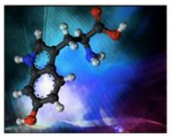
17th conference of the INTERNATIONAL SOCIETY FOR TRYPTOPHAN RESEARCH

JUNE 10-12, 2026 | PADOVA, ITALY



ISTRY
International Society for Tryptophan Research

UNIVERSITÀ DI PADOVA
Dipartimento
di Scienze del Farmaco

2026 ISTRY MEETING *abstract book*

SUMMARY

ISTRY COMMITTES

Executive committee

President	**Prof. Stefano Comai** - University of Padua, Italy
Vice-President	**Prof. Ana Pocivavsek** - University of South Carolina School of Medicine, Columbia, South Carolina, USA
President Elect	**Prof. Sophie Erhardt** - Karolinska Institutet, Stockholm, Sweden
Past President	**Prof. Florian Zepf** - Friedrich Schiller University, Jena, Germany
Secretary & Treasurer	**Prof. Edwin Lim** - Jena University Hospital, Germany
Member	**Prof. Tsutomu Fukuwatari** - University of Shiga Prefecture, Japan
Advisor	**Prof. Emeritus Trevor Stone** - University of Oxford, UK

Local organizing committee

Prof. Stefano Comai - University of Padua, Italy
Prof. Antonella Bertazzo - University of Padua, Italy
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Prof. Monica Montopoli - University of Padua, Italy
Prof. Sara De Martin - University of Padua, Italy
Prof. Cecilia Giron - University of Padua, Italy
Dr. Sofia Nasini - University of Padua, Italy
Dr. Antonino Casile - University of Camerino, Italy
Ms. Benedetta Barzon - University of Padua, Italy

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Prof. Edwin Lim - Jena University Hospital, Germany
Prof. Sarah Beggiato - University of Ferrara, Italy
Prof. Florian Zepf - Friedrich Schiller University, Jena, Germany
Prof. Johanna Gostner - Medical University of Innsbruck, Austria
Prof. Francesca Fallarino - University of Perugia, Italy

Media & Communication Team

Dr. Samara Walpole	Head of Media & Communication Team (since Nov 2025); Communication Lead (2023–Current)
Dr. Amanda Burmeister	Senior Editor (2019–Current)
Dr. Ananda Staats Pires	Editor (2024–Current)
Ms. Lorraine Tan	Event Coordinator (2019–Current)
Dr. Sandra Tatchum	Media Assistant (2024–Current)
Ms. Benedetta Barzon	Media Assistant (2024–Current)
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Ms. Courtney Wright	Media Assistant (2024–Current)
Ms. Maria Piroli	Media Assistant (2024–Current)
Prof. Edwin Lim	Media Team Advisor (2019–Current)

WELCOME MESSAGE

Dear colleagues, ISTRY delegates, and friends,

It is my great pleasure to welcome you to the ISTRY 2026 Conference here in Padua.

Returning to Padua carries a special meaning for our community. This city is not only one of Europe's oldest academic centers, but also the birthplace of ISTRY, where the first meeting was held more than five decades ago under the visionary leadership of Professor Luigi Musajo. His pioneering contributions to tryptophan research continue to shape our field today, and it is particularly meaningful that the Society honors his legacy through the Musajo Medal, a recognition of outstanding scientific achievement inspired by his work

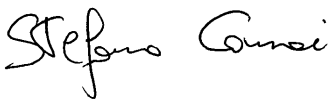
Since its foundation, the International Society for Tryptophan Research has served as a unique forum for scientists exploring the diverse roles of tryptophan and its metabolites. Over the years, our field has evolved from fundamental biochemical investigations to a highly interdisciplinary area spanning neuroscience, immunology, oncology, metabolism, and beyond. Today, tryptophan metabolism stands at the crossroads of many biological systems, with growing relevance for understanding human health and disease.

From the serotonin and kynurenine pathways to microbiome-derived indoles, research in this area is rapidly expanding our knowledge of neuropsychiatric disorders, neurodegeneration, cancer, immune regulation, and the gut–brain axis. At the same time, advances in systems biology and computational approaches are opening new opportunities to integrate these complex networks and translate them into meaningful clinical insights.

The scientific program of ISTRY 2026 reflects this breadth and dynamism. Over the coming days, we will explore topics ranging from cancer biology and central nervous system disorders to metabolism, ageing, nutrition, and immunometabolism, alongside emerging themes such as microbiome interactions and translational approaches. The meeting brings together established leaders and early-career researchers from across disciplines, fostering dialogue that is essential for advancing our field.

Beyond the science, we hope this conference will provide an opportunity to reconnect, exchange ideas, and build new collaborations in an open and collegial atmosphere. Padua, with its rich scientific heritage and vibrant cultural life, offers an inspiring setting for these interactions.

On behalf of the organizing committee and the ISTRY community, I warmly welcome you in Padua and wish you a stimulating and enjoyable conference.



Stefano Comai
President of ISTRY
Chair, ISTRY 2026 Conference

GENERAL INFORMATIONS

HOUSEKEEPING RULES AT THE CONFERENCE VENUE

Badge

Please kindly wear your conference badge at the conference venue so that our staff can easily identify you as an ISTRY meeting delegate in case you need further assistance around the venue.

Language

The official language for this meeting is English. There will be no translation or interpretation provided.

Smoking policy

Smoking is prohibited at all times around the conference venue; it is only allowed outside the compound of the University of Padua.

Mobile devices

Please observe minimal disruption to the presenters and audience by either switching off or putting your device in silent mode while attending the meeting. Please note that audio and visual recordings are not permitted during the meeting.

Internet connection

The conference venue is covered by the eduroam network. Participants from affiliated institutions can connect using their home university credentials. We recommend ensuring your device is configured for eduroam before arrival.

Safety and Emergency Procedures

Your safety is our priority. Please take a moment to familiarize yourself with the safety procedures of the venue:

- Emergency Exits: All emergency exits are clearly marked with green signs.
- Evacuation Plans: Floor plans showing emergency exits, evacuation routes, and assembly points are posted in the corridors near the entrance of each meeting room.
- In Case of Emergency: Should the alarm sound, please remain calm and follow the instructions provided by the University staff or the organizing committee. Do not use the elevators.
- Emergency Number: The general emergency number in Italy (and the EU) is 112.

The University of Padua and ISTRY assume no liability regarding lost or stolen personal belongings.

GETTING AROUND THE VENUES

VENUE FOR DAY 1 (10 JUNE 2026)

Conference venue address: Palazzo Bo, University of Padua, Via VIII Febbraio, 2, 35122 Padova PD, Italy.

Palazzo Bo lies in a *limited traffic area* (ZTL) where cars are not allowed without special permission. The nearest parking lots can be found in Prato della Valle area at the Park Rabin (15 minutes, on foot), piazza Insurrezione (often crowded) and at Padova Centro Park, near the Scrovegni Chapel.

VENUE FOR DAYS 2 & 3 (11 – 12 JUNE 2026)

Conference venue address: Centro Culturale Altinate/San Gaetano, Via Altinate, 71, 35121 Padova PD, Italy

Travel by tram from the train station

Take the streetcar to the Stazione stop, direction Guizza – Capolinea Sud. On leaving the Station, you will find stops on both sides of the overpass: the direction is to get off the overpass towards the city center. Get off at the PONTI ROMANI stop. Go up Rivera toward the station. Turn right onto Via Altinate (near Porta Altinate: it is on the left). Walk down Via Altinate until you find house number 71, on the left.

Travel by bus from the train station

You can take buses 3 and 12. Get off at the second stop, near Porta Altinate. Turn left onto via Altinate. Walk along Via Altinate until you find house number 71, on the left. Tickets are purchased at the station and are the same for buses and streetcars.

Travel by car from Strada del Santo

Take exit 18 bis. Go along Via San Marco, toward the center, which then becomes Via Venezia. At the Stanga traffic light, continue along via Venezia – Fiera – Stazione. After passing the Fiera and a traffic light (intersection with via Gozzi), turn left at the traffic circle onto via Valeri.

At the end of this street turn left onto via Trieste. After two traffic lights, past the intersection with via Gozzi, you will find the entrance to the Autosilo (paid parking lot) on the right. From the parking lot, walk down Via Morgagni, then turn right onto Via Alessio. Past a few steps, you will find the entrance to the Cultural Center on the left.

Other useful information

The nearest airport to Padua is the Marco Polo International Airport (about 30 Km) Connections are provided by a bus service (Busitalia), running every half an hour to the Padua train Station (Trenitalia; Italo), which is close to the city centre. From there you can reach Palazzo Bo on foot in about 15 minutes. There is also a tram service – Sir 1 line – running every 10 minutes from the station to the vicinity of Palazzo Bo (Ponti Romani tram stop).

PROGRAM

Wednesday 10 JUNE 2026 • Day 1

13:00 - 14:00 **REGISTRATION**

13:30 - 14:00 **OPENING CEREMONY**

14:00 - 14:45 **MUSAJO LECTURE**

From kynurenine pathway to psychiatric vulnerability: neuroinflammation, dopamine and new therapeutic horizons
Prof. Sophie Erhardt, Karolinska Institutet, Stockholm, Sweden

Chair: Prof. Robert Schwarcz, University of Maryland School of Medicine, USA. Musajo Medal Awardee in 2015 at the 14th ISTRY Meeting.

14:45 - 15:30 **Session 1 – 2-min DATA BLITZ POSTER PRESENTATIONS**

Chairs: Prof. Johanna Gostner, Medical University of Innsbruck, Austria.
Prof. Francesca Fallarino, University of Perugia, Italy

- VARIATION IN KYNURENINE PATHWAY GENE EXPRESSION IN NON-ALCOHOLIC FATTY PANCREATIC DISEASE (NAFPD)
  Mika Kittaka, Notre Dame Seishin University, Okayama, Japan.
- DIFFERENTIAL EFFECTS OF TEMPOL AND ASPIRINE TREATMENTS ON MEMORY AND KYNURENINE PATHWAY ALTERATIONS IN APP23 MICE
  Alessandro Ieraci, eCampus University, Novedrate, Italy.
- THE DELETERIOUS EFFECTS OF NEUROTOXIN QUINOLINIC ACID ON SVZ NSCS
  Michael D. Lovelace, St. Vincent's Centre for Applied Medical Research, Darlinghurst, Sydney, NSW, Australia
- DEVELOPMENT OF A FLUOROPHORE-BOUND L-TRYPTOPHAN DERIVATIVE FOR EVALUATING INDOLEAMINE 2, 3-DIOXYGENASE ACTIVITY BY HPLC WITH FLUORESCENCE DETECTION
  Mayu Onozato, Faculty of Pharmaceutical Sciences, Toho University, Japan
- THE INVOLVEMENT OF RENAL NMDA RECEPTORS IN THE DEVELOPMENT OF QUINOLINIC ACID INDUCED RENAL FIBROSIS
  Mamiko Ishikawa, Notre Dame Seishin University, Okayama, Japan
- KYNURENINE AMINOTRANSFERASE III AS THE KEY ENZYME DRIVING IMMUNE-INDUCED KYNURENIC ACID SYNTHESIS: A NOVEL TARGET FOR COGNITIVE DYSFUNCTIONS AND PSYCHOTIC DISORDER
  Varvara Louvrou, Karolinska Institutet, Stockholm, Sweden
- EFFECTS OF KYNURENIC ACID AND ITS ANALOG SZR-104 IN A SOCIAL ISOLATION-INDUCED DEPRESSION MOUSE MODEL: A PRELIMINARY STUDY
  Ágnes Szabó, University of Szeged, Szeged, Hungary

- LONG-TERM GAN DIET-FED MASLD MODEL MICE ENHANCE RENAL TRYPTOPHAN METABOLISM AND RENAL AGEING
  Misaki Omori, Notre Dame Seishin University, Okayama, Japan
- KYNURENINE PATHWAY ACTIVATION AND NEUROTOXIC IMBALANCE IN MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS ACROSS PERIPHERAL AND CENTRAL BIOMATRICE
  Lorraine Sue Ying Tan, Macquarie University, Sydney, Australia
- INDOLE-3-LACTATE AND THE ILA/IAA REDOX INDEX CORRELATE WITH DISEASE SEVERITY AND RESPOND TO ACUTE EXERCISE IN PERSONS WITH MULTIPLE SCLEROSIS
  Tiffany Wences Chirino, TU Dortmund University, Dortmund, Germany
- ALTERED TRYPTOPHAN AND KYNURENINE METABOLISM IN SCHIZOPHRENIA: IMPLICATIONS FOR PRAGMATIC IMPAIRMENTS AND LINK WITH TREATMENT-RESISTANCE
  Michele Francesco D'Incalci, Vita-Salute San Raffaele University, Milan, Italy
- DISSECTING THE INHIBITORY EFFECTS OF KYNA ON PREFRONTAL PARVALBUMIN-POSITIVE INTERNEURONS AND PYRAMIDAL CELLS THROUGH AN OPTIMIZED EX VIVO CALCIUM IMAGING APPROACH
  Edoardo Tiziani, University of Ferrara, Ferrara, Italy

Monitoring tryptophan catabolism: current tools and future directions
Dr. Alban Bessede, IMMUSMOL, Bordeaux, France

15:30 - 16:00 COFFEE BREAK

16:00 - 17:00 Session 2 – CANCER 1

Chairs: Prof. Christiane A. Opitz, German Cancer Research Center, Germany
Prof. Edwin Lim, Jena University Hospital, Germany

16:00 - 16:15 NEOADJUVANT IDO1 INHIBITION COMBINED WITH SHORT COURSE RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER: EFFICACY AND SAFETY FROM A PHASE 2 TRIAL
Dr. Matthew A Ciorba, Washington University in Saint Louis, Saint Louis, USA

16:15 - 16:30 mregDC-RESTRICTED IL4I1 PROGRAMS AN IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT
Prof. Marco Gargaro, University of Perugia. Italy

16:30 - 16:45 THE INTERPLAY OF TRYPTOPHAN METABOLISM AND IMMUNOREGULATORY STIMULATION IN GLIOBLASTOMA
Dr. Verena Panitz, Heidelberg University Hospital, Heidelberg, Germany

16:45 - 17:00 THE IN VITRO EFFECTS OF KYNURENINE METABOLITES AND A CHEMOKINE INHIBITOR CTCE-9908 ON CELL ADHESION IN B16-F10 MELANOMA AND SEND-2 ENDOTHELIOMA CELLS AND THE IN VIVO EFFECT IN C57BL/6 MICE
Dr. Sandra Tatchum, University of Pretoria, Pretoria, South Africa

17:00 - 18:00 **Session 3 – CENTRAL NERVOUS SYSTEM**

Chairs: Dr. Tina Notter, University of Zurich, Switzerland
Prof. Sarah Beggiato, University of Ferrara, Italy

17:00 - 17:15 NEUROTOXIC KYNURENINE PATHWAY METABOLITE QUINOLINIC ACID PREFERENTIALLY LOCALISES TO MS LESIONS, ACCUMULATES IN ASTROCYTES AND MYELOID CELLS, AND IS ELEVATED IN THE CEREBROSPINAL FLUID OF PROGRESSIVE MULTIPLE SCLEROSIS PATIENTS
Dr. Michael Lovelace, St. Vincent's Centre for Applied Medical Research, Darlinghurst, Sydney, NSW, Australia

17:15 - 17:30 MODULATION OF SEROTONIN 5-HT1A RECEPTORS BY BERGAMOT ESSENTIAL OIL: A STEP TOWARD NANOBEO DEVELOPMENT FOR NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE
Prof. Damiana Scuteri, University "Magna Graecia" of Catanzaro, Catanzaro, Italy

17:30 - 17:45 PLASMA LEVELS OF NEUROPROTECTIVE KYNURENINES ARE NEGATIVELY ASSOCIATED WITH SUICIDAL BEHAVIOR AND SUICIDE RISK FACTORS
Prof. Teodor T. Postolache, University of Maryland School of Medicine, Baltimore, MD, USA

17:45 – 18:00 HIGH ANTENATAL MATERNAL MENTAL STRESS ASSOCIATES WITH INCREASED PLACENTAL IDO2 MRNA EXPRESSION
Dr. Hannah E.J. Yong, Institute for Human Development and Potential, Agency for Science, Technology and Research, Singapore

18:00–19:30 **WELCOME RECEPTION**

Thursday 11 JUNE 2026 • Day 2

09:00 - 10:30 SYMPOSIUM

Kynurenic acid: positive aspects of therapeutic promise

Chairs: Prof. Trevor Stone, University of Oxford, UK
Prof. Laszlo Vecsei, University of Szeged, Szeged, Hungary

9:00 - 9:20 EFFECTS OF SOME KYNURENIC ACID ANALOGUES ON PRECLINICAL MODELS OF NEUROLOGICAL DISORDERS
Prof. Laslo Veczo, University of Szeged, Szeged, Hungary

9:20 - 9:40 MODULATION OF KYNURENIC ACID METABOLISM: DIFFERENT APPROACHES TO TREATING MEMORY AND COGNITIVE IMPAIRMENT
Prof. Halina Baran, Karl Landsteiner Research Institute, Lower Austria, Austria

9.40 - 9:55 ELEVATIONS IN KYNURENIC ACID IN THE LATERAL HYPOTHALAMUS DISRUPT SLEEP AND AROUSAL STATES IN RATS
Dr. Maria V. Piroli, University of South Carolina School of Medicine, Columbia, South Carolina, USA

9:55 - 10:10 ASTROGLIAL DISINHIBITION OF CORTICAL CIRCUITS DISRUPTS COGNITION VIA KYNURENIC ACID
Dr. Viktor Beilmann, University of Zurich, Zurich, Switzerland

10:10 - 10:55 LECTURE

The essentials of the microbiome-gut-brain axis: focus on microbial regulation of tryptophan metabolism
Prof. Gerard Clarke, University College Cork, Ireland

Chair: Prof. Maria Cecilia Giron, University of Padua, Italy

10:55 - 11:30 COFFEE BREAK

11:30 - 13:00 SYMPOSIUM

Tryptophan metabolism in psychiatry: key mechanisms and therapeutic potential

Chair: Prof. Sophie Erhardt, Karolinska Institutet, Sweden

11:30 - 11:50 KYNURENINE AND SEROTONIN PATHWAYS IN MOOD DISORDERS: DISSECTING BRAIN REGION AND SEX-SPECIFIC CHANGES
Dr. Samara Walpole, University of Wollongong, Wollongong, NSW, Australia

11:50 - 12:10 MODELING THE KYNURENINE PATHWAY IN NEUROINFLAMMATION USING IPSC-DERIVED BRAIN ORGANOIDS AND ASTROCYTE SPHEROIDS
Dr. Funda Orhan, Karolinska Institute, Sweden

12:10 - 12:30 PRECLINICAL INSIGHTS INTO THE ROLE OF KYNURENINE AND SEROTONIN/MELATONIN PATHWAYS IN SCHIZOPHRENIA
Ms. Benedetta Barzon, University of Padua, Padua, Italy

12:30 - 12:50 THE THERAPEUTIC POTENTIAL FOR MODULATING THE KYNURENINE PATHWAY THROUGH INHIBITION OF KYNURENINE TRANSPORT ACROSS THE BLOOD BRAIN BARRIER
Dr. Adam Walker, University of New South Wales, Sydney, NSW, Australia.

13:00 - 14:30 LUNCH BREAK AND POSTER SESSION 1

14:30 - 15:50 SYMPOSIUM

Physical exercise and nutrition - spotlight on the kynurenine pathway

Chairs: Prof. Philipp Zimmer, TU Dortmund University, Dortmund, Germany
Prof. Simone Eussen, Maastricht University, Maastricht, The Netherlands

14:30 - 14:50 MYELOID CELL GPR35 AND THE SYSTEMIC EFFECTS OF KYNURENIC ACID
Prof. Jorge Ruas, University of Michigan Medical School, Ann Arbor, MI, USA

14:50 - 15:10 KYNURENIC ACID AND XANTHURENIC ACID CAN BE INDUCED SYSTEMICALLY BY ACUTE EXERCISE: WHAT ABOUT AHR ACTIVATION?
Dr. Niklas Joisten, TU Dortmund University, Dortmund, Germany

15:10 - 15:30 THE IMPACT OF DIETARY INTAKE ON PLASMA KYNURENINES AND SUBSEQUENT DOMAINS OF QUALITY OF LIFE IN COLORECTAL CANCER SURVIVORSHIP
Prof. Simone Eussen, Maastricht University, Maastricht, The Netherlands

15:30 - 15:50 PHYSICAL EXERCISE AND TRYPTOPHAN METABOLISM IN MULTIPLE SCLEROSIS: KYNURENINES, INDOLES, AND BEYOND
Ms. Marie Kupjetz, TU Dortmund University, Dortmund, Germany

15:50 - 16:20 COFFEE BREAK

16:20 - 18:05 SYMPOSIUM

The role of tryptophan metabolism in healthspan: molecular and physiological insights

Chair: Dr. Anna Ainslie, European Research Institute for the Biology of Ageing, UMCG, Groningen, The Netherlands

16:20 - 16:40 INVESTIGATING HEALTHY AGEING MECHANISMS MEDIATED BY THE KYNURENINE PATHWAY
Dr. Anna Ainslie, European Research Institute for the Biology of Ageing, UMCG, Groningen, The Netherlands

16:40 - 17:00 ELEVATING PHYSIOLOGICAL 3 - HYDROXYANTHRANLIC ACID LEVELS TO EXTEND HEALTHY LIFESPAN
Prof. George Sutphin, University of Arizona, Tucson, AZ, USA.

17:00 - 17:20 TRYPTOPHAN METABOLIC FLEXIBILITY IN HEALTH AND DISEASE
Dr. Maralice Conacci Sorrell, University of Texas Southwestern Medical Center, Dallas, USA

17:20 - 17:50 SESSION 3 – CANCER 2

Chair: Prof. Marco Gargaro, University of Perugia, Italy

17:20 - 17:35 SPATIAL ORCHESTRATION OF TRYPTOPHAN METABOLISM REVEALS SELF - REINFORCING LOOPS DRIVING IMMUNE SUPPRESSIVE MICROENVIRONMENTS IN GLIOBLASTOMA
Dr. Ahmed Sadik, German Cancer Research Center, Heidelberg, Germany

17:35 - 17:50 RETHINKING IDO1 IN THE TUMOR MICROENVIRONMENT: NEW INSIGHTS INTO NON - CANONICAL TARGETING OF IDO1 IN CANCER IMMUNOTHERAPY
Dr. Sofia Rossini, University of Perugia, Perugia, Italy

17:50 - 18:20 SESSION 4 – VARIOUS TOPICS

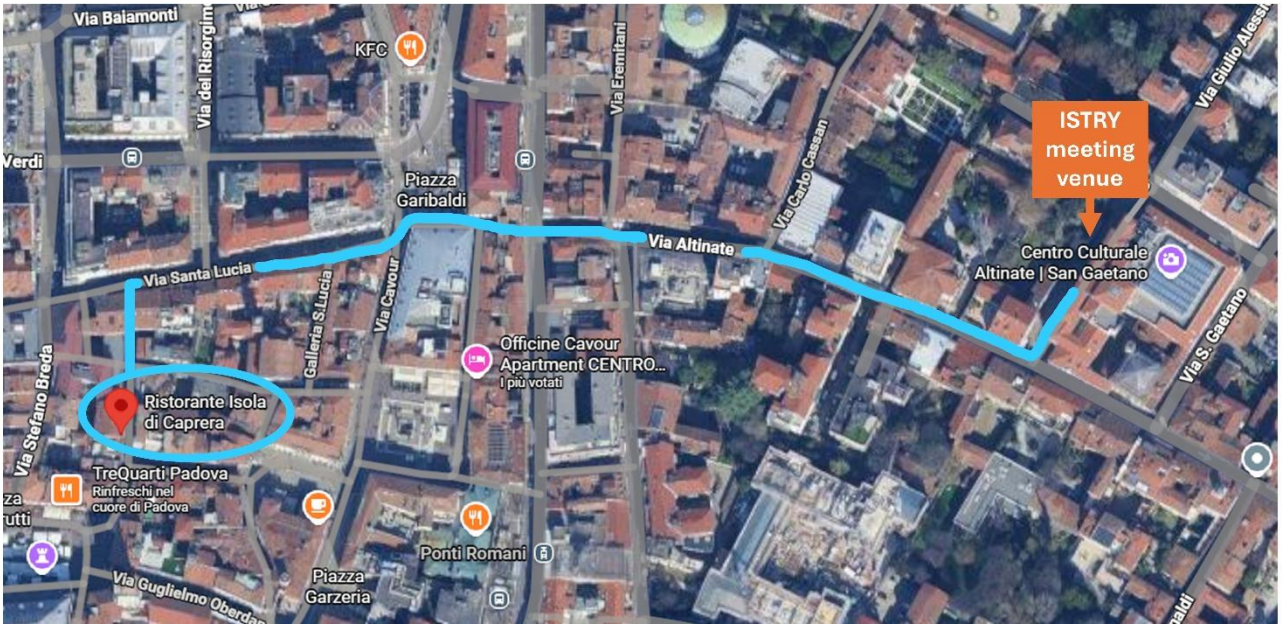
Chair: Funda Orhan, Karolinska Institutet, Sweden

17:50 - 18:05 COMPARTMENTALIZED REGULATION OF THE TRYPTOPHAN METABOLISM ACROSS BLOOD, URINE, SALIVA, AND SEBUM
Prof. Chai K Lim, Jena University Hospital, Jena, Thuringia, Germany

18:05 - 18:20 EDARAVONE MODULATES IDO1-DEPENDENT TRYPTOPHAN METABOLISM
Dr. Chiara Suvieri, University of Perugia, Perugia, Italy

from 19:30 SOCIAL DINNER

Restaurant "Isola di Caprera"
Via Marsilio da Padova, 11, 35139 Padova PD



Friday 12 JUNE 2026 • Day 3

09:00 - 10:30 **JOINT SYMPOSIUM CO-ORGANIZED BY ICAAS, JSTRY AND ISTRY**

Lifestyle factors: diet and nutrition

Chairs: Prof. Tsutomu Fukuwatari, The University of Shiga Prefecture, Japan
Prof. Hideki Matsumoto, Institute for Innovation, Ajinomoto Co., Tokio, Japan

9:00 - 9:20 METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH) IN NIACIN INSUFFICIENCY
Prof. Tsutomu Fukuwatari, The University of Shiga Prefecture, Japan

9:20 - 9:40 EFFECTS AND MECHANISMS OF ANTI-INFLAMMATORY FOOD COMPONENTS ON TRYPTOPHAN METABOLIC KEY ENZYMES AND THE BRAIN-GUT AXIS
Prof. Yukari Egashira, Chiba University, Chiba, Japan

9:40 - 10:00 RELEVANCE AND SAFE INTAKE OF AMINO ACIDS IN SUPPLEMENTS FOR HUMAN NUTRITION
Dr. François Blachier, Université Paris - Saclay, France

10:00 - 10:15 THE IMPACT OF GUT MICROBIOTA ON NAD^+ METABOLISM
Prof. Keisuke Yaku, University of Toyama, Japan

10:15 - 10:30 CONCEPT - A PHASE II, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF ORAL CONTROLLED-ILEAL-RELEASE NICOTINIC ACID (CIR - NA) FOR INDUCING REMISSION IN SUBJECTS WITH PREDIABETES
Dr. Corinna Geisler, University Medical Center Schleswig - Holstein, Kiel, Germany

10:30 - 11:15 **LECTURE**

Serotonergic modulation of emotional processing
Prof. Catherine Harmer, University of Oxford, UK

Chair: Prof. Florian Zepf, Friedrich Schiller University, Jena, Germany

11:15 - 11:40 **COFFEE BREAK**

11:40 - 13:00 **SYMPOSIUM**

Tryptophan metabolism and neurodevelopmental risk: models and mechanisms

Chairs: Prof. Ana Pocivavsek, University of South Carolina School of Medicine, Columbia, South Carolina, USA
Prof. Alexandre Bonnin, Keck School of Medicine of USC, USA

11:40 - 12:00 PRENATAL INFLAMMATION ALTERS SEROTONERGIC AND BLOOD BRAIN BARRIER DEVELOPMENT
Prof. Alexandre Bonnin, Keck School of Medicine of USC, USA

12:00 - 12:20 DYSREGULATED PREFRONTAL ASTROCYTES MEDIATE COGNITIVE DEFICITS VIA KYNURENINE ACID
Prof. Tina Notter, University of Zurich, Zurich, Switzerland

12:20 - 12:40 SLEEP DISRUPTIONS IN PREGNANCY TRIGGER INFLAMMATION AND TRYPTOPHAN-KYNURENINE PATHWAY ACTIVATION: RELEVANCE TO NEURODEVELOPMENTAL DISORDERS
Prof. Ana Pocivavsek, University of South Carolina School of Medicine, Columbia, South Carolina, USA

12:40 - 13:00 GESTATIONAL CANNABINOID EXPOSURE RESHAPES EXTRACELLULAR KYNURENIC ACID SIGNALING IN THE VENTRAL TEGMENTAL AREA OF PERIADOLESCENT OFFSPRING: A SCHIZOPHRENIA-RELATED ENDOPHENOTYPE
Prof. Sarah Beggiato, University of Ferrara, Ferrara, Italy

13:00 - 14:30 LUNCH BREAK AND POSTER SESSION 2

14:30 - 16:25 SYMPOSIUM

Discerning the AhR cytosolic and genomic pathway engaged by tryptophan metabolites

Chairs: Prof. Laura Santambrogio, Weill Cornell Medicine, New York, NY, USA
Prof. William Bourguet, Center for Structural Biology, Montpellier, France

14:30 - 14:50 STRUCTURAL INSIGHTS INTO THE ACTIVATION MECHANISM OF THE ARYL HYDROCARBON RECEPTOR, A RECEPTOR FOR TRYPTOPHAN-DERIVED METABOLITES
Prof. William Bourguet, Center for Structural Biology, Montpellier, France

14:50 - 15:10 DISCERNING THE AHR CYTOSOLIC AND GENOMIC PATHWAY ENGAGED BY TRYPTOPHAN METABOLITES
Prof. Laura Santambrogio, Weill Cornell Medicine, New York, NY, USA

15:10 - 15:25 EXPLORING THE ANTI-TUMOR POTENTIAL OF 3HKA THROUGH DISTINCT AHR SIGNALING ROUTES
Prof. Ciriana Orabona, University of Perugia, Perugia, Italy

15:25 - 15:40 DC-DEPENDENT AhR SIGNALING CONTROLS BREAST CANCER PROGRESSION
Prof. Aitziber Buque, Fox Chase Cancer Center and Lewis Katz School of Medicine Temple University, Philadelphia, PA, USA

15:40 - 15:55 DIETARY L-TRYPTOPHAN DETERMINES THE NUMBER OF COLONIC GPR15+ REGULATORY T CELLS AND SUSCEPTIBILITY TO COLITIS
Prof. Sangwon Kim, Thomas Jefferson University, Philadelphia, PA, USA

15:55 - 16:10 AhR-DRIVEN IMMUNE SUPPRESSION IN SOFT TISSUE SARCOMAS: IMPLICATIONS FOR CDC1 ANTITUMOR IMMUNITY AND THERAPEUTIC TARGETING
Dr. Estevão Carlos Silva Barcelos, University of Perugia, Perugia, Italy

16:10 - 16:25 AhR ACTS AS A METABOLIC GATEKEEPER IN CROSS-PRESENTING CDC1 DURING ANTITUMOR IMMUNITY
Ms. Doriana Ricciuti, University of Perugia, Perugia, Italy

16:25 - 16:55 COFFEE BREAK

16:55 - 18:10 SESSION 5 – IMMUNOMETABOLISM

Chairs: Prof. Antonella Bertazzo, University of Padua, Italy
Prof. Teodor T. Postolache, University of Maryland School of Medicine, USA

16:55 - 17:10 CHARACTERIZATION OF THE GENETICALLY MODIFIED IDO1H350A MOUSE MODEL EXPRESSING A LOSS-OF-FUNCTION MUTANT OF INDOLEAMINE 2,3-DIOXYGENASE 1 ENZYME
Ms. Sara Ambrosino, University of Perugia, Perugia, Italy

17:10 - 17:25 CYP1A1 CONTROLS THE BALANCE BETWEEN INFLAMMATORY AND IDO1-DEPENDENT PROGRAMS IN TYPE-2 DENDRITIC CELLS
Ms. Manola Mezzanotte, University of Perugia, Perugia, Italy

17:25 - 17:40 IDO-1–DRIVEN IMMUNOTOXICITY OF BPA AND ALTERNATIVES: A PATHWAY LEVEL DOSE-RESPONSE PERSPECTIVE
Dr. Pablo Monfort - Lanzas, Medical University of Innsbruck, Innsbruck, Austria

17:40 - 17:55 TRYPTOPHAN CATABOLISM VIA IDO1 SHAPES METABOLIC ADAPTATION IN MIGRATORY cDC1
Dr. Giada Mondanelli, University of Perugia, Perugia, Italy

17:55 - 18:10 AN IDO1-KYNURENINE-AHR METABOLIC CIRCUIT BETWEEN DENDRITIC CELL SUBSETS CONTROLS FVIII-SPECIFIC IMMUNE TOLERANCE
Dr. Francesco Sarnari, Biomedical Campus University, Rome, Italy

18:10 - 18:25 AMNIOTIC FLUID STEM CELL–DERIVED EXTRACELLULAR VESICLES CARRY FUNCTIONAL IDO1 AND KYNURENINE TO METABOLICALLY REPROGRAM DENDRITIC CELLS
Dr. Giorgia Manni, University of Perugia, Perugia, Italy

18:25 - 19:00 CLOSING REMARKS AND AWARDS

MUSAJO LECTURE
Wednesday, June 10th, 14.00 – 14.45

Abstract 01

From kynurenine pathway to psychiatric vulnerability: neuroinflammation, dopamine and new therapeutic horizons

Sophie Erhardt

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Over nearly three decades, our collaborative work has helped elucidate how inflammation-driven disturbances in the kynurenine pathway contribute to psychosis, cognitive impairment and suicidality. Early studies from our group demonstrated that levels of the tryptophan metabolite kynurenic acid (KYNA), are elevated in the cerebrospinal fluid (CSF) of patients with schizophrenia, providing some of the first evidence that increased brain KYNA may contribute to the pathophysiology of the disorder. These findings helped shape the “KYNA hypothesis” of schizophrenia, linking glutamatergic and dopaminergic dysfunction to cognitive deficits and poor functional outcomes. Combining clinical and preclinical approaches, this line of research has shown that elevated KYNA levels are associated with cognitive impairments in patients and causally impair cognition and neural circuit function in animal models, whereas lowering KYNA can normalize such deficits.

A central focus has been to define how immune activation drives KYNA synthesis in the brain. We have demonstrated that inflammatory signaling stimulates the kynurenine pathway and induces specific kynurenine aminotransferases, showing that not only KAT II but also KAT III is upregulated by immune activation and may contribute to pathological KYNA elevations and cognitive dysfunction, particularly in conditions characterized by pronounced neuroinflammation. In parallel, genetic studies, have implicated variants in genes such as SNX7 and GRK3 in the regulation of kynurenine metabolism and psychosis risk, providing a bridge between inflammatory, metabolic and genetic vulnerability factors.

Further work has linked downstream branch points of the kynurenine pathway to suicidality, demonstrating reduced levels of the neuroprotective metabolite picolinic acid (PIC) and elevated quinolinic acid (QUIN) in suicidal patients, suggesting deficient ACMSD activity. These findings highlight PIC as a potential biomarker of suicide risk and underscore that a fine balance between neuroprotective and neurotoxic kynurenine metabolites is crucial for mental health. Collectively, our studies have provided a mechanistic framework for novel therapeutic strategies targeting KYNA synthesis and kynurenine pathway regulation in major psychiatric disorders.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 02

Variation in Kynurenine Pathway Gene Expression in Non- Alcoholic Fatty Pancreatic Disease (NAFPD)

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Objective: Metabolic dysfunction-associated steatohepatitis (MASH), previously termed non-alcoholic fatty liver disease, has become a major global health concern associated with obesity. Recent studies indicate that a similar obesity-related pathological condition may also develop in the pancreas, known as non-alcoholic fatty pancreatitis (NAFPD), though its underlying mechanisms remain unclear. The kynurenine (KYN) pathway, the main metabolic route of tryptophan, generates metabolites that regulate inflammation and immune responses. Our previous studies demonstrated that KYN pathway-related gene expression was uniformly reduced in the livers of Gubra Amylin NASH diet (GAN)-induced obesity mice. However, it remains unclear whether KYN metabolism in the pancreas is similarly affected. This study examined the effects of GAN-induced obesity on NAFPD development and pancreatic KYN metabolism.
Methods: Male C57BL/6J mice aged 7 weeks were fed GAN for 55 weeks (GAN-55). Serum from GAN-55 underwent biochemical analysis, and pancreatic tissues were evaluated using hematoxylin and eosin staining and Sirius red staining. Gene expression levels of inflammatory, fibrotic markers, and KYN pathway enzymes were measured by qPCR.
Results: Histological analysis of GAN-55 pancreas revealed clear inflammation and fibrosis. Correspondingly, qPCR demonstrated increased expression of inflammation- and fibrosis-related genes. Interestingly, while most KYN metabolic enzymes were downregulated in the liver, their expression was upregulated in the pancreas.
Conclusion: These findings indicate that GAN-induced obesity contributes to both MASH and NAFPD, and that KYN metabolism shows organ-specific alterations, suggesting distinct regulatory mechanisms between hepatic and pancreatic pathology

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 03

Differential Effects of Tempol and Aspirine Treatments on Memory and Kynurenine Pathway Alterations in APP23 Mice

Mauro Vismara [1], Antonietta Licursi [2,3], Martina Galazzi [2,3], Silvia Stella Barbieri [2,4], Mauro Torti [1], Ilaria Canobbio [1], Alessandro Ieraci [2,3]

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Introduction: Alzheimer's disease (AD), the most common cause of dementia, is characterized by progressive cognitive decline associated with neuroinflammation, oxidative stress, and metabolic dysfunction. Increasing evidence indicates that alterations in the kynurenine pathway (KP), the main route of tryptophan metabolism, contribute to AD pathophysiology. In this study, we investigated the effects of the antioxidant Tempol and low-dose of aspirin on cognitive performance and KP-related gene expression in the APP23 mouse model of AD.

Methods: APP23 mice were treated with tempol (10 mg/kg) or aspirin (25 mg/kg) starting at 3 months of age for 6 or 15 months. Cognitive function was assessed using the Novel Object Recognition test. The expression of genes involved in the KP, together with markers of inflammation and oxidative stress, was analyzed by real-time PCR in the hippocampus of 9- and 18-month-old mice.

Results: Tempol, but not aspirin, significantly improved recognition memory in APP23 mice. Notably, Tempol selectively reversed the dysregulation of KP-related genes and normalized oxidative stress markers, whereas aspirin had no significant effects on cognitive performance or KP gene expression. These effects were especially evident in 9-month-old APP23 mice.

Conclusion: Our findings support a key role for kynurenine pathway dysregulation in the early stages of cognitive impairment in AD. By restoring KP-related gene expression and reducing oxidative stress, Tempol effectively ameliorates memory deficits in APP23 mice. These results highlight modulation of the kynurenine pathway as a potential therapeutic target in AD and identify antioxidant-based strategies as promising disease-modifying approaches.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 04

The deleterious effects of neurotoxin Quinolinic acid on SVZ NSCs

Michael D. Lovelace

Peter Duncan Neuroscience Research Unit, St. Vincent's Centre for Applied Medical Research, Darlinghurst, Sydney, NSW, Australia

Current treatments for Multiple Sclerosis (MS) reduce the autoimmune-driven relapses, but are ineffective at preventing neurological disability arising in the progressive phase, where brain cells die. Mouse neural stem cells (NSCs) constitute a pool of multipotent cells available for repair but are vulnerable to neuroinflammation. Quinolinic acid (QUIN) is a Kynurenine Pathway (KP) excitotoxin that our group previously showed potently kills brain cells, particularly oligodendrocytes. We further hypothesised QUIN might damage the cellular health of mNSCs. Via Muse flow cytometry (24-72 hours) and microscopy across different assays we have comprehensively mapped the impact of QUIN on mouse adult NSCs and progenitors. The Mitogenie platform was used to analyse mitochondria at the single cell level from Mitotracker-stained images. Our principle findings include a common pattern of acute benefit to ATP and NAD generation with QUIN treatment at 24-hours (only at low doses), followed by a significant and detrimental effects at 48-hours at the high (2mM) dose. A significant decline in the cellular health of NSCs was manifested by increased mitochondrial depolarisation, oxidative stress, and caspase expression at low and high doses, which became more pronounced at the 72-hr timepoint. Analysis of 500nM QUIN-treated mitochondria showed a significantly greater area per cell at the 24-hr timepoint vs controls, suggesting less mitochondrial turnover, in agreement with the ATP results. The effect was abolished at later timepoints. Therefore reducing QUIN production could reduce cell death, potentially improve the regenerative capacity of NSCs and in turn be effective in treating the neurodegeneration in MS.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 05

Development of a fluorophore-bound L-tryptophan derivative for evaluating indoleamine 2, 3-dioxygenase activity by HPLC with fluorescence detection

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Background: It is important to evaluate the activity of indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme for tryptophan (Trp) metabolism, because IDO is involved in immune tolerance, and some Trp metabolites are involved in the development of some psychiatric diseases and cancer. This study aimed to design and develop a novel fluorescent L-Trp derivative to fluorometrically monitor Trp-catabolizing enzyme activity via IDO.
Methods: To evaluate IDO activity *in vivo*, 7-*N*,*N*-dimethylamino-2,1,3-benzoxadiazole (DBD), a fluorophore, was covalently bound at the 5-position of the indole ring in Trp to produce 5-DBD-L-Trp. An *in vivo* microdialysis (MD) study was conducted using Sprague- Dawley rat kidney. Specifically, 5.0 μM 5-DBD-L-Trp in phosphate-buffered Ringer's solution was infused into the rats, and the MD sample was analyzed via high-performance liquid chromatography with fluorescence detection.
Results and discussion: In the MD sample, two fluorescence peaks other than 5-DBD-L- Trp were observed during the 5-DBD-L-Trp infusion, and the main metabolite peak was proposed to be 5-DBD-kynurenine, verified by liquid chromatography-tandem mass spectrometry. The intensity of the fluorescent peak was significantly attenuated by co-infusion with an IDO inhibitor, 1-methyl-D-tryptophan. These results suggest that 5-DBD-L- Trp may be metabolized by renal IDO and can be used to evaluate IDO activity *in vivo*. Currently, *in vitro* studies on 5-DBD-L-Trp using a commercially available human recombinant IDO1 or IDO2 are being carried out.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 06

The Involvement of Renal NMDA Receptors in the Development of Quinolinic Acid Induced Renal Fibrosis

Mamiko Ishikawa [1], Yoshiko Yasuhara [2], Shin-Ichi Fukuoka [3], Ken-Ichi Kobayashi [1]

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Objective: Quinolinic acid (QA), a tryptophan metabolite and N-methyl-D-aspartate receptor (NMDAR) agonist, accumulates in neurodegenerative diseases and neurotoxicity. QPRT-KO mice, which accumulate QA, develop renal fibrosis and anemia-like symptoms, but the mechanism is unclear. On the other hand, NMDAR is expressed not only in the brain but also in renal structures such as the glomerulus and tubules, and its association with diabetic nephropathy and nephrotoxicity has attracted attention. Nevertheless, many aspects of the relationship between NMDAR and renal pathology remain unclear. This study examined the relationship between QA accumulation–type renal fibrosis and NMDAR.
Methods: DNA microarray analysis was performed using kidneys from 60-week-old QPRT-KO mice. Gene expression of NMDAR subunits (NR1, 2A, 2B, 2C, 2D, 3A) in 14- and 60-week-old mice was assessed by quantitative PCR. Immunohistochemistry using antibodies against NMDAR subunits and QA was conducted to evaluate localization. HK-2 cells were treated with QA, and NMDAR subunit expression was analyzed by quantitative PCR.
Results: Microarray analysis showed reduced expression (>50%) of NR1, 2A, 2B, 2D, 3A, and downstream calpain genes in 60-week-old mice. PCR confirmed significant decreases in NR2C and 3A at 60 weeks, while 14-week-old mice showed increased NR2C and upward trends in NR1 and 3A. Immunohistochemistry revealed strong tubular staining at 14 weeks, with less pronounced changes at 60 weeks. QA localized to tubules and interstitium. In HK-2 cells, QA ≥500 μM significantly decreased NR1, 2B, 2C, and 2D expression.
Conclusion: Altered NMDAR expression and localization associated with QA accumulation may contribute to renal fibrosis.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 07

Kynurenine Aminotransferase III as the Key Enzyme Driving Immune-Induced Kynurenic Acid Synthesis: A Novel Target for Cognitive Dysfunctions and Psychotic Disorders

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Elevated central levels of kynurenic acid (KYNA) are associated with psychosis and cognitive deficits. KYNA is synthesized by four kynurenine aminotransferase (KAT I-IV) enzymes, among which KAT II is considered the primary enzyme under physiological conditions. During immune activation, pro-inflammatory cytokines induce the kynurenine pathway, including the synthesis of KYNA. Analysis of publicly available bulk and single-cell RNA-sequencing datasets reveals a consistent upregulation of KAT III in postmortem brain tissue from individuals with infectious or psychiatric disorders associated with cognitive dysfunction. In these datasets, inflammatory markers positively correlate with KAT III and KAT II gene expression. Network analysis further indicates that KAT III occupies a more critical synaptic role than KAT II, and cell-type-specific analyses show that KAT III is upregulated in neurogranin-expressing neurons and oligodendrocyte progenitor cells, both implicated in synaptic plasticity. Experimental validation demonstrates that KAT III expression is upregulated in human-derived monocytes following stimulation with Poly (I:C) and in vivo, immune-challenged rodents exhibit increased KYNA levels accompanied by elevated KAT III expression. In contrast, physiological increases in KYNA induced by kynurenine administration do not upregulate KAT III and, pharmacological KAT II inhibition fails to reduce KYNA levels in immune-challenged rodents. Consistent with this, KYNA levels in immune-challenged KAT II knockout mice are indistinguishable from those in wild-type controls. Together, these findings identify KAT III as the key enzyme driving KYNA production during immune activation, and position KAT III as a promising therapeutic target for cognitive impairment associated with immune-mediated conditions.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 08

Effects of Kynurenic Acid and Its Analog SZR-104 in a Social Isolation-Induced Depression Mouse Model: A Preliminary Study

Ágnes Szabó [1,2,3], Zsolt Galla [4], Bálint Lőrinczi [5], Diána Martos [1], Péter Monostori [4], István Szatmári [5], Tanaka Masaru [1,2,3], László Vécsei [1,2]

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Background: Major depressive disorder is linked to dysregulation of the tryptophan (Trp)- kynurenine (KYN) pathway, including altered levels of kynurenic acid (KYNA), a metabolite with concentration-dependent neuroactive properties. Social isolation (SI) induces depression-like phenotypes in rodents, yet SI-related KYN shifts remain incompletely defined. This study examined the behavioral and metabolic outcomes of SI and compared the effects of KYNA and its synthetic analog, SZR-104.
Methods: Male C57BL/6N mice (n = 4-7 per group) were socially isolated from weaning or group-housed as controls. Mice received acute intraperitoneal injections of saline, KYNA, or SZR-104 at 75 or 150 mg/kg before behavioral testing or sample collection. Behavioral tests were performed at 8 and 12 weeks of age following 4 or 8 weeks of SI using the open-field test, forced swim test, and Y-maze. Plasma samples were collected at 13 weeks, and Trp- KYN metabolites were quantified by mass spectrometry.
Results: SI increased forced swim immobility and impaired spontaneous alternation by 8 weeks, with a12 weeks. SI reduced plasma KYNA without changing Trp and shifted downstream KYN metabolism toward a neurotoxic profile. Acute KYNA administration increased peripheral KYNA yet failed to reverse depression-like behavior. In contrast, SZR-104 lowered neurotoxic metabolites and reduced immobility, with more consistent effects at 75 mg/kg.
Conclusion: Here we show that SI-driven depression reflects selective KYN imbalance rather than KYNA deficiency per se. Pathway-selective modulation may offer a translational route from stress-induced metabolic bias to new antidepressant strategies.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 09

Long-term GAN Diet-fed MASLD Model Mice Enhance Renal Tryptophan Metabolism and Renal Ageing

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Background: Metabolic dysfunction-associated steatohepatitis (MASLD) is a disease caused by obesity. It is known that progression increases the risk of cirrhosis and hepatocellular carcinoma. Furthermore, MASLD has been reported as a risk factor not only for liver disease but also for chronic kidney disease and renal cell carcinoma. Although it has been suggested that the onset of MASLD may accelerate cellular ageing, many aspects remain unclear. The kynurenine pathway is a metabolic pathway synthesising NAD from tryptophan, and many of its metabolites possess neurotoxicity and physiological activity, which is implicated in various diseases. We have previously demonstrated reduced gene expression of kynurenine pathway enzymes and ageing factors in the livers of MASLD mice. However, alterations in renal kynurenine pathway and their impact on renal ageing remain unclear.
Objective: Using Gubra Amylin NASH (GAN) diet-induced obese model mice (GAN mice), we investigated the effects of MASLD on overall renal kynurenine pathway and renal ageing.
Methods: Real-time PCR was performed on kidneys from C57BL/6J mice fed the GAN diet for 55 weeks (GAN55). β-actin was used as the internal standard.
Results: Gene expression analysis in GAN55 kidneys revealed increased expression of numerous kynurenine pathway enzyme genes. Furthermore, in the kidney of GAN55, the ageing-related genes p16, p21, and p53 were significantly elevated, and Klotho showed tendency to increase.
Discussion: These results suggest that MASLD induces renal inflammation, fibrosis, and cellular senescence, while kynurenine metabolism may be altered in contrast to hepatic metabolism.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 10

Kynurenine Pathway Activation and Neurotoxic Imbalance in Multiple Sclerosis: A Systematic Review and Meta-Analysis Across Peripheral and Central Biomatrices

Lorraine Sue Ying Tan [1], Ananda Staats Piers [2], Hanna Melzer [2], Soraya Wille [2], Josefin Thielow [2], Emma Bluethgen [2], Simona Beham [2], Chai Lim [2]

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Background: The kynurenine pathway (KP) represents a putative mechanistic bridge between inflammatory and neurodegenerative processes in the autoimmune disease multiple sclerosis (MS). However, KP dynamics are heterogeneous across disease stages and cross-compartmental matrices, requiring systematic synthesis to clarify consistent patterns.
Methods: A systematic review and meta-analysis was conducted across three databases from February 2021 to June 2025 (PROSPERO CRD42021239617). Case–control studies reporting tryptophan (TRP) and downstream KP metabolites in people with MS compared to healthy controls were included. Standardised mean differences (Hedges' g) were pooled using random-effects models, with meta-regression and risk of bias analyses conducted to identify moderators of effect size variability and assess methodological quality.
Results: Twenty-four studies (1,404 MS participants; 815 controls) were included, with 15 of these contributing 85 effect sizes for quantitative synthesis. Pooled analysis revealed elevated KYN and KYN:TRP ratios in blood, in MS and relapsing remitting MS. There were also pooled elevations of QA and QA:KA ratios in blood in MS, with significantly increased KA concentrations found in CSF compared to controls. Meta-regression identified clinical and methodological moderators. Between-study heterogeneity was high across pooled analyses, and the majority of studies were classified as high risk of reporting bias.
Conclusions: KP alterations in MS are characterized by peripheral pathway activation and a shift toward neurotoxic metabolite balance, alongside compartmentalized central neuroprotection, supporting their potential relevance as biomarkers of disease activity and progression.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 11

Indole-3-lactate and the ILA/IAA redox index correlate with disease severity and respond to acute exercise in persons with multiple sclerosis

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Purpose: Multiple sclerosis (MS) is an autoimmune neurodegenerative disease marked by differences in the taxonomic abundance of gut microbiota. The resulting changes in the microbiota-gut-brain axis are increasingly considered to be relevant to neuroinflammation. Key mediators of this axis include tryptophan (TRP)-derived indoles. Particularly indole-3- acetate (IAA), indole-3-lactate (ILA) and the ILA/IAA index, reflecting a predominantly reductive/oxidative metabolism, have been associated with MS-related disability, as measured by the Expanded Disability Status Scale (EDSS) score. Exercise can alleviate several disease-related symptoms in persons with MS (pwMS) and has the potential to induce changes in indole metabolism. Our aim is to confirm associations between indoles and MS-related severity and to investigate if an acute bout of exercise can increase the systemic concentrations of indoles.
Methods: We performed Pearson correlations of baseline indoles measured via HPLC-MS/MS and MS-disease-related information of 233 pwMS enrolled in three studies. We additionally performed a mixed-model analysis to evaluate the effect of a 60-minute bout of exercise (before 10-minute warm-up, after 30-minute resistance and at the end of the 20- minute strength and endurance) in a cohort of 17 pwMS.
Results: We found a negative association of the EDSS and both ILA ($r=-0.15$, $p=0.038$) and ILA/IAA ($r=-0.29$, $p<.001$). After an acute bout of exercise, ILA ($p<.001$) concentrations and the ILA/IAA ($p=.007$) increased.
Conclusions: MS-related disability is negatively associated with ILA and ILA/IAA. Acute exercise transiently increases the circulating concentrations of ILA, and the ILA/IAA index and chronic exercise could potentially play a modulating role in the microbiota-gut-brain axis in MS.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 12

Altered tryptophan and kynurenine metabolism in schizophrenia: implications for pragmatic impairments and link with treatment-resistance

Michele Francesco D'Incalci [1], Jacopo Sapienza [1,2], Giulia Agostoni [2], Marco Spangaro [2], Margherita Bechi [2], Francesca Martini [2], Carmelo Guglielmino [2], Federica Cocchi [2], Stefano Dall'Acqua [3], Roberto Cavallaro [1,2], Valentina Bambini [4], Stefano Comai [3,5], Marta Bosia [1,2]

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The kynurenine pathway (KP) is increasingly recognized as a key biological mechanism in schizophrenia and a potential treatment target, particularly in patients resistant to first-line antipsychotics. KP dysregulation has been extensively reported in patients and associated with cognitive impairments typical of the disorder, including basic linguistic abilities. However, no previous study has so far investigated whether the effects of KP alterations are also linked to more complex linguistic abilities, such as pragmatics, whose deficits are a core feature of schizophrenia. This cross-sectional study included 78 patients with schizophrenia, who were assessed for circulating tryptophan, KP metabolites, serotonin, and melatonin, as well as psychopathology, cognitive functioning, and pragmatic abilities. Results showed significant correlations between several pragmatic domains and circulating levels of KP metabolites. Notably, the relationship between tryptophan metabolism and linguistic-pragmatic abilities varied according to treatment-resistance status. Indeed, in treatment-resistant patients receiving clozapine treatment, peripheral levels of quinolinic acid showed a positive correlation with pragmatic comprehension and were significantly associated with global pragmatic competence ($\beta = 0.39$, $p = 0.03$). A positive association was also found between melatonin levels and global pragmatics in treatment-resistant patients ($\beta = 0.37$, $p = 0.03$). These findings underscore the relevance of the KP in schizophrenia and provide novel insights into the potential biological correlates of pragmatic deficits. Importantly, this study highlights the relationship between these dimensions and treatment-resistance status, which may help guide the development of personalized interventions targeting pragmatic impairment and its impact on global functioning in schizophrenia.

Session 1 – 2-min DATA BLITZ POSTER PRESENTATION
Wednesday, June 10th, 14.45 – 15.30

Abstract 13

Dissecting the inhibitory effects of KYNA on prefrontal parvalbumin-positive interneurons and pyramidal cells through an optimized ex vivo calcium imaging approach

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Kynurenic acid (KYNA) is a neuroactive metabolite of the kynurenine pathway known to modulate multiple neurotransmitter receptor systems, including inhibition of the N-methyl- D-aspartate (NMDA) receptor. While KYNA can have neuroprotective effects, elevated KYNA levels in the prefrontal cortex (PFC) have been associated with cognitive deficits in schizophrenia and related disorders. Recent evidence in mice suggests that elevated KYNA alters local neural circuits by suppressing the activity of fast-spiking parvalbumin-positive (PV) interneurons, which in turn disinhibits excitatory pyramidal cells. However, the impact of elevated KYNA on these neuronal populations remains to be fully elucidated. To assess the effects of KYNA on PV interneurons and pyramidal cells, we developed an optimized two-photon calcium imaging approach to measure neuronal activity in acute brain slices. We used a dual-sensor imaging strategy where a green-shifted Ca^{2+} sensor and a red-shifted Ca^{2+} sensor were selectively expressed in PV interneurons and pyramidal cells. Ca^{2+} activity was recorded simultaneously in both cell types following exposure to escalating concentrations of KYNA (0.1, 1, 10, 100 µM). Calcium dynamics were quantified using a custom Python script computing a noise baseline (3_{σ} threshold) to extract a multiparametric profile of cellular activity. Preliminary data suggest that KYNA may exert a dose-dependent inhibitory effect on both neuronal populations. The most prominent trend is a reduction in the frequency of high-amplitude Ca^{2+} spikes and in total active time (%), with a possible preferential effect on PV interneurons. This approach provides a robust, high-temporal- resolution platform to dissect the neuropharmacological impact of KYNA on cortical microcircuits.

Session 2 – CANCER 1
Wednesday, June 10th, 16.00 – 17.00

Abstract 14

Neoadjuvant IDO1 inhibition combined with short course radiotherapy in patients with locally advanced rectal cancer: Efficacy and safety from a phase 2 trial

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Background: In preclinical studies, IDO1 promotes resistance to radiation in colorectal cancer, and IDO1 inhibition with epacadostat improves tumor radiosensitivity. In a phase 1 trial, patients (pts) with locally advanced rectal cancer (LARC, n=17) were treated with epacadostat in combination with short course radiotherapy (SCRT) and CAPOX which was well-tolerated, and the recommended phase 2 dose (RP2D) of epacadostat was 400mg BID. Here we report efficacy and safety from the NCI-supported phase 2 (NCT03516708) multicenter, open-label trial (treatment cohort).
Methods: Pts were treated with standard of care (SOC) SCRT and then neoadjuvant chemotherapy (NAC). Epacadostat (400 mg BID) started with SCRT and continued until starting NAC. Eight pts were enrolled prior to discontinuation of epacadostat by Incyte in March 2025. The primary endpoint is Neoadjuvant Rectal (NAR) score and MRI-based tumor regression grade (MR-TRG). Secondary endpoints are pathologic complete response (pCR) rate, complete clinical response (cCR) rate, and progression free survival (PFS).
Results: Non-operative management (NOM) was pursued in 7/8 pts and surgical resection was performed on 1/8. At median follow-up (12-months), local tumor regrowth occurred in 1 pt initially treated with NOM. Epacadostat treatment was interrupted in 2/8 patients due to grade 3 maculopapular rash. Treatment-emergent adverse events (TEAEs) regardless of causality (all grades (G)/G3-4) were bloating (75%/0%), increased ALT (62.5%/0%), nausea (50%/0%), and constipation (50%/0%). Grade 3 diarrhea and non-cardiac chest pain occurred in 1 patient each (unrelated to epacadostat)
Conclusions: Epacadostat demonstrates promising efficacy and manageable safety in patients with LARC. The biomarker cohort and correlative studies are ongoing.

Session 2 – CANCER 1
Wednesday, June 10th, 16.00 – 17.00

Abstract 15

mregDC-Restricted IL4i1 Programs an Immunosuppressive Tumor Microenvironment

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In the tumor microenvironment (TME), amino acid metabolism, particularly tryptophan catabolism, is closely linked to immune tolerance and poor clinical outcomes. IL4i1, an enzyme involved in tryptophan degradation, has recently emerged as a critical regulator of the TME, promoting immune suppression and resistance to ferroptosis. However, the cellular sources and mechanisms underlying IL4i1-driven tumor progression remain incompletely understood. Using single-cell RNA sequencing, we identified IL4i1 expression as highly restricted to mature regulatory dendritic cells (mregDCs) within the TME of a transplantable fibrosarcoma model. IL4i1$^+$ mregDCs expressed canonical markers of DC maturation, including CCR7 and Zbtb46. Metabolomic analyses revealed enrichment of IL4i1-derived tryptophan metabolites, notably indole-3-pyruvate and 3-indole-acetaldehyde, within the TME. Consistently, *Il4i1-/-* mice exhibited reduced tumor growth accompanied by enhanced CD8$^+$ T cell–mediated antitumor responses. Conditional deletion of IL4i1 in mregDCs recapitulated this phenotype, resulting in impaired tumor growth and diminished accumulation of IL4i1-derived metabolites in the TME. Mechanistically, IL4i1 metabolites actively suppressed CD8$^+$ T cell effector functions and conferred resistance to ferroptosis in tumor cells. Moreover, we identified AhR- expressing target cells responsive to IL4i1-derived metabolites, revealing a metabolic signaling network through which mregDCs shape tumor immunity. Importantly, analysis of the TCGA-SARC dataset identified IL4i1 as a negative prognostic factor in specific sarcoma subtypes, a finding further validated by immunohistochemical detection of IL4i1 in human tumor biopsies. Collectively, these findings establish IL4i1 as a key metabolic driver of immune suppression and tumor persistence, highlighting its potential as a therapeutic target to reprogram the TME and enhance antitumor immunity.

Session 2 – CANCER 1
Wednesday, June 10th, 16.00 – 17.00

Abstract 16

The interplay of tryptophan metabolism and immunoregulatory stimulation in glioblastoma

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Glioblastoma is the most aggressive primary brain tumor in adults. It is marked by a highly immunosuppressive tumor microenvironment. Nevertheless, immunotherapies like immune checkpoint inhibitors did not show promising results in clinical trials so far. However, novel immunotherapies such as CAR-T cells are under investigation in glioblastoma. Metabolism of tryptophan by tryptophan-catabolizing enzymes (TCEs) generates metabolites such as kynurenine or kynurenic acid that can act as ligands of the cytosolic transcription factor aryl hydrocarbon receptor (AHR). In glioblastoma, AHR activation enhances cancer cell-intrinsic malignant features and leads to immunosuppression and associates with worse overall survival. As therapies targeting TCEs and AHR are becoming available, it is of high importance to better understand the regulation of TCEs and AHR activation in glioblastoma. Amongst others, TCEs can be induced by pro-inflammatory stimuli. These might be induced by immunotherapies. Hence, our special interest lies in investigating the regulation and the potential interplay of TCE and AHR activation and immunoregulatory stimuli in glioblastoma. A better understanding of these complex interactions might help to improve the stratification of glioblastoma patients to future combination therapies targeting tryptophan metabolism, AHR and immunosuppression in the glioblastoma tumor microenvironment.

Session 2 – CANCER 1
Wednesday, June 10th, 16.00 – 17.00

Abstract 17

The in vitro effects of kynurenine metabolites and a chemokine inhibitor CTCE-9908 on cell adhesion in B16-F10 melanoma and sEnd-2 endothelioma cells and the in vivo effect in C57BL/6 mice

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South Africa has the second highest incidence of skin cancer in the world after Australia. Despite recent advances in targeted therapies, there are still no reliable treatments to assist with managing disease progression. The effect of CTCE-9908 (a chemokine inhibitor) in combination with kynurenine metabolites (quinolinic acid and L-kynurenine) was investigated on cell adhesion in melanoma and endothelioma cells. L-kynurenine (L-kyn) was identified as a promising antiproliferative metabolite, therefore L-kyn was used in combination with CTCE-9908 to investigate tumor adhesion by quantifying adhesion proteins, E-cadherin, paxillin and focal adhesion kinase *in vitro* in melanoma cells and *in vivo* in murine models using immunohistochemistry and enzyme-linked immunosorbent assay. A statistically significant decrease in the percentage cell number in L-kyn- and CTCE-9908- treated sEnd-2 cells when compared to the vehicle control was observed. In control cell lines, immortalized keratinocyte (HaCaT) and endothelial (EA. hy926), there was a decrease in percentage cell number after treatment with L-kyn and CTCE-9908. The *in vivo* research revealed a decrease in tumor volume in the CTCE-9908/L-kyn combination treatment when compared to the treatments alone in C57BL/6 mice inoculated with B16-F10 cells. Cell morphology showed an increase in E-cadherin staining in mice treated with CTCE-9908 when compared to control. This was confirmed by an increase in E- cadherin in mice serum. Data from this study provides novel insights into the mechanism of action of CTCE-9908 and kynurenine metabolites and suggests that CTCE-9908 and L-kyn represent promising adjunct chemotherapeutic agents against melanoma and endothelioma.

Session 3 – CENTRAL NERVOUS SYSTEM
Wednesday, June 10th, 16.00 – 17.00

Abstract 18

Neurotoxic kynurenine pathway metabolite quinolinic acid preferentially localizes to MS lesions, accumulates in astrocytes and myeloid cells, and is elevated in the cerebrospinal fluid of progressive Multiple Sclerosis patients

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The kynurenine pathway (KP) metabolizes tryptophan, producing metabolites including neuroprotective kynurenic and picolinic acid, and neurotoxic quinolinic acid (QUIN). Multiple sclerosis (MS) serum metabolomics show dysregulation towards QUIN accumulation. Neurodegeneration predominates in progressive MS, but understanding CSF dysregulation in active/inactive subtypes and QUIN's localization in tissue and CSF concentrations is unknown. KP dysregulation is observed in progressive MS serum, but to date, limited studies have compared active/inactive forms. We analytically analyzed metabolite concentrations in CSF from different MS subtypes, and histologically localized QUIN in post-mortem patient brain tissue samples - 36 CSF and 12 cortical age-matched healthy controls, inactive relapsing-remitting MS (RRMS), and active and nonactive secondary progressive MS (SPMS). Chromogenic immunohistochemistry localized QUIN to glial fibrillary acid protein (GFAP+) astrocytes, IBA1+ microglia and in grey matter, presumed neurons in healthy controls and MS tissue. Kruskal-Wallis ANOVA with Dunn's pairwise comparison used; $p<0.05$. We undertook the first characterization of CSF and immunostaining for KP metabolites/enzymes in brain tissue. MS CSF showed significantly higher kynurenine/tryptophan ratio than controls ($p<0.001$), while QUIN/kynurenic acid ratio, and QUIN was significantly higher in active-SPMS (62.96nM, $p<0.001$) or remitting- RRMS (45.47nM, $p<0.05$) than controls (36.32nM). This confirms KP CSF activation/dysregulation, favoring QUIN to »2-fold>controls (SPMS), versus picolinic acid (decreased). QUIN preferentially localized to neurons/glia in lesions vs border/normal tissue. Detoxifying enzyme QPRT was restricted to astrocytes and downregulated in lesions. Severe QUIN in active/inactive SPMS suggests sustained neurotoxicity fuels neurodegeneration during persistent neuroinflammation. High QUIN/low QPRT lesion staining is supportive. Reducing QUIN/increasing catabolism are novel potential MS therapies.

Session 3 – CENTRAL NERVOUS SYSTEM
Wednesday, June 10th, 16.00 – 17.00

Abstract 19

Modulation of Serotonin 5-HT1A Receptors by Bergamot Essential Oil: A Step Toward NanoBEO Development for Neuropsychiatric Symptoms in Alzheimer's Disease

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Over 55 million people worldwide suffer from dementia and Alzheimer's disease (AD) account for over half cases. Some 99% of patients are affected by neuropsychiatric symptoms (NPS) and agitation is the most challenging. Currently approved therapies have limited efficacy and are endowed with doubled cardio- and cerebro-vascular mortality risk. Pain, often under-diagnosed and -treated, is a major trigger for agitation. Bergamot essential oil (BEO) showed strong preclinical efficacy in pain. Serotonergic (5-HT) neurotransmission appears fundamental to anxiety regulation, and pharmacological studies suggest that several essential oils can influence this pathway. Our studies proved that BEO exerts anxiolytic–relaxant effects distinct from benzodiazepines, contraindicated for patients suffering from dementia. Particularly, modulation of 5-HT1A receptors by selective agonist ((±)8-OH-DPAT) or antagonist (WAY-100635) was proven to influence BEO-induced anxiolytic–relaxant effects in the Open Field and Elevated Plus Maze tests. This study aimed to develop a preclinical-to-clinical pathway for translation of NanoBEO, a nanotechnological BEO-based device (patent number 102019000013353) now at the European Regional stage (EP4003294A1). The pilot study of the clinical trial BRAINAID (NCT04321889) randomized, quadruple masked, controlled vs placebo and following SPIRIT and CONSORT guidelines demonstrated that NanoBEO significantly reduced frequency (28%) and disruptiveness of agitated behaviors after 2 weeks, with long-lasting effects and no need for psychotropic rescue medications. Additionally, NanoBEO was well tolerated and induced a significant analgesic effect (45% decrease in pain intensity). NanoBEO might represent the first effective and safe need-oriented treatment for agitation in AD.

Session 3 – CENTRAL NERVOUS SYSTEM
Wednesday, June 10th, 16.00 – 17.00

Abstract 20

Plasma levels of neuroprotective kynurenines are negatively associated with suicidal behavior and suicide risk factors

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Suicide among US Veterans represents a critical public health crisis with rates significantly exceeding the general population (US Department of Veterans Affairs, 2023). After linking suicidal self-directed violence (SSDV) to inflammation centrally and peripherally, we first reported associations between SSDV and kynurenine pathway molecules. Specifically, SSDV was associated positively with kynurenine (KYN) and quinolinic acid (QUIN) positively, and kynurenic acid (KYNA) and picolinic acid (PIC) negatively. We now studied 407 Veterans (203 with suicidal self- directed violence [SSDV], 204 without) enrolled in mental health treatment across three VA sites. KYNA/KYN ratio ($p<0.01$), and PIC ($p<0.05$) were negatively associated with SSDV, resisting multiple comparison adjustments. KYNA/QUIN and PIC were negatively associated with depression ($p<0.05$) in attempters. KYNA/QUIN and PIC/QUIN were negatively associated with impulsivity ($p=0.01$, $p<0.001$, respectively) and sleep disturbance ($p<0.05$). QUIN was positively associated with daytime sleepiness ($p=0.007$); Neuroprotective kynurenines were associated with cognitive control (Stroop Test interference: KYNA $p<0.05$, PIC $p<0.001$); only the PIC- Stroop performance association resisted multiple comparison adjustment. Additionally, high PIC levels flattened strong positive associations between childhood maltreatment and SSDV. Limitations included the cross-sectional design and peripheral blood-only measurement. The results confirm and extend our previously reported SSDV-tryptophan pathway links and call for better mechanistic understanding and potential interventional targeting of SSDV risk elevation by low blood levels of neuroprotective kynurenines.

Session 3 – CENTRAL NERVOUS SYSTEM
Wednesday, June 10th, 16.00 – 17.00

Abstract 21

High antenatal maternal mental stress associates with increased placental IDO2 mRNA expression

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Maternal mental stress signals transmitted via the placenta can programme the fetal brain and influence neurodevelopmental trajectories. As past studies of impaired offspring neurodevelopment implicate altered placental tryptophan metabolism, we hypothesised that altered placental tryptophan metabolism may mediate such links. Nevertheless, human studies linking maternal mental stress with placental tryptophan metabolism remain limited. This study aimed to determine whether antenatal maternal mental stress levels are associated with placental mRNA expression of tryptophan catabolic enzymes in the GUSTO mother- offspring cohort. Mid-pregnancy maternal mental stress was assessed by a combined stress score integrating the Beck Depression Inventory-II, State-Trait Anxiety Inventory and Edinburgh Postnatal Depression Scale. Placental mRNA expression of upstream tryptophan catabolic enzymes in the serotonin/kynurenine pathway (*IDO1*, *IDO2*, *TPH1* and *TPH2*) was examined by RT-qPCR in 549 term placental samples. Following log-transformation and standardisation of gene expression data, statistical analyses utilised multiple regression with adjustment for covariates including maternal age, ethnicity, education, household income, parity, gestational age at delivery, child sex and placental collection time. Higher maternal mental stress levels associated with increased placental *IDO2* mRNA expression (adjusted estimate: 0.16 standard deviation in expression per standard deviation increase in stress score, p=0.0017). No association was observed between stress levels and expression of the other genes. Increased placental *IDO2* expression with high maternal mental stress may reflect upregulation of placental tryptophan catabolism along the kynurenine pathway. Ongoing work is exploring placental expression of downstream tryptophan catabolic enzymes and placental tryptophan metabolites, and the link of these tryptophan measures with longitudinal child neurodevelopmental outcomes.

Symposium – KYNURENC ACID: POSITIVE ASPECTS OF THERAPEUTIC PROMISE
Thursday, June 11th, 9.00 – 10.00

Abstract 22

Effects of some kynurenic acid analogues in preclinical models of neurological disorders

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Purpose: The purpose of our research is to investigate novel kynurenic acid analogues in different experimental models of central nervous system and some other disorders and perform a Phase I human study.
Methods: Transgenic mouse model of Huntington's disease, cuprizone animal model of multiple sclerosis, pentylenetetrazole-induced epileptiform seizures, in vitro hippocampal slices, cortical spreading depression, in vivo long-term potentiation induction, experimentally induced inflammation in the trigeminal ganglion, formalin model of trigeminal activation, dural inflammatory soup application, Complete Freund's Adjuvant-induced dural inflammation, electrical-stimulation-induced elevated polypeptide expression in the trigeminal nucleus caudalis, nitroglycerin-induced neuronal activation and hyperalgesia, permeability through the blood-brain-barrier, neonatal hypoxic ischemic encephalopathy, corticocerebral blood flow, acute mouse brain slice preparation, middle cerebral occlusion model of focal ischemia, nanoscale containers for biomedical application, surface plasmon resonance, microglia enriched cultures of newborn rat brains, sepsis-associated neutrophil activation.
Results: Our results suggest that kynurenic acid analogues have significant effects in these models.
Conclusion: Based on the preclinical findings we have several patents with kynurenic acid analogues. Furthermore, we performed Phase 1 study to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of kynurenine in healthy volunteers. This first-in-human study of kynurenine showed that the substance was safe and well tolerated after intravenous infusion up to 5 mg/kg over 20 minutes.

Symposium – KYNURENC ACID: POSITIVE ASPECTS OF THERAPEUTIC PROMISE
Thursday, June 11th, 9.00 – 10.00

Abstract 23

Modulation of Kynurenic Acid Metabolism: Different Approaches to Treating Memory and Cognitive Impairment

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An increased metabolism of kynurenic acid (KYNA) has been associated with memory and cognitive impairment in people with neuropsychiatric disorders. Our research aims to develop various approaches to combat these impairments. KYNA is a by-product of the breakdown of the amino acid L-tryptophan, which is synthesized from L-kynurenine by kynurenine aminotransferases. Experimental pharmacological studies have demonstrated a link between elevated KYNA levels in the brain and learning disabilities. Physical activity significantly influences KYNA metabolism through stochastic resonance therapy. Lowering KYNA levels alleviates the associated symptoms. Inhibiting kynurenine aminotransferases could provide a new treatment for memory disorders and cognitive impairment. We used a newly developed memory model of the snail (Helix pomatia) to evaluate these strategies. The data revealed a correlation between reduced KYNA levels and enhanced memory function. We hypothesize that dietary supplementation with natural plant extracts and physical activity can influence endogenous pharmacology by reducing KYNA synthesis and modulating steady-state biological conditions. This could delay the negative consequences of ageing and the onset of pathological processes.

Symposium – KYNURENC ACID: POSITIVE ASPECTS OF THERAPEUTIC PROMISE
Thursday, June 11th, 9.00 – 10.00

Abstract 24

Elevations in kynurenic acid in the lateral hypothalamus disrupt sleep and arousal states in rats

Maria V. Piroli, Charles A. Grant, Sujit Pujhari, Ana Pocivavsek

Dept. of Pharmacology, Physiology, and Neuroscience, University of South Carolina School of Medicine, Columbia, South Carolina

Individuals with neuropsychiatric disorders, like schizophrenia and bipolar disorder, often experience sleep disturbances. The pathophysiology of these disorders indicates dysregulated metabolism of the kynurenine pathway, notably elevated kynurenic acid (KYNA). In astrocytes, KYNA is synthesized from kynurenine predominantly by kynurenine aminotransferase II (KAT II). We hypothesize that elevated brain KYNA plays a role in sleep disturbances via activation of orexinergic neurons in the lateral hypothalamus (LH), which have been implicated in neuropsychiatric disorders. To test this hypothesis, adult rats were injected with an astrocyte-targeting adeno-associated virus serotype 5 (AAV5) encoding rat *Aadat* (KAT II) with mCherry reporter (denoted "KAT II sense") or control virus (denoted "control") into the LH. Immunofluorescence confirmed viral expression five weeks post- injection. In vivo microdialysis performed at baseline and after kynurenine challenge revealed an increase in extracellular KYNA in KAT II sense animals compared to controls. Separate animals were implanted with telemetry devices to record EEG/EMG polysomnography for the analysis of wake, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. During the latter half of the light phase, KAT II sense rats showed a 27% increase in wake duration and a 31% decrease in REM duration compared to controls. Our findings demonstrate for the first time that virus-mediated transduction can overexpress KAT II locally in the brain, resulting in increased extracellular KYNA and sleep disturbances.

Symposium – KYNURENC ACID: POSITIVE ASPECTS OF THERAPEUTIC PROMISE
Thursday, June 11th, 9.00 – 10.00

Abstract 25

Astroglial disinhibition of cortical circuits disrupts cognition via kynurenic acid

Viktor Beilmann [1], Johanna Furrer [1], Sina M. Schalbetter [2], Ron Schaer [2], Edoardo Tiziani [3], Kim D. Ferrari [1], Felisa Herrero [2], Alexandra von Faber-Castell [1], Ulrike Weber-Stadlbauer [1], Jacqueline Condrau [2], Matthias T. Wyss [1], Aiman S. Saab [1], Sarah Beggiato [3], Urs Meyer [2], Bruno Weber [1], Tina Notter [1]

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Astrocyte dysfunctions are increasingly implicated as central contributors to circuit-level abnormalities in psychiatric disorders, yet the mechanisms through which altered glial activity shapes cognitive impairment remain poorly defined. Here, we identify astrocyte-derived kynurenic acid (KYNA), a neuroactive kynurenine-pathway metabolite and endogenous antagonist of N-methyl-D-aspartate (NMDA) receptors, as a regulator of prefrontal cortical function. Using a combination of chemogenetic stimulation, pharmacological rescue strategies, and astrocyte-specific knockdown of kynurenine aminotransferase II (KAT II) in mice, we show that elevated KYNA profoundly disrupts prefrontal circuit dynamics by suppressing the activity of parvalbumin-positive interneurons. This suppression leads to disinhibition of pyramidal neurons and causes a broad spectrum of deficits in cognitive processes, including temporal order memory, working memory, and sensorimotor gating. Together, these findings define a mechanistic astrocyte-KYNA-interneuron axis that governs cortical excitability and cognitive integrity. They further provide a conceptual framework for understanding how astrocyte-derived metabolites contribute to cognitive dysfunction in major psychiatric disorders.

LECTURE
Thursday, June 11th, 10.10 – 10.55

Abstract 26

The essentials of the microbiome-gut-brain axis: focus on microbial regulation of tryptophan metabolism

Gerard Clarke [1,2]

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The microbiome-gut-brain axis is sustained by a multilayered network of neural, endocrine, immune, and metabolic signalling pathways that integrate microbial activity within the gastrointestinal tract with central nervous system function. Among these mechanisms, microbial regulation of tryptophan metabolism represents a pivotal molecular interface linking gut microbiota composition to neuromodulatory and immunological outcomes. Tryptophan availability and metabolic partitioning are governed by the coordinated activity of host enzymes, including tryptophan hydroxylase and indoleamine- and tryptophan-2,3-dioxygenases (IDO and TDO), together with microbial enzymatic pathways that generate a diverse array of bioactive metabolites. Gut microbes influence host serotonergic signalling both indirectly, by modulating luminal tryptophan pools that determine substrate availability for serotonin biosynthesis, and directly, through the production of tryptophan-derived metabolites such as indoles, tryptamine, and short-chain fatty acids. These microbial products engage host receptors including the aryl hydrocarbon receptor (AhR), G protein–coupled receptors, and ligand-gated ion channels, thereby shaping epithelial barrier function, immune activation, and vagal afferent signalling. In parallel, altered microbial control of tryptophan flux through the kynurenine pathway can shift the balance between neuroprotective and neurotoxic metabolites, influencing glutamatergic neurotransmission, neuroinflammation, and stress-related behavioural outcomes. Perturbations in these tightly regulated metabolic networks have been observed in stress-related psychiatric disorders and in irritable bowel syndrome (IBS), a disorder of gut-brain interaction characterised by prominent affective comorbidity. Changes in microbiota composition and functional capacity are associated with dysregulated tryptophan metabolism, aberrant immune-metabolic signalling, and altered expression of genes critical to neurotransmitter systems involved in anxiety and mood regulation. Emerging multilevel experimental approaches integrating genomic, metabolomic, and neurobehavioural analyses are beginning to resolve how specific microbial metabolic functions intersect with host signalling cascades to modulate brain function. A detailed molecular understanding of microbial regulation of tryptophan metabolism across the microbiome-gut-brain axis is therefore essential for advancing mechanistically informed therapeutic strategies. Defining how microbial enzymes, host metabolic checkpoints, and receptor-mediated signalling pathways interact will be critical for translating basic discoveries into targeted interventions aimed at restoring metabolic and neurochemical homeostasis in psychiatric and gastrointestinal disorders.

Symposium – TRYPTOPHAN METABOLISM IN PSYCHIATRY: KEY MECHANISMS AND THERAPEUTIC POTENTIAL
Thursday, June 11th, 11.30 – 13.00

Abstract 27

Kynurenine and Serotonin Pathways in Mood Disorders: Dissecting Brain Region and Sex-Specific Changes

Samara Walpole

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Growing evidence highlights a critical role for tryptophan metabolism, and the subsequent production of neuroactive compounds, in the neurobiology of major depressive disorder (MDD) and bipolar disorder (BD). Moreover, there are significant sex differences in the presentations of both disorders, however, the investigation of sex differences in the molecular mechanisms of these disorders is lacking. Therefore, this project aimed to investigate tryptophan metabolism in MDD and BD, with a specific focus on assessing both sex and diagnostic differences. Human postmortem hippocampus and anterior cingulate cortex (ACC) tissue were obtained from the NIH NeuroBioBank from individuals with MDD, BD and nonpsychiatric controls. Gene expression of targets related to tryptophan metabolism were investigated via RT-qPCR and metabolites were measured using liquid chromatography-mass spectrometry. Region-, sex-, and diagnosis-specific alterations in tryptophan metabolism were identified. In BD, the ACC showed disruptions within the kynurenine pathway, with increased 3-hydroxykynurenine, whereas serotonin metabolism was reduced in the hippocampus. In MDD, sex-specific differences varied by brain region, suggesting distinct regional vulnerabilities. In the ACC, kynurenic acid was reduced in females with MDD, whereas in the hippocampus KAT mRNAs were increased in males with MDD. These findings highlight disorder-, regional- and sex-specific differences in tryptophan metabolism. They are now informing ongoing work examining how these molecular disruptions affect glutamate receptor expression using patient-derived induced pluripotent stem cells from individuals with BD. Together, this work aims to clarify how tryptophan metabolism pathways contribute to excitatory neurotransmission abnormalities in mood disorders, ultimately informing more targeted therapeutic strategies.

Symposium – TRYPTOPHAN METABOLISM IN PSYCHIATRY: KEY MECHANISMS AND THERAPEUTIC POTENTIAL
Thursday, June 11th, 11.30 – 13.00

Abstract 28

Modeling the kynurenine pathway in neuroinflammation using iPSC-derived brain organoids and astrocyte spheroids.

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Background: Kynurenic acid (KYNA), a neuroactive metabolite primarily produced by glial cells, is elevated in the brains of individuals with neuropsychiatric disorders such as schizophrenia, particularly under inflammatory conditions. KYNA is synthesized via four kynurenine aminotransferases (KATs), with KAT II recognized as the dominant enzyme under physiological conditions. However, emerging evidence from our group implicates KAT III as a key contributor during immune activation. To better understand KYNA regulation in human brain cells, relevant experimental models are needed. This study aimed to establish human brain cellular platforms to investigate kynurenine pathway metabolism and KYNA release.
Methods: Human primary astrocytes were cultured as spheroids and exposed to cytokines (IL-1β, IFN-γ) with or without the pan-KAT inhibitor PF-04859989. Spheroids were pooled to enhance metabolite detection. In parallel, iPSC-derived dorsal forebrain organoids were generated and subjected to the same treatments. KYNA and other tryptophan metabolites were measured in conditioned media by mass spectrometry.
Results: Both astrocyte spheroids and brain organoids produced detectable levels of kynurenine pathway metabolites. Inflammatory stimulation increased KYNA release in both models, whereas treatment with the KAT inhibitor attenuated this response. In astrocyte spheroids, stimulation increased KYNA levels from approximately 3.9 to 25.6 nmol/L (~6.5 fold). Application of PF-04859989 resulted in a dose-dependent reduction in KYNA levels.
Conclusion: Astrocyte spheroids and iPSC-derived organoids provide complementary, human-relevant platforms for studying KYNA regulation under inflammatory conditions. Both models respond to inflammatory stimulation and KAT inhibition, supporting their use for mechanistic studies and potential drug testing.

Symposium – TRYPTOPHAN METABOLISM IN PSYCHIATRY: KEY MECHANISMS AND THERAPEUTIC POTENTIAL
Thursday, June 11th, 11.30 – 13.00

Abstract 29

Preclinical insights into the role of kynurenine and serotonin/melatonin pathways in schizophrenia

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Cognitive deficits and the high prevalence of metabolic syndrome in schizophrenia (SCZ) may share biological mechanisms involving disruptions in tryptophan (Trp) metabolism, inflammation, and gut microbiome function. To investigate these interactions, we conducted two complementary studies integrating behavioral, electrophysiological, and metabolic analyses. In the first study, we examined how endogenous melatonin availability influences vulnerability to psychosis-like and metabolic alterations. Melatonin-deficient (C57BL/6) and melatonin-proficient (C3H/HeN) mice were exposed to either a standard or high-fat diet and treated with MK-801 or vehicle. MK-801 produced genotype- and diet-dependent behavioral changes in the Open Field Test and T-maze, accompanied by altered dorsal raphe 5-HT neuron activity. Peripheral analyses showed distinct inflammatory profiles and shifts in Trp metabolites along the serotonin/melatonin and kynurenine pathways, indicating interactions among melatonin physiology, metabolic state, and glutamatergic perturbation. In the second study, we assessed how gut microbial factors shape SCZ-like phenotypes by performing fecal microbiota transplantation (FMT) from patients with severe or mild SCZ symptoms into C57BL/6 and C3H/HeN mice. FMT produced graded behavioral differences reflecting donor symptom severity and modulated ventral tegmental area dopaminergic firing. Serum and brain measurements revealed changes in Trp metabolism and inflammatory cytokines, supporting a microbiota-driven influence on neuroimmune and monoaminergic pathways. Together, these findings suggest that dysregulated Trp metabolism and inflammation integrate genetic background, metabolic conditions, and microbiota-derived signals to shape behavioral and neurophysiological vulnerability relevant to SCZ. Targeting these interacting pathways may offer novel opportunities for precision medicine in SCZ.

Symposium – TRYPTOPHAN METABOLISM IN PSYCHIATRY: KEY MECHANISMS AND THERAPEUTIC POTENTIAL
Thursday, June 11th, 11.30 – 13.00

Abstract 30

The therapeutic potential for modulating the kynurenine pathway through inhibition of kynurenine transport across the BBB

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During inflammation the majority of brain kynurenine crosses the blood-brain barrier from the blood via the large amino acid transporter-1 (LAT-1). Mitigating LAT-1-mediated transport of excess kynurenine may offer a novel intervention strategy for inflammatory psychiatric disorders, such as depression and schizophrenia, by reducing the amount of brain kynurenine available for metabolism into neurotoxic metabolites. To test this hypothesis, we induced inflammation using lipopolysaccharide (LPS vs saline) in mice and assessed behaviors relevant to depressive/negative symptoms and hyperdopaminergia. To inhibit kynurenine blood-to-brain transport, mice were treated with leucine (vs vehicle). Leucine has a higher LAT-1 affinity than kynurenine, and we have previously shown that leucine reduces brain kynurenine concentrations and depressive/negative relevant behaviors in mice. Here, we found that two injections of LPS (0.84 mg/kg, ip, 16 h apart) exacerbates dexamphetamine-induced hyperlocomotion at 40 h during peak sickness, indicative of inflammation-induced hyperdopaminergia. When LPS injections are spaced 24 h apart and mice are tested at 72 h, exacerbated hyperlocomotion is retained in the absence of sickness behavior, suggesting that dopamine dysregulation triggered by inflammation persists. Leucine reduced LPS-induced hyperlocomotion in response dexamphetamine. To explore whether increased kynurenine alone is sufficient to induce hyperdopaminergia- relevant behaviors, we injected exogenous kynurenine (33 mg/kg, ip) 2h prior to dexamphetamine. Preliminary data indicate that kynurenine increased hyperlocomotion even in the absence of inflammation. Together, these findings support further investigation into targeting LAT-1 mediated kynurenine transport to mitigate the positive and negative symptoms of inflammatory schizophrenia.

Symposium – PHYSICAL EXERCISE AND NUTRITION - SPOTLIGHT ON THE KYNURENINE PATHWAY
Thursday, June 11th, 14.30 – 15.50

Abstract 31

Myeloid cell Gpr35 and the systemic effects of kynurenic acid

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Kynurenic acid (Kyna) is an immunoregulatory metabolite known to promote the resolution and restraint of inflammatory responses. In peripheral tissues, Kyna exerts context- dependent effects that include anti-inflammatory actions in the gastrointestinal tract and adipose tissue, as well as improvements in insulin sensitivity and energy metabolism. Notably, circulating Kyna levels are elevated in seemingly disparate contexts, such as during acute physical exercise and in states of chronic inflammation. Emerging evidence suggests that not only the magnitude, but also the temporal pattern of Kyna exposure (intermittent versus persistent), critically influences its biological effects. Here, we investigated the extent to which the peripheral actions of Kyna are mediated by the immune system, with a particular focus on its receptor Gpr35. Strikingly, pan-hematopoietic deletion of Gpr35 resulted in a metabolic phenotype closely resembling that of whole-body Gpr35 knockout mice. This phenotype was recapitulated by Cx3cr1-Cre–mediated deletion of Gpr35, which preferentially targets monocytes and macrophages, with additional recombination in dendritic and iNKT cells. Using a combination of FACS and RNA-seq immune cell profiling in the circulation and adipose tissue, we will present new insights into how Kyna–Gpr35 signaling modulates mononuclear myeloid cell function and downstream tissue responses. Given the central role of immune cell recruitment and regulation in tissue homeostasis, these findings suggest a broader mechanism by which Kyna may regulate peripheral tissue function across physiological and pathological contexts.

Symposium – PHYSICAL EXERCISE AND NUTRITION - SPOTLIGHT ON THE KYNURENINE PATHWAY
Thursday, June 11th, 14.30 – 15.50

Abstract 32

Kynurenic acid and xanthurenic acid can be induced systemically by acute exercise: What about AHR activation?

Niklas Joisten

TU Dortmund University, Dortmund, Germany

The kynurenine pathway of tryptophan metabolism can be influenced by acute physical exercise in skeletal muscle, immune cells, and systemically, with endurance exercise being the most potent stimulus. To increase systemic levels of both kynurenic acid (KA) and (XA) xanthurenic acid, either longer-term moderate continuous exercise (i.e. 40 min.) or shorter- term high-intensity exercise (~12 min) can be performed. The subsequent physiological actions of systemically elevated KA and XA levels are insufficiently understood. Both metabolites, KA and XA, serve as ligands of the aryl hydrocarbon receptor (AHR), which is ubiquitously expressed in the human body and has been described to regulate anti- inflammatory actions. In this talk, we will present unpublished data on an acute exercise bout, investigating systemic tryptophan metabolite levels and potential AHR activation in peripheral blood mononuclear cells and in circulating CD4+ T-cells.

Symposium – PHYSICAL EXERCISE AND NUTRITION - SPOTLIGHT ON THE KYNURENINE PATHWAY
Thursday, June 11th, 14.30 – 15.50

Abstract 33

The impact of dietary intake on plasma kynurenines and subsequent domains of quality of life in colorectal cancer survivorship

Simone JPM Eussen

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The tryptophan-kynurenine pathway is the primary route to metabolize the essential amino acid tryptophan, while several vitamins and minerals are required for enzyme activity within this pathway. The metabolites of this pathway (also referred to as kynurenines) potentially have inflammatory, oxidative, and neuroactive properties. This suggests that the tryptophan-kynurenine pathway is an underlying mechanism explaining the relationship between diet and chronic disease. Specifically, this presentation will focus on the role of neuro-inflammatory metabolites of the kynurenine pathway in colorectal cancer survivorship presenting showing results of longitudinal associations on (1) dietary intake (e.g. dietary patterns, specific food groups, and macro- and micronutrients) with plasma kynurenines; of (2) plasma kynurenines with domains of quality of life, fatigue, anxiety and depression; and of (3) dietary intake with domains of quality of life, in which kynurenines served as potential mediators. These results are derived from the Energy for Life after ColoRectal cancer (EnCoRe) study, a multicenter, prospective cohort study among newly diagnosed stage I-III CRC patients being followed up until 12-months after the end of CRC-treatment. Repeated measurements of dietary intake, plasma kynurenines, and outcomes were performed at 6- weeks, 6-months, and 12-months post-treatment. Confounder-adjusted linear mixed models and mediation analyses were used to analyze all longitudinal associations. Furthermore, the rationale for future research directions will be discussed, including proposed work on the synergistic impact of dietary intake and physical activity on plasma kynurenines among diverse study populations, alongside a more comprehensive panel of biomarkers and a broader spectrum of health outcomes.

Symposium – PHYSICAL EXERCISE AND NUTRITION - SPOTLIGHT ON THE KYNURENINE PATHWAY
Thursday, June 11th, 14.30 – 15.50

Abstract 34

Physical exercise and tryptophan metabolism in multiple sclerosis: kynurenines, indoles, and beyond

Marie Kupjetz

TU Dortmund University, Dortmund, Germany

Kynurenine pathway imbalance is a common hallmark of inflammation-related and neurodegenerative diseases, including multiple sclerosis (MS). Several studies have meanwhile been conducted to decipher if MS-related kynurenine pathway imbalance is merely a passive bystander or plays an active role in disease pathophysiology and clinical expression. This talk will first focus on current knowledge linking kynurenine pathway imbalance to disease severity, established MS biomarkers and symptoms, as well as body composition and performance metrics. Building on that, an overview will be given of physical exercise as a powerful means to modulate kynurenine pathway imbalance, distinguishing between different exercise modalities, and between the effects of *acute* exercise (i.e., immediate effects of a single session) and *chronic* exercise (i.e., sustained effects of regular training) over intervention periods up to 24 weeks. An emphasis will be placed on our recently discovered kynurenine pathway patterns, which provide a novel framework to study the kynurenine pathway metabolome and possess translational potential to address various other research questions. Beyond the kynurenine pathway, this talk will also touch upon two important metabolic interfaces of the kynurenine pathway: B vitamins and tryptophan-derived indoles formed by the gut microbiota. First insights will be shared on how physical exercise can modulate both the systemic levels of B vitamins and indoles, along with a translational perspective on the potential relevance of these exercise-induced changes in MS.

Symposium – THE ROLE OF TRYPTOPHAN METABOLISM IN HEALTHSPAN: MOLECULAR AND PHYSIOLOGICAL INSIGHTS
Thursday, June 11th, 16.20 – 17.20

Abstract 35

Investigating healthy ageing mechanisms mediated by the kynurenine pathway

Anna Ainslie [1], Renée Seinstra [1], Yifan van Hasselt [1], Emma Westenberg [1], Martijn van Faassen [2], Claude van der Ley [2], Lisanne van der Molen [2], Ido Kema [2], Ellen Nollen [1]

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A promising target for aging intervention is the Kynurenine Pathway (KP) enzyme tryptophan 2,3-dioxygenase (TDO-2). Depletion of TDO-2 increases motility and lifespan in ageing C. elegans, and in other neurodegenerative disease (ND) models. However, our understanding of the mechanisms and tissue-specificity of neuroprotection by TDO-2 depletion is still limited. By combining transcriptomic analysis, metabolomics, proteomics, and live imaging data we have identified a common expression pattern in the hypodermis during ageing of KP enzyme genes. In contrast, the localization patterns of the KP branch enzymes (that produce neuroactive metabolites) diverge, suggesting that there is a dynamic and tissue-specific regulation of metabolite production that also shifts during ageing. We have also optimized the auxin-inducible degron tool to elucidate the dynamic local and systemic changes that are induced by TDO-2 depletion. We are analyzing transcriptomic, metabolomic and proteomic changes after degrading TDO-2 somatically during adulthood. These analyses will help us develop further insights to the protective effect due to metabolic shifts that occur after losing TDO-2. Overall, we aim to understand the tissue-specific role of KP enzymes and metabolites in neuroprotection and thus elucidate potential mechanisms to help fight neurodegeneration in ageing.

Symposium – THE ROLE OF TRYPTOPHAN METABOLISM IN HEALTHSPAN: MOLECULAR AND PHYSIOLOGICAL INSIGHTS
Thursday, June 11th, 16.20 – 17.20

Abstract 36

Elevating Physiological 3-Hydroxyanthranlic Acid Levels to Extend Healthy Lifespan

George Sutphin

University of Arizona, Tucson, AZ, USA

Tryptophan metabolism through the kynurenine pathway becomes dysregulated during normal aging and is implicated in many age-associated diseases, including chronic inflammation, atherosclerosis, neurodegeneration, and cancer. Kynurenine pathway enzymes and metabolites influence a range of molecular processes critical to healthy aging, including regulation of inflammatory and immune responses. Kynurenine metabolism is active in immune cells and activated in response to proinflammatory cytokine signaling. We discovered that elevating physiological levels of the kynurenine pathway metabolite 3- hydroxyanthranilic acid (3HAA) via either direct supplementation or inhibition of the enzyme that degrades 3HAA, 3HAA dioxygenase (HAAO), extends lifespan and delays age- associated health decline in both roundworms and mice. In recent work, we find that elevating physiological 3HAA can beneficially enhance both stress resilience and the immune response of *C. elegans* to bacterial pathogens during aging. In the absence of HAAO, 3HAA accumulates in lysosome related organelles (LROs) in the intestinal cells of *C. elegans*, the same subcellular compartment that contains engulfed bacteria. LROs are a cellular repository for both iron and zinc, and we further find that iron chelation or zinc supplementation dramatically enhances the bactericidal properties of 3HAA. Here we present a mechanistic model in which age-dependent accumulation of 3HAA in intestinal LROs combines with changes to iron and zinc homeostasis to enhance stress and bacterial pathogen resistance with age in *C. elegans*.

Symposium – THE ROLE OF TRYPTOPHAN METABOLISM IN HEALTHSPAN: MOLECULAR AND PHYSIOLOGICAL INSIGHTS
Thursday, June 11th, 16.20 – 17.20

Abstract 37

Tryptophan Metabolic Flexibility in Health and Disease

Maralice Conacci Sorrell

University of Texas Southwestern Medical Center, Dallas, USA

Cancer cells exhibit metabolic programs and nutrient dependencies that differ fundamentally from those of normal tissues. Defining these tumor-specific nutrient demands can uncover selective metabolic vulnerabilities with therapeutic potential. We have discovered that MYC-driven liver tumors display an increased reliance on tryptophan (Trp) uptake. Although Trp is the largest and most structurally complex amino acid-and the least abundant in the proteome, its indole ring supports metabolism through the serotonin, kynurenine (Kyn), and indole-3-pyruvate (I3P) pathways. We will discuss Trp as an alternative source of energy and signaling molecules in cancer cells.

Session 3 – CANCER 2
Thursday, June 11th, 17.20 – 17.50

Abstract 38

Spatial orchestration of tryptophan metabolism reveals self- reinforcing loops driving immune suppressive microenvironments in glioblastoma

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The importance of tryptophan (Trp) metabolism extends beyond protein synthesis and the production of neurotransmitters. In cancers, Trp catabolizing enzymes (TCEs) produce a plethora of metabolites that drive immune suppression and cell motility. In particular indoleamine-2,3-dioxygenase 1 (IDO1) and tryptophan-2,3-dioxygenase 2 (TDO2) that produce kynurenine (Kyn), and interleukin-4 induced 1 (IL4I1) that produces indole-3- pyruvate (I3P) mediate these immune suppressive effects by activating the aryl hydrocarbon receptor (AHR). The activity of the Trp-AHR axis is more pronounced in mesenchymal GB tumors. Studies have shown that transforming growth factor beta (TGFB) is important for the transition of GB tumors to aggressive mesenchymal subtypes. We set out to investigate if TGFB and the Trp-AHR axis interact to maintain immune suppression in GB patients. Single cell RNAseq analysis shows that TCEs are preferentially expressed in tumor and immune cell types. Spatial analysis of GB tissues shows the compartmentalized induction of TCEs by TGFB, which leads to AHR activation. We describe for the first time a self- sustaining TGFB-TCE-AHR loop in GB and highlight the importance of introducing spatial diagnostics in patient stratification.

Session 3 – CANCER 2
Thursday, June 11th, 17.20 – 17.50

Abstract 39

Rethinking IDO1 in the tumor microenvironment: new insights into non-canonical targeting of IDO1 in cancer immunotherapy.

Sofia Rossini, Sara Ambrosino, Ciriana Orabona

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Indoleamine 2,3-dioxygenase 1 (IDO1) is a plastic immune checkpoint molecule that potently orchestrates immune responses within the tumor microenvironment. As a heme- containing enzyme, IDO1 converts the essential amino acid tryptophan into immunoactive kynurenines, generating an immunosuppressive microenvironment through both tryptophan depletion and kynurenine-mediated regulatory functions. Although the enzymatic activity of IDO1 in cancer critically participates to tumor-escape processes, clinically trialed IDO1 catalytic inhibitors disappointed the expected anti-tumor efficacy. Therefore, we here revised the "on-target" mechanism of these compounds, with the aim of clarifying and overcoming the pitfalls of current IDO1 targeting strategies in cancer. Specifically, the most promising IDO1 catalytic inhibitors – epacadostat, linrodostat, and navoximod – beside blocking its enzymatic activity, persistently stabilize a non-enzymatic conformation of IDO1 in human tumor models, suggesting an unexpected "on-target" adverse effect of these compounds. Of note, in the tumor cells, the stabilized non-enzymatic IDO1 protein triggers a pro-tumorigenic signaling, enhancing the intrinsic tumor proliferation and overcoming the expected anti-cancer potential of IDO1 catalytic inhibition. By contrast, the use of IDO1 protein degraders significantly abrogates the pro-tumorigenic phenotype of cells, unveiling the importance of targeting the dual function of IDO1 – i.e., enzymatic and non-enzymatic – within the tumor. Overall, our results uncover an adverse pro-tumorigenic effect of conventional IDO1 catalytic inhibitors in the tumor microenvironment and suggest protein degradation, rather than enzymatic inhibition, as a novel therapeutic approach to efficiently target enzymatic and non-enzymatic IDO1 in cancer.

Session 4 – VARIOUS TOPICS
Thursday, June 11th, 17.50 – 18.20

Abstract 40

Compartmentalized regulation of the tryptophan metabolism across blood, urine, saliva, and sebum

Najwa-Joelle Metri [1], Sonia Bustamante [2], Chunguang Liang [3], Genevieve Z Steiner-Lim [1], Chai K Lim [4]

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Introduction: Tryptophan metabolism is a key regulator of immune, metabolic, and neurobiological processes and is widely implicated in many health conditions. Most human studies rely on blood-based measurements, implicitly assuming that circulating metabolites reflect global kynurenine pathway (KP) activity. Whether KP regulation is instead structured across distinct biological compartments remains poorly understood.
Methods: We performed targeted metabolomic profiling of tryptophan metabolism, encompassing both serotonin- and kynurenine-pathway metabolites and enzyme-derived ratios, in matched serum, plasma, saliva, urine, and sebum samples from 20 healthy individuals. Multi-omics factor analysis (MOFA+) was used to identify latent metabolic axes across biofluids, and structural equation modeling (SEM) was applied to test biologically informed relationships between these latent components.
Results: MOFA+ identified three robust and biologically interpretable latent factors underlying KP metabolism across the five biofluids. These factors captured distinct and largely non- overlapping sources of variation, indicating that KP regulation is partitioned into multiple metabolic domains rather than governed by a single systemic process. One factor was predominantly expressed in sebum-derived metabolites, a second showed coordinated variation across blood and saliva, and a third was dominated by urinary KP metabolites. No latent factor corresponded to a global blood-dominated inflammatory KP signature. SEM supported a structured relationship among these latent components.
Conclusions: KP metabolism comprises multiple compartmentalized regulatory domains extending beyond what can be inferred from blood alone. Multi-fluid profiling therefore provides a powerful framework for resolving tissue-specific KP biology and for developing non-invasive biomarkers.

Session 4 – VARIOUS TOPICS
Thursday, June 11th, 17.50 – 18.20

Abstract 41

Edaravone Modulates IDO1-Dependent Tryptophan Metabolism

Chiara Suvieri [1], Sara Ambrosino [1], Valeria Valsecchi [2], Luca Regazzoni [3], Michele Protti [4], Laura Mercolini [4], Elva Morretta [5], Mariachiara Monti [5], Ciriana Orabona [1], Claudia Volpi [1]

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease involving neuroinflammation and metabolic dysfunction. Beyond oxidative stress, which drives neurodegeneration and glial/endothelial impairment, increasing attention has focused on alterations in tryptophan metabolism and the kynurenine pathway (KP). Indoleamine 2,3- dioxygenase 1 (IDO1), the rate-limiting enzyme of the KP, has emerged as a critical regulator of immune responses and neuronal survival. Recent evidence suggests that edaravone (EDA), an approved ALS therapy, can inhibit 3-hydroxyanthranilate 3,4-dioxygenase (3HAO), a downstream KP enzyme generating quinolinic acid precursors. Therefore, we investigated whether EDA also modulates the KP through IDO1. Preliminary in vitro studies were performed in p1HTR cells transfected with murine IDO1 or empty vector. EDA exhibited a dose-dependent inhibition of kynurenine production (IC_{50}= 27 μM), independent of its antioxidant activity, as ascorbic acid had no effect at similar concentrations. Cytotoxicity and protein stability were excluded by cell counting, MTT, and CHX-chase assays. Notably, inhibition was absent in biochemical assays using recombinant IDO1, indicating that EDA does not exert a direct inhibitory effect on IDO1 catalytic activity. We thus investigated whether EDA might decrease kynurenine production by favoring the signaling conformation of IDO1 over its catalytically active form. Indeed, immunoprecipitation analysis revealed increased IDO1 tyrosine phosphorylation upon EDA treatment, without altering total expression, in both p1HTR and IFN_{γ}-stimulated BV2 microglial cells. These findings indicate that EDA could modulate IDO1 signaling independently of its antioxidant properties, highlighting a potential additional therapeutic mechanism. Understanding EDA's impact on the KP, particularly IDO1, may identify novel avenues for ALS intervention.

Joint symposium co-organized by ICAAS, JSTRY and ISTRY – LIFESTYLE FACTORS: DIET AND NUTRITION
Friday, June 12th, 9.00– 10.30

Abstract 42

Metabolic dysfunction associated steatohepatitis (MASH) in niacin insufficiency

Tsutomu Fukuwatari

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Purpose: Metabolic dysfunction-associated steatohepatitis (MASH), a progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD), increases the risk of cirrhosis and hepatocellular cancer. NAD regulates a variety of processes including lipid accumulation, ER stress, inflammation and fibrosis in fatty liver diseases, and enhancement of NAD levels improves fatty liver diseases. However, relationships between niacin nutritional status and fatty liver diseases remains to be elucidated. We have recently established the model mice to show several niacin nutritional statuses. In the present study, we investigated the effects of niacin insufficiency on MASH in mice.
Methods: Adult kynurenine 3-monooxygenase knock out (KMO-/-) mice were fed choline- deficient methionine-reduced high-fat diet (CDAHFD) or control diet containing insufficient or sufficient nicotinic acid for 12 weeks. Niacin nutritional status, MASH pathology and MASH related genes expressions were evaluated.
Results: Niacin insufficient diets caused low NAD levels in the blood and liver without any niacin deficient symptoms. Liver histology showed CDAHFD-induced fibrosis in the niacin sufficient, and severe fibrosis and necrosis in the insufficient mice. CDHFD also enhanced MASH related genes expressions such as fibrosis, inflammation, inflammasome and ER stress markers in the liver, and further their expressions were found in the niacin insufficient MASH mice.
Conclusion: Niacin insufficiency develops MASH pathology with severe fibrosis and inflammation. Our findings suggest that low NAD status cannot properly regulate ER stress, inflammation and fibrosis in MASH.

Joint symposium co-organized by ICAAS, JSTRY and ISTRY – LIFESTYLE FACTORS: DIET AND NUTRITION
Friday, June 12th, 9.00– 10.30

Abstract 43

Effects and Mechanisms of Anti-Inflammatory Food Components on Tryptophan Metabolic Key Enzymes and the Brain-Gut Axis

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Purpose: Chronic inflammation causes various diseases, including lifestyle-related diseases and neurodegenerative disorders. Therefore, it is important to prevent chronic inflammation. Some dietary components have anti-inflammatory effects in vivo. Indole amine 2,3 dioxygenase (IDO) and 2-Amino-3-carboxymuconate-6-semialdehyde decarboxylase (ACMSD) are metabolic key enzymes that play pivotal role in tryptophan degradation via kynurenine pathway. Induction of IDO and suppression of ACMSD lead to an increase in neurotoxin quinolinic acid production. In this study, we examined the effects of water- soluble dietary fiber (SDF) on expression of tryptophan-NAD metabolic key enzymes, brain inflammation and gut microbiota in mice fed a high-fat diet.
Methods: The mice were fed a standard diet (ST), a high fat diet (HF), or a high fat diet + SDF (HF- SDF) for 16 weeks. Expression of genes involved in tryptophan key enzymes, tight junction and inflammatory cytokines was assayed by real-time quantitative PCR. The gut microbiota composition was analyzed by 16S rRNA gene sequencing.
Results: Body weight gain and mesenteric fat tissue were significantly higher in the HF group than in the ST group. HF group induced the expression of *TNF-α* and *IDO* in hippocampus. Their expression was significantly suppressed in HF-SDF group. SDF increased the expression of tight junctions in the hippocampus. The abundance of some short chain fatty acid-producing gut bacteria was altered by SDF feeding.
Conclusion: SDF suppresses inflammation by altering the gut environment, further increases tight junction expression in the hippocampus, and also affects tryptophan metabolism in the brain. SDF may contribute to preventing brain inflammation.

Joint symposium co-organized by ICAAS, JSTRY and ISTRY – LIFESTYLE FACTORS: DIET AND NUTRITION
Friday, June 12th, 9.00– 10.30

Abstract 44

Relevance and safe intake of amino acids in supplements for human nutrition

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From clinical trials and experimental studies, it appears that supplementation with one or several specific amino acids may be relevant to correct for amino acid inadequate intake in case of insufficient supply, mostly from dietary proteins. Such supply is considered as insufficient by comparison with the amounts needed for optimal metabolism and physiological functions in different specific situations. However, it is essential not to overdose with excessive quantities of amino acids in supplements, thus beyond the upper level of safe intake (ULSI). In this presentation, I will recapitulate the protein and amino acid requirements for the general population and for subgroups of population including vulnerable subgroups, and these requirements will be compared to the usual consumption. Typical examples of clinical studies showing beneficial effects from amino acid supplementation in different pre-pathological and pathophysiological contexts will be presented together with results obtained from experimental studies performed in that field. Finally, parameters such as the No-Observed-Adverse-Effect-Level (NOAEL) values used to determine the ULSI for amino acid supplementation will be defined, and values determined in clinical trials will be given and discussed.

Joint symposium co-organized by ICAAS, JSTRY and ISTRY – LIFESTYLE FACTORS: DIET AND NUTRITION
Friday, June 12th, 9.00– 10.30

Abstract 45

The impact of gut microbiota on NAD⁺ metabolism

Keisuke Yaku, Takashi Nakagawa

Department of Molecular and Medical Pharmacology, Faculty of Medicine, University of Toyama, Japan

Nicotinamide adenine dinucleotide (NAD⁺) is one of the terminal metabolites of tryptophan metabolism via the de novo NAD⁺ synthesis pathway. Beyond its biosynthetic origin, NAD⁺ functions as an essential coenzyme in a wide range of cellular processes, including redox reactions, DNA repair, post-translational protein modifications, calcium signaling, and mRNA processing. Age-associated declines in NAD⁺ levels have been linked to metabolic dysfunction and increased vulnerability to age-related diseases, stimulating interest in strategies aimed at restoring NAD⁺ availability. Because NAD⁺ itself is not directly transported across cell membranes, nutritional precursors such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are widely used to enhance NAD⁺ biosynthesis. These intermediates have shown beneficial effects in animal models of metabolic and neurodegenerative disorders, and NMN supplementation has been reported to improve skeletal-muscle insulin sensitivity in prediabetic women. Nevertheless, the in vivo metabolic fate of orally administered NAD⁺ precursors remains incompletely understood. In this study, we examined NAD⁺ metabolic dynamics in mice following oral administration of NAD⁺ precursors, with particular attention to contributions from the gut microbiota. Our findings indicate the presence of distinct utilization pathways and suggest revisions to current models of NAD⁺ precursor metabolism that incorporate host–microbial interactions. Together, these results provide new insight into NAD⁺ homeostasis in relation to tryptophan metabolism and may inform future nutritional and therapeutic approaches.

Joint symposium co-organized by ICAAS, JSTRY and ISTRY – LIFESTYLE FACTORS: DIET AND NUTRITION
Friday, June 12th, 9.00– 10.30

Abstract 46

CONCEPT - A Phase II, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of oral controlled-ileal-release nicotinic acid (CIR-NA) for inducing remission in subjects with prediabetes

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Background: Prediabetes, affecting nearly 20% of Germans, is a growing health concern, with 5-10% of cases advancing annually to type 2 diabetes mellitus (T2DM). The gut microbiome plays a vital role in regulating energy homeostasis and mediating the negative effects of obesity and is marked by an increased *Firmicutes*/*Bacteroidetes* ratio and reduced diversity. T2DM is also linked to changes in tryptophan metabolism, including NAD+ and nicotinic acid (NA). The relationship between gut microbiota and tryptophan is bidirectional and contributes to systemic inflammation, insulin resistance, and metabolic dysfunction in T2DM. Gut-targeted supplementation of NA by CIR-NA appears warranted.
Study design: The CONCEPT trial is a multi-center, prospective, randomized, double-blind, placebo-controlled study with a 26-week intervention period and a 4-week follow-up. A total of 390 participants with BMI ≥ 20 kg/m² and prediabetes will be randomly assigned to three groups of 130 participants each: 100 mg/d CIR-NA, 200 mg/d CIR-NA, or placebo. The primary objective is to assess the efficacy of CIR-NA on the remission of prediabetes at week 26. Secondary objectives are to assess the progression of prediabetes to T2DM and the individual levels of fasting plasma glucose, glycated hemoglobin and the 2-h oral glucose tolerance test at week 26. Participants will receive standardized lifestyle recommendations on nutrition and physical activity.
Scientific perspective: The proposed use of CIR-NA aims to enhance metabolic parameters by modifying intestinal microbiota through targeted NA release in the terminal ileum, thereby supplementing the intestinal epithelium and microbiota.

LECTURE
Friday, June 12th, 10.30– 11.15

Abstract 47

Serotonergic modulation of emotional processing

Catherine Harmer

University of Oxford, UK

Drugs targeting the serotonin system remain among the most widely prescribed treatments for depression, yet the mechanisms through which they exert their therapeutic effects continue to be refined. Traditional accounts have emphasised gradual neurochemical adaptations associated with delayed clinical improvement. However, an emerging body of work supports a more dynamic model in which serotonergic interventions act early in treatment on cognitive and affective processes that maintain depressive symptoms.

In particular, manipulations of central serotonin - through selective serotonin reuptake inhibitors (SSRIs) and dietary precursors such as tryptophan - have been shown to modify emotional processing biases. These biases influence how individuals perceive, attend to, and remember emotional information, and are typically skewed toward the negative in depression. Increasing serotonin availability typically reduces negative biases and enhances the processing of positive social cues, whereas depletion of tryptophan can induce the opposite pattern. Notably, these effects of SSRIs can emerge within hours to days, preceding measurable changes in mood. Neuroimaging studies implicate modulation of frontolimbic circuitry, including reduced amygdala reactivity to negative stimuli, supporting a model in which serotonergic treatments recalibrate emotional processing systems and facilitate more positive interactions with the social environment over time.

While emotional biases are increasingly recognised as a key target of antidepressant action, cognitive impairments are also a core feature of depression and are less consistently improved by standard treatments. Evidence from pharmacological challenge studies suggests that under some circumstances serotonergic manipulations can also affect non-emotional (or 'cold') cognitive function. In particular, the serotonin releaser fenfluramine, and the 5HT4 partial agonist prucalopride, have been shown to produce pro-cognitive effects across multiple domains, indicating that serotonergic modulation can extend beyond affective processing to influence cognitive function.

In this talk, I will review converging evidence from behavioural, pharmacological, and neuroimaging studies examining the effects of serotonergic manipulations - including SSRIs, tryptophan, and fenfluramine - on emotional and cognitive processes. I will discuss how these findings refine our understanding of antidepressant mechanisms and consider their implications for the development of novel treatments targeting the neurocognitive substrates of depression.

Symposium – TRYPTOPHAN METABOLISM AND NEURODEVELOPMENTAL RISK: MODELS AND MECHANISMS
Friday, June 12th, 11.40– 13.00

Abstract 48

Prenatal inflammation alters serotonergic and blood brain barrier development

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Keck School of Medicine of USC, USA

Well-defined transcription factors regulate the specification and axon outgrowth of fetal serotonergic neurons. However, the mechanisms by which extrinsic factors such as prenatal inflammation influence serotonergic neurodevelopment are not well characterized. We demonstrated that maternal immune activation (MIA) increases tryptophan metabolism to 5- HT in the placenta leading to elevated fetal blood and forebrain 5-HT concentration and delayed maturation of fetal serotonergic neurons *in vivo* (Goeden et al., 2016). Recent results also show that exogenous 5-HT regulates serotonergic neuron development *in vitro.* Furthermore, recent data obtained using a novel *ex vivo* whole mouse fetus umbilical perfusion system reveal a permeability gradient of the fetal blood-brain barrier (BBB) to 5- HT, leading to differential exposure of growing serotonergic axons and neurons to circulating 5-HT. Thus, fetal BBB maturation, which is directly affected by MIA (Zhao et al., 2022), and progressive changes in permeability to circulating 5-HT occur during a critical period of the endocrine regulation of serotonergic neuron development. BBB developmental timing could therefore influence normal serotonergic growth. This novel mechanism could be critical to understand how prenatal insults such as maternal inflammation, which affects both BBB formation and the establishment of the 5-HT system, leads to neurodevelopmental disorders in offspring.

Symposium – TRYPTOPHAN METABOLISM AND NEURODEVELOPMENTAL RISK: MODELS AND MECHANISMS
Friday, June 12th, 11.40– 13.00

Abstract 49

Dysregulated Prefrontal Astrocytes Mediate Cognitive Deficits via Kynurenine Acid

Viktor Beilmann [1], Johanna Furrer [1], Sina Schalbetter [2], Ron Schaer [2], Edoardo Tiziani [3], Matthias Wyss [4], Aiman Saab [4], Sarah Beggiato [3], Urs Meyer [2], Bruno Weber [1], Tina Notter [1]

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Astrocyte dysfunction is increasingly implicated in psychiatric disorders, yet the mechanisms linking glial activity to cognitive impairments remain poorly understood. Here, we identify astrocyte-derived kynurenic acid (KYNA), a neuroactive metabolite of the kynurenine pathway, as a key regulator of prefrontal circuits and behavior. In a mouse model of maternal immune activation, elevated peripheral kynurenine was associated with increased prefrontal astrocyte reactivity and impaired temporal order memory. These deficits were recapitulated in a model in which prefrontal astrocyte activity was selectively manipulated using chemogenetic DREADDs. Astrocyte stimulation increased central KYNA levels and the KYNA/KYN ratio, while other kynurenine pathway metabolites remained unchanged. By combining chemogenetic activation with pharmacological inhibition and astrocyte-specific knockdown of kynurenine aminotransferase II (KAT II), we demonstrate that astrocyte-derived KYNA suppresses parvalbumin-positive interneuron activity in the prefrontal cortex, leading to disinhibition of pyramidal neurons and cognitive impairments. These findings define a mechanistic astrocyte-KYNA-interneuron axis underlying cognitive dysfunction and highlight altered glial metabolism as a potential driver of circuit-level deficits in major psychiatric disorders.

Symposium – TRYPTOPHAN METABOLISM AND NEURODEVELOPMENTAL RISK: MODELS AND MECHANISMS
Friday, June 12th, 11.40– 13.00

Abstract 50

Sleep Disruptions in Pregnancy Trigger Inflammation and Tryptophan-Kynurenine Pathway Activation: Relevance to Neurodevelopmental Disorders

Ana Pocivavsek, Courtney J Wright

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Sleep impairments are common during pregnancy and are linked to adverse offspring outcomes. We presently investigate the impact of prolonged sleep fragmentation during pregnancy in rats on tryptophan metabolism via the kynurenine pathway. We hypothesize that prenatally elevated kynurenic acid (KYNA), an endogenous inhibitor of glutamatergic and cholinergic neurotransmission, is a mechanistic link between disturbed maternal sleep, inflammation, and poor offspring health. Wistar rats were experimentally manipulated the last week of pregnancy (embryonic day 15-21). Experiment 1: Chronic sleep fragmentation occurred via a novel paradigm that disrupted maternal sleep 18hrs/day. Experiment 2: Maternal diet was supplemented with kynurenine (100 mg/day), direct KYNA bioprecursor, to elevate kynurenine metabolism only. On embryonic day 21, we assessed maternal sleep, maternal plasma cytokines (27 multi-plex assay), and metabolites (kynurenine, KYNA) in maternal (plasma, brain) and male and female fetal (placenta, brain) samples. Sleep fragmentation reduced sleep (-62%) and significantly elevated maternal plasma IL-1beta, an activator of kynurenine metabolism, and IL-10, a pro-inflammatory cytokine. Sleep fragmentation did not alter maternal brain or plasma metabolites, yet elevated kynurenine in placenta and KYNA in fetal brain. Kynurenine diet impaired sleep quality (-10% sleep duration; elevated cage activity), yet plasma cytokines were unaffected. Kynurenine diet elevated KYNA systemically (maternal plasma; maternal brain; placenta; fetal brain). Kynurenine pathway activation was more pronounced in male fetal brain across experimental paradigms. Our prenatal models identify elevated fetal KYNA as a molecular consequence of inflammation and sleep disturbances translationally relevant for psychiatric illness.

Symposium – TRYPTOPHAN METABOLISM AND NEURODEVELOPMENTAL RISK: MODELS AND MECHANISMS
Friday, June 12th, 11.40– 13.00

Abstract 51

Gestational cannabinoid exposure reshapes extracellular kynurenic acid signaling in the ventral tegmental area of periadolescent offspring: a schizophrenia-related endophenotype

Sarah Beggiato

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Cannabis is the most commonly abused illicit drug during pregnancy, and epidemiological evidence links prenatal cannabis exposure (PCE), particularly to Δ9-tetrahydrocannabinol (THC), with increased schizophrenia (SZ) risk in offspring. Yet the mechanisms remain unclear, limiting biomarker discovery and prevention. The kynurenine pathway (KP) of tryptophan metabolism, especially kynurenic acid (KYNA), a neuromodulator associated with cognitive dysfunction and psychosis, is a candidate mechanism. Elevated KYNA levels in patients with psychotic disorders and in PCE male rats suggest KP dysregulation as a bridge between maternal THC use and later psychopathology. We therefore investigated whether PCE induces sex-specific alterations via KYNA dysregulation in the ventral tegmental area (VTA). Primiparous Sprague Dawley rats received THC (2 mg/kg, s.c., once daily) from gestational day 5–20. One periadolescent [postnatal day 24–28] rat of each sex per litter was used to determine extracellular KYNA levels by in vivo microdialysis in the VTA. In separate animals from the same cohorts, biochemical analyses of KP-related targets were performed. Basal VTA KYNA levels were significantly higher in male PCE periadolescent rats than in controls ($p<0.05$). An acute kynurenine challenge produced a selectively greater KYNA increase in males prenatally exposed to THC, a pattern also observed after short restraint and tail pinch stress ($p<0.05$). These findings suggest that VTA KYNA dysregulation may represent a sex-specific, SZ-related endophenotype of PCE and point to the KP as a promising target for intervention in vulnerable offspring.

Symposium – DISCERNING THE AhR CYTOSOLIC AND GENOMIC PATHWAY ENGAGED BY TRYPTOPHAN METABOLITES

Friday, June 12th, 14.30– 16.25

Abstract 52

Structural insights into the activation mechanism of the aryl hydrocarbon receptor, a receptor for tryptophan-derived metabolites

William Bourguet

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The aryl hydrocarbon receptor (AHR) is a ligand-dependent transcription factor playing key roles in a wide array of (patho)physiological processes in response to hundreds of external and natural substances. Historically, AHR has been recognized as the receptor for pollutants such as dioxins, polycyclic aromatic hydrocarbons (PAHs), or polychlorinated biphenyls (PCBs), where it mediates their metabolism and, in some cases, their harmful effects. In addition, many dietary components and derivatives, including a broad spectrum of tryptophan-derived metabolites produced both by the host and the microbiota, have been identified as inducers of AHR functions in development, immune regulation, or barrier tissue integrity. Dysregulation of AHR activity is associated with the development of various diseases, including autoimmunity, inflammatory diseases, endocrine disruption, metabolic disorders and cancer. Recent structural studies from our group and others have revealed key determinants of AHR ligand-binding affinity, specificity, and promiscuity, along with new mechanistic insights into receptor activation. We will highlight the most impactful results.

Symposium – DISCERNING THE AhR CYTOSOLIC AND GENOMIC PATHWAY ENGAGED BY TRYPTOPHAN METABOLITES
Friday, June 12th, 14.30– 16.25

Abstract 53

Discerning the AhR Cytosolic and Genomic Pathway Engaged by Tryptophan Metabolites

Laura Santambrogio

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The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that plays a central role in diverse (patho)physiological processes triggered by various environmental chemicals and naturally occurring substances, among which several Tryptophan Metabolites. Canonical AhR signaling involves the translocation of ligand bound AhR to the nucleus in complex with chaperone proteins, culminating with the formation of an active heterodimeric transcription factor encompassing AhR and ARNT. This will initiate a transcription program which includes transcription of *CYP1B1* as well as several other pro or anti-inflammatory transcription programs (genomic pathways). However, part of the anti- inflammatory AhR activity is also associated with AhR cytosolic signaling (cytosolic pathway) which include Ca2+ release from the ER/Golgi, c-Src kinase and PKA activation. Herein, using different biochemical and biophysical assays we will discuss how different AhR ligands engage the cytosolic vs the genomic(s) AhR-signaling pathways, by differently engaging the PAS-B-AhR domain. The immunological relevance of each transcription program and their therapeutic relevance will also be discussed.

Symposium – DISCERNING THE AhR CYTOSOLIC AND GENOMIC PATHWAY ENGAGED BY TRYPTOPHAN METABOLITES
Friday, June 12th, 14.30– 16.25

Abstract 54

Exploring the Anti-Tumor Potential of 3HKA Through Distinct AhR Signaling Routes

Sofia Rossini, Sara Ambrosino, Ciriana Orabona

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Background: 3-Hydroxy-kynurenamine (3HKA) is an amine derived from a lateral branch of tryptophan catabolism through the decarboxylation of 3-l-OH-kynurenine. Similar to the main tryptophan-derived metabolite l-kynurenine (KYN), 3HKA binds to the aryl hydrocarbon receptor (AhR) and exerts context-dependent biological effects. Previous studies have shown that 3HKA displays an anti-inflammatory profile in both mouse and human dendritic cells, reducing pro-inflammatory cytokine production and inhibiting the generation of effector $CD8^+$ T cells.
Objective: Despite its immunomodulatory activity, the direct impact of 3HKA on tumor cells has not yet been investigated.
Results: In this study, we explore for the first time the intrinsic effects of 3HKA on tumor cells expressing AhR. We observed that 3HKA exerts an anti-proliferative effect on tumor cells, reducing anchorage-dependent growth and slowing their migratory capacity. This anti- proliferative activity is associated with the activation of a canonical AhR genomic pathway, culminating in the induction of IDO1 expression and subsequent KYN production. In parallel, 3HKA also triggers a non-canonical cytosolic AhR pathway, leading to Src kinase phosphorylation.
Conclusions: These findings reveal that 3HKA directly modulates tumor cell behavior through both canonical and non-canonical AhR-dependent mechanisms, highlighting a previously unrecognized role for this tryptophan-derived metabolite in cancer biology. Discerning the AhR cytosolic and genomic pathways engaged by 3HKA in tumor cells will contribute to defining its potential role in shaping cancer cell behavior and its relevance within the broader framework of tryptophan-derived metabolites in cancer biology.

Symposium – DISCERNING THE AhR CYTOSOLIC AND GENOMIC PATHWAY ENGAGED BY TRYPTOPHAN METABOLITES
Friday, June 12th, 14.30– 16.25

Abstract 55

DC-Dependent AhR Signaling Controls Breast Cancer Progression

Aitziber Buque

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Hormone receptor-positive (HR⁺) breast cancer (BC) is the most prevalent BC subtype, and although CDK4/6 inhibitors have improved progression-free survival, resistance to standard therapies remains inevitable for most patients. Emerging evidence suggests that metabolic dysregulation within the tumor microenvironment (TME), particularly involving tryptophan metabolism and aryl hydrocarbon receptor (AhR) signaling, contributes to immune dysfunction and therapeutic failure. However, how distinct tryptophan-derived metabolites engage cytosolic versus genomic AhR pathways in specific immune compartments remains poorly understood. Here, we characterize the antitumor activity of 3-hydroxy-L-kynurenamine (3HKA), a tryptophan-derived biogenic amine internalized through AhR. In an endogenous, carcinogen-driven and hormone-accelerated model of HR⁺BC, systemic administration of 3HKA significantly delayed tumor onset and reduced subsequent tumor growth kinetics. Mechanistically, the antitumor effect of 3HKA was preserved in mice lacking B, T, and NK cells, demonstrating independence from adaptive and cytotoxic lymphocyte-mediated immunity. In contrast, depletion of DCs abrogated 3HKA efficacy. Consistent with a non- tumor-intrinsic mechanism, 3HKA displayed no direct cytotoxicity toward tumor cells in vitro and did not induce hallmarks of cellular stress or immunogenic cell death. Together, these findings identify 3HKA as a DC-dependent, non-cytotoxic metabolite that modulates antitumor immunity through AhR engagement independently of adaptive immune cells. Notably, tumor control does not require adaptive immune engagement typically associated with canonical, transcriptional AhR signaling, thereby functionally implicating a DC-intrinsic, predominantly non-genomic AhR signaling axis. This provides new insight into how distinct tryptophan metabolites differentially activate cytosolic versus genomic AhR pathways with functional consequences for cancer progression and therapeutic response.

Symposium – DISCERNING THE AhR CYTOSOLIC AND GENOMIC PATHWAY ENGAGED BY TRYPTOPHAN METABOLITES
Friday, June 12th, 14.30– 16.25

Abstract 56

Dietary L-Tryptophan determines the number of colonic GPR15+ regulatory T cells and susceptibility to colitis

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Environmental factors contribute to the onset of immunological disorders such as ulcerative colitis, but the mechanisms underlying this contribution remain unclear. Here, we demonstrate the effect of the ubiquitous dietary component L-tryptophan (L-Trp) on mucosal immune responses. We show that the amount of ingested L-Trp determines the number of colonic CD4+ T cells through the aryl hydrocarbon receptor (AhR), which activates transcription of the colon T-cell homing receptor GPR15. The default pathway linking L-Trp, AhR, GPR15, and T-cells is microbiota-independent and involves host IDO1/2 enzymes, selectively increasing GPR15+ Tregs. Two weeks of L-Trp supplementation nearly doubled the number of colonic GPR15+ Tregs and significantly reduced the risk of future colitis. Our extensive in vitro screening of AhR ligands suggests that AhR ligand-specific variations in target gene expression may account for the Treg-selective response to L-Trp. Thus, we uncovered unique, microbiota-independent mechanisms linking dietary L-Trp and colonic Tregs that may offer therapeutic promise.

Symposium – DISCERNING THE AhR CYTOSOLIC AND GENOMIC PATHWAY ENGAGED BY TRYPTOPHAN METABOLITES
Friday, June 12th, 14.30– 16.25

Abstract 57

AhR-Driven Immune Suppression in Soft Tissue Sarcomas: Implications for cDC1 Antitumor Immunity and Therapeutic Targeting

Estevão Carlos Silva Barcelos [1], Andrea Marra [2], Giada Mondanelli [1], Doriana Ricciuti [3], Francesco Sarnari [1], Manola Mezzanotte [1], Giorgia Manni [3], Alessandro Pinzi [3], Giulia Mencarelli [3], Benedetta Pieroni [3], Giulia Scalisi [4], Martina Mandanaro [3], Anna La Rosa [3], Kenneth M. Murphy [5], Francesca Fallarino [3], Marco Gargaro [1]

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Soft tissue sarcomas (STS) are characterized by an immunosuppressive tumor microenvironment that limits effective antitumor immunity. Aryl hydrocarbon receptor (AhR) signaling, driven by metabolites of tryptophan metabolism, promotes immune evasion, whereas conventional type 1 dendritic cells (cDC1) are key mediators of tumor control. This study evaluates the interplay between AhR activation and cDC1 function to determine how this metabolic axis governs patient prognosis in STS. Cox regression analysis of 259 TCGA- SARC samples showed that high cDC1 gene signature expression was associated with improved overall survival ($p = 0.008$), while AhR activation alone had no prognostic impact ($p = 0.118$). Notably, elevated AhR activation significantly attenuated the protective effect of cDC1 (coef = 0.323, HR = 1.382, $p = 0.018$). Transcriptomic profiling of cDC1/AhR^{high} versus AhR^{low} tumors revealed immune-related pathways consistent with potential immune exhaustion. To define the metabolic basis of AhR activation, we generated a single-cell transcriptomic atlas of 51 primary STS samples. cDC1 were rare but consistently expressed *AHR* and AhR activation gene signatures. Canonical tryptophan-catabolizing enzymes were minimally expressed in the TME: *IDO1* (1.18%) was found in immune cells, *TDO2* (2.07%) was found mainly in non-immune cells, and *IDO2* (0.38%) showed minimal expression. In contrast, *IL4I1*, a secreted L-amino acid oxidase protein capable of producing AhR-active metabolites, was enriched in the myeloid compartment (2.43%). *AHR* expression correlated with its activation signature across STS samples and varied among histological subtypes. Our findings suggest that AhR suppresses cDC1-mediated immunity in STS, revealing a potential target to enhance antitumor responses.

Symposium – DISCERNING THE AhR CYTOSOLIC AND GENOMIC PATHWAY ENGAGED BY TRYPTOPHAN METABOLITES
Friday, June 12th, 14.30– 16.25

Abstract 58

AhR Acts as a Metabolic Gatekeeper in Cross-Presenting cDC1 During Antitumor Immunity

Doriana Ricciuti [1], Estevão Carlos Silva Barcelos [2], Andrea Marra [3], Giada Mondanelli [2], Giorgia Manni [1], Francesco Sarnari [2,3], Giulia Mencarelli [1], Alessandro Pinzi [1], Benedetta Pieroni [1], Giulia Scalisi [4], Anna La Rosa [1], Manola Mezzanotte [2], Antonio Macchiarulo [2], Marco Colonna [5], Kenneth M. Murphy [5], Francesca Fallarino [1], Marco Gargaro [2]

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Tumor therapy relies on invasive procedures and nonselective cytotoxic drugs, and many patients fail to respond to current treatments. Conventional dendritic cells (DCs) are regulators of antitumor immunity in cancer immunosurveillance, with cDC1 being essential for early $CD8^+$ T-cell priming. The aryl hydrocarbon receptor (AhR) is an environmental sensor of endogenous and exogenous metabolites implicated in tumor immune escape and immune regulation. Here, we investigated the impact of AhR deletion in cDC1 on antitumor immune responses.Genome-wide analyses revealed that AhR is preferentially expressed in mature cDC1 compared with cDC2 and plasmacytoid DCs. Promoter analysis identified five AP1–IRF composite elements (AICEs), with ChIP-seq confirming IRF8 binding in cDC1. Using an integrated retroviral reporter system, we found that a single region containing the AICE1 motif selectively enhanced AhR transcription in cDC1. CRISPR–Cas9–mediated disruption of this AICE1 site suppressed AhR expression in cDC1. Functional ablation of AhR in cDC1 reduced the expression of the tryptophan-catabolizing enzyme IDO1 while enhancing IL-12 and TNF-α production. Consistently, in cDC1–$CD8^+$ T-cell co-cultures, AhR- deficient cDC1 increased proliferation and IFN-γ production by OT-I T cells. In a fibrosarcoma mouse model, single-cell RNA sequencing revealed high AhR expression in tumor-infiltrating cDC1. Selective AhR deletion in $XCR1^+$ cDC1 accelerated spontaneous rejection of progressive tumors, accompanied by increased intratumoral cDC1 accumulation and IFN-γ–producing $CD8^+$ T cells. These findings identify AhR as a metabolic gatekeeper restraining cDC1-mediated antitumor immunity and highlight AhR targeting in cDC1 as a strategy to overcome tumor immune tolerance and resistance to immunotherapy.

Session 5 – IMMUNOMETABOLISM
Friday, June 12th, 14.30– 16.25

Abstract 59

Characterization of the genetically modified IDO1H350A mouse model expressing a loss-of-function mutant of Indoleamine 2,3-dioxygenase 1 enzyme

Sara Ambrosino, Sofia Rossini, Ciriana Orabona

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Indoleamine 2,3-dioxygenase 1 (IDO1) is a key immunoregulatory enzyme that catalyzes the conversion of tryptophan (Trp) into kynurenine (Kyn) and participates in signal transduction pathways within immune and tumor cells, influencing cellular responses. To better understand the molecular mechanisms underlying IDO1's dual role, we resorted to an IDO1 loss-of-function mutant mouse model ($IDO1^{H350A}$), obtained by the replacement of histidine with alanine at position 350 in the IDO1's catalytic site. Serum analysis revealed a markedly reduced Kyn/Trp ratio in $IDO1^{H350A}$ mice, confirming loss of enzymatic activity. Although IDO1 protein expression was similarly inducible by pro-inflammatory stimuli in splenocytes and conventional dendritic cells (cDCs) from both genotypes, enzymatic activity was undetectable in immune cells from $IDO1^{H350A}$ mice. Moreover, $IDO1^{H350A}$ protein displayed increased stability in cDCs, with a prolonged half-life of 16 hours compared with 7.6 hours for $IDO1^{WT}$. Functional analyses further demonstrated a similar inflammatory phenotype in LPS-stimulated splenocytes and cDCs expressing $IDO1^{H350A}$ compared to WT controls. To investigate the IDO1 non-enzymatic functions in the tumor microenvironment, $IDO1^{H350A}$ mice were used as recipients for B16 melanoma cells. $IDO1^{H350A}$ mice showed a slower tumor growth and improved survival compared with $IDO1^{WT}$ recipients, while tumor progression was similar to that observed in $IDO1^{KO}$ animals. Notably, $IDO1^{H350A}$ mice exhibited enhanced survival respect to $IDO1^{KO}$ mice despite comparable tumor growth rates, suggesting an improved resistance to tumor burden. Collectively, the $IDO1^{H350A}$ model represents a powerful tool to dissect the *in vivo* contribution of IDO1's non-enzymatic functions in regulating immune activation and shaping the tumor microenvironment.

Session 5 – IMMUNOMETABOLISM
Friday, June 12th, 14.30– 16.25

Abstract 60

Cyp1a1 Controls the Balance Between Inflammatory and IDO1-Dependent Programs in Type-2 Dendritic Cells

Manola Mezzanotte [1], Alessandro Pinzi [2], Francesco Sarnari [1], Benedetta Pieroni [2], Giorgia Manni [2], Giulia Mencarelli [2], Doriana Ricciuti [2], Estevão Carlos Silva Barcelos [1], Giada Mondanelli [1], Carsten Schmidt-Weber [3], Caspar Ohnmacht [3], Anna La Rosa [2], Francesca Fallarino [2], Marco Gargaro [1]

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Aim: Dendritic cells (cDCs) are professional antigen-presenting cells that orchestrate immune responses against pathogens and tumors and adapt to environmental cues. The aryl hydrocarbon receptor (AhR) senses environmental signals and regulates immune responses by inducing cytochrome P4501 enzymes to metabolize AhR ligands. The role of Cyp1a1 in cDC subsets is not fully understood. We investigated its functional role and impact on immune responses.
Methods: cDC1 and cDC2 were generated from WT and *Cyp1a1 -/-* bone marrow and analyzed by flow cytometry. Cyp1a1 expression, unstimulated or LPS-stimulated, was measured by real-time PCR. Cytokine production was quantified in supernatants using Luminex. Antigen presentation was tested by co-culturing sorted cDC2 with CellTrace Violet–labeled OT-II T cells and soluble OVA.
Results: We demonstrated that Cyp1a1 deficiency doesn't alter the DC development. Cyp1a1 deficiency did not affect cDC development. Upon LPS stimulation, Cyp1a1 expression was selectively induced in cDC2 compared to cDC1. WT cDC2 displayed a proinflammatory cytokine profile characterized by robust IL-6 production, whereas *Cyp1a1 -/-* cDC2 showed a marked reduction of IL-6 and other inflammatory mediators. Notably, IL-6–producing cDC2 failed to induce Ido1 expression in response to LPS. In contrast, Cyp1a1-expressing cDC2 upregulated Ido1 following LPS stimulation, indicating a functional link between Cyp1a1 activity and engagement of immunoregulatory pathways. Consistently, Cyp1a1-deficient cDC2 exhibited a reduced capacity to sustain OT-II T cell proliferation.
Conclusion: Cyp1a1 controls cDC2 functional polarization by coupling AhR ligand metabolism to the balance between inflammatory cytokine production and IDO1 induction, highlighting a novel pathway to fine-tune cDC2-driven immune responses.

Session 5 – IMMUNOMETABOLISM
Friday, June 12th, 14.30– 16.25

Abstract 61

IDO-1–Driven Immunotoxicity of BPA and Alternatives: A Pathway-Level Dose–Response Perspective

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Bisphenol A (BPA) and its analogues are established endocrine disruptors with emerging roles in immune modulation. Previously it was shown that BPA in suppressed tryptophan breakdown and cellular immune responses in human peripheral blood mononuclear cells and other immune cell models. An indoleamine 2,3-dioxygenase (IDO-1) transcriptomic signature for detecting immune-disruptive properties of environmental chemicals has been developed to complement current assessments based on the detection of biochemical markers. A robust gene signature was developed based on the combination of publicly available gene sets focusing on IDO-1 related signaling, and candidate genes were optimized though multiple feature selection approaches to reduce redundancy and enhance the specificity of the signature. For evaluation of the IDO-1 signature public RNA-seq data (MCF-7, GSE211183) from cells exposed to 16 bisphenols analogues were analyzed. Four compounds (BPA, BPAF, BPS, 4,4'-BPF) were selected for detailed analysis. Dose-response analysis using DoseRider revealed consistent downregulation of immune checkpoint genes and upregulation of proliferation-associated markers within the IDO-1 signature. Pathway enrichment confirmed disruption of tryptophan metabolism and interferon-related signaling. These results support that a transcriptomic signature provides a sensitive and mechanistic readout of IDO-1 inhibition induced by environmental chemicals such as BPA and analogues.

Session 5 – IMMUNOMETABOLISM
Friday, June 12th, 14.30– 16.25

Abstract 62

Tryptophan catabolism via IDO1 shapes metabolic adaptation in migratory cDC1

Giada Mondanelli [1], Estevao Carlos Silva Barcelos [1], Doriana Ricciuti [2], Francesco Sarnari [3], Manola Mezzanotte [2], Giorgia Manni [2], Francesca Fallarino [2], Fabrizia Bonacina [4], Marco Gargaro [1]

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The functional specialization of dendritic cells (DCs) during their migration from peripheral tissues to lymph nodes requires a coordinated metabolic adaptation. While indoleamine 2,3-dioxygenase 1 (IDO1) is well recognized for its immunoregulatory properties via tryptophan degradation, its role in shaping DC bioenergetics during homeostasis and immune activation remains poorly defined. To investigate the relationship between tryptophan metabolism and cellular metabolic states, we analyzed type 1 conventional DCs (cDC1) undergoing the acquisition of a CCR7^{+} migratory phenotype. Transcriptomic and functional analyses revealed that CCR7^{-} cDC1 are metabolically expanded, displaying upregulation of oxidative phosphorylation, glycolysis, and lipid metabolism pathways. In contrast, CCR7^{+} cDC1 induced IDO1 and exhibited a restrained energetic profile. In *Ido1 -/-* mice, migratory DCs failed to repress anaerobic glycolysis, as indicated by increased *Ldha* expression and lactate accumulation, reflecting a loss of metabolic control. Notably, the CCR7^{+} migratory state was associated with a selective induction of *Ido1*, whereas CCR7^{-} *Ido1*$^{-}$ cDC1 retained a metabolically active and immunostimulatory profile, suggesting a close link between activation of tryptophan catabolism and metabolic adaptation. Together, these findings position IDO1-mediated tryptophan metabolism as a central regulator of cDC1 metabolic reprogramming and function. They also reveal a unique window of vulnerability in cDC1 that could be exploited to modulate immunogenicity and optimize immunotherapeutic strategies.

Session 5 – IMMUNOMETABOLISM
Friday, June 12th, 14.30– 16.25

Abstract 63

An IDO1–Kynurenine–AhR Metabolic Circuit Between Dendritic Cell Subsets Controls FVIII-Specific Immune Tolerance

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Background: The development of neutralizing antibodies against therapeutic FVIII is an immunological complication of replacement therapy in haemophilia A. As FVIII is considered a non-self-antigen, immune unresponsiveness relies on peripheral tolerance mechanisms mediated by dendritic cells (DCs). Among these, indoleamine 2,3-dioxygenase 1 (IDO1) plays a key role by metabolizing tryptophan into kynurenine metabolites, thereby promoting regulatory T-cell differentiation.
Purpose: Although the role of the IDO1–kynurenine–AhR axis in immune regulation is well known, its specific contribution to FVIII-specific tolerance remains unclear. This study aimed to identify the roles of cDC1 and cDC2 in influencing FVIII-specific immune responses and to explore the cellular and metabolic mechanisms driving immune tolerance to FVIII.
Results: Using conditional mouse models that allow selective depletion of DC subsets, we demonstrate that cDC1 protects against inhibitor development, while cDC2 promotes anti- FVIII antibody formation. In vivo activation of TLR9 by CpG specifically induced IDO1 expression in cDC1, leading to a significant decrease in inhibitor titers. Genetic removal of IDO1 in cDC1 eliminated this protective effect. Mechanistically, we identified a metabolic crosstalk between DC subsets mediated by L-kynurenine, produced by IDO1+ cDC1. L- Kynurenine activated AhR in neighboring cDC2, reprogramming them toward an immunoregulatory phenotype and limiting T follicular helper cell differentiation. This tolerogenic effect was antigen-specific and did not impair immune responses to unrelated antigens.
Conclusion: These findings identify the IDO1–kynurenine–AhR axis as a crucial metabolic pathway regulating FVIII-specific immune tolerance and emphasize its potential as a target to prevent inhibitor development in haemophilia A.

Session 5 – IMMUNOMETABOLISM
Friday, June 12th, 14.30– 16.25

Abstract 64

Amniotic Fluid Stem Cell–Derived Extracellular Vesicles Carry Functional IDO1 and Kynurenine to Metabolically Reprogram Dendritic Cells

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Purpose: Extracellular vesicles (EVs) derived from human amniotic fluid stem cells (HAFSCs) exhibit immunomodulatory properties, yet the contribution of immunometabolic pathways to their activity remains poorly defined. Since indoleamine 2,3-dioxygenase 1 (IDO1) and the kynurenine pathway are central regulators of immune tolerance, we investigated whether HAFSC-EVs transport tryptophan-degrading enzymes and metabolites and how they functionally affect target dendritic cells (DCs).
Methods: HAFSC-EVs were isolated and characterized by standard biophysical and molecular approaches. Proteomic analyses and targeted metabolomics were used to detect IDO1 and kynurenine within EVs. EV uptake by DCs was assessed, together with intracellular kynurenine levels and induction of endogenous IDO1 expression. Functional consequences were evaluated using antigen-specific T cell proliferation assays with OT-II $CD4^+$ T cells.
Results: HAFSC-derived EVs contained IDO1 protein that retained enzymatic activity within the vesicular compartment. Consistently, kynurenine was detected in EV preparations, indicating the presence of a functional tryptophan catabolic axis. Upon uptake by DCs, HAFSC-EVs delivered kynurenine, resulting in rapid intracellular accumulation of the metabolite. In addition, EV exposure induced de novo IDO1 expression in DCs, suggesting metabolic and transcriptional reprogramming of recipient cells. Functionally, DCs conditioned with HAFSC-EVs showed a significant reduction in antigen-driven OT-II T cell proliferation, demonstrating the acquisition of a tolerogenic phenotype.
Conclusion: HAFSC-derived EVs act as carriers of functional IDO1 and kynurenine and reprogram DCs toward an immunoregulatory state. These findings reveal a novel EV-mediated immunometabolic mechanism with potential relevance for immune tolerance–based therapies.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 65

Prenatal Choline Supplementation Rescues Learning and Memory Deficits in Mice Exposed to Elevated Kynurenic Acid during Neurodevelopment

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Elevated brain levels of kynurenic acid (KYNA) are implicated in the pathophysiology of schizophrenia (SZ). By antagonizing cholinergic and glutamatergic neurotransmission, increased KYNA levels may be causally related to cognitive dysfunctions in SZ. In mice, ingestion of the KYNA precursor kynurenine [50 mg/day in the diet from embryonic days (ED) 11-18; "EKyn"] raises brain KYNA during neurodevelopment and results in cognitive impairments in adulthood compared to animals on a control diet ("ECon"). Here we investigated if perinatal supplementation with choline, an essential nutrient and agonist of α7nACh receptors, would affect the adverse learning observed in adult EKyn mice. Pregnant C57Bl/6J mice were fed a standard diet (0.1% choline chloride) or a choline-supplemented diet (0.5% choline chloride) from ED 11 to postnatal day (PD) 21. Upon weaning, all offspring received control chow until experimental testing in adulthood (PD 56-85). Adult offspring were assessed biochemically (microdialysis in prefrontal cortex), electrophysiologically (ex vivo recordings of interhemispheric transmission), and behaviorally (Barnes maze). Adult EKyn mice had significantly higher KYNA in the prefrontal cortex, delayed interhemispheric transmission, and showed increased latency to find the escape box and the number of errors in the Barnes maze. The behavioral impairment was not observed in offspring of EKyn mothers that received the high choline diet. The mitigation of cognitive impairments in adult EKyn offspring by choline supplementation early in life suggests a translationally relevant mechanism linking prenatal risk factors with cognitive dysfunction in SZ.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 66

Untangling the involvement of the Kynurenine Pathway in Drosophila models of neurodevelopmental disorders

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The kynurenine pathway is the major route of tryptophan catabolism, producing neuroactive metabolites that influence neuronal excitability, oxidative stress, and immune signalling. Alterations to this pathway have been extensively associated with neurodegenerative disorders, but the link with autism spectrum disorder and intellectual disability remains largely unexplored. Two key genes implicated in autism spectrum disorder and intellectual disability are *FMR1* (Fragile X), an RNA-binding protein regulating synaptic protein synthesis, and *RAB39B*, a small GTPase involved in vesicle trafficking. Loss of *d*FMR1 in *Drosophila* results in synaptic overgrowth, altered neuronal circuitry and behavioural changes such as disrupted circadian-rhythms, and social interaction deficits. Similar behavioural changes have been observed by our group in flies carrying a knockout for *d*RAB39. These flies display locomotor impairments, circadian-rhythm defects and mitochondrial dysfunction. Whether these phenotypes intersect with tryptophan-kynurenine metabolism and its downstream metabolites remains unknown. We aim to determine whether loss of *d*RAB39 or *d*FMR1 affects kynurenine pathway activity, and whether modulating this pathway could influence behavioural phenotypes in *Drosophila melanogaster*. To achieve this, we will manipulate kynurenine pathway activity by exploiting RNA interference and the GAL4/UAS system in the *Drosophila* central nervous system, including targeted manipulation of specific glial cell types such as astrocytes. We also aim to enhance specific branches of the pathway by overexpressing enzymes responsible for the production of 3-hydroxykynurenine (3-HK) and kynurenic acid (KYNA), or by directly treating these models with the two metabolites. This project will provide novel insights into the involvement of the kynurenine pathway in these neurodevelopmental diseases.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 67

Synthesis and modification of kynurenic acid-3-carboxylate derivatives

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Kynurenic acid (KYNA) is a metabolic product of L-tryptophan. The molecule is endogenous ligand of numerous receptors and its local concentration in the central nervous system correlates with several neurodegenerative diseases (e.g. Parkinson's disease, Alzheimer's disease, schizophrenia, migraine). Due to the diverse role of KYNA in wide variety of neurological diseases, it is important to investigate kynurenic acid derivatives' pharmacological properties and synthesize more compounds as potential new drug candidates. It is already known that KYNA has cytoprotective and neuroprotective effects, but its pharmacodynamical properties are not perfect. Our aim was to synthesize KYNA analogues that are 2,3-dicarboxylic acid derivatives by the reaction of isotonic anhydride and diethyl-acetylene dicarboxylate. Further these compounds were planned to react with primary amines to synthesize KYNA amides and imides. These newly synthesized molecules could act as neuroprotective agents as the mother compound and hopefully have more advanced pharmacodynamic properties.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 68

Assessment of an Anticancer Effect of the Simultaneous Administration of MM-129, a 1,2,4-triazine derivative and Indoximod in the Colorectal Cancer Model

Dariusz Pawlak, Iwona Kwiatkowska, Justyna Hermanowicz

Medical University of Bialystok, Poland

Background: The purpose of the given study was to examine the antitumor activity of the simultaneous administration of MM-129, a 1,2,4-triazine derivative (pyrazolo[4,3-e]tetrazolo[4,5-b][1,2,4]triazine sulfonamide), and indoximod (IND), the kynurenine pathway inhibitor, toward colon cancer.
Methods: The efficiency of the coadministration of the compounds studied was assessed in xenografted zebrafish embryos. Then, the effects of the combined administration of compounds on cellular processes such as cell viability, apoptosis, and intracellular signaling pathways were evaluated. In vitro studies were performed using two colorectal cancer cell lines, namely, DLD-1 and HT-29.
Results: The results indicated that the simultaneous application of MM-129 and indoximod induced a stronger inhibition of tumor growth in zebrafish xenografts. The combination of these compounds intensified the process of apoptosis by lowering the mitochondrial potential, enhancing the externalization of phosphatidylserine (PS) and activation of caspases. Additionally, the expression of protein kinase B (AKT) and indoleamine 2,3-dioxygenase-(1IDO1) was disrupted under the applied compound combination.
Conclusions: Simultaneous targeting of ongoing cell signaling that promotes tumor progression, along with inhibition of the kynurenine pathway enzyme IDO1, results in the enhancement of the antitumor effect of the tested compounds against the colon cancer cells.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 69

Disturbances of tryptophan metabolism in bone may inhibits PTH-dependent bone turnover in young rats with chronic kidney disease.

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Purpose: Disturbances in tryptophan (TRP) metabolism and secondary hyperparathyroidism are common features of chronic kidney disease (CKD). This study aimed to evaluate potential interactions between the bone kynurenine pathway (KP) and endogenous parathyroid hormone (PTH) in relation to bone turnover in young rats with experimental CKD.
Methods: TRP, kynurenine (KYN), the KYN/TRP ratio, and bone turnover markers (BTMs): alkaline phosphatase (ALP) and tartrate-resistant acid phosphatase 5b (TRAP-5b were measured in bone homogenates. Serum PTH concentrations were assessed after one month (CKD-1) and three months (CKD-3) of experimental CKD.
Results: Serum PTH levels were slightly elevated in the CKD-3 group compared with healthy controls ($p < 0.05$). Over the three-month course of CKD development, KP activation reflected by the KYN/TRP ratio increased in trabecular bone ($p < 0.05$), while a reduction in KP activity was observed in cortical bone ($p < 0.01$). Both bone KYN levels and serum PTH concentrations were inversely associated with BTMs in trabecular bone. However, in cortical bone, PTH was positively correlated with TRAP-5b activity and the TRAP-5b/ALP ratio, whereas KYN remained inversely associated with BTMs.
Conclusions: Endogenous PTH may attenuate bone turnover in trabecular bone while enhancing this process in cortical bone. In contrast, bone-derived KYN appears to suppress bone turnover regardless of anatomical site. Together, these findings suggest that the paracrine KP in bone may interfere with the anabolic effects of PTH on cortical bone turnover in young rats with CKD.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 02

Variation in Kynurenine Pathway Gene Expression in Non- Alcoholic Fatty Pancreatic Disease (NAFPD)

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Objective: Metabolic dysfunction-associated steatohepatitis (MASH), previously termed non-alcoholic fatty liver disease, has become a major global health concern associated with obesity. Recent studies indicate that a similar obesity-related pathological condition may also develop in the pancreas, known as non-alcoholic fatty pancreatitis (NAFPD), though its underlying mechanisms remain unclear. The kynurenine (KYN) pathway, the main metabolic route of tryptophan, generates metabolites that regulate inflammation and immune responses. Our previous studies demonstrated that KYN pathway-related gene expression was uniformly reduced in the livers of Gubra Amylin NASH diet (GAN)-induced obesity mice. However, it remains unclear whether KYN metabolism in the pancreas is similarly affected. This study examined the effects of GAN-induced obesity on NAFPD development and pancreatic KYN metabolism.
Methods: Male C57BL/6J mice aged 7 weeks were fed GAN for 55 weeks (GAN-55). Serum from GAN-55 underwent biochemical analysis, and pancreatic tissues were evaluated using hematoxylin and eosin staining and Sirius red staining. Gene expression levels of inflammatory, fibrotic markers, and KYN pathway enzymes were measured by qPCR.
Results: Histological analysis of GAN-55 pancreas revealed clear inflammation and fibrosis. Correspondingly, qPCR demonstrated increased expression of inflammation- and fibrosis-related genes. Interestingly, while most KYN metabolic enzymes were downregulated in the liver, their expression was upregulated in the pancreas.
Conclusion: These findings indicate that GAN-induced obesity contributes to both MASH and NAFPD, and that KYN metabolism shows organ-specific alterations, suggesting distinct regulatory mechanisms between hepatic and pancreatic pathology

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 03

Differential Effects of Tempol and Aspirine Treatments on Memory and Kynurenine Pathway Alterations in APP23 Mice

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Introduction: Alzheimer's disease (AD), the most common cause of dementia, is characterized by progressive cognitive decline associated with neuroinflammation, oxidative stress, and metabolic dysfunction. Increasing evidence indicates that alterations in the kynurenine pathway (KP), the main route of tryptophan metabolism, contribute to AD pathophysiology. In this study, we investigated the effects of the antioxidant Tempol and low-dose of aspirin on cognitive performance and KP-related gene expression in the APP23 mouse model of AD.

Methods: APP23 mice were treated with tempol (10 mg/kg) or aspirin (25 mg/kg) starting at 3 months of age for 6 or 15 months. Cognitive function was assessed using the Novel Object Recognition test. The expression of genes involved in the KP, together with markers of inflammation and oxidative stress, was analyzed by real-time PCR in the hippocampus of 9- and 18-month-old mice.

Results: Tempol, but not aspirin, significantly improved recognition memory in APP23 mice. Notably, Tempol selectively reversed the dysregulation of KP-related genes and normalized oxidative stress markers, whereas aspirin had no significant effects on cognitive performance or KP gene expression. These effects were especially evident in 9-month-old APP23 mice.

Conclusion: Our findings support a key role for kynurenine pathway dysregulation in the early stages of cognitive impairment in AD. By restoring KP-related gene expression and reducing oxidative stress, Tempol effectively ameliorates memory deficits in APP23 mice. These results highlight modulation of the kynurenine pathway as a potential therapeutic target in AD and identify antioxidant-based strategies as promising disease-modifying approaches.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 04

The deleterious effects of neurotoxin Quinolinic acid on SVZ NSCs

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Current treatments for Multiple Sclerosis (MS) reduce the autoimmune-driven relapses, but are ineffective at preventing neurological disability arising in the progressive phase, where brain cells die. Mouse neural stem cells (NSCs) constitute a pool of multipotent cells available for repair but are vulnerable to neuroinflammation. Quinolinic acid (QUIN) is a Kynurenine Pathway (KP) excitotoxin that our group previously showed potently kills brain cells, particularly oligodendrocytes. We further hypothesised QUIN might damage the cellular health of mNSCs. Via Muse flow cytometry (24-72 hours) and microscopy across different assays we have comprehensively mapped the impact of QUIN on mouse adult NSCs and progenitors. The Mitogenie platform was used to analyse mitochondria at the single cell level from Mitotracker-stained images. Our principle findings include a common pattern of acute benefit to ATP and NAD generation with QUIN treatment at 24-hours (only at low doses), followed by a significant and detrimental effects at 48-hours at the high (2mM) dose. A significant decline in the cellular health of NSCs was manifested by increased mitochondrial depolarisation, oxidative stress, and caspase expression at low and high doses, which became more pronounced at the 72-hr timepoint. Analysis of 500nM QUIN-treated mitochondria showed a significantly greater area per cell at the 24-hr timepoint vs controls, suggesting less mitochondrial turnover, in agreement with the ATP results. The effect was abolished at later timepoints. Therefore reducing QUIN production could reduce cell death, potentially improve the regenerative capacity of NSCs and in turn be effective in treating the neurodegeneration in MS.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 05

Development of a fluorophore-bound L-tryptophan derivative for evaluating indoleamine 2, 3-dioxygenase activity by HPLC with fluorescence detection

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Background: It is important to evaluate the activity of indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme for tryptophan (Trp) metabolism, because IDO is involved in immune tolerance, and some Trp metabolites are involved in the development of some psychiatric diseases and cancer. This study aimed to design and develop a novel fluorescent L-Trp derivative to fluorometrically monitor Trp-catabolizing enzyme activity via IDO.
Methods: To evaluate IDO activity *in vivo*, 7-*N*,*N*-dimethylamino-2,1,3-benzoxadiazole (DBD), a fluorophore, was covalently bound at the 5-position of the indole ring in Trp to produce 5-DBD-L-Trp. An *in vivo* microdialysis (MD) study was conducted using Sprague- Dawley rat kidney. Specifically, 5.0 μM 5-DBD-L-Trp in phosphate-buffered Ringer's solution was infused into the rats, and the MD sample was analyzed via high-performance liquid chromatography with fluorescence detection.
Results and discussion: In the MD sample, two fluorescence peaks other than 5-DBD-L- Trp were observed during the 5-DBD-L-Trp infusion, and the main metabolite peak was proposed to be 5-DBD-kynurenine, verified by liquid chromatography-tandem mass spectrometry. The intensity of the fluorescent peak was significantly attenuated by co-infusion with an IDO inhibitor, 1-methyl-D-tryptophan. These results suggest that 5-DBD-L- Trp may be metabolized by renal IDO and can be used to evaluate IDO activity *in vivo*. Currently, *in vitro* studies on 5-DBD-L-Trp using a commercially available human recombinant IDO1 or IDO2 are being carried out.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 06

The Involvement of Renal NMDA Receptors in the Development of Quinolinic Acid Induced Renal Fibrosis

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Objective: Quinolinic acid (QA), a tryptophan metabolite and N-methyl-D-aspartate receptor (NMDAR) agonist, accumulates in neurodegenerative diseases and neurotoxicity. QPRT-KO mice, which accumulate QA, develop renal fibrosis and anemia-like symptoms, but the mechanism is unclear. On the other hand, NMDAR is expressed not only in the brain but also in renal structures such as the glomerulus and tubules, and its association with diabetic nephropathy and nephrotoxicity has attracted attention. Nevertheless, many aspects of the relationship between NMDAR and renal pathology remain unclear. This study examined the relationship between QA accumulation–type renal fibrosis and NMDAR.
Methods: DNA microarray analysis was performed using kidneys from 60-week-old QPRT-KO mice. Gene expression of NMDAR subunits (NR1, 2A, 2B, 2C, 2D, 3A) in 14- and 60-week-old mice was assessed by quantitative PCR. Immunohistochemistry using antibodies against NMDAR subunits and QA was conducted to evaluate localization. HK-2 cells were treated with QA, and NMDAR subunit expression was analyzed by quantitative PCR.
Results: Microarray analysis showed reduced expression (>50%) of NR1, 2A, 2B, 2D, 3A, and downstream calpain genes in 60-week-old mice. PCR confirmed significant decreases in NR2C and 3A at 60 weeks, while 14-week-old mice showed increased NR2C and upward trends in NR1 and 3A. Immunohistochemistry revealed strong tubular staining at 14 weeks, with less pronounced changes at 60 weeks. QA localized to tubules and interstitium. In HK-2 cells, QA ≥500 μM significantly decreased NR1, 2B, 2C, and 2D expression.
Conclusion: Altered NMDAR expression and localization associated with QA accumulation may contribute to renal fibrosis.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 07

Kynurenine Aminotransferase III as the Key Enzyme Driving Immune-Induced Kynurenic Acid Synthesis: A Novel Target for Cognitive Dysfunctions and Psychotic Disorders

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Elevated central levels of kynurenic acid (KYNA) are associated with psychosis and cognitive deficits. KYNA is synthesized by four kynurenine aminotransferase (KAT I-IV) enzymes, among which KAT II is considered the primary enzyme under physiological conditions. During immune activation, pro-inflammatory cytokines induce the kynurenine pathway, including the synthesis of KYNA. Analysis of publicly available bulk and single-cell RNA-sequencing datasets reveals a consistent upregulation of KAT III in postmortem brain tissue from individuals with infectious or psychiatric disorders associated with cognitive dysfunction. In these datasets, inflammatory markers positively correlate with KAT III and KAT II gene expression. Network analysis further indicates that KAT III occupies a more critical synaptic role than KAT II, and cell-type-specific analyses show that KAT III is upregulated in neurogranin-expressing neurons and oligodendrocyte progenitor cells, both implicated in synaptic plasticity. Experimental validation demonstrates that KAT III expression is upregulated in human-derived monocytes following stimulation with Poly (I:C) and in vivo, immune-challenged rodents exhibit increased KYNA levels accompanied by elevated KAT III expression. In contrast, physiological increases in KYNA induced by kynurenine administration do not upregulate KAT III and, pharmacological KAT II inhibition fails to reduce KYNA levels in immune-challenged rodents. Consistent with this, KYNA levels in immune-challenged KAT II knockout mice are indistinguishable from those in wild-type controls. Together, these findings identify KAT III as the key enzyme driving KYNA production during immune activation, and position KAT III as a promising therapeutic target for cognitive impairment associated with immune-mediated conditions.

POSTER SESSION 1
Thursday, June 11th, 13.00– 14.30

Abstract 08

Effects of Kynurenic Acid and Its Analog SZR-104 in a Social Isolation-Induced Depression Mouse Model: A Preliminary Study

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Background: Major depressive disorder is linked to dysregulation of the tryptophan (Trp)- kynurenine (KYN) pathway, including altered levels of kynurenic acid (KYNA), a metabolite with concentration-dependent neuroactive properties. Social isolation (SI) induces depression-like phenotypes in rodents, yet SI-related KYN shifts remain incompletely defined. This study examined the behavioral and metabolic outcomes of SI and compared the effects of KYNA and its synthetic analog, SZR-104.
Methods: Male C57BL/6N mice (n = 4-7 per group) were socially isolated from weaning or group-housed as controls. Mice received acute intraperitoneal injections of saline, KYNA, or SZR-104 at 75 or 150 mg/kg before behavioral testing or sample collection. Behavioral tests were performed at 8 and 12 weeks of age following 4 or 8 weeks of SI using the open-field test, forced swim test, and Y-maze. Plasma samples were collected at 13 weeks, and Trp- KYN metabolites were quantified by mass spectrometry.
Results: SI increased forced swim immobility and impaired spontaneous alternation by 8 weeks, with a12 weeks. SI reduced plasma KYNA without changing Trp and shifted downstream KYN metabolism toward a neurotoxic profile. Acute KYNA administration increased peripheral KYNA yet failed to reverse depression-like behavior. In contrast, SZR-104 lowered neurotoxic metabolites and reduced immobility, with more consistent effects at 75 mg/kg.
Conclusion: Here we show that SI-driven depression reflects selective KYN imbalance rather than KYNA deficiency per se. Pathway-selective modulation may offer a translational route from stress-induced metabolic bias to new antidepressant strategies.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 70

Targeting Kynurenine aminotransferase III: Discovery of a Selective and Brain-Penetrant Inhibitor for reducing synthesis of immune-induced kynurenic acid.

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Kynurenic acid (KYNA) is a neuroactive metabolite produced via the kynurenine pathway and an endogenous NMDAR and possibly α7nAChR antagonist. Elevated KYNA levels are observed in several conditions where interference with glutamatergic and dopaminergic neurotransmission contributes to psychosis and cognitive decline. Under physiological conditions, kynurenine aminotransferase II (KAT II) is the main enzyme responsible for KYNA synthesis in the brain. However, our recent findings demonstrate that immune activation induces KAT III expression and establishing KAT III as the principal contributor to immune-induced KYNA production, for which no inhibitors exist. We set out to develop a potent, selective, and brain-penetrant inhibitor of human KAT III. To initiate this effort, we developed a high-throughput screening assay for KAT III to identify candidate compounds. Structure-activity relationship (SAR) studies identified key positions amendable to chemical modifications, generating a portfolio of KAT III inhibitors. Our lead compound, SLL-9183, exhibits nanomolar potency against human and rat KAT III, and nanomolar affinity for both species determined by surface plasmon resonance (SPR), with over 100-fold selectivity against the other KAT isoforms. The X-ray crystal structure of our inhibitor in complex with KAT III revealed no interaction with the enzyme's cofactor. Pharmacokinetic evaluation in rodents confirmed brain exposure, with free brain concentrations of SLL-9183 exceeding 10 times its Kd value measured by SPR. Preliminary data show that systemic administration of our inhibitor consistently and robustly suppresses immune-induced KYNA synthesis in mice, with reductions observed across several distinct brain regions, including the hippocampus (-51%), frontal cortex (-56%), and striatum (-78%).

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 71

Effects of Coffee Beverage Consumption on Inflammation, Fibrosis, and Kynurenine Metabolism in the Liver and Adipose Tissue of High-fat Diet-induced Obese Model Mice

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Purpose: The kynurenine (KYN) pathway, which converts tryptophan to NAD^+, generates metabolites such as KYN and quinolinic acid (QA) that play roles in neurological and peripheral health. Coffee contains bioactive compounds like chlorogenic acid, caffeic acid, and caffeine, but its effects on fat accumulation and fatty liver under high-fat diet (HFD) conditions remain unclear. This study aimed to examine the impact of unsweetened coffee consumption on liver and adipose tissue fibrosis and KYN metabolism in HFD-induced obese mice.
Methods: Seven-week-old male C57BL/6J mice were divided into two groups: one received a high-fat, high-cholesterol, high-fructose diet (GAN) with unsweetened coffee (Coffee group), and the other received GAN with distilled water (Control group) for 14 weeks. Serum biochemical markers were analyzed. Liver and adipose tissues were examined using hematoxylin and eosin (HE) and Sirius red staining. Quantitative PCR was performed to assess gene expression of KYN metabolic enzymes and the fibrosis marker Col1a1.
Result: Coffee group showed significantly reduced body, liver, and fat weights. Histological analysis revealed suppressed hepatic steatosis and adipocyte hypertrophy. Col1a1 expression and serum TP, AST, ALT, and LDH levels were significantly lower in Coffee group. In the liver of Coffee group, KATs, KYNU, and ACMSD were upregulated, while QPRT was downregulated. In adipose tissue of Coffee group, ACMSD was downregulated and IDO2, QPRT showed a decreasing trend.
Conclusion: Unsweetened coffee reduced fibrosis and inflammation in liver and adipose tissue of HFD-fed mice, with tissue-specific modulation of KYN metabolism suggesting distinct regulatory mechanisms.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 72

Inhibition of Tryptophan/Kynurenine pathway enzyme, Alpha- amino-beta-carboxymuconate-epsilon-semialdehyde decarboxylase (ACMSD) improves Muscle Function and Bone Integrity in Aged Mice

Sandeep Kumar [1], Sagar Vyavahare [2], Bharati Mendhe [2], Roger Zhong [2], Cooley Marion [2], Carlos M. Isales [2], Sadanand Fulzele [2]

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Background: Aging drives progressive deterioration of muscle and bone, partly through altered tryptophan metabolism and inflammation. Alpha-amino-beta-carboxymuconate- epsilon-semialdehyde decarboxylase (ACMSD) regulates a critical branch of the kynurenine pathway, influencing NAD synthesis and cellular energy balance.
Objective: To determine whether pharmacological inhibition of ACMSD with TES1025 improves musculoskeletal health in aged mice.
Methods: In the current study, Male and female (C57BL6) mice (n=10/group) were obtained at 16 months and housed in a 12-h light/dark cycle, and had free access to food and water throughout the study. The TES 1025 ACMSD inhibitor (0.5 mg/kg/body weight) and DMSO were administered subcutaneously twice a week for 12 weeks. Muscle function, muscle fiber morphology, bone parameters, serum cytokines, NAD levels, lymph node immune profiles, and molecular markers of senescence and metabolism (p21, p16) were assessed.
Results: ACMSD inhibitor **(**TES1025) treated mice displayed increased muscle fiber size and strength, enhanced bone health metrics, elevated NAD levels, and reduced circulating pro-inflammatory cytokines. Flow cytometry revealed a shift toward a less pro-inflammatory immune phenotype. Molecular analyses showed suppression of senescence markers, restoration of antioxidant and sirtuin proteins, and reduced FOXO-1 expression changes consistent with improved musculoskeletal integrity.
Conclusion: ACMSD inhibition (TES1025) attenuates age-related musculoskeletal decline by modulating inflammation, preserving cellular function, and enhancing metabolic resilience. TES1025 represents a potential therapeutic candidate for improving muscle and bone health in aging.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 73

Inflammatory cytokines trigger the activation of the Kynurenine Pathway of Tryptophan Metabolism: Effects on embryonic mouse neural stem cell proliferation, health and NAD state

Michael Lovelace

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New regulators of neural stem cell (NSC) proliferation underpin future cell therapies, while understanding NSC vulnerabilities during disease states could explain why innate repair in neurodegenerative/neuroinflammatory diseases fails. The kynurenine pathway (KP) regulates essential amino acid tryptophan (TRP)'s bioavailability, notably induced by stimuli including interferons-components of antiviral defences. In neurodegenerative diseases the KP becomes dysregulated, producing high levels of metabolites like potent neurotoxin Quinolinic acid (QUIN). QUIN metabolism by enzyme quinolinate phosphoribosyltransferase (QPRT) into cofactor NAD is rate-limiting, favouring QUIN accumulation during chronic KP activation. We characterized KP/NAD synthesis gene expression, and hypothesized KP modulation by interferons alters embryonic mouse (emNSC) proliferation and cell health. Tryptophan-2,3-dioxygenase (TDO2) is the master regulator of TRP catabolism, showing substantial basal expression while modestly upregulated (IFN-gamma->2.7-fold)/IFN- beta->2.1-fold). IFN-gamma slightly upregulates alloenzyme indoleamine-2,3-dioxygenase (4.1±0.38-fold); IFN-beta no effect. NSCs varyingly express all KP genes basally including QPRT; upregulated by both IFNs. While IFN-gamma significantly increased mean neurosphere size (10IU/mL, 287.3±32.73mm; p=0.0032; 100IU/mL, 305.7±10.64mm; p=0.0005) versus controls (180.5±42.1mm), it increased oxidative stress/caspase-activation, suggesting compromised cell health. Conversely, 50nM KYNA significantly increased neurosphere size (307.5±11.45mm; p=0.0004) while retaining cell health. Strikingly, both IDO-1/TDO2 are intrinsically linked with NAD metabolic state, as their siRNA-knockdown with IFN-gamma co-treatment resulted in increased NAD+/NADH ratio. We undertook the first KP/NAD gene expression characterization. emNSCs are vulnerable to deleterious effects of interferons-particularly IFN-gamma, which preferentially reduces (while IFN-beta enhances) enzyme expression producing protective KP metabolites KYNA/Picolinic acid. Selective KP inhibition, increasing KYNA could minimize cell death, improve regeneration during inflammation, and optimize NSC proliferation in therapeutic applications.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 74

Gaming Disorder induces central and peripheral remodeling of tryptophan metabolism: evidence from a rat model

Antonino Casile [1], Brigitta Bonaldo [2], Sofia Nasini [3], Benedetta Barzon [3], Stefano Comai [3], Stefano Dall'Acqua [3], Maria Vittoria Micioni Di Bonaventura [1], Stefano Gotti [4], Carlo Cifani [1]

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Gaming disorder (GD) is associated with alterations in neurobiological systems involved in mood regulation and reward processing; however, its impact on tryptophan (Trp) metabolism remains poorly characterized. In the present study, we used a rat model of GD to investigate central and peripheral changes in the serotonergic and kynurenine pathways, also considering sex-specific differences. Compared to control rats, GD rats of both sexes exhibited increased plasma Trp levels accompanied by a marked reduction in serotonin and dopamine, suggesting impaired Trp utilization rather than substrate deficiency. GD also induced a profound remodeling of the kynurenine pathway, characterized by reduced KYN levels, a decreased KYN/Trp ratio indicative of lower IDO/TDO activity, and an imbalance in downstream metabolites. In control conditions, several Trp metabolites displayed a clear sexual dimorphism, which was completely abolished in GD rats, indicating the emergence of a convergent pathological phenotype. Pharmacological validation of the model using fluoxetine, a drug currently employed in the treatment of GD patients, resulted in normalization of Trp-related inflammatory pathways at the peripheral level. However, untargeted plasma metabolomic analysis revealed that, despite functional improvement, the metabolic profile of fluoxetine-treated GD rats did not overlap with that of control rats. Overall, these findings indicate that GD induces a systemic and persistent reorganization of tryptophan metabolism, linking central neurotransmitter deficits to peripheral metabolic alterations. Pharmacological treatment restores functional balance without fully reverting the underlying metabolic phenotype, suggesting tryptophan metabolism as a potential biomarker and therapeutic target in GD.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 09

Long-term GAN Diet-fed MASLD Model Mice Enhance Renal Tryptophan Metabolism and Renal Ageing

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Background: Metabolic dysfunction-associated steatohepatitis (MASLD) is a disease caused by obesity. It is known that progression increases the risk of cirrhosis and hepatocellular carcinoma. Furthermore, MASLD has been reported as a risk factor not only for liver disease but also for chronic kidney disease and renal cell carcinoma. Although it has been suggested that the onset of MASLD may accelerate cellular ageing, many aspects remain unclear. The kynurenine pathway is a metabolic pathway synthesising NAD from tryptophan, and many of its metabolites possess neurotoxicity and physiological activity, which is implicated in various diseases. We have previously demonstrated reduced gene expression of kynurenine pathway enzymes and ageing factors in the livers of MASLD mice. However, alterations in renal kynurenine pathway and their impact on renal ageing remain unclear.
Objective: Using Gubra Amylin NASH (GAN) diet-induced obese model mice (GAN mice), we investigated the effects of MASLD on overall renal kynurenine pathway and renal ageing.
Methods: Real-time PCR was performed on kidneys from C57BL/6J mice fed the GAN diet for 55 weeks (GAN55). β-actin was used as the internal standard.
Results: Gene expression analysis in GAN55 kidneys revealed increased expression of numerous kynurenine pathway enzyme genes. Furthermore, in the kidney of GAN55, the ageing-related genes p16, p21, and p53 were significantly elevated, and Klotho showed tendency to increase.
Discussion: These results suggest that MASLD induces renal inflammation, fibrosis, and cellular senescence, while kynurenine metabolism may be altered in contrast to hepatic metabolism.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 10

Kynurenine Pathway Activation and Neurotoxic Imbalance in Multiple Sclerosis: A Systematic Review and Meta-Analysis Across Peripheral and Central Biomatrices

Lorraine Sue Ying Tan [1], Ananda Staats Piers [2], Hanna Melzer [2], Soraya Wille [2], Josefin Thielow [2], Emma Bluethgen [2], Simona Beham [2], Chai Lim [2]

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Background: The kynurenine pathway (KP) represents a putative mechanistic bridge between inflammatory and neurodegenerative processes in the autoimmune disease multiple sclerosis (MS). However, KP dynamics are heterogeneous across disease stages and cross-compartmental matrices, requiring systematic synthesis to clarify consistent patterns.
Methods: A systematic review and meta-analysis was conducted across three databases from February 2021 to June 2025 (PROSPERO CRD42021239617). Case–control studies reporting tryptophan (TRP) and downstream KP metabolites in people with MS compared to healthy controls were included. Standardised mean differences (Hedges' g) were pooled using random-effects models, with meta-regression and risk of bias analyses conducted to identify moderators of effect size variability and assess methodological quality.
Results: Twenty-four studies (1,404 MS participants; 815 controls) were included, with 15 of these contributing 85 effect sizes for quantitative synthesis. Pooled analysis revealed elevated KYN and KYN:TRP ratios in blood, in MS and relapsing remitting MS. There were also pooled elevations of QA and QA:KA ratios in blood in MS, with significantly increased KA concentrations found in CSF compared to controls. Meta-regression identified clinical and methodological moderators. Between-study heterogeneity was high across pooled analyses, and the majority of studies were classified as high risk of reporting bias.
Conclusions: KP alterations in MS are characterized by peripheral pathway activation and a shift toward neurotoxic metabolite balance, alongside compartmentalized central neuroprotection, supporting their potential relevance as biomarkers of disease activity and progression.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 12

Indole-3-lactate and the ILA/IAA redox index correlate with disease severity and respond to acute exercise in persons with multiple sclerosis

Tiffany Wences Chirino [1], Marie Kupjetz [1], Marit L. Schlagheck [1], Sebastian Proschinger [1], Annette Rademacher [2], Adrian McCann [3], Per Magne Ueland [3], Lars Hvid [4], Ulrik Dalgas [4], Niklas Joisten [1], Philipp Zimmer [1]

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Purpose: Multiple sclerosis (MS) is an autoimmune neurodegenerative disease marked by differences in the taxonomic abundance of gut microbiota. The resulting changes in the microbiota-gut-brain axis are increasingly considered to be relevant to neuroinflammation. Key mediators of this axis include tryptophan (TRP)-derived indoles. Particularly indole-3- acetate (IAA), indole-3-lactate (ILA) and the ILA/IAA index, reflecting a predominantly reductive/oxidative metabolism, have been associated with MS-related disability, as measured by the Expanded Disability Status Scale (EDSS) score. Exercise can alleviate several disease-related symptoms in persons with MS (pwMS) and has the potential to induce changes in indole metabolism. Our aim is to confirm associations between indoles and MS-related severity and to investigate if an acute bout of exercise can increase the systemic concentrations of indoles.
Methods: We performed Pearson correlations of baseline indoles measured via HPLC-MS/MS and MS-disease-related information of 233 pwMS enrolled in three studies. We additionally performed a mixed-model analysis to evaluate the effect of a 60-minute bout of exercise (before 10-minute warm-up, after 30-minute resistance and at the end of the 20- minute strength and endurance) in a cohort of 17 pwMS.
Results: We found a negative association of the EDSS and both ILA ($r=-0.15$, $p=0.038$) and ILA/IAA ($r=-0.29$, $p<.001$). After an acute bout of exercise, ILA ($p<.001$) concentrations and the ILA/IAA ($p=.007$) increased.
Conclusions: MS-related disability is negatively associated with ILA and ILA/IAA. Acute exercise transiently increases the circulating concentrations of ILA, and the ILA/IAA index and chronic exercise could potentially play a modulating role in the microbiota-gut-brain axis in MS.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 13

Altered tryptophan and kynurenine metabolism in schizophrenia: implications for pragmatic impairments and link with treatment-resistance

Michele Francesco D'Incalci [1], Jacopo Sapienza [1,2], Giulia Agostoni [2], Marco Spangaro [2], Margherita Bechi [2], Francesca Martini [2], Carmelo Guglielmino [2], Federica Cocchi [2], Stefano Dall'Acqua [3], Roberto Cavallaro [1,2], Valentina Bambini [4], Stefano Comai [3,5], Marta Bosia [1,2]

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The kynurenine pathway (KP) is increasingly recognized as a key biological mechanism in schizophrenia and a potential treatment target, particularly in patients resistant to first-line antipsychotics. KP dysregulation has been extensively reported in patients and associated with cognitive impairments typical of the disorder, including basic linguistic abilities. However, no previous study has so far investigated whether the effects of KP alterations are also linked to more complex linguistic abilities, such as pragmatics, whose deficits are a core feature of schizophrenia. This cross-sectional study included 78 patients with schizophrenia, who were assessed for circulating tryptophan, KP metabolites, serotonin, and melatonin, as well as psychopathology, cognitive functioning, and pragmatic abilities. Results showed significant correlations between several pragmatic domains and circulating levels of KP metabolites. Notably, the relationship between tryptophan metabolism and linguistic-pragmatic abilities varied according to treatment-resistance status. Indeed, in treatment-resistant patients receiving clozapine treatment, peripheral levels of quinolinic acid showed a positive correlation with pragmatic comprehension and were significantly associated with global pragmatic competence ($\beta = 0.39$, $p = 0.03$). A positive association was also found between melatonin levels and global pragmatics in treatment-resistant patients ($\beta = 0.37$, $p = 0.03$). These findings underscore the relevance of the KP in schizophrenia and provide novel insights into the potential biological correlates of pragmatic deficits. Importantly, this study highlights the relationship between these dimensions and treatment-resistance status, which may help guide the development of personalized interventions targeting pragmatic impairment and its impact on global functioning in schizophrenia.

POSTER SESSION 2
Friday, June 12th, 13.00– 14.30

Abstract 14

Dissecting the inhibitory effects of KYNA on prefrontal parvalbumin-positive interneurons and pyramidal cells through an optimized ex vivo calcium imaging approach

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Kynurenic acid (KYNA) is a neuroactive metabolite of the kynurenine pathway known to modulate multiple neurotransmitter receptor systems, including inhibition of the N-methyl- D-aspartate (NMDA) receptor. While KYNA can have neuroprotective effects, elevated KYNA levels in the prefrontal cortex (PFC) have been associated with cognitive deficits in schizophrenia and related disorders. Recent evidence in mice suggests that elevated KYNA alters local neural circuits by suppressing the activity of fast-spiking parvalbumin-positive (PV) interneurons, which in turn disinhibits excitatory pyramidal cells. However, the impact of elevated KYNA on these neuronal populations remains to be fully elucidated. To assess the effects of KYNA on PV interneurons and pyramidal cells, we developed an optimized two-photon calcium imaging approach to measure neuronal activity in acute brain slices. We used a dual-sensor imaging strategy where a green-shifted Ca^{2+} sensor and a red-shifted Ca^{2+} sensor were selectively expressed in PV interneurons and pyramidal cells. Ca^{2+} activity was recorded simultaneously in both cell types following exposure to escalating concentrations of KYNA (0.1, 1, 10, 100 µM). Calcium dynamics were quantified using a custom Python script computing a noise baseline (3_{σ} threshold) to extract a multiparametric profile of cellular activity. Preliminary data suggest that KYNA may exert a dose-dependent inhibitory effect on both neuronal populations. The most prominent trend is a reduction in the frequency of high-amplitude Ca^{2+} spikes and in total active time (%), with a possible preferential effect on PV interneurons. This approach provides a robust, high-temporal- resolution platform to dissect the neuropharmacological impact of KYNA on cortical microcircuits.

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To our dear delegates,

Thank you so much for being here and for your continued support of the ISTRY society. We truly hope you enjoyed the conference and had a wonderful stay in Padua. It was a pleasure hosting you, and we look forward to seeing you at the next meeting! In the meantime, stay tuned and keep following our updates.

Thank you!