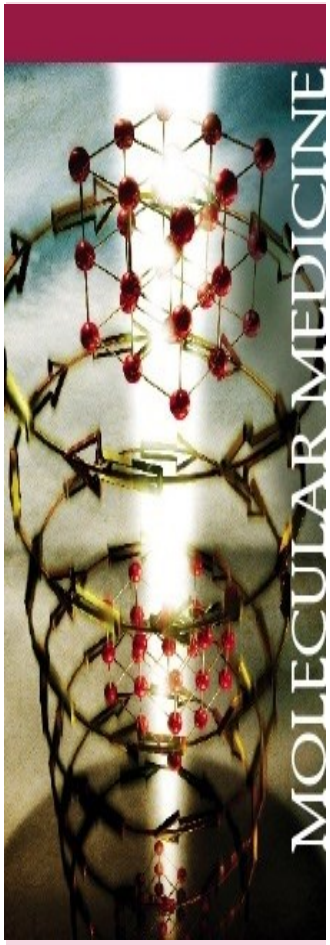

CENTER FOR
MOLECULAR MEDICINE AND GENETICS
Fall 2022/Winter 2023

Role of ER-Associated Degradation in Regulating Fibrinogen Biogenesis

Faculty spotlight—Shengyi (Iris) Sun

Protein folding defects cause disease

Dr. Shengyi (Iris) Sun is currently focused on studying endoplasmic reticulum associated degradation (ERAD) *in vivo* such as in the liver and germline stem cells. Aided by a new NIH grant, Dr. Sun is researching the function of ERAD in regulating an important coagulation factor, fibrinogen.

The endoplasmic reticulum (ER) is a key organelle in every cell, where all secretory and membrane proteins are synthesized before they are exported for function. "It's like a factory making products—errors can happen. In the cellular

Sun

context, errors in production result in misfolded proteins, which require quality control mechanisms in the ER," Dr. Sun explains. Protein misfolding can have broad pathological implications, from liver diseases to diabetes. Dr. Sun and her lab study one such quality control mechanism, specifically ER-associated protein degradation (ERAD), which recognizes misfolded proteins in the ER and extracts them to the cytosol for degradation. The protein complex consisting of SEL1L

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Mitochondrial Regulation in Breast Cancers

MNRR1 protein in metastasis role

Faculty spotlight—Siddhesh Aras

Dr. Siddhesh Aras brings a mitochondrial focus to his research on human disease. Currently he is focused on breast cancer, the subject of a new grant award from the Department of Defense. Breast cancer is the second leading cause of cancer-related mortalities in women. A specific subset of breast cancer – triple negative – accounts for about 15-20% of all breast cancer cases and has no targeted therapies. Metastasis, the migration elsewhere of cancerous cells from the primary tumor, is usually the underlying cause of mortality in cancer. Since increased mitochondrial activity accompanies metastasis, Dr. Aras is seeking to identify

mechanistic and druggable targets for mitochondrial regulation. "There is no cure once metastasis has occurred," he says. "We are interested in the mitochondria because there are currently no therapies that target this organelle."

One target Dr. Aras is investigating is the protein product of the gene *MNRR1* (also called *CHCHD2*). As a postdoctoral fellow, Dr. Aras

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Aras Spotlight:

Regulation in Breast Cancers

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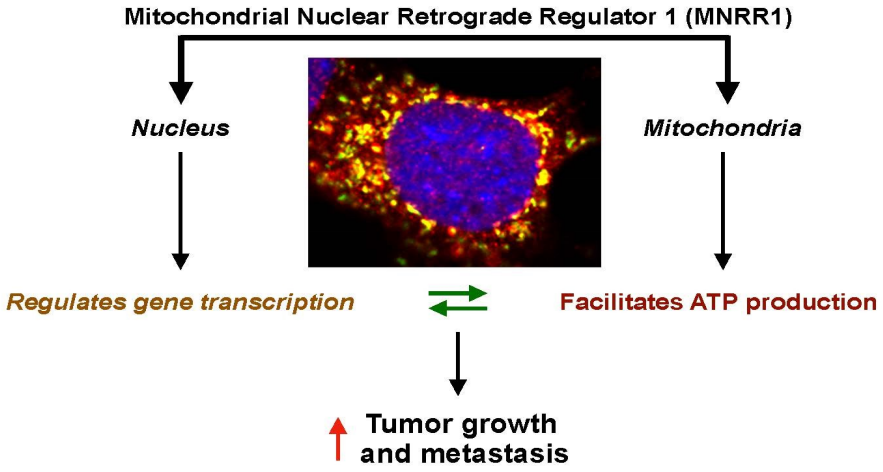

characterized the MNRR1 protein, and then discovered that its level is increased in breast cancer cells, roughly in proportion to the aggressiveness of the tumor. According to Dr. Aras, the MNRR1 protein "is one of a kind since it can be found both in the mitochondria and the cell nucleus." The MNRR1 protein was previously thought to be found only in the mitochondria, but Dr. Aras, along with CMMG Director Lawrence Grossman, discovered this protein to be present in the cell nucleus as well, where it regulates transcription of about 1000 genes. Dr. Aras explains the MNRR1 protein is sort of a "moonlighting protein, in that it has multiple functions," owing to its presence both in the mitochondria and the cell nucleus. The implications of this discovery are significant because now the MNRR1 protein can be understood to play a key role in both compartments, making it "an attractive target for influencing multiple functions within the cell." Interrupting the function of the MNRR1 protein will hopefully reduce proliferation and metastasis of cancerous cells, thus uncovering a promising direction for limiting the spread of breast cancer .

Preliminary analyses have shown that inhibitors of the MNRR1 protein reduce the tumor burden in animal models. Dr. Aras and his team are currently characterizing additional compounds to target the MNRR1 protein. His work thus has the potential to improve outcomes and quality of life for breast cancer patients, especially those with triple negative breast cancer.

In addition to its role in cancer, the MNRR1 protein has been associated with neurodegenerative diseases such as ALS and Parkinson's. In those cases, mutations of are found to be present. Overall, this underscores the importance of Dr. Aras' work in researching the MNRR1 protein as an attractive target for therapeutic treatments.

SURP Symposium 2022—Highlights

The Summer Undergraduate Research Program (SURP) hosted by the Center for Molecular Medicine and Genetics is the hallmark of mentorship in research. Every year, students accepted into the program conduct research under the mentorship of CMMG faculty in a variety of projects related to faculty members' research such as mitochondrial genetics, evolutionary genetics, neuroscience, inflammation, and more. This summer marked a return to an in-person program for the first time since 2019. Students then had the opportunity to present their research projects live at the 2022 Summer Undergraduate Research Symposium in August.

SURP has been running for the past 22 years at CMMG and has mentored numerous undergraduate students to promote their research capabilities and interests. The mentor-mentee relationships fostered during the program lasts beyond the summer and has a lasting impacts on the students. The CMMG faculty who acted as mentors to this year's cohort were again dedicated to advancing the research skills of the students, taking the time to teach the foundational skills of research, and reviewing students' work with them. Matthew Pang, a student at Michigan State University who was mentored by Dr. James Granneman, said that he "not only gained many important lab skills, but also learned how to approach problems with a research mindset."

Students delivering slide presentations at the symposium were judged by a committee of four faculty members: Dr. Maik Hüttemann, Dr. Henry Heng. Dr. Iris Sun, and Dr. Russell Finley. Presenters were judged upon a variety of factors about their poster presentation, and the top two presenters received an award. All

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Sun Spotlight

From Page 1

and HRD1, located on the ER membrane, is a key complex carrying out ERAD activity. Past research has focused on the biochemistry of this complex, studying it *in vitro*. "However, we are really interested in the significance of this complex *in vivo,* in a cell-type specific manner," Dr. Sun says.

"If you think of our body," Dr. Sun goes on to say, "we have all kinds of cells with many different functions because of the different proteins they make. So, thinking about different cell types, the ERAD mechanism must carry out different functions in a cell-type specific manner."

Thus, in the current study, Dr. Sun and her team aim to better understand the function of ERAD specifically in hepatocytes (liver cells). They are researching the function of SEL1L-HRD1 ERAD in "ensuring the proper maturation and secretion of fibrinogen, a coagulation factor abundantly produced in the liver." According to Dr. Sun, the fibrinogen protein is "very large and complex," since it is composed of six polypeptide chains, making it prone to misfolding and requiring ERAD activity. In addition, mutations in the fibrinogen genes lead to the presence of misfolded fibrinogen and cause fibrinogen storage disease. The misfolded fibrinogen is trapped in the ER of hepatocytes rather than being secreted, thus motivating the investigation of how "ERAD can regulate the disease-causing fibrinogen mutants," says Dr. Sun.

Initially, Dr. Sun came across this study on the ERAD regulation of fibrinogen biogenesis through a bizarre observation made while studying mice containing a hepatocyte-specific knockout of SEL1L (which have deficient ERAD activity in the liver).

"We found very large and 'bubble-like' inclusion bodies within the hepatocytes of the knockout mice," Dr. Sun says. "Through literature studies we found that fibrinogen may be a protein retained in the inclusion bodies and that's how we started to look at how ERAD regulates fibrinogen biogenesis."

A curious observation and the hard work of Dr. Sun and her team led to their recent grant funding. Most of all, Dr. Sun feels grateful about the hard work and support of her lab and colleagues. "I'm really fortunate to have such wonderful lab members and colleagues working with me…through everyone's hard work we landed these grants and I hope to keep good things happening in the future."

Mentorship is key in academia and Dr. Sun prioritizes this aspect with the students working in her lab. She hopes that anyone who works in her lab takes away "not only the techniques but also the way of scientific thinking. It's not just working in the lab, but also driving a study to the end with a view of the bigger picture." When asked about advice for future graduate students or any student interested in research, Dr. Sun states that motivation, hard work, and keeping an open mind is important. "In research we must be motivated, have an open mind, and not be afraid of trying something new. This is true for anything in life, and very important in research."

ERAD is implicated in a wide variety of functions in different cells by "regulating the biogenesis of specific proteins." The Sun lab is studying a variety of ERAD functions such as in the regulation of iron metabolism in germline stem cells and spermatogenesis, and in many protein misfolding diseases. In addition, Dr. Sun is interested in investigating "if the ERAD is dysregulated in a disease and, if so, whether there is a possibility to target it."

"Our research is really curiosity driven – we are open to many possibilities in the future."

Honors

Awards/Promotions

Erin Carmany, MS, CGC was promoted to Associate Professor—Clinical.

Roger Pique-Regi, PhD, was promoted to Professor.

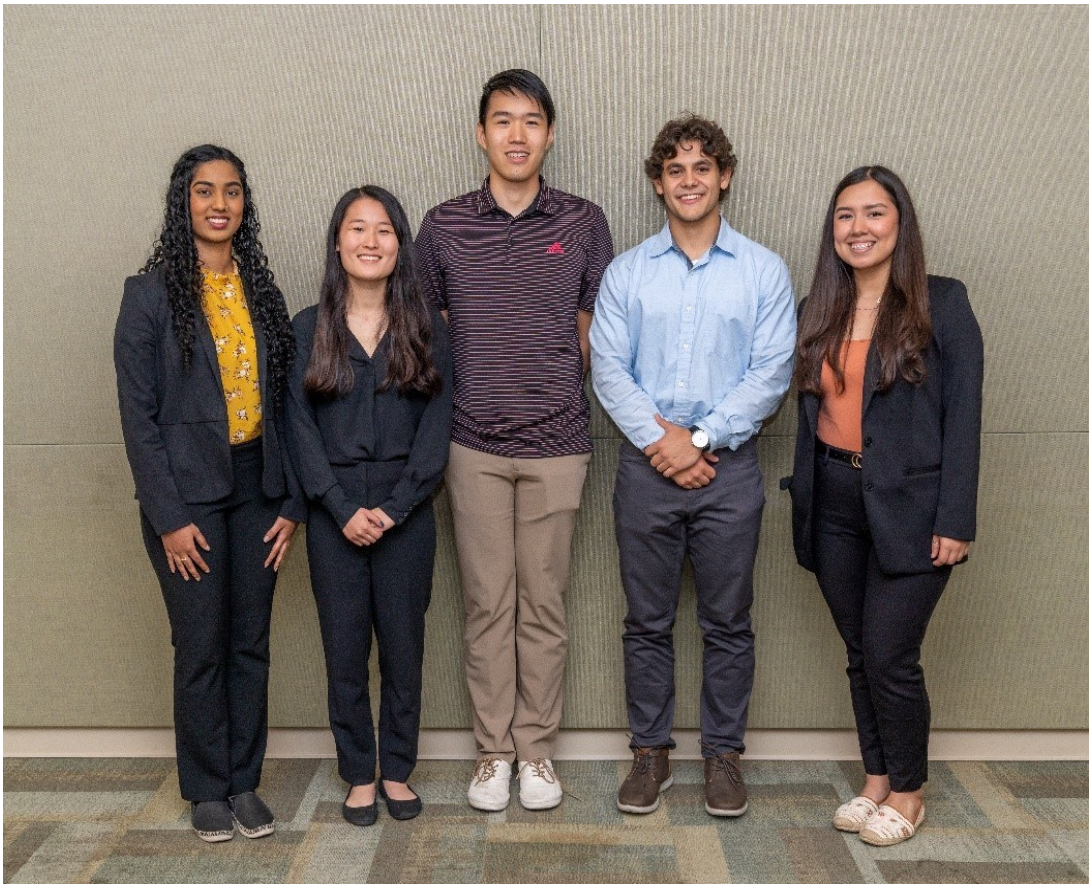
Siddhesh Aras, MBBS, PhD, was awarded the 2022 SoM Teaching Award.

Francesca Luca, PhD, was promoted to Professor and received both the 2022 Outstanding Graduate Mentor Award and 2022 SOM Research Excellence Award.

Iris Sun, PhD, was awarded the 2022 SOM Research Excellence Award.

Kezhong Zhang PhD, was awarded the Dean's Office Award for Outstanding Research.

SURP Symposium cont.



Pictured above are the 2022 SURP Cohort. (L to R) **Geetika Kancharla**, Virginia Commonwealth University; **Emma Kramer**, Central Michigan University; **Matthew Pang**, Michigan State University; **Pietro Elliot**, Pennsylvania State University; **Daniela Rodriguez**, University of Texas Rio *Grande Valley (Not pictured: **Vasudha Nimmagadda**, Michigan State University). These students successfully completed research projects under the mentorship of CMMG faculty and presented posters at the SURP Symposium.*

participants received a certificate of completion signed by the SURP Symposium Chair, Dr. James Granneman and CMMG Director, Dr. Lawrence Grossman.

1st Place: Emma Kramer, Central Michigan University

Mentor: Tiffany Cook, PhD

"Variables Influencing Retinal Degeneration and Recovery in Drosophila Melanogaster"

2nd Place: Matthew Pang, Michigan State University

Mentor: James Granneman, PhD

"Interplay of PPARα and PPARɣ in Thermogenic Brown Adipose Tissue During Cold Conditions"

Suzanne Shaw, SURP Program Coordinator, explained the importance of hosting this program every year, stating that it helps expand student interest in graduate programs here at WSU while also fostering their research skills. She emphasized the competitive nature of this program, which has about a 6-7% acceptance rate and attracts a diverse and talented group of undergraduate students from across the country. Ms. Shaw matches students with faculty members based on the students' research interests and the availability of mentors. According to Pietro Elliott, a student at Pennsylvania State University, this summer was his first research experience and that, under the mentorship of Dr. Alexander Gow, he developed a computational model "that simulates the spinal dorsal network in a health versus diseased state" and has given him a new perspective on research.

Future symposiums will likely continue to use Zoom for increased accessibility in addition to the traditional in-person format. Interested undergraduate students can find more information on how to apply for the 2023 SURP cohort on the CMMG website.

Pictured above:
Ms. Vasudha Nimmagadda

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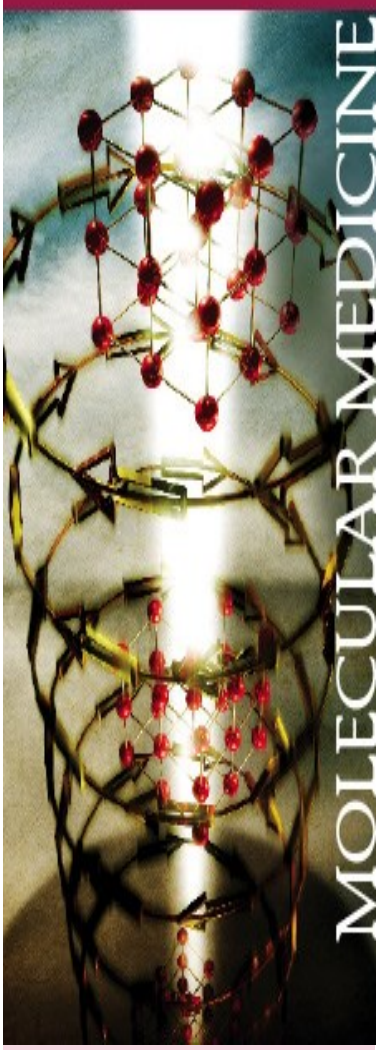

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Tiffany Cook, PhD

Gerald L. Feldman, MD, PhD

Russell L. Finley, Jr., PhD

Alexander Gow, PhD

James G. Granneman, PhD

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