories resulted in the discovery and X-ray structure of dimeric α-cobratoxin [1], isolation of αδ-bungarotoxin (more reversible action than of α-bungarotoxin) [2], design of α-conotoxin PnIA analogs having a 50-fold higher affinity for α7 nAChR [3], identification of some residues explaining distinct type of epibatidine interaction with α7 and α9 nAChR [4], interaction of novel d-tubocurarine analogs with the above-listed Cys-loop receptors [5]. Available rich information on the nAChR interaction with the TFP neurotoxins may be utilized to better understand nAChR interactions with human TFPs Lynx1 and SLURP-1. The difference between rSLURP-1 (heterologously expressed and having additional N terminal Met) and synthetic sSLURP-1 (identical to natural protein) resulted in the selectivity shift from α7 to α9/α10 nAChR [6].

Molecular interactions of 5-HT3 receptors

Sarah Lummis (1)

(1) University of Cambridge, Tennis Court Road, Cambridge, England.

The 5-HT3 receptor is part of a large family of 5-HT receptors, but it is structurally and functionally distinct because, unlike all other 5-HT receptors, it is a Cys-loop receptor. Cys loop receptors, which are part of the larger pentameric ligand gated ion channel (pLGIC) family, are neurotransmitter-gated ion channels responsible for fast excitatory or inhibitory transmission in the CNS, and are the site of action of many of our most widely prescribed drugs. A number of high resolution structures of the 5-HT3 receptor have been published recently (1-3), and thus we are beginning to understand the molecular interactions both within the receptor, and between the receptor and the many compounds that activate or modulate this critical protein. This presentation will reveal some of the exciting new data which is helping to clarify the mechanism of action and potential for novel therapeutic agents acting at this and related receptors.

S8.4

Allosteric regulation of pentameric ligand-gated ion channels by phospholipids

Chris Ulens (1)

(1) KU Leuven, Herestraat 49, PB601, Leuven, Belgium.

Pentameric ligand-gated ion channels (pLGICs) or Cys-loop receptors belong to a class of ion channels involved in fast synaptic signaling in the central and peripheral nervous systems. Molecules acting as allosteric modulators target binding sites which are remote from the neurotransmitter binding site, but functionally affect coupling of ligand binding to channel opening. In this presentation, I will give an overview of the structural and functional studies carried out in our lab in recent years and which focus on a better understanding of the mechanism of allosteric modulation in several model ion channels. These include the human alpha7 nicotinic acetylcholine receptor (nAChR) and the prokaryote GABA-activated ion channel ELIC. The main focus will be on modulation of these channels by phospholipids, and the relationship with other known modulators, such as nanobodies (antibody fragments) and small molecules. Together, the results from these studies provide new strategies for structure-based drug design and the development of new therapies in ion channel-related disorders.
S9.1

ADNP/NAP (CP201): From Gene to Clinical Development

Illana Gozes (1)

(1) Tel Aviv University, Einstein Street, Tel Aviv, Israel.

Twenty years ago, we discovered a new protein to science and named it activity-dependent neuroprotective protein (ADNP). We then showed that it has transcription factor properties regulating >400 genes during development and microtubule function, essential for neuronal and brain formation. ADNP contains the NAPVSIPQ (NAP) domain, including a SxIP motif, which interacts with microtubule end binding proteins to regulate axonal transport and synapse formation. NAP (davunetide, CP201), enhancing/replacing ADNP-microtubule interactions, is currently an investigational drug candidate. NAP (CP201) future clinical trials intend to treat children carrying de novo ADNP mutations and suffering from intellectual disabilities within the autism spectrum disorders.

Characterizing the ADNP syndrome

(https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=404448), we discovered pleotropic actions of ADNP including brain regulation of senses, addictive behaviors and peripheral regulation of skin function. Our recent findings show that Adnp deficiency in mice mimics the ADNP syndrome in terms of speech, cognitive and motor functions. Importantly, NAP treatment provides protection against developmental and behavioral impediments and protects the Adnp-deficient glutamatergic synapse. Mechanistically, NAP enhances dynamic Tau interaction with microtubules through microtubule end binding proteins, providing a promising drug candidate for developmental disorders, such as the ADNP syndrome and beyond. CP201 (NAP) received an orphan drug designation from the US-FDA (http://www.coronisns.com/) and is currently being developed for the ADNP syndrome.

S9.2

Clinical presentation of a complex neurodevelopmental disorder caused by mutations in ADNP

Frank Kooy (1)

(1) Department of Medical Genetics, University of Antwerp, Prins Boudewijnlaan 43/6, Edegem, Belgium.

BACKGROUND: In genome-wide screening studies for de novo mutations underlying autism and intellectual disability, mutations in the ADNP gene are consistently reported among the most frequent. ADNP mutations have been identified in children with autism spectrum disorder comorbid with intellectual disability, distinctive facial features, and deficits in multiple organ systems. However, a comprehensive clinical description of the Helsmoortel-Van der Aa syndrome is lacking.

METHODS: We identified a worldwide cohort of 78 individuals with likely disruptive mutations in ADNP from January 2014 to October 2016 through systematic literature search, by contacting collaborators, and through direct interaction with parents. Clinicians filled in a structured questionnaire on genetic and clinical findings to enable correlations between genotype and phenotype. Clinical photographs and specialist reports were gathered. Parents were interviewed to complement the written questionnaires.

RESULTS: We report on the detailed clinical characterization of a large cohort of individuals with an ADNP mutation and demonstrate a distinctive combination of clinical features, including mild to severe intellectual disability, autism, severe speech and motor delay, and common facial characteristics. Brain abnormalities, behavioral problems, sleep disturbance, epilepsy, hypotonia, visual problems, congenital heart defects, gastrointestinal problems, short stature, and hormonal deficiencies are common comorbidities. Strikingly, individuals with the recurrent p.Tyr719* mutation were more severely affected.

CONCLUSIONS: This overview defines the full clinical spectrum of individuals with ADNP mutations, a specific autism subtype. We show that individuals with mutations in ADNP have many overlapping clinical features that are distinctive from those of other autism and/or intellectual disability syndromes. In addition, our data show preliminary evidence of a correlation between genotype and phenotype.
De humani corporis fabrica: organoid-based deconvolution of neuropsychiatric disorders at single cell resolution

Giuseppe Testa (1)(2)

(1) Dipartimento di Oncologia ed Emato-Oncologia, Università degli Studi di Milano, via Adamello 1, 20139 Milan, Italy.
(2) Dipartimento di Oncologia Sperimentale, Istituto Europeo di Oncologia, via Santa Sofia 9, 20122 Milan, Italy.

Over the last years my lab has been spearheading the modelling of a particularly informative set of neurodevelopmental disorders caused by point mutations or dosage imbalances in chromatin regulators that operate in inter-related pathways. To this end we harness panels of patient-specific disease-relevant lineages derived by cell reprogramming, including 3D brain organoids that recapitulate salient features of human corticogenesis, to enable a multi-layered genome-wide analysis of the gene expression deficits that are either convergent or divergent across different chromatinopathies. Here I discuss the latest insights from our work, focusing on the single-cell level deconvolution of dosage-dependent alterations in developmental pathways and the integration of our transcriptomic profiles within a cutting-edge meta-analysis of available transcriptomic data. Specifically, the latter allows to empirically assess how far brain organoids can recapitulate human brain development and which protocols of differentiation best suit specific experimental needs. To this end, we have assembled an extensive transcriptome database of human cortical development, combining multiple available published works to be used as a robust standard against which to benchmark the transcriptomes of both early and mature stages organoids, encompassing the most relevant aspects of currently available protocols (patterning versus no patterning, matrigel embedding versus not, and combinations thereof). Our analysis shows that patterned cortical organoids recapitulate faithfully the patterns of expression unfolding in fetal corticogenesis and validate the use of this benchmarking resource for comparative evaluations of brain organoid results deriving from different origins and preparations.
A transcription factor implicated in autism locally constrains chromatin looping

Kaaij Lucas (1), Mohn Fabio (1), Bühler Marc (1)(2)

(1) Friedrich Miescher Institute for Biomedical Research, Maulbeerstrasse 66, 4058 Basel, Switzerland.
(2) University of Basel, Petersplatz 10, 4003 Basel, Switzerland.

In studies screening for mutations underlying autism and intellectual disability, mutations in the ADNP gene are reported among the most frequent. Importantly, ADNP mutations have been found comorbid with intellectual disability, distinctive facial features, and deficits in multiple organ systems in children with autism spectrum disorder. This condition is now commonly referred to as Helsmoortel-VanderAa syndrome.

We have recently shown that ADNP forms a chromatin regulatory complex, which we refer to as ChAHP. Besides mediating complex assembly, ADNP recognizes DNA motifs that specify ChAHP binding to euchromatin. Ablation of ChAHP components in mouse embryonic stem cells results in spontaneous differentiation concomitant with premature activation of lineage-specific genes and in a failure to differentiate towards the neuronal lineage. Although this may explain comorbidity in patients with Helsmoortel-Van der Aa syndrome, ADNP’s precise role in transcriptional regulation and development is not understood.

I will present data showing that ChAHP acts as a local modulator of chromatin organization. Our results not only help explain ChAHP-mediated regulation of gene expression but also strongly suggest that ChAHP functions to prevent rewiring of chromatin folding by specifically recognizing novel emerging CTCF sites.
De Novo and Inter-tissue Somatic Mosaicism of ADNP Mutations in Autistic Individuals


(1) Program of Genetics and Genome Biology, The Hospital for Sick Children, 686 Bay St, Toronto Ontario, Canada.
(2) Department of Experimental Oncology, Istituto Europeo di Oncologia (IEO), IFOM-IEO Campus, via Adamello 16, Milan, Italy.
(3) Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Einstein Street, Tel Aviv, Israel.
(4) Department of Medical Genetics, University of Antwerp, Prins Boudewijlnaam 43, B-2650, Edegem, Belgium.
(5) University Hospital Centre Zagreb, Kispaticeva 12, 10000, Zagreb, Croatia.
(6) Department of Molecular Genetics, University of Toronto, Toronto, Canada.

The molecular genetic causes of autism is poorly understood. Autism can be caused by de novo mutations in the ADNP gene, as defined by the absence of mutations in the parents. Mutation events can arise as early as in the parental germline, during embryonic, or fetal development, or as late as post-natally. Timing of mutations could lead to mosaicism of less than heterozygosity to approaching homozygosity. Degrees of mosaicism of mutations between tissues could reveal mutation timing and may shed light on disease etiology and clinical variability. To date ADNP mutation analyses focused upon blood DNA (mesodermal lineage) rather than of ectodermal lineage tissues giving rise to the brain. We developed an ultra-sensitive, highly quantitative droplet digital PCR assay to assess the mutation levels of the ADNP gene in DNA extracted from a broad-range of ADNP patient-derived tissues from multiple patients, including blood, teeth, hair root cells (ectodermal), iPSCs, and many tissues from a post-mortem de novo ADNP mutated child, including the transplanted liver received from a non-mutant donor. Striking levels of somatic mosaicism of ADNP mutations were evident between tissues of the same individual: in one case ADNP mutation loads approached homozygosity in the hair but were less than heterozygosity in the teeth. Mosaicism was evident between clonal iPSC lines - indicating rapid evolution of mosaicism. Tissue-specific ADNP mutation load differences were observed between the post-mortem tissues, both above and below heterozygosity, but not in the transplanted liver. Where ADNP mosaicism approached homozygosity, these may have arisen by parental germ line mutations or extremely high rates of post-zygotic mutations. Since in some cases ADNP mutations were less than heterozygosity supports post-zygotic mutation events, and that variable ADNP mosaicism loads between tissues can arise during development and possibly post-natally, and ongoing mutations may contribute to clinical variation.
S10.1

How to make money with a PhD - Introductory talk: general ideas on career planning

Eva-maria Blumrich (1)

(1) Centre for Discovery Brain Sciences, University of Edinburgh, George Square, EH8 9XD, Edinburgh, Scotland, UK, England.

To get on the career path just right for you is an enormous task and every scientist is confronted with it at least once. One of the major problems is finding a starting point and a way through the numerous ideas, options and suggestions distributed online, by word of mouth or friendly advice. The aim of this workshop is to help managing this task on various different levels, such as information, take-home-tips and direct exchange of experiences with those who have mastered this challenge for themselves already. It is addressed to students and early career researchers in particular, but everyone interested is welcome to join the discussion. The introductory talk will give an overview on the current ideas, coaching approaches and strategies in career planning. In order to give the participants hands on techniques to find their personal starting point for career planning, key questions will be raised and explained alongside introducing various expert-recommended online resources of information. This will invite participants to elucidate what their skills are, what they want to do in the future and what would fit their lifestyle may it be in- or outside of academia. Following this general start the workshop will focus on more senior scientists sharing their experiences of different working environments, such as publishing, academia and industry. This more personal approach will allow participants to ask their questions and engage in an interactive exchange of experiences in the final Q&A session.
At a certain point of your scientific qualification path you will be confronted with a harsh question - What happens after graduation? For some young scientists the way is directed towards academia following the career path of PhD, postdoc and professorship. Nevertheless, pursuing a career outside academia is also a valid option. Both career opportunities have their benefits and downsides. It requires some preparation before following a career track outside academia. Crucial to this is self-reflection and the translation of the scientific skill set gathered during your training to the qualifications desired by the hiring employer. This talk will give an insight about the capabilities you already obtained but might not be aware of. Further, if an employer wants to hire you as an asset to his company, you as well should have some requirements. What basics and benefits can and should you expect as employee? Facing those questions as PhD in biochemistry with 3 years experience working in the industry, I will give you a personal review.
Starting a career in academia

Alessandro Prinetti (1)

(1) Department of Medical Biotechnology and Translational Medicine, University of Milano, Milan, Italy.

After a M.Sc. in pharmaceutical Chemistry, I enrolled in a 4-yeard PhD course at the University of Milano and eventually in 1997 I got my PhD in Biochemistry (with 8 papers in my records, including one as first author; but I had to wait until 2001 for my first J. Neurochem paper).

After that, I moved in Seattle, WA in the lab of Sen-itiroh Hakomori, where I met some of the persons who still are my best collaborators and friends.

I came back to my alma mater at the end of 1998, and in 1999, I became Researcher at the University of Milano, at that time the first step in the academic career in Italy. The rest of my career has developed in the same institution where I became Full Professor of Biochemistry in 2008.

Since the time of my PhD, things have changed dramatically in the Italian academic scenario. The PhD course in Biochemistry shrunk to 3 years. Several private Medical Universities research institutions appeared in Italy, flanking the State Universities and the government-led National Research Council.

The legislation regulating the access to academia and the progression along the academic career has changed twice.

In my presentation, I will try to explain what I do have in common with my PhD students, and why I am convinced that a career in academia is still a possible and rewarding choice.
S10.4

From science to science publishing: opportunities and challenges

Anthony J Turner (1), Natalia N Nalivaeva (1)(2), Jackie Jones (3)

(1) School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Mount Preston Street, Leeds, LS2 9JT, England.
(2) I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry, RAS, 44 Thorez av, Saint Petersburg, Russia.

A PhD in a science discipline can deliver broad career opportunities outside of the academic and industrial research worlds while still utilising the acquired skills and knowledge. One such opportunity is in science publishing, which provides an interface between a scientific background and knowledge communication. It can offer frontline opportunities close to science, for example in dealing with authors, processing of scientific manuscripts, managing the review process itself and working closely with scholarly societies. Opportunities range from roles as journal editorial co-ordinators/managers that work closely in the editorial office supporting a Chief Editor who is often a busy and active scientist or can be a Professional Editor-in-Chief, through to roles in marketing and commissioning. “Back-office” roles can range from graphic design to web editing, PR and social media yet still remain close to the science itself. An editorial manager/co-ordinator not only deals directly with authors and editors but also oversees editorial board meetings as well as journal statistics, bibliometric analysis, and can facilitate new scientific directions, workflows and policies for the journal. Where it is linked to a scientific society (like Journal of Neurochemistry), the journal can provide opportunities for conference travel and staying close to the cutting edge of the science itself. It can also allow for flexible work location. For the active scientist/academic, direct involvement in publishing, for example as a journal handling editor, provides insight into all aspects of science communication, including ethics, open research initiatives, science impact and value. It is currently an exciting and challenging time to enter the science publishing world as it transitions to a completely open access environment. This is already opening up opportunities and providing new initiatives among the traditional publishing groups and the many new entrants to the field.
Ret protects the midbrain dopaminergic system against α-synuclein toxicity by influencing mitochondrial integrity and autophagy

Edgar R. Kramer (1)(2), Helia Aboutalebi (2)(3), Karsten Tillack (2)(4), Eva Van Well (5), Barbara Finckh (6), Simone Feldengut (7), Kelly Del Tredici (7), Konstanze F. Winklhofer (5)

(1) Institute of Translation and Stratified Medicine, Faculty of Medicine and Dentistry, University of Plymouth, Derriford Research Facility, 14 Research Way, PL6 8BU, Plymouth, United Kingdom.
(2) Development and Maintenance of the Nervous System, Center for Molecular Neurobiology, University Medical Center Hamburg-Eppendorf, Falkenried 94, 20251, Hamburg, Germany.
(3) German Center for Neurodegenerative Diseases (DZNE) within the Helmholtz Association, Venusberg-Campus 1, Building 99, 53127, Bonn, Germany.
(4) Evotec AG, 22419, Hamburg, Germany.
(5) Department of Molecular Cell Biology, Institute of Biochemistry and Pathobiochemistry, Ruhr-University Bochum, Building MA 2/143, Universitätsstraße 150, 44801, Bochum, Germany.
(6) Neonatal Screening/Metabolic Laboratory, Diagnostic Center, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246, Hamburg, Germany.
(7) Clinical Neuroanatomy Section, Department of Neurology, Center for Biomedical Research, University of Ulm, Helmholtzstrasse 8/1, 89081, Ulm, Germany.

Despite the positive effect of glial cell line-derived neurotrophic factor (GDNF) and its receptor Ret in different Parkinson disease (PD) animal models on maintenance, protection and regeneration of dopaminergic (DA) neurons, clinical trials on PD patients with Ret ligands are still inconclusive. This discrepancy emphasizes the need to analyze in vivo Ret/GDNF signalling in more detail under physiological and pathophysiological conditions in improved PD models.

Here we show the requirement of postnatal Ret signalling in mice especially for the maintenance of substantia nigra DA neurons preferentially dying in PD patients. We developed an inducible α-synuclein transgenic PD mouse model with progressive DA neuron degeneration and additional PD hallmarks and found unaltered Nurr1 and Ret protein levels. This challenges the physiological relevance of α-synuclein mediated Nurr1 and Ret down-regulation reported for viral overexpression of α-synuclein in rodents. Ret protein is also detected in human PD brains at all Braak stages. Additional deletion of the Ret receptor in these α-synuclein PD mice resulted in a more severe DA neuron degeneration and increased autophagy problems proving the occurrence and benefit of Ret signalling under this PD-like conditions. Ret signalling also counteracts α-synucleins negative effect on mitochondrial integrity and autophagy.

These data prove the in vivo neuroprotective function of Ret signalling even in α-synuclein accumulating DA neurons and they underpin the importance to continue with the ongoing clinical PD trials using Ret activators.
S11.2

From dysfunction of PINK1/Parkin-mediated mitochondrial quality control to Parkinson’s disease.

Olga Corti (1)

(1) Institut du Cerveau et de la Moelle épinière, Hôpital de la Pitié-Salpêtrière, 75013 Paris, France.

Mitochondrial quality control is orchestrated by a series of fundamental mechanisms aimed at preserving mitochondrial activity and adapting it to the changing environment in order to promote cell survival. The relevance of these mechanisms is highlighted by the dramatic consequence of the genetic alteration of intrinsic or regulatory components of these pathways. One example is illustrated by loss-of-function mutations in the PARK2 and PINK1 genes, which lead to autosomal recessive forms of Parkinson’s disease. These genes encode the E3 ubiquitin ligase Parkin and the mitochondrial serine/threonine kinase PINK1, which jointly regulate the degradation of dysfunctional mitochondria by autophagy, a process termed mitophagy. Despite the remarkable advances in our understanding of the molecular mechanisms by which these proteins cooperate in sensing mitochondrial damage and activating mitophagy, whether dysfunction of this pathway is central to neuronal degeneration in Parkinson’s disease remains debated. I will present recent efforts from our laboratory to investigate more broadly the role of the PINK1/Parkin system in mitochondrial quality control, with a focus on mitochondrial protein import. I will also illustrate our approaches to address more globally the consequence of PINK1/Parkin dysfunction on the biology of neuronal and glial cells, with a focus on the response to mitochondrial stress and to proinflammatory stimuli. Finally, I will discuss the possibility that PINK1/Parkin-dependent mechanisms play a role beyond autosomal recessive Parkinson’s disease.
S11.3

Functional genomic analysis uncovers mitophagy regulators associated with Parkinson’s disease risk

Helene Plun-Favreau (1)

(1) University College London, Institute of Neurology, Queen Square, WC1N 3BG, London, England.

Parkinson’s disease (PD) is a common neurodegenerative disease, for which there is no cure. Until recently, the genetic basis for PD was limited to family-based linkage studies, favouring the identification of rare Mendelian genes of high penetrance and effect. The identification of common genetic variants linked to disease via genome wide association studies (GWAS) has led to a rapid improvement of our understanding of the genetic architecture of PD, but has resulted in two major challenges for the research community. First, conclusively identifying the causal gene(s) for a given risk locus, and secondly dissecting their contribution to disease pathogenesis. Addressing these challenges is critical for moving beyond genetic insights to developing new disease modifying strategies for PD. Based upon extensive data implicating impaired mitophagy in the aetiology of familial PD, we developed a mitophagy screening assay as a tool to evaluate candidate genes identified through GWAS. Using our screening pipeline, we identified two new PD risk genes, that were previously shown to interact at the mitochondria, that regulate mitophagy. These findings establish mitophagy as a contributing factor to idiopathic PD and provide a proof of principle for the value of screening approaches to identify causative genes in GWAS loci. Finally, these results enrich our understanding of physiological events regulating mitochondrial quality control and establish a novel pathway for drug targeting in neurodegeneration.
Decoding PINK1/Parkin signalling in Parkinson’s disease

Miratul Muqit (1)

(1) MRC Protein Phosphorylation and Ubiquitylation Unit, School of Life Sciences, University of Dundee, Dundee DD1 5eh, United Kingdom.

The Parkinson’s disease-associated protein kinase, PINK1, and ubiquitin E3 ligase, Parkin function in a common signalling pathway known to regulate mitochondrial network homeostasis and quality control including mitophagy. The multistep activation of this pathway has expanded our understanding of cellular damage responses during human disease. To explore the physiological role of PINK1-Parkin signalling we have undertaken proteomic analysis of wild-type and PINK1 knockout neurons. This reveals new downstream substrates of the Parkin E3 ligase. These substrates will be valuable for validating small molecular activators of Parkin as potential therapeutics against Parkinson’s.
S12.1

The NMDA receptor co-agonist D-serine is essential for dopamine modulations of prefrontal neuronal activity and cognitive function

Jean-Pierre Mothet (1)

(1) UMR9188 CNRS - ENS Paris Saclay, 505 rue du Belvédère, Orsay, France.

Dopaminergic modulation of glutamatergic neurotransmission in the prefrontal cortex (PFC) plays an important role in the control of cognitive functions. Accordingly, disruption of frontocortical dopamine (DA)-glutamate cross-talk is a hallmark of several neuropsychiatric disorders, including schizophrenia. In addition, hypoactivity of NMDA receptors due to reduced availability of the co-agonist D-serine is implicated in schizophrenia. Whether dopaminergic modulations of neuronal activity and cognitive functions involve D-serine is not known. Herein, we show that pharmacologically- and genetically-driven depletions of D-serine impair positive and negative modulations of glutamatergic transmission, neuronal excitability and plasticity by D₁ and D₃-receptor activation, respectively. Furthermore, we report that the selective blockade of the D₃-receptors increases global PFC activity and cognition in wild-type but not in null-mutant mice for serine racemase the enzyme that synthesizes D-serine. All these aberrant electrophysiological and behavioral signatures found in the mutant mice are fully alleviated when D-serine is administered to mice. Finally, we reveal that D₁R and D₃R activations coordinately regulate in opposite directions the extracellular levels of D-serine in the PFC and identify the cAMP/PKA pathway as a molecular hub. Collectively, these results reveal a key role for D-serine in the neuromodulation by dopamine of PFC activity, findings highly relevant to the etiology and treatment of schizophrenia but also to disease where the dopamine-glutamate cross-talk is disrupted.
S12.2

Learning from failures: A novel framework for presynaptic plasticity

Rudi Tong (1), Nigel Emptage (1)


Glutamate is thought to play a crucial role in Hebbian plasticity. However, glutamate release is known to be very unreliable, which is seemingly inefficient for learning. Here, we show that long-term potentiation of presynaptic release probability (LTPpre) is independent of glutamate and is in fact driven by release failures. We find that the induction of LTPpre requires the retrograde messenger nitric oxide, which is released upon strong postsynaptic depolarisation and activation of L-type voltage-gated Ca2+ channels and is therefore independent of glutamate signalling. Instead, release of glutamate promotes presynaptic long-term depression via a negative feedback through presynaptic NMDA receptors. These findings reveal a novel framework for presynaptic plasticity, which is distinct from conventional models of postsynaptic plasticity.
NMDA receptor C-terminal domain signaling in health and disease

Giles Hardingham (1)(2)

(1) University of Edinburgh, England.
(2) UK Dementia Research Institute, England.

The GluN2 subtype (2A vs. 2B) determines key biophysical properties of forebrain NMDA receptors. During development, GluN2A becomes incorporated into previously Glu2NB-dominated NMDARs, but both are highly expressed in the adult forebrain. In addition to controlling channel properties, GluN2A and GluN2B have large and highly divergent cytoplasmic C-terminal domains. Using genetically modified mice with targeted mutation of exchange of GluN2 C-terminal domains, we are investigating their role in development and disease. Key questions include their role in directing the switch in NMDA receptor subunit composition, and in pro-death signaling in acute and chronic neurological conditions.

Emergence of mTOR-dependent protein translation is controlled by non-conventional NMDA receptors

Maria Jose Conde-dusman (1), Partha Narayan Dey (2), Luis García-rabaneda (3), Oscar Elía-zudaire (1), Victor Briz (4), Isabel Perez-otaño (1)

(1) Instituto de Neurociencias (CSIC-UMH), Instituto de Neurociencias, Campus de Sant Joan, Avda Santiago Ramón y Cajal s/n, San Juan De Alicante, Spain.
(2) Johannes Gutenberg University, Mainz, Germany.
(3) Institute of Science and Technology Austria, Klosterneuburg, Austria.
(4) Centro de Biología Molecular, Universidad Autónoma, Madrid, Spain.

Early brain development is characterized by an overproduction of synapses which make weak functional connections between neurons. Neuronal activity later refines this basic circuitry by strengthening and maintaining subsets of connections but suppressing others, ultimately resulting in the formation of more precise and durable connections. Juvenile NMDARs containing GluN3A subunits have emerged as key regulators of this kind of postnatal circuit refinements by preventing premature synapse maturation/ stabilization until the arrival of sensory experience, and later targeted certain synapses for pruning (see Pérez-Otaño, Larsen and Wesseling, Nat Rev Neuroscience 2016). Here we investigated the signaling pathways whereby GluN3A expression tunes the balance between synapse maturation and pruning, and their impact on the emergence of cognitive functions. We found that GluN3A inhibits the induction of a subset of activity-regulated pathways, most prominently the mammalian target of rapamycin (mTOR) pathway, placing constraints on the developmental emergence of mTOR-dependent di novo protein synthesis. Conversely, mTOR activation is potentiated in GluN3A KO mice, and correlates with enhanced performance of GluN3A KOs in the Morris water maze relative to wild-type littermates. GluN3A KO mice also formed stronger aversive memories in the fear conditioning and conditioned taste aversion paradigms, but this advantage was suppressed by pharmacological reduction of mTOR with rapamycin. Current work aims to elucidate the differentially translated mRNA transcripts, and whether the observed cognitive phenotypes reflect developmental effects of GluN3A on circuit configuration or adult roles.

Work was funded by the UTE project CIMA, a Tatiana Pérez de Guzmán el Bueno fellowship (to M.J.C.D.), a Juan de la Cierva-Incorporation Fellowship (IJC1-2014-19056) (to L.G.R), a NARSAD Independent Investigator Award and grants from the MINECO (CSD2008-00005, SAF2013-48983R, SAF2016-80895-R) (to I.P.O).
S13.1

Brain metabolic alterations in neuronal ceroid lipofuscinosis juvenile CLN7 Batten disease

Irene Lopez-fabuel (1)(5), Costantina Buondelmonte (1), Nicolo Bonora (1)(2), Stephan Storch (3), Sara Mole (4), Angeles Almeida (5), Juan P. Bolanos (1)(5)

(1) Institute of Functional Biology and Genomics (IBFG), Universidad de Salamanca, Salamanca, Spain.
(2) Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain.
(3) Section Biochemistry, Children’s Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
(5) Institute of Biomedical Research of Salamanca (IBSAL), Hospital Universitario de Salamanca, Salamanca, Spain.

Neuronal ceroid lipofuscinoses (NCL), known as Batten disease, is the most common of the rare neurodegenerative disorders in children. Families affected by all types of NCL are found throughout Europe, with the exact distribution of genetic sub-types varying from country to country. The incidence of CLN7 disease, caused by mutation in MFSD8 gene, is the highest in southern and Mediterranean Europe. CLN7/MFSD8 encodes a lysosomal membrane glycoprotein that seems to transport small substrates across the lysosomal membrane. However, the precise function of CLN7 and therefore the molecular mechanism that leads to neuronal death in CLN7 disease is yet uncertain. Lysosomal function is critical for nutrient sensing and signalling pathways regulating cell metabolism, in part by controlling the degradation of damaged mitochondria, hence suggesting that neuronal energy metabolism might be affected in CLN7 disease. Here, we aimed to ascertain this issue by characterizing the bioenergetic metabolism of neurons in primary culture obtained from CLN7 knockout (KO) (CLN7Δex2) mice. Employing radiometric approaches, we found that the rate of glucose consumption through the pentose-phosphate pathway (PPP) is decreased in CLN7-KO neurons, which accompanies increased mitochondrial reactive oxygen species (mROS) glycolysis. Experiments performed to understand the mechanism responsible for this metabolic rewiring in CLN7-KO neurons revealed that damaged mitochondria, by producing excess mROS, upregulated the hypoxia-inducible factor-1 (HIF1), which accounted for the induction of key glycolytic genes upregulating glycolysis and shifting down the PPP. Since PPP is a major antioxidant mechanism in neurons, the molecular mechanism that reprograms neuronal metabolism herein deciphered also explains the redox stress associated with neuronal loss in CLN7 disease. Thus, reprogramming of neuronal metabolism through this mROS-HIF-1 pathway may explain the neurodegeneration associated with CLN7 disease and pinpoints a potential novel therapeutic target against this disorder.
S13.2

APC/C-Cdh1 regulates X fragile protein FMRP and dendrite stability during brain development

Bobo-Jimenez Veronica (1)(2), Gomila Silvia (1)(2), Bolaños Juan P (1)(2), Almeida Angeles (1)(2)

(1) Institute of Biomedical Research of Salamanca (IBSAL), Calle Zacarías González 2, Salamanca, Spain.
(2) University of Salamanca, Calle Zacarías González 2, Salamanca, Spain.

Fragile X Syndrome (FXS) is the most common single-gene cause of intellectual disability and autistic spectrum disorders. The molecular cause of FXS arises from loss-of-function mutations in the X-chromosome gene, FMR1, which encodes the RNA binding protein FMRP (Fragile X Mental Retardation Protein). FXS is a synaptic plasticity disorder, associated with impaired structural development of neuronal dendrites and spines. During development, an adequate synapse formation and maintenance are essential processes for proper brain function, including cognitive activity, such as learning and memory. We recently described that the E3 Ubiquitin Ligase Anaphase Promoting Complex/Cyclosome (APC/C) is essential for dendrite network and synapse integrity in the adult brain. However, the role of APC/C in postnatal dendrite and synapse development and its impact in FXS are still unknown. Here, we study the function of Cdh1, the activator of APC/C, on dendrite and synapse stability in the developing brain.

Cdh1 loss promoted alterations in brain structure, including brain weight reduction and increased lateral ventricle volume. Moreover, the length of cortex and hippocampus were shorter in the Cdh1 knock-out (Cdh1 KO) mice, which correlated with dendrite disruption and neuronal loss. The ultrastructure analysis of CA1 hippocampus layer revealed a disbalance between synaptic clefts and synaptic vesicles in the Cdh1 cKO mice. Furthermore, the lack of Cdh1 decreased level expression of pre (Basson) and post-synaptic (PSD95) proteins, while increased FMRP levels. Then, Cdh1 depletion prevents synaptogenesis and dendrite stability in the developing brain.

Here we describe a key role of APC/C-Cdh1 in postnatal synaptogenesis and integrity of dendritic network in the developing brain. Moreover, APC/C-Cdh1 regulates FMRP levels in the developing brain, which highlights the impact of Cdh1 in the molecular pathogenesis of FXS.

The work was funded by The Ramon Areces Foundation.
S13.2

APC/C-Cdh1 regulates X fragile protein FMRP and dendrite stability during brain development

Bobo-Jimenez Veronica (1)(2), Gomila Silvia (1)(2), Bolaños Juan P (1)(2), Almeida Angeles (1)(2)
(1) Institute of Biomedical Research of Salamanca (IBSAL), Calle Zacarías González 2, Salamanca, Spain.
(2) University of Salamanca, Calle Zacarías González 2, Salamanca, Spain.

Fragile X Syndrome (FXS) is the most common single-gene cause of intellectual disability and autistic spectrum disorders. The molecular cause of FXS arises from loss-of-function mutations in the X-chromosome gene, FMR1, which encodes the RNA binding protein FMRP (Fragile X Mental Retardation Protein). FXS is a synaptic plasticity disorder, associated with impaired structural development of neuronal dendrites and spines. During development, an adequate synapse formation and maintenance are essential processes for proper brain function, including cognitive activity, such as learning and memory. We recently described that the E3 Ubiquitin Ligase Anaphase Promoting Complex/Cyclosome (APC/C) is essential for dendrite network and synapse integrity in the adult brain. However, the role of APC/C in postnatal dendrite and synapse development and its impact in FXS are still unknown. Here, we study the function of Cdh1, the activator of APC/C, on dendrite and synapse stability in the developing brain.

Cdh1 loss promoted alterations in brain structure, including brain weight reduction and increased lateral ventricle volume. Moreover, the length of cortex and hippocampus were shorter in the Cdh1 knock-out (Cdh1 KO) mice, which correlated with dendrite disruption and neuronal loss. The ultrastructure analysis of CA1 hippocampus layer revealed a disbalance between synaptic clefts and synaptic vesicles in the Cdh1 cKO mice. Furthermore, the lack of Cdh1 decreased level expression of pre (Basson) and post-synaptic (PSD95) proteins, while increased FMRP levels. Then, Cdh1 depletion prevents synaptogenesis and dendrite stability in the developing brain after birth.

Here we describe a key role of APC/C-Cdh1 in postnatal synaptogenesis and integrity of dendritic network in the developing brain. Moreover, APC/C-Cdh1 regulates FMRP levels in the developing brain, which highlights the impact of Cdh1 in the molecular pathogenesis of FXS.

The work was funded by The Ramon Areces Foundation.

S13.3

Lysosomal disorders provide valuable insight into neurodegenerative conditions

Simon Heales (1)

There is a growing body of evidence to support the concept that perturbation of lysosomal metabolism plays a key role in the pathogenesis of neurodegenerative conditions such as Parkinson’s diseases (PD). This is exemplified by the intriguing link between mutations affecting the lysosomal enzyme glucocerebrosidase (GBA1) and PD; homozygous mutations in GBA1 cause Gaucher Disease (GD) and convey an increased risk of PD. Furthermore, heterozygote carriers, whilst not developing GD, have a comparable risk of getting PD. How a loss of lysosomal GBA1 activity leads to degeneration of neuronal cells is not known. However, a number of mechanisms have been proposed and these include secondary loss of mitochondrial function (failure of mitophagy), ER stress, oxidative stress and alpha-synuclein accumulation. Additionally, in idiopathic PD, where no GBA1 mutations can be identified, loss of GBA1 activity can be demonstrated suggesting that the neurodegenerative process in PD negatively impacts on lysosomal metabolism. In PD, loss of GBA1 can be demonstrated in brain tissue and also dried blood spots and white cells suggesting peripheral involvement of the lysosomal system. Whilst the link between GBA1 activity and dopamine (the neurotransmitter deficient in PD) is not known, marked alterations in dopamine turnover can be demonstrated in GD patients and in cultured cells following chemical inhibition of GBA1. Finally, it is now emerging that other lysosomal disorders convey a risk factor for developing PD and hence are providing further mechanistic insights and treatment targets for PD.
S13.4

The role of cholesterol metabolism in Huntington's disease: from molecular mechanism to therapeutics

Marta Valenza (1)(2), Giulia Biolini (1)(2), Elena Vezzoli (1)(2), Francesca Pederzoli (3), Claudia Maniezzi (4), Francesca Talpo (4), Gerardo Biella (4), Andrea Falqui (5), Barbara Ruozzi (3), Giovanni Tosi (3), Elena Cattaneo (1)(2)

(1) Department of Biosciences, University of Milan, Milan, Italy.
(2) IINGM, Istituto Nazionale di Genetica Molecolare “Romeo ed Enrica Invernizzi”, Milan, Italy.
(3) Nanomedicine and Pharmaceutical technology, Dept. of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy.
(4) 4Dept. of Biology and Biotechnology, University of Pavia, Pavia, Italy.
(5) 5King Abdullah University of Science and Technology (KAUST), Thuwal, Saudi Arabia.

Huntington's disease (HD) is a genetic, neurodegenerative disorder caused by a CAG repeat expansion in the gene encoding the huntingtin (HTT) protein. Clinically, HD is characterized by motor defects, cognitive decline and psychiatric disturbances and is associated with neuronal and synaptic dysfunction and progressive loss of striatal and cortical neurons.

One affected pathway in HD implicates brain cholesterol. Brain cholesterol biosynthesis is reduced across different HD animal models supporting the hypothesis that newly cholesterol is less available to neurons. This might be detrimental for neuronal cells, especially given that cholesterol from periphery is not able to cross the blood-brain barrier and locally synthesized cholesterol is critical for neurite outgrowth, synapses formation, maintenance and activity, and optimal neurotransmitter release.

Here we present our findings indicating that astrocytes carrying the HD mutation are the major responsible of cholesterol dysfunction in HD as they contribute to supply less cholesterol to the surrounding neurons. Finally, I will show our in vivo studies demonstrating that delivery of exogenous cholesterol to the brain of HD mice rescues molecular, functional and behavioral aspects of the disease.
Activity-dependent neuroprotective protein (ADNP) was discovered and first characterized in the laboratory of Prof. Illana Gozes as vital for mammalian brain formation, while its haploinsufficiency causes cognitive impairments. ADNP was recently discovered as one of the leading genes mutated de novo causing an autistic syndrome, namely the ADNP syndrome, characterized by global developmental delays, intellectual disabilities, speech impediments and motor dysfunctions. In this respect, the Adnp-deficient mouse was found to mimic the human ADNP syndrome patient in terms of synapse density and gene expression patterns, as well as at the developmental, motor, and cognitive levels. Furthermore, an alternate formulation tested in our lab for the effective delivery of NAP showed improvements using daily intranasal NAP treatment at the behavioral and brain structural levels (diffusion tensor imaging). Additional significant effects were observed in the hippocampus and cerebral cortex at the level of expression of proteins important for synaptic plasticity and cognition. These results complemented the findings of reduced dendritic spine density, improved by NAP, in the Adnp-deficient mouse model and showed sex differences in social activities. Altogether, ADNP may be unveiled as a possible biomarker, identifying autistic individuals suffering from the ADNP syndrome. Moreover, a better understanding of the ADNP syndrome may be provided, paving the path to its clinical early diagnosis, and suggesting NAP for further clinical development.

References:

1. The autism/neuroprotection-linked ADNP/NAP regulate the excitatory glutamatergic synapse.


S14.2

Metabolic heterogeneity of astrocytes in grey and white matter

Susanne Köhler (1), Ulrike Winkler (1), Johannes Hirrlinger (1)(2)

(2) Max-Planck-Institute for Experimental Medicine, Department of Neurogenetics, Hermann-Rein-Straße, 3, Göttingen, 37075, Germany.

Astrocytes are the most abundant glial cell type in the central nervous system crucially contributing to brain function. Astrocytes are a phenotypical heterogeneous cell population, which is classically divided into protoplasmic astrocytes of the grey matter and fibrous astrocytes of the white matter. Besides this morphological diversity, they also have distinct functional specializations adapting to their local environment. Astrocytes in grey matter support and modulate neuronal information transmission as part of the tripartite synapse whereas astrocytes in white matter are in close contact with axons, myelin and oligodendrocytes. However, it is still a matter of debate how astrocytic energy metabolism reflects these structural and functional differences and which underlying mechanisms regulate these processes. To address this issue we investigated in acutely isolated brain slices the energy metabolism of astrocytes from grey and white matter using genetically encoded fluorescent biosensors for key metabolites and studied the dynamics of the NADH/NAD⁺ redox state (“Perodox” sensor) and ATP (“ATeam1.03YEMK” sensor). Astrocytes in cortex and corpus callosum differed in their basal redox state as well as showed distinct responses upon application of neurotransmitters, enhancement of extracellular potassium concentration and neuronal depolarization, suggesting different local mechanisms of coordinating signaling and metabolism. These results show that the metabolic state of astrocytes in different brain regions is rather heterogeneous, thereby contributing to adjust astrocytic function to the local energetic demands within the brain.
S14.3

Maternal hyperhomocysteinemia disturbs development of brain cortex and hippocampus and affects memory in rat offspring

Anastasiia Shcherbitskaia (1)(2), Dmitryi Vasilev (1), Natalia Tumanova (1), Julia Milyutina (2), Irina Zaloznyaya (2), Natalia Nalivaeva (1), Alexander Arutjunyan (2), Igor Zhuravin (1)

(1) I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Academy of Sciences, M.Thorez av., 44, Saint-petersburg, Russia.
(2) The Research Institute of Obstetrics, Gynecology and Reproductology named after D.O. Ott, Mendeleevskaya l., 3, Saint-petersburg, Russia.

The action of different stressors during pregnancy leads to various complications both in the maternal organism and in the fetus increasing the risk of abnormal brain development and function in later life. Here we examined the effects of maternal hyperhomocysteinemia (HHC) on brain development and memory in rat offspring. HHC was induced in pregnant rats by administration of methionine (0.6mg/kg) in drinking water on the 4th-21st days of pregnancy. 5’ethynyl-2’dexoxyuridine was used to label neurons generated in the fetal brain on E14. In the group of pups subjected to HHC the total number of labeled cells in the parietal cortex was decreased while the number of labeled neurons scattered within the superficial cortical layers was increased, suggesting that HHC causes a disruption in neuroblast generation and migration. In the first 20 days after birth the reduction in the total number of neurons and an increase in the number of glial cells was observed in the cortex and hippocampus of HHC rat offspring. At the ultrastructural level there were also some features of delayed brain development: an increased number of growth cones, larger volume of intercellular spaces and decreased number of developed synapses. Along with morphological changes, at this age, caspase-3 activation and increased levels of NRG1 and proBDNF were observed in the brain of HHC rat pups as well as an elevation in the levels of pro-inflammatory cytokines. Later in life (P60) HHC rats demonstrated memory impairment when examined by various tests. The data obtained indicate that maternal HHC during pregnancy affects formation of fetal brain cytoarchitecture, in particular of the hippocampus and cortex, leading to the disruption of their development in postnatal ontogenesis, which results in impaired cognitive functions of adult rat offspring.

Supported by RFBR 18-015-00099 and Russian state budget assignment (AAAA-A19-119021290116-1, AAAA-A18-118012290373-7).
IDENTIFICATION OF THE ANTIGEN RECOGNIZED IN VITRO BY RHIGM22, A REMYELINATION-PROMOTING HUMAN MONOCLONAL ANTIBODY

Livia Cabitta (1), Sara Grassi (1), Simona Prioni (1), Laura Mauri (1), Maria Grazia Ciampa (1), Yana Zorina (2), Sandro Sonnino (1), Alessandro Prinetti (1)

(1) Università di Milano, Dipartimento di biotecnologie mediche e medicina traslazione, Via Fratelli Cervi 93, Segrate, Milan, Italy.
(2) Acorda Therapeutics, Inc, Ardsley, Ny, United States of America.

Recombinant human IgM22 (rHlgM22) binds to myelin and oligodendrocytes (OLs), and promotes remyelination in models of multiple sclerosis. rHlgM22 preferentially reacts with sulfatide-positive (O^+4) OLs, and its binding is abolished in brain slices from Cst (-/-) mice, suggesting its binding requires the presence of a product of cerebroside sulfotransferase. However, literature suggests that cell populations lacking sulfatide expression, such as microglia and oligodendrocyte precursor cells, are responsive to rHlgM22, thus the identity of the antigen recognized by this antibody remains to be elucidated.

We tested the binding of rHlgM22 to purified lipids and lipid extracts from various sources using TLC immunostaining and surface plasmon resonance (SPR) with lipid monolayers. Our results show that IgM22 binds to sulfatide and lysosulfatide in vitro, while it does not bind to other myelin sphingolipids. In addition, rHlgM22 also reacts with phosphatidylinositol, phosphatidylserine and phosphatidic acid, present in lipid extracts from various sources, including CST ko mice brains, mixed glial cultures, isolated astrocytes and microglia.

These data suggest that sulfatide at the OLs surface might be important for the binding of rHlgM22 to these cells. On the other hand, its ability to bind some glycerophospholipids could explain the biological responses elicited by rHlgM22 in cells lacking sulfatide expression. The in vitro reactivity of rHlgM22 suggests that binding of rHlgM22 to intact cells might require a complex molecular arrangement, and, in particular, sulfatide and other membrane lipids might be part of the functional rHlgM22 antigen localized at the cell surface.
S15.1

Long-Lasting Impairment of Neuroplastic Gene Expression as a Mechanism of Cognitive Deficit Caused by Neonatal LPS Exposure

Alexander Trofimov (1), Olga Zubareva (1)(2), Alexander Schwarz (1)(3), Ekaterina Veniaminova (1)(4), Kevin Fomalont (1), Victor Klimenko (1)

(1) Laboratory of Neurobiology of the Brain Integrative Functions, I.P. Pavlov Department of Physiology, Institute of Experimental Medicine, Akademika Pavlova st. 12, Saint Petersburg, Russia.

(2) Laboratory of Molecular Mechanisms of Neuronal Interactions, I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, Thorez Avenue 44, Saint Petersburg, Russia.

(3) Multidisciplinary Laboratory of Neurobiology, I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Science, Thorez Avenue 44, Saint Petersburg, Russia.

(4) Laboratory of Psychiatric Neurobiology, Institute of Molecular Medicine, Sechenov First Moscow State Medical University, Mokhovaya st. 11/4, Moscow, Russia.

Perinatal pathology is known to impair the CNS formation and increase the risk of chronic cognitive deficit. Overexpression of pro-inflammatory cytokines by the cells of immune and nervous systems is a key detrimental factor for the developing brain. Particular molecular mechanisms of the action of pro-inflammatory factors on the cells of CNS are yet not fully elucidated. One of possible mechanisms of long-term cognitive impairments evoked by early-life inflammation is an altered neuroplastic gene expression.

In our studies on Wistar rats that were treated with moderately pyrogenic doses of LPS during the 3rd week of postnatal development, we focused on the prefrontal and hippocampal gene expression of fibroblast growth factor-2 (Fgf2), matrix metalloproteinase-9 (Mmp9), and tissue inhibitor of metalloproteinases-1 (Timp1). These genes are implicated in the development of CNS and memory formation, as well as their expression was described to be affected by inflammation-related events. LPS-treated animals demonstrated decreased exploratory activity and increased static movement, impaired active avoidance learning and spatial memory formation compared to the control animals that were injected with saline. Impaired behavior was associated with decreased Fgf2 expression in the medial prefrontal cortex in comparison with vehicle-treated control. Adolescent and adult LPS-treated animals demonstrated increased anxiety-like behavior and decreased exploratory behavior in the open field arena. Gene expression of Mmp9 and Timp1 was differentially altered in the cortex and hippocampus of pups vs. adult untrained rats and remained unchanged in rats trained in either learning task, revealing that prolonged pro-inflammatory challenge during early postnatal development negatively affects the plasticity factors involved in memory acquisition in adulthood. These results suggest that an increase in cognitive stimulation might be an effective approach to reduce the negative effects of neonatal immune challenges on brain functioning. Supported by RFBR 17-04-02116.
S15.2

GM1 oligosaccharide modulation of calcium signaling in neuronal function

Giulia Lunghi (1), Erika Di Biase (1), Maria Fazzari (1), Margherita Maggioni (1), Gabriella Tedeschi (2), Elisa Maffioli (2), Francesca Grassi Scalvini (2), Sandro Sonnino (1), Elena Chiricozzi (1)

(1) University of Milano, Via Fratelli Cervi 93, Segrate, Milan, Italy.
(2) University of Milano, Via Celoria 2, Milan, Italy.

Recently, we demonstrated that the oligosaccharide portion of GM1 (OligoGM1) is responsible, via the direct activation of the TrkA-MAPK pathway, for the ability of GM1 to induce neuritogenesis and to confer neuroprotection, in a mouse neuroblastoma cell line N2a. This suggests that the specific role of ganglioside GM1 in neuronal functions described in the past, is determined by a direct interaction of its oligosaccharide portion with specific proteins expressed on the plasma membranes (PM). Among them, an important GM1 property would regards the activation of PM ion channels that permit the regulation of cytosolic calcium concentration necessary for neuronal functions. Thus, we investigated if GM1 oligosaccharide could be involved also in the regulation of calcium signaling using murine neuroblastoma cell line, N2a. Firstly, proteomic analysis identified 324 proteins expressed only in OligoGM1 treated cells and, interestingly, many of them are involved in the regulation of calcium homeostasis. Administration of OligoGM1 to undifferentiated N2a cells resulted in an increased calcium influx measured by calcium imaging. To determine whether OligoGM1 neuritogenesis is mediated by the calcium-integrin mediated signaling, we focused on the activation of the integrin-coupled nonreceptor tyrosine kinase, FAK, and its downstream effectors. Western blotting analysis revealed an increase in β1 and α5 integrin levels, followed by an activation of PLCγ, and in paxillin protein, involved in the remodeling of axonal cytoskeleton. Moreover, we observed that OligoGM1 neurite induction in N2a cells was blocked by subtoxic administration of extracellular and intracellular calcium chelators. Our results suggest that GM1 oligosaccharide could be responsible for GM1 regulation of calcium signaling and homeostasis in neuronal functions.
S15.3

Mushroom bodies development and abnormalities in defective Wnt pathway models

Paolo Grazioli (1), Chiara Parodi (1), Daniele Bottai (1), Thomas Vaccari (2), Valentina Massa (1)

(1) Dipartimento di Scienze della Salute; Università degli Studi di Milano, Via Antonio Di Rudini, 8, Milan, Italy.
(2) Dipartimento di Bioscienze; Università degli Studi di Milano, Via Celoria, 26, Milan, Italy.

Mushroom bodies (MB) are arthropods paired prominent neuropil structures which play a pivotal role in olfactory learning, courtship behavior, and elementary cognitive functions. The MB cell bodies (Kenyon cells) are located in the dorsal brain cortex and receives olfactory information from the antennal lobes. MB are composed of two inter-winded lobes α and α′ dorsally, and three parallel lobes β, β′ and γ medially. Developmental studies have shown that Kenyon cells are produced by the division of the four MB neuroblasts, which are generated at an early embryonic stage and divide continuously throughout development.

MB have been extensively studied in *Drosophila melanogaster* and have been shown to be abnormal in disease models such as those modelling Cornelia de Lange syndrome (CdLS), a rare genetic disorder affecting among other organs, the neurodevelopment. Our laboratory previously demonstrated that CdLS models show an impairment in the canonical Wnt pathway. Therefore, we aimed at assessing development and morphology of the MB in a *Drosophila* CdLS model mutated in *Nipped-B* (*NIPBL* ortholog, a gene mutated in about 60% of patients) by chemically activating canonical Wnt pathway. Remarkably, our results show that upon feeding on lithium—a widely known Wnt activator—*Drosophila* CdLS mutants reveal rescue of MB morphology in the adult offspring.

Moreover, we validated our results in immortalized lymphoblastoid cell lines in which LiCl treatments restored the proliferation rate and induced *CyclinD1* gene (found reduced in CdLS cells); and mammalian Neural Stem Cells CdLS model (CdLS-NSCs) that upon treatment with LiCl showed a rescue in the significant reduction of proliferation rate and differentiation capabilities toward the neuronal lineage, restoring their physiological levels.

Overall, our data could possibly explain the neurodevelopmental alterations of CdLS patients and could pave the way for future therapeutic strategies.
S15.4

How we used Wfs1 deficient rat to develop treatment strategies for Wolfram Syndrome patients?

Kadri Seppa (1)(2), Maarja Toots (2), Riin Reimets (2), Toomas Jagomäe (1), Tuulikki Koppel (2), Maia Pallase (2), Jens Nyengaard (3), Eero Vasar (1)(4), Anton Terasmaa (1), Mario Plaas (1)(2)

(1) Institute of Biomedicine and Translational Medicine, Department of Physiology, University of Tartu, Ravila 19, Tartu, Estonia.

(2) Institute of Biomedicine and Translational Medicine, Laboratory Animal Centre, University of Tartu, Ravila 14b, Tartu, Estonia.

(3) Stereology and Electron Microscopy Laboratory, Center for Stochastic Geometry and Advanced Bioimaging, Aarhus University Hospital, Palle Juul Jensens Boulevard 99, Aarhus, Denmark.

(4) Centre of Excellence for Genomics and Translational Medicine, University of Tartu, Ravila 19, Tartu, Estonia.

Wolfram syndrome (WS) is a rare autosomal recessive neurodegenerative disorder and is caused by biallelic mutations of the Wfs1 gene. WS first symptom is diabetes mellitus followed by optic nerve atrophy, deafness and progressive brainstem degeneration. Currently, there is no cure for WS and death usually occurs by respiratory failure due to brainstem atrophy. For that reason, it is important to find therapies that could protect against the progression of the disease. By our research group, the rat model of WS has been developed and characterized. Deletion of exon 5 of the Wfs1 gene resulted in development of the main symptoms of WS: diabetes mellitus, optic nerve atrophy and medullary degeneration. Wfs1-KO rat is the only WS animal model that develops both diabetes mellitus and neurological symptoms; therefore, Wfs1-KO rat is a valuable pre-clinical tool to evaluate treatment strategies. GLP-1 (glucagon-like peptide-1) receptor agonists have been accepted as a promising class of anti-diabetic drugs, having the potential to delay or even reverse disease progression. Previously our group has demonstrated that chronic liraglutide treatment prevented the development of glucose intolerance in Wfs1-KO rats. Moreover, such treatment reduced ER stress and inflammation in Wfs1 KO rats Langerhans islets, which seems to result from overall better health of islet cells and a possible protective effect of liraglutide. In my presentation, I will present you our recent results of long-term liraglutide treatment effect on aged Wfs1 deficient rats. Our data suggest that liraglutide treatment has also neuroprotective effects on WS.
S16

Blood brain barrier model, mechanism and metabolism in health and disease

Sikha Saha (1)

(1) University of Leeds, Leeds Institute of Cardiovascular and Metabolic Medicine, LIGHT Laboratories, Clarandon Way, Leeds, United Kingdom.

The blood brain barrier (BBB) is a highly specialised structural and biochemical barrier that regulates the entry of compounds between blood and brain. Disruption and dysfunction of the BBB result in many central nervous system (CNS) diseases including stroke, vascular dementia and Alzheimer’s disease. A major drawback to the current development of novel therapeutic molecules for CNS disorders is our inability to effectively study the mechanisms and metabolisms of the BBB to develop better therapeutics for central nervous system diseases. There is also lack of a physiologically relevant in vitro BBB model for drug delivery and toxicity testing. At present, the majority of studies on BBB are performed using in vivo models which are expensive and are not aligned with the aim of animal-free screening. Current in vitro models primarily use rodent and bovine brain cells cultured in two dimensional (2D) static conditions, which do not mimic the in vivo situation. In the proposed symposium, we will highlight recent development of BBB model and novel findings on its mechanism and metabolism in health and disease. So, this symposium will provide the most recent and comprehensive overview on the development of BBB models and its function and metabolism in normal and disease situations, thus attracting interest across the broader neuroscience and neurology communities attending the ESN meeting.

S16.1

please find this Abstract at the page 201
In vitro modeling of the human blood-brain barrier - recent developments in stem cell-based human models

Lasse Saaby (1)

(1) Bioneer A/S, Kogle Alle 2, Hørsholm, Denmark.

The blood-brain barrier (BBB) regulates the exchange of nutrients, gases, endogenous metabolites and xenobiotic compounds between the blood and the brain parenchyma. The BBB therefore plays a crucial role in maintaining the general homeostasis of the central nervous system. The BBB is formed by the endothelial cells lining the microvessels of the brain, supported by neighboring cells, such as astrocytes and pericytes, within the neurovascular unit. The BBB is both a physical and a functional barrier, and can be a major obstacle for drug delivery to the brain. Tight junctions between the brain endothelial cells effectively separates the blood from the brain parenchyma, while transport proteins intercepts most lipophilic compounds able to partition into the cell membrane and metabolic enzymes enables inactivation and elimination of a wide range of compounds. In vivo investigations of the BBB function and biology in humans and animal models is largely limited by ethical considerations and costly experimental designs. Cell culture models of immortalized and primary brain endothelial cells of different animal origin has been established to enable in vitro research of blood-brain barrier function and screening of potential drug compounds for the treatment of diseases of the CNS. This presentation aims to give an overview of existing cellular blood-barrier models with a focus on human stem cell-based models. As the field of stem cell-based models is still emerging, the presentation will also include a summary of the experience with stem cell-based human models of the BBB obtained so far and will try to address the issues that should be resolved through further development.
S16.3

In vitro and in vivo models of brain metastasis formation

Istvan Krizbai (1), Janos Hasko (1), Csilla Fazakas (1), Kinga Molnar (1), Attila Gergo Vegh (1), Imola Wilhelm (1)

(1) Institute of Biophysics, Biological Research Centre, Temesvari krt. 62, Szeged, Hungary.

Brain metastases are life threatening pathologies with limited therapeutic options, representing a major cause of death in patients with lung cancer, breast cancer and melanoma. Since the CNS lacks a classical lymphatic system, metastasis formation depends on the ability of tumor cells to migrate through cerebral endothelial cells, which form the morphological basis of the blood-brain barrier.

In our investigations we have used in vitro BBB models and in vivo models to decipher the complex interactions between cells of the neurovascular unit and metastatic tumor cells originating from melanoma and breast cancer (4T1).

Using different in vitro BBB models we have shown that melanoma cells can transmigrate more rapidly and in a higher number through brain endothelial monolayers than breast cancer cells. Moreover, melanoma cells have an increased ability to impair the tight junctions of the brain endothelium than mammary carcinoma cells. During extravasation, brain metastatic cells activate the Rac and PI3K pathways, release proteolytic enzymes and use the mesenchymal type of cell movement.

In in vivo models we observed marked vascular changes during transmigration of 4T1 cells, including vessel constriction, endothelial plug formation up- and downstream of the tumor cell, vacuolization of the endothelium and new vessel formation. After extravasation, triple negative breast cancer cells started to migrate and proliferate along the capillaries, co-opting them. Reactive astrocytes and microglia were observed in the vicinity of metastatic tumor cells, while distant glial cells appeared to be normal. In human breast cancer brain metastatic samples, triple negative tumor cell islands incorporated and invaded abnormal microvessels.

Our results obtained in in vitro and in vivo models provide direct evidence of an active role of the neurovascular unit in the transmigration of metastatic cells through the BBB and reveal important signalling mechanisms involved in this process.
S16.4

Blood-brain barrier in health & disease - in vitro modelling

Adjanie Patabendige (1)(2)

(1) University of Newcastle, School of Biomedical Sciences & Pharmacy, Newcastle, Nsw, Australia.
(2) Institute of Infection & Global Health, University of Liverpool, Liverpool, United Kingdom.

The blood-brain barrier (BBB) formed by brain capillary endothelial cells, is the protective interface between the blood and the brain, which prevents toxin and pathogen entry into the central nervous system (CNS). While the physical barrier is formed by complex tight junctions between endothelial cells that restrict the paracellular permeability to small hydrophilic solutes, resulting in high transendothelial electrical resistance (TEER), the transcellular movement of small and large molecules is regulated by several transporters, receptors and enzymes. In addition, the BBB maintains a low level of immune surveillance of the CNS by restricting the entry of leukocytes. However, during certain neurological infections and diseases, the entry of circulating leukocytes into the CNS is increased due to inflammation at the BBB. Due to the difficulty in direct investigation of the BBB in vivo, and with growing evidence of BBB disruption in many CNS pathologies, good in vitro models that closely mimic the BBB in vivo for studying BBB dysfunction is vital. Generally, endothelial cells derived from porcine brains give the highest TEER in monoculture, while brain endothelial cells derived from other species require co-culture with astrocytes and/or pericytes to generate high TEER. Immortalised brain endothelial cells derived from several species are available, though these usually display relatively low TEER compared to BBB models derived from primary cells. However, culturing under flow conditions, which exposes brain endothelial cells to physiological shear stress leads to a significant increase in TEER. Recently, brain endothelial cells derived from human induced pluripotent stem cells have been shown to generate TEER approaching in vivo levels, and offer the advantage of avoiding species-specific differences. While there is no ‘gold standard’ BBB model, in vitro BBB models have contributed tremendously to our current understanding of the BBB during health and disease, and are essential for CNS drug screening programmes.
S17.1

Development of selective CB2 receptor inhibitors as potential probes for molecular imaging with positron emission tomography

Peter Brust (1), Rares Moldovan (1)

(1) Helmholtz-Zentrum Dresden-Rossendorf, Permoserstraße 15, Leipzig, Saxony, Germany.

Targeting of cannabinoid (CB) receptors represents a new promising tool in the possible pharmacological treatment of several brain-related disorders including brain cancer. Of the two different CB receptor types the CB₂ receptor is comparably less investigated although assumed to be of major impact for selected brain diseases, e.g. traumatic brain injury, multiple sclerosis, and glioblastoma. Therefore, molecular imaging of CB₂ receptors with positron emission tomography (PET) may provide a significant contribution to the understanding of the cross-talk between CB₂ receptors and inter- and intracellular signaling mechanisms. New insights into these functional interrelationships will allow a better diagnosis of brain diseases and direct a rational development of new therapeutic concepts. PET uses biomolecules as probes which are labeled with radionuclides of short half-lives, synthesized prior to the imaging studies. These probes are called radiotracers. Fluorine-18 is a radionuclide that is routinely used in the radiolabeling of neuroreceptor ligands for PET because of its favorable half-life of 109.8 min. The talk will mainly focus on the strategy of radiotracer development for CB₂ receptors bridging from basic science to biomedical application. Successful radiotracer design provides molecular probes which are not only useful for imaging of human brain diseases, they will also allow molecular CB₂ receptor imaging studies in various small-animal models of disease. Furthermore, they provide a powerful tool for in vivo pharmacology during the development of new drugs targeting CB₂ receptors.
Endocannabinoid signalling in neuroprotection: Key-role of CB2 receptor

Mauro Maccarrone (1)

(1) Campus Bio-Medico University of Rome, Via alvaro del Portillo 21, Rome, Italy.

Extracts of cannabis (Cannabis sativa and Cannabis indica) have been used to treat human disease for thousands of years, but the recent ability to isolate biologically active cannabinoids and identify the targets of these molecules has led to great interest in cannabinoid treatments among the scientific, medical and pharmaceutical community, particularly for neurological disorders. In my lecture, I shall summarize the latest understanding of the actions of plant-derived cannabinoids (phytocannabinoids) as mimetics or disruptors of the endogenous signalling network made of bioactive lipids, their receptors, metabolic enzymes and transporters, collectively known as “endocannabinoid system”. In particular, based on its wide expression in immune cells, the endocannabinoid-binding G protein-coupled type-2 cannabinoid receptor (CB2) was traditionally thought to act as a “peripheral receptor” with an almost exclusively immunomodulatory function. However, its recent identification in mammalian brain areas, as well as in distinct neuronal cells, has opened the way to a re-consideration of CB2 signalling in the context of brain pathophysiology, synaptic plasticity and neuroprotection. In my lecture I shall focus on the pivotal role of CB2 as a neuroprotective and anti-inflammatory mediator within the central nervous system, and hence endowed with potential as drug target to treat neurologic disorders like Alzheimer's disease, Parkinson’s disease, Huntington’s chorea, and amyotrophic lateral sclerosis. Moreover, preclinical and clinical data suggest that phytocannabinoids may be used to control symptoms of multiple sclerosis such as spasticity and chronic pain, whereas preclinical data indicate that these compounds and their endogenous counterparts, i.e. the endocannabinoids, may also exert neuroprotective effects and slow down disease progression. Thus, endocannabinoid signalling (especially CB2-dependent) in multiple sclerosis will be addressed as a paradigm to better discuss its therapeutic exploitation also in other neuroinflammatory disorders.
S17.3

Relevance of CB2 receptors in motor neuron disease

Eva De Lago (1)(2)

(1) Departamento de Bioquímica y Biología Molecular, Instituto Universitario de Investigación en Neuroquímica, Facultad de Medicina, Universidad Complutense, Madrid, Spain.
(2) Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain.

Motor neuron diseases are a group of neurodegenerative disorders that selectively affect motor neurons. The most common disorder of this group is amyotrophic lateral sclerosis (ALS) in which both upper and lower motor neurons are affected. ALS is a progressive and fatal disorder which unfortunately has no cure or useful treatments to date. Therefore, there is an urgent need for new treatment options that prevent/delay disease progression.

Recent data suggests that targeting the cannabinoid receptor type-2 (CB2) affords neuroprotection in experimental models of ALS. Under pathological events, the CB2 expression in the central nervous system rapidly increases, which is considered as an neuroprotective and anti-inflammatory response. The receptor has been found to be elevated particularly in glial elements, as found in the post-mortem spinal cord of ALS patients, dogs affected by a canine variant, and two murine genetic models of ALS (SOD-1(G93A) and TDP-43(A315T) transgenic mice). Selective treatments with the synthetic CB2 agonist AM-1241 were able to delay disease progression in SOD1 transgenic mice whereas other CB2 agonist, HU-308 improved the neurological status of TDP-43 mice by reducing glial reactivity and by preserving spinal motor neurons. We have crossed TDP-43 transgenic mice with knock-out mice for the CB2 receptor and investigated the progression of the pathological phenotype in these double mutants compared with the different controls. Preliminary results proved that the genetic ablation of the CB2 receptor accelerated and aggravated the deterioration in the neurological status. Moreover, the histological analysis of the spinal cords revealed a more intense death of motor neurons, which was accompanied also by a greater inflammatory response.

In summary, all the data to date confirm the important neuroprotective role of the CB2 receptor in ALS, and possibly other MND, and strongly support the need to progress towards a clinical evaluation of this potential in ALS patients.
The Role of CB2 Receptor in the Recovery of Mice after Traumatic Brain Injury

Esther Shohami (1), Lital Magid (1), Sigal Liraz-zaltsman (2), Raphael Mechoulam (1)

(1) The Hebrew University of Jerusalem, School of Pharmacy, Jerusalem, Israel.
(2) Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel Aviv, Israel.

Following the discovery of the structure of THC and CBD, in the Cannabis Sativa plant, and the CB1 and CB2 receptors in the mammalian brain, it was a matter of time for the discovery of the endocannabinoid (eCB, e.g. 2-Arachidonoyl-glycerol and Anandamide) and of the eCB structural-related analogs (eCB-like small lipid bioactive molecules). It is now well established that the eCB system, which also includes the enzymes for the synthesis and degradation of these molecules, is found in most organs of the body, and plays a role in health and disease. We have investigated the beneficial effects on recovery after traumatic brain injury (TBI) of various classes of cannabinoids, such as eCB that bind to both receptor types, eCB-like molecules that do not bind the either of these receptors, plant derived phytocannabinoids and synthetic selective CB2 agonists. The talk will mainly focus on the role that CB2 receptor plays as a mediator of neuroprotection and recovery by the tested cannabinoids. The effects exert by these compound include improved motor and cognitive functions, reduced edema, lesion volume and BBB disruption, reduced neuro-inflammation and neuronal cell loss, enhanced synaptic plasticity and potent vasodilation of cerebral arterioles, which leads to improved cerebral circulation. The improved functional recovery was abrogated by CB2 antagonists while CB2 knockout mice did not respond to treatment. Taken together, our results suggest that at least in part, the neuroprotective effects of cannabinoids molecules are mediated via the CB2 receptors and that targeting drugs, which are devoid of psychoactive side-effects, to stimulate this receptor could be developed as a new treatment modality for TBI.
S18.1

S100B as a biomarker and therapeutic target in Multiple Sclerosis

Adelaide Fernandes (1)(2)

(1) Neuron-Glia Biology in Health and Disease, Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Avenida Professor Gama Pinto, Lisboa, Portugal.

(2) Department of Biochemistry and Human Biology, Faculty of Pharmacy, Universidade de Lisboa, Avenida Professor Gama Pinto, Lisboa, Portugal.

Neuroinflammation is a primary hallmark of Multiple Sclerosis (MS) and has long been associated with demyelination. We recently showed that the pro-inflammatory molecule S100B is highly increased in the cerebrospinal fluid and serum of MS patients at diagnosis, and that both S100B and its receptor RAGE are markedly overexpressed in active demyelinating post-mortem MS lesions. Subsequent studies showed that S100B is highly released upon demyelination of ex vivo cerebellar organotypic slice cultures from an astroglial source, playing an important role in the inflammatory milieu, microglia activation and in demyelination pathogenesis, showing a detrimental effect on oligodendrogenesis. Ongoing studies in EAE models are shedding some light on the use of S100B as a potential therapeutic target in MS in order to reduce both clinical and pathological signs, indicating a potential use in demyelinating disorders associated with neuroinflammation.
S18.2

The S100b story: from biomarker to active factor in neural injury

Fabrizio Michetti (1)

(1) Università Cattolica S. Cuore, Largo Francesco Vito, 1 00168, Rome, Italy.

S100B is a Calcium-binding protein mainly concentrated in astrocytes. Its levels in biological fluids (cerebrospinal fluid, peripheral and cord blood, urine, saliva, amniotic fluid) are recognized as a reliable biomarker of active neural distress. Mounting evidence now points to S100B as a Damage-Associated Molecular Pattern molecule which, when released at high concentration, triggers tissue reaction to damage in a series of different neural disorders, such as acute brain injury, neurodegenerative diseases, inflammatory bowel disease, congenital/perinatal disorders, psychiatric disorders. In many cases, overexpression/administration of the protein induced worsening of the disease, whereas its deletion/inactivation produced amelioration, both for clinical and neuropathological/biomolecular parameters (for review, 1). In particular, our recent results indicated a role of S100B in experimental models of amyotrophic lateral sclerosis, including overexpression of the protein in astrocytes of diseased rats correlated to neurodegeneration level, increase of S100B synthesis/release in astrocytes transfected with SODG93A, downregulation of proinflammatory genes after S100B silencing in SODG93A-derived astrocytes (2). Our current studies also indicate an active role of the protein in pathogenic processes occurring in an in vivo model of multiple sclerosis (relapsing remitting experimental autoimmune encephalomyelitis in SJL mice) and, more in general, indicate the participation of the protein in processes leading to the activated inflammatory phenotype in astrocytes. This scenario opens the perspective that S100B may be regarded as a therapeutic target for different neural disorders, which appear to share some common features, reasonably attributable to neuroinflammation, regardless their origin.

Supported by Nando and Elsa Peretti Foundation, Fondazione Italiana Sclerosi Multipla, and Università Cattolica S.Cuore


S18.3

Roles of S100B in schizophrenia and affective disorders

Johann Steiner (1)

(1) University of Magdeburg, Leipziger Str 44, 39120 Magdeburg, Magdeburg, Germany.

Scientific evidence for increased S100B concentrations in the peripheral blood of acutely ill patients with schizophrenia and affective disorders is very consistent. In the past, this finding was mainly considered to reflect astroglial or blood-brain barrier dysfunction.

The talk will summarize previous results on this topic. S100B is potentially associated with the dopamine and glutamate hypotheses. Supporting the glial hypothesis, an increased expression of S100B has been detected in cortical astrocytes of paranoid schizophrenia cases. In opposite, S100B-immunopositive astrocytes were bilaterally decreased in the CA1 pyramidal layer of Major Depression and bipolar disorder compared to controls. Recently, the neuroinflammation hypothesis of schizophrenia and depression has gained growing attention. Accordingly, S100B may act as a cytokine after secretion from glial cells, CD8+ lymphocytes and NK cells, activating monocytes and microglial cells. Moreover, S100B exhibits adipokine-like properties and may be dysregulated in schizophrenia due to disturbances in insulin signaling, leading to the increased release of S100B and free fatty acids from adipose tissue.

In conclusion, S100B is expressed in different cell types and is involved in many regulatory processes. Currently, “the most important” mechanism related to schizophrenia and depression cannot be determined.
S18.4

Development of S100B small molecule inhibitors

David Weber (1)

(1) University of Maryland School of Medicine, 108 N. Greene St, Baltimore, United States of America.

Developing small molecule inhibitors that target S100B is underway, and they have potential for treating neurodegenerative disorders, cancers, and other diseases. For S100B, its up-regulation is established in cancer and in neurodegenerative states. Upon the binding calcium, three binding pockets are exposed that are important for S100B target complexes. Site 1 was discovered in via structural biology techniques of S100B-target peptide complexes, and sites 2 and 3 were identified via studies with the FDA approved drug pentamidine. Pentamidine was repurposed and used in a phase II clinical trial for treatment of relapsed and/or refractory melanoma in patients with wild-type p53 and elevated S100B. While p53 protein levels were restored in patients receiving pentamidine, the toxicity profile was problematic due to known off-target effects. For these reasons, structure-activity relationship (SAR) studies were initiated to improve the affinity and selectivity of pentamidine analogues for binding to Ca2+-S100B and to reduce toxicity. In this regard, hundreds of S100B inhibitors (SBiXs) were prepared. Of importance, structural studies of S100B•SBiX complexes showed that S100B adopts two conformations. In one, Phe-88 occludes a hydrophobic channel between Sites 1 and 2 comprising residues in helix 4 and loop 2 termed the “hinge”, and in a second conformation, the channel between Sites 1 and 2 is open with Phe-88 and Phe87 found to be reoriented so both aromatic rings are outside this groove. Thus, it is now understood what molecular entities are needed to target the “open” form of the S100B “FF-gate”. These studies together with how dynamic properties of S100B and other S100 proteins will be presented, as will how these data were used to develop next generation SBiX molecules having high affinity (KD<50 nM) and specificity (>1000-fold versus S100A1).
Acetyl-CoA – direct regulator of acetylations in the brain?

Andrzej Szutowicz (1), Agnieszka Jankowska-kulawy (1), Anna Ronowska (1), Sylwia Gul-hinc (1)

(1) Department of Laboratory Medicine, Medical University of Gdańsk, Dębinki 7, 80-211 Gdańsk, Poland.

Brain neurons, to support their neurotransmitter functions require a several times higher supply of glucose than non-excitible cells. Pyruvate, the end product of glycolysis, through pyruvate dehydrogenase complex reaction, is a principal source of acetyl-CoA, which is a direct energy substrate, in all brain cells. Several neurodegenerative conditions result in the inhibition of pyruvate dehydrogenase and decrease of acetyl-CoA synthesis in mitochondria. This attenuates metabolic flux through TCA, yielding energy deficits, and inhibition of diverse synthetic acetylation reactions in all neuronal subcompartments. The acetyl-CoA concentrations in neuronal mitochondrial and cytoplasmic compartments are in the range of 10 and 7 µmol/L, respectively. They appear to be from 2 to 20 times lower than its Km values for carnitine acetyltransferase, acetyl-CoA carboxylase, aspartate acetyltransferase, choline acetyltransferase, sphingosine kinase1 acetyltransferase, acetyl-CoA hydrolase, and acetyl-CoA acetyltransferase, respectively. Therefore, alterations in acetyl-CoA levels alone may significantly change the rates of metabolic fluxes through multiple acetylation reactions in brain cells in different physiologic and pathologic conditions. Such substrate-dependent alterations in cytoplasmic, endoplasmic reticulum or nuclear acetylations, may directly affect ACh synthesis, aminoacid/protein acetylations and gene expression. The excitotoxicity-evoked intracellular zinc excess hits several intracellular targets, decreasing acetyl-CoA and yielding the collapse of energy balance and impairment of the functional and structural integrity of postsynaptic cholinergic neurons. Acute disruption of brain energy homeostasis activates slow accumulation of amyloid-β1-42 (Aβ). Extra and intracellular oligomeric deposits of Aβ affect diverse transporting and signaling pathways in neuronal cells. Different neuro-glial and neuronal cell types display differential susceptibility to similar pathogenic insults depending on individual proportions between rates of acetyl-CoA provision and utilization in their energy producing and diverse synthetic acetylations compartments. Thereby, alterations in acetyl-CoA availability may regulate functional and adaptative properties of neuronal and non-neuronal brain cells in diverse physiologic and pathologic conditions.
Nε-lysine acetylation within the endoplasmic reticulum: a fundamental role for brain physiology and pathology

Luigi Puglielli (1)

(1) University of Wisconsin-Madison, 1500 Highland Avenue, Madison, Wi, United States of America.

The import of acetyl-CoA into the lumen of the endoplasmic reticulum (ER) by AT-1/SLC33A1 regulates Nε-lysine acetylation of ER-cargo proteins and is essential for the efficiency of the secretory pathway. Specifically, it regulates both quality control and autophagy-mediated disposal of protein aggregates (J Cell Sci 2010, 123, 3378; J Biol Chem 2014, 289, 32044; J Biol Chem 2012; 287: 29921; Brain 2016, 139, 937). Mice with reduced ER influx of acetyl-CoA display excessive induction of autophagy while mice with increased influx display increased efficiency of the secretory pathway. In both cases, lack of homeostatic balance leads to drastic phenotypes (J Neurosci 2014, 34, 6772; J Exp Med 2016, 213,1267; Aging Cell 2018, 17:e12820). Importantly, a dysfunctional ER-acetylation machinery, as caused by mutation and duplication events affecting AT-1/SLC33A1, is associated with different human diseases, including developmental delay, spastic paraplegia, autism spectrum disorder, intellectual disability and dysmorphism. To expand upon our findings, we generated six new mouse models targeting the ER acetylation machinery and associated metabolic pathways. Here, we will describe the autistic-like phenotype of the above mice and report novel findings on the molecular mechanisms that regulate metabolic crosstalk and protein homeostasis down-stream of the ER acetylation machinery. We will also discuss the impact of these events on brain physiology and pathology.
S19.3

Inborn errors of Coenzyme A metabolism in neurodegeneration with brain iron accumulation

Valeria Tiranti (1), Ivano Di Meo (1)

(1) Fondazione IRCCS Istituto Neurologico C. Besta, Via Temolo 4, Milan, Italy.

Neurodegeneration with Brain Iron Accumulation (NBIA) is a highly heterogeneous group of seriously devastating rare diseases characterized by iron accumulation in the brain, progressive movement disorder, mental disability and early death. Inborn errors of Coenzyme A (CoA) biosynthesis are responsible for two distinct forms of NBIA, PKAN and CoPAN (Pantothenate Kinase and CoA synthase Associated Neurodegeneration), caused by mutations in PANK2 and COASY genes, coding for enzymes essentials for CoA biosynthesis. CoA is one of the most important metabolic cofactors that functions as an acyl group carrier and carbonyl-activating group, regulating numerous biological processes, such as energy production, cell growth and death, autophagy, signal transduction, as well as protein acetylation and epigenetics. Recent findings showed that CoA reduction in different PKAN models leads to defects in proteins acetylation. We recently generated a conditional brain-specific CoPAN null mouse model. First-born animals showed the early-onset appearance of typical neurodegenerative signs, such as a pronounced hind limb clasping phenotype, reduction of spontaneous motor activity and of motor coordination, and movement disorders. This model could be very useful to gain new insights into the pathogenic mechanisms of neurodegenerative disorders associated to defective CoA biosynthesis.
S19.4

Histone acetylation in myelinating glia

David Dansu (1)(2), Sami Sauma (1)(3), Hye-jin Park (1), Patrizia Casaccia (1)(2)

(1) ASRC at GC-CUNY, 85 St. Nicholas Terrace, New York, Ny, United States of America.
(2) Graduate Program Biochemistry, New York, Ny, United States of America.
(3) Graduate Program Biology, New York, United States of America.

Myelinating glial function is fundamental for brain health and its impairment is detected in a growing number of psychiatric and neurological disorders. Studying the basic mechanisms regulating the progression of progenitors into myelinating oligodendrocytes in the developing and adult brain therefore has substantial implications for providing the framework for the design of novel therapeutic strategies. Our lab has pioneered the concept of epigenetic regulation of oligodendrocyte progenitor differentiation and identified histone deacetylation as a critical driver of the differentiation process. We defined the important role of histone deacetylases in developmental myelination and reported impaired mechanisms of recruitment in aging rodents and in post-mortem human brains from Multiple Sclerosis patients. Since histone acetylation is driven by the nuclear levels of acetyl-CoA, we have recently focused on the characterization of acetyl-CoA synthetic enzymes, in response to decreased glucose bioavailability. Preliminary results in primary cultures of oligodendrocyte progenitors suggest that – in these conditions - the enzyme ATP-citrate lyase, a key nucleocytosolic acetyl-CoA producing enzyme, exits from the nucleus of these cells, which are also characterized by differential levels of acetylation of specific histone lysine residues. Ongoing studies are investigating the potential role of additional enzymes and transporters which may impact the levels and subcellular distribution of acetyl-CoA in oligodendrocyte progenitor cells. The goal is to identify a specific epigenetic signature in these cells, in response to age and to changes of metabolic conditions.
Interplay between misfolded proteins and membraneless organelles: implications in age-related neurodegenerative diseases

Laura Mediani (1), Jordina Guillén-boixet (2), Jonathan Vinet (1), Titus M. Franzmann (2), Daniel Mateju (2), Federica F. Morelli (1), Tatiana Tiago (1), Poser Ina (2), Simon Alberti (3), Serena Carra (1)

(1) Centre for Neuroscience and Nanotechnology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, G Campi 287, 41125, Modena, Italy.
(2) Max Planck Institute of Molecular Cell Biology and Genetics, 01307, Dresden, Germany.
(3) Technische Universität Dresden, Center for Molecular and Cellular Bioengineering (CMCB), Biotechnology Center (BIOTEC), Tatzberg 47/49, 01307, Dresden, Germany.

Errors occurring during DNA replication, transcription and translation lead to the production of mutated or truncated polypeptides that cannot acquire their native folding state, impairing protein homeostasis. Imbalances in protein homeostasis, in turn, lead to cell dysfunction, aging and disease. The main source of misfolded proteins in mammalian cells are newly synthesized polypeptides that have not yet reached their native state and defective ribosomal products (DRiPs), which result from the misincorporation of amino acids, premature translation termination, damaged mRNAs or DNA mutations.

Regardless of their origin, once DRiPs are synthesized, they are recognized by specific protein quality control (PQC) machineries. These include the chaperones of the HSP70 family, which co-translationally bind to nascent polypeptides, and VCP. Both HSP70s and VCP bind to DRiPs, assist their ubiquitination, and promote their degradation by the proteasome. Surprisingly, although DRiPs represent the major source of misfolded proteins in cells, how DRiPs are handled and cleared, and the consequences of mishandling them are largely unknown.

We recently showed that DRiPs can accumulate inside membraneless compartments called stress granules (SGs) and promote their conversion from a liquid-like dynamic state into a solid-like aggregated state. Here, we will discuss the pathological implications of altered SG dynamics in cell dysfunction and neurodegeneration.

Next, we report that DRiPs rapidly diffuse into the nucleus, where they accumulate in nucleoli and PML bodies, which are membraneless organelles similar to cytoplasmic SGs. If not properly cleared with the assistance of chaperones, DRiPs convert nucleoli and PML bodies from a dynamic state into a solid state and compromise nuclear proteostasis. We will discuss the functional effects caused by prolonged sequestration of protein quality control factors in nuclear compartments and their potential involvement in age-related neurodegenerative diseases characterized by the presence of nuclear protein aggregates, proteostasis impairment and genome instability.
Remodeling proteostasis networks in Caenorhabditis elegans aging

Nufar Shpigel (1), Netta Shemesh (1), Lana Meshnik (1), Mor Kishner (1), Anat Ben-zvi (1)

(1) Ben-Gurion University if the Negev, Beer-sheva, Israel.

Aging is associated with the accumulation of damaged and misfolded proteins due to a functional decline in cellular quality control machineries. In Caenorhabditis elegans, protein homeostasis (proteostasis) is remodeled at the onset of reproduction, resulting in a rapid and widespread decline in folding capacity and stress response activation. However, endocrine signals that modulate aging progression, such as the gonadal signaling and nutrient-sensing signaling, can reshape the quality control network, remodeling the ability of cells to cope with chronic and acute stresses. Directly comparing germline arrested animals with dietary restricted animals showed that they do not restore youthful proteostasis, but rather remodel the quality control network using at least two different strategies. Whereas signaling from the gonad rescued acute stress response activation, dietary restriction only mildly enhanced it. In contrast, dietary restriction, transformed the response to chronic stress and enhanced folding maintenance, while gonadal signaling only mildly affected them. Moreover, commitment to proteostasis remodeling occurred during larval development in germline arrested animals, while, dietary-dependent proteostasis remodeling was induced post-developmental, and even late in adulthood. Finally, rescue of quality control functions by these two pathways required different transcription factors, potentially affecting the capacity and functions of the quality control network. Such remodeling can strongly impact the ability of an organism to withstand acute or chronic stresses and thus affect its’ vulnerability to age-dependent accumulation of damage proteins and aging associated diseases.
Deciphering the proteostasis network's response to the accumulation of toxic protein aggregates in the aging brain

Ehud Cohen (1)
(1) The Hebrew University of Jerusalem, Ein Karem campus, Jerusalem, Israel.

The ability to maintain proper protein homeostasis (proteostasis) is critical for organismal functionality and viability. Cells have evolved sophisticated mechanisms that act in concert to maintain the integrity of the proteome. These mechanisms, which are known as "the proteostasis network", assist protein folding, supervise the integrity of mature proteins and direct damaged polypeptides for degradation. Nevertheless, as the organism ages, subsets of aggregation-prone proteins challenge the proteostasis network by escaping degradation and forming insoluble aggregates. In some cases, these aggregates underlie the development of late-onset neurodegenerative disorders such as Alzheimer's disease (AD) and Huntington's disease (HD). How the proteostasis network responds to dissimilar challenges and whether the nature of the aggregating protein or the cell type where the aggregates accumulate, shape this response, are largely unanswered questions. Employing nematodes that express different neurodegeneration-linked, aggregative proteins, we found that while Torsin chaperones (Torsin 1 and 2) protect model worms from the aggregation of the HD-causing, abnormally long poly-glutamine (polyQ) stretches, the same chaperones expose nematodes to the toxicity of the AD-causing peptide, Aβ. These opposing effects were observed in both, neurons and muscles cells, indicating that the nature of the toxic polypeptide rather than the tissue of expression, shapes the proteostasis network's response to dissimilar aggregative proteins. These opposing effects on proteotoxicity are accompanied by differential modulations of gene expression, including of a subset of neuropeptides. Our results indicate that the proteostasis network differentially responds to dissimilar proteotoxic challenges, show that neurons regulate these activities and highlight the importance of understanding the accurate response to specific aggregative proteins, to design specifically tailored therapies for different neurodegenerative maladies.
S20.4

Protein aggregation is the prime driver of most neurodegenerative diseases

Harm Kampinga (1)

(1) UMCG, BSCS, Ant. Deusinglaan 1, Groningen, Netherlands.

Protein aggregates are main hallmark of cellular ageing and age-related disease, including a series of muscular and neurodegenerative diseases. The idea that these aggregates are causal to these diseases has recently been challenged. Whereas there is evidence that sequestration of aggregated material may be protective and that certain amyloids may be functional rather than toxic, this does not reject the possibility that an (uncontrolled) aggregation process is not key to the initiation of most of these diseases. In fact, genetic forms of theses disease nearly always are linked to mutations that make the related protein more aggregation-prone. Moreover, in experimental models systems, boosting protein quality control can alleviated toxicity and degeneration associated with such disease-causing proteins. Inversely, mutations in components of protein quality control pathways that normally maintain protein homeostasis also lead to degenerative neuronal or muscular that are associated with protein aggregation. In my talk, I provide evidence for imbalances in protein homeostasis indeed is the prime driver in many muscular and neurodegenerative diseases. In addition, I will present recent data from our lab on how mutations in molecular chaperones, so-called chaperonopathies, lead to protein aggregation disease via different mechanisms, ranging from (minimal) loss-of-function (haplo-insufficiency) to dominant-negative mechanisms and self-perpetuating, progressive declines in protein homeostasis.
Ultrastructure and chemical compositon of neuromelanin in the human substantia nigra

Antje Biesemeier (1), Oliver Eibl (2), Gianni Pezzoli (3), Fabio A. Zucca (4), Ulrich Schraermeyer (1), Luigi Zecca (4)

(1) Center for Ophthalmology, Division for Experimental Vitreoretinal Surgery, University Eye Hospital, Tuebingen, Germany.
(2) USTEM and Institute for Solid State Physics, Technische Universität, Wien, Austria.
(3) Parkinson Institute, Via Bignami 1, Milan, Italy.
(4) Institute of Biomedical Technologies, Via Fratelli Cervi, 93, Milan, Italy.

Catecholaminergic neurons of the substantia nigra (SN) selectively degenerate in Parkinson's disease (PD), probably due to iron intoxication. Neuromelanin organelles (NM organelles), accumulating the pigment neuromelanin together with lipid bodies and proteins, are thought to play a role in this pathological process. Therefore, investigating the composition and iron storing capacity of NM organelles is important for understanding Fe metabolism and PD disease mechanisms.

Analytical Electron Microscopy (AEM) and Nano Secondary Ion Mass Spectrometry (NanoSIMS) were used to investigate NM-containing organelles of human SN tissue sections with respect to ultrastructure and elemental composition. Individual NM granules and lipid bodies within the NM organelles had sizes of about 200-600 nm. Energy dispersive x-ray microanalysis (EDX) spectra of the NM granules and lipid bodies were acquired with 100 nm beam diameter in AEM. Elemental maps with a field of view of 40 µm x 40 µm and a lateral resolution of less than 150 nm were obtained using NanoSIMS. AEM yielded the elemental composition of NM granules and bound metals, e.g. iron with about 0.15 at%. The qualitative chemical analyses by NanoSIMS were consistent to the quantitative EDX data, allowing (semi)quantification of the nanoSIMS measurements.

In NM granules of SN from healthy subjects, a significant amount of Fe and Cu, but also S, indicative for pheomelanin, were found. P, a marker for phospholipids, was measured in lipid bodies. The improved detection limits of nanoSIMS offer new possibilities for chemical mapping, high-sensitivity trace element detection and reduced acquisition times as compared to EDX alone. Variations between individual NM granules can now be investigated effectively and quantitatively by NanoSIMS mapping of Cu and Fe. With this setup, new insight into the changes of chemical composition of NM pigments during healthy aging and disease can be obtained in future, also allowing the investigation of other melanized brain tissues like caudate nucleus and locus coeruleus.
S21.2

Neuromelanin-Sensitive MRI: A Novel, Non-Invasive Proxy Measure of Dopamine Function in Psychiatric Illness

Clifford Cassidy (1), Zecca Luigi (2), Horga Guillermo (3)

(1) The University of Ottawa Institute of Mental Health Research, 1145 Carling Ave, Ottawa, On, Canada.
(2) Istituto di Tecnologie Biomediche, Via Fratelli Cervi, 93, Milan, Italy.
(3) Columbia University, 1051 Riverside Dr, New York, Ny, United States of America.

Background

Neuromelanin-sensitive magnetic resonance imaging (NM-MRI) has proven to be a sensitive neuroimaging marker for degeneration of dopamine neurons in Parkinson’s disease but its utility as a marker of dopamine function in non-neurodegenerative conditions remains unclear.

Methods

We validated NM-MRI in the substantia nigra (SN) against a Positron Emission Tomography (PET)-based measure of dopamine release capacity (based on amphetamine-induced displacement of the radiotracer [11C]raclopride) obtained in individuals without a neurodegenerative condition (n=18). To test its utility as a proxy for psychosis-related dopamine dysfunction, we collected data in 33 unmedicated individuals with schizophrenia, 25 individuals at high risk for psychosis, and 50 healthy controls. For voxelwise analyses, we used a permutation-based method for correction for multiple comparisons.

Results

Voxelwise analysis within the SN in vivo revealed a cluster where NM-MRI signal-to-noise positively correlated with striatal dopamine release capacity (rho=0.55, p<0.05). Voxelwise analyses in the psychiatric populations identified overlapping clusters where higher NM-MRI signal-to-noise in the SN correlated with more severe psychotic symptoms both in patients with schizophrenia and in individuals at clinical high risk (conjunction p<0.0001).

Conclusions

Our results indicate that NM-MRI signal reflects dopamine system function and captures a psychosis-related phenotype. Future work should evaluate the utility of NM-MRI as a predictive biomarker for treatment response or illness conversion in at-risk populations.
S21.3

Locus coeruleus imaging: correlations to pathology and cognition in dementia

Heidi Jacobs (1)(2)

(1) Maastricht University, PO BOX 616, Maastricht, Netherlands.
(2) MGH, Fruit Street 55, Boston, United States of America.

The key pathological hallmarks of Alzheimer’s disease are amyloid-beta and tau accumulation. These proteinopathies start to accumulate decades prior to the first clinical symptoms. In fact, autopsy studies reported that the locus coeruleus is the first site accumulating tau pathology and approximately 80-90% of the 40-year old cases show tau pathology in this brainstem nucleus. Visualizing tau pathology in the locus coeruleus is currently impossible, partly because of its small size, but mostly because of the off-target binding of the tau-tracers to neuromelanin and iron. To image the locus coeruleus, we developed neuromelanin-sensitive imaging methods for 7T MRI and translated this to the 3T environment. In this talk, I will discuss the region-of-interest and voxel-wise relationships between locus coeruleus integrity, age, amyloid and tau, by focusing on Pittsburg Compound B-PET (amyloid-beta), Flortaucipir-PET (tau) imaging and locus coeruleus MR imaging data from the Harvard Aging Brain Study and patient data. Furthermore, I will also discuss the clinical relevance of locus coeruleus imaging by discussing relationships between locus coeruleus functional and structural measures, heart rate variability, noradrenergic measures and memory performance in young and older individuals. Finally, the potential of considering locus coeruleus imaging as a biomarker for Alzheimer’s disease will be discussed.
S21.4

Neurochemistry and neurobiology of human brain neuromelansins

Fabio A. Zucca (1), Chiara Bellei (1), Pierluigi Mauri (1), Michela Sturini (2), Luigi Casella (2), Kazumasa Wakamatsu (3), Shosuke Ito (3), Alessandro Prinetti (4), David Sulzer (5)(6), Luigi Zecca (1)(5)

(1) Institute of Biomedical Technologies, National Research Council of Italy, Segrate, Milan, Italy.
(2) Department of Chemistry, University of Pavia, Pavia, Italy.
(3) Department of Chemistry, Fujita Health University School of Health Sciences, Toyoake, Aichi, Japan.
(4) Department of Medical Biotechnology and Translational Medicine, University of Milan, Segrate, Milan, Italy.
(5) Department of Psychiatry, Columbia University Medical Center, New York State Psychiatric Institute, New York, Ny, United States of America.
(6) Department of Neurology and Pharmacology, Columbia University Medical Center, New York, Ny, United States of America.

The investigation of aging mechanisms is mandatory for understanding processes involved in neurodegeneration of Parkinson’s disease. One event observed during brain aging is the accumulation of neuronal organelles filled with dark-brown pigment, known as neuromelanin, together with lipid bodies, proteins and metals in various brain regions, especially in substantia nigra which is selectively targeted in Parkinson’s disease. The neuromelanin pigment derives from melanized-dopamine metabolites and has been long discussed as critical factor underlying neuronal vulnerability in Parkinson’s disease. To clarify the biogenesis of neuromelanin-containing organelles and their role in neurodegeneration of Parkinson’s disease, protein and lipid systems were investigated in these organelles of human substantia nigra by mass spectrometry, western blot and immunoelectron microscopy. In neuromelanin-containing organelle, membrane and matrix proteins characteristic of lysosomes were found although in lower number than in normal lysosomes, consistent with reduced enzymatic activity and likely indicating impaired capacity to fuse with lysosomes and autophagosomes. The presence of proteins involved in lipid transport may explain the accumulation of lipid bodies within the organelle and the lipid component in neuromelanin structure. Proteins of aggregation and degradation pathways were also present, suggesting a role for this organelle when ubiquitin-proteasome-system is inadequate. The presence of storage proteins associated with aging and storage diseases is likely a result of impaired autophagy or impaired function of lysosomal enzymes. The finding of typical autophagy proteins and double membranes demonstrates the organelle’s autophagic nature and indicates that has engulfed neuromelanin precursors from cytosol. Then, it appears that neuromelanin-containing organelle has a very slow turnover during the life of neuron and represents an intracellular compartment of final destination for different molecules. The major histocompatibility complex class I, which is involved in antigen presentation, was also identified in neuromelanin-containing organelles, thus explaining the preferential vulnerability of pigmented neurons in Parkinson's disease.
P1

192IgG-Saporin Influences the State of Microglia in the Neocortex

Vladimir Markevich (1), Maria Volobueva (1), Yuliya Dobryakova (1), Anna Manolova (1), Michael Stepanichev (1), Alexey Kvichansky (1), Natalia Gulyaeva (1), Alexey Bolshakov (1)

(1) Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, 5-a, Butlerova st., Moscow, Russia.

Immunotoxin 192IgG-saporin is a conjugate of antibody against NGFR and ribosomal toxin saporin. Injection of this immunotoxin into the ventricles induces a selective death of cholinergic neurons in the basal nuclei. It was shown that immunotoxin leads to activation of microglial cells in the dorsal hippocampus and death of pyramidal neurons in the CA3 neurons. Here, we studied the effect of intracerebroventricular administration of the immunotoxin on microglia in brain areas adjacent to the ventricles (striatum and parietal cortex) as well as brain areas that are located more distantly from the ventricles but are innervated by neurons from the medial septal area and diagonal band of Broca (entorhinal cortex and olfactory bulbs). We performed immunohistochemical staining of brain slices with antibodies to the microglial IBA-1 protein and to the astrocyte marker protein GFAP to evaluate the state of glial cells. We found an increase in the number of microglial cells in the parietal cortex, however, the state of astrocytes was not altered. Analysis of the expression of the Ncf1 and Cx3Cr1 genes, which are predominantly expressed by microglial cells, showed that the expression of Ncf1 increased both in the parietal and in the entorhinal cortex without any changes in the expression of Cx3Cr1. No changes in the expression of these two genes were observed in the striatum and olfactory bulbs. We also analyzed the expression of the Ptprb and Slc22a8 genes which are expressed in blood vessels. Slc22a8 expression decreased only in the striatum. Our data suggest that 192IgG-Saporin alters the state of microglia in the neocortex 1.5 months after its administration, but does not influences the glial state in the striatum or olfactory bulbs. Supported by grant RSF No 16-15-10403-Π.
P2

A new perspective on Alzheimer's disease as a brain expression of a complex metabolic disorder.

Baruh Polis (1), Abraham Samson (1)

(1) The Azrieli Faculty of Medicine, Bar-Ilan University, Henrieta Tzold, 8, 1311502, Safed, Israel.

Alzheimer's disease (AD) is an irredeemable chronic neurodegenerative disorder and the predominant cause of dementia. The disease progression is associated with amyloid plaques’ deposition and neurofibrillary tangles’ formation in the brain, yet clinical dementia is the end and culminating stage of the enduring pathology.

Recent evidence indicates that AD is characterized by distinctive abnormalities apparent on systemic, histological, macromolecular, and biochemical levels. Besides the well-described characteristic hallmarks, the AD pathology includes substantial neuronal loss, inflammation, extensive DNA damage, considerable mitochondrial malfunction, impaired energy metabolism, and chronic oxidative stress. Moreover, severe metabolic dysfunction leading to oxidative stress is a possible cause and hallmark of AD that is apparent decades before the disease manifestation. State-of-the-art metabolomics studies prove that arginine and branched-chain amino acids (BCAA) metabolism disturbances accompany AD and contribute to its pathogenesis. Local arginine deprivation caused by arginase over-activation leads to NO synthase uncoupling and superoxide anion production. Lower plasma valine levels are associated with accelerated cognitive decline, and, conversely, an increase in valine concentration is associated with a significantly reduced risk of AD.

We provided the 3xTg-AD mice with arginase inhibitor non-proteinogenic BCAA norvaline, which is an isoform of valine. The animals treated with norvaline demonstrated significantly improved memory acquisition, associated with an increase in hippocampal spine density, reduced neuroinflammation, alleviated BBB integrity and tissue glucose uptake. Moreover, the rate of the brain amyloidosis was significantly diminished due to a reduction in the expression levels of the APP, which was followed by a significant increase in superoxide dismutase levels suggesting improvement of the internal antioxidant mechanisms.

We suggest that hyperphosphorylated Tau and deposited β-amyloid are just hallmarks, not the ultimate causes of AD. Accordingly, the modern scientific vision of AD etiology and pathogenesis must reach beyond the hallmarks and look for alternative strategies and areas of research.
A Role for Autophagy in Prion-Like Tau Propagation

Giona Pedrioli (6)(2), Marialuisa Barberis (6)(3), Sandra Pinton (6), Maurizio Molinari (4)(5), Stephanie Papin (6), Paolo Paganetti (6)

(1) Laboratory for Biomedical Neurosciences, Neurocentro della Svizzera Italiana, Ente Opedaliero Cantonale, Taverne-torricella, Switzerland.
(2) Biozentrum, University of Basel, Basel, Switzerland.
(3) Università dell’Insubria, Varese, Italy.
(4) Institute for Research in Biomedicine, Bellinzona, Switzerland.
(5) Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland.
(6) Laboratory for Biomedical Neurosciences, Neurocentro della Svizzera Italiana, Ente Opedaliero Cantonale, Taverne-torricella, Switzerland.

Neurodegenerative disorders progress with a well-defined pattern of affected brain regions, which starts from a restricted vulnerable region and then gradually spreads along the neuronal connectivity paths to invade the whole brain. Indeed, the temporal and spatial distribution of pathologic protein deposits defines the disease stage. At the cellular and molecular level, a prion-like mechanism is required for cell-to-cell and protein-to-protein propagation of pathogenic protein forms. We revisited the role of secreted extracellular vesicles (EVs) as possible vectors for transcellular protein transport. In particular, we questioned how EVs release their protein cargo, once internalized by the cell. The data obtained demonstrate that mammalian cells efficiently internalize and accumulate EVs within the endocytic pathway. However, cytosolic release of EV protein cargo into the cytosol is a rare event, independently to the presence of pathological Tau forms. Instead, the accumulation of EVs carrying pathogenic Tau cause lysosomal dysfunction, which in turn stimulate the biogenesis of new lysosomes and activate macroautophagy possibly to impede the buildup of toxic proteins. In conflict with this anticipation, EVs also cause the endosomal accumulation of endogenous Tau by a process impaired by genetic inactivation of autophagy. The coexistence of extracellular and intracellular Tau molecules in endo-lysosomes favor their direct interaction and trigger the propagation of pathological epitopes. Thus, our data demonstrate a role of autophagy in prion-like transcellular propagation of pathological Tau forms and question the value of autophagy activation as an approach to halt neurodegeneration.
ADNP: a pivotal factor in neuronal fate commitment and syndromic autism onset

Ludovico Rizzuti (1)(2), Alessandro Vitriolo (1), Michele Gabriele (1), Pierre-luc Germain (1), Giuseppe Testa (1)(2)

(1) European Institute of Oncology, Via Adamello, 16, Milan, Italy.
(2) University of Milan "La Statale", Via Festa del Perdono, 7, Milan, Italy.

ADNP encodes Activity-Dependent Neuroprotective Protein, whose de novo mutations cause Helsmoortel-Van der Aa Syndrome, a rare developmental genetic disorder mainly affecting brain formation and neuronal functions. This condition is clinically considered a form of syndromic autism, involving mild to severe intellectual disability with speech and behavioral impairment. Although ADNP mutation frequency accounts for 0.17% of all autism spectrum disorder cases (making it one of the most common genetic causes of this condition), its precise role in the onset of the syndrome has yet to be clarified. Our research aims to understand the genomic and epigenomic mechanisms underlying this neurodevelopmental disorder harnessing cell reprogramming in order to develop meaningful models for the pathology. ADNP structure strongly suggests a role as a transcription factor and has been recently found to be a component of a newly identified chromatin remodeler complex called ChAHP. This includes also CHD4 and HP1γ and recognizes euchromatin regions establishing local heterochromatic domains independently of H3K9me3. We performed RNA-seq on a cohort of patient-derived iPSCs samples and iPSCs from healthy controls, highlighting differential expression of genes associated with cell fate decision and neuronal lineage commitment. We also performed ATAC-seq and ChIP-seq in order to understand how ADNP haploinsufficiency alters iPSCs enhancers state, affecting their wiring with promoters in selective disease-relevant regions, and score possible chromatin abnormalities that will ultimately impact neuronal development and functionality.
ALS-Associated VPC-Mutants alter proteinostasis by inducing lysosome damage

Veronica Ferrari (1), Paola Rusmini (1), Valeria Crippa (1), Riccardo Maria Cristofani (1), Barbara Tedesco (1), Elena Casarotto (1), Marta Chierichetti (1), Mariarita Galbiati (1), Elio Messi (1), Margherita Piccolella (1), Angelo Poletti (1), Maria Elena Cicardi (2)

(1) Dipartimento di Scienze Farmacologiche e Biomolecolari-Centre of Excellence on Neurodegenerative Diseases, Università degli Studi di Milano, Via Balzaretti 9, Milan, Italy.
(2) Jefferson Weinberg ALS Center, Vickie and Jack Farber Institute for Neurosciences, Department of Neuroscience, Sidney Kimmel Medical College - Jefferson University, Philadelphia, United States of America.

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease caused by motoneuron death. All ALS-forms are characterized by presence of protein aggregation in brain of affected patients, representing a hallmark of alteration in proteinostasis. In fact, many mutated genes express proteins that misfold and aggregate. Aggregates, if not removed, lead to toxicity and cell death. Moreover, various ALS forms are associated to the mutation of genes involved in the protein quality control system. One of this genes is Valosin Containing Protein (VCP). VCP has a key role in proteinostasis by regulating degradation of misfolded proteins and the turnover of damaged organelles like mitochondria and lysosomes. Lysosomes damage is deleterious for cells for their loss of function and for the toxic effects induced by lysosome leakage.

In this study, we analyzed lysosomal-damage response in presence of overexpressed wt VCP, and its ALS-associated mutants (VCP R155H; VCP R191Q) in motoneuron immortalized cell line. To study VCP contribute in this pathway we chemically and biologically induced lysosome damage. We demonstrated that the overexpressed wt VCP reduces lysosomal damage after it is chemically and biologically induced. Conversely, VCP R155H prevents the clearance of damaged lysosomes when the damage is induced. VCP R191Q can partially reduce lysosomal damage, but it significantly loses its functionality compared to overexpressed VCP WT. Moreover, we demonstrated that both VCP-mutants induce lysosome damage in basal condition. Correlated to damage of lysosomes, we demonstrate that the overexpression of the VCP-mutants leads the translocation of a specific transcription factor, TFE3, but not of TFEB, that activates the expression of genes involved autophagy. The translocation of TFE3 over-activates the autophagic flux.

These data demonstrate a novel pathogenic mechanism of mutants-VCP. The presence of these mutants alter proteinostasis leading to lysosome damage, preventing their removal and activate the autophagic flux.
Alterations of lysosomal activity in Charcot-Marie-Tooth 2B neuropathy

Roberta Romano (1), Cristina Rivellini (2), Maria De Luca (1), Rossana Tonlorenzi (2), Raffaella Beli (1), Fiore Manganelli (3), Maria Nolano (4), Lucio Santoro (3), Eeva-liisa Eskelinen (5), Stefano C. Previtali (2), Cecilia Bucci (1)

(1) Department of Biological and Environmental Sciences and Technologies (DiSTeBA), University of Salento, Lecce, Italy.
(2) INSPE-Institute of Experimental Neurology, San Raffaele Scientific Institute, Milan, Italy.
(3) Department of Neurosciences, University of Naples “Federico II”, Naples, Italy.
(4) Salvatore Maugeri Foundation, Institute of Telese Terme, Benevento, Italy.
(5) Department of Biosciences, Division of Biochemistry and Biotechnology, University of Helsinki, Helsinki, Finland.

Charcot-Marie-Tooth type 2B (CMT2B) is a rare autosomal-dominant axonal disorder affecting the peripheral nervous system and characterized by distal weakness, muscle atrophy, prominent sensory loss, foot ulcerations and recurrent infections leading to toe amputations. CMT2B is caused by 5 mutations (L129F, K157N, N161T/I, V162M) of the RAB7A gene, encoding a small GTPase that controls late endocytic trafficking and plays also important roles in neurons, regulating neurotrophin trafficking and signaling, neurite outgrowth and neuronal migration. RAB7A controls maturation of early endosomes in late endosomes, transport from late endosomes to lysosomes, biogenesis of lysosomes and clustering and fusion of late endosomes and lysosomes in the perinuclear region. As several neurodegenerative diseases are caused by lysosomal disfunctions, we decided to investigate whether CMT2B-causing RAB7A mutations alter the activity of these organelles. Thus, we used healthy and CMT2B skin fibroblasts carrying the Rab7V162M mutation and we investigated expression of endocytic proteins, signaling receptor degradation and lysosomal enzyme activity. We found that CMT2B fibroblasts exhibited higher expression of late endocytic protein and of lysosomal enzymes, higher cathepsins activity and higher receptor degradation compared to control fibroblasts. In addition, we found in CMT2B cells an increased number of lysosomes. Therefore, our data demonstrate higher lysosomal activity in CMT2B cells. Furthermore, we differentiated sensory neurons from induced pluripotent stem cells (iPSC) of healthy control and patients and we confirmed these data demonstrating that patient cells show higher lysosomal activity. Thus, as hyperactivation of degradation could induce a premature termination of signaling possibly contributing to axonal degeneration, our data suggest that higher lysosomal activity leads to neurodegeneration.
Analysis of Tau-KO cells reveals a new role of Tau protein in modulating cell death

Martina Sola (1)(2), Claudia Magrin (1)(2), Paolo Paganetti (1), Stephanie Papin (1)

(1) Neurocenter of Southern Switzerland, Laboratory for Biomedical Neurosciences, Taverne-Torricella, Canton Ticino, Switzerland.

(2) Università della Svizzera Italiana, faculty of Biomedical Sciences, PhD in Neurosciences, Lugano, Canton Ticino, Switzerland.

Tauopathies define a group of age-dependent neurodegenerative disorders characterized by intracellular deposits of abnormally phosphorylated Tau. Pathological tau deposition holds both a gain-of-function effect in the form of toxic tau species a loss-of-function effect considering the role of tau on microtubules. Beside dominant hereditary tau mutation, the triggers leading to the formation of pathogenic Tau forms and neurodegeneration remain poorly appreciated. One well-demonstrated risk factor is aging, e.g. characterized by accumulating DNA damage. Cells are exposed daily to a high numbers of DNA lesions and thus cells had to evolve a molecular machinery, the DNA damage response (DDR), in order to cope with these adverse events. The relevance of the DDR in health and disease is illustrated by the large variety of pathologies, including cancer, linked to mutations of DDR genes, in particular p53 mutations cause 50% of human cancers. In order to explore a possible link between the DDR and Tau, we first generated Tau-KO SH-SYSY neuroblastoma cells and then exposed them to the DNA damaging drug Etoposide, a topoisomerase-II inhibitor. Our first observation was that the absence of Tau protected cells from DNA damage-induced programmed cell death, which was balanced by increased induction of cell senescence. Detailed analysis of the DDR allowed excluding a role of Tau in the early phases of the DDR whilst highlighting a new role of Tau as a p53 modulator, in particular for its stabilization. Indeed, the use of nutlin-3, a compound interfering with MDM2-mediated degradation of p53, restored p53 expression in Tau-KO cells and partly reversed cell death-induction. A p53-dependent loss-of-function of Tau in cellular senescence highlights a new mechanism in neurodegeneration but also implicates Tau in cancer.
Astrocytic mitochondrial ROS modulate brain metabolism and mouse behaviour


(1) Institute of Functional Biology and Genomics (IBFG), Universidad de Salamanca, CSIC, Salamanca, Spain.
(2) Institute of Biomedical Research of Salamanca (IBSAL), Hospital Universitario de Salamanca, Universidad de Salamanca, CSIC, Salamanca, Spain.
(3) Commissariat à l’Energie Atomique et aux Energies Alternatives (CEA), Département des Sciences du Vivant (DSV), Institut d’Imagerie Biomédicale (I2BM), Molecular Imaging Center (MIRCen), CNRS UMR 9199, Université Paris-Sud, Université Paris-Saclay, Fontenay-aux-Roses, Paris, France.
(4) Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain.
(5) Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain.

To satisfy its high energetic demand, the brain depends on the metabolic cooperation of various cell types. For example, astrocytic-derived lactate sustains memory consolidation by serving both as an oxidizable energetic substrate for neurons and as a signalling molecule. Astrocytes and neurons also differ in the regulation of glycolytic enzymes and in the organization of their mitochondrial respiratory chain. Unlike neurons, astrocytes rely on glycolysis for energy generation and, as a consequence, have a loosely assembled mitochondrial respiratory chain that is associated with a higher generation of mitochondrial reactive oxygen species (ROS). However, whether this abundant natural source of mitochondrial ROS in astrocytes fulfils a specific physiological role is unknown. Here we show that astrocytic mitochondrial ROS are physiological regulators of brain metabolism and neuronal function. We generated mice that inducibly overexpress mitochondrial tagged catalase in astrocytes and show that this overexpression decreases mitochondrial ROS production in these cells during adulthood. Transcriptomic, metabolomic, biochemical, immunohistochemical and behavioural analysis of these mice revealed alterations in brain redox, carbohydrate, lipid and amino acid metabolic pathways associated with altered neuronal function and mouse behaviour. We found that astrocytic mitochondrial ROS regulate glucose utilization via the pentose-phosphate pathway and glutathione metabolism, which modulates the redox status and potentially the survival of neurons. Our data provide further molecular insight into the metabolic cooperation between astrocytes and neurons and demonstrate that mitochondrial ROS are important regulators of organismal physiology in vivo.

*Nature Metabolism* DOI: https://doi.org/10.1038/s42255-018-0031-6
BDNF upregulates synaptic NMDA receptors by enhancing local translation of Pyk2 in cultured hippocampal neurons

Pasqualino De Luca (1)(2), Pedro Afonso (1), Rafael Carvalho (1), Paulo Pinheiro (1)(2), Miranda Mele (1)(2), Carlos Duarte (1)(3)

(1) CNC-Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal.
(2) Institute for Interdisciplinary Research, University of Coimbra, Coimbra, Portugal.
(3) Department of Life Sciences, University of Coimbra, Coimbra, Portugal.

Brain derived neurotrophic factor (BDNF) plays a key role in long-term synaptic potentiation (LTP) in the hippocampus, in part due to the upregulation of translation activity. However, the molecular mechanisms involved are not fully understood. In this work we investigated the mechanisms underlying the BDNF-induced alterations in the synaptic proteome that are coupled to synaptic strengthening. BDNF induced the synaptic accumulation of GluN2B-containing NMDA receptors (NMDARs) and increased the amplitude of NMDAR-mediated miniature excitatory postsynaptic currents (mEPSCs) in cultured rat hippocampal neurons by a mechanism requiring activation of the protein tyrosine kinase Pyk2 and dependent on cellular protein synthesis. Single-particle analysis using quantum dot imaging revealed that the increase in the abundance of synaptic NMDAR currents correlated with their enhanced stability in the synaptic compartment. Furthermore, BDNF increased the local synthesis of Pyk2 at the synapse, as determined by the FUNCAT-PLA method, and the observed increase in Pyk2 protein abundance along dendrites of cultured hippocampal neurons was mediated by a mechanism dependent on the ribonucleoprotein hnRNP K, which bound to Pyk2 mRNA and dissociated from it upon BDNF application. Knocking down hnRNP K reduced the BDNF-induced synaptic synthesis of Pyk2 protein, whereas its overexpression enhanced it. Together, these findings indicate that hnRNP K mediates the synaptic distribution of Pyk2 synthesis, and hence the synaptic incorporation of GluN2B-containing NMDARs, induced by BDNF, which may affect LTP and synaptic plasticity.

(Supported by FCT, COMPETE and Mais Centro Program [Grants POCI-01-0145-FEDER-028656 and UID/NEU/04539/2019])
C9ORF72 arginine rich poly-dipeptides induce transcriptional alterations in ALS/FTD cell model.

Riccardo Cristofani (1), Andrea Grilli (2), Giulia Vezzoli (1), Nausica Valentina Licata (3), Valeria Crippa (1), Maria Elena Cicardi (4), Paola Rusmini (1), Barbara Tedesco (1), Veronica Ferrari (1), Elena Carasotto (1), Marta Chierichetti (1), Mariarita Galbiati (1), Serena Carra (2), Silvio Bicciato (2), Alessandro Provenzani (3), Angela Poletti (1)

(1) Dipartimento di Scienze Farmacologiche e Biomolecolari (DiSFeB), Centro di Eccellenza sulle Malattie Neurodegenerative, Università degli Studi di Milano, Milan, Italy.

(2) Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Università degli Studi di Modena e Reggio Emilia, Modena, Italy.

(3) Laboratory of Experimental Neurobiology, Department of Cellular, Computational and Integrative Biology (CIBIO), Università degli Studi di Trento, Trento, Italy.

(4) Department of Neuroscience, Sidney Kimmel Medical College, Jefferson University, Philadelphia, United States of America.

Amyotrophic Lateral Sclerosis (ALS) and frontotemporal dementia (FTD) are associated with several mutated proteins such as: mutant SOD1, TDP-43, FUS, VCP, OPTN and C9ORF72. Expanded (G4C2) stretch of C9ORF72 give rise to poly di-peptide repeats (DPRs) that are produced by repeat-associated non-ATG (RAN) translation, a mechanism originally identified for CAG triplet repeat sequences.

DPRs misfold and aggregate into cytoplasm or nuclei of motor neuron as it has been already demonstrated in polyQ containing proteins. DPRs alter the protein quality control system which maintains protein homeostasis by re-folding (by chaperone) or by degradation (by autophagy or proteasome) and it clears misfolded proteins to counteract proteotoxicity. Chaperone assisted selective autophagy (CASA) is involved in misfolded protein degradation and is mediated by the HSPB8-BAG3-HSP70 complex. We previously demonstrated that DPRs aggregation and toxicity are prevented by autophagy facilitation through HSPB8 overexpression.

We developed a novel inducible human neuronal model to identify aberrant mechanisms altered by RAN-DPR and PolyQ peptides. We first evaluated DPRs and polyQ stability and induced toxicity. RTqPCR show that DPRs mRNA are less expressed than polyQ. This is also recapitulated in toxicity assay where only polyQ cells shows marked cell death. We performed differential genetic profiling of neuronal transcriptional response to DPRs and polyQ, followed by bioinformatics analyses. We found a selective alteration of specific transcripts in cells expressing the two most highly aggregation prone DPRs; polyGR and Poly PR. Gene set enrichment analysis showed specific pathways modulated by polyGR and/or polyPR expression. Notably, PCSK1N related to ALS and FTD and TOMM5 related to mitophagy and protein metabolism are influenced by polyGR and/or polyPR expression.

Collectively, these data showed that aggregating prone DPRs overexpression alters gene expression in our cell model.

GRANTS: FONDAZIONE TELETHON; FONDAZIONE CARIPLO; FONDAZIONE ARISLA; Joint Programme Neurodegenerative Disease and Kennedy's disease association.
Dissecting homodimeric oxytocin receptor pathways regulation through OT-derived bivalent ligands.

Francesca Santini (1)(2), Alessandro Gori (3), Arianna Costanzo (4), Bice Chini (1), Marta Busnelli (1)
(1) CNR Institute of Neuroscience, Via Luigi Vanvitelli, 32, Milan, Italy.
(2) University of Milan, Dept. of Biotechnology and Translational Medicine, Via Luigi Vanvitelli, 32, Milan, Italy.
(3) Istituto di Chimica del Riconoscimento Molecolare (ICRM), Via Bianco Mario, 9, Milan, Italy.
(4) University of Milan, Dept. of Pharmacological and Biomolecular Sciences, Via Balzaretti, 9, Milan, Italy.

Oxytocin is a peptidic neurohormone secreted in the hypothalamus and released centrally and peripherally. In the central nervous system, it is a key regulator of different social behaviours, and it is also involved in stress, memory and learning. Alterations in the oxytocinergic system have been detected in a wide variety of neuropsychiatric and neurodevelopmental disorders. Therefore, there is great interest into the development of specific and innovative oxytocin-centered therapies to revert social dysfunctions in these pathologies.

Oxytocin binds to a G protein coupled receptor (OTR), that upon ligand binding activates different G protein subtypes to transduce its signal intracellularly. As many other members of their family, OTRs can form homo or heterodimers; however, their functional and structural characteristics haven’t been fully elucidated yet. In order to better characterize the pharmacological features of homodimeric OTRs, we generated a series of homobivalent ligands, linking two identical OT analogs with a carboxylic spacer. We showed that two of these compounds could specifically target the dimeric OTRs, behaving as superagonists activating the OTR/G_s signaling pathway at a concentration 1000 times lower than their monomeric counterpart, and rescuing social deficits in mouse and zebrafish.

Here, we demonstrated that all our bivalent ligands are also functional agonists, because differently from endogenous oxytocin, they can only activate certain G protein subtypes, but not others. We are now in the process of completing the characterization of the whole series, unveiling its features in terms of G protein activation and β arrestin recruitment.

Understanding in detail all the peculiar pharmacological features of OTRs in their monomeric and dimeric forms will help to dissect the different signaling pathways that they regulate, to better define the pathogenetic processes that are responsible of neuropsychiatric conditions, and consequently to develop new therapeutic molecules with improved efficacy and less side effects.
Dopamine and Serotonin Metabolism in Parkinsonian Disorders:

Haya Alrashidi (1)(2), Simon Heales (1)(3), Simon Eaton (1)

(1) University College London, London, United Kingdom.
(2) Kuwait University, Kuwait.
(3) Great Ormond Street Hospital (GOSH), London, United Kingdom.

The major pathological feature of Parkinson’s Disease (PD) is dopamine depletion and death of dopaminergic neurons of the substantia nigra. Dysregulations to the serotonin system are also reported. The cause of neuronal death is still unknown. Loss mitochondrial of complex 1 is well documented. Furthermore, compromised lysosomal glucocerebrosidase (GBA) enzyme activity has also been described in brain tissue of sporadic PD patients and patients with GBA mutations. Recent work, by our group, also suggests the importance of functional mitochondria and lysosomes for optimal dopamine and serotonin metabolism. In addition, decreased levels of glutathione, the cell’s major antioxidant, are also reported. However, the pathological mechanism of PD remains unclear. Appropriate models are imperative for any scientific study. Dopaminergic neuronal cell models are necessary for studying PD mechanism and for development of therapeutics. The SH-SY5Y cell line is one of the most widely used cell model for PD research, however reports of its dopaminergic nature are conflicted in literature. A more neuronal like cell model can be generated by differentiation of SH-SY5Y cells using retinoic acid and 12-O-Tetradecanoylphorbol-13-acetate (TPA). In this study, we have compared dopamine-serotonin metabolism in these cells and compared this to undifferentiated cells. Notable differences were 79% decrease in extracellular dopamine and a 160% increase in its turnover. Serotonin metabolism however was comparable. These data further indicate the importance of utilising an appropriate model system for studying parkinsonian disorders.
P13

Effect of cobalt chloride on death induced by inhibition of ubiquitin proteasome system

Mária Brodňanová (1), Simona Saksonová (1), Katarína Dibdiaková (1), Ivana Pilchová (2), Katarína Klačanová (2), Jozef Hatok (1), Peter Račay (1)(2)

(1) Institute of Medical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovakia, Malá Hora 4, 03601 Martin, Martin, Slovakia.
(2) Biomedical Center Martin, Division of Neurosciences, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovakia, Malá Hora 4D, 03601 Martin, Martin, Slovakia.

Background: Accumulation and aggregation of aberrant proteins are characteristic for diverse human pathologies including neurodegenerative disorders such as Alzheimer’s, Parkinson’s or Huntington’s disease. In addition to important regulatory functions, ubiquitin proteasome system (UPS) plays a prominent role in elimination of abnormal and aged proteins. Proteasome stress resulting from either UPS overload or dysfunction is considered to be important mechanism implicated in pathophysiology of mentioned neurodegenerative diseases. Cobalt (Co) is essential to human health. Toxic effect of Co\(^{2+}\) is also recognized, but the mechanism of Co\(^{2+}\)-mediated cellular response is not completely understood. In models of neurodegenerative diseases, it has been proposed that heat shock proteins can suppress protein aggregation and therefore protect the cells from cytotoxic effects of protein aggregates.

Objectives: The purpose of this study was to investigate protective effect of CoCl\(_2\) chloride in the model of proteasome stress of neuroblastoma SH-SY5Y. Our interest was focused on role of Hsp70 and caspase 3 in this process.

Methods: In our study we used a model of proteasome stress of neuroblastoma cell line SH-SY5Y induced by bortezomib, an inhibitor of 26S proteasome. The relative viability of cells was determined by MTT test. Western blot was used for detection of expression changes of selected genes.

Results: Our results indicate that incubation of SH-SY5Y cells with CoCl\(_2\) is associated with significant increase of hsp70 expression. We have shown that pre-treatment of the cells with CoCl\(_2\) 24h prior to application of bortezomib was associated with significant delay of the cell death induced by proteasome stress and with inhibition of bortezomib-induced caspase 3 activation in the cells pre-treated with CoCl\(_2\). We suppose that protective effect CoCl\(_2\) might be partially attributed to the Hsp70-mediated effect.

Acknowledgement: This study was supported by the Slovak Research and Development Agency under the contract No. APVV-16-0033 to PR.
Effects of prenatal hypoxia on expression of the amyloid-degrading enzyme neprilysin in the olfactory bulb and entorhinal cortex, and behavior of rats

Igor Zhuravin (1), Nadezhda Dubrovskaya (1), Dmitrii Vasilev (1), Ekaterina Kochkina (1), Natalia Tomanova (1), Natalia Nalivaeva (1)

(1) I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Academy of Sciences, 44 Thorez av, Saint Petersburg, Russia.

Deficit of the major amyloid-degrading enzyme neprilysin (NEP) plays an important role in pathogenesis of late-onset Alzheimer’s disease (AD) in which neurodegeneration first affects the olfactory bulbs (OB), entorhinal cortex (EC) and later the hippocampus (Hip) with smell impairment being one of the earliest manifestations of AD. We suggest that these pathological processes might be linked to the deficit of NEP in OB and EC caused by normal ageing or, in early life, by prenatal stress such as hypoxia. Accumulation of amyloid Aβ peptide (Aβ) in OB and EC due to NEP deficit can in turn result in neuronal cell death in these brain areas and loss of their peptidergic interaction with Hip leading to its structural and biochemical impairment and cognitive deficit. To test this hypothesis we analyzed NEP mRNA expression in OB, EC, Hip, cortex (Cx) and striatum (Str) of male Wistar rats, either control or subjected to prenatal hypoxia (PH) on the 14th day of embryogenesis (E14, 7% O₂, 3 h) at various stages of postnatal life. Rat memory was tested in the novel object and smell recognition tests. We found that although there was a steady increase in NEP expression during the first month of life in all studied structures, PH resulted in a statistically significant decrease of NEP mRNA levels in EC, Cx and Hip compared to controls. PH also led to impaired memory and olfactory deficit in aged animals. Further studies of NEP expression and Aβ content in the olfactory system and other brain structures during advanced ageing, after PH and administration of an HDAC inhibitor valproic acid, which up-regulates NEP expression, will help us to identify the pathways via which NEP is linked to olfactory deficit and can be regulated pharmacologically. Supported by RFBR 19-015-00232 and Russian state budget assignment (AAAA-A18-118012290373-7).
P15

Effects the remyelination-promoting antibody rHIgM22 on sphingolipid metabolism in primary cultured glial cells

Sara Grassi (1), Simona Prioni (1), Livia Cabitta (1), Sandro Sonnino (1), Alessandro Prinetti (1)

(1) Department of Medical Biotechnology and Translational Medicine, University of Milano, Via Fratelli Cervi 93, Segrate, Italy.

Recombinant human IgM22 (rHIgM22) binds to myelin and oligodendrocytes (OLs) and promotes remyelination in mouse models of multiple sclerosis. Literature suggests that rHIgM22 recruits a multimolecular complex formed by Lyn, integrin αvβ3 and PDGFRα, triggering Lyn activation and promoting oligodendrocyte precursor cells (OPCs) survival and proliferation. However, its exact mechanism of action remains to be elucidated. We have shown the involvement of different sphingolipids in rHIgM22 binding at the cell surface, suggesting that reorganization of lipid membrane microenvironment might be relevant in its biological activity.

Thus, we assessed the effect of a 24 hours, single dose treatment with rHIgM22 on sphingolipid metabolism in cultured rat mixed glial cells (MGC), OPCs and OLs. The treatment had no significant effects on the lipid pattern of MGC. However, in OPCs and OLs it determined an increase in the levels of gangliosides GD3 and GM3, both known for their ability to interact with and modulate the activity of different growth factor receptors.

In addition, rHIgM22 determined a reduced activity of the acid sphingomyelinase (ASMase), with a consequent reduction of ceramide (Cer) generation. Ceramide generated by the action of ASMase represents an important pro-apoptotic signal, but also potent regulator for the organization of sphingolipid-rich signaling platforms. Remarkably, genetic deficiency or pharmacological inhibition of ASMase effectively protect against demyelination and other detrimental effects in MS models. Altogether, our results support the notion that rHIgM22 protective effects might be mediated by alterations of lipid-dependent membrane organization and/or signalling in different cell types present in the nice of MS lesions.
P16

Endovanilloids stimulate neuronal and glial differentiation via GPR55 and CB1 receptors

Mikhail Akimov (1), Polina Dudina (1), Anastasia Cherkasova (1), Marina Gretskaya (1), Galina Zinchenko (1), Leonid Khaspekov (2), Vladimir Bezuglov (1), Mikhail Akimov (1), Polina Dudina (1), Anastasia Cherkasova (1), Marina Gretskaya (1), Galina Zinchenko (1), Leonid Khaspekov (2), Vladimir Bezuglov (1)

(1) Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, RAS, Miklukho-Maklaya, 16/10, Moscow, Russia.
(2) Research Center of Neurology, Volokolamskoye shosse, 14, Moscow, Russia.

Endovanilloids, of which anandamide and acyl dopamines are most known, are a family of endogenous bioactive lipids. Their key receptors are CB1 and TRPV1; recently GPR55 was also proposed as an endovanilloid target. Endovanilloids modulate differentiation of various cell types, however, their activity during neuronal and astrocytic differentiation remains controversial. The aim of this work was to evaluate the activity of acyldopamines during neuronal and astrocytic differentiation in culture of neuroblastosmas, astrocytomas, and cerebellar neurons.

Neuroblastosmas Neuro-2a, IMR-32, SH-SY5Y, NGP, HT-22, teratocarcinoma NT2D1, pheochromocytoma PC12, glioblastomas C6, U-87 MG, and 1321N1 were used as a model. After the treatment with DHA-DA and AA-EA both alone and in combination with various receptor blockers for 14 days, the morphology and differentiation marker expression was analyzed using microscopy, qPCR, and immunocytochemistry.

In HT-22, SH-SY5Y, and IMR-32 acyldopamines induced only cell death. In Neuro-2a and NT2D1, a pronounced neurite outgrowth was observed, accompanied by intensive cell death. In PC12, NGP, C6, U-87 MG, and 1321N1 the core response was neurite outgrowth. Anandamide exerted a similar activity. In the aggregates of newborn rat cerebellar neurons, acyldopamines significantly increased the speed of neurite outgrowth. The morphology changes of the cell lines were accompanied by an increase of neuronal (beta-III tubulin, MAP-2, NF160) markers for neuroblastomas, NT2D1 and PC12, and astrocytic (EAAT2, GFAP) markers for glioblastomas.

The inhibitors of CB2 and TRPV1 receptors reduced the acyldopamine induced neurite length by 50%, and their combination by 70%. The addition of GPR55 inhibitor to this combination completely prevented neurite outgrowth; therefore, concomitant activation of these receptors is required for acyldopamines activity.

Thus, endovanilloids indeed are able to work as differentiation inducers for both neurons and astrocytes, and could play a role during embryogenesis and tissue regeneration.

The work was in part supported by the RFBR grant #17-00-00105.
P17

Epigenetic features of C9orf72 gene promoter as RNA foci modifiers in iPSCs and iPSC-MNs

Clara Volpe (1)(2), Claudia Colombrita (1), Patrizia Bossolasco (1), Valentina Gumina (1), Cinzia Tiloca (1), Silvia Peverelli (1), Anna Maria Maraschi (1), Donatella Bardelli (1), Vincenzo Silani (1)(3), Antonia Ratti (1)(2)

(1) Department of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, Via Zucchi, 18, Cusano Milanino, Milan, Italy.
(2) Dept. Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Via Vanvitelli, 32, Milan, Italy.
(3) Department of Pathophysiology and Transplantation, Dino Ferrari Center, Università degli Studi di Milano, Via Festa del Perdono, 7, Milan, Italy.

The repeat expansion (RE) of the hexanucleotide sequence GGGGCC (>30 repeats) in the first intron of C9orf72 gene is the main genetic cause of Amyotrophic lateral sclerosis and Frontotemporal lobar degeneration. The 5’ CpG island of C9orf72 is methylated in 30% of C9orf72 positive (C9+) patients compared to C9 patients and healthy controls, suggesting a neuroprotective role for promoter methylation. C9orf72 promoter methylation is detectable in blood, dermal fibroblasts and brain of C9”individuals. Hydroxymethylation, another epigenetic modification with an opposite effect on chromatin condensation compared to methylation, is widespread in the nervous system, but it has not been fully investigated in neurodegeneration.

C9” patients show RNA foci in the nucleus and cytoplasm containing the expanded repeat sequence which is also RAN-translated into dipeptide repeats (DPRs). Both RNA foci and DPRs are hallmarks of C9orf72 pathology and are considered toxic for neurons.

We analyzed the relationship between the epigenetic state of C9orf72 promoter (methylation and hydroxymethylation) and C9orf72 gene expression and RNA foci formation in C9+ induced pluripotent stem cells (iPSCs) and iPSC-derived motor neurons (iPSC-MNs). Our results show that methylation state correlates with a lower number of RNA foci and with a down-regulation of the two pathologic C9orf72 mRNA isoforms (V1 and V3), although also hydroxymethylation and repeat expansion length seem to account for RNA foci number variability. Since we characterized eight different C9” iPSC lines, their original fibroblasts and the differentiated iPSC-MNs, we could observe that the epigenetic pattern of C9orf72 promoter could change after iPSC reprogramming and switch again during differentiation into MNs.

Our data suggest that druggable RNA foci in C9” patient-derived iPSCs are variable in number among patients and seem to depend on a complex interplay of epigenetic and genetic factors influencing the transcription of pathologic RNA isoforms.
Exploiting targeted epigenetic editing to increase efficiency and safety of oligodendroglial progenitor cell (OPC) generation from human iPSC

Marco Luciani (1), Eleonora Maria Ciccarelli (1), Alessandro Migliara (1), Angelo Lombardo (1), Angela Gritti (1)

(1) San Raffaele Scientific Institute, San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), Via Olgettina, 60, Milan, Italy.

Oligodendroglial progenitor cells (OPCs) are a promising cell source for the treatment of demyelinating disorders, but their generation at clinical purity and efficiency still poses several hurdles (e.g., immunogenicity, low purity, and difficult large-scale production). Human induced pluripotent stem cells (hiPSCs) may generate large numbers of allogeneic or autologous OPCs, provided the development of safe and effective differentiation protocols. The transient and/or stable overexpression of oligodendroglial (OL) master Transcription Factors (TFs) may enhance OPC commitment and/or differentiation from hiPSCs. We hypothesize that a timely epigenetic modulation of key OL genes may better recapitulate a physiological differentiation and decrease the genotoxic risk, thus producing OPC populations at increased yield and homogeneity. Here, we will exploit state-of-the technologies for epigenetic editing to modulate the expression of OL-related genes in hiPSC-derived Neural Stem Cells (hiPS-NSCs). We have selected genes known to drive (Olig2, Sox10) or suppress (BMP2/4, Sox2) OL commitment, and we have exploited the DNA acetylation and methylation profile of their promoter/enhancers in iPSC-NSCs to select a panel of target sites for epigenetic modulators (epieffectors). The epieffectors are designed according to the RNA-guided, catalytically dead Cas9 (dCas9) or TALEN DNA-binding architecture, and fused to an enzymatic or scaffolding domain able to activate (e.g., P300, VP160, TET1 for Olig2 and Sox10) or repress (e.g., KRAB, DNMTs for BMP2/4, Sox2) gene transcription (Amabile et al., Cell 2016). Epieffectors will be transiently delivered in hiPSC-NSCs. The setting resulting in optimum gene activation/repression will be selected to treat iPSC-NSCs during their differentiation into neuronal/glial progeny (Frati et al., Cell Death Dis., 2018). We expect an enhancement in OPC yield, purity, and maturation in the epieffector-treated vs. untreated iPSC-NSC-derived cultures. If successful, this work will allow obtaining high-yield, homogeneous and pure transplantable OPC populations to be used for cell therapy of demyelinating diseases.
P19

Exposure to decanoic acid increases mitochondrial DNA content in a human neuronal-like cell line

Tomas Baldwin (1), Aziza Khabbush (1), Michael Orford (1), Simon Heales (2), Simon Eaton (1)

(1) UCL Great Ormond Street Hospital Institute for Child Health, 30 Guilford St, London, England.
(2) Chemical Pathology, Great Ormond Street Children's Hospital, NHS Foundation Trust, Great Ormond St, London, England.

The Medium Chain Triglyceride (MCT) diet can be effective in the treatment of children and adults with refractory epilepsy and metabolic conditions such as glucose transporter defects (GLUT1) pyruvate dehydrogenase (PDH) deficiency. Furthermore, it may have positive application in neurodegenerative conditions such as Alzheimer's disease. The MCT diet is composed predominantly of octanoic (C8) and decanoic acids (C10) and it is our hypothesis that C10 has significant biological activity with regards to explaining the efficacy of the diet. Our research, to date has shown that C10, but not C8, can elicit, via PPAR γ activation, neuronal mitochondrial biogenesis, increase mitochondrial complex I and catalase activity. Furthermore, we have found that C10 is oxidised at an inferior rate to C8 raising the possibility that C10 may build up in neuronal tissue thereby maximising its effect upon PPARγ. Building on our findings, we have, in this study, analysed changes in mitochondrial DNA (mtDNA) content following exposure (6 days) of SHSY5Y cells to 250 uM C10 or C8. Using qPCR, we found a statistically significant (p <0.05) increase in the relative abundance of mtDNA in the C10 treated cells. These findings provide further evidence that C10 has the capacity to stimulate mitochondrial biogenesis.
FUS (Fused in Sarcoma) facilitates the recruitment of the DNA Damage Response Machinery contributing to genome stability

Brunno R. Levone (1), Silvia C. Lenzken (1), Marco Antonaci (1), Francesca Conte (1), Giuseppe Filosa (1), Fabio Biella (1), Cise Kızılırmak (1), Marc-david Ruepp (2), Silvia M.l. Barabino (1)

(1) University of Milan-Bicocca, Piazza della Scienze, 2, Milan, Italy.

Elevated levels of double strand breaks (DSB) have been observed in several neurodegenerative diseases. The source of these DSBs can derive from mutations in components of the DNA repair pathway, including RNA-binding proteins, such as fused in sarcoma (FUS). FUS is an intrinsically disordered protein, involved in the maintenance of the genome stability by preventing R-loops formation and helping the DNA Damage Response (DDR) machinery. However, the specific roles of FUS in R-loops-mediated DNA damage are still poorly understood. Thus, the present study aims to assess the specific roles of FUS in DDR and R-loops metabolism. We used HeLa cell lines FUS knock-out (FUS-KO) to study the effects of the absence of FUS on R-loops metabolism and DNA damage repair. We observed that FUS-KO cells are more sensitive to genotoxic stress and show higher levels of R-loops under basal conditions than WT cells. Upon DNA damage, FUS-KO cells show an inefficient repair of DSB, as well as major changes in the recruitment of components of the DDR pathways. Normal R-loops levels and a response to genotoxic stress comparable to WT cells was obtained in FUS-KO cells upon overexpression of RNaseH1, enzyme which degrades R-loops. Taken together, we dissected novel roles of FUS in DDR and R-loops metabolism, which emphasises its contributions in protecting the genome by repairing the DSB. The elucidation of these molecular mechanisms might aid future studies to find a more efficient treatment for neurodegenerative diseases.
Genetic interplay between vitamin D hydroxylase and major histocompatibility factor as a novel preventive individualized approach in the multiple sclerosis

Jan Lehotsky (1), Daniel Cierny (1), Maria škereňová (1), Egon Kurca (1)

(1) Comenius Univ., Jess Fac Med Martin Slovakia, Italy.

Clinical course of multiple sclerosis (MS) in man is remarkably affected by the effect of vitamin D. Synthesis of biologically active calcitriol is catalyzed by 1α-hydroxylase (CYP27B1). Promotor region of HLA-DRB1*15 gene contains vitamin D responsive element. Our aim was to analyze association inrs703842 (C/T) v CYP27B1 gene mutation with the risk of diseases onset, severity of disease progression and the serum level of vitamin D, and in parallel to find possible influence of the allele HLA-DRB1*15:01 on these association. We have analyzed cohort of 496 SM patients of Slovak origin with the relaps-remitting and secondary progressive form and 521 healthy control individuals. Rate of disease progression was analyzed from index of progression as well as MSSS scores. Genotypization for rs703842 in CYP27B1 gene was done by restriction analysis, genotypes of HLA-DRB1*15:01 was detected by the analysis of melting temperature curves, serum level of vitamin D was assessed by chemiluminiscence immunoanalysis. Allele C of rs703842 polymorphism was identified as significant protective (OR = 0.482, p = 1.09 × 10^{-5}) and allele HLA-DRB1*15:01 as a risk factor of MS development (OR = 3.795, p = 7.9 × 10^{-30}). In individuals with the genotypes TT and CT (carriers of allele T) was found an increased risk of MS development, and the presence of allele HLA-DRB1*15:01 aggravates this association (OR = 2.82 vs. 4.86, p < 0.0001). Association of rs703842 with the disease progression as well as with the serum vitamin D level was not proved. The strong association of rs 703842 polymorphisms in CYP27B1 gene with the risk of MS development and concomitant effect of allele HLA-DRB1*15:01 presence suggets for a novel preventive individualizedgenetic approach in predisposed MS individuals.

This work was supported by the grant of APVV 15/0107.
Gestational exposure to lipopolysaccharide results in mitochondrial respiratory chain complexes alterations in the adolescent offspring

Aleksandra Zawadzka (1), Magdalena Cieślik (1), Agata Adamczyk (1)

(1) Mossakowski Medical Research Centre Polish Academy of Sciences, 02-106, 5 Pawinskiego Street, Warsaw, Poland.

Maternal immune activation (MIA) is a risk factor for psychiatric and neurodevelopmental disorders like autism or schizophrenia. Inflammation and elevated levels of pro-inflammatory cytokines may contribute to mitochondrial dysfunction and mitochondria-mediated oxidative stress. However, a causal link between MIA during pregnancy and mitochondria changes in the brain of adolescent offspring remain obscure. Therefore, we investigated the inflammatory processes and mitochondria function in the brain of adolescent rats prenatally exposed to MIA.

We used rat model of MIA which was evoked in pregnant females by i.p. administration of lipopolysaccharide at gestation day 9.5. Cerebral cortex and hippocampi of offspring (52 days old rats) were analyzed by using transmission electron microscopy (TEM), qPCR and Western blotting. Moreover, mitochondrial membrane potential, activity of respiratory complexes and glutathione levels were measured.

In cerebral cortex we observed increased expression of proinflammatory cytokines (IL6 and Tnfa) and other mediators of inflammation like cyclooxygenase-2 (Ptgs2) and 12-lipoxygenase (ALOX12), however no change in the hippocampus was observed. Enhanced oxidative stress, measured by glutathione levels, was detected in both structures. TEM study showed altered mitochondrial structure including fragmented cristae with evidence of an expanded matrix compartment or disrupted membrane. Moreover, reduced mitochondrial membrane potential and alterations of ETC complexes were observed. In the cerebral cortex of MIA rats the expression of complex I (mt-Nd1), complex III (mt-Cyb) and complex IV (mt-Co1) subunit was decreased, however in hippocampus only mt-Co1 was reduced. In addition, we showed lower activity of complexes I and IV in cerebral cortex and complex I in hippocampus.

These are the first studies demonstrating widespread changes in mitochondrial function in adolescent offspring prenatally exposed to maternal immune activation. MIA alters the expression of genes related to proinflammatory processes and mitochondria function in the brain region-specific manner.

Supported by the NSC grant 2016/23/D/NZ4/03572 and POWR.03.02.00-00-1028/17-00
GM1 oligosaccharide as mitochondrial regulator in neuronal cells

Maria Fazzari (1), Giulia Lunghi (1), Erika Di Biase (1), Matteo Audano (2), Elisa Maffioli (3), Francesca Grassi Scalvini (3), Gabriella Tedeschi (3), Nico Mitro (2), Sandro Sonnino (1), Elena Chiricozzi (1)

(1) University of Milano, via Fratelli Cervi, 93, Segrate, Milan, Italy.
(2) University of Milano, via Balzaretti, 9, Milan, Italy.
(3) University of Milano, via Celoria, 10, Milan, Italy.

Functional data and clinical studies suggest the existence of a positive loop between the age-dependent GM1 deficiency and alpha-synuclein (αS) accumulation determining the neurodegeneration onset of sporadic Parkinson Disease (PD). This loop is triggered by the plasma membrane GM1 deficiency, which leads to a failure of trophic signaling and to the αS accumulation, increasing the susceptibility to neuronal death. Recently we shed new light on the molecular basis underlying GM1 effects highlighting that GM1 oligosaccharide (OligoGM1) directly binds TrkA receptor, triggering TrkA-MAPK pathway activation which leads to neuronal differentiation and protection. Following its administration to B4galnt1⁺/+ PD mouse model, OligoGM1 was found to completely rescue the physical symptoms, reduce αS aggregates and restore tyrosine-hydroxylase neurons. Since the mitochondrial dysfunction plays a central role in the exacerbation of nigrostriatal degeneration in PD, we decide to evaluate the putative OligoGM1 mitochondrial modulation in murine neuroblastoma cells, N2a. Following its exogenous administration, proteomic analysis revealed an increased expression of proteins involved in mitochondrial bioenergetics and in oxidative stress protection. By biochemical studies we found that OligoGM1 protects N2a cells from MPTP toxic effect as well as from mitochondrial oxidative stress. Moreover, by immunoblotting we identified an increased expression of Tom20/HtrA2 mitochondrial proteins, whose reduced expression has been associated with PD. At functional level, we found increased basal and uncoupled mitochondrial respiration following OligoGM1 administration. Collectively our data indicate a possible role of OligoGM1 as mitochondrial regulator that by inducing mitochondriogenesis and enhancing mitochondrial activity could determine mitochondrial restoration in PD neurons.
GSK3-mediated phosphorylation of PI4KII-alpha regulates ADBE via control of protein interactions

Eva-maria Blumrich (1), Jessica C. Nicholson-fish (1), Dominic Kurian (2), Karen J. Smillie (1), Michael A. Cousin (1)

(1) Center for Discovery Brain Sciences, The University of Edinburgh,, Hugh Robson Building, George Square, EH8 9XD, Edinburgh, Scotland, United Kingdom.

(2) The Roslin Institute, The University of Edinburgh,, Easter Bush, Midlothian, EH25 9RG, Edinburgh, Scotland, United Kingdom.

Activity dependent bulk endocytosis (ADBE) is triggered during high neuronal activity in central neurons. It is a two-step process that generates synaptic vesicles from large bulk endosomes, which are directly invaginated from the presynaptic plasma membrane. The activity of glycogen synthase kinase 3 (GSK3) is essential for ADBE, however how this control is mediated is still incompletely understood. One GSK3 substrate that is present at the synapse is phosphatidylinositol 4-kinase IIa (PI4KIIα). Depletion of PI4KIIα using shRNA in cultured cerebellar granule neurons (CGNs) arrested ADBE. Delivery of exogenous PI4KIIα to these neurons fully restored ADBE, highlighting an important role of PI4KIIα. Interestingly, molecular replacement of endogenous PI4KIIα with a GSK3- phospho-mimetic mutant failed to rescue ADBE. However, kinase-dead and phospho-null mutants both fully restored ADBE, suggesting that GSK3-dependent phosphorylation of PI4KIIα negatively regulates this endocytosis mode. To determine potential phosphorylation-specific interactions, GST-PI4KIIα pull downs were performed. Mass spectrometry analysis revealed 5 presynaptic molecules that displayed an increased interaction with the phospho-mimetic PI4KIIα mutant, which were confirmed by Western blotting. Truncation and domain swap mutations revealed that mock phosphorylation of Ser-47 on PI4KIIα is critical in controlling these interactions. Intriguingly, individual depletion of two of these phospho-dependent interaction partners greatly reduced ADBE in CGNs. These results indicate a key role for PI4KIIα in ADBE and confirm the constitutively active GSK3 as a master regulator of this process. We propose that activity-dependent dephosphorylation of Ser-47 on PI4KIIα induces the release of key molecules which are crucial for the initiation of ADBE.
Heterogeneity of neuroinflammatory responses in Amyotrophic Lateral Sclerosis (ALS) revealed at single-cell resolution: a roadmap for new target discovery

Danilo Pellin (1), Andrea Protti (2), Daniela Curti (3), Alessandra Biffi (1)(4), Marco Peviani (4)(1)

(1) Dana-Farber/Boston Children's Cancer and Blood Disorder Center, 450 Brookline ave, Boston, Ma, United States of America.

(2) Lurie Family Imaging Center - Dana Farber Cancer Institute, 27 Drydock ave, Boston, Ma, United States of America.

(3) University of Pavia, Via Ferrata 9, Pavia, Italy.

(4) Harvard Medical School, 450 Brookline ave, Boston, Ma, United States of America.

ALS is a complex pathology; i) the neurodegeneration is progressive; it starts focally in specific CNS areas and spreads to different districts; ii) the heterogeneous/multifaceted responses occurring in different CNS regions during the disease reflect not only the extent of neuronal demise but also variable engagement of astrocytes, microglia, immune cells in the attempt to cope with the neurodegeneration.

To better investigate the neuroinflammatory responses in ALS, we ran a study in the SOD1.G93A rat model where we correlated the pathological alterations highlighted by MRI with the pattern of expression of known microgliosis markers (CD11b, TSPO and CB2) measured by flow cytometry in cells from CNS areas characterized by different extent of neurodegeneration (lumbar, thoracic and cervical spinal cord; brainstem; cortex and hippocampus). Interestingly, we highlighted different microglia phenotypes (characterized by variable combinations of the three analyzed markers) depending on the extent of region-specific neuronal demise and on type of onset, hind- vs fore-limb. To further investigate this phenomenon, we performed a single-cell RNAseq analysis: a total of 36000 microglia cells retrieved from different CNS regions of WT or symptomatic SOD1.G93A (TG) rats were barcoded using a droplet-based technology (InDrop). Notably, by running an unbiased analysis based only on the genetic signature of each cell, TG microglia was very efficiently discriminated from WT cells. More importantly, when we classified each cell according to the CNS region, we identified two very different cell-clusters composed of TG microglia derived either from spinal cord or from brainstem and we found a few novel gene candidates that were specifically overexpressed only in TG spinal cord. Validation on human samples is in progress. Overall, our approach unraveled new insights into the complexity of ALS and opened the way for discovery of novel markers for cell-targeting approaches or for future druggable targets for therapy.
History and evolution of Molecular Neuroscience in modern didactics research for High School

Marina Minoli (1)

(1) National Biologists Order - Royal Society of Biology, Dalmazia street, Milan, Italy.

The mission of this project was to develop didactic research about teaching and learning Molecular Neuroscience with interdisciplinary methods important to realize "Neuroscience with Society". For development of Molecular Brain Science are necessary collaboration between scientists with different skills and it is useful for success of didactics actions to transfer these approaches in Scientific High School classes. Working as biologist didactic researcher - principal investigator in scientific international community were realized innovative learning by doing didactics strategies about Molecular Mechanisms of Neuroscience for inclusive bioscience education with enquire methods approaches. Surfing and searching in scientific selected international data base was possible to start scientific project, to guide students in analyzing historical aspects and modern biological concepts about molecular brain researches, scientific literacy also about elements of biochemisty and cellular physiology for neurodegenerative diseases. Modern Brain Science with molecular mechanism regulation researches for innovative STEM activities introducing Systems Neuroscience: elements of Brain Science Evolution were promoted motivating students and educating to correct interpretation of modern neuroscience discoveries about channel proteins, cellular neurooxidative stress conditions and biomolecules implicated in neurodegenerative processes, manipulation of protein receptors with optogenetics methodology. Neuroscience modern researches with innovative setting class were present two core concepts:neuroplasticity and neuroconnectivity, creating also some interconnections between Nanoscience-Neuroscience, modern researches about brain impact (nanotoxicity) of innovative nanomaterials. In this innovative Educational path were useful STEM didactic approaches to realize contamination between different disciplines analyzing also the role of TAU protein in pathology of local microcircuits in the brain. Different Neuroscience Molecular didactic research activities were realized linking important concepts with historical elements and laboratory neurobiology experimental technique, strategic cooperative teaching and learning practices to realize constructive Modern Brain Science education also with collaborative academic Unimi and Royal Society of Biology for terminal evaluation of student' works.
Impact of Endoplasmic reticulum (ER) stress on expression of ER specific E3 ubiquitin ligase Hrd1

Peter Račay (1)(2), Katarína Dibdiaková (2), Simona Saksonová (2), Ivana Pilchová (1), Katarína Dačanová (1), Zuzana Tatarková (2)

(1) Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin (JFM CU), Biomedical Center Martin JFM CU
(2) Department of Medical Biochemistry JFM CU Martin, Slovakia

Endoplasmic reticulum (ER) stress is often implicated in pathophysiology of neurodegenerative diseases such as Parkinson’s and Alzheimer’s diseases since chronic ER stress is associated with the initiation of multiple cell death mechanisms. ER stress induces also intracellular protective responses termed the unfolded protein response (UPR). With respect to protein synthesis and quality control, UPR induces both the repression of protein synthesis via activation of protein kinase RNA-like ER kinase (PERK), which phosphorylates the α subunit of the eukaryotic initiation factor 2 (eIF2α) and the degradation of the unfolded proteins by ER-associated degradation (ERAD). We have investigated the impact of ER stress on the expression of Hrd1, an E3 ubiquitin ligase that plays a central role in the process of ERAD. SH-SY5Y neuroblastoma cells that are frequently used as a model for studying the mechanisms of neurodegeneration associated with Parkinson’s disease and parental SK-N-SH cells were studied. We have demonstrated that ER stress, induced by thapsigargin or tunicamycin, correlates with the increased expression of Hrd1 in both SH-SY5Y and SK-N-SH cells. Inhibition of PERK did not significantly suppress the thapsigargin- or tunicamycin-induced expression of Hrd1. PERK inhibition had a positive effect on the survival of SH-SY5Y cells treated with thapsigargin but not on those treated with tunicamycin. Inhibition of IRE1α associated with the inhibition of XBP1 splicing did not affect the survival of SH-SY5Y cells treated with either thapsigargin or tunicamycin but resulted in the complete suppression of both the thapsigargin- and tunicamycin-induced expression of Hrd1. Thus, the ER-stress-induced expression of Hrd1 in SH-SY5Y depends on Hrd1 transcription activation, which is a consequence of IRE1α activation. Finally, we suppose that overexpression of Hrd1 is universal cell response to ER stress.

This study was supported by the Slovak Research and Development Agency under the contract No. APVV-16-0033 to PR.
Impaired approach to novelty and altered striatal responsiveness in the oxytocin receptor deficient mouse model of autism

Valentina Gigliucci (1), Marianna Leonzino (1)(2), Luisa Ponzoni (2), Marta Busnelli (1)(2), Ilaria Ceresini (1), Daniela Braida (2), Natalia Duque-wilckens (3), Brian C. Trainor (3), Katsuhiko Nishimori (4), Mariaelvina Sala (1)(2), Bice Chini (1)(2)

(1) Institute of Neuroscience - Consiglio Nazionale delle Ricerche, via Vanvitelli 32, Milan, Italy. 
(2) Dept. of Biotecnologie Mediche e Medicina Traslazionale, University of Milan, via Vanvitelli 32, Milan, Italy. 
(3) Animal Behavior Graduate Group, Psychology Department, University of California, Davis, California, United States of America. 
(4) Laboratory of Molecular Biology, Graduate School of Agricultural Science, Tohoku University, Sendai 981-8555, Japan.

The role of oxytocin (OXT) in sociability and social memory has been widely characterized, however the role(s) of OXT outside the social domains remain to be addressed. In particular, the role of OXT in novelty and habit formation, contributing to autistic-relevant behaviors such as cognitive inflexibility, is still to be established.

Methods: Behavioral tests (marble burying, spontaneous alternation in the Y maze, novel object recognition) were conducted in Oxtr-/- and Oxtr+/+ mice; experiments were also conducted on Oxtr+/+ mice after pharmacological manipulation ofOXTR. In the hippocampus and dorsolateral striatum, two areas involved in spatial learning, novelty and habit formation, neuronal arborization and dendritic spines number and morphology were analyzed; in the same areas, the expression level of synaptic excitatory and inhibitory (E/I) markers was also determined.

Results: Our data indicate that Oxtr-/- mice display impaired behavioral responses that could be rescued after longer habituation to the object and/or to the test environment, suggesting a defective approach to novelty that impairs cognitive performances in unfamiliar situations. At the morphological and biochemical levels, Oxtr-/- mice display altered E/I markers and an increased dendritic arborization, with a subsequent increased number of excitatory synapses, in the dorsolateral striatum. No alterations of pyramidal neurons’ morphology and E/I markers expression were found in the hippocampus.

Conclusions: All together, these data indicate that the genetic disruption of OXT receptor signaling results in abnormal remodeling in the dorsolateral striatum, a likely substrate for increased neophobia and cognitive rigidity in this animal model of autism. The present study highlights an impaired approach to novelty as one of the possible target mechanisms for OXT-induced rescue of complex autistic manifestations.
P29

JNK role in animal and human Rett Syndrome models: its inhibition is an innovative therapeutic strategy

Clara Alice Musi (1), Lucia Buccarello (1), Tiziana Borsello (1)(2)
(1) Università degli Studi di Milano, Italia.
(2) IRCCS- Istituto di Ricerche Farmacologiche Mario Negri, Italia.

Rett syndrome (RTT) is an autistic-spectrum disorder and one of the most common genetic causes of cognitive impairment in females. RTT is characterized by normal early growth followed by neurodevelopment regression within the first 3 years. RTT is caused by heterozygous mutations in the X-linked MECP2 gene encoding methyl-CpG-binding protein-2. MeCP2 protein is involved in regulation of neural circuits and, importantly, in synaptic deficits. However, the molecular mechanisms related with these defects are largely unknown. Here, we showed that c-Jun N-terminal kinase (JNK), a stress-activated protein kinase, plays an important role in RTT.

We studied different RTT models: MeCP2-knockout (Mecp2\(^{-/-}\)) male mice, MeCP2-heterozygous (Mecp2\(^{+/-}\)) female mice and human neurons differentiated from MeCP2-mutated iPSCs (Mecp2\(^{mut}\)). We proved that JNK was powerfully activated in all three models.

Mecp2\(^{-/-}\) mice presented JNK activation in whole homogenate and dendritic spines. In spines glutamate receptors, PSD95 and PSD93 levels were higher than wt mice and SHANK3 and Drebrin levels were lower, these results correlated with locomotor impairments. Mecp2\(^{-/-}\) mice were characterized also by glia deregulation since GFAP and IBA-1 levels were altered.

Even Mecp2\(^{+/-}\) mice presented higher P-JNK/JNK in dendritic spines than in wt; in this model the spine pathology involved increases in PSD95, PSD93 and SHANK3 levels, with decreased Drebrin level. These mice also showed locomotor impairments.

Using hiPSCs differentiated in neurons we demonstrated that in Mecp2 control allele the JNK signaling is not activated, while in hMecp2\(^{mut}\) we found a strong activation of JNK, c-Jun phosphorylation and neuronal death.

The specific JNK inhibitor, D-JNK1, prevents clinical symptoms recovering body weight and locomotor impairments in both male and females models. D-JNK1, inhibiting JNK activation, rescued dendritic spine alterations, glial dysfunctions and, importantly, in hiPSCs-Mecp2\(^{mut}\) inhibiting c-jun phosphorylation prevents induced-cell death.

These results suggest that JNK inhibition represent an attractive therapeutic strategy against RTT.
Let’s make maths about lactate in the brain!

Nicolas Bourmeyster (1)(2), Angélique Perrillat-mercerot (3), Alain Miranville (3), Carole Guillemin (3), Rémy Guillemin (1)(4)

(1) CHU Poitiers, 2, rue de la Milétrie, 86021 Poitiers, France.
(2) Laboratoire Signalisation et Transports Ioniques Membranaires, ERL CNRS 7003, Equipe 4CS, Université de Poitiers, 1, rue Georges Bonnet, 86022 Poitiers, Francia.
(3) Laboratoire de Mathématiques et Applications, UMR CNRS 7348, SP2MI, Equipe DACTIM MIS, Université de Poitiers,, Boulevard Marie et Pierre Curie Téléport 2,, 86073 Poitiers, France.
(4) Laboratoire de Mathématiques et Applications, UMR CNRS 7348, SP2MI, Equipe DACTIM MIS, Université de Poitiers,, Boulevard Marie et Pierre Curie Téléport 2,, 86073 Poitiers, Francia.

Everything that lives is born, eats, reproduces and dies. For the brain, the question is more complex because neurons have to survive and to support brain activity. Energy management is also particular because brain cells evolve together with no competition. First seen as a waste, it is now commonly admitted that lactate is a substrate appreciated by brain cells and in particular tumor cells. To go further, lactate kinetics seem to be very impacted by common brain health problems such as glioma or neurodegenerative diseases. Mathematics and in particular modeling of energy substrates is useful to describe and predict energetic kinetics and changes. Mathematical models could get with clinical and medical results to describe, explain or predict lactate kinetics and therefore bring informations on tumor growth. They can help to characterize and quantify a tumor evolution, then leading to improve their therapeutical management. Our works deal with several approaches of substrates dynamics in healthy and gliomatous brains. These researches are based on systems of equations. We model local lactate exchanges (ODE, fast slow systems), global substrates exchanges (ODE), glutamate/glutamine cycle (RDE) and local lactate exchanges in higher dimensions (PDE). We briefly describe, analyze and give simulations of these models. Simulations are fitted on patient MRI data or literature data. Lactate is necessary for your brain to live. But if your neighbor consumes a part of your resources, can you still survive?
Linking Phospho-HDAC6 to protein aggregation in Parkinsonisms

Samanta Mazzetti (1)(2), Mara De Leonardis (1), Gloria Gagliardi (1), Alessandra Maria Calogero (1)(2), Milo Jarno Basellini (1)(2), Emanuela Maderna (3), Francesca Cacciatore (3), Sonia Spinello (3), Manuela Bramerio (4), Giorgio Giaccone (3), Gianni Pezzoli (5)(2), Graziella Cappelletti (1)

(1) Dipartimento di Bioscienze Università degli Studi di Milano, via celoria 26, Milan, Italy.
(2) Fondazione Grigioni per il Morbo di Parkinson, Via Zuretti 35, Milan, Italy.
(3) Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria 11, Milan, Italy.
(4) ASST Grande Ospedale Metropolitano Niguarda, Piazza Ospedale Maggiore, 3, Milan, Italy.
(5) Parkinson Institute, ASST “G.Pini-CTO”, via Bignami 1, Milan, Italy.

HDAC6 is a peculiar histone deacetylase, whose functions include deacetylase activityon cytoplasmic not-histonic proteinsand ubiquitin-binding activity. Both these activities are required for HDAC6 triggering the formation of the so-called “aggresome”,a specific and active cellular response to aggregate misfolded protein that finally leads to autophagic degradation. Its deacetylase activity is increased by phosphorylation on serine 22 (Phospho-HDAC6). In autoptic human brains, HDAC6 has been localized also in Lewy bodies in neurons in Parkinson’s disease (PD) and in Papp-Lantos bodies in oligodendrocytes in Multiple System Atrophy (MSA), while, up to now, no data are available concerning Phospho-HDAC6 localization. Based on these considerations, the aim of this work was to evaluate and compare the distribution of HDAC6 and its phosphorylated form in human brains obtained from patients affected by three different Parkinsonisms, including two synucleinopathies, i.e. PD and MSA, and also a tauopathy,Progressive Supranuclear Palsy (PSP), never analysed before.

The results obtained using immunohistochemical techniques associated with confocal microscopy, revealed that both HDAC6 and its phosphorylated form (HDAC6P) are present together with the aggregated a-Synuclein or the Phospho-Tau in Lewy bodies (PD), Papp-Lantos bodies (MSA) and neurofibrillary tangles (PSP), thus representing a converging point between synucleinopathies and tauopathies. The regions we analysed in this study include inferior olivary nucleus, dorsal motor nucleus of vagus, substantia nigra, mesencephalic reticular formation, putamen, pallido, hippocampus and enthorinal cortex. Finally, to evaluate if HDAC6 directly interact with a-Synuclein, we performed proximity ligation assay (PLA), confirming their interaction. In particular, PLA signal was abundant in Lewy bodies or Pale bodies, but was also present as a diffuse staining in neuropil.

In conclusion, this study suggested that both HDAC6 and Phospho-HDAC6 could be a key component for protein homeostasis in Parkinsonisms.
Long and very long chain ceramides correlate with a more aggressiveness behavior in skull base chordomas

Emanuele La Corte (1)(4), Michele Dei Cas (1)(5), Monica Patanè (2), Chiara Calatozzolo (2), Bianca Pollo (2), Alberto Raggi (3), Giuseppe Campisi (1)(5), Paolo Ferroli (4), Rita Paroni (5), Riccardo Ghidoni (1)(6)

(1) PhD School in Molecular and Translational Medicine, Department of Health Sciences, University of Milan, Milan, Italy.
(2) Neuropathology Unit, Fondazione IRCCS Istituto Neurologico “Carlo Besta”, Milan, Italy.
(3) Neurology, Public Health and Disability Unit, Fondazione IRCCS Istituto Neurologico “Carlo Besta”, Milan, Italy.
(4) Department of Neurosurgery, Fondazione IRCCS Istituto Neurologico “Carlo Besta”, Milan, Italy.
(5) Clinical Biochemistry & Mass Spectrometry Laboratory, Department of Health Sciences, University of Milan, Milan, Italy.
(6) Biochemistry and Molecular Biology Laboratory, Department of Health Sciences, University of Milan, Milan, Italy.

Introduction. Skull base chordomas are rare slow-growing neoplasms that arise from notochord. Sphingolipids analysis is emerging as a new approach in many cancers and it has never been applied in chordomas. Our aim is to investigate chordoma biological behavior and the role of ceramides.

Patients and Methods. Sphingolipids were extracted from frozen tissues and total ceramides and dihydroceramides were evaluated by liquid chromatography and mass spectrometry in a cohort of patients treated for a skull base chordoma at the Fondazione IRCCS Istituto Neurologico “Carlo Besta”. Clinical and radiological data have been also collected. Survival analysis was performed according to Kaplan-Meier method. Simple linear regression and correlation analyses were conducted.

Results. Total ceramides and dihydroceramides were significantly higher in “intense MR contrast enhancement” chordomas in comparison to the “no/mild enhancement” chordomas (p=0.0290 and p=0.0186, respectively). Analyzing the association between ceramides level and MIB-1, total ceramides level showed a strong association (r=0.7257, r²=0.5267) with MIB-1 staining (p=0.0033). Analyzing the association between DHCer level and MIB-1 within each skull base chordoma patient, total DHCer level showed also strong association (r=0.6733, r²=0.4533) with MIB-1 staining (p=0.0083). Among the single ceramides species Cer C24:1 (r=0.8814, r²=0.7769, p≤0.0001), DHCer C24:1 (r=0.8429, r²=0.7104, p=0.0002) and DHCer C18:0 (r=0.9426, r²=0.8885, p≤0.0001) levels showed a significant correlation with MIB-1 staining. Final candidate predictive factors that well fitted the regression model were: cer24:1 (r=0.824, p≤0.001), and DHCer C18:0 (r=0.748, p=0.002).

Conclusion. Our lipid analysis showed ceramides as promising tumoral bio-markers in skull base chordomas. Long and very long chain ceramides, such as Cer C24:1 and DHCer C24:1, may be related to a prolonged tumor survival, aggressiveness and the understanding of their effective biological role will hopefully shed lights on the mechanisms of chordoma radio-resistance, tendency
Spinal muscular atrophy (SMA) is a severe autosomal recessive disease characterized by selective motor neuron degeneration and progressive amyotrophic paralysis. SMA is the leading genetic cause of infant mortality, with an incidence of about 1 in 10,000 neonates. The novel SMN enhancing drugs are demonstrating extremely promising results, but also only partial efficacy, emphasizing the need for understanding the mechanisms of SMA pathogenesis, in order to find targets for additional therapies. SMA being a complex disease, combined therapies providing SMN-targeted and SMN-independent medications probably represent the best approaches for treatment. There is also need of biomarkers to monitor disease progression and treatment efficacy. MicroRNAs (miRNAs) are small non-coding RNAs that bind to complementary target sequences and modulate gene expression. miRNAs are functional for nervous system development, differentiation and survival, but they are also involved in neurodegeneration and motor neuron diseases. In the attempt to identify specific miRNAs as SMA biomarkers and therapeutic targets, we demonstrated up-regulation of miR-21 in SMA delta7 mice as a compensatory mechanism set in motion by degenerating motor neurons. We then analyzed the expression levels of specific miRNAs involved in neurogenesis and neuronal development by RT-qPCR, observing a significant decrease of miR-124a and miR-219 in spinal cord, but not brain, of SMA versus wt mice. A negative correlation was evidenced between miR-219 and its target gene Foxj3, and between miR-124 and Sox9. Western blot analysis showed alteration of glial and neuronal markers such as GFAP, Olig2, SMI311. As miR-219 is necessary in promoting neural and oligodendrocyte differentiation through regulation of Foxj3, and altered levels of miR-124 in ALS mice are associated with astrocyte/neuron differentiation unbalance, we hypothesize a possible disease mechanism shared by SMA and ALS, where altered expression of miR-219 and miR-124a might affect neurogenesis and neural stem cell differentiation, thus contributing to SMA pathogenesis.
Microtubule cytoskeleton and alpha-Synuclein: new data for an emerging interplay

Alessandra Maria Calogero (1), Samanta Mazzetti (1)(3), Francesca Cantele (1), Sara Pizzi (1), Delia Tarantino (1), Alida Amadeo (1), Giorgio Giaccone (2), Gianni Pezzoli (3)(4), Graziella Cappelletti (1)(5)

(1) Dept. of Biosciences, Università degli Studi di Milano, Milan, Italy.
(2) Foundation IRCCS Carlo Besta Institute of Neurology, Milan, Italy.
(3) Fondazione Grigioni per il Morbo di Parkinson, Milan, Italy.
(4) Parkinson Institute, ASST G. Pini-CTO, ex ICP, Milan, Italy.
(5) Center of Excellence on Neurodegenerative Diseases, Università degli Studi di Milano, Milan, Italy.

Microtubules are key elements of cytoskeleton, being fundamental in many cellular functions, including cell morphology, differentiation, polarity and migration. In neurons, they are essential for intracellular trafficking along axons and dendrites, and regulation of dendritic spines and synaptic morphology. Microtubules are highly dynamic structures, whose assembly and functions are strictly regulated also by post-translational modifications. Many neurodegenerative diseases are characterized by microtubule alterations, so much so that microtubule dysfunctions are emerging as one of possible actors in neurodegenerative processes, including Parkinson’s disease (PD). Interestingly, some of the gene linked to familial forms of PD are also involved in microtubule functions or regulations. Many data indicate that α-Synuclein, the main component of Lewy Body, the pathological hallmark of PD, is able to regulate microtubule dynamics. Here, we deeply investigated the interplay between tubulin and α-Synuclein using different approaches from in vitro assays with pure proteins to analyses of mouse or human brain. First we found that some of the pathogenic mutations lead to alteration of microtubule cytoskeleton assembly compared to wild-type α-Synuclein in vitro, probably due to their reduced affinity for tubulin. Then, in wild type mice, we deeply investigate α-Synuclein distribution and colocalization with post-translationally modified α-tubulin, highlighting interestingly differences among different brain regions. Finally, we moved to post-mortem human brains from PD patients, focusing on those brain regions involved in the disease. We found that a region-specific redistribution of acetylated tubulin occurs in patient samples and this seems to be correlated with the pathological oligomerization and aggregation of α-Synuclein. Collectively, our data support the concept that the interaction of tubulin/microtubules with α-Synuclein might be crucial for α-Synuclein in physiological but also in pathological contexts.
P35

Mitochondrial dysfunction increases fatty acid β-oxidation and impairs neuroblast maturation

Silvia Pedretti (1), Matteo Audano (1), Maurizio Crestani (1), Donatella Caruso (1), Emma De Fabiani (1), Nico Mitro (1)

(1) Università degli Studi di Milano, Dipartimento di Scienze Farmacologiche e Biomolecolari, via Balzaretti, 9, Milan, Italy.

Neurogenesis is a biological process beginning from neural stem cells to mature neuron formation. This process is necessary for the development of the nervous system to ensure proper cognitive functions, such as behavior, mood, memory, and brain plasticity.

During neurogenesis, progenitor cells undergo several stages such as quiescent neural stem cells, proliferative neural progenitor cells, followed by neuronally committed neuroblasts, and finally mature neurons. The metabolic transition from anaerobic glycolysis and fatty acid β-oxidation to glycolysis coupled to oxidative phosphorylation is a key process for neuron development. Previous works demonstrated the importance of mitochondrial function and metabolic pathways regulation in the transition of quiescent neural stem cells to proliferative neural progenitor cells. Moreover, the importance of glycolysis and pentose phosphate pathway has been reported during the differentiation of neural progenitor cells to neurons. However, a full characterization of the metabolic shift and the involvement of mitochondria occurring during neuroblasts to neurons maturation is still elusive.

We describe a model of neuroblasts (N2a cells) with dysfunctional mitochondria to investigate the contribution of mitochondria and energy metabolism to the maturation from neuroblast to neuron. Using a detailed biochemical characterization consisting of steady state metabolomics and metabolic flux analysis, we found increased fatty acid β-oxidation as peculiar feature of neuroblasts with altered mitochondria. The consequent metabolic switch favored neuroblast proliferation at the expense of neuron maturation.
Modulation of sphingolipids by non-invasive myriocin administration: potential treatment for Retinitis Pigmentosa

Michele Dei Cas (1), Federico Rubino (1), Jessica Rizzo (1), Paola Signorelli (1), Enrica Strettoi (2), Chiara Platania (3), Claudio Bucolo (3), Rosario Pignatello (4), Rita Paroni (1), Riccardo Ghidoni (1)

(1) Dept. Health Sci. Univ MilanUniversity of Milan, via A. di Rudinì, 8, Milan, Italy.
(2) Institute of Neuroscience CNR, Pisa, Italy.
(3) NANO-i, Dept. Drug Sci. Univ Catania, Catania, Italy.
(4) edical and Biotechnological Sciences, Univ Catania, Catania, Italy.

Introduction. Myriocin (Myr) acts as a suicide inhibitor of serine-palmitoyl-transferase, the first and rate-limiting enzyme in the de novo sphingolipids biosynthetic pathway. Myr is currently in the pre-clinical study phase for the treatment of different diseases characterized by an abnormal ceramide levels such as retinitis pigmentosa. Its biological activity is exerted at very low doses, and thus a highly performing quantitative method for its determination is needed. The pharmacological development of Myr to modulate ceramide levels also requires currently unavailable ADME information in healthy and pathological animal models.

Results. Tissue levels of Myr are related to the pharmaceutical formulation, administration route, and administration schedule. In particular, lipid nanoparticles were found to be extremely more efficacious than the other formulations for the delivery of Myr to different districts of the eye. The NLC slow release formulation produced a T\(_{\text{max}}\) between 180-240 minutes, with a maximum concentration respectively of 10 \(\pm\) 0.1 mg/mL in vitreous and 1.7 \(\pm\) 0.05 mg/g in retina (n=4). Biological activity of Myr was confirmed in rabbit’s retina by a significant decrease (about 3-folds at 180 min) in total ceramides and dihydroceramides levels, compared to the levels measured in untreated animals.
P37

Modulation of the constitutive activity of melanocortin 4 receptors by zinc and copper ions

Reet Link (1), Santa Veiksina (1), Maris-johanna Tahk (1), Sergei Kopanchuk (1), Ago Rinken (1)

(1) Institute of Chemistry, University of Tartu, Ravila 14a, Tartu, Estonia.

Melanocortin 4 receptors (MC₄R) are involved in energy homeostasis, neuroprotection, and neurogenesis and therefore have become as important targets for the regulation of body weight and neurological performance. The signal transduction of MC₄ receptors is initiated by a complex ligand binding process, which involves conformational adjustments, oligomerization, and effects of different modulators [1]. MC₄R is unique among GPCRs as they have endogenous ligands that can exhibit inverse agonistic properties in the case of elevated basal activity. Implementation of fluorescence anisotropy (FA) assay has enabled on-line monitoring of ligand-receptor binding process that allows characterization of kinetic peculiarities of different modulators [2]. We have designed two novel red-shifted fluorescent ligands for the MC₄ receptors, UTBC101 and UTBC102, which have a high binding affinity and suitable kinetic properties for this kind FA studies [3]. The presence of at least submillimolar concentration of Ca²⁺ was essential to achieve high-affinity specific binding of ligands to MC₄R. The Zn²⁺ and Cu²⁺ also regulated ligand binding to MC₄ receptors, but they acted as negative allosteric modulators. In functional assays, Zn²⁺ acted as an activator, but Cu²⁺ acted as an inhibitor of the basal activity of MC₄ receptors, and this already at low micromolar concentrations.

These findings indicate that at physiologically relevant concentrations, Zn²⁺ and Cu²⁺ can function as MC₄ receptor agonists or inverse agonists, respectively, and are involved in the regulation of constitutive activity level of the receptor.

References:

Supported by ETAG (IUT20-17 and PSG230)
P38

Myelinosomes enable cell to cell transfer of mutant huntingtin-exon1 causing aggregate formation in neuronal cells

Nicolas Bourmeyster (1)(2), Marina Yefimova (1)(3), Emile Béré (4), Anne Cantereau-becq (4), Agnès Burel (5), Marie-thérèse Lavault (5), Annie-claire Meunier (1), Celia Ravel (6), Frédéric Becq (1)

(1) Université de Poitiers/CNRS, Laboratoire Signalisation et Transports Ioniques Membranaires, 1, rue Georges Bonnet, 86022, Poitiers, France.
(2) CHU de Poitiers, 2, rue de la Milétrie, 86021 Poitiers, France.
(3) Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, 44, Prosp. Maurice Thorez, St Petersbourg, 194233, Russia.
(4) Plateforme IMAGE-UP, 1 rue Georges Bonnet, 86022 Poitiers, France.
(5) Plateforme Mric TEM, BIOSIT UMS 34 80. Université de Rennes1, 2 av Pr Léon Bernard, 35043 Rennes Cedex, France.
(6) Laboratoire de Biologie de la Reproduction-CECOS, Hôpital SUD, 16 Bd de Bulgarie, 35 000 Rennes, France.

In a previous report (Yefimova et al., 2016), we uncovered a new mechanism of misfolded protein elimination through myelinosome secretion. Myelinosome-driven secretion (MDS) mechanism prevents the accumulation of aggregate-prone mHtt exon1 in the somatic Sertoli cells from HD testis. MDS relies upon secretory organelles myelinosomes, which load mHtt exon1 in cell cytoplasm, and then are released outside of the cells. Here we aimed to unveil the impact of MDS on the neighboring cells and its significance for CNS and other tissues. Using several cell lines from CNS and extra-CNS origin (human glial retinal Müller cells, human neuroblastoma SH-SY5Y cells, somatic Sertoli cells from mouse testis), we demonstrate that mHtt-exon1-bearing myelinosomes undergo cell-to-cell transfer. The mechanism of myelinosome delivery in the cytoplasm of acceptor cell depends on cell specialization. Non-professional phagocytes glial retinal Müller cells and somatic Sertoli cells capture myelinosomes through phagocytosis; while membrane fusion mechanism is required for the handling of myelinosomes in neuroblastoma SH-SY5Y cells. Moreover, being transferred into neuronal SH-SY5Y cells, myelinosome-delivered mHtt exon1 exerts a prion-like activity, contributing to the formation of insoluble mHtt aggregates. We propose MDS as one of potential mechanisms, involved in the propagation of HD.
Novel gene therapy for GM2 gangliosidoses with AAV9/3-CMV-modHEXB vector

Kohji Itoh (1), Yukiya Ohnishi (1), Daisuke Tsuji (1), Ryo-suke Watanabe (1), Katsuhito Asai (2), Shin-ichi Muramatsu (3)

(1) Graduate School of Pharmaceutical Science, Tokushima University, 1-78 Sho-machi, Tokushima, Tokushima, Japan.
(3) Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, Japan.

Tay-Sachs disease (TSD) and Sandhoff disease (SD) are autosomal recessive GM2 gangliosidoses, caused by the recessive gene mutations of HEXA and HEXB encoding the alfa and beta-subunits of lysosomal beta-hexosaminidase (Hex), respectively. These incurable diseases associate with the HexA (alfa/beta heterodimer) deficiency and excessive accumulation of GM2 gangliosides (GM2) in brains of the patients and neurological symptoms. Although high incidence of TSD in Ashkenazy-Jewish populations is well-known, there are 27 of Japanese TSD patients according to the report in 2017. We constructed an adeno-associated viral vector (AAV9/3-CMV-modHEXB) encoding the modified HEXB to produce the modified HexB (modHexB) composed of homodimeric beta-subunits carrying 9 amino acid residues substituted to those of the alfa-type involving GM2 degradation. We demonstrated that the intracerebroventricular and intravenous administration of AAV9/3-CMV-modHEXB to adult and neonatal SD model mice could restore the GM2-degrading activity, reduce the GM2 accumulated in the brain regions, repress the motor dysfunctions and prolong the life span as Proof of Concept (POC) for efficacy. We also found that the neuronal cells induced from iPS cells derived from a TSD patient secreted the human active modHexB after treatment with AAV9/3-CMV-modHEXB, suggesting the "cross-correction" effect. Furthermore, we performed intrathecal injection to Cynomologus monkey and confirmed the safety for at least three months. From these findings, the intrathecal gene therapy using AAV-CMV-modHEXB is expected to be clinically applicable as a low-invasive treatment for TSD and SD.
Novel mutations in the asparagine synthetase gene (ASNS) associated with microcephaly

Ulrike Winkler (1), Grit Marx (1), Dorit Schleinitz (2), Katrin Hoffmann (3), Peter Kovacs (2), Johannes Hirrlinger (1)(4)

(1) Carl-Ludwig-Institute for Physiology, Faculty of Medicine, University of Leipzig, Liebigstrasse 27, 04103 Leipzig, Germany.
(2) Leipzig University Medical Center, IFB AdiposityDiseases, Liebigstraße 20, 04103 Leipzig, Germany.
(3) Institute of Human Genetics, Martin-Luther-University Halle-Wittenberg, Magdeburger Straße 2, 06112 Halle (saale), Germany.
(4) Max-Planck-Institute for Experimental Medicine, Department of Neurogenetics, Hermann-Rein-Strasse 3, 37075 Göttingen, Germany.

Microcephaly is a devastating condition defined by a small head and small brain compared to the age- and sex-matched population. Mutations in genes involved the synthesis of several non-essential amino acids have been described which cause a severe neurological and/or neurodevelopmental phenotype. This includes the gene encoding the enzyme asparagine synthetase (ASNS). Mutations in the ASNS gene were recently identified as causal mutations for rare forms of microcephaly and several different mutations in ASNS have been described worldwide. In a family with two affected girls, we identified novel compound heterozygous variants in ASNS (c.1165G>C, p.E389Q and c.601delA, p.M201Wfs*28). The first mutation (E389Q) is a missense mutation resulting in the replacement of a glutamate residue evolutionary conserved from *Escherichia coli* to *Homo sapiens* by glutamine. Protein modeling based on the known crystal structure of ASNS of E. coli predicted a destabilization of the protein by E389Q. The second mutation (p.M201Wfs*28) results in a premature stop codon after amino acid 227, thereby truncating more than half of the protein. While, the pathophysiological mechanisms linking mutations in the ASNS gene to the development of microcephaly remain enigmatic so far, these novel variants expand the growing list of microcephaly causing mutations in ASNS.
Nuclear accumulation of WRAP53 maintains genome integrity in neurons after ischemia

Cristina Rodríguez (1)(2), Irene Sánchez Morán (1)(2), Angeles Almeida (1)(2)

(1) Institute of Biomedical Research of Salamanca (IBSAL), University Hospital of Salamanca, University of Salamanca, CSIC, Spain.
(2) Institute of Functional Biology and Genomics (IBFG), University of Salamanca, CSIC, Spain.

Ischemic stroke causes DNA damage in neurons, thereby contributing to cell death unless promptly repaired. An adequate DNA damage response is essential to survive after cerebral ischemia, therefore is indispensable to preserve the integrity of the transcribed genome in neurons. However, the molecular mechanism underlying neuronal survival remains unknown.

Here we describe that WRAP53 (WD40 encoding RNA Antisense to p53), a scaffold protein implicated in DNA repair in replicative cells, also plays an essential role in post-mitotic neurons after ischemia. We observed that ischemia induces oxidative stress and promotes DNA double strand breaks (DSBs), as revealed by the nuclear accumulation of γH2AX in neurons. The ischemic insult also promoted a time-dependent increase in Wrap53 gene expression and protein abundance. Remarkably, the ischemic-induced oxidative stress triggers WRAP53 traffic to the nucleus, where WRAP53 is involved in DNA repair processes. We confirm that WRAP53 depletion prevents 53BP1 foci formation, therefore increasing neuronal susceptibility to ischemia-induced apoptosis. Conversely, WRAP53 expression in ischemic neurons promotes DNA repair events and neuronal survival.

Our results provide new molecular insights into DSB DNA repair in neurons and demonstrate the key role of nuclear accumulation of WRAP53 to maintain genome integrity in neurons and preserve neuronal survival after ischemia.

This work was funded by The Instituto de Salud Carlos III (PI18/00265; RD16/0019/0018); European Regional Development Fund (FEDER); European Union’s Horizon 2020 Research and Innovation Programme (Grant Agreement 686009); and Junta de Castilla y León (IIES007P17; Escalera de Excelencia CLU-2017-03 Cofinanciado por el P.O. FEDER de Castilla y León 14-20)
P209 point mutations in the Bcl-2-Associated Athanogene 3 impact on the Chaperone-Assisted Selective Autophagy

Barbara Tedesco (1), Elias Adriaenssens (4), Laura Mediani (3), Valeria Crippa (1), Serena Carra (3), Vincent Timmerman (4), Angelo Poletti (1)

(1) Dipartimento di Scienze Farmacologiche e Biomolecolari, Centro di Eccellenza sulle Malattie Neurodegenerative, Università degli Studi di Milano, Milan, Italy.
(2) Peripheral Neuropathy Research Group, Department of Biomedical Sciences, Institute Born Bunge, University of Antwerp, Antwerpen, Belgium.
(3) Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, and Center for Neuroscience and Neurotechnology, Modena, Italy.
(4) Peripheral Neuropathy Research Group, Department of Biomedical Sciences, Institute Born Bunge, University of Antwerp, Antwerpen, Belgium.

Misfolded and aggregated proteins are the major hallmark of neurodegenerative diseases (NDs), suggesting that proteostasis failure occurs in affected neurons. To cope with proteotoxic stress, cells, including neurons, rely on the Protein Quality Control (PQC) system, a network of proteins that acts in the refolding or the disposal of damaged and misfolded proteins. The Chaperone Assisted Selective Autophagy (CASA) pathway protects neurons and muscle cells from proteotoxicity, by promoting the disposal of misfolded and aggregate prone substrates. Essential players of CASA are the Bcl-2-Associated Athanogene 3 (BAG3) and the small Heat Shock Protein B8 (HSPB8), which interact together through two IPV domains of BAG3. By HSPB8 recognition and dynein-mediated retrograde transport, misfolded substrates are concentrated to the perinuclear aggresome. Mutations of BAG3 and HSPB8 are related to myopathies and neuropathies, while the induction or the overexpression of the wild-type forms of these CASA members enhance the clearance of proteins aggregates both in cell and animal models of Amyotrophic Lateral Sclerosis (ALS) and other NDs. Here, we investigate the biochemical behaviour of three BAG3 mutations in the second IPV domain (P209L/S/Q) responsible of myopathies or neuropathies. By using complementary techniques, we show that P209 mutants accumulate forming high molecular weight species, which are insoluble in mild detergents. By analysing protein localization, we show that P209 mutants form aggregates, partly dispersed in the cytoplasm and often associated to the nuclear envelope, resembling aggresomes. Furthermore, we show that the presence of these mutants is associated with an increase of insoluble species of the ALS-related misfolded SOD1G93A protein, which is a substrate of CASA complex. In conclusion, mutations at position P209 are characterized by a CASA dysfunction, which could dysregulate proteostasis maintenance.
PKCɛ regulates H-Ras activation via the recruitment of the RasGEF SOS1 and of the RasGAP neurofibromin in the lipid rafts of neurons

Charoula Peta (1), Sofia Karouzaki (1), Emmanouella Tsirimonaki (1), Dimitra Mangoura (1)

(1) Biomedical Research Foundation of the Academy of Athens, 4 Soranou Ephessiou, Athens 11527, Greece.

The spatial organization of plasma membrane proteins is a key factor in the generation of distinct signal outputs, especially for the PKC/Ras/ERK signalling pathway. Regulation by membrane receptor agonism of the membrane-bound Ras, critical for neuronal differentiation and highly specialized functions, is controlled by guanine nucleotide exchange factors (GEFs) that promote the exchange of GDP for GTP and thereby activation of Ras, whereas the other side is controlled by RasGAPs that lead to activation of the intrinsic GTPase activity of Ras and thus to its inactivation. PKCs are potent Ras activators yet the mechanistic details of this event and its topology, or the involvement of specific PKC isoforms are now beginning to be addressed.

Towards this, we isolated lipid rafts from chick embryo neural tissue and primary neuronal cultures when PKCɛ is the prominent isoform, and, in combination with in vitro kinase assays, we now show that, in response to the PKCɛ-specific activating peptide ψεRACK, an activated PKCɛ is recruited to lipid rafts; similar mobility was established when PKCɛ was activated with the Cannabinoid receptor 1 (CB1) agonist methanandamide. Activation of H-Ras by both agents was then established for the first time with in vivo RasGAP activity assays. Moreover, we found that the GEF SOS1 and the PKCɛ substrate RasGAP neurofibromin were both transiently enriched in the rafts. Taken together, these results suggest that PKCɛ activation regulates the enrichment of both RasGEFs and the RasGAP neurofibromin in rafts, thus controlling the activation-deactivation cycles of H-Ras in neurons.
Preconditioning-promoted PI3K/Akt activation regulates MDM2/p53 complex and triggers ischemic tolerance

Emilia Barrio (1)(2), Rebeca Vecino (1)(2), Irene Sanchez-moran (1), Alberto Suarez-pindado (1), Juan P. Bolaños (2)(3), Angeles Almeida (1)(2), Maria Delgado-esteban (1)(2)

(1) Institute of Biomedical Research of Salamanca, University Hospital of Salamanca, University of Salamanca, CSIC, Salamanca, Salamanca, Spain.
(2) Institute of Functional Biology and Genomics, University of Salamanca, CSIC, Salamanca, Salamanca, Spain.
(3) Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Instituto de Salud Carlos III, Madrid, Madrid, Spain.

Attenuation of cell apoptosis has been involved in endogenous neuroprotection induced during brain tolerance related to ischemic preconditioning (IPC). The PI3K/Akt pathway regulates cell development, growth, and survival. Several studies have reported that activated Akt, a serine-threonine specific protein kinase B enhances MDM2-mediated p53 destabilization triggering survival in cancer cells. Recently, we demonstrated that IPC prevents the activation of p53/PUMA/Caspase-3 apoptotic pathway by increasing MDM2/p53 interaction in cortical neurons. Here, we aimed to clarify the role of Akt in the IPC-induced neuronal tolerance against lethal ischemia.

To do that, primary cortical neurons were exposed to a validated in vitro model of IPC (oxygen glucose deprivation; OGD; 20 min) prior to prolonged ischemia (OGD, 90min). Akt levels were modulated by specific siRNA and PI3K/Akt activity was inhibited by wortmannin. Protein levels were determined by Western blotting. Neuronal apoptosis (Annexin-V-staining and caspase-3 activation) was analyzed by flow cytometry and fluorimetry. For ectopic human MDM2 expression, a plasmid construction expressing YFP-tagged Mdm2 was used.

Our results show that IPC promoted early phosphorylation of Akt, followed by an increase in Akt-MDM2 interaction. Indeed, Akt activation promoted stabilization of phosphorylated MDM2, which enhanced IPC-promoted nuclear MDM2-p53 complex at 4 hours of reoxygenation after ischemia. Furthermore, PI3K/Akt specific inhibition by wortmannin and siRNA against Akt, completely induced a cytosolic MDM2 translocation, leading to the prevention of IPC-mediated neuroprotection.

In conclusion, the PI3K/Akt signaling pathway is involved in neuronal ischemic tolerance, through controlling the MDM2/p53 interaction.

The work was funded by The Instituto de Salud Carlos III (PI18/00103 and RD16/0019/0018); FEDER (European regional development fund); and Junta de Castilla y Leon (IES007P17; Escalera de Excelencia CLU-2017-03 Cofinanciado por el P.O. FEDER de Castilla y León 14-20).
Prenatal hypoxia-induced premature aging is accompanied with malfunction of glutamatergic system in rat hippocampus

Oleg Vetrovoy (1)(2), Victor Stratilov (1), Ekaterina Tyulkova (1)

(1) Pavlov Institute of Physiology, Russian Academy of Sciences, Makarova emb., 6, St. Petersburg, Russia.
(2) St. Petersburg State University, Faculty of Biology, Universitetskaya emb., 7-9, St. Petersburg, Russia.

Prenatal hypoxia (PH) is one of the most common causes of developing brain pathologies. This study was aimed to analyze the characteristics of the glutamate system and behavior during early (2-week), adult (3-month) postnatal ontogenesis and in the process of aging (18-month) of rats subjected to hypoxic stress (5% O2, 3 h) during 14-16 days of prenatal development. We have shown progressive with age decrease in the amount of glutamate in the hippocampus of rats subjected to PH, which is accompanied by a decrease in the number of NeuN+ cells, as well as a decrease in long-term memory and learning ability in the Morris water maze. A gradual decrease in the amount of glutamate inversely correlates with, apparently, a compensatory increase in the levels of mGluR1, IP3R1 and polyphosphoinositides. At the same time, the use of mGluR1 agonists normalizes the cognitive ability of rats subjected to PH. 18-month animals subjected to PH demonstrate decreased activity of liver glucose-6-phosphatase, the product of glucocorticoid-dependent transcription. This enzyme contributes to increase of glucose blood level and thus to reaction of glutamate synthesis in the brain. Glucocorticoid receptor levels, similarly, decrease with age in rats subjected to PH. These results indicate a significant contribution of the dysfunction of the glutamatergic system to the formation of early aging caused by PH. The mechanism of glutamatergic deficit can be glucocorticoid-dependent.

Scientific research was performed with involvement of the Research park of SPbU Observatory of Environmental Safety Center and Centre for Molecular and Cell Technologies. The work was supported by RFBR grant no. 17-04-01118.
P46

Protective effects of coffee metabolites against oxidative stress

Tatiana Carrozzini (1), Elena Lonati (1), Laura Botto (1), Michele Tassotti (2), Mena Pedro (2), Daniele Del Rio (2), Paola Palestini (1), Alessandra Bulbarelli (1)

(1) University of Milano-Bicocca, via cadore 48, Monza, Italy.
(2) University of Parma, parco area delle scienze 27/A, Parma, Italy.

Nowadays, since life expectancy has increased and the quality of the environment has worsened, the attention to neurodegenerative diseases has grown. Aging is a major predisposing factor for the most common neurodegenerative disorders, including Alzheimer's disease. The aetiology and pathogenesis of neurodegenerative disorders is not fully understood, but inflammation and oxidative damage are a key component. Several studies, indeed, demonstrated that oxidative stress and neuroinflammatory responses can cause Blood Brain Barrier break-down: the main cause of ischemia. Therefore, in an elderly subject living in a polluted environment, ischemic attacks may arise and this condition causes an increase in ROS. In this scenario, nutrition can modify the oxidant impacts and a healthy diet with adequate intake of micronutrients with antioxidant properties may be crucial to prevent the development of chronic diseases.

In particular, several epidemiological studies have revealed that polyphenol-rich diets can provide beneficial effects in humans and coffee has been described as probably the most relevant source of dietary antioxidant compounds.

For these reasons, phytocomplexes derived from coffee modified by the intestinal microbiome (Dihydrocaffeic Acid, Dihydroferulic Acid, Dihydroferulic Acid-4-sulfate, Ferulic Acid-4-sulfate, Caffeic acid, Caffeic acid-3-glucuronide, Caffeic acid-4-glucuronide, Dihydrocaffeic acid-3-glucuronide) have been used to test their antioxidant activities. Moreover, considering that BBB constitutes the cerebral vascular district with a fundamental role in CNS homeostasis and that injurious states can be triggered by ROS, the substances are tested on a blood-brain barrier model using rat brain endothelial cells (RBE4).

Preliminary data show that RBE4 can be treated with different amount of different compounds, with statistically significance in activating antioxidant defence system after oxygen and glucose deprivation and reperfusion (OGD) a treatment mimicking the ischemia. Coffee metabolites appear to have an antioxidant power, especially when the metabolites are used in a mix reflecting the amount detected in the plasma after the coffee intake.
Neuronal cells are competent in sensing nanotopographical features of their microenvironment. The perceived microenvironmental information will be “interpreted” by mechanotransductive processes and impacts on neuronal functioning and differentiation. Attempts to influence neuronal differentiation by engineering substrates that mimic appropriate extracellular matrix (ECM) topographies are hampered by the fact that profound details of mechanosensing/-transduction complexity remain elusive. Introducing omics methods into these biomaterial approaches has the potential to provide a deeper insight into the molecular processes and signaling cascades underlying mechanosensing/-transduction.

Supersonic cluster beam deposition (SCBD) allows the fabrication of nanostructured substrates characterized by a quantitatively controllable ECM-like nanoroughness that has been recently shown to foster neuron differentiation and maturation. Exploiting the capacity of SCBD, we characterized by a proteomic approach the differentiative behavior and neuronal maturation of neuron-like PC12 cells and hippocampal neurons induced by appropriate nanorough zirconia surfaces. We found that neonatal rat hippocampal neurons show accelerated and enhanced maturation and synaptogenesis on zirconia substrates by the earlier and stronger presence of synaptic markers, electrophysiological activity and a protein profile confirming an advanced state of neurogenic events. In accordance, the proteomic data suggest a strong involvement of cytoskeleton- and integrin adhesome-related processes. The same results were also obtained on PC12 cells suggesting furthermore an involvement of ILK, mTOR, Wnt, and calcium signaling in these nanotopography- and/or cell mechanics-related processes. Altogether, our results strongly suggest that tailored nanostructured substrates coupled to proteomic approaches may provide a unique strategy to identify novel hints for cell replacement strategies and tissue engineering to treat neurodegenerative diseases.
Proteomic mapping of cellular processes affected by the overexpression of Na+/Mg2+ exchanger SLC41A1 in HEK-293 cells.

Ivana Pilchova (1), Zuzana Tatarkova (2), Michal Cibulka (2), Maria Brodnanova (2), Peter Racay (1)(2), Martin Kolisek (1)

(1) Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Mala Hora 4D, Martin, Slovakia.

(2) Department of Medical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Mala Hora 4D, Martin, Slovakia.

A cross-talk between cellular Mg2+ transport mechanisms define the intracellular Mg homeostasis. Na+/Mg2+ exchanger (NME) SLC41A1 (A1) is the only known Mg2+ transporter integral to plasma membrane able to conduct Mg2+ efflux. The overexpression of A1 enhances cellular Mg2+ extrussion and leads to intracellular hypomagnesemia – the pathophysiological state associated with broad spectrum of serious illnesses in human (mammals).

Design of this study is based on the comparative proteomic profiling of HEK-293 cells with inducible overexpression of A1. The aim was to profile proteome changes evoked by inducing intracellular hypomagnesemia (by overexpressing A1) and to reveal the most affected cellular metabolic pathways. Significant increase of A1 protein amount was observed already 6 hours after induction of A1 overexpression and the A1 accumulation continued with prolonged incubation time. Visible changes at the level of cellular morphology were obvious 16 hours after induction of A1 overexpression, while the negative effect on cell viability manifested 48 hours after induction of A1 overexpression.

In total, 45 significantly deregulated proteins predominantly with binding and catalytic activity were identified. The string analysis identified as the most affected cellular pathways those covering the cellular stress response, detoxification of reactive oxygen species and pathways related to neurodegenerative processes. Further experimentation revealed that A1 overexpression induced intracellular hypomagnesemia is associated with increase of total antioxidant capacity of the cell and suppression of the total glutathion level. Moreover, the dysregulation of enzymatic activities of individual mitochondrial respiratory complexes outlines the link between Mg2+ homeostasis and its impact on mitochondrial function.

These data in accordance with previously published data clearly demonstrate link between functional status of A1 and the crucial cellular processes involved in mitochondrial homeostasis. However, yet the precise molecular mechanism(s) behind this link remain(s) elusive.

Supported by the APVV-16-0033 and VEGA1/0554/19 projects.
P48

Proteomic mapping of cellular processes affected by the overexpression of Na+/Mg2+ exchanger SLC41A1 in HEK-293 cells.

Ivana Pilchova (1), Zuzana Tatarkova (2), Michal Cibulka (2), Maria Brodnanova (2), Peter Racay (1)(2), Martin Kolisek (1)

(1) Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Mala Hora 4D, Martin, Slovakia.
(2) Department of Medical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Mala Hora 4D, Martin, Slovakia.

A cross-talk between cellular Mg2+ transport mechanisms define the intracellular Mg homeostasis. Na+/Mg2+ exchanger (NME) SLC41A1 (A1) is the only known Mg2+ transporter integral to plasma membrane able to conduct Mg2+ efflux. The overexpression of A1 enhances cellular Mg2+ extrussion and leads to intracellular hypomagnesemia – the pathophysiological state associated with broad spectrum of serious illnesses in human (mammals).

Design of this study is based on the comparative proteomic profiling of HEK-293 cells with inducible overexpression of A1. The aim was to profile proteome changes evoked by inducing intracellular hypomagnesemia (by overexpressing A1) and to reveal the most affected cellular metabolic pathways. Significant increase of A1 protein amount was observed already 6 hours after induction of A1 overexpression and the A1 accumulation continued with prolonged incubation time. Visible changes at the level of cellular morphology were obvious 16 hours after induction of A1 overexpression, while the negative effect on cell viability manifested 48 hours after induction of A1 overexpression.

In total, 45 significantly deregulated proteins predominantly with binding and catalytic activity were identified. The string analysis identified as the most affected cellular pathways those covering the cellular stress response, detoxification of reactive oxygen species and pathways related to neurodegenerative processes. Further experimentation revealed that A1 overexpression induced intracellular hypomagnesemia is associated with increase of total antioxidant capacity of the cell and suppression of the total glutathion level. Moreover, the dysregulation of enzymatic activities of individual mitochondrial respiratory complexes outlines the link between Mg2+ homeostasis and its impact on mitochondrial function.

These data in accordance with previously published data clearly demonstrate link between functional status of A1 and the crucial cellular processes involved in mitochondrial homeostasis. However, yet the precise molecular mechanism(s) behind this link remain(s) elusive.

Supported by the APVV-16-0033 and VEGA1/0554/19 projects.

P49

Quantitative analysis of OCT-A foveal scans from healthy volunteers and AMD patients according to signal amount and dispersion of caliber-classified vessels.

Marco Righi (1), Alessandro Arrigo (2), Luisa Pierro (2)

(1) CNR-Institute of Neuroscience, via Vanvitelli 32, 20129, Milan, Italy.
(2) Department of Ophthalmology, Vita-Salute University, San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milan, Italy.

Description of vascular angioarchitectures observed in different plexa of physio-pathological retinas is a complex task. Recently, a new analytical approach based on the amount and dispersion of caliber-classified vessels was validated in tumors and more physiological samples. Here we applied this image-analysis approach to retinal tissues developing a semi-automatic quantitative protocol for descriptions of microvascular angioarchitectures on the basis of a small set of interdependent parameters. The ensuing analyses of automatically segmented retinal tissues from OCT-A scans were carried out on physiological eyes and on a minimal sample of untreated patients suffering from macular degeneration (AMD). Healthy volunteers showed a very close quantification for both controlateral eyes, although we could trace differences among individuals in results from the deep retinal plexus. In AMD patients we highlighted the expected increase in the microvascularization of choriocapillar tissues and, in some cases, quantified a reduction in vascular amounts of the corresponding deep plexus. This reduction was linked to increased microvascular distances thus betraying a local anti-angiogenic response. Considering that vascular alterations in retinal samples are a hallmark of different neurodegenerative diseases, this new approach candidate itself as a potential tool to investigate and monitor vascular alterations along with disease progression.
Spine developmental defect and cognitive impairment in Rab39b mouse, model for human Intellectual Disability

Maria Lidia Mignogna (1), Stefano Musardo (2), Camilla Bellone (2), Patrizia D'Adamo (1)

(1) IRCCS Ospedale San Raffaele, Via Olgettina 58, 20126, Milan, Italy.
(2) University of Geneva, CMU, Rue Michel-Servet 1, 1211, Geneva, Switzerland.

Mutations on RAB39B gene cause Intellectual Disability (ID), and it results in comorbidity with Autism Spectrum Disorders (ASD) or early-Parkinson Disease. RAB39B is a neuronal RAB GTPase which drives the GluA2/GluA3 AMPA receptor trafficking throughout the secretory pathway, to achieve the correct AMPAR composition at the neuronal glutamatergic post-synaptic terminals. After a detailed in vitro RAB39B characterization, a Rab39b KO mouse model was generated to establish the mechanistic link between the lack of RAB39B and ID. Preliminary data confirm that the absence of RAB39B alters the GluA2/GluA3 AMPAR trafficking across neuronal cellular compartments leading as a final step to a Ca2+-permeable AMPAR and hyper-excitable glutamatergic synapses. This scenario prompts to an altered actin-mediated morphological organization of dendritic spines, resulting in a long-lasting restless and immature morphology. Finally, the behavioral characterization shows hyperactive behavior and lack of cognitive flexibility, in agreement with the molecular and morphological defects. These results highlight the role of GluA2/GluA3 AMPAR RAB39B-mediated trafficking in covering the gap in the knowledge of the mechanisms regulating the maturation of spines, which is the significant signature in the majority of ID models.
The alternative splicing regulation of the schizophrenia-associated TNIK gene during neuronal differentiation

Valentina Gumina (1), Claudia Colombrita (1), Claudia Fallini (2), Patrizia Bossolasco (1), Annamaria Maraschi (1), John E. Landers (2), Vincenzo Silani (1)(3), Antonia Ratti (1)(4)

(1) Istituto Auxologico Italiano, IRCCS, Department of Neurology-Stroke Unit and Laboratory of Neuroscience, Milan, Italy.
(2) Department of Neurology, University of Massachusetts Medical School, Worcester, United States of America.
(3) Department of Pathophysiology and Transplantation, “Dino Ferrari” Center, Università degli Studi di Milano, Milan, Italy.
(4) Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Milan, Italy.

TNIK gene, a genetic risk factor for schizophrenia, encodes for a Ser/Thr kinase highly expressed in the brain, regulating cytoskeleton dynamics and synapse formation. We previously demonstrated that the alternative splicing of TNIK exon 15, encoding for an in-frame 29 aminoacidic region, is regulated by TDP-43, an ubiquitous RNA-binding protein (RBP) associated to amyotrophic lateral sclerosis and frontotemporal dementia, which promotes exon 15 skipping. Although both TNIK isoforms including/excluding exon 15 have been described, their tissue-expression and their biological significance are unknown. Here, we further characterized TNIK alternative exon 15 splicing in human adult tissues and during neuronal differentiation in vitro of human iPSCs. Our data showed that TNIK exon 15 inclusion is the main splicing event in human brain, spinal cord and skeletal muscle, suggesting a prevalent neuronal function of exon 15-containing (TNIKex15) isoforms. During neuronal differentiation of iPSCs, TNIK exon 15 inclusion increased, independently of TDP-43 protein content. By studying the possible interplay of TDP-43 with brain-specific splicing factors, we found that the neuronal NOVA-1 RBP competitively inhibits TDP-43 skipping activity on TNIK pre-mRNA. To investigate the biological significance of the 29 aminoacidic sequence encoded by exon 15, we focused on TNIK regulatory role in cytoskeleton organization, by overexpressing TNIKex15 and TNIKΔ15 protein isoforms in HEK293T cells and primary cortical neurons. We found that TNIKΔ15 isoform did not induce the HEK293T cell morphology changes and the defective neurite development of primary cortical neurons already described for the TNIK full-length protein, suggesting that the exon 15-encoded sequence is important for TNIK-mediated cytoskeleton organization. In conclusion, our results suggest that TNIK exon 15 alternative splicing is tightly regulated in human brain and during neuronal differentiation in vitro and a dysregulation of this splicing event may contribute to defective neuronal activities that may account for the cognitive deficits observed in schizophrenia.
P52

The assessment of the autophagy markers expression in the rat brain under severe hypobaric hypoxia

Anna Churilova (1), Mihail Zenko (1)

(1) Pavlov Institute of Physiology of Russian Academy of Sciences, Makarova emb. 6, St-petersburg, Russia.

Autophagy is an intracellular regulated mechanism of degradation of cytoplasmic molecules and organelles in autophagosomes and is thought to be one of the key mechanisms for maintaining intracellular homeostasis during various stresses, including hypoxia. According to current literature, autophagy can be associated either with death or survival of neurons under hypoxia/ischemia challenge what depends to a large extent on the type of autophagy (macroautophagy or chaperone-mediated) being activated. So far, the question of whether the increased activity of autophagy in response to injurious exposure is a mechanism of cell death or a part of an adaptive strategy aimed at eliminating damaged organelles, proteins and toxic substances is under debate. The aim of the present study was to characterize the activation rate of two different types of autophagy (macro- and chaperone-mediated) in response to hypoxia in the paradigm of severe hypobaric hypoxia (SHH, 180 mm Hg, 3 hours). The expression of key markers of the macroautophagy (LC3) and chaperone-mediated autophagy (LAMP2A) has been estimated after SHH alone or SHH in combination with administration of autophagy inhibitor chloroquine in the rat neocortex and hippocampus using immunohistochemistry. As chloroquine prevents the fusion of autophagosome and lysosome it has been used as an inhibitor of macroautophagy. The data obtained are important for understanding the interaction between the pathological and adaptive processes competing in the cell under hypoxia and have translational potential for development of the new approaches to treatment of post-hypoxic states.

The work is supported by RFBR grant № 19-04-01152.
The effect of a coenzyme Q10 deficiency on neuronal cell lysosomal acidity

Robert Heaton (1), Iain Hargreaves (1)(2), Simon Heales (2), Khalid Rahman (1)

(1) school of Pharmacy, Liverpool John Moores University, Byrom St, Liverpool, United Kingdom.
(2) Neurometabolic Unit, National Hospital, Great Ormond Street, Queen Square and Enzyme Unit, Department of Paediatric Laboratory Medicine, London, United Kingdom.

Together with the mitochondria, lysosomes are also a major site of coenzyme Q10 (CoQ10) localisation within the cell where it plays an essential role in the transport of protons across the lysosomal membrane. Proton translocation into the interior of the lysosome is linked to the activity of the tentative electron transport (ETC) chain of this organelle where CoQ10 is believed to act as both an electron carrier and proton translocator. The acidic environment maintained by the ETC is essential for the activity of the lysosomal enzymes which are acidic hydrolases and active at acidic pH rather than the neutral, pH of the cytosol. The inability to maintain the acidic environment of the lumen would be expected to impair lysosomal activity and given the essential ‘housekeeping’ role these organelles perform, this would be anticipated to adversely impact upon cellular function. At present, no studies have assessed the effect of a CoQ10 deficiency on lysosomal acidity and therefore, this was the aim of the current investigation.

In order to investigate the effect of a neuronal cell CoQ10 deficiency on lysosomal function we established a pharmacologically induced CoQ10 deficiency in SH-SY5Y neuroblastoma cells by treatment with para-aminobenzoate (PABA). PABA treatment (1mM) induced a 46% decrease in cellular CoQ10 status. The effect of this CoQ10 deficiency was assessed on lysosomal acidity by incubating cells with Lysotracker red DND-99 and Lysosensor blue DND-167. The diminution in CoQ10 status was resulted in a decrease in fluorescence intensity (PABA treated: 884.424au and control: 1122.29au p<0.05) indicating an increase in lumen pH which was reversed by CoQ10 treatment (5µM).

In conclusion, these results indicate evidence of an impairment in lysosomal acidification as the result of a cellular CoQ10 deficiency. Therefore, lysosomal dysfunction may be an important factor to consider in diseases associated with a CoQ10 deficiency.
The effect of global brain ischemia on proteins of mitochondrial dynamics

Katarína Klačanová (1), Mária Kovalská (2), Mária Chomová (3), Ivana Pilchová (1), Peter Račay (1)(4)

(1) Division Neuroscience of Biomedical Center, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia, Malá Hora 4D, 036 01, Martin, Slovakia.
(2) Department of Histology and Embryology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia, Malá Hora 4, 036 01, Martin, Slovakia.
(3) Institute of Medical Chemistry, Biochemistry and Clinical Biochemistry, Faculty of Medicine, Comenius University in Bratislava, Slovakia, Sasinkova 2, 811 08, Bratislava, Slovakia.
(4) Department of Medical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia, Malá Hora 4D, 036 01, Martin, Slovakia.

Permanent brain damage caused by ischemia followed by reperfusion is a global health and socio-economic problem. Therefore, understanding of processes leading to neuronal cell death following ischemia/reperfusion injury of various types is of great interest of current neuroscience. Mitochondrial dysfunction is considered to be important mechanism involved in several serious human diseases, including neurodegenerative diseases, such as Parkinson’s and Alzheimer’s disease and ischemic neurodegeneration.

The aim of our work was to study impact of transient global brain ischemia on the expression of selected proteins involved in mitochondrial dynamics and mitochondria-associated membranes. We have focused our interest on Mfn2, DRP1, VDAC1 and GRP75 proteins performing the Western blot analysis of total cell extracts and mitochondria isolated from either cerebral cortex or hippocampus of experimental animals. In addition, analysis of Mfn2 intracellular localisation was performed using laser scanning confocal microscopy. We have shown that 15 min ischemia and 15 min ischemia followed by 1, 3, 24 and 72 h of reperfusion, was associated with significant decrease of Mfn2 in mitochondria isolated from cerebral cortex but not in hippocampal mitochondria. The translocation of Mfn2 to cytoplasm was documented immediately after global brain ischemia in neurones of cerebral cortex. This translocation was followed by decreased expression of Mfn2 during reperfusion. In addition, significantly elevated levels of VDAC1, were also documented in total cell extracts, isolated from hippocampus of rats after 15 min ischemia followed by 3 h of reperfusion, and from cerebral cortex of rats after 15 min ischemia followed by 72 h of reperfusion.

Our results have shown that release of Mfn2 from mitochondria that was observed in early periods of reperfusion might represent an important mechanism of mitochondrial dysfunction associated with neuronal dysfunction or death induced by global brain ischemia.

This work was supported by grants: APVV-16-0033 and VEGA 1/0171/18.
P55

The metabolic transition during neuronal maturation

Matteo Audano (1), Silvia Pedretti (1), Maurizio Crestani (1), Donatella Caruso (1), Emma De Fabiani (1), Nico Mitro (1)

(1) Università degli Studi di Milano, Dept. of Pharmacological and Biomolecular Sciences, Via Balzaretti, 9, Milan, Italy.

Energy metabolism is the set of reactions that leads to energy fuels oxidation. Mitochondria are the milestone of central energy metabolism being the main hub of principal metabolic pathways (i.e. oxidative glutaminolysis and fatty acid β-oxidation) and ATP production. For these reasons, such organelles are key regulators of neurogenesis, where they are crucial for neural progenitor exit from quiescence, proliferation and migration. On the other hand, less is known about mitochondria role in neuroblast maturation, the last step of neuron differentiation. In light of these premises, we investigated the role of central metabolism during neuron maturation. Our results indicated that mitochondrial function was upregulated in differentiated neurons compared to neuroblasts. Also, both glycolysis and glutaminolysis were increased, while β-oxidation was downregulated during neuron maturation. Metabolomic analyses confirmed these findings showing increased levels of several glycolysis metabolites, like glucose, glucose/fructose 6-phosphate, glyceraldehyde 3-phosphate/dihydroxyacetone phosphate, phosphoenolpyruvate pyruvate and lactate. In addition, we observed higher levels of glutamine, NADPH and malonyl-CoA in neurons compared to neuroblasts, suggesting increased fatty acid synthesis. This latter data was corroborated by reduced levels of several acyl-carnitines in differentiated compared to undifferentiated cells, which demonstrate a reduction of fatty acid oxidation. Next, we tested if one or more pathways of central energy metabolism was/were the driving force(s) of neuron maturation. The treatment with etomoxir, an antagonist of carnitine palmitoyl transferase 1a, the limiting step of β-oxidation, increased mitochondrial function and neuron maturation. On the other hand, neuroblasts exposed to glycolysis and glutaminolysis antagonists, such as 2-deoxyglucose and CB-839, showed lower mitochondrial activity and impaired capacity to differentiate into neurons. Taken together, these results demonstrate that a specific and coordinated rewiring of central energy metabolism occurs in the transition from neuroblasts to neuron to ensure proper maturation.
THE OLIGOSACCHARIDE OF GM1 GANGLIOSIDE ACTS AS A NEUROTROPHIC AGENT FOR NEURONAL DEVELOPMENT

Erika Di Biase (1), Margherita Maggioni (1), Giulia Lunghi (1), Maria Fazzari (1), Simona Prioni (1), Sandro Sonnino (1), Elena Chiricozzi (1)

(1) University of Milano, Via Fratelli Cervi 93, Segrate, Milan, Italy.

GM1 ganglioside, plays a pivotal role during neuronal development and its neurotrophic properties have been largely reported both in vitro and in vivo. In cultured neurons, the GM1 enrichment in plasma membrane microdomains contributes to the activation of neurotrophin receptors belonging to Trk family. This triggers a specific signaling cascade resulting in actin depolymerization, axon protrusion and elongation. Despite this evidence, the GM1 mechanism of action is still unknown. In neuroblastoma cells we demonstrated that GM1 oligosaccharide (OligoGM1) directly binds NGF specific receptor TrkA, triggering the TrkA-MAPK pathway activation which leads to neurodifferentiation and protection against neurotoxins. Here, we characterize OligoGM1 effect on the developmental process of mouse primary neurons. Time-lapse recordings of plated neurons showed that exogenously administered OligoGM1 enhances neuron clustering, arborization and networking. Accordingly, treated cells expressed increased level of specific neuronal markers. Moreover, the higher phosphorylation rate of FAK and Src proteins, the intracellular key regulators of neuronal motility, confirms OligoGM1 impact on the migration process. Beside the observed migratory phenotype, preliminary results suggest that in the presence of OligoGM1, neurons express higher amount of more complex gangliosides and lower level of simpler ones. Overall OligoGM1 showed to prompt neuronal maturation in culture. OligoGM1 effects was found to be due to an interaction with neuronal surface resulting in an early TrkA-MAPK pathway activation. Our data reveal that the GM1 specific role in neuronal differentiation and maturation is due to its oligosaccharide portion which, by interacting with the cell surface, triggers the activation of intracellular biochemical pathways responsible for neuronal migration, dendrites emission and axon growth.
The role of extracellular vesicles in the removal of aggregated TDP-43 responsible for ALS/FTD diseases

Elena Casarotto (1), Daisy Sproviero (2), Stella Gagliardi (2), Barbara Tedesco (1), Riccardo Cristofani (1), Veronica Ferrari (1), Marta Chierichetti (1), Paola Rusmini (1), Mariarita Galbiati (1), Cristina Cereda (2), Angelo Poletti (1), Valeria Crippa (1)

(1) Dipartimento di Scienze Farmacologiche e Biomolecolari (DiSFeB), Department of excellence 2018-2022, Università degli Studi di Milano, Via Balzaretti 9, Milan, Italy.
(2) Mondino Foundation – IRCCS, Via Mondino 2, Pavia, Italy.

Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) are two related neurodegenerative diseases, with a continuous clinical spectrum. A common feature between the two diseases is the abnormal cytoplasmic localization and the aggregation of the TAR DNA binding protein 43 (TDP-43), in affected cells (i.e both upper and lower motoneurons for ALS and neurons of the frontal and temporal lobes, for FTD). Pathological TDP-43 aggregates are mainly composed by its C-terminal fragments of 35 kDa (TDP-35) and 25 kDa (TDP-25), as a result of caspase 3-dependent cleavage. These species are highly aggregation-prone and are thought to be neurotoxic. Thus, the removal of TDP-35 or TDP-25 fragments is protective for cells. The clearance of aberrantly folded or misfolded proteins is mediated by the intracellular protein quality control (PQC) system, composed by chaperone/co-chaperone proteins, the ubiquitin proteasome system and the autophagy. Recent data underlined that also the extracellular secretory pathway, mainly represented by exosomes (EXOs) and microvesicles (MVs), might be involved in misfolded proteins clearance from affected cells.

We investigated the role of both EXOs and MVs in the secretion of TDP-43 and its C-terminal fragments, in the motoneuronal NSC34 cell model. Using an ultracentrifugation approach, we separated larger (MVs) from smaller (EXOs) vesicles. The vesicles were analysed by i) the NanoSight, Nanoparticle Tracking Analysis, to establish the size and the count, and ii) western blot analysis, to characterize the protein content. Our preliminary results show that all TDP-43 species are secreted in EVs, mainly in MVs. Very interestingly, we found that some PQC-components, involved in TDP-43s clearance, are present in EVs, suggesting an interplay between PQC and EVs.

GRANTS: Fondazione Cariplo, Italy (n. 2017_0747); Università degli Studi di Milano e piano di sviluppo UNIMI - linea B.
Transcytosis of Protein-based Nanoparticles to the Brain: A New Insight into the Role of Astroglia

David J Begley (1)

(1) Institute of Pharmaceutical Science, Kings College London, Franklin-Wilkins Building, 150 Stamford Street SE1 9NH, London, United Kingdom.

Human serum albumin (HSA) nanoparticles, modified with apolipoprotein E coating, cross the blood-brain barrier (BBB) \textit{in vivo} after intra-jugular injection. The biodegradable and non-antigenic nanoparticles were produced at a size of 200nm diameter using a desolvation method and their surface modified with ApoE.

Electron microscopy showed the brain intracellular localization of the modified nanoparticles 15 min after intra-jugular injection. Whereas unmodified HSA nanoparticles were not seen within the brain tissue. The BBB crossing ability of the modified nanoparticles is mediated by receptor-mediated endocytosis followed by transcytosis involving the LRP1 receptor as demonstrated \textit{in vitro}. However, the rapid speed of nanoparticle movement within the brain tissue remains surprising. Confocal microscopy confirmed electron microscopic findings, underlining the rapid movement of the modified HSA nanoparticles through the brain tissue following brain BBB endothelial cell internalization. Furthermore, it allowed for the precise quantification of the number of nanoparticles per cell in the brain and calculation of injected dose subsequently found in the brain. Surface modified HSA nanoparticles were located over 4μm from the closest vessel 15 min after injection.

With an average size of 200 nm the nanoparticles are far too big to travel freely through the highly tortuous extracellular space. Furthermore, the modified nanoparticles were never seen extracellularly within brain, except for the basal lamina. Astrocytic end-feet covering the brain endothelial cells are well positioned to mediate further transport through the brain tissue. Published cytoplasmic flow rates of 2-16 mm/hr would explain the rapid rate of intracellular movement observed. Furthermore, the modified HSA nanoparticles were highly concentrated in the astrocytic end-feet 5 min after injection, shown by confocal microscopy, and localized in the distal astrocytic processes 15 min after injection, as shown by 3D reconstruction. Within 30 minutes the HSA nanoparticles are distributed within the cytoplasm of neurons. These observations lead to a re-evaluation of the role of astrocytes in the rapid movement of large constructs within the brain.
Human serum albumin (HSA) nanoparticles, modified with apolipoprotein E coating, cross the blood-brain barrier (BBB) in vivo after intra-jugular injection. The biodegradable and non-antigenic nanoparticles were produced at a size of 200nm diameter using a desolvation method and their surface modified with ApoE. Electron microscopy showed the brain intracellular localization of the modified nanoparticles 15 min after intra-jugular injection. Whereas unmodified HSA nanoparticles were not seen within the brain tissue. The BBB crossing ability of the modified nanoparticles is mediated by receptor-mediated endocytosis followed by transcytosis involving the LRP1 receptor as demonstrated in vitro. However, the rapid speed of nanoparticle movement within the brain tissue remains surprising. Confocal microscopy confirmed electron microscopic findings, underlining the rapid movement of the modified HSA nanoparticles through the brain tissue following brain BBB endothelial cell internalization. Furthermore, it allowed for the precise quantification of the number of nanoparticles per cell in the brain and calculation of injected dose subsequently found in the brain. Surface modified HSA nanoparticles were located over 4μm from the closest vessel 15 min after injection. With an average size of 200 nm the nanoparticles are far too big to travel freely through the highly tortuous extracellular space. Furthermore, the modified nanoparticles were never seen extracellularly within brain, except for the basal lamina. Astrocytic end-feet covering the brain endothelial cells are well positioned to mediate further transport through the brain tissue. Published cytoplasmic flow rates of 2-16 mm/hr would explain the rapid rate of intracellular movement observed. Furthermore, the modified HSA nanoparticles were highly concentrated in the astrocytic end-feet 5 min after injection, shown by confocal microscopy, and localized in the distal astrocytic processes 15 min after injection, as shown by 3D reconstruction. Within 30 minutes the HSA nanoparticles are distributed within the cytoplasm of neurons. These observations lead to a re-evaluation of the role of astrocytes in the rapid movement of large constructs within the brain.
<table>
<thead>
<tr>
<th>PAGE</th>
<th>SESSION</th>
<th>TYPE OF PRESENTATION</th>
<th>TITLE</th>
<th>AUTHORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>PL1</td>
<td>Plenary Lecture</td>
<td>PRINCIPLES OF ASTROGLIOPATHOLOGY: FROM REACTIVITY TO ATROPHY AND DEGENERATION</td>
<td>Verkhratsky Alexei</td>
</tr>
<tr>
<td>59</td>
<td>PL2</td>
<td>Plenary Lecture</td>
<td>AXONAL TRANSPORT AS A THERAPEUTIC TARGET</td>
<td>Schiavo Giampietro</td>
</tr>
<tr>
<td>60</td>
<td>YSLA1</td>
<td>YSLA Lecture</td>
<td>PRESYNAPTIC NANOMACHINES: REGULATION OF THE QUANTAL RELEASE OF GLUTAMATE</td>
<td>Martineau Magalie</td>
</tr>
<tr>
<td>61</td>
<td>YSLA2</td>
<td>YSLA Lecture</td>
<td>EXPLORING MECHANISMS OF NEURON-GLIAL SIGNALLING AND METABOLIC INTERACTIONS</td>
<td>Saab Aiman</td>
</tr>
<tr>
<td>62</td>
<td>PL3</td>
<td>Bachelard Award Lecture</td>
<td>ESN - A KEY START TO MY SCIENTIFIC AND ACADEMIC CAREER</td>
<td>Fredman Pam</td>
</tr>
<tr>
<td>63</td>
<td>S1.1</td>
<td>Symposium</td>
<td>NEUROPLASTICITY IN AN ANIMAL MODEL OF SPS: EVIDENCE FROM RATS LACKING THE SEROTONIN TRANSPORTER</td>
<td>Fumagalli Fabio, Telese Francesca, Bottan Giorgia, Caffino Lucia</td>
</tr>
<tr>
<td>64</td>
<td>S1.2</td>
<td>Symposium</td>
<td>THE CONTRIBUTION OF ENVIRONMENTAL SENSITIVITY TO VULNERABILITY TO COCAINE ADDICTION: A PRECLINICAL STUDY</td>
<td>Homberg Judith, Seegers Stephanie, Verheij Michel</td>
</tr>
<tr>
<td>65</td>
<td>S1.3</td>
<td>Symposium</td>
<td>SENSORY PROCESSING SENSITIVITY AND DRUG USE RECOVERY PATHWAYS</td>
<td>Mary-krause Murielle, Herranz Joel, Melchior Maria</td>
</tr>
<tr>
<td>66</td>
<td>S1.4</td>
<td>Symposium</td>
<td>SENSORY-PROCESSING SENSITIVITY IN SUBSTANCE USE DISORDERS AND ITS RELATION TO COGNITION AND BEHAVIOR</td>
<td>Quednow Boris</td>
</tr>
<tr>
<td>67</td>
<td>S2.1</td>
<td>Symposium</td>
<td>ARE OLIGODENDROCYTE PROGENITORS ALL BORN EQUAL? A LESSON FROM A MICROCEPHALY MODEL</td>
<td>Boda Enrica</td>
</tr>
<tr>
<td>68</td>
<td>S2.2</td>
<td>Symposium</td>
<td>POST-TRANSCRIPTIONAL REGULATION IN OLIGODENDROCYTES: THE STRATEGY OF MIR-125A-3P</td>
<td>Lecca Davide, Marangon Davide, Boda Enrica, Parolisi Roberta, Negri Camilla, Montarolo Francesca, Perga Simona, Giorgi Corinna, Buffo Annalisa, Abbraccchio Maria Pia</td>
</tr>
<tr>
<td>69</td>
<td>S2.3</td>
<td>Symposium</td>
<td>ENHANCING D-ASPARTATE SIGNALING TO PROMOTE REMYELINATION</td>
<td>De Rosa Valeria, Agnese Secondo, Anna Pannacionne, Roselia Ciccone, Luigi Formisano, Natalia Guida, Roberta Crispino, Annalisa Fico, Roman Polishchuk, Antim D’Aniello, Lucio Annunziato, Francesca Boscia</td>
</tr>
<tr>
<td>70</td>
<td>S2.4</td>
<td>Symposium</td>
<td>DECLINE OF OLIGODENDROGENESIS IN THE AGEING BRAIN</td>
<td>Rivera Andrea Domenico, Pieropan Francesca, Arthur Buttf</td>
</tr>
<tr>
<td>71</td>
<td>S3</td>
<td>Symposium</td>
<td>MY FIRST CONFERENCE – HOW TO MAKE THE BEST OF IT</td>
<td>Blumrich Eva maria, Pieropev Frevesca, Orthus lutt</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>----------</td>
<td>----------------------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>72</td>
<td>S4.1</td>
<td>Symposium</td>
<td>MOLECULES CAPABLE TO INDUCE NEUROPROTECTION VIA LYSOPLAGY ACTIVATION</td>
<td>Rusmini Paola, Cortese Katia, Crippa Valeria, Cristofani Riccardo, Ferrari Veronica, Tedesco Barbara, Casarotto Elena, Chierichetti Marta, Messi Ello, Piccoletta Margherita, Galliati Mariarita, Basso Manuela, Garre' Massimiliano, Morelli Elena, Vaccari Thomas, Poletti Angelo</td>
</tr>
<tr>
<td>73</td>
<td>S4.2</td>
<td>Symposium</td>
<td>GLUCOCEREBROSIDASE AND PARKINSON DISEASE</td>
<td>Schapira Anthony</td>
</tr>
<tr>
<td>74</td>
<td>S4.3</td>
<td>Symposium</td>
<td>INHIBITING AMYLOID PROTEIN AGGREGATION RELEASES LYSOSOMAL-AUTOHAGIC DYSFUNCTION AND PROTECTS AGAINST NEURODEGENERATION IN LYSOSOMAL STORAGE DISEASES</td>
<td>Monaco Antonio, Sorrentino Nicola Cristina, Casace Vincenzo, Sambri Irene, De Leonibus Elvira, Bilan Gal, Fraldi Alessandro</td>
</tr>
<tr>
<td>75</td>
<td>S4.4</td>
<td>Symposium</td>
<td>AUTOPHAGY AND NEURODEGENERATION</td>
<td>Rubinszttein David</td>
</tr>
<tr>
<td>76</td>
<td>S5.1</td>
<td>Symposium</td>
<td>FROM THE NOSE TO THE BRAIN: SEMAPHORIN SIGNALLING IN THE CONTROL OF GNRH NEURON DEVELOPMENT</td>
<td>Cariboni Anna, Oleari Roberto, Lettieri Antonella, Paganoni Alyssa</td>
</tr>
<tr>
<td>77</td>
<td>S5.2</td>
<td>Symposium</td>
<td>UNDERSTANDING THE MOLECULAR MECHANISMS OF ANGIOGENESIS IN THE BRAIN AND RETINA</td>
<td>Fantin Alessandro</td>
</tr>
<tr>
<td>78</td>
<td>S5.3</td>
<td>Symposium</td>
<td>NON-MONOTONIC REGULATION OF GENE EXPRESSION, NEURAL PROGENITOR FATE AND BRAIN GROWTH BY THE CHROMATIN REMODELLER CHD8</td>
<td>Hurle Sham, Mohan Conor, Sutterlin Philipp, Pagani Marco, Ellegood Jacob, Gallouera Alberto, Rudari Fabrizio, Lherch Jaison, Gozzi Alessandro, Fernandes Cathy, Basso M. Albert</td>
</tr>
<tr>
<td>79</td>
<td>S5.4</td>
<td>Symposium</td>
<td>MOLECULAR CONTROL OF CORTICAL LAYER DEVELOPMENT BY TRANSMEMBRANE SEMAPHORINS</td>
<td>Verhagen Marieke, Lemstra Suzanne, Zwaan Melissa, Reihberg Kati, Adolfs Youri, Pasterkamp Jeroen</td>
</tr>
<tr>
<td>80</td>
<td>S6.1</td>
<td>Symposium</td>
<td>HOW DOES AN OXYTOCIN TREATMENT IN EARLY LIFE IMPACT SOCIAL BEHAVIOR AND HIPPOCAM-PAL ALTERATIONS IN MAGEL2 DEFICIENT MICE?</td>
<td>Bertoni Alessandra, Gaillard Stephanie, Tyzio Roman, Diabira Diabé, Vaidyanathan S Radhika, Matarazzo Valery, Hammock Elizabeth, Chini Bice, Galarsa Jean-luc, Muscatelli Françoise</td>
</tr>
<tr>
<td>81</td>
<td>S6.2</td>
<td>Symposium</td>
<td>OXYTOCIN SIGNALING IN THE CENTRAL AMYGDALA MODULATES EMOTION DISCRIMINATION IN MICE</td>
<td>Papaleo Francesco</td>
</tr>
<tr>
<td>82</td>
<td>S6.3</td>
<td>Symposium</td>
<td>INTERPLAY BETWEEN OXYTOCIN AND SENSORY SYSTEMS IN ORCHESTRATION OF SOCIAL BEHAVIOUR</td>
<td>Grinevich Valery</td>
</tr>
<tr>
<td>83</td>
<td>S6.4</td>
<td>Symposium</td>
<td>PROLONGED OPTOGENETIC ACTIVATION OF OXYTOCIN NEURONS IN GROUPS OF MICE INCREASES PROSOCIAL AND AGONISTIC BEHAVIORS</td>
<td>Shemesh Yair, Anpilov Sergey, Chen Alon</td>
</tr>
<tr>
<td>84</td>
<td>S7.1</td>
<td>Symposium</td>
<td>AXONAL METABOLIC SUPPORT AND ENERGY DYNAMICS IN ACTIVE WHITE MATTER TRACTS</td>
<td>Trevisiol Andrea, Kusch Kathrin, Nave Klaus, Hirrlinger Johannes</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>----------------------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>85</td>
<td>S7.2</td>
<td>Symposium</td>
<td>CELLULAR MECHANISMS REGULATING AXONAL ENERGY METABOLISM IN COMPACT WHITE MATTER</td>
<td>Saab Aiman</td>
</tr>
<tr>
<td>86</td>
<td>S7.3</td>
<td>Symposium</td>
<td>CORRELATION BETWEEN ACTIVITY-RELATED CHANGES IN INTRACELLULAR SODIUM AND ATP IN MOUSE HIPPOCAMPAL NEURONS</td>
<td>Rose Christine R.</td>
</tr>
<tr>
<td>87</td>
<td>S7.4</td>
<td>Symposium</td>
<td>CELL TYPE SPECIFICITY OF NEUROVASCULAR COUPLING IN CEREBRAL CORTEX</td>
<td>Thunemann Martin</td>
</tr>
<tr>
<td>88</td>
<td>S8.1</td>
<td>Symposium</td>
<td>PHOTOCHROMIC MODULATORS OF CYS-LOOP RECEPTORS</td>
<td>Bregestovski Piotr, Maleeva Galina, Rustler Karin, Petukhova Elena, Nin-hill Alba, Alfonso-Prieto Mercedes, Rovira Carme, Gorostiza Pau</td>
</tr>
<tr>
<td>89</td>
<td>S8.2</td>
<td>Symposium</td>
<td>FROM NEUROTOXIC PEPTIDES AND PROTEINS TO ENDOSOMAL MODULATORS OF CYS-LOOP RECEPTORS</td>
<td>Tsetlin Victor, Kashcheverov Igor, Utkin Yuri</td>
</tr>
<tr>
<td>90</td>
<td>S8.3</td>
<td>Symposium</td>
<td>MOLECULAR INTERACTIONS OF 5-HT3 RECEPTORS</td>
<td>Lummis Sarah</td>
</tr>
<tr>
<td>91</td>
<td>S8.4</td>
<td>Symposium</td>
<td>ALLOSTERIC REGULATION OF PENTAMERIC LIGAND-GATED ION CHANNELS BY PHOSPHOLIPIDS</td>
<td>Ulen Chris</td>
</tr>
<tr>
<td>92</td>
<td>S9.1</td>
<td>Symposium</td>
<td>ADNP/NAP (CP201): FROM GENE TO CLINICAL DEVELOPMENT</td>
<td>Gozes Illana</td>
</tr>
<tr>
<td>93</td>
<td>S9.2</td>
<td>Symposium</td>
<td>CLINICAL PRESENTATION OF A COMPLEX NEURODEVELOPMENTAL DISORDER CAUSED BY MUTATIONS IN ADNP</td>
<td>Kooy Frank</td>
</tr>
<tr>
<td>94</td>
<td>S9.3</td>
<td>Symposium</td>
<td>DE HUMANI CORPORIS FABRICA: ORGANOID-BASED DECONVOLUTION OF NEUROPSYCHIATRIC DISORDERS AT SINGLE CELL RESOLUTION</td>
<td>Testa Giuseppe</td>
</tr>
<tr>
<td>95</td>
<td>S9.4</td>
<td>Symposium</td>
<td>A TRANSCRIPTION FACTOR IMPlicated IN AUTISM LOCALLY CONSTAINS CHROMATIN LOOPING</td>
<td>Lucas Kasaj, Fabio Mohn, Marc Bühler</td>
</tr>
<tr>
<td>96</td>
<td>S9.5</td>
<td>Symposium</td>
<td>DE NOVO AND INTER-TISSUE SOMATIC MOSAICISM OF ADNP MUTATIONS IN AUTISTIC INDIVIDUALS</td>
<td>Mohiuddin Mohiuddin, Germain Pierre-luc, Pallotta Danila, Hacohen Kleiman Gal, Grigg Iris, Van Dijck Anke, Cappuyns Elisa, Kooy Frank, Gozes Illana, Testa Giuseppe, Marusic Zlatko, Pearson Christopher E</td>
</tr>
<tr>
<td>97</td>
<td>S10.1</td>
<td>Symposium</td>
<td>HOW TO MAKE MONEY WITH A PHD - INTRODUCTORY TALK: GENERAL IDEAS ON CAREER PLANNING</td>
<td>Blumrich Eva-maría</td>
</tr>
<tr>
<td>98</td>
<td>S10.2</td>
<td>Symposium</td>
<td>GRADUATED AND NOW? - A PERSONAL REVIEW ABOUT WORKING IN THE INDUSTRY</td>
<td>Bulcke Felix</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>99</td>
<td>S10.3</td>
<td>Symposium</td>
<td>STARTING A CAREER IN ACADEMIA</td>
<td>Prinetti Alessandro</td>
</tr>
<tr>
<td>100</td>
<td>S10.4</td>
<td>Symposium</td>
<td>FROM SCIENCE TO SCIENCE PUBLISHING: OPPORTUNITIES AND CHALLENGES</td>
<td>Turner Anthony J, Nalivaeva Natalia N, Jones Jackie</td>
</tr>
<tr>
<td>102</td>
<td>S11.2</td>
<td>Symposium</td>
<td>FROM DYSFUNCTION OF PINK1 PARKIN-MEDIATED MITOCHONDRIAL QUALITY CONTROL TO PARKINSON’S DISEASE.</td>
<td>Cotti Olga</td>
</tr>
<tr>
<td>103</td>
<td>S11.3</td>
<td>Symposium</td>
<td>FUNCTIONAL GENOMIC ANALYSIS UNCOVERS MITOPHAGY REGULATORS ASSOCIATED WITH PARKINSON’S DISEASE RISK</td>
<td>Plun-Favreau Helene</td>
</tr>
<tr>
<td>104</td>
<td>S11.4</td>
<td>Symposium</td>
<td>DECODING PINK1/PARKIN SIGNALLING IN PARKINSON’S DISEASE.</td>
<td>Miratul Muqit</td>
</tr>
<tr>
<td>105</td>
<td>S12.1</td>
<td>Symposium</td>
<td>THE NMDA RECEPTOR CO-Agonist D-Serine IS ESSENTIAL FOR DOPAMINE MODULATIONS OF PREFRONTAL NEURONAL ACTIVITY AND COGNITIVE FUNCTION</td>
<td>Mothet Jean-Pierre</td>
</tr>
<tr>
<td>106</td>
<td>S12.2</td>
<td>Symposium</td>
<td>LEARNING FROM FAILURES: A NOVEL FRAMEWORK FOR PRESYNAPTIC PLASTICITY</td>
<td>Tong Rudi, Emptage Nigel</td>
</tr>
<tr>
<td>107</td>
<td>S12.3</td>
<td>Symposium</td>
<td>NMDA RECEPTOR C-TERMINAL DOMAIN SIGNALING IN HEALTH AND DISEASE</td>
<td>Hardingham Giles</td>
</tr>
<tr>
<td>108</td>
<td>S12.4</td>
<td>Symposium</td>
<td>EMERGENCE OF Mtor-DEPENDENT PROTEIN TRANSLATION IS CONTROLLED BY NON-CONVENTIONAL NMDA RECEPTORS</td>
<td>Conde-dusman Maria Jose, Dey Partha Narayan, Garcia-rabaneda Luis, Elia-zudaire Oscar, Briz Victor, Perez-otazo Isabel</td>
</tr>
<tr>
<td>109</td>
<td>S13.1</td>
<td>Symposium</td>
<td>BRAIN METABOLIC ALTERATIONS IN NEURONAL CEROID LIPOFUSCINOSIS JUVENILE CLN7 BATTEN DISEASE</td>
<td>Lopez-fabuel Irene, Buonelmonte Costantina, Bonora Nico, Storch Stephan, Mole Sara, Almeida Angeles, Bolanos Juan P.</td>
</tr>
<tr>
<td>110</td>
<td>S13.2</td>
<td>Symposium</td>
<td>APC/C-CDH1 REGULATES X FRAGILE PROTEIN FMRF AND DENDRITE STABILITY DURING BRAIN DEVELOPMENT</td>
<td>Veronica Bobo-jimenez, Silvia Gomila, Juan P Bolaños, Angeles Almeida</td>
</tr>
<tr>
<td>111</td>
<td>S13.3</td>
<td>Symposium</td>
<td>LYSOSOMAL DISORDERS PROVIDE VALUABLE INSIGHT INTO NEURODEGENERATIVE CONDITIONS</td>
<td>Heales Simon</td>
</tr>
<tr>
<td>112</td>
<td>S13.4</td>
<td>Symposium</td>
<td>THE ROLE OF CHOLESTEROL METABOLISM IN HUNTINGTON’S DISEASE: FROM MOLECULAR MECHANISM TO THERAPEUTICS</td>
<td>Valenza Marta, Biolini Giulia, Vezzoli Elena, Pederzoli Francesca, Maniezzi Claudia, Talpo Francesca, Biella Gerardo, Falqui Andrea, Ruozzi Barbara, Tosi Giovanni, Cattaneo Elena</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>113</td>
<td>S14.1</td>
<td>Symposium</td>
<td>THE ADNP-DEFICIENT MOUSE MODELS SYNAPTIC AND BEHAVIORAL PHENOTYPES OF AN AUTISM-LIKE SYNDROME</td>
<td>Sragogovich Shlomo, Hacothen-kleiman Gal, Gozes Illana</td>
</tr>
<tr>
<td>114</td>
<td>S14.2</td>
<td>Symposium</td>
<td>METABOLIC HETEROGENEITY OF ASTROCYTES IN GREY AND WHITE MATTER</td>
<td>Köhler Susanne, Winkler Ulrike, Hirrlinger Johannes</td>
</tr>
<tr>
<td>115</td>
<td>S14.3</td>
<td>Symposium</td>
<td>MATERNAL HYPERHOMOCYSTEINEMIA DISTURBS DEVELOPMENT OF BRAIN CORTEX AND HIPPOCAMPUS AND AFFECTS MEMORY IN RAT OFFSPRING</td>
<td>Shcherbitskaia Anastasiia, Vasilev Dmitry, Tumanova Natalia, Milyutina Julia, Zalozyiyya Irina, Nalievea Natalia, Aruljunnay Alexander, Zhuravin Igor</td>
</tr>
<tr>
<td>116</td>
<td>S14.4</td>
<td>Symposium</td>
<td>IDENTIFICATION OF THE ANTIGEN RECOGNIZED IN VITRO BY RHIM22, A REMYELINATION-PROMOTING HUMAN MONOCLONAL ANTIBODY</td>
<td>Cabitita Livia, Grassi Sara, Prioni Simona, Maur Laura, Ciampa Maria Grazia, Zorina Yana, Sonnino Sandro, Piniatti Alessandro</td>
</tr>
<tr>
<td>117</td>
<td>S15.1</td>
<td>Symposium</td>
<td>LONG-LASTING IMPAIRMENT OF NEUROPLASTIC GENE EXPRESSION AS A MECHANISM OF COGNITIVE DEFICIT CAUSED BY NEONATAL LPS EXPOSURE</td>
<td>Trofimov Alexander, Zubareva Olga, Schwarz Alexander, Veniaminovova Ekatkerina, Formalont Kevin, Klimenko Victor</td>
</tr>
<tr>
<td>118</td>
<td>S15.2</td>
<td>Symposium</td>
<td>GM1 OLIGOSACCHARIDE MODULATION OF CALCIUM SIGNALING IN NEURONAL FUNCTION</td>
<td>Lunghi Giulia, Di Blase Erika, Fazzari Maria, Maggioni Margherita, Tedeschi Gabriella, Mattioli Elisa, Grassi Scalvini Francesca, Sonnino Sandro, Chiricozzi Elena</td>
</tr>
<tr>
<td>119</td>
<td>S15.3</td>
<td>Symposium</td>
<td>MUSHROOM BODIES DEVELOPMENT AND ABNORMALITIES IN DEFECTIVE W1T PATHWAY MODELS</td>
<td>Grisazio Paolo, Parodi Chiara, Bottai Daniele, Vaccari Thomas, Massa Valentina</td>
</tr>
<tr>
<td>120</td>
<td>S15.4</td>
<td>Symposium</td>
<td>HOW WE USED WFS1 DEFICIENT RAT TO DEVELOT TREATMENT STRATEGIES FOR WOLFRAM SYNDROME PATIENTS?</td>
<td>Seppa Kadri, Toots Maarja, Reimets Riin, Jagomåe Tomas, Koppel Tiiulikki, Pallase Maia, Nyengaard Jens, Vasar Eero, Terasmaa Anton, Pleas Mário</td>
</tr>
<tr>
<td>121</td>
<td>S16</td>
<td>Symposium</td>
<td>BLOOD BRAIN BARRIER MODEL, MECHANISM AND METABOLISM IN HEALTH AND DISEASE</td>
<td>Saha Siska</td>
</tr>
<tr>
<td>202</td>
<td>S16.1</td>
<td>Symposium</td>
<td>THE BLOOD-BRAIN BARRIER, TRANSCYTOSIS OF PROTEIN-BASED NANOPARTICLES TO THE BRAIN: A NEW INSIGHT INTO THE ROLE OF ASTROGLIA</td>
<td>Begley David</td>
</tr>
<tr>
<td>122</td>
<td>S16.2</td>
<td>Symposium</td>
<td>IN VITRO MODELING OF THE HUMAN BLOOD-BRAIN BARRIER - RECENT DEVELOPMENTS IN STEM CELL-BASED HUMAN MODELS</td>
<td>Saaby Lasse</td>
</tr>
<tr>
<td>123</td>
<td>S16.3</td>
<td>Symposium</td>
<td>IN VITRO AND IN Vivo MODELS OF BRAIN METASTASIS FORMATION</td>
<td>Krizbai Istvan, Hasko Jano, Fazakas Cailia, Molnar Kinga, Vegh Attila Gerge, Wilhelm Imola</td>
</tr>
<tr>
<td>124</td>
<td>S16.4</td>
<td>Symposium</td>
<td>BLOOD-BRAIN BARRIER IN HEALTH &amp; DISEASE – IN VITRO MODELLING</td>
<td>Patabendige Adjianie</td>
</tr>
<tr>
<td>125</td>
<td>S17.1</td>
<td>Symposium</td>
<td>DEVELOPMENT OF SELECTIVE CB2 RECEPTOR INHIBITORS AS POTENTIAL PROBES FOR MOLECULAR IMAGING WITH POSITRON EMISSION TOMOGRAPHY</td>
<td>Brust Peter, Moldovan Rares</td>
</tr>
<tr>
<td>126</td>
<td>S17.2</td>
<td>Symposium</td>
<td>ENDOCAANABINOID SIGNALLING IN NEUROPROTECTION: KEY-ROLE OF CB2 RECEPTOR</td>
<td>Maccarrone Mauro</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>---------------------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>127</td>
<td>S17.3</td>
<td>Symposium</td>
<td>RELEVANCE OF CB2 RECEPTORS IN MOTOR NEURON DISEASE</td>
<td>De Lago Eva</td>
</tr>
<tr>
<td>128</td>
<td>S17.4</td>
<td>Symposium</td>
<td>THE ROLE OF CB2 RECEPTOR IN THE RECOVERY OF MICE AFTER TRAUMATIC BRAIN INJURY</td>
<td>Shohami Esther, Magid Lital, Liraz-zaltsman Sigal, Mechoulam Raphael</td>
</tr>
<tr>
<td>129</td>
<td>S18.1</td>
<td>Symposium</td>
<td>S100B AS A BIOMARKER AND THERAPEUTIC TARGET IN MULTIPLE SCLEROSIS</td>
<td>Fernandes Adelaide</td>
</tr>
<tr>
<td>130</td>
<td>S18.2</td>
<td>Symposium</td>
<td>THE S100B STORY: FROM BIOMARKER TO ACTIVE FACTOR IN NEURAL INJURY</td>
<td>Michetti Fabrizio</td>
</tr>
<tr>
<td>131</td>
<td>S18.3</td>
<td>Symposium</td>
<td>ROLES OF S100B IN SCHIZOPHRENIA AND AFFECTIVE DISORDERS</td>
<td>Steiner Johann</td>
</tr>
<tr>
<td>132</td>
<td>S18.4</td>
<td>Symposium</td>
<td>DEVELOPMENT OF S100B SMALL MOLECULE INHIBITORS</td>
<td>Weber David</td>
</tr>
<tr>
<td>134</td>
<td>S19.2</td>
<td>Symposium</td>
<td>N -LYSINE ACETYLATION WITHIN THE ENDOPLASMIC RETICULUM: A FUNDAMENTAL ROLE FOR BRAIN PHYSIOLOGY AND PATHOLOGY</td>
<td>Puglielli Luigi</td>
</tr>
<tr>
<td>135</td>
<td>S19.3</td>
<td>Symposium</td>
<td>INBORN ERRORS OF COENZYME A METABOLISM IN NEURODEGENERATION WITH BRAIN IRON ACCUMULATION</td>
<td>Tiranti Valeria, Di Meo Ivano</td>
</tr>
<tr>
<td>136</td>
<td>S19.4</td>
<td>Symposium</td>
<td>HISTONE ACETYLATION IN MYELINATING GLIA</td>
<td>Dansu David, Sauma Sami, Park Hye-jin Casaccia Patrizia</td>
</tr>
<tr>
<td>138</td>
<td>S20.2</td>
<td>Symposium</td>
<td>REMODELING PROTEOSTASIS NETWORKS IN CAENORHABDITIS ELEGANS AGING</td>
<td>Shpigel Nufar, Shemesh Netta, Meshnik Lana, Klahner Mor, Ben-zvi Anat</td>
</tr>
<tr>
<td>139</td>
<td>S20.3</td>
<td>Symposium</td>
<td>DECIPHERING THE PROTEOSTASIS NETWORK’S RESPONSE TO THE ACCUMULATION OF TOXIC PROTEIN AGGREGATES IN THE AGING BRAIN</td>
<td>Cohen Ehud</td>
</tr>
<tr>
<td>140</td>
<td>S20.4</td>
<td>Symposium</td>
<td>PROTEIN AGGREGATION IS THE PRIME DRIVER OF MOST NEURODEGENERATIVE DISEASES</td>
<td>Kampinga Harm</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>----------------------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>141</td>
<td>S21.1</td>
<td>Symposium</td>
<td>ULTRASTRUCTURE AND CHEMICAL COMPOSITION OF NEUROMELANIN IN THE HUMAN SUBSTANTIA NIGRA</td>
<td>Bießemeier Antje, Ebli Oliver, Pozzoli Gianni, Zucca Fabio A., Schraermeyer Ulrich, Zecca Luigi</td>
</tr>
<tr>
<td>142</td>
<td>S21.2</td>
<td>Symposium</td>
<td>NEUROMELANIN-SENSITIVE MRI: A NOVEL, NON-INVASIVE PROXY MEASURE OF DOPAMINE FUNCTION IN PSYCHIATRIC ILLNESS</td>
<td>Cassidy Clifford, Luigi Zecca, Guillermo Horga</td>
</tr>
<tr>
<td>143</td>
<td>S21.3</td>
<td>Symposium</td>
<td>LOCUS COERULEUS IMAGING: CORRELATIONS TO PATHOLOGY AND COGNITION IN DEMENTIA</td>
<td>Jacobs Heidi</td>
</tr>
<tr>
<td>144</td>
<td>S21.4</td>
<td>Symposium</td>
<td>NEUROCHEMISTRY AND NEUROBIOLOGY OF HUMAN BRAIN NEUROMELANINS</td>
<td>Zucca Fabio A., Bellei Chiara, Mauri Pierluigi, Sturini Michela, Casella Luigi, Wakamatsu Kazumasa, Ito Shosuke, Prinetti Alessandro, Sulzer David, Zecca Luigi</td>
</tr>
<tr>
<td>145</td>
<td>P1</td>
<td>Poster</td>
<td>192IOD-SAPORIN INFLUENCES THE STATE OF MICROGLIA IN THE NEOCortex</td>
<td>Markевич Vladimir, Volobueva Maria, Dobryakova Yuliya, Manoova Anna, Stepanichev Michael, Kvitkonsky Alexey, Gulyaeva Natalia, Bolshakov Alexey</td>
</tr>
<tr>
<td>146</td>
<td>P2</td>
<td>Poster</td>
<td>A NEW PERSPECTIVE ON ALZHEIMER’S DISEASE AS A BRAIN EXPRESSION OF A COMPLEX METABOLIC DISORDER.</td>
<td>Polis Baruh, Samson Abraham</td>
</tr>
<tr>
<td>147</td>
<td>P3</td>
<td>Poster</td>
<td>A ROLE FOR AUTOPHAGY IN PRION-LIKE TAU PROPAGATION</td>
<td>Pedriolo Giona, Barberis Marialuisa, Pinton Sandra, Molinari Maurizio, Papin Stephanie, Paganetti Paolo</td>
</tr>
<tr>
<td>148</td>
<td>P4</td>
<td>Poster</td>
<td>ADNP: A PIVotal FACTOR IN NEURONAL FATE COMMITMENT AND SYNDROMIC AUTISM ONSET</td>
<td>Rizzuti Ludovico, Vitriolo Alessandro, Gabriele Michele, Germain Pierre-luc, Testa Giuseppe</td>
</tr>
<tr>
<td>149</td>
<td>P5</td>
<td>Poster</td>
<td>ALS-ASSOCIATED VCP-MUTANTS ALTER PROTEINOSTASIS BY INDUCING LYSOSOMAL DAMAGE</td>
<td>Ferrari Veronica, Rusmini Paola, Crippa Valeria, Cristofani Riccardo Maria, Tedesco Barbara, Casarotto Elena, Chierichetti Marta, Galibrait Marialita, Messi Eli, Piccolessa Margherita, Poletti Angelo, Cicardi Maria Elena</td>
</tr>
<tr>
<td>150</td>
<td>P6</td>
<td>Poster</td>
<td>ALTERATIONS OF LYSOSOMAL ACTIVITY IN CHARCOAT-MARIE-TOOTH 2B NEUROPATHY</td>
<td>Romano Roberta, Rivellini Cristina, De Luca Maria, Tonlorenzi Rossana, Belli Raffaella, Manganelli Fiore, Nolano Maria, Santoro Lucio, Eskelinen Eeva-Iliisa, Previtali Stefano C., Bucci Cecilia</td>
</tr>
<tr>
<td>151</td>
<td>P7</td>
<td>Poster</td>
<td>ANALYSIS OF TAU-KO CELLS REVEALS A NEW ROLE OF TAU PROTEIN IN MODULATING CELL DEATH</td>
<td>Sola Martina, Magrin Claudia, Paganetti Paolo, Papin Stephanie</td>
</tr>
<tr>
<td>152</td>
<td>P8</td>
<td>Poster</td>
<td>ASTROCYTIC MITOCHONDRIAL ROS MODULATE BRAIN METABOLISM AND MOUSE BEHAVIOUR</td>
<td>Vicente-gutiérrez Carlos, Bonora Nicolò, Bobo-jimenez Veronica, Jimenez-blasco Daniel, Lopez-fabuel Irene, Emilio Fernandez Emilio, Josephine Charlene, Bonvento Gilles, Enriquez Jose A., Almeida ángeles, Bolaños Juan P.</td>
</tr>
<tr>
<td>153</td>
<td>P9</td>
<td>Poster</td>
<td>BDNF UPREGULATES SYNAPTIC NMDA RECEPTORS BY ENHANCING LOCAL TRANSLATION OF PYK2 IN CULTURED HIPPOCAMPAL NEURONS</td>
<td>De Luca Pasqualino, Afonso Pedro, Carvalho Rafael, Pinheiro Paulo, Mele Miranda, Duarte Carlos</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>----------</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>154</td>
<td>P10</td>
<td>Poster</td>
<td>C9ORF72 ARGinine RICH POLY-Dipeptides Induce Transcriptional Alterations in ALS/FTD Cell Model.</td>
<td>Cristofani Riccardo, Grilli Andrea, Vezzoli Giulia, Licata Nausica Valentina, Crippa Valeria, Cicardi Maria Elena, Rusmini Paola, Tedesco Barbara, Ferrari Veronica, Casarotto Elena, Chierichetti Marta, Gabiati Mariarita, Carra Serena, Bicciato Silvio, Provenzani Alessandro, Poletti Angelo</td>
</tr>
<tr>
<td>155</td>
<td>P11</td>
<td>Poster</td>
<td>Dissecting Homodimeric oxytocin Receptor Pathways Regulation through Ot-Derived Bivalent Ligands.</td>
<td>Santini Francesca, Gori Alessandro, Costanzo Arianna, Chini Bice, Busnelli Marta</td>
</tr>
<tr>
<td>156</td>
<td>P12</td>
<td>Poster</td>
<td>Dopamine and Serotonin Metabolism in Parkinsonian Disorders.</td>
<td>Alrashidi Haya, Heales Simon, Eaton Simon</td>
</tr>
<tr>
<td>157</td>
<td>P13</td>
<td>Poster</td>
<td>Effect of Cobalt Chloride on Death Induced by Inhibition of Ubiquitin Proteasome System.</td>
<td>Brod anová Mária, Saksonová Simona, Dibaaková Katárina, Plíchová Ivana, Kla anová Katárina, Hatók Jozef, Ra ay Peter</td>
</tr>
<tr>
<td>158</td>
<td>P14</td>
<td>Poster</td>
<td>Effects of Prenatal Hypoxia on Expression of the Amyloid-Degrading Enzyme Neprilysin in the Olfactory Bulb and Entorhinal Cortex, and Behavior of Rats.</td>
<td>Zhuravin Igor, Dubrovskaya Nadezhda, Vasilev Dmitri, Kochkina Ekaterina, Tomanova Natalia, Nalivkova Natalia</td>
</tr>
<tr>
<td>159</td>
<td>P15</td>
<td>Poster</td>
<td>Effects the Remyalination-Promoting Antibody RHGIM22 on Spingolipid Metabolism in Primary Cultured Glial Cells.</td>
<td>Grassi Sara, Priori Simona, Capitta Livia, Sonnino Sandro, Prinetti Alessandro,</td>
</tr>
<tr>
<td>160</td>
<td>P16</td>
<td>Poster</td>
<td>Endovanilloids Stimulate Neuronal and Glial Differentiation Via GPR55 and CB1 Receptors.</td>
<td>Akimov Mikhail, Dudina Polina, Cherkasova Anastasia, Kapkaeva Marina, Gretskaya Natalia, Zinchenko Galina, Khashpekov Leonid, Bezuglov Vladimir</td>
</tr>
<tr>
<td>161</td>
<td>P17</td>
<td>Poster</td>
<td>Epigenetic Features of C9ORF72 Gene Promoter as RNA Foci Modifiers in iPSCs and iPS-MNS.</td>
<td>Volpe Clara, Colombrita Claudia, Bossoasco Patrizia, Gumina Valentina, Tilco Cinzia, Peverelli Silvia, Maraschi Anna Maria, Bardelli Donatella, Silani Vincenzo, Ratti Antonia</td>
</tr>
<tr>
<td>162</td>
<td>P18</td>
<td>Poster</td>
<td>Exploiting Targeted Epigenetic Editing to Increase Efficiency and Safety of Oligodendroglial Progenitor Cell (OPC) Generation from Human iPSC.</td>
<td>Luciani Marco, Ciccarelli Eleonora Maria, Migliara Alessandro, Lombardo Angelo, Gritti Angela</td>
</tr>
<tr>
<td>163</td>
<td>P19</td>
<td>Poster</td>
<td>Exposure to Decanoid Acid Increases Mitochondrial DNA Content in a Human Neuronal-Like Cell Line.</td>
<td>Baldwin Tomas, Khubbush Aziza, Orford Michael, Heales Simon, Eaton Simon</td>
</tr>
</tbody>
</table>
| 164  | P20      | Poster               | FUS (Fused in Sarcoma) Facilitates the Recruitment of the DNA Damage Response Machinery Contributing to Genome Stability. | Levone Bruno R., Lenzken Silvia C., Antonaci Marco, Conte Francesca, Filosa Giuseppe, Biella Fabio, Kızılırmak Cise, Ruepp Marc-david, Barabino Silvia M.
<p>| 165  | P21      | Poster               | Genetic Interplay Between Vitamin D Hydroxylase and Major Histocompatibility Factor as a Novel Preventive Individualized Approach in the Multiple Sclerosis. | Lehotsky Jan, Cierny Daniel, Škere ová Maria, Kurca Egon |
| 166  | P22      | Poster               | Gestational Exposure to Lipopolysaccharide Results in Mitochondrial Respiratory Chain Complexes Alterations in the Adolescent Offspring. | Zawadzka Aleksandra, Cie Iik Magdalena, Adamczyk Agata |</p>
<table>
<thead>
<tr>
<th>PAGE</th>
<th>SESSION</th>
<th>TYPE OF PRESENTATION</th>
<th>TITLE</th>
<th>AUTHORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>167</td>
<td>P23</td>
<td>Poster</td>
<td>GM1 OLIGOSACCHARIDE AS MITOCHONDRIAL REGULATOR IN NEURONAL CELLS</td>
<td>Fazzani Maria, Lunghi Giulia, Di Biasi Erika, Audano Matteo, Maffioli Elisa, Orsini Scalvini Francesca, Tedeschi Gabriella, Mitro Nico, Sonnino Sandro, Chiricozzi Elena</td>
</tr>
<tr>
<td>169</td>
<td>P25</td>
<td>Poster</td>
<td>HETEROGENEITY OF NEUROINFLAMMATORY RESPONSES IN AMYOTROPIC LATERAL SCLEROSIS (ALS) REVEALED AT SINGLE-CELL RESOLUTION: A ROADMAP FOR NEW TARGET DISCOVERY</td>
<td>Pellin Danilo, Protti Andrea, Biffi Alessandra, Curti Daniele, Peviani Marco</td>
</tr>
<tr>
<td>170</td>
<td>P26</td>
<td>Poster</td>
<td>HISTORY AND EVOLUTION OF MOLECULAR NEUROSCIENCE IN MODERN DIDACTICS RESEARCH FOR HIGH SCHOOL</td>
<td>Minoli Marina</td>
</tr>
<tr>
<td>171</td>
<td>P27</td>
<td>Poster</td>
<td>IMPACT OF ENDOPLASMIC RETICULUM (ER) STRESS ON EXPRESSION OF ER SPECIFIC E3 UBIQUITIN LIGASE HRD1</td>
<td>Racay Peter, Dibdibakova Katarina, Sojkova Simona, Pilchova Ivana, Klacanova Katarina, Tatarkova Zuzana</td>
</tr>
<tr>
<td>172</td>
<td>P28</td>
<td>Poster</td>
<td>IMPAIRED APPROACH TO NOVELTY AND ALTERED STRIATAL RESPONSIVENESS IN THE OXYTOCIN RECEPTOR DEFICIENT MOUSE MODEL OF AUTISM</td>
<td>Gigliucci Valentina, Leonzino Marianna, Ponconi Luisa, Busneli Marta, Ceresini Ilaria, Braida Daniela, Duque-wilckens Natalia, Trainor Brian C., Nishimori Katsuhiko, Sala Mariaelvina, Chini Bice</td>
</tr>
<tr>
<td>173</td>
<td>P29</td>
<td>Poster</td>
<td>JNK ROLE IN ANIMAL AND HUMAN RETT SYNDROME MODELS: ITS INHIBITION IS AN INNOVATIVE THERAPEUTIC STRATEGY</td>
<td>Musi Clara Alice, Buccaneo Lucia, Borsello Tiziana,</td>
</tr>
<tr>
<td>174</td>
<td>P30</td>
<td>Poster</td>
<td>LET’S MAKE MATHS ABOUT LACTATE IN THE BRAIN !</td>
<td>Bourmeyster Nicolas, Perrillat-mercorot Angélique, Miranville Alain, Guillemin Carole, Guillemin Rémy</td>
</tr>
<tr>
<td>175</td>
<td>P31</td>
<td>Poster</td>
<td>LINKING PHOSPHO-HDAC6 TO PROTEIN AGGREGATION IN PARKINSONSIMS</td>
<td>Mazzetti Samanta, De Leonidas Mara, Gagliardi Gloria, Calogero Alessandra Maria, Basellini Milo Jarno, Maderna Emanuela, Cacciatore Francesca, Spinello Sonia, Bramerio Manuela, Giaccone Giorgio, Pezoli Gianni, Cappelletti Graziella</td>
</tr>
<tr>
<td>176</td>
<td>P32</td>
<td>Poster</td>
<td>LONG AND VERY LONG CHAIN CERAMIDES CORRELATE WITH A MORE AGGRESSIVENESS BEHAVIOR IN SKULL BASE CHORDOMAS</td>
<td>La Corte Emanuele, Dei Cas Michele, Patanè Monica, Calatuzzolo Chiara, Pollo Bianca, Raggi Alberto, Campisi Giuseppe, Ferroli Paolo, Paroni Rita, Ghidoni Riccardo</td>
</tr>
<tr>
<td>177</td>
<td>P33</td>
<td>Poster</td>
<td>MICRONIA ALTERATIONS AS A PATHOGENETIC MECHANISM IN A MOUSE MODEL OF SPINAL MUSCULAR ATROPHY.</td>
<td>Cagnoli Cinzia, Marcuzzo Stefania, Cipelletti Barbara, Colciaghi Francesca, Locatelli Denise, Bernasconi Pia, Mantegazza Renato, De Curtis Marco</td>
</tr>
<tr>
<td>178</td>
<td>P34</td>
<td>Poster</td>
<td>MICROTUBE CYTOSKELETAL AND ALPHA-SYNUCLEIN: NEW DATA FOR AN EMERGING INTERPLAY</td>
<td>Calogero Alessandra Maria, Mazzetti Samanta, Cantele Francesca, Pizzi Sara, Tarantino Delia, Amadeo Alida, Gamone Giorgio, Pezoli Gianni, Cappelletti Graziella</td>
</tr>
<tr>
<td>179</td>
<td>P35</td>
<td>Poster</td>
<td>MITOCHONDRIAL DYSFUNCTION INCREASES FATTY ACID OXIDATION AND IMPAIRS NEUROBLAST MATURATION</td>
<td>Pedretti Silvia, Audano Matteo, Crestani Maurizio, Caruso Donatella, De Fabbian Emma, Mitro Nico</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>----------------------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>180</td>
<td>P36</td>
<td>Poster</td>
<td>MODULATION OF SPHINGOLIPIDS BY NON-INVASIVE MYRIOCIN ADMINISTRATION: POTENTIAL TREATMENT FOR RETINITIS PIGMENTOSA</td>
<td>Dei Cas Michele, Rubino Federico, Rizzo Jessica, Signorelli Paola, Strettoi Enrica, Platania Chiara, Bucolo Claudio, Pignatello Rosario, Paroni Rita, Ghidoni Riccardo</td>
</tr>
<tr>
<td>181</td>
<td>P37</td>
<td>Poster</td>
<td>MODULATION OF THE CONSTITUTIVE ACTIVITY OF MELANOCORTIN 4 RECEPTORS BY ZINC AND COPPER IONS</td>
<td>Link Reet, Veiskina Santa, Tahk Maria-Johanna, Kopanchuk Sergei, Rinken Ago</td>
</tr>
<tr>
<td>182</td>
<td>P38</td>
<td>Poster</td>
<td>MYELINOSOMES ENABLE CELL TO CELL TRANSFER OF MUTANT HUNTINGTIN-EXON 1 CAUSING AGGREGATE FORMATION IN NEURONAL CELLS</td>
<td>Bourmeyster Nicolas, Yefimova Marina, Béré Emile, Cantereau-becq Anne, Burel Agnès, Lavaut Marie-thérèse, Meunier Annie-claire, Ravel Celia, Becq Frédéric</td>
</tr>
<tr>
<td>183</td>
<td>P39</td>
<td>Poster</td>
<td>NOVEL GENE THERAPY FOR GM2 GANGLIOSIDOSES WITH AAV9/3-CMV-MDHDIX VECTOR</td>
<td>Itoh Kohji, Ohnishi Yuko, Tsuji Daisuke, Watanabe Ryo-suke, Asai Katsuhiko, Muramatsu Shin-ichi</td>
</tr>
<tr>
<td>184</td>
<td>P40</td>
<td>Poster</td>
<td>NOVEL MUTATIONS IN THE ASPARAGINE SYNTHETASE GENE (ASNS) ASSOCIATED WITH CYTOARCHITECTURAL ABNORMALITIES</td>
<td>Winkler Ulrike, Marx Grit, Schweinritz Dorit, Hoffmann Katrin, Kovacs Peter, Hrllinger Johannes</td>
</tr>
<tr>
<td>185</td>
<td>P41</td>
<td>Poster</td>
<td>NUCLEAR ACCUMULATION OF WRAP53 MAINTAINS GENOME INTEGRITY IN NEURONS AFTER ISCHEMIA</td>
<td>Rodríguez Cristina, Sánchez Morán Irene, Almeida Angeles</td>
</tr>
<tr>
<td>186</td>
<td>P42</td>
<td>Poster</td>
<td>P209 POINT MUTATIONS IN THE BCL-2-ASSOCIATED ATANOGENE 3 IMPACT ON THE CHAPERONE-ASSISTED SELECTIVE AUTOPHAGY</td>
<td>Tedesco Barbara, Adriaenssens Elias, Mediani Laura, Crippa Valeria, Carrà Serena, Timmerman Vincent, Poletti Angelo</td>
</tr>
<tr>
<td>187</td>
<td>P43</td>
<td>Poster</td>
<td>PKC REGULATES H-RAS ACTIVATION VIA THE RECRUITMENT OF THE RASGAP NEUROFIBROMIN IN THE LIPID RAFTS OF NEURONS</td>
<td>Peta Charoula, Karouzaki Sofia, Tsirimonaki Emmanouella, Mangoura Dimitra</td>
</tr>
<tr>
<td>188</td>
<td>P44</td>
<td>Poster</td>
<td>PRECONDITIONING-PROMOTED P38/AKT ACTIVATION REGULATES MDM2/P53 COMPLEX AND TRIGGERS ISCHEMIC TOLERANCE</td>
<td>Barrio Emilia, Vecino Rebeca, Sanchez-moran Irene, Suarez-pindado Alberto, Bolaños Juan P., Almeida Angeles, Delgado-esteban Maria</td>
</tr>
<tr>
<td>189</td>
<td>P45</td>
<td>Poster</td>
<td>PRENATAL HYPOXIA-INDUCED PREMATURE AGING IS ACCOMPANIED WITH MALFUNCTION OF GLUTAMATMERIC SYSTEM IN RAT HIPPOCAMPUS</td>
<td>Vetrovoy Oleg, Stratilov Victor, Tyulkova Ekaterina</td>
</tr>
<tr>
<td>190</td>
<td>P46</td>
<td>Poster</td>
<td>PROTECTIVE EFFECTS OF COFFEE METABOLITES AGAINST OXIDATIVE STRESS</td>
<td>Carozzini Tatiana, Lonati Elena, Botto Laura, Tassotti Michele, Pedro Meni, Del Rio Daniele, Palestini Paola, Bulbarelli Alessandra,</td>
</tr>
<tr>
<td>191</td>
<td>P47</td>
<td>Poster</td>
<td>PROTEOMIC APPROACHES TO CHARACTERIZE DIFFERENTIATION AND MATURATION EVENTS INDUCED BY NANOSTRUCTURED ZIRCONIA SURFACES IN DIFFERENT NEURONAL CELLS</td>
<td>Maffioli Elisa, Schulte Carsten,Grassi Scalvini Francesca, Nonnis Simona, Negri Armando, Puricelli Luca, Malgaroli Antonio, Podestà Alessandro, Lenardi Cristina, Milani Paolo, Tedeschi Gabriella</td>
</tr>
<tr>
<td>192</td>
<td>P48</td>
<td>Poster</td>
<td>PROTEOMIC MAPPING OF CELLULAR PROCESSES AFFECTED BY THE OVEREXPRESSION OF NA+/Mg2+ EXCHANGER SLC41A1 IN HEK-293 CELLS.</td>
<td>Pilchova Ivan, Tatarkova Zuzana, Cibulka Michal, Brodhanova Maria, Racay Peter, Kolisek Michal</td>
</tr>
<tr>
<td>193</td>
<td>P49</td>
<td>Poster</td>
<td>QUANTITATIVE ANALYSIS OF OCT-A FOVEAL SCANS FROM HEALTHY VOLUNTEERS AND AMD PATIENTS ACCORDING TO SIGNAL AMOUNT AND DISPERSION OF CALIBER-CLASSIFIED VESSELS.</td>
<td>Righi Marco, Arrigo Alessandro, Piero Luisa,</td>
</tr>
<tr>
<td>PAGE</td>
<td>SESSION</td>
<td>TYPE OF PRESENTATION</td>
<td>TITLE</td>
<td>AUTHORS</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>194</td>
<td>P50</td>
<td>Poster</td>
<td>SPINE DEVELOPMENTAL DEFECT AND COGNITIVE IMPAIRMENT IN RAB39B MOUSE, MODEL FOR HUMAN INTELLECTUAL DISABILITY</td>
<td>Mignogna Maria Lidia, Musardo Stefano, Bellone Camilla, D’Adamo Patrizia,</td>
</tr>
<tr>
<td>195</td>
<td>P51</td>
<td>Poster</td>
<td>THE ALTERNATIVE SPLICING REGULATION OF THE SCHIZOPHRENIA-ASSOCIATED TN1K GENE DURING NEURONAL DIFFERENTIATION</td>
<td>Gumina Valentina, Colombrita Claudia, Fallini Claudia, Bossofa Patrizia, Maraschi Annamaria, Landers John E., Silani Vincenzo, Ratti Antonia</td>
</tr>
<tr>
<td>196</td>
<td>P52</td>
<td>Poster</td>
<td>THE ASSESSMENT OF THE AUTOPHAGY MARKERS EXPRESSION IN THE RAT BRAIN UNDER SEVERE HYPOBARIC HYPOXIA</td>
<td>Churilova Anna, Zenko Mihail</td>
</tr>
<tr>
<td>197</td>
<td>P53</td>
<td>Poster</td>
<td>THE EFFECT OF A COENZYME Q10 DEFICIENCY ON NEURONAL CELL LYSOSOMAL ACIDITY</td>
<td>Heaton Robert, Hargreaves Iain, Heales Simon, Rahman Khalid</td>
</tr>
<tr>
<td>198</td>
<td>P54</td>
<td>Poster</td>
<td>THE EFFECT OF GLOBAL BRAIN ISCHEMIA ON PROTEINS OF MITOCHONDRIAL DYNAMICS</td>
<td>Klačanová Katarína, Kovalská Mária, Chomová Mária, Pilchová Ivana, Ra ay Peter</td>
</tr>
<tr>
<td>199</td>
<td>P55</td>
<td>Poster</td>
<td>THE METABOLIC TRANSITION DURING NEURONAL MATURATION</td>
<td>Audano Matteo, Pedretti Silvia, Crestani Maurizio, Caruso Donatelli, De Fabiani Emma, Mitro Nico</td>
</tr>
<tr>
<td>200</td>
<td>P56</td>
<td>Poster</td>
<td>THE OLIGOSACCHARIDE OF GM1 GANGLIOSIDE ACTS AS A NEUROTROPHIC AGENT FOR NEURONAL DEVELOPMENT</td>
<td>Di Biase Erika, Maggioni Margherita, Lunghi Giulia, Fazzari Maria, Prioni Simona, Sonnino Sandro, Chiricozzi Elena</td>
</tr>
<tr>
<td>201</td>
<td>P57</td>
<td>Poster</td>
<td>THE ROLE OF EXTRACELLULAR VESICLES IN THE REMOVAL OF AGGREGATED TDP-43 RESPONSIBLE FOR ALS/FTD DISEASES</td>
<td>Casarotto Elena, Sproviero Daisy, Gagliardi Stella, Tedesco Barbara, Cristofani Riccardo, Ferrari Veronica, Chierichetti Marta, Rusmini Paolo, Galiati Marialia, Cereda Cristina, Poletti Angelo, Crippa Valeria</td>
</tr>
</tbody>
</table>
194
P50
Poster
SPINE DEVELOPMENTAL DEFECT AND COGNITIVE IMPAIRMENT IN RAB39B MOUSE, MODEL FOR HUMAN INTELLECTUAL DISABILITY
Mignogna Maria Lidia, Musardo Stefano, Bellone Camilla, D'Adamo Patrizia

195
P51
Poster
THE ALTERNATIVE SPLICING REGULATION OF THE SCHIZOPHRENIA-ASSOCIATED TNIK GENE DURING NEURONAL DIFFERENTIATION
Gumina Valentina, Colombrita Claudia, Fallini Claudia, Bossolasco Patrizia, Maraschi Annamaria, Landers John E., Silani Vincenzo, Ratti Antonia

196
P52
Poster
THE ASSESSMENT OF THE AUTOPHAGY MARKERS EXPRESSION IN THE RAT BRAIN UNDER SEVERE HYPOBARIC HYPOXIA
Churilova Anna, Zenko Mihail

197
P53
Poster
THE EFFECT OF A COENZYME Q10 DEFICIENCY ON NEURONAL CELL LYSOSOMAL ACIDITY
Heaton Robert, Hargreaves Iain, Heales Simon, Rahman Khalid

198
P54
Poster
THE EFFECT OF GLOBAL BRAIN ISCHEMIA ON PROTEINS OF MITOCHONDRIAL DYNAMICS
KlaÅnanová Katarína, Kovalská Mária, Chomová Mária, Pilchová Ivana, RaÅray Peter

199
P55
Poster
THE METABOLIC TRANSITION DURING NEURONAL MATURATION
Audano Matteo, Pedretti Silvia, Crestani Maurizio, Caruso Donatella, De Fabiani Emma, Mitro Nico

200
P56
Poster
THE OLIGOSACCHARIDE OF GM1 GANGLIOSIDE ACTS AS A NEUROTROPHIC AGENT FOR NEURONAL DEVELOPMENT
Di Biase Erika, Maggioni Margherita, Lunghi Giulia, Fazzari Maria, Prioni Simona, Sonnino Sandro, Chiricozzi Elena

201
P57
Poster
THE ROLE OF EXTRACELLULAR VESICLES IN THE REMOVAL OF AGGREGATED TDP-43 RESPONSIBLE FOR ALS/FTD DISEASES
Casarotto Elena, Sproviero Daisy, Gagliardi Stella, Tedesco Barbara, Cristofani Riccardo, Ferrari Veronica, Chierichetti Marta, Rusmini Paola, Galbiati Mariarita, Cereda Cristina, Poletti Angelo, Crippa Valeria