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INSTITUTE FOR INTEGRATIVE TOXICOLOGY

Tewari-Singh Awarded R01 **Grant by National Eye Institute**



TIT-affiliated fac-Lulty member, Dr. Neera Tewari-Singh, was recently awarded a R01 grant from the National Eye Institute for her project, "Understanding Mustard Vesicants Distribution and Toxicity in the Eye Using In Vivo and In Silico Models."

Tewari-Singh will receive \$1,380,587 to perform this research over the next three years.

For over 15 years the major long-term goal of Dr. Tewari-Singh's research has been to pursue both basic and translational studies to develop approved and more effective targeted countermeasures and therapies against dermal and ocular injuries from chemical threat agent exposures. Mustard gas (sulfur mustard) has historically been one of the most commonly used chemical warfare agents and remains a potential agent of warfare and terrorism. Consequently, many governments and research agencies have prioritized researching and developing countermeasures to mustard gas toxicity. Tewari-Singh's research has focused on discovering signaling pathways that could lead to mustard gas toxicity to identify the targeted therapeutic treatments that could help treat these exposures.

The eye is the most sensitive organ to mustard gas exposure, resulting in devastating biphasic ocular injury and impaired vision or blindness. The dose and time related severity of symptoms of this eye injury in mass casualty situations poses a challenge in mechanistic research and identification of therapeutic targets. Injury involving damage mainly to the cornea and possibly other ocular tissues is not well understood. With her new R01 grant, Tewari-Singh will be collaborating with Dr. Carrie German at CFD Research, a company that specializes in computational modeling. Her research will use in vivo studies and CFD Research's existing in silico rabbit ocular model to determine how mustard gas and various other chemical agents penetrate the eye at various concentrations and timings. This is an exciting step in addition

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Tewari-Singh RO1 Grant cont.

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to her current in vivo research, that will use a synergistic in vivo-in silico approach to determine mustard vesicant eye distribution and the resulting corneal injury and repair mechanisms.

The combination of experimental and computational approaches will provide a more cost and time efficient platform for the evaluation of mustard vesicant exposure for multiple concentrations and durations. These studies will allow Tewari-Singh to answer a lot of questions on time- and tissue-dependent eye toxicity mechanisms by mus-

tards that were previously unattainable using only in vivo methods. Her studies will also combine in vivo analyses of injury and repair pathology with time-and concentration-dependent transcriptomics (RNA sequencing analysis-based bioinformatics) to identify the biochemical changes and their associated pathways. The proposed study could serve as a more efficient and potentially more insightful novel approach to evaluate mustard vesicating agents' induced tissue-specific toxicity mechanisms.

Tewari-Singh will use newly ac-

quired data from these studies to further develop countermeasures and treatment modalities for the future, especially for mass casualty scenarios from eye exposure to chemical threat agents. This research can then be applied to predict toxicity and treatment modalities for exposures to other organs as well. Developing effective and targeted medical interventions is a critical component of the modern global strategy to overcome the challenges of chemical emergencies in both civilian and military populations, making her research highly significant.

EITS Student Isha Khan Publishes Exciting Research on the Role of AHR in Human Hematopoiesis



Environmental and Integrative Toxicological Sciences (EITS) graduate student, Isha Khan, in collaboration with a team of scientists including Peer Karmaus, Anthony Bach, Robert Crawford and Norbert Kaminski,

recently published exciting research on the role of the aryl hydrocarbon receptor (AHR) in human hematopoiesis, the process by which blood cells are formed. The paper, "An in vitro model of human hematopoiesis identifies a regulatory role for the aryl hydrocarbon receptor," was published in October 2023 in the journal, Blood Advances.

Human hematopoietic stem cells undergo successive rounds of differentiation and give rise to different types of blood cells, including the immune cells, in the body. A good balance between the different branches of the hematopoietic cell lineages is necessary for healthy living. AHR is a protein that regulates gene expression in cells and has important physiological functions. However, the role of AHR in human hematopoiesis is not well understood. Khan's research works to explain the role played by AHR in altering human hematopoietic stem and progenitor cell (HSPC) differentiation.

Khan recognized that current in vitro models to study concurrent immune cell development from hematopoietic

stem cells in a single system were scarce. He took this opportunity to identify and characterize, using single cell modalities, a model of human hematopoiesis in an in vitro platform that, without the need for any other supporting cells, allows the development of most major immune cell types, except for T cells. Using this model, Khan demonstrated that 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD), a highly potent activator of the AHR, even at very low concentrations, skews human hematopoietic stem and progenitor cell differentiation towards certain immune cell lineages, specifically granulocytes and monocytes, at the expense of other immune lineages such as lymphoid progenitors, B lymphocytes, dendritic cells, and megakaryocytes. This is an interesting finding and may have important repercussions. Lymphocytes, for example, help orchestrate specific adaptive immune responses against invading agents such as pathogenic microorganisms. As sufficient lymphocyte production is crucial for developing holistic immune competence, an imbalance in lymphocyte production induced by TCDD may have pathological consequences. His research further showed that cellular expression of key genes such as BCL11A and IRF8 that are involved in the development of lymphoid and dendritic cells from HSPCs were suppressed by TCDD which may explain the TCDD mediated perturbation of hematopoiesis.

Khan's research has also been an integral part of the ongoing work of the

MSU Superfund Research Program. One of the goals of the program is to identify molecular responses to environmental contaminants that act as agonists for the AHR in different systems, such as in the context of the immune system. Khan's research contributes to a better understanding of the adverse effects of TCDD on the developing human immune system.

"To my knowledge, this is the first time that the effect of TCDD on gene regulation during human hematopoietic stem and progenitor cell (HSPC) differentiation has been studied at the single cell transcriptomic level," commented Khan. "Specific signaling pathways and genes that have been found to be altered by TCDD in HSPCs may be useful to understand the mechanisms by which AHR activators exert toxicity and help develop strategies in the future to counteract such phenomena."

Khan is also interested in testing the functional capabilities of some of the immune cells that develop in the developmental assay. Using different approaches, Khan hopes to test the effect of TCDD on immune cell function as well as delineate the role of different signaling pathways in TCDD mediated alterations in hematopoiesis. Moreover, with the increasing adoption of new approach methodologies to replace animal models, the multilineage model of human hematopoiesis that Khan has identified and characterized could be useful to test the effects of other toxicants on human hematopoiesis.

Li Receives Two Prestigious Awards this Fall



IIT-affiliated faculty member Dr. Hui Li has been selected for two prestigious awards this fall.

Li was selected as the recipient of the Impact Award for the 2023 CANR Excellence in Re-

search Awards. The CANR Excellence in Research Award Program recognizes the outstanding contriubtions of CANR researchers to the research misson of Michigan State University. In particular, the awards focus on the impact that their achievements have had on academic and external stakeholder communities. Award recipients were selected based on evidence of dedication to research

through experimentation and discovery, innovation of techniques that contribute to research scholarship, evidence of excellence in scholarly outputs, as well as evidence of impacts in academic and/or external stakeholder communities. The Impact Award, co-sponsored by MSU AgBioResearch and MSU Extension, was awarded to Li for his project, "SARS-CoV-2 Epidemiology-Wastewater Evaluation and Reporting (SEWERS) Network."

Li is also being honored with the 2023 Environmental Quality Research Award from the American Society of Agronomy (ASA). Li was formally recognized Oct. 30 at the society's annual meeting in St. Louis, Missouri. Researchers are presented ASA awards each year for contributions to agronomy through education, national and international service, and research. According to the ASA, the Environmental Quality Research Award is given to scientists

who enhance basic understanding of environmental sciences in the areas of agriculture, soil quality, water and air resources. Candidates are evaluated on creativity and originality of research, as well as contributions to the field of environmental quality. There have been 40 recipients since the award's inception in 1984.

Li is a professor in the Department of Plant, Soil and Microbial Sciences as well as a co-investigator on Project 5 of the MSU Superfund Research Program. Dr. Li's research expertise is in the area of environmental soil chemistry, and the fate and transport of contaminants in plant-soil-water systems.

To read more about the ASA award, please visit: https://www.canr.msu.edu/news/msu-soil-scientist-recognized-for-outstanding-environmen-tal-quality-research.

Wu Named University Distinguished Professor



IIT-affiliated faculty member Dr. Felicia
Wu was recently named as a University Distinguished Professor in recognition of her outstanding achievements in teaching, research and pub-

lic service. Wu was one of ten faculty to receive the honor this year.

The recognition is among the highest honors that can be bestowed on a faculty member by the university. Those selected for the title have been recognized nationally and internationally for

their exceptional teaching, outstanding record of public service, and scholarly and creative achievements.

The designations were recommended by Interim Provost Thomas D. Jeitschko, Ph.D., and Interim President Teresa K. Woodruff, Ph.D., and approved by the MSU Board of Trustees at its June 16 meeting. Designations were effective immediately.

Individuals holding the professorship will receive, in addition to their salary, a stipend of \$5,000 per year for five years to support professional activities.

A reception to honor the newly designated University Distinguished Professors was held on Nov. 16.

Wu is a John A. Hannah Distinguished Professor in the Department of

Food Science and Human Nutrition and the Department of Agricultural, Food, and Resource Economics. Wu's research examines the national and global burden of foodborne disease, how improved nutrition can counteract the harmful effects of toxins, and how cost-effective strategies can improve food safety in the United States and worldwide. Recently, her work has expanded to examine the risk of antimicrobial resistance from antibiotic use in livestock production, as well as how we can curb these risks.

To read more about the University Distinguished Professorships awarded this year, please visit: https://msutoday.msu.edu/news/2023/2023-university-distinguished-professor-designation.

Bhattacharya Receives Promotion and Tenure

Dr. Sudin Bhattacharya, Ph.D., has been promoted to Associate Professor with Tenure in the Departments of Biomedical Engeering and Pharmacology & Toxicology, effective July 1, 2023.

Bhattacharya's research focuses on applying computational methods to

study the signaling and transcriptional regulatory networks that determine cell fate and how these networks are disturbed by environmental pollutants like dioxin. His lab uses quantitative tools and genomic data sets to map and model these regulatory networks. His

work also includes spatial multi-scale modeling of tissue-level phenomena like toxicity in a liver injury. His lab primarily relies on mathematical and statistical modeling as research tools, and he works closely with other experimental scientists.

Center for Research on Ingredient Safety News

Research Partnership - MSU, Corewell Health Partner to Investigate Effects of Lead Exposure on Pregnant Women, Newborns

Researchers with Michigan State University and Corewell Health are partnering to study the health effects of lead poisoning in the Grand Rapids area where about one in 10 children has elevated lead levels in their blood, according to state data.

Researchers will employ a new assay using umbilical cord-derived stem cells to evaluate the effects of lead exposure on the developing immune system during early life stages. In parallel, clinicians and researchers at Corewell Health in Grand Rapids, Michigan, will explore any impacts of lead exposure on maternal health outcomes. Lead is a toxic metal that can cause various health problems, including developmental delays, intellectual disabilities and behavioral issues in children.

"We know lead exposure can cause a variety of adverse health outcomes. However, there's little research on the developing immune system. Our new assay will allow us to explore lead's impact on our most vulnerable populations," said Norbert Kaminski, the director of the MSU Center for Research on Ingredient Safety and the project's principal investigator.

Lead exposure during pregnancy has been associated with adverse obstetrical outcomes, but additional research is needed to fully determine the effects of maternal lead exposure on mother and fetus.

"We will monitor pregnancy complications in the study participants. Any correlation between complications and lead levels will be studied, helping us better understand the relationship between lead levels and adverse pregnancy outcomes," said Marcos Cordoba, an obstetrician and gynecologist and co-principal investigator from Corewell Health.

In addition to the study's potential scientific impact, MSU and Corewell Health are collaborating to minimize lead poisoning by boosting community awareness of lead exposure risk and available supportive services in Kent County and surrounding areas. Participating clinics will offer pregnant mothers educational materials on lead risks during pregnancy and breastfeeding and ways to reduce those risks as well as connect families with services from the Kent County Health Department for lead mitigation and removal. The study will offer no-cost lead testing and equip local physicians with tools for lead-exposure-related health counseling.

"By providing no-cost lead testing and lead-exposure-related health counseling, as well as utilizing a new way to evaluate the impacts of lead exposure, this partnership strives to make a positive impact on community health and address health equity disparities simultaneously," said Austin Goodyke, research scientist and co-investigator at Corewell Health.

The research is part of a larger effort to develop new tools and technologies to assess the effects of heavy metal and chemical exposure on the developing immune system.

"Our first focus with this assay explores lead, but it has the potential to transform how we evaluate safety to chemical exposure, whether environmental or otherwise," said Kaminski, a professor of Pharmacology and Toxicology at the MSU College of Human Medicine.

To read the original press release, please visit: https://www.canr.msu.edu/news/research-partnership-msu-corewell-health-partner-to-investigate-effects-of-lead-exposure-on-pregnant-women-newborns.

CRIS Science Day 2023

The 2023 Center for Research on Ingredient Safety Science Day held on September 12, 2023 at the MSU Union, focused on new approach methodologies in support of weight of evidence assessments for regulatory decisions. Speakers included:

- » Amber Goetz, Ph.D., Sygenta Implementing Modern Approaches to Testing and Evaluation into Weight-of-Evidence
- » Barbara Kaplan, Ph.D., Mississippi State University

NAMs and In Vitro Assays for Immunotoxicity with Focus on the IL-2 Luc Assay

- » Zhichao Liu, Ph.D., Boehringer Ingelheim Pharmaceuticals, Inc. Generative AI Promoting New Approach Methodologies (NAMs) Development
- » Kelly Magurany, M.S., NSF International Applying NAMs in Risk Assessment - A Framework Approach and Case Study
- » Lindsay Marshall, Ph.D., Humane Society International

Replicating the Human Airways in Vitro - From Normal Physiology to Disease Models for Drug Testing

» M. Sue Marty, Ph.D., Dow Chemical Company Using NAMs in a NextGen Safety Assessment for a Cosmetic Ingredient

For more information on the Center for Research on Ingredient Safety, please visit: https://cris.msu.edu.

Three EITS Students Receive Awards at MI SOT Annual Fall Meeting

The Michigan Regional Chapter of the Society of Toxicology recently held their annual fall meeting, "One Health in Toxicology," on October 13, 2023. Three Environmental and Integrative Toxicological Sciences (EITS) graduate students received awards at this meet-

ing.



EITS graduate student Kelsi Morris received the 1st Place Oral Platform Presentation Award for her presentation, "Associations of glyphosate and aminomethylphosphonic acid (AMPA)

with early second-trimester inflammatory biomarkers." Strickland is mentored by Dr. Rita Strakovsky.

Morris is interested in understanding the extent to which pregnant women are exposed to various environmental chemicals through their diets, and how this exposure could impact their health

and the health of their baby. Specifically, she is interested in studying the endocrine and metabolic health of women during pregnancy.



EITS graduate student Ebenezar Okoyeocha received the Ist Place Graduate/Postdoctoral Poster Presentation Award for his poster, "Chloropicrin-induced ocular toxicity; In-vivo injury model and the role of the Nrf2

pathway." Okoyeocha is mentored by Dr. Neera Tewari-Singh.

Okoyeocha's research interests involve elucidating the mechanism of chemical induced injury, and identifying targeted treatment options. His current research in Dr. Neera Tewari-Singh's lab is focused on establishing an in vivo mouse ocular injury model with Chloropicrin (Trichloronitromethane, CP). He

is working to further define the role of the Nrf2 pathway in CP-induced ocular injury using Nrf2 knockout (KO) mice.



EITS graduate student Maria Cinzori received the 2nd Place Graduate/Postdoctoral Poster Presentation Award for her poster, "Associations of per- and polyfluoroalkyl substances with maternal metabolic

and inflammatory biomarkers in mid-pregnancy." Cinzori is mentored by Dr. Rita Strakovsky.

Cinzori's research interests center around the intersection between nutrition, toxicology, and pregnancy. She has a particular interest in the relationship between maternal obesity and endocrine disrupting chemicals (EDCs) and their impact on the anogenital distance (AGD) and 2:4 finger digit ratio (2:4D) of the offspring.

IIT Seminar Series Fall 2023

The IIT was excited to host a wonderful lineup of speakers for the Fall 2023 IIT Seminar Series.



The semester-long series began with Dr. Honglei Chen, Michigan State University on September 19. He spoke on, "The Study of Olfaction: Environment, Prodromal Neurodegeneration, and Beyond." The study of

olfaction in older adults may present a novel way to understand and maintain healthy aging. In this talk, Dr. Chen discussed how novel research on olfactory impairment may help dissect the complexity of prodromal neurodegeneration and define roles of environmental factors. He also identified potential challenges and solutions. and then presented novel findings on how olfaction may affect the health of older adults above and beyond neurodegenerative diseases.



On October 14, the IIT hosted **Dr. David Tonucci**, Principal Consultant, Product Safety and Stewardship, Ramboll Americas. Tonucci is also an Adjunct Professor with the IIT. Dr. Tonucci is an experienced regulatory

toxicologist with over 30 years of experience developing a comprehensive background in global regulatory affairs focusing on new ingredient technologies in the food industry. He has focused his work on developing regulatory and toxicology programs to support the regulatory approval of novel ingredients, genetically modified enzymes, fermentation products as well as ingredients manufactured through biotechnology. Tonucci spoke on, "Cultivated Meat: Technical Approaches, Safety Considerations and Regulatory Implications."

The final seminar of the series



was given by Dr. Stephen Safe, Texsas A&M University, on November 14. He spoke on, "Nuclear Receptor 4A (NR4A) as a Traget for Inhibition of Tumor Growth and Reversal of T cell Exhaustion." Research in the Safe laboratory focuses

on developing and discovering compounds for mechanism-based drug development that targets both cancer and non-cancer endpoints. The major target for cancer chemotherapy includes specific protein (Sp) transcription factors, the aryl hydrocarbon receptor (AhR), the estrogen receptor (ER), and orphan nuclear receptors NR4Al (Nur77, TR3) and NR4A2 (Nurr1).

The IIT was excited to be able to offer such a diverse array of learning opportunities through the wide variety of seminars this fall.

Recent EITS Graduates



Lauren HeinePharmacology and Toxicology
Mentor, Jack Harkema

Dr. Lauren Heine received her Ph.D. after completing the dual major program in Pharmacology and Toxicology and Environmental Toxicology. Her dissertation was, "Glucocorticoid and Omega-3 Fatty Acid Interventions in Environmental Triggered Inflammation and Autoimmune Disease."

Heine has recently accepted a postdoctoral position with the Biochemistry and Biotechnology (B-TEK) Group at Los Alamos National Labs in New Mexico.



Omar Kana Pharmacology and Toxicology Mentor, Sudin Bhattacharya

Dr. Omar Kana received his Ph.D. after completing the dual major program in Pharmacology and Toxicology and Environmental Toxicology. His dissertation was, "Application of Deep Generative Modeling to Single Cell RNA Sequencing Data in Toxicology."

Kana is now a Scientist I in Spatial Transcriptomics at the Allen Institute for Brain Science in Seattle, Washington.



Isha KhanPharmacology and Toxicology
Mentor, Norbert Kaminski

Dr. Isha Khan received his Ph.D. after completing the dual major program in Pharmacology and Toxicology and Environmental Toxicology. His dissertation was, "Role of aryl hydrocarbon receptor activation by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in an in vitro model of human hematopoiesis."

Khan will be continuing his postdoctoral education in the laboratory of Dr. Norbert Kaminski where he will be evaluating the effect of different immunotoxicants on human hematopoiesis using

an in vitro model of human hematopoietic stem cell differentiation. He will also be involved in developing new in vitro human cell-based culture systems that may be useful to study the interaction of different immune cells with other cell types. Potentially, Khan would also like to study the effects of aryl hydrocarbon receptor agonists on functional responses of myeloid immune cells. In the long term, he is interested in a research career in the pharmaceutical and biotechnology industries and would like to be involved in drug development with a focus on translational biomarker technologies.



Michelle Steidemann Pharmacology and Toxicology Mentor, John LaPres

Dr. Michelle Steidemann received her Ph.D. after completing the dual major program in Pharmacology and Toxicology and Environmental Toxicology. Her dissertation was, "The Role of Crosstalk between the Aryl Hydrocarbon Receptor and Translocator Protein in Modulation of Gene Expression and Cellular Homeostasis."

Steidemann is continuing her postdoctoral education at MSU in the laboratory of Dr. John

LaPres. Based on previous RNA-sequencing results, Steidemann is working to understand how environmental sensing proteins AHR and TSPO can influence the expression of LRRK2, the most commonly mutated gene in familial Parkinson's disease. As TSPO is a known mitochondrial protein, Steidemann's research aims to determine how LRRK2 could be interacting with mitochondria as well as if any other organelles, such as lysosomes, or ER are involved. This research could provide a clearer mechanism for how Parkinson's disease might progress.

IIT Welcomes New EITS Students

The IIT is pleased to welcome the following students who have joined the EITS program in the past several months:

- » Antryg Benedict, training with Dr. Cheryl Rockwell
- » Kelsi Morris, training with Dr. Rita Strakovsky
- » Samantha Musso, training with Dr. Jamie Bernard
- » Andrew Roney, training with Dr. Neera Tewari-Singh

EITS Research Evening Celebrates Student Research

The Institute for Integrative Toxicology's Annual Research Evening showcased trainees in the Environmental and Integrative Toxicological Sciences Graduate Training program and their accomplishments. This year's event took place on Wednesday, November 29, 2023 in the Lincoln Room at the MSU Kellogg Center. The event included dinner, student posters and platform presentations.

Three EITS graduate students presented the platform presentations:



Morgen Clark, training in the lab of Dr. Gemma Reguera, spoke on, "Uranium detoxification by electric bacteria." Clark is a doctoral student in the Department of Microbiology and Molecular Genetics and has

focused her graduate research on metal detoxification mechanisms by met-

al-reducing bacteria. Using Geobacter sulfurreducens as a model organism, Clark explores how conductive type IV pili, lipopolysaccharide, and outer membrane vesicles play a role in metal reduction and detoxification.



Isha Khan, training in the lab of Dr. Norbert Kaminski, spoke on, "Role of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in an in vitro model of human hematopoiesis." Khan is a doctoral student in the Department of Pharmacology and

Toxicology and has focused his research on investigating the effects of certain xenobiotics on human hematopoietic stem cell differentiation in vitro. Khan also plans to use different functional assays to evaluate the immunocompetence of several hematopoietic lineages that develop in vitro from human hematopoietic stem cells.



Brad Ryva, training in the lab of Dr. Rita Strakovsky, spoke on, "All Mixed Up: Modeling cumulative and non-linear associations of endocrine disrupting chemical mixtures with maternal hormone levels in pregnant women." Ryva is a doctoral

student in the Department of Pharmacology and Toxicology and has focused his graduate research on non-persistent endocrine disrupting chemicals found in common consumer products and their potential impacts on women's health during pregnancy. Specifically, he is exploring the hormonal and environmental determinants of persistent nausea during pregnancy.

To those who attended, thank you for joining us for this special evening of celebration, camaraderie, and learning!



EITS Student Jennifer Hinman Receives Accolade



EITS graduate student Jennifer Hinman, training with Dr. Kin Sing Lee, received best poster award for her work, "The Molecular Crosstalk Between Aging, Polyunsaturated Fatty Acid Oxidative Metabolism, and Neurodegenera-

tion in C. elegans," at the 19th International Winter Eicosanoid Conference. The annual conference serves as a forum for exchange of ideas and learning of exciting new developments in the field of eicosanoids with a focus on cancer, inflammation, and cardiovascular disease. This year's meeting was held October 15 - 17 in Baltimore, Maryland.

HInman's research interests include studying how endogenous oxidized polyunsaturated fatty acid (PUFA) metabolites, also called oxylipins, affect age-associated neurodegenerative diseases. Throughout this work she hopes to identify and study the corresponding mechanism of oxylipins that either accelerate or alleviate age-associated neurodegeneration, specifically the epoxy- and dihydroxy-metabolites of omega-3 (ω -3) and omega-6 (ω -6) fatty acids.

Tewari-Singh Receives Promotion and Tenure

Dr. Neera Tewari-Singh, Ph.D., has been promoted to Associate Professor with Tenure in the Department of Pharmacology & Toxicology, effective July 1, 2023.

Her research focuses on under-

standing the mechanisms of toxicity and inflammation associated with toxic chemical exposures with the goal of developing effective targeted countermeasures. Her lab employs a combination of state-of-the-art molecular techniques and systematic toxicology approaches to develop effective medical interventions. This two-pronged approach is critical and makes her research highly significant.



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