FEBRUARY 2022, ISSUE 2

ISTRY NEWSLETTER

International Society for Tryptophan Research

INTRODUCTION

Wishing a very happy 2022 to the tryptophan research community!

Welcome to our second issue of the newsletter. Since the release of our first issue, we have faced many challenges and changes around the world and for ISTRY. It seems like yesterday when the world raced for the first vaccine and now we are seeing movement for the 3rd dose of vaccines – hinting a near future to co-exist with COVID-19 as we shift from pandemic to endemic. There's much to speculate about what the long-term health effects of COVID-19 will bring about and this was certainly a topic of interest in our last online webinar where Dr. Mary Collier from the University of Leicester, UK talked about the potential involvement of the kynurenine pathway in COVID-19.

In this issue, we will provide some recent updates of activities organized by ISTRY, followed by a themed topic for this issue on "Cancer and tryptophan metabolism", and lastly, a brief interview with one of our very prominent TRP researchers who was the latest Musajo Memorial Medalist, Emeritus Professor Trevor Stone.

ISTRY CONFERENCE UPDATE

It has been two years since the intended in-person ISTRY meeting was meant to happen in 2020. As we begin to live with COVID thanks to the vaccination roll-out, our international borders are starting to open up. However, the EC felt that international travel for academic conferences has yet to go back to pre-COVID days. Hence, there was a lot of uncertainty as to whether an in-person ISTRY meeting could take place this year. After seeing a successful first online webinar last year in late September 2021, we acknowledge the need for the TRP research community to stay connected globally. The EC decided that the in-person meeting will be replaced by 2 online webinar meetings this year to foster every opportunity for increased connectivity amongst TRP researchers. Hopefully, an in-person meeting in 2023 will be possible. The tentative dates for the two webinars are late March (based on Pan-Asia time zone) and early October (based on US time zone). More details will follow closer to the date via email.

WHAT'S INSIDE THIS ISSUE:

SOME UPDATES OF ISTRY

Despite the challenges faced with traveling, the ISTRY EC and the media team have been working hard to keep colleagues in the TRP research field connected. Other than the ongoing newsletter publication, we have a monthly update of interesting research articles on TRP research featuring a diverse range of fields – mental health, cancer biology, gut microbiome, plant immunology, etc. We organized our first online webinar in late Sept 2021 to unite TRP researchers for some interesting talks on neuroscience and COVID-19. During this webinar, we also presented the Musajo Memorial medal award to Emeritus Professor Trevor Stone. For those who missed the webinar, you can view the recordings here (ISTRY members-only).

It was reassuring to have the continued support of the TRP research community with about 120 registrations and 75% attendance at the webinar, despite the time difference (European time), which we initially thought to be a big hurdle. We had delegates from 13 countries covering the US, Germany, Italy, UK, Japan, Australia, and India (see Fig 1A for detail). Our delegates in terms of career stage were well spread covering a good mix of postgraduates, early, mid, and senior career researchers, and PIs (see Fig 1B). A post-webinar survey was conducted with 93% indicating that they would like to attend a future online webinar. Over 70% of the attendees rated the overall webinar as good-excellent and over two-thirds of the attendees were current ISTRY members.

As an academic focus organization, we acknowledge the financial implications and challenges faced by ECRs especially during this difficult time, it is of utmost importance to ISTRY that we promote and cultivate the next generation of researchers in TRP research for the continual growth and success of the society. Hence, in the coming months, the TRP research community will be able to see some new features that are exclusive to members-only on our website to support our ECRs. Stay tuned!

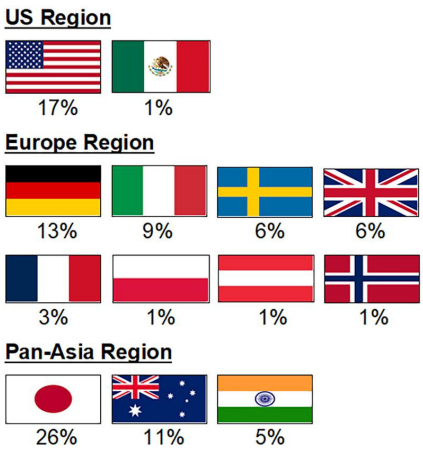


Figure 1A: Geographic Representation of Delegates (%)

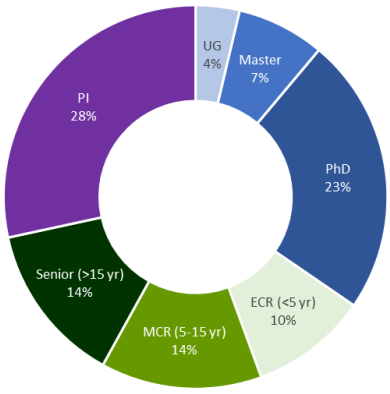


Figure 1B: Career Stage Representation

CANCER AND TRYPTOPHAN METABOLISM

The discovery of IDO mediated immunosuppression by Munn et al. (1998) in fetal placenta was integral in establishing the role of tryptophan (TRP) metabolism in immune tolerance. Consequently, this has built a foundation for the expansion of TRP research in the field of cancer, where it is evident that TRP metabolism promotes tumor progression via suppressing anti-tumor immune responses in the tumor microenvironment. To date, the most studied enzyme in TRP depletion is indoleamine 2,3-dioxygenase (IDO) given it is expressed in around 58% of the human cancers including melanoma, gynecological cancers, colon cancer and hematological malignancies and is linked to poorer clinical outcomes. This has led to the development of competitive IDO inhibitors, namely 1-methyl-tryptophan (1MT), that have been demonstrated to slow tumor progression in rodent models of liver, prostate and lung cancer, leading to clinical trials of both standalone and combinational regimens with monoclonal antibody medication (see the most recent trial watch). Progress in the development of TRP-related biomarkers, and therapies in cancer have advanced in the last 10 years, particularly when it comes to more downstream metabolites of the kynurenine (KYN) pathway.

Recent research has moved beyond quantifying KYN/TRP levels (as a way of measuring IDO activity) and have found more nuanced changes in the KYN pathway are linked to cancer progression. Liu et al. (2019) showed that overexpression of the enzyme kynureninase (KYNU), suppresses breast cancer cell proliferation, colony formation and xenograft tumor growth which indicates KYNU might play a crucial role in breast cancer cell proliferation and differentiation. The relationship between KYN metabolites and anti-inflammatory properties have also been explored. In particular, several studies have investigated the immunomodulatory role of kynurenic acid (KYNA). Early studies on KYNA established its biological importance as a neuroprotective metabolite but recently its role in carcinogenesis has been investigated and KYNA was detected in different cancers including glioblastoma, renal cell carcinoma and colon adenocarcinoma. Interestingly, the function of KYNA differs when conditions are inflammatory or homeostatic. The action of KYNA under non-inflammatory conditions suggests that the treatment has a temporal and/or cell type-dependent effect. However, KYNA appears to have a more consistent impact under inflammatory circumstances. KYNA has been shown to reduce inflammation elicited by diverse stimuli in several *in vitro* investigations employing several primary or immortalized leukocyte cell types (e.g., LPS). KYNA can reduce inflammation by inhibiting HMGB1 protein release and suppressing cytokine expression such as tumor necrosis factor expression and secretion in monocytes and interleukin-4 release in T-cell receptor activated invariant natural killer-like T cells. There is growing data showing a relationship between KYNA and carcinogenesis however it is still too early to conclude on a final decision of KYNA's importance in cancer.

The newest KYN metabolite of interest is anthrallinic acid (AA). In a recent study by Gęca et al. (2022), AA levels were significantly higher in gastric cancer patients in the peritoneum than controls and it showed correlation with the cancer stage. The potential role of AA in cancer biology as an anti-inflammatory agent and whether it is produced by the host response or by cancer cells is not well established and more investigation is needed.

Regarding the latest immunotherapies, preclinical research has established targeted approaches that intervene with the downstream catabolism of KYN. Studies in breast cancer have demonstrated that inhibiting KMO, the enzyme that breaks down KYN into 3HK, is related to reduced tumor proliferation, metastasis and promoted longer survival outcomes (Chiu et al., 2019, Huang et al., 2020, Liu et al., 2019). Similarly, inhibition of KMO in blood borne cancer cell cultures can increase T cell cytotoxicity against

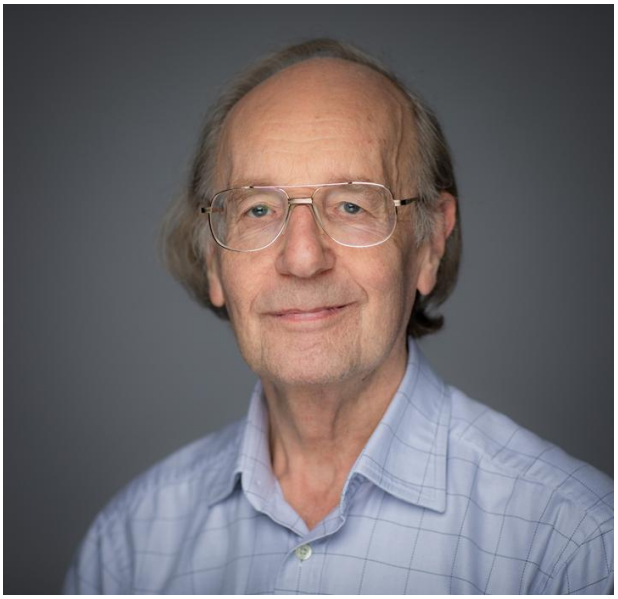
tumor cells (Ray et al., 2020). There has also been a larger focus on exogenous KYN-degrading enzymes that can deplete KYN with the intent of maximizing TRP levels and breaking KYN down into AA, an immunologically benign metabolite. Studies have established that engineered KYNUs are an effective monotherapy in colon cancer and melanoma mouse model. KYNUs have been shown to reduce KYN levels in both serum and the tumor microenvironment without affecting TRP concentrations, leading to retarded tumor growth due to T cell proliferation (Triplett et al., 2017, Stone et al., 2015). Further, combination with immune checkpoint inhibitors can fortify clinical results, leading to total tumor eradication. Lastly, there is emerging research exploring the effects of lifestyle factors on tryptophan metabolism in cancer and studies have found that resistance training can downregulate KYN/TRP levels in pancreatic and breast cancer (Zimmer et al. 2019, Pal et al. 2020). Taken together, these findings implicate the importance of upcoming research on KYN metabolism and metabolite accumulation in the tumor microenvironment which offers a promising avenue for future cancer immunotherapies.

RESEARCHER HIGHLIGHT: PROF. TREVOR STONE

Written by: Dr Amanda R Burmeister

Prof. Trevor Stone was recognized for his contribution to the tryptophan field and was recently awarded with the Musajo Memorial Medal at our 2018 ISTRY conference. Prof. Stone's work covers a wide range of topics with a central theme on understanding tryptophan metabolism and its role in disease.

I recently sat down for a talk with Prof. Stone to learn more about him as a researcher and as an individual. He recently retired from the University of Glasgow and moved to the University of Oxford where he is excited to expand his research repertoire. His colleagues at Oxford University are experts in the fields of Immunology and Pharmacology and he is starting to investigate kynurenine metabolites outside of the brain and is looking into the interactions between the immune system, brain, and microbes in the context of tryptophan metabolism. Exciting new projects have recently been published and we can expect more great things to come. Last year Prof. Stone published in PNAS looking at the epigenetic control of IDO and soon work will be published on novel mechanisms of activating IDO.



When asked about his work and which project or publication stood out above the rest, Prof. Stone shared details behind one of his most well-known publications (TW Stone and MN Perkins, 1981). At the time biochemists thought that tryptophan metabolism was important for the generation of NAD+ and none of the kynurenine metabolites had known biological effects. He was trying to find antagonists for the glutamate receptor and as he was testing a rigid molecular analog (now known to be Quinolinic acid) he found that it was having an effect however, as an agonist not an antagonist. Additionally, as he increased the dose this excitation also increased. Prof. Stone had a post-doc in his laboratory repeat this experiment without disclosing his own results and was excited to see that it was reproducible. He immediately wrote the short manuscript as he knew that this finding would be very important for neurophysiology and neurodegeneration and he was keen to disseminate the information as soon as possible. With this study in mind, Prof. Stone offered some advice to all the young researchers. He suggests that you not throw away any results even if they are not what you expected. Some of the most interesting results can come from this or from mistakes in experimental protocols. What makes a great researcher is asking how these results could be relevant in other fields or in other ways than what was hypothesized.

Due to the monumental discovery of QUIN and its biological relevance, Prof. Stone wanted to investigate other tryptophan metabolites to see whether their structures were more suited for antagonizing glutamate leading him to his next big discovery of kynurenic acid (MN Perkins and TW Stone 1982). While he is mainly interested in tryptophan metabolism, he has always had an interest in serine proteases and adenosine. In fact, he credits his wife for his success in the tryptophan metabolism field. The couple met at a scientific meeting and Prof. Stone mentioned his interest in exploring other areas however, his wife said that he had already made an impact in the tryptophan metabolism field and that he should continue exploring the pathway. Luckily, Prof. Stone took her advice and has gone on to impact this field in countless ways.

Prof. Stone has seen many changes in the field over the years noting that the interest in the kynurenine pathway has really started to span disciplines, where previously it was of scientific interest and now it is being recognized more often by clinicians and pharmaceutical companies. He does note that one of the biggest hurdles of his career has been getting funding and this is in part due to tryptophan metabolism being a niche field. This is overcome by having other areas of interest in conjunction with kynurenine pathway research. As this field becomes more immersive in the clinics and is commercialized, he hopes that researchers will be more able to gain funding for projects that have this pathway as its main focus.

Prof. Stone is dedicated to his work and takes great joy in spending most of his time doing research. He and his wife love to keep up with research and tend to be surrounded by research articles. However, when he steps away from the research, he loves photography and playing the piano. He enjoys photographing landscapes and animals, including hedgehogs and deer in the garden as well as hummingbirds. He is fond of classical music and opera and has also done oil painting. He loves whiskey and many people don't know that he also enjoys playing snooker, "an adult form of pool". When asked if he had plans on officially retiring from tryptophan research, he said that he would continue to work as long as he could (physically/mentally) and until he is no longer allowed to. With that said, we will continue to see more from Prof. Stone and look forward to his future studies.

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