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ISTRY NEWSLETTER

International Society for Tryptophan Research

INTRODUCTION

Dear ISTRY members, friends, colleagues, and the tryptophan research community,

I hope everyone has had a great start to 2025 and is busy generating new findings for the next ISTRY meeting (more on that below). As I work diligently with our ISTRY media team—now with a few new members—the ISTRY Executive Committee (EC) is actively preparing for the next ISTRY meeting. The EC has decided that the 17th ISTRY meeting will be held in Padua, Italy, from June 10th to 12th, 2026. Stay tuned for the official announcement regarding registration and abstract submission on our website.

Late last year, we had a successful turnout for our online webinar featuring early- to mid-career researchers from Europe and America. For those who missed it or would like to revisit the talks, the recording is available here—please log in as a member to access it. The 7th online webinar is scheduled for May 14th, with registration expected to open in early to mid-April. Our President, Prof. Stefano Comai, will share firsthand insights about the upcoming ISTRY meeting in Padua during the webinar. Please mark your calendars and plan ahead for these exciting events!

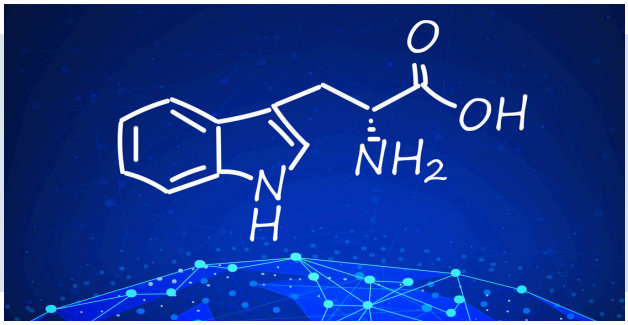
In this issue of the newsletter, the ISTRY media team has put together a short overview on the theme of IDOs, reminding us why we examine the kynurenine pathway in the first place. I hope you find some interesting facts and insights into the role of IDOs beyond tryptophan catabolism. In our final section, we would like to take this opportunity to introduce the ISTRY community to one of our longstanding tryptophan researchers and a dedicated supporter of ISTRY—Prof. Emeritus Hans Steinhart.

Lastly, let's take a moment to reflect on the great time we had at the ISTRY meeting in Jena, Germany, and stay connected until we meet again in Italy. I wish you all the best in your research and look forward to seeing you at our next event.

Best wishes,

Prof Edwin Lim
ISTRY Secretary & Treasurer

WHAT'S INSIDE THIS ISSUE:



BEYOND TRYPTOPHAN CATABOLISM: PAST, PRESENT, AND FUTURE OF IDOS

Written by: Dr. Ananda Christina Staats Pires and Mrs. Sandra Tatchum

IDO manipulation as a therapeutic target: What we know so far

Indoleamine 2,3-dioxygenase (IDO) has intrigued scientists for years, yet many of its secrets remain undiscovered. Initially linked to maternal-fetal immune tolerance, IDO plays a much larger role in immune regulation and evasion, making it a key target in medical research, especially cancer treatment.

Three main enzymes—IDO1, IDO2, and tryptophan 2,3-dioxygenase (TDO)—break down tryptophan along the kynurenine pathway. While TDO primarily controls tryptophan levels in the liver, IDO1 and IDO2 respond to inflammation. IDO2 supports IDO1 in immune tolerance, but its exact role remains unclear. Recent research suggests IDO2 has a non-enzymatic role in autoimmune diseases by interacting with Runx1 in B cells, disrupting immune regulation and contributing to autoimmune arthritis (December 2024 Featured Article).

Beyond breaking down tryptophan, IDO1 also acts as a messenger inside immune cells, influencing their long-term behavior. Dr. Giada Mondanelli (Webinar 6) discussed how IDO1's role shifts based on its environment. When inflammatory molecules like IL-6 take over, IDO1 degrades, pushing immune cells into a more aggressive state. Blocking IL-6 can restore IDO1 function and reduce disease symptoms, opening new therapeutic avenues.

One of IDO's most well-known effects is its ability to suppress the immune system by depleting tryptophan. Without enough tryptophan, immune cells struggle to survive and function, giving cancer cells an advantage. However, this explanation has been debated—some researchers argue that tryptophan levels don't drop low enough to trigger this response. Instead, new evidence suggests that when IDO1 depletes tryptophan, cells may replace it with phenylalanine, altering protein production. This surprising effect could actually make tumor cells more visible to the immune system, showing that IDO's role in cancer is more complex than previously thought (See March 2022 Featured Article).

This duality—helping tumors evade the immune system while also potentially making them more detectable—reveals how IDO fine-tunes immune responses. Researchers now believe that IDO's immunosuppressive effects are driven more by the byproducts of tryptophan metabolism, rather than tryptophan depletion itself. These byproducts, particularly kynurenine and kynurenic acid, activate a receptor called aryl hydrocarbon receptor (AhR), which plays a major role in regulating immune responses. AhR activation suppresses immune attacks while promoting regulatory T cells, ultimately dampening the immune response. In cancer, this forms a vicious cycle—IDO1 fuels AhR activity, which in turn strengthens tumor defenses.

But IDO's impact extends beyond cancer. Research shows that in newborns, IDO1 is essential for heart regeneration after injury. By producing molecules that activate AhR, IDO1 promotes blood vessel growth and heart repair. When AhR is blocked, these healing effects disappear, showing that the IDO1-AhR connection is crucial not just for immune regulation but also for regenerative medicine (See November 2022 Featured Article).

As scientists continue to explore its mechanisms, IDO remains a promising target for future therapies—whether in fighting cancer, managing autoimmune diseases, or even promoting organ regeneration. Understanding IDO's complex role brings us one step closer to unlocking new, groundbreaking treatments.

IDO inhibitors in cancer therapy: Progress and setbacks

More than 50% of human tumors overproduce IDO1, making it a key player in immune suppression. High IDO1 levels correlate with poor outcomes in melanoma, gynecological tumors, colon cancer, and blood malignancies. This led to the development of IDO1 inhibitors, including epacadostat, BMS986205, which progressed through over 100 clinical trials. Early studies showed that these drugs were safe, but when tested alone, they had little effect against cancer. This led to a shift toward combination therapies, particularly with immune checkpoint inhibitors like pembrolizumab (a PD-1 blocker). However, hopes were dampened when a key phase III trial showed that adding an IDO1 inhibitor to pembrolizumab provided no additional benefit [1].

Why didn't these inhibitors work as expected? One reason lies in the close relationship between IDO1 and PD-1, a critical immune checkpoint in cancer. Our June/July 2021 Featured Article explored this connection in ovarian cancer, showing that IDO1 increases the number of PD-1+ CD8+ T cells within tumors. This happens because kynurenine, a byproduct of IDO1 activity, activates AhR, which then enhances PD-1 expression. Blocking AhR with a specific inhibitor (i.e., CH223191) reversed this effect, suggesting that targeting IDO1 and AhR together could improve cancer immunotherapy.

The failure may also be due to alternative pathways like TDO and IL4I1, which maintain immune suppression even when IDO1 is blocked. Additionally, IDO1 expression varies across tumors, making a one-size-fits-all approach ineffective. Moving forward, researchers are developing stronger IDO1 inhibitors, reliable biomarkers, and combination therapies targeting AhR, IL4I1, and TDO to enhance immune responses.

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IDO beyond cancer: groundwork evidence arising from preclinical studies

From cancer to neurodegeneration, chronic pain to autoimmune diseases, IDO1 has emerged as a powerful regulator of inflammation and immune responses. While its role in cancer immunotherapy has been widely explored, its involvement in other diseases is gaining attention. By refining our understanding of IDO1's functions and interactions, researchers are uncovering new therapeutic strategies that could transform treatment for a wide range of inflammation-driven conditions.

Neurodegenerative diseases—such as Alzheimer's, Parkinson's, Huntington's, and ALS—may have different causes, but they share a common problem: harmful protein buildup that leads to cellular stress and toxic immune reactions. One key factor driving this process is neuroinflammation. While scientists are still uncovering the exact mechanisms, growing evidence suggests that blocking IDO1 could help slow or even prevent disease progression.

Exciting insights into this were featured in our August 2024 Featured Article, which revealed that Alzheimer's-associated peptides (Aβ and tau) increase IDO1 activity, activating AhR signaling and disrupting energy production in brain cells. By inhibiting IDO1, researchers restored astrocytic metabolism, improved lactate production, and even reversed memory deficits in preclinical Alzheimer's models. This suggests that targeting IDO1 could be a new therapeutic strategy for neurodegenerative diseases.

Beyond neurodegeneration, IDO1 has been linked to neuropathic pain. Our October 2022 Featured Article showed that inhibiting IDO1—either through drugs like 1-MT or genetic modifications—prevented pain development. The study found that IDO1-expressing immune cells accumulate in the spinal cord, producing kynurenine, which astrocytes then convert into pain-inducing molecules. These findings suggest that targeting IDO1 could lead to new treatments for chronic pain conditions.

Interestingly, IDO1 may also play a role in psychiatric disorders. Our April 2022 Featured Article explored how lithium, a well-known mood stabilizer, reduces IDO1 activity in brain immune cells while increasing anti-inflammatory signals like IL-10. This suggests that lithium's effectiveness in bipolar disorder may be partly due to its ability to inhibit IDO1 and regulate inflammation.

IDO1's influence isn't limited to the brain—it also plays a role in inflammatory bowel disease (IBD). Research highlighted in our February 2023 Featured Article found increased IDO1 levels in ulcerative colitis patients and in mouse models of colitis. These findings suggest that IDO1 contributes not only to gut inflammation but also to the psychiatric symptoms often linked to IBD, making it a potential target for dual-treatment strategies.

In the kidneys, IDO1 activation has been linked to polycystic kidney disease (PKD). Our December 2022 Featured Article reported that IDO1 levels were significantly higher in PKD models. Blocking IDO1 reduced disease severity and altered the immune environment in the kidneys, hinting at a promising new treatment approach. All in all, IDO1 inhibition opens a new avenue of approach to treating inflammation-driven diseases and conditions, as well as affording opportunities to synergize with emerging oncological interests in IDO1-based immunotherapy.

Beyond IDO inhibition: IDO as a therapeutic target in autoimmunity disorders

Our immune system is designed to protect us, but sometimes it mistakenly attacks the body's own cells, leading to autoimmune diseases like multiple sclerosis, lupus, and Crohn's disease. IDO1 helps regulate immune responses, preventing excessive inflammation and maintaining tolerance. While its absence doesn't always trigger autoimmunity, it can worsen disease severity. In some cases, immune cells fail to activate IDO1 properly, and genetic variations in IDO1 have been linked to a higher risk of developing certain autoimmune conditions.

Research in animal models of multiple sclerosis, lupus, rheumatoid arthritis, and diabetes has shown that IDO1 plays a role in controlling disease severity. In Webinar 6, Dr. Giulia Mencarelli explained how IDO1-derived kynurenine helps immune cells become more tolerant. Her study found that kynurenine activates AhR in certain immune cells, reducing inflammation and shifting them toward a more tolerant state. In multiple sclerosis models, kynurenine significantly reduced disease symptoms—but only in mice with a functioning AhR pathway. This highlights the importance of the IDO1-AhR connection in maintaining immune balance and suggests new treatment possibilities for autoimmune diseases.

Researchers are exploring various strategies to harness IDO1's immunoregulatory potential for treating autoimmune diseases. While most efforts have focused on developing drugs that mimic kynurenine pathway metabolites, new approaches target IDO1 activity directly to limit immune attacks on the body's tissues. One promising strategy involves using nanoparticles to deliver mRNA encoding IDO1, which enhances and prolongs IDO1 protein expression, supporting regulatory T cell function. This technique has successfully modulated immune responses and improved rodent models of multiple sclerosis and lupus [2].

Other innovative approaches include cell-based and gene therapies. Transferring IDO1-producing fibroblasts or immune cells has shown promise in preclinical models of autoimmune diabetes [3; 4]. Meanwhile, viral vector-based gene therapy delivering IDO1 directly to tissues has demonstrated potential for preventing transplant rejection and treating autoimmune diseases [5].

As a key immunoregulatory enzyme, IDO1 has implications beyond autoimmunity, including cancer, neurodegeneration, and regenerative medicine. Originally studied for maternal-fetal tolerance, its broader role in immune modulation makes it a compelling therapeutic target. Future progress will depend on a deeper understanding of IDO1's mechanisms, advanced delivery technologies, and personalized treatment strategies, paving the way for innovative interventions across multiple diseases.

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For more details on each reference, please click on the DOI or hyperlinks provided in the text.

RESEARCHER HIGHLIGHT: PROF. EMERITUS HANS STEINHART

Written by: Mrs. Sandra Tatchum and Dr. Ananda Christina Staats Pires

Our ISTRY media team had the privilege of interviewing Prof. Dr. Hans Steinhart, a distinguished figure in the field of biochemistry and food chemistry, who has made significant contributions to the study of tryptophan metabolism. He has contributed significantly to the success of ISTRY, serving in multiple leadership roles—including Treasurer, Secretary, and President—on the executive committee from 1983 to 2006. His contributions to the field of tryptophan research were recognized with the prestigious Musajo Memorial Medal. Prof. Steinhart reflects on a remarkable scientific career that spans decades and a journey from agricultural science to biochemistry, with a lasting impact on both food chemistry and the broader scientific community.

Having studied agriculture in Munich and biochemistry in Zurich, Prof. Steinhart held professorships in Munich and Kassel before assuming the Chair of Biochemistry and Food Chemistry in Hamburg. His work is an exemplary mix of curiosity-driven research and practical application, combining both fields in impactful ways.

What inspired you to conduct research on Tryptophan metabolism?

Prof. Steinhart shared that his journey into tryptophan research was unconventional. "I am an atypical member of ISTRY," he began. "Most of the members are medical doctors, but I started my career in agriculture before transitioning to biochemistry." In the late 1960s, as a doctoral student at the Technical University of Munich, Prof. Steinhart worked at the Institute of Animal Nutrition, where he focused on optimizing nutrient requirements for farm animals. His initial task was to determine the tryptophan requirements of poultry. At the time, analyzing tryptophan posed considerable challenges due to its instability during protein hydrolysis. "The amino acid analyzers available were cumbersome and prone to failure," he recalls. His innovative approach to developing more reliable analytical methods helped shape the foundation of his research into tryptophan metabolism.

Reflecting on your career, what are some of the highlights or publications you are most proud of?

Looking back on a career that spans over 600 scientific publications and the supervision of 136 doctoral students, Prof. Steinhart highlights several key accomplishments. "One of my most significant contributions is related to the metabolism of tryptophan in grapes and wine yeasts," he explains. Tryptophan, in stressful conditions, can lead to the formation of aminoacetophenone, a compound responsible for a foul aroma in wine, often referred to as the “atypical aging note.” "Through our work, we identified the stress factors in vineyards and wine cellars that trigger this metabolic change and developed methods to prevent it. This has led to a significant reduction in wine spoilage, saving millions of euros for winegrowers in Germany alone." This work stands out not only for its scientific novelty but also for its real-world impact.

What advice would you give to early-career researchers?

Prof. Steinhart offers invaluable advice to those starting their scientific careers. "Young researchers should not be discouraged by setbacks. Tenacity is key, and those who persist will eventually succeed," he states. He emphasizes the importance of good mentorship, sharing that experienced scientists can quickly recognize when a research topic is viable or needs refinement. "Collaboration within research groups is vital for generating new ideas and troubleshooting experiments. Reliable results should be published in peer-reviewed journals, and young researchers should present their findings at international conferences to build a network of colleagues and expand their career opportunities."

Now in retirement, how do you spend your time?

At 85 years old, Prof. Steinhart continues to remain active in the academic world. Though officially retired, he still has a room at the university where he keeps up with the latest literature and participates in scientific meetings. "I still attend congresses when possible and regularly meet with colleagues, particularly in the field of food chemistry," he notes. He also maintains close relationships with former colleagues in Korea and China, where he holds honorary professorships. Outside of academia, Prof. Steinhart enjoys spending time with his family, playing the accordion, and participating in his church community. "As I originally come from Bavaria, my musical focus is on alpine folk music" he adds, showing a well-rounded passion for life beyond research.

Prof. Steinhart remains passionate about his work and continues to make invaluable contributions to the field of tryptophan metabolism. His dedication to both the scientific community and his personal hobbies demonstrates the depth of his curiosity and commitment to lifelong learning. As he reflects on a career filled with groundbreaking discoveries and mentorship, he remains an inspiring figure to early-career researchers and seasoned scientists alike.

CONTACT US

Webpage: istry.org

Email: media_team@istry.org

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