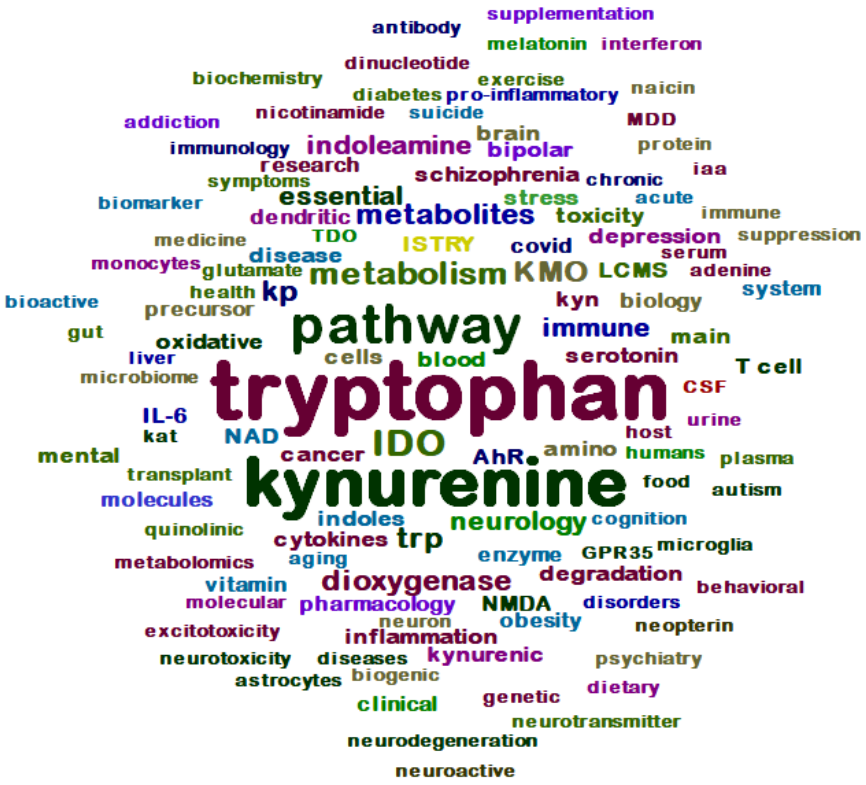
*I*NTERNATIONAL *S*OCIETY FOR *TRY*PTOPHAN RESEARCH



ISTRY ONLINE WEBINAR

ISTRY 6TH ONLINE WEBINAR AGENDA
18 DECEMBER 2024 (CET)

Introduction

From 16.45	Virtual Reception by Host – Zoom login
17:00 - 17:10	Welcome and Opening remarks by ISTRY President, Prof Stefano COMAI

Early & Mid Career Speakers

CHAIR	**Prof. Emeritus Trevor STONE, ISTRY Executive Committee Advisor**
17:10 - 17:25	**The Power of Place: how the microenvironment shapes IDO1 expression and dendritic cells function** Dr. Giada MONDANELLI University of Perugia, Italy
17:25 - 17:30	Q & A Session
17:30 - 17:45	**Endogenous tryptophan metabolite L-Kyn reprograms inflammatory type 2 conventional dendritic cells in a model of multiple sclerosis** Dr. Giulia MENCARELLI University of Perugia, Italy
17:45 - 17:50	Q & A Session
17:50 - 18:05	**Investigating kynurenic acid and sleep during development for maternal and child health** Miss Courtney WRIGHT University of South Carolina, USA
18:05 - 18:10	Q & A Session

Research in focus

CHAIR	**Prof. Ana Pocivavsek, ISTRY Vice-President**
18:10 - 18:35	**High Baseline plasma anthranilic acid predicts remission upon acute-series ketamine infusion for treatment-resistant depression** Dr. Stephen MURATA Pine Rest Christian Mental Health Services, USA
18:35 - 18:40	Q & A Session

Closing

18:40 - 18:45	Acknowledgment and closing remark by ISTRY President

ISTRY 6TH ONLINE WEBINAR AGENDA
18 DECEMBER 2024 (EST)

Introduction

From 10.45	Virtual Reception by Host – Zoom login
11:00 - 11:10	Welcome and Opening remarks by ISTRY President, Prof Stefano COMAI

Early & Mid Career Speakers

CHAIR	**Prof. Emeritus Trevor STONE, ISTRY Executive Committee Advisor**
11:10 - 11:25	**The Power of Place: how the microenvironment shapes IDO1 expression and dendritic cells function** Dr. Giada MONDANELLI University of Perugia, Italy
11:25 - 11:30	Q & A Session
11:30 - 11:45	**Endogenous tryptophan metabolite L-Kyn reprograms inflammatory type 2 conventional dendritic cells in a model of multiple sclerosis** Dr. Giulia MENCARELLI University of Perugia, Italy
11:45 - 11:50	Q & A Session
11:50 - 12:05	**Investigating kynurenic acid and sleep during development for maternal and child health** Miss Courtney WRIGHT University of South Carolina, USA
12:05 - 12:10	Q & A Session

Research in focus

CHAIR	**Prof. Ana Pocivavsek, ISTRY Vice-President**
12:10 - 12:35	**High Baseline plasma anthranilic acid predicts ketamine response in treatment resistant depression** Dr. Stephen MURATA Pine Rest Christian Mental Health Services, USA
12:35 - 12:40	Q & A Session

Closing

12:40 - 12:45	Acknowledgment and closing remark by ISTRY President

The Power of Place: how the microenvironment shapes IDO1 expression and dendritic cells

Giada MONDANELLI, *Ph.D*
Senior Researcher

Dept. of Medicine and Surgery (Pharmacology)
University of Perugia, Perugia, ITALY

Abstract:
Conventional dendritic cells (cDCs) are antigen presenting cells playing a critical role in innate and adaptive host immunity. cDCs are plastic cells in nature, as they adapt their phenotype and function depending on the signals perceived in the microenvironment. cDCs are in charge of educating T lymphocytes whether initiate an immune response or maintain self-tolerance. One of the mechanisms by which cDCs regulate tolerance involves indoleamine 2,3-dioxygenase 1 (IDO1). Besides the most famous catalytic activity (i.e., tryptophan degradation along the kynurenine pathway), IDO1 behaves also as an intracellular transducing protein, and the microenvironment dictates which of the two activities prevails over the other. Under steady-state conditions, cDCs consist of two major subset – namely, cDC1and cDC2 – that are characterized by distinct developmental origin, surface markers and functions. Recently, we showed that at homeostasis IDO1 was expressed only in mature cDC1 in IRF8-dependent manner, and that lipopolisaccaride (LPS) treatment induced IDO1-dependent tolerogenic activity only in isolated cDC1. Accordingly, the specific deletion of IDO1 in cDC1 in vivo worsened disease severity in experimental autoimmune encephalomyelitis (EAE). As opposed to cDC1, cDC2 treated with LPS expressed and produced higher amount of IL-6, i.e., the cytokine responsible for the proteasomal degradation of IDO1. As a matter of the fact, the pharmacologic neutralization of IL-6 in vitro and the genetic deletion in vivo respectively restored the expression of IDO1 protein in cDC2 and mitigated the EAE disease severity. These insights will offer a novel therapeutic angle for cell-specific targeting of inflammation in autoimmune demyelinating diseases.

Endogenous tryptophan metabolite L-Kyn reprograms inflammatory type 2 conventional dendritic cells in a model of multiple sclerosis

Giulia MENCARELLI, *Ph.D.*
Post-Doctoral Researcher

Dept. of Medicine and Surgery
University of Perugia, Perugia, ITALY

Abstract:
Tryptophan metabolites are pivotal messengers for immune cells interactions, and among those, l-kynurenine (l-kyn) stands out for it acts rapidly and efficiently in mediating tolerogenic activity in conventional dendritic cells (cDCs). Recently, we found that a mechanism of DCs tolerance, the enzyme indoleamine 2,3-dioxygenase 1, is selectively expressed by cDC1 but not in cDC2. However, cDC2 are involved in the differentiation and maintenance of Th17 cells, a highly plastic subset of T lymphocytes playing a central role in immunopathogenesis of autoimmune diseases such as Multiple Sclerosis, and its experimental model, experimental autoimmune encephalomyelitis (EAE). All considered, we wished to assess the capability of endogenous l-kyn in spreading immune tolerance in other DC subtypes aiming at discovering new potential drugs able to modulate cDC2 activity in Multiple Sclerosis pathogenesis. Initially

we induced EAE in mice where IDO1 was selectively ablated in cDC2, and surprisingly we found that they showed a worsened symptomatology suggesting the relevance of IDO1 in this dendritic cell subset. Therefore, we assessed in vitro the immunoregulatory properties of IDO1-derived metabolite, L-Kyn, in cDC2 obtained from bone marrow. We demonstrated that l-kyn induces IDO1 in LPS-primed cDC2 via Aryl Hydrocarbon Receptor (AhR) activation, which cooperates with its cofactor RelB. The AhR-RelB axis allows IDO1 expression, binding to two canonical AhR responsive elements, located at +1340 bp and +1601 bp. Importantly, AhR competent cDC2 showed a reduction in IL-6 production. In vivo experiments were carried out to understand whether l-kyn supplementation could reduce EAE symptoms. Surprisingly, l-kyn reduced EAE scores only in AhR competent mice, conferring a regulatory phenotype in the CNS; as proof, selective deletion of AhR in cDC2 impaired l-kyn protective effect.
Collectively, these findings show that cDCs use a pathway of metabolic communication to maintain self-tolerance, in which the cDC1 subset controls the ability of cDC2 subset to become tolerogenic in a model of Multiple Sclerosis.

Investigating kynurenic acid and sleep during development for maternal and child health

Courtney WRIGHT,
Ph.D. Candidate

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

Abstract:
Prenatal insults such as infection or stress linked to neurodevelopmental disorders (NDDs) and psychiatric illness elevate tryptophan degradation via the kynurenine pathway and increase levels of kynurenic acid (KYNA). Elevations in KYNA are observed in adult patients with NDDs such as schizophrenia and bipolar disorder. As an antagonist of NMDA and α7nACh receptors, elevated KYNA has been causally linked to the cognitive disturbances experienced by patients with NDDs. Our lab has shown that elevated KYNA also disturbs sleep (Pocivavsek et al., Sleep 2017). As sleep disturbances are common among NDD patients and can worsen clinical symptoms, we are currently investigating the novel hypothesis that elevated KYNA represents a key molecular link between sleep disturbances and cognitive dysfunction in NDDs. To model prenatal elevations in KYNA that occur from etiologically relevant insults (stress, infection), we employ the embryonic kynurenine (EKyn) paradigm, wherein pregnant Wistar rat dams are fed a control diet (ECon) or a diet laced with kynurenine (100 mg/day), the direct KYNA bio-precursor from embryonic day (ED) 15 to ED 22. EKyn rat offspring express sex-specific and translationally relevant biochemical, sleep, and cognitive disturbances during young adulthood. However, sleep disturbances often precede clinical diagnoses and can exacerbate disease progression and symptom severity in human patients. Early changes to sleep in EKyn offspring have not yet been explored. Therefore, we evaluated sleep-wake parameters of EKyn and ECon offspring across development to elucidate the postnatal developmental time course of sleep dysfunction in our translational EKyn rat model. We also evaluated immunometabolic responses to sleep deprivation in these offspring. We found early developmental changes to sleep in male EKyn offspring and sex-specific alterations in kynurenine pathway metabolites and inflammatory markers following sleep deprivation in pre-pubertal female EKyn offspring. Future studies will investigate translational therapeutic strategies to treat early sleep problems associated with elevated brain KYNA, which may effectively improve long-term health outcomes for patients with NDDs.

High Baseline plasma anthranilic acid predicts ketamine response in treatment resistant depression

Stephen MURATA, MD
Child-Adolescent Psychiatry Fellow

Pine Rest Christian Mental Health Services,
Michigan State University College of Human Medicine, Grand Rapid, USA

Abstract:
Treatment-resistant depression (TRD) poses significant challenges, but intravenous racemic ketamine has shown promise as a rapid-acting antidepressant. However, responses are highly variable, highlighting the need for reliable biomarkers. The Bio-K study, a multi-center, open-label clinical trial, explored plasma kynurenine pathway (KP) metabolites and cytokines as predictors of remission in TRD. Among the 74 participants, 52% achieved remission (defined as MADRS < 9) after three ketamine infusions.

Results revealed that elevated baseline anthranilic acid (AA) was strongly associated with remission, independent of age, sex, BMI, and benzodiazepine use. Composite biomarker ratios, such as AA:ICAM-1 and AA:TRP, significantly improved predictive accuracy. This study underscores the role of immune-metabolic dysregulation in moderating ketamine response and supports the potential of biomarkers like AA to guide personalized treatment strategies for TRD.

SPEAKERS

Dr Giada Mondanelli
University of Perugia

The Power of Place: how the microenvironment shapes IDO1 expression and Dendritic Cells function.

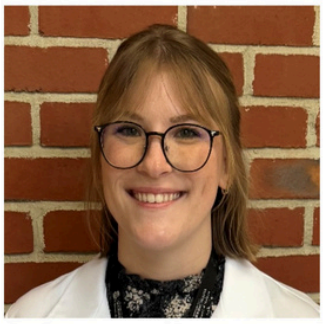
Dr Mondanelli's research focuses on exploring the role of amino acid metabolism, particularly arginine and tryptophan, in the immunoregulation mediated by dendritic cells.

Endogenous Tryptophan metabolite L-Kyn reprograms inflammatory type 2 conventional dendritic cells in a model of multiple sclerosis.

Dr Giulia Mencarelli
University of Perugia

Miss Mencarelli's PhD focused on studying amino acid catabolizing enzymes and unravelling their contributions to autoimmune and neoplastic diseases.

Miss Courtney Wright
University of South Carolina



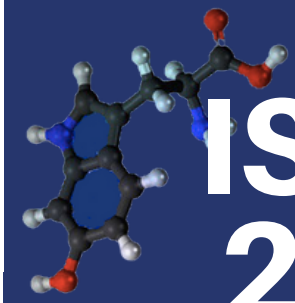
Investigating kynurenic acid and sleep during development for maternal and child health.

Miss Wright's PhD focuses on the impacts of elevated kynurenic acid during the prenatal period in rats, studying its effect on sleep and immuno-metabolism during development

High baseline plasma anthranillic acid predicts remission upon acute-series ketamine infusion for treatment-resistant depression.

Dr Stephen Murata
Pine Rest Christian Mental Health Services

Dr Murata is a Child and Adolescent Psychiatrist, and his research focuses on neuro-progression and psychoneuro-immunology.



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