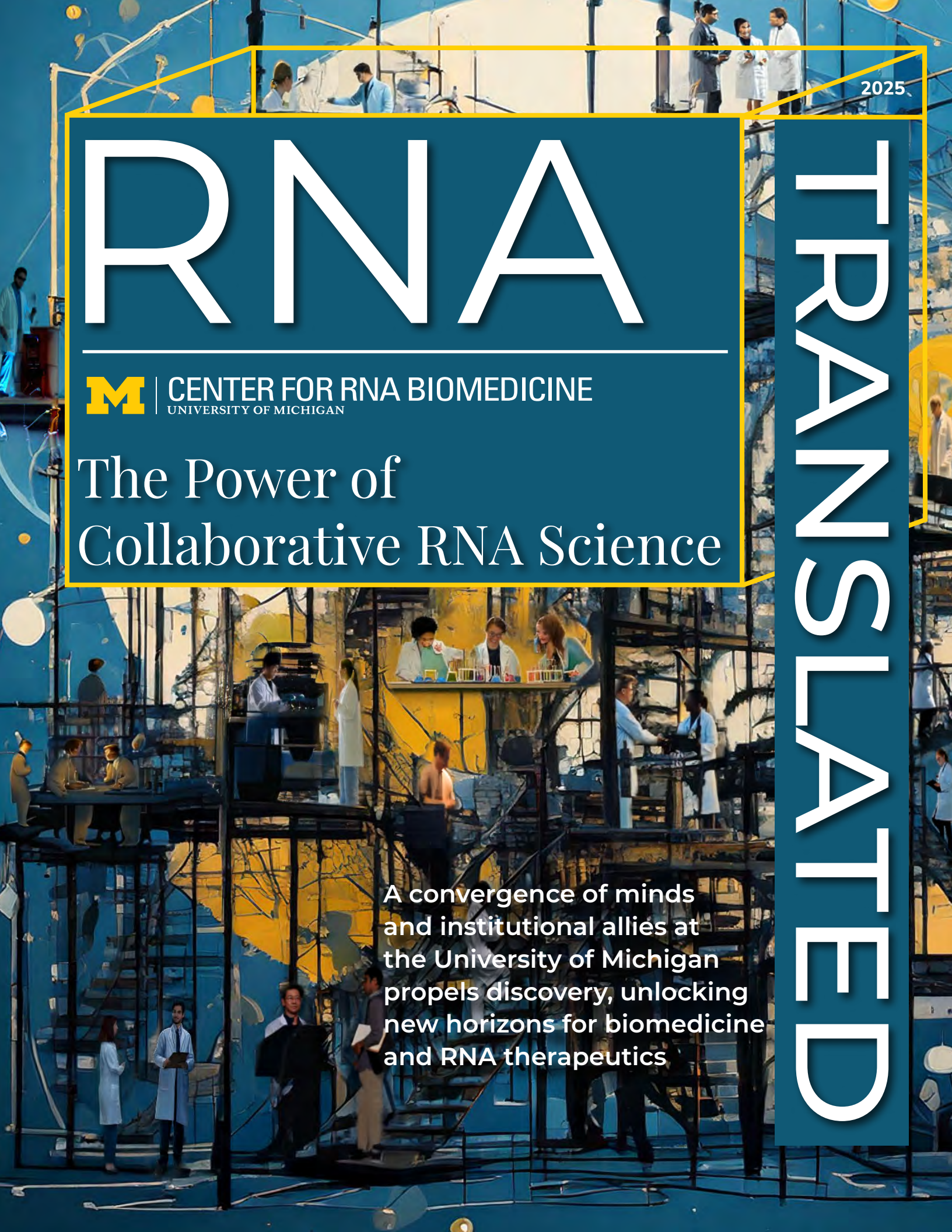

2025

RNA TRANSLATED

CENTER FOR RNA BIOMEDICINE
UNIVERSITY OF MICHIGAN

The Power of Collaborative RNA Science

A convergence of minds and institutional allies at the University of Michigan propels discovery, unlocking new horizons for biomedicine and RNA therapeutics

CENTER FOR RNA BIOMEDICINE
UNIVERSITY OF MICHIGAN

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External Leadership Council

Formed in 2023, the External Leadership Council comprises leading experts in RNA science who help shape our overall strategy in support of the center's mission. Additionally, they provide strategic guidance and scientific advice and support us in growing our professional networks through introductions to contacts in industry, academia and government.

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Huntington Sheldon Professor in Medical Discover, Professor of Molecular Biology and Genetics, Johns Hopkins School of Medicine

Nils Walter welcomes John Cooke at the 2024 RNA Symposium.

Mission

The University of Michigan Center for RNA Biomedicine seeks to:

- Promote and develop cross-disciplinary collaborations on RNA across campus.
- Mentor the next diverse generation of RNA scientists in an equitable and inclusive way.
- Enrich the U-M's intellectual and training environment around RNA biomedicine.
- Leverage and promote the strengths of the U-M RNA community, ranging from single-cell and single-molecule biophysics to RNA therapeutics and across RNA-mediated diseases such as cancer, neurodegeneration and viral infection.
- Provide a central organizational structure to help recruit and develop common resources, including collaborative research grants and shared equipment, as well as domestic and international researchers.

Photo: Scott C. Soderberg, Michigan Photography

Mats Ljungman, Ph.D., Professor of Radiation Oncology and of Environmental Health, Medical School

Nils G. Walter, Ph.D., Francis S. Collins Collegiate Professor of Chemistry, Biophysics and Biological Chemistry, Professor of Chemistry, Professor of Biophysics, College of Literature, Science, and the Arts

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Michelle Hastings, Ph.D., Pfizer Upjohn Research Professor of Pharmacology, Professor of Pharmacology, Medical School and Professor of Medicinal Chemistry, College of Pharmacy

Introduction

The rapid progress in RNA biology and therapeutics is remarkable. While the widespread use of mRNA vaccines has subsided, they remain poised for a resurgence in the next pandemic, even as their impact expands into anticancer vaccines and protein replacement therapies. Meanwhile, high-throughput technologies such as genomics, transcriptomics, artificial intelligence (AI)-driven pattern recognition and patient-derived organoid screening are accelerating the clinical translation of fundamental discoveries. Driving these advances is the power of collaboration, a core mission of the Center for RNA Biomedicine at the University of Michigan (U-M).

This newest issue of our RNA Translated magazine celebrates and contextualizes this progress. We highlight the vital role of cross-disciplinary collaboration, bringing together foundational researchers, clinicians and administrators to unlock mysteries in RNA biology and realize the full potential of RNA therapeutics. Through exemplary stories of success, we explore breakthroughs ranging from the harnessing of microRNAs in cancer to the role of stress granules in neurodegenerative diseases, single-cell spatial transcriptomics and synergistic small-molecule drug discovery efforts across a range of pathologies.

In parallel, to fully unlock the potential of RNA therapeutics, we are actively fundraising for a new RNA Synthesis Core. This initiative aims to provide high-quality, cost-effective enzymatically and chemically synthesized RNAs for preclinical research accessible to researchers and clinicians at the University of Michigan and beyond. Free from commercial constraints, this resource will further accelerate breakthroughs in personalized RNA medicines, positioning the U-M as a "leaders and best" community at the forefront of innovation, both nationally and globally.

As we look ahead, the field of RNA biosciences continues to redefine the limits of medicine, offering unprecedented opportunities for discovery and innovation. The breakthroughs highlighted in this issue of RNA Translated underscore the transformative power of interdisciplinary collaboration, cutting-edge technology and a shared commitment to advancing RNA research for the benefit of human health. With the launch of new initiatives like the RNA Synthesis Core and the relentless pursuit of foundational research and novel therapeutics, the U-M will remain at the forefront of this revolution. We invite you to explore these stories, celebrate the progress made and join us in shaping the future of the RNA biosciences.

Photo opposite: Daryl Marshke, Michigan Photography

The Power of Collaborative RNA Science

It takes a village

Aristotle famously said, “The whole is greater than the sum of its parts.” But the Greek philosopher most likely never imagined how great that whole could become as manifested by the Center for RNA Biomedicine at the University of Michigan.

Each spring, the center hosts its annual symposium, bringing together top leaders in RNA science and medicine to present their latest work and share ideas with colleagues.

It’s fuel for the fire for RNA researchers and clinicians, drawing them out of their labs and examination rooms and into an electrified environment where the collective consciousness of kindred spirits sparks thought and feeds the imagination.

The annual event represents a mere facet of a word that each of the nearly 170 faculty members of the center would undoubtedly consider an unequivocally essential component of their work: collaboration.

However, collaboration takes on an entirely new dimension when applied to the Center for RNA Biomedicine, which fosters not only cooperative alliances between members and other faculty but also partnerships with myriad supportive centers, institutes and initiatives scattered throughout U-M’s diverse landscape.[1]

[1] https://provost.umich.edu/resources-policies/academic-program-center-planning/centers-institutes/list-of-institutes-centers/

Photo: Paul Avedisian

This cross-disciplinary, collaborative interconnectedness and interdependency is central to fulfilling the center’s mission, expanding its human capital, compounding its resources and, most importantly, connecting people.

To provide a snapshot of this dynamic, we’ve highlighted a selection of these U-M units and spoke to a core group of Center for RNA Biomedicine faculty and student members affiliated with each. Their combined work encompasses a veritable cross-section of RNA scientific research — a kaleidoscope of seemingly disparate areas of focus, all intersecting at a common point: RNA.

The conversations presented here offer views into the groundbreaking work of some of the world’s leading experts at the forefront of RNA science and medicine. And for the first time, insight from junior researchers provides an additional perspective from the next generation of thought leaders, as we shine the spotlight on those who carry the torch and are poised at the front lines of the inevitable exponential scientific advancement to come.

The collaborative network generated within the Center for RNA Biomedicine and throughout the University of Michigan campus is strong. In the following pages, you’ll learn how a few inhabitants of the largest, most diverse and overall best-funded RNA centers in the United States harness that power to drive current discoveries and guide them to their next path.

As English naturalist, geologist and biologist Charles Darwin said, “In the long history of humankind (and animal kind, too) those who learned to collaborate and improvise most effectively have prevailed.”

Ratchet up your senses. Put your finger on the pulse.

Feel the power …

… of collaboration.

Photo: Scott C. Soderberg, Michigan Photography

Rogel Cancer Center

The University of Michigan Rogel Cancer Center seeks to reduce cancer burden and improve cancer outcomes through research, innovation and transdisciplinary collaboration. A comprehensive cancer center designated by the National Cancer Institute, Rogel Cancer Center follows a team-based approach to cancer not only in patient care but also in research and education.

ROGEL CANCER CENTER
UNIVERSITY OF MICHIGAN HEALTH

"Why? But why? So, then ... why?"

Analisa DiFeo, Ph.D.

Analisa DiFeo, Ph.D., Professor of Pathology, Professor of Obstetrics and Gynecology and Associate Director Academic Program, Cancer Biology Graduate Program, Medical School

Questions, not answers, brought Analisa DiFeo, Ph.D., professor in the Departments of Pathology and Obstetrics and Gynecology, to science.

She recalls one of her first childhood memories: her sister returning home from the hospital after undergoing a successful operation to correct a cleft palate. Four-year-old Analisa was more fascinated than upset and curious than cautious. Reaching rather than recoiling, Analisa asked her parents why her sister had this condition when she didn't, what the doctors did and how they did it. Inquisitive? Absolutely. Probing? Positively!

Analisa's natural curiosity propelled her forward and into not only the "whys," but also the "hows," "whos," "whens," "whats" and "ifs" of it all — the science — where she's lived ever since.

DiFeo is an affiliate faculty member of the University of Michigan Rogel Cancer Center and the associate director of the Cancer Biology Graduate Program, supported jointly by the Rogel Cancer Center and the U-M Medical School's interdisciplinary Ph.D. Programs in Biomedical Science (PiBS).[1]

Honored as a 2024 Rogel Scholar for her dedication to achieving impact through novel breakthroughs in cancer research, DiFeo is a translational scientist, committed to research that directly impacts the lives of the pa-

Opposite: Dr. DiFeo advocating for more federal funding for biomedical research on Hill Day, 2024 at the U.S. Capitol in Washington, D.C. Image courtesy of Analisa DiFeo, Ph.D.

[1] https://medschool.umich.edu/programs-admissions/phd-programs/pibs

DiFeo headshot image courtesy of Analisa DiFeo., Ph.D.

tients with the disease — and collaboration is key. “The motto of my lab is, ‘Teamwork makes the dream work,’” DiFeo says. “We can’t do it alone.”

Her passion for science is fueled by the driving principle: “We know what we don’t know.” “This is especially important in science,” DiFeo says. “There’s a tendency for investigators to believe that they know everything there is to know about a certain topic or area. They tend to get tunnel vision, which is detrimental for scientists because they don’t reach out and remain stuck.

“That is one of the reasons why we have high school students, undergraduate and graduate students, medical fellows, post-docs, staff scientists, literally the entire continuum of researchers working in our lab. Diverse minds help with the diversity of your research, and cancer is very diverse. Any question from anyone can impact the way we do our work.”

DiFeo “making the dream work” with members of her lab. Image courtesy of Analisa DiFeo, Ph.D.

For Analisa DiFeo, it’s personal. Cancer research, that is.

DiFeo’s work centers on cancer genetics, the field in which she earned her Ph.D. However, she began her studies working on rare genetic diseases, until receiving unsettling news that some family members were diagnosed with ovarian cancer as a graduate student at Icahn School of Medicine at Mount Sinai in New York — an unwelcome catalyst steering her in a new direction.

Though less common than breast or lung cancer, ovarian cancer is much more lethal, with a five-year survival rate of just 29-30%. It’s a silent cancer. Many patients receive misdiagnoses of gastrointestinal issues early; 80% receive the ovarian cancer diagnosis at stage three or four when treatment is much more of a challenge.

“I found out that very little was known about ovarian cancer, particularly its genetic makeup, and, of course, being true to my nature, I asked myself, ‘Why?’” says DiFeo. “Fortunately I had a mentor at the time who gave me the latitude and encouraged me to explore this area even though it was something completely novel in his laboratory.”

Early in her investigation, DiFeo learned that many of the cell lines, or cells grown in a lab, used in ovarian cancer research and to test drugs had their origins in samples collected from patient tumors in the 1970s-80s. Several groups had published that these cells had stopped accurately recapitulating, or reproducing, the tumors in human disease because of genetic drift, or genetic shifts, over time. This widening divergence made these cells significantly different from their original source.

DiFeo recognized that to begin her investigation of ovarian cancer properly required a much firmer foundation, identifying the immediate need to build a better mousetrap: a cell line from new human ovarian cancer tissue that would replicate the tumors much more accurately. Furthermore, she set out to build an entire repository of cell lines, a “biobank” of frozen tissue samples, and make them freely available to the ovarian cancer research community at large.

DiFeo began establishing a biobank at Mount Sinai and then at Case Western Reserve University, teaming up with clinicians to obtain patient samples from those performing the operations. In a brilliant feat, three departments coordinated their efforts to bring Analisa to U-M when she joined the faculty in 2018: Eric Fearon, M.D., Ph.D., director of the Rogel Cancer Center and affiliate faculty and Strategic Advisory Board (SAB) member of the Center for RNA Biomedicine (CRB); Charles Parkos, M.D., Ph.D., chair of the Pathology Department; and Dee Fenner, M.D., chair of the Department of Obstetrics and Gynecology at Michigan Medicine.

In collaboration with Zhen Ni Zhou, M.D., Ph.D., clinical assistant professor in the Departments of Gynecological Oncology and Obstetrics and Gynecology, and a team of gynecological oncology surgeons, DiFeo continued to build a gynecological cancer biobank. This joint venture would prove instrumental in acquiring as many samples as possible.

“Sigourney Weaver ain’t got nothin’ on her”

The groundwork set, DiFeo plunged in headfirst. Once she and her team collected the tumor cell samples, they earmarked them for various purposes: growing cancer cell lines, implanting them into immunodeficient mice (mice bred to lack an immune response to allow for unimpeded growth), conducting RNA sequencing to study the genetics, or freezing in the biobank for later analysis (see Figure 1 on page 12).

DiFeo next focused on what would become her breakthrough work — replicating, or mirroring, the human tumor environment in mice to study ovarian cancer genetic profiles and test the effectiveness of drugs and other intervening methodologies. Enter the avatars. Mouse avatars.

In movies and video games, avatars act as stand-ins for real people. In cancer research, avatars enable scientists to test treatments for humans in mice, ergo mouse avatars.

DiFeo and her team needed to prove that the new cell lines were growing tumors that closely resembled their human counterparts. Vetting began by looking at the histology (the microscopic structure of biological tissues) of the patient

Eric Fearon, M.D., Ph.D., Emanuel N. Maisel Professor of Oncology, Director, Rogel Cancer Center, Associate Dean for Cancer Programs, University of Michigan Medical School, Professor, Departments of Internal Medicine, Human Genetics, and Pathology

(PT) tumor and patient-derived xenograft (PDX) mouse tumor cells side by side, staining them with various proteins and confirming that the protein was consistent.

Next, RNA-sequencing revealed that overall RNA expression (information encoded in a gene that’s turned into a function) mapped similarly, providing additional proof that the PT tumor was extremely similar to the PDX mouse tumor (see Figure 2 on page 13). This gave the team confidence that they could recapitulate the human tumor in the mouse avatars.

Narrowing down the avatar field then turned into an inverted game of “survival of the fittest.” Explains DiFeo, “Normal human tissue will die after four or five passages (transfers or subcultures into dishes). Cancer cells are different, they can grow indefinitely and therefore be passaged indefinitely. It’s also one of the reasons a cure has been so elusive.

“As we passage the cells from six, seven, up to 20 times, genetic drift will still occur because cancer cells are aggressive survivors, adapting well to their environment. So with each passage, we selected the most aggressive cells — those with the highest survival rate — because these are the tumor cells most likely to come back in a patient.”

Eric Fearon photo courtesy of Eric Fearon, M.D., Ph.D.

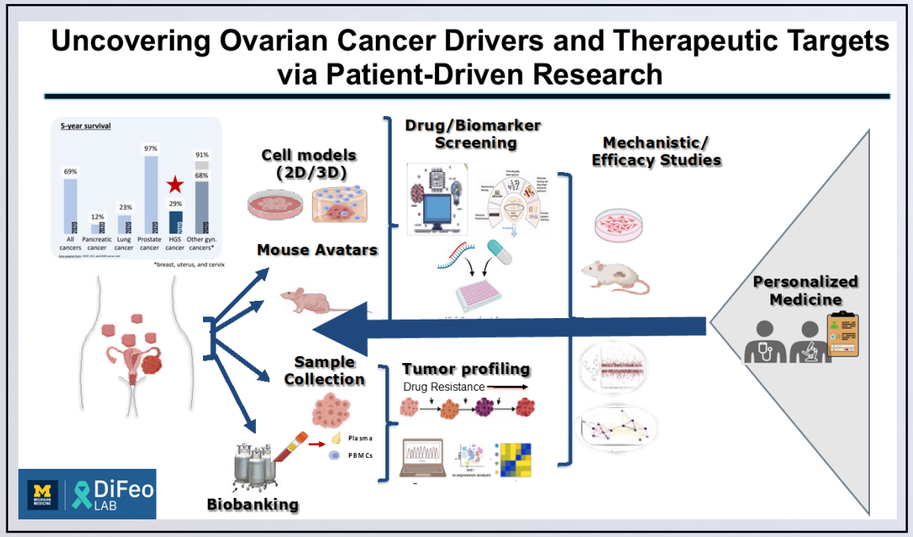


Figure 1. Schematic showing ovarian cancer tumor cell samples earmarked for multiple purposes. Courtesy of Analisa DiFeo, Ph.D.

Tumor tissue profiling (checking for the presence of certain genes, proteins, molecules) infused another level of criteria to the Darwinian hypothesis. Determining what genetic factors seemed to get enriched or lost, for instance in patients who don't respond to chemotherapy or whose tumors come back much faster than others, provided crucial data that helped the DiFeo selection committee further evaluate contenders.

Approximately 30-35 different PDX mouse avatar models have made the final cut, representing a field of the most aggressive ovarian cancer tumor profile environments.

"Operation Avatar" continues with advances on two fronts. The first front involves testing existing small molecule drugs (think aspirin, antihistamines) to see which tumors respond best. Those genetic profiles could then be translated to predict response to that drug in the future.

The second front, developing and testing new drugs and other ways to intervene such as RNA-based or RNA-targeting medicines, is inherently rife with challenges, the least of which is identifying which drugs, compounds (chemicals, not yet drugs) or molecules are most effective.

Finding out the mechanisms of where and how they work — that's the moonshot. But for Team DiFeo, the spaceship is locked, loaded, and ready to blast off for a lunar landing. Destination? Collaboration Crater.

Cue: RNA. Specifically, microRNA.

Biologists Victor Ambros and Gary Ruvkun received the 2024 Nobel Prize in Physiology or Medicine for their 1993 discovery of microRNA (miRNA) and its role in post-transcriptional gene regulation.

First recognized by the scientific community as a distinct class of biological regulators in the early 2000s, miRNAs are "non-coding" RNAs that don't translate into protein but are "helper" molecules that function to assist cells in regulating gene expression.

Background photo: Austin Thomason, Michigan Photography - University of Michigan

In 2012, DiFeo began exploring genetic pathways that might disrupt ovarian cancer initiation and progression in earnest and uncovered that miRNAs were located in regions commonly amplified or lost in tumors. She discovered that one of these miRNAs, 181a (miR-181a), regulates a protein called STING (stimulator of interferon genes), which was decreased in the worst tumors in ovarian cancer cells — the ones that came back. DiFeo and her team knew they were on to something significant.[2,3,4]

The finding catapulted DiFeo's foray into RNA biology and represents the reason U-M became an important player in that trajectory. DiFeo reports, "I was enthralled at the infrastructure in place at U-M to help me probe the mechanisms of this miRNA target to learn about basic RNA biology, most notably the Center for RNA Biomedicine faculty cohort. To study what something is doing in cancer, you first need to study what it's doing in normal cells."

Further investigation confirmed miR-181a's involvement in early-stage and recurrent ovarian cancer. DiFeo found that increased presence of miR-181a and STING critically deactivated the body's natural defenses to fight the invader and that inhibiting this miRNA and its protein STING re-activates the immune system — the most powerful weapon to vanquish the enemy.

But DiFeo needed to find out how and where to target miR-181a, and what drugs or molecules would work to inhibit the translation of the toxic protein. In a coup of perfect timing, Michelle Hastings, Ph.D., RNA Therapeutics director and expert in the field, arrived at U-M in May 2023.

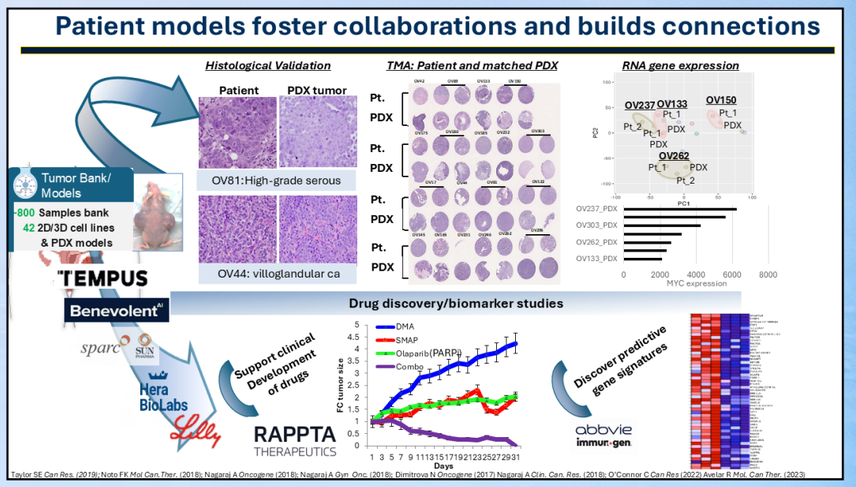


Figure 2. Schematic showing how RNA expression in human tumor cells and mouse tumor cells mapped similarly. Courtesy of Analisa DiFeo, Ph.D.

[2] Parikh, A., Lee, C., Joseph, P. et al. microRNA-181a has a critical role in ovarian cancer progression through the regulation of the epithelial–mesenchymal transition. Nat Commun 5, 2977 (2014). https://doi.org/10.1038/ncomms3977

[3] Knarr, M., Avelar, R.A., Sekhar, S.C. et al. miR-181a initiates and perpetuates oncogenic transformation through the regulation of innate immune signaling. Nat Commun 11, 3231 (2020). https://doi.org/10.1038/s41467-020-17030-w

[4] https://www.cancer.gov/news-events/cancer-currents-blog/2020/ovarian-cancer-form-microrna

Says DiFeo, “I don’t have expertise in that area, but I was so excited when I heard that Michelle was coming here [to U-M] because that’s exactly what she does. One of my students, Grace McIntyre, has taken up the reins on the miR-181a target project, and Michelle is on her Ph.D. committee, so there’s a perfect tie-in there.” (For more on Grace McIntyre’s work, see the separate article, “A Doctoral Journey.”)

DiFeo also enlisted McIntyre to help run point and navigate the rigorous territory of new drug discovery. However, to identify small-molecule drugs that would perturb the function of miR-181, DiFeo needed to bring in the big guns and teamed up with colleagues with expertise in screening projects of this magnitude.

One key collaborator is Peter Toogood, Ph.D., a faculty member of the CRB and the director of Michigan Drug Discovery (MDD) at U-M’s Life Sciences Institute (LSI). Toogood has extensive expertise in medicinal chemistry as well as a background in the commercial pharmaceutical industry. (For more on Peter Toogood’s work, see the separate article, “Leading the Discovery of Small-Molecule Miracles.”)

Another crucial partner is Andrew Alt, Ph.D., the director of the Center for Chemical Genomics (CCG) at LSI. Alt specializes in chemical biology and has notable expertise in high-throughput screening and assay (a laboratory test to measure substance amount) development.

DiFeo with McIntyre (front row, third from left) and members of the DiFeo Lab. Image courtesy of Analisa DiFeo, Ph.D.

MDD refines the compounds into a more drug-like state, removing toxicity. The compounds are tested in the DiFeo Lab and then handed over for screening by the CCG. Together, they’ve identified 32 potential candidates out of 55,000 screened.

In a highly collaborative game of football, DiFeo and her teammates go back and forth to find out exactly how and where each compound affects miR-181a. Finding an effective treatment would be equivalent to a field goal — a solid three points. A viable therapy would deliver the touchdown, and a cure would clinch the coveted extra point and final win.

“That’s what’s so exciting — this neural network involved in getting a drug made to help people,” says DiFeo. “I love sharing these discoveries from my lab with colleagues and clinicians, and the hope is to one day have them developed further in clinical trials as FDA-approved therapies.”

Trying to hit a moving target

The dream is to find a drug that targets the exact location where the genome goes wrong with each person’s ovarian cancer. “We have a gene mutation, we have a drug, we hit it and that’s it,” DiFeo relays. “That’s what we thought in the beginning. But tumor cells adapt, cancer finds a way.”

Many cancers have genetic mutations common amongst a large population of patients, such as breast cancer, which has over 20 FDA-approved targeted drugs that are effective, compared to ovarian cancer’s three FDA-approved drugs. High-throughput analysis of over 600-700 ovarian cancer patients showed approximately 30,000 mutations, with less than six percent sharing the same mutation.

Similarly, leukemia tumors have few mutations. Gleevec is a therapy that targets the BCR-ABL tyrosine kinase protein in chronic myeloid leukemia. People have been cured, and stay cured. So while gene targeting won’t work for ovarian cancer, there is a silver lining.

Says DiFeo, “The beauty of miRNAs is that they can target up to 100 genes at once to shut down multiple pathways — even compensatory pathways activated by cancer cells to circumvent a drug — contributing to tumor growth, and potentially minimizing recurrence and resistance to the therapy.”

DiFeo focuses on creating “tumor blueprints” using the mouse avatars for testing treatments across the diverse genetic alterations of ovarian cancer tumors and predicting drug responses based on tumor profiles.

“That’s where the mouse avatars importantly come into play — if you have enough of these, you can do a ‘mouse avatar clinical trial’ with these treatments,” says DiFeo. “If a new patient comes in with that same blueprint, we’ll have an idea of what they responded to in the past.”

As a boon, the availability of these mouse avatars has generated interest and investment from private pharmaceutical companies who partner with the DiFeo Lab to test whether their newly developed drug targeting another disease will be effective against ovarian cancer.

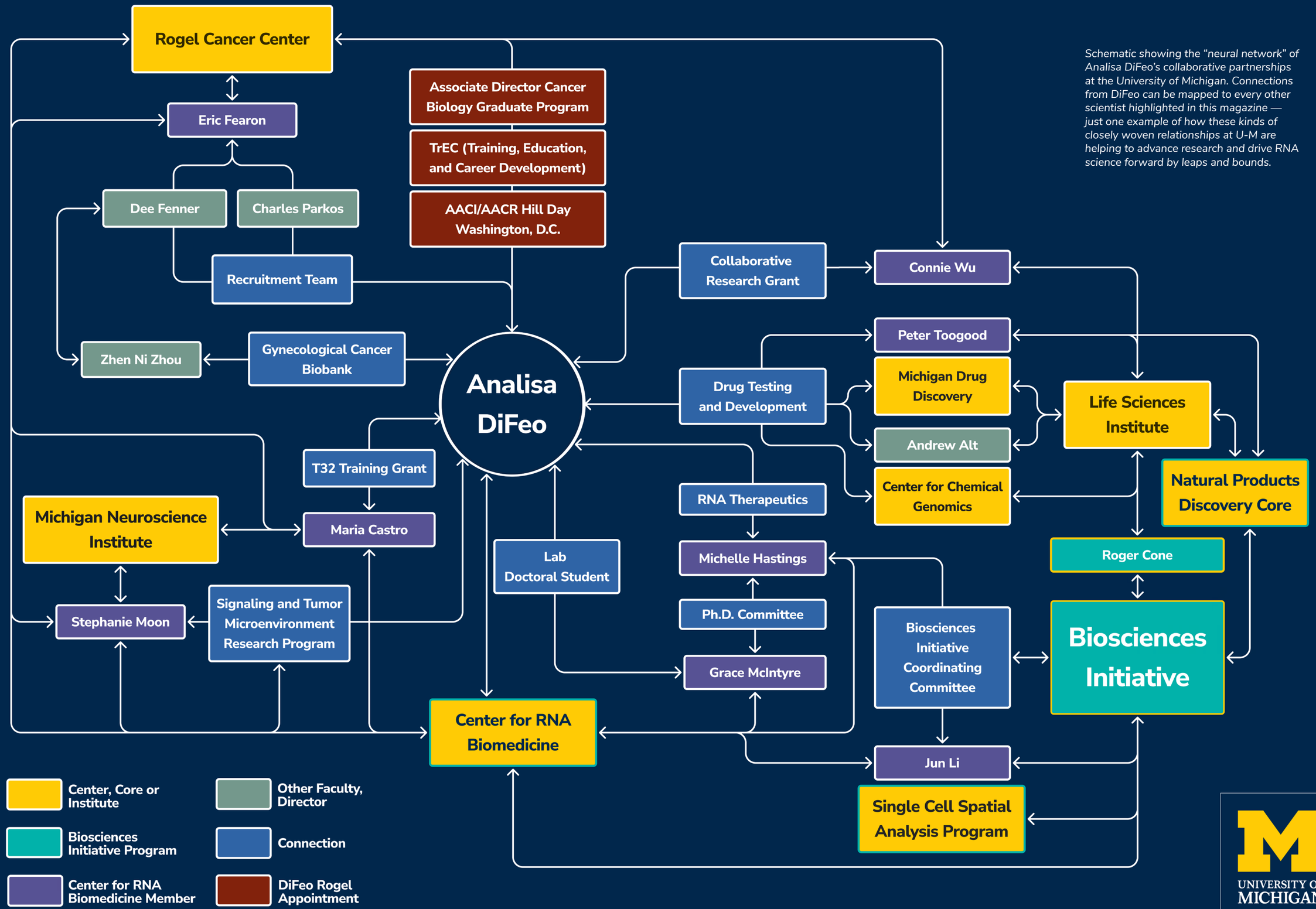
Championing community, education and patient advocacy

“At Michigan, there’s an opportunity for everything, and an expert in everything, and I’ve tried to utilize that to the best of my ability,” DiFeo says.

“The Center for RNA Biomedicine is vital in connecting students, scientists and clinicians across campus and helps us move our research forward.”

DiFeo's passion for mentorship led to securing a National Institutes of Health T32 Training Grant to support predoctoral and postdoctoral students in tumor microenvironment, which she shares with her co-principal investigator Maria Castro, Ph.D.[5] (For more on Maria Castro’s work, see the article, “The Brain,” in the 2024 issue of RNA Translated.)

[5] https://researchtraining.nih.gov/programs/training-grants/T32-a



Schematic showing the "neural network" of Analisa DiFeo's collaborative partnerships at the University of Michigan. Connections from DiFeo can be mapped to every other scientist highlighted in this magazine — just one example of how these kinds of closely woven relationships at U-M are helping to advance research and drive RNA science forward by leaps and bounds.

UNIVERSITY OF MICHIGAN

DiFeo engaging the community at a Michigan Ovarian Cancer Alliance (MIOCA) outreach event. Image courtesy of Analisa DiFeo, Ph.D.

Moreover, DiFeo supports training students and early-career scientists, from middle school to post-graduate levels, through the Rogel Training, Education and Career Development (TrEC) Trainee Advisory Council.[6] She encourages early hands-on lab experiences and aims to foster a compassionate, diverse scientific community equipped to tackle the complexities of cancer.

In May 2024, DiFeo was selected to represent the Rogel Cancer Center on Hill Day, speaking to Congress about the importance of supporting cancer research.[7] The Association of American Cancer Institutes (AACI) and the American Association for Cancer Research (AACR) co-host this annual event.

DiFeo is also committed to educating patients about the latest medications and research developments — something routinely practiced at Michigan Medicine, less so particularly in rural areas where information may be limited. For example, she emphasizes that due to their delicate nature, ovarian cancer surgeries should be performed by gynecological oncologists, as surgery plays a critical role in improving survival outcomes.

Advocating for health equity, DiFeo sits on the board of Michigan Ovarian Cancer Alliance (MIOCA), which builds awareness of ovarian cancer through community outreach programs such as lab visits.[8] DiFeo recalls one memorable occasion with a lab visitor whose own cells were being grown in her lab. "It was a moment I'll never forget," she states.

DiFeo and colleagues on Hill Day, 2024. Image courtesy of Analisa DiFeo, Ph.D.

"Though the patient may not have known it was her cells growing in the incubators, it brought the patient a lot of hope because she knew she contributed her samples to our study and the possibility of these new drugs being tested on her cells was overwhelming," DiFeo adds. "Doctors may have told her they've exhausted every option, but here was something that might work on her cancer, or could potentially help the next generation. It was a really touching time for us."

[6] https://rogeltrainees.med.umich.edu/trainees/early-career-faculty

[7] https://www.aaci-cancer.org/hill-day

[8] https://www.mioca.org/

Background photo: Michigan Medicine

Rogel Cancer Center

A Doctoral Journey

Grace McIntyre, B.S., Rackham Graduate School Student, Molecular & Cellular Pathology Ph.D. Student, Bioinformatics M.S. Student

Grace McIntyre, B.S., Ph.D. Student

Grace McIntyre, B.S., is a Ph.D. candidate in the Department of Molecular & Cellular Pathology at the University of Michigan. Scientist. Student. Researcher. Leader. Mentor. Mentee.

Mix in a climate of creativity, collaboration, teamwork, ingenuity, inventiveness, independence, interdependence, exploration, initiative, inclusivity and diversity on a level playing field.

That's because Grace McIntyre is a Ph.D. candidate in the lab of Dr. Analisa DiFeo, one of the world's leading experts in ovarian cancer research and an inspiring mentor. Now we're talking.

Grace earned her Bachelor of Science degrees in Biology and Public Health at Marian University in Indianapolis. She distinguished herself by publishing two papers on her work in the journals BMC Research Notes and Aging.[1,2] While completing her undergraduate studies, Grace drew up a required list of professors whose work she followed and admired for her U-M graduate school application. Analisa DiFeo's name sat at the top of that list.

"I actually met Analisa during my interview," Grace says. "I loved the work she was doing in her lab, it was RNA therapeutics-based, women-focused, and she works on gynecological cancers — everything I'm passionate about. I really wanted to interview with her and was so fortunate to have been given that opportunity." (For more on DiFeo's work, see the separate article, "Why? But why? So then … why?")

Grace McIntyre was accepted into the Ph.D. program at U-M, and in July of 2022, began a rotation in the DiFeo Lab. She's never looked back.

[1] McIntyre, G., Wright, J., Wong, H.T. et al. Effects of FUdR on gene expression in the C. elegans bacterial diet OP50. BMC Res Notes 14, 207 (2021). https://doi.org/10.1186/s13104-021-05624-6

[2] Staab TA, McIntyre G, Wang L, Radeny J, Bettcher L, Guillen M, Peck MP, Kalil AP, Bromley SP, Raftery D, Chan JP, . The lipidomes of C. elegans with mutations in asm-3/acid sphingomyelinase and hyl-2/ceramide synthase show distinct lipid profiles during aging. Aging (Albany NY). 2023 Feb 13; 15:650-674. https://doi.org/10.18632/aging.204515

McIntyre instantly became energized by the electricity in the air. She discovered a scientific environment infused with an infectious zeal for translational work focused on the patient and relevant to the clinic — elements she sometimes noticed lacking in other labs. She had found her academic home, a community that shared her values and one in which she could thrive.

Embarking on an ambitious journey, she firmly established herself as a dedicated leader and emerging RNA scientist. DiFeo harnessed that trajectory and enlisted McIntyre to help run point on a two-front project that sprang from DiFeo's groundbreaking discovery of a microRNA, miR-181a, as a driving mechanism behind ovarian cancer.

One front involved investigating the use of 1,2-Dioleoyl-sn-Glycero-3-Phosphocholine (DOPC, pronounced "dopp-cee") lipid nanoparticles (LNPs) to deliver a synthetically engineered RNA molecule called an antagomir, or anti-miR, to cancerous tumor cells to counteract the pathological functioning of miR-181a.

LPNs are tiny, spherical particles made of lipids, or fatty molecules, that can transport therapeutic substances into cells. The mRNA COVID-19 vaccine was delivered this way. DOPC is a helper phospholipid that promotes a more stable structure that assists in LNP delivery.

"'Naked' RNAs are negatively charged, complicating their passage through the cell membrane," explains McIntyre. "They also degrade rapidly in the body. DOPC lipid nanoparticles help us deliver RNA into cells much more efficiently."

McIntyre began collaborating with Dr. Gabriel Lopez-Berestein, M.D., a professor of experimental therapeutics, and his laboratory team at the University of Texas MD Anderson Cancer Center in Houston. Lopez-Berestein's group had demonstrated strong efficacy for delivering short interfering RNAs (siRNAs) via DOPC LPNs in ovarian cancer models.

"We wanted to find out if the same methodology could be tailored to deliver anti-miRs to target miR-181a," McIntyre says. "Their siRNA study has now advanced to the clinical trial phase."

"Tiny pieces of tumor tissue are implanted into the peritoneal cavity in mice, which is the fluid-filled space in the abdomen, to mimic the predominant location where ovarian cancer metastasizes in humans," McIntyre explains.

The Lopez-Berestein team designed an anti-miR-181a, which they then encapsulated in DOPC LPNs and injected intraperitoneally into the mice. The anti-miRs bind with the miR-181a molecules, preventing them from attaching to the larger mRNA molecules, thus leaving the body's stalwart tumor-suppressing machinery intact.

"So far, we've seen a strong reduction in tumor burden and a fifteen to twenty percent longer lifespan in the animals treated with this RNA therapeutic," says McIntyre. Promising signs.

The other front and main focus of her research comprises a large drug screen: testing various compounds (chemicals, not yet drugs) on ovarian tumor cell lines grown in a culture dish (*in vitro*) for their effectiveness against the culprit microRNA.

McIntyre at work in the DiFeo Lab. Photo courtesy of Anastazia Hartman, M.B.A., M.S., and U-M Department of Pathology.

Headshot image opposite courtesy of Grace McIntyre, B.S.
Background photo: Scott C. Soderberg, Michigan Photography

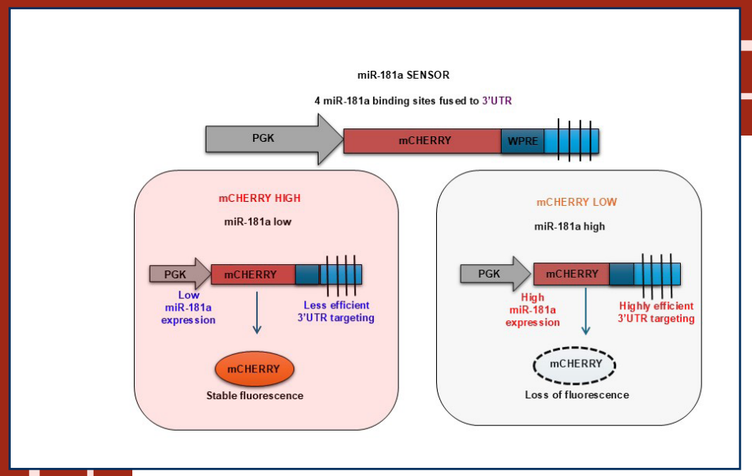


Figure 1. Illustration of miR-181a sensor platform showing the cherry fluorescent reporter. Image courtesy of Grace McIntyre, B.S., DiFeo Lab.

"We're trying to find out if a compound is 'suppressing the suppressors,'" McIntyre says. "We want the tumor suppressors to exist, but these microRNAs are knocking them down, allowing unfettered tumor growth."

McIntyre collaborated with Andrew Alt, Ph.D., director of the U-M Center for Chemical Genomics (CCG), who specializes in high throughput compound screening projects of this scale. (For more on Alt's work, see the separate article, "Why? But why? So then … why?")

In preparation, McIntyre and her colleagues introduced a "fluorescent reporter" into highly aggressive ovarian cancer cells. This fluorescent reporter is a molecule, or protein, that emits a red cherry-like color and serves as an indicator of miR-181a's activity, the study of which was previously published by the DiFeo Lab in the journal Stem Cell Reports.[3] Reporters like this allow scientists to visualize and track protein expression (or in this case, microRNA activity) within the cells. McIntyre used this reporter to identify which compounds reduce miR-181a activity. (See Figures 1 and 2.)

Alt and Research Laboratory Specialist Aaron Robida, Ph.D., pipetted the cells delivered by McIntyre and her team into 384-well plates (a microplate with 384 individual cells) and monitored and measured fluorescent activity over a 24- to 48-hour period.

No observed fluorescence indicated that the microRNA was highly active and that the compound was ineffective at knocking out the miR-181a and was subsequently eliminated from the study. High fluorescence signaled that the microRNA was inactive, indicating that the compound had the desired effect and was earmarked as a candidate for further characterization.

Back in the DiFeo Lab, McIntyre began performing various orthogonal assays (applying different methods to test the various characteristics for each compound of interest) to measure miR-181a expression, cell viability and changes in expression of known downstream pathways.

"We're trying to validate whether or not these compounds might be good fits for our ultimate goal, which is to reduce this microRNA's activity and kill the cancer cells," McIntyre says.

McIntyre brings one or two compounds of interest to Peter Toogood, Ph.D., at Michigan Drug Discovery (MDD), for evaluation. Toogood looks at the structure-activity relationship of each compound, identifies which have more preferable properties and provides adjustments that change their structures slightly. (For more on Peter Toogood's work, see the separate article, "Leading the Discovery of Small-Molecule Miracles.")

McIntyre then goes back to the lab to test each new structural iteration and determine which

[3] Belur Nagaraj A, Joseph P, Ponting E, Fedorov Y, Singh S, Cole A, Lee W, Yoon E, Baccarini A, Scacheri P, Buckanovich R, Adams DJ, Drapkin R, Brown BD, DiFeo A. A miRNA-Mediated Approach to Dissect the Complexity of Tumor-Initiating Cell Function and Identify miRNA-Targeting Drugs. Stem Cell Reports. 2019 Jan 8;12(1):122-134. https://doi.org/10.1016/j.stemcr.2018.12.002

functions best to elicit the greatest change in activity of microRNA of interest.

Despite the fact that drug development typically takes 15 to 20 years, McIntyre remains enthusiastic and optimistic about her work. "My goal is to have one or two of these compounds in the preclinical state — characterized very well and efficacy shown *in vivo* (animal models) — by the time I complete my Ph.D.," she says.

"MicroRNAs were only recognized as prevalent in cancer in the early 2000s. They're a relatively new discovery, but remarkable strides have been made in such a short time. It's really exciting to be on the brink of clinical trial therapeutics in just 20 years. It's nothing short of amazing!"

McIntyre teamed up with Center for RNA Biomedicine (CRB) affiliate faculty member Amanda Garner, Ph.D., who also studies microRNAs. Together, they've been exploring various RNA binding proteins associated with miR-181a — a collaboration McIntyre looks forward to developing further.

Outside of the lab, McIntyre allocates time for the myriad additional responsibilities that come with being a graduate student, including advanced coursework, grant writing and checking in with her Ph.D. committee which guides her progress and gauges her scientific development. DiFeo serves as her primary advisor and Ph.D. committee chair, with CRB affiliate faculty members Sethu Pitchaya, Ph.D., assistant professor in the urology and pathology departments, and Maureen Sartor, Ph.D., sitting alongside.

Sartor is a professor of computational medicine and bioinformatics as well as biostatistics. McIntyre is concurrently earning her dual Master of Science degree in bioinformatics.

Michelle Hastings, Ph.D., professor of Pharmacology and CRB RNA Therapeutics director, is a cognate committee member. As a subject matter expert, Hastings provides mentorship and confirmation that McIntyre's experiments align well with her Ph.D. focus on RNA therapeutics.

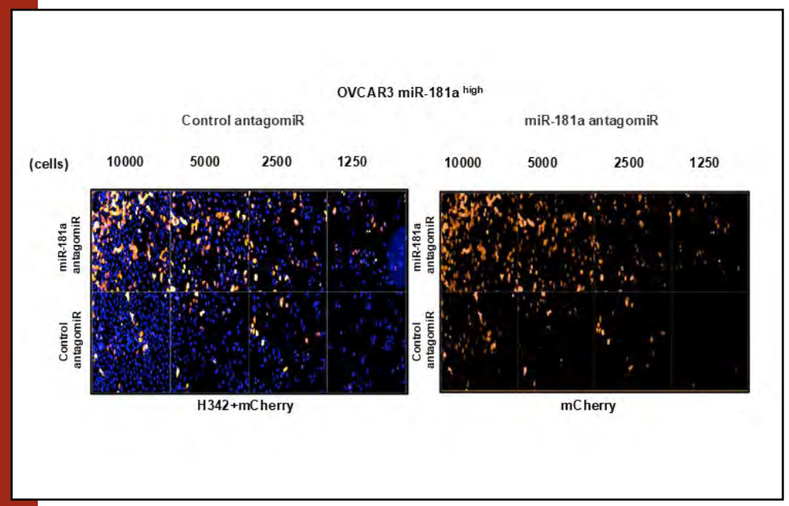


Figure 2. The top half of each image shows the cells treated with the antagomir, indicating how knockdown of the microRNA induces fluorescence, whereas the lower (control) half of each image shows a lack of fluorescence. The numbers across the top indicate different seeding densities, or the number of cells put on the plate. Image courtesy of Grace McIntyre, DiFeo Lab.

In her spare time, McIntyre enjoys volunteering with Project SHORT (Students for Higher Education Opportunities and Representation in Training), an organization that helps students apply to graduate school.[4] "I do a lot of work with international students, who might not know a lot about the process of applying to schools in the U.S., and help them create a competitive application package," she says.

McIntyre also relishes mentoring three undergraduate students in the DiFeo Lab and helping them prepare for their poster presentations. One student accompanied her to Washington, D.C., to present at an RNA therapeutics conference at the National Cancer Institute, and the others presented posters at a symposium for the U-M pathology department in the Fall of 2024.

"I do love mentoring all around," McIntyre shares. "We have one high school student right now, a senior, who gets an early release from school to work in the lab. It's incredible to see how much they can learn in such a short amount of time. It's an inspiration, and I'm likewise able to grow and learn much faster in this incredibly supportive space."

McIntyre is mid-way through the Ph.D. program but has already gained accolades as a National Science Foundation Graduate Research Fellowship and a Rackham Graduate Pre-Candidate Student Research Grant recipient. She was also the only graduate student asked to give an oral presentation at the National Cancer Center's RNA Therapeutics Workshop in 2024.

In December 2024, she published a review on miR-181a pathways and targetability in cancer in the journal Expert Opinion on Therapeutic Targets, which has been downloaded over 275 times since publication.[5,6] She also co-authored two other papers in the lab that are currently going through the submission and revision process. Continuing the trend, McIntyre was recently selected as U-M's only nominee for the prestigious National Cancer Institute Predoctoral to Postdoctoral Fellow Transition Award (F99/K00) — an opportunity afforded to a select few, with 24 funded applications from approximately 100 submitted applications. The award supports outstanding Ph.D. candidates to help them complete their dissertation research training and transition to cancer-focused postdoctoral career development.

[4] https://www.project-short.com/

[5] McIntyre, G., Jackson, Z., Colina, J., Sekhar, S., & DiFeo, A. (2024). miR-181a: regulatory roles, cancer-associated signaling pathway disruptions, and therapeutic potential. Expert Opinion on Therapeutic Targets, 28(12), 1061–1091. https://doi.org/10.1080/14728222.2024.2433687

[6] https://www.tandfonline.com/doi/metrics/10.1080/14728222.2024.2433687?scroll=top

McIntyre preparing samples in the DiFeo Lab. Photo courtesy of Anastazia Hartman, M.B.A., M.S., and U-M Department of Pathology.

"To be selected as the Rogel Cancer Center's nominee for this highly competitive award is a huge honor!" McIntyre says. "It is incredible to know how much support I have from the cancer center and all of the faculty I have met since I have been here. It has also really helped boost my own confidence and helped me recognize all of the skills I have developed since I started my graduate career.

"To be thought of as a top graduate student at the University of Michigan is something I didn't ever expect for myself coming from such a small undergraduate program, but I am really proud of myself and how far I have come. Most importantly, I am so thankful for all of the incredible support I have received from my mentors and my lab mates. I wouldn't be in this position without them."

Michigan Neuroscience Institute

The Michigan Neuroscience Institute (MNI) is a cross-campus institute that catalyzes interdisciplinary neuroscience research across labs, departments and schools at the University of Michigan. MNI's mission is to leverage advances across all fields of science and engineering to solve the mysteries of the brain, advance human health, and address society's challenges.

MICHIGAN NEUROSCIENCE INSTITUTE
UNIVERSITY OF MICHIGAN

Under Pressure

Stephanie Moon, Ph.D.

Stephanie Moon, Ph.D., Assistant Professor of Human Genetics, Medical School, Faculty Scholar, Center for RNA Biomedicine

"Pressure, pushin' down on me, pressin' down on you ... under pressure."

The iconic 1981 Queen and David Bowie song lyrics depict — albeit poetically — a few familiar conditions associated with what those in the popular zeitgeist might describe as "stress."

To a molecular biologist, stress is quite another thing.

Stephanie Moon, Ph.D., is an assistant professor of human genetics and faculty scholar at the University of Michigan Center for RNA Biomedicine (CRB), and she's studying how mRNA translation is regulated during the stress response in cells.

Most people think of stress as the physiological and psychological responses to real or perceived challenges or threats. The cell stress response on the other hand encompasses the molecular changes that an individual cell undergoes when it encounters harmful conditions, or "stressors," such as extreme temperature, viruses, toxins, and UV radiation, among a host of other intervening factors.

"Stress to a cell is different from our body's reaction to stress as an entire organism," Moon explains.

"Cells are in a very defined space and have a specific job. They will encounter situations that they must react to and adapt to because they can't simply run away."

The cell enters a state of self-preservation or, in extreme cases, programs its own death to prevent further damage.

Moon adds, "Viruses, for instance, have evolved multiple mechanisms to inhibit the stress pathway. This suggests that the stress pathway doesn't help the virus to replicate and make new viruses."

During these stressful conditions in cells, protein production can ramp up, taper down, or cease altogether. Moon relays, "Red blood cells, for example, make the protein hemoglobin, and when those cells are low on iron, it activates the stress pathway and shuts down translation. The RNA does not make protein, and that's pretty much the only protein red blood cells make, so it's critical."

The neuro-genetics roadway

Moon first became interested in genetic neurologic disease systems as a postdoctoral fellow studying a mutation in the genes that make eIF2B — a group of proteins that help cells regulate the stress response — and their involvement in a neurologic condition known as Vanishing White Matter disease (VWM).

VWM is incurable and mostly affects children, causing them to lose the white matter in their brains rather suddenly.

"During the stress response, normal cells shut off translation but not all the way," Moon explains. "They shut it off enough that certain stress-induced genes will get translated but most will not. In VWM, the mutated genes cause the cells to have too much translation suppression during stress, and the stress-induced genes necessary for cell resilience do not get translated.

"That project used this genetic disease system as a platform to show how translation control has to be regulated very tightly in order to allow all of these processes to take place," Moon recalls. "It sparked my interest in interacting with researchers focused on the genetic determinants of diseases, and that's how I came to join the human genetics group at the University of Michigan."

Moon is also an affiliate faculty member of the U-M Michigan Neuroscience Institute (MNI), which offers additional resources. She shares, "We're not neuroscientists, so it's great to network and communicate with researchers in neuroscience to study these gene mutations in the stress response pathway that cause so many neurologic disorders and diseases such as VWM and how that affects translation control."

Moon and her team focus on what happens along these stress pathways during translation, where it's happening and how that could be useful for finding genetic targets to help treat disease.

Moon and members of the Moon Lab attending the annual Rustbelt RNA Meeting at Michigan State University. Photo courtesy of Stephanie Moon, Ph.D.

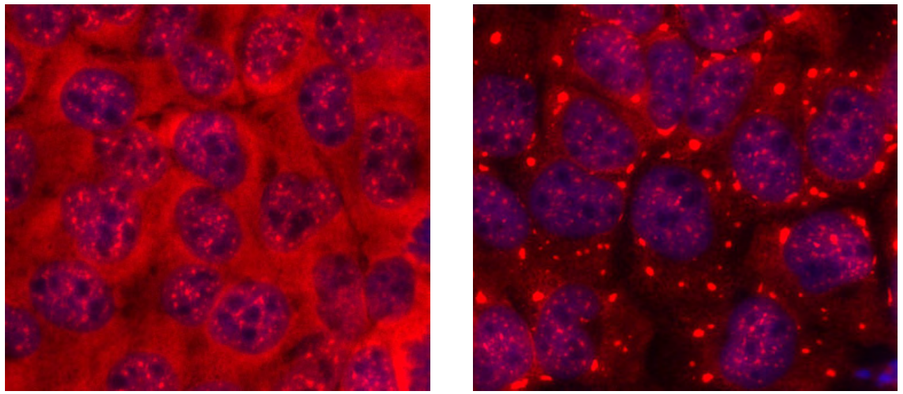
More specifically, Moon studies the genetic mutations that affect the stress pathway and cause or are associated with rare, neurodegenerative diseases. This focus is why she also relishes being an affiliate faculty member of MNI.

Her investigation of neurodegenerative diseases spans three areas. The first area involves studying the mechanisms behind protein aggregation and granule formation.

Many neurodegenerative diseases share two primary commonalities: first, proteins that aggregate or clump together randomly in the cell, known as aggregates, and second, an activated stress response.

Headshot photo: Austin Thomason, Michigan Photography. Image courtesy of Stephanie Moon, Ph.D.

Background photo: Eric Bronson, Michigan Photography



RNA forms blob-like stress granules when cells are stressed. RNA (red) in unstressed human cells (left) and stressed human cells (right). Image courtesy of Stephanie Moon, Ph.D.

During stress, ribonucleoprotein (RNP) stress granules similar to protein aggregates, known as condensates, form in cells as a more organized, "normal" response to stress.[1,2]

Since stress granules share some of the same proteins and RNAs found in the aggregates, Moon is interested in the interplay between the two and in learning about the fundamentals of how translation is coordinated. She and her team want to find out if the aggregates resemble the granules, how the granules regulate and affect the aggregates and what role RNA plays in aggregate formation, stability and disassembly.

Recently, scientists discovered that the stress pathway was chronically on in many neurodegenerative diseases — like a valve stuck open. Moon wanted to know why, and this became her second area of research in neurodegenerative diseases.

"In cell samples taken from Alzheimer's, Parkinson's, and ALS [amyotrophic lateral sclerosis] patients with different mutated genes, evidence showed that there's a problem with reversing the stress pathway, and it's causing cells in the brain to act in a stressed-out state all the time," Moon explains. "They can't do their normal job because they're too busy responding to a stress that either is or isn't there."

Moon's third area of study looks at the fundamental mechanisms of the integrated stress response in neurodegenerative diseases, particularly the effect of protein degradation pathways.

"In neurodegenerative disease as well as in aging — its primary risk factor — you lose activity of a protein complex known as the proteasome," Moon says. "It's the garbage disposal of the cell that rids it of damaged or old proteins. Many scientists theorize that the reason we see the protein aggregates in the cells is because this garbage dump is not working properly."

Moon and her team were awarded a National Institutes of Health grant to study how the proteasome's loss of function affects the stress response pathway and to find out how the proteasome helps the stress pathway proceed on a fundamental level.

[1] English AM, Green KM, Moon SL. A (dis)integrated stress response: Genetic diseases of eIF2α regulators. Wiley Interdiscip Rev RNA. 2022 May;13(3):e1689. doi: 10.1002/wrna.1689. Epub 2021 Aug 31. PMID: 34463036. https://doi.org/10.1002/wrna.1689

[2] https://themoonlab.org/wp-content/uploads/2021/08/2021_English_WIRES_RNA.pdf

"Elementary, my dear Watson."

Often interacting with neuroscientists at MNI to gain more insight into studying neurodegeneration, Moon and her team lean on their MNI colleagues' expertise in basic, or fundamental, science to investigate the processes involved in gene programming during stress.

"We create cell culture systems and use microscopy and various molecular biology assays to test our ideas and hypotheses," Moon explains. "Using CRISPR-Cas9 [clustered regularly interspaced short palindromic repeats] technology in human cells, neural stem cells or iPSCs [induced pluripotent stem cells] that can be reprogrammed into any type of cell, we mimic the same genetic mutations found in patients with neurodegenerative diseases in cells in a dish."

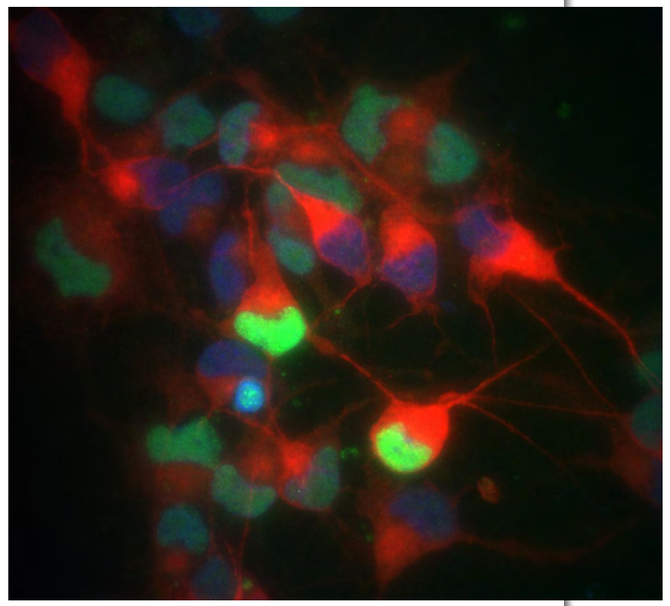
In addition to protein aggregation, inflammation, hypoxia, oxidative stress, nutrient deprivation and starvation also activate the stress response pathway. Moon and her team recognize with increasing regularity that these influences are relevant not only to the individual cell but to the entire human body, particularly when it's in a disease state.

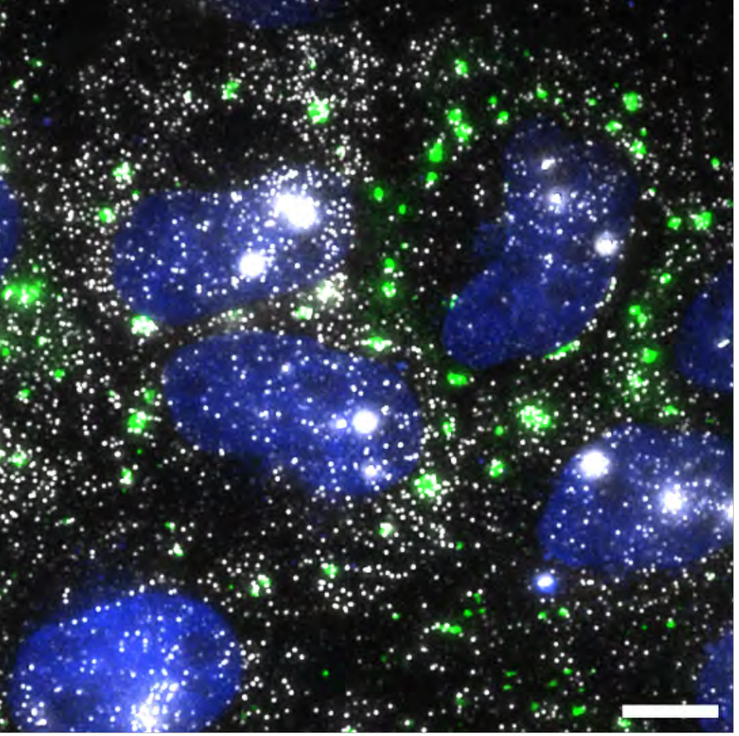
When a body is fighting a systemic disease, the stress response can activate in multiple areas in a cascading fashion, with potentially catastrophic results. "It's a signaling pathway," Moon says. "In other words, if something happens in a cell that appears to be an isolated event, it can cause what's known as a signaling event where everything gets shut down. A few genes get prioritized to be expressed and will still translate, but most genes are not expressed at all."

Many aspects of the stress response pathway continue to baffle scientists, including Moon. She adds, "What we do know, however, is that if you try to express some of the genes that are normally promoted during the stress state — the ones the stressed cell makes — in healthy cells, they can die. But if you knock them out in the stressed cell, the stressed cell can die." Cells must react to acute stress — albeit in an event that happens briefly and is not too severe. It's an important biological process. Cells create proteins that clean up messes, such as heat shock proteins, a "chaperone" that helps cells survive stress by unfolding and refolding proteins before degradation. They also clear aggregates which could become toxic over time. Moon explains, "The stress response is helping the cell upregulate those types of genes to manage the stress."

Evolutionarily, the stress response in cells has been around for a very long time, and Moon avers that it exists for good reason. The key for Moon and her team then is to learn as much as possible about the stress response pathway and to find ways to intervene with drugs or RNA therapeutics that keep the stress response within the normal range, or even turn it off completely, without causing toxicity to humans.

Human induced pluripotent stem cell (iPSC)-derived motor neurons. Image courtesy of Stephanie Moon, Ph.D.





Single molecules of RNA (white) can coalesce into stress granules (green) in stressed human cells (nuclei in blue). Image courtesy of Stephanie Moon, Ph.D.

"For the VWM project during my postdoc, we tested drugs that targeted the stress pathway in VWM cells and were successful in stopping the cell from completely shutting off translation just enough for the stress-induced genes to do their beneficial work," Moon recalls. "These and similar new drugs that target the stress pathway to turn it off are also being tested in ALS. The small molecules attack the proteins that translate the RNA, telling the cell to ignore that stress is happening and translate normally."

Thinking globally; acting locally

What sets the Moon Lab apart from other groups is its global perspective. Moon shares, "Rather than looking at how one mRNA from one gene is regulated, we're looking at the big picture: How are mRNAs regulated, and how can we change that on a global scale within the cell?"

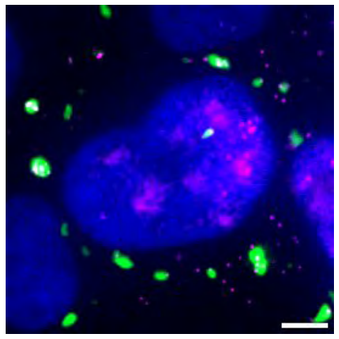
Though not limited to studying mRNAs since RNP stress granules also contain noncoding RNAs that don't translate into proteins, Moon's long-term goal is to create cell culture models for diseases that she and her team could use to test drugs that target the stress pathway.

"Right now, however, we're at the basic science level," she states.

"We're making cell culture systems to study the stress response pathway — how it works, how RNA is regulated, how RNA regulation goes wrong in disease — which will give us much-needed insight into what to target, and which types of drugs to create."

While examining how to manipulate the stress response, Moon and her team also work on drug development tools in the lab, supported by a pilot grant from the Michigan Medicine Research Scouts program.[3] They look forward to collaborating with the U-M Life Science Institute's (LSI) Chemical Genomics Core (CGC), whose expertise in chemistry will augment their drug discovery efforts.

A stressed human cell with the nucleus in blue, messenger RNA in pink, and stress granules in green. Image courtesy of Stephanie Moon, Ph.D.



Moon was the very first Biosciences Initiative-funded hire of a faculty scholar into the CRB in 2020. She cemented her induction by becoming a joint recipient of the prestigious Chan Zuckerberg Initiative (CZI) Collaborative Pairs Pilot Project Award, teaming up with CRB Co-Director Nils Walter, Ph.D., to peer deeper into RNP granules.[4,5]

Moon also collaborates closely with fellow CRB, MNI and Department of Human Genetics faculty member Anthony Antonellis, Ph.D., who works with transfer RNA (tRNA) synthetases, essential enzymes crucial for protein synthesis. Moon finds this work highly complementary to her own, because mutations in tRNA synthetases also cause neurodegenerative disease.

She's also part of the U-M Protein Folding Disease Initiative, a cross-university interdisciplinary interest group that meets regularly to share protein folding disease-related research. Interdisciplinary is the name of the game for the Moon Lab. Trainees in the lab have diverse backgrounds and interests. Arya Menon, a Ph.D. candidate in chemical biology, currently interfaces extensively with the Paul F. Glenn Center for Aging Research at the U-M as part of a T32 Training Grant in biogerontology.

"Noah Helton is a Ph.D. candidate in genetics and genomics, and Max Baymiller is a postdoctoral fellow trained in biochemistry," Moon shares. "I want to build a highly diverse research group that has lots of different interests and perspectives, so we can come at these challenges from many different angles. It's been really fun!"

Nowhere is this benevolent philosophy manifested more clearly than on the homepage of the Moon Lab website.[6] The video loop filling the screen beckons visitors to embark on a tranquil journey inside a lush, verdant forest rife with life and teeming with mysteries. It's the blissful antithesis to stress, and indeed the kind of environment that sparks wonder and rewards curiosity. It's the Moon ethos at its core. Welcome aboard!

The Moon Lab, University of Michigan. Photo courtesy of Stephanie Moon, Ph.D.

[3] https://medschool.umich.edu/department-news/research-scouts-grants-awarded-stephanie-moon-lev-prasov-and-tom-wilson

[4] https://rna.umich.edu/6323-2/

[5] https://chanzuckerberg.com/science/programs-resources/neurodegeneration-challenge/projects/regulation-of-mrna-and-rnp-granules-by-vcp-in-motor-neuron-degeneration/

[6] https://themoonlab.org/

Biosciences Initiative

The Biosciences Initiative (BSI) aims to advance interdisciplinary research across the biological sciences. BSI's goal is to bring together diverse expertise from across the university to tackle significant challenges in bioscience, develop innovative solutions, and educate future leaders in the field. The BSI supports a diverse range of scientific initiatives, fostering innovation and collaboration across various fields.

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Connecting the Dots

Jun Li, Ph.D.

Jun Li, Ph.D., Associate Chair, Department of Computational Medicine and Bioinformatics, Professor of Human Genetics and Professor of Computational Medicine and Bioinformatics, Medical School

Landing an interview with a faculty member of the University of Michigan Center for RNA Biomedicine (CRB) is a distinct privilege for any journalist. Full schedules, ongoing research, academic responsibilities and various and sundry other obligations oftentimes make it understandably difficult for them to squeeze in the time. So, to have a moment to sit down and talk with Dr. Jun Li about his work, research and teaching philosophy is a rare opportunity indeed.

Jun Li, Ph.D., is a professor in the Department of Human Genetics, and professor and associate chair for research in the Department of Computational Medicine and Bioinformatics at U-M. His engagement, however, reaches across campus.

Li opens the conversation by providing a broad overview of his position and responsibilities at U-M, highlighting collaborations with several U-M initiatives, centers and institutions and contributions as a member of several committees and advisory panels at the U-M Medical School and beyond. But as the discussion zeroes in on his approach to science and education and how the two are inherently intertwined, it becomes clear that Li is not only a passionate computational scientist, but a passionate scholar who holds education — holistic, inclusive, integrative — in the highest regard.

Being a supportive mentor is an important part of that mix for Li. He encourages students to become well-rounded individuals who can face the most perplexing problems with acuity and aplomb. He views the ideal approach to graduate education as challenging students to develop superior critical thinking skills, measured patience and earnest respect for diligently vetted research essential for moving science forward step-by-step and by leaps and bounds.

“Some beginning students may have an inaccurate understanding of the computational biologist’s way of life,” Li says. “Instead of thoroughly examining each process in a decision tree, for example, they may have an image in their minds of simply ‘turning a key’ at one end of a ‘machine’ and then jumping to the other end to get ‘the result.’

“I try to inject a thinking process infused with investigative intent and skill, so that they can graduate not just as operators or informants, but as true investigators.”

Li is also a strong advocate of interdisciplinary research, exemplified by his association with a broad spectrum of U-M centers and institutions: The Rogel Cancer Center, the Eisenberg Family Depression Center, the Caswell Diabetes Institute, and the Michigan Institute for Data and AI in Society (MIDAS).

In addition, he recently served as a co-chair of the research working group for the Medical School Generative AI (GenAI) Task Force, helping to forge guiding principles to direct the Medical School’s approach to GenAI for all faculty, staff and learners.

“The AI Task Force brought me another connection to e-HAIL [E-Health and Artificial Intelligence] and the campus-wide generative AI effort,” Li shares. “That certainly includes MIDAS as well, but also parallel efforts in other schools and colleges, including Engineering and Literature, Science and the Arts.”

The birth of the Single Cell Spatial Analysis Program

The U-M Biosciences Initiative (BSI) was established in 2017 to advance interdisciplinary research across the biological sciences. Li now sits on the BSI Coordinating Committee (BICC), helping to shape its practices, policies and investments.

Nine Scientific Research Initiatives (SRI) were born from the BSI, including The Single Cell Spatial Analysis Program (SCSAP), established in 2019, whose mission is to “develop the University of Michigan into a recognized leader in applying high-resolution spatially resolved multi-omic analysis … to drive next-generation solutions in biology and human health.”[1] Li is part of the SCSAP leadership team, along with Evan Keller, Tom Wilson, Sunitha Nagrath, Arvind Rao, and Justin Colacino. Keller, Nagrath and Colacino are also faculty members of the CRB.

[1] https://singlecellspatialanalysis.umich.edu/

Background: Image generated using DALL-E 3, part of the University of Michigan's AI Services.
Headshot image courtesy of Jun Li, Ph.D.

Li observed — by proxy or perhaps sheer proximity — the evolution of the CRB which was formed in 2019 as one of initiatives in BSI, and the progression of its many successes, highlighted by Michelle Hasting's recruitment as RNA Therapeutics director, the center's fifth and final faculty appointment. Hasting also serves on the current BICC.

Li and Colacino led the recruitment efforts for SCSAP, which has placed three faculty in different U-M units — the final appointment inducted in early 2025. By connecting both existing and new faculty, the SCSAP is positioned to fully realize the potential of single-cell spatial analysis technologies — a bona fide game-changer for research scientists and a new way to tap into the power of RNA biology.

In the early 2000s, The Human Genome Project mapped and sequenced the DNA of the entire human genome. DNA carries all genetic information encoded inside its familiar double-helix physical structure. Those "instructions" are copied, or transcribed, into RNA molecules which then translate that information when a cell begins synthesizing proteins that determine its function, such as how, when, and where to grow, proliferate, differentiate, migrate, or die. When there is a misstep in transcription or an error in the code itself, the result can be disorder in the cell, malfunction of the tissue and even disease.

In parallel with DNA sequencing, scientists also sequence RNA to determine how genes are being expressed. RNA sequencing (RNA-Seq) is a technique developed in the mid-2000s that uses next-generation sequencing to discover the type and amount of different RNA molecules in a sample, known as its "transcriptome." This allows scientists to understand the biology of the sample more fully, see what genes are turned on or off and to what degree and assess how that manifests downstream, for instance, in disease.

RNA-Seq of tissue samples, however, has been limited in its resolution. Li explains, "RNA sequencing traditionally uses bulk samples ground up in a tube. It's a mixture, consisting of millions of cells from dozens of different cell types, like a smoothie made up of many different fruits. For example, the data may show that approximately 10,000 genes are expressed in the entire sample, but we don't know which genes are expressed in which cell types."

Breaking down a breakthrough technology

In 2009, single-cell RNA-Seq (scRNA-Seq) technology introduced an innovation that allowed scientists to measure gene expression not only in the entire sample but for individual cells.

"The aim of single-cell sequencing is to not break up those fruits in the smoothie," Li says. "While each cell gets sequenced less deeply — you may measure 500 to 1,000 genes for each cell rather than 10,000 for the bulk sample — you spread out your measurement resources from hundreds to thousands of individually isolated cells."

Single-cell technology provides data on individual cells, but it has its own limitation, in that the cells have been dissociated. Their spatial arrangement within the original "tissue field" is lost. That's where spatial technology comes into play. It ups the ante, measuring 1,000s, or more than 100,000 cells, within one tissue section while the cells are still in their native environment.

Spatial analysis first began as a high-resolution-low-content technology. Li explains, "In the past, you'd put a thin slice of tissue on a glass slide and look at it under a microscope, sometimes collaging images together to get 100,000 cells in a wider field of view. But the old technologies only measure two to three types of molecules, such as when you use three antibodies to measure three proteins to see if a breast cancer sample is triple-negative or not."

The new technologies can measure hundreds of different types of molecules at the same time. "It's like looking at a starry sky, each star representing a single RNA molecule," Li explains. Multiplexed error-robust fluorescence *in situ* hybridization (MERFISH) is one of the technologies his group has been working on. "A cell may have 300 dots, and that's 300 RNA molecules that may represent some of the 500 genes you have selected to tell you a lot about the tissue's biology. You can classify the 100,000 cells in the same view into 30 or more cell types, which is not possible when you only measure three types of molecules."

This new generation of spatial technologies is thus both high-resolution and high-content. They provide a more powerful "telescope" that allows researchers to peer deeper into the tissue's function — a major breakthrough sparking a groundswell of interest that culminated in the birth of the SCSAP.

The magic for measuring many types of RNA happens via DNA encoding — attaching unique barcodes to each molecule to track 100s to 1000s of them simultaneously. It's scRNA-Seq in tissue space, providing scientists with more in-depth information about the entire community of cells: their properties such as gene expression and protein activity, their dynamics and interactions among neighboring cells. That knowledge helps researchers to understand how a tissue or an organ works normally, how they fail in disease or at old age and may also help them discover and design more precisely targeted treatment options.

"In this original tissue slice we can see if fibroblast cells like to have other fibroblasts, or immune or blood vessel cells as neighbors," Li says. "We're then able to describe the characteristics of a neighborhood, and observe which cells like to fellowship with their own kind and which like to infiltrate or socialize with other cell types."

Jun Li attending a reception for the 2024 Class of American Institute for Medical and Biological Engineering (AIMBE) College of Fellows. Photo courtesy of Jun Li, Ph.D.

Applications for studying diseases

Before single-cell and spatial analysis, comparative analysis of bulk samples was the go-to methodology for scientists studying diseases. Tissue samples from five patients, for instance, would be compared with similar samples from five healthy control individuals. Researchers would then report which genes were upregulated or downregulated in the samples with disease, yet had no notion of which cells got affected or whether the cell number had changed.

In contrast, single-cell analysis allows scientists to study which cell types are affected. Further, spatial analysis can reveal the arrangement of many single cells in healthy tissues, to determine "the norm and variation around the norm,"

as Li says. That way, researchers are better positioned to detect a distinct departure from the norm that may be the key reason underlying pathology. Li adds, “In diseased tissue, we commonly hope to discover if the spatial pattern has been rearranged.

“With single-cell analysis, if each of the five healthy samples has 2,000 cells sequenced, and each of the five diseased samples also has 2,000 cells sequenced, we can use the data to ask two questions. The first is which cell type rose or fell in number in the diseased condition, which previously we couldn’t know. The second is to detect if there is something slightly wrong, or off-color, in cells of each recognizable cell type, by comparing cells from diseased and healthy samples for each cell type separately.”

In a more extreme scenario, if the relative cell numbers don’t change, and if each cell type appears to be normal, it may be discovered that it is the spatial arrangement of the cell community that is errant — something scientists can only determine with high-content spatial data for single cells. In dissociated cell data alone, that spatial context is lost.

“Quite simply, the conclusions we can draw are qualitatively better than what is possible with dissociated single-cell sequencing,” Li says. He also cautions that not all biomedical problems require single-cell technology, such as when cellular heterogeneity is not at play. Likewise, spatial analysis technology may not be needed if spatial disruption is not a factor.

Jun Li with his student Xianing Zheng (far left), and Saher (Sue) Hammoud with her student Gabe Manske. Both Xianing and Gabe have now graduated with Ph.D.s

“A lot of brain disorders, such as autism, bipolar disorder, and schizophrenia, have always been mysterious,” Li reports. “It’s often difficult to say how the brain is affected, such as having too many neurons or glial cells in a brain region. It could be much more subtle: the cell numbers are normal, and individual cells are healthy, but the “circuitry” — how cells talk with each other — is malfunctioning, underlying the abnormalities in emotion or behavior.”

“There are different mechanisms underlying the transition from health to disease, and many could involve cellular heterogeneity or spatial heterogeneity,” Li explains.

“These new genomic tools we have now are empowering us to visit the old mysteries. If the real story demands cell-level data or spatial data, we have a much better chance than any time in the past to pull that story out.”

Multi-scale biology

Genomic, single-cell, and now high-content spatial analysis opened up new possibilities. It gave scientists new knowledge about cell types, their characters and physical arrangement, how “functional units” make up a tissue and how tissues make up an organ. Such data reveal the inner workings of healthy organisms over a succession of scales: from “the micro,” to “the meso,” to “the macro.” However, different biological scales have traditionally been studied in different fields and have been challenging to integrate.

Academic disciplines — molecular biology, cell and developmental biology, physiology, pathology, ecological and evolutionary biology — specialize in studying their own scales. The rules learned for one scale — say how a protein is folded — tend to be based on data for that scale and won’t automatically reveal how things work at the next scale — say how a fibroblast is made.

Jun Li and Sue Hammoud celebrating D. Ford Hannum’s Ph.D. defense (seated center, front), with students from both labs. Photo courtesy of Jun Li, Ph.D.

Single-cell and spatial technologies provide a new hope to link across adjacent scales.

“A spatial dataset for a hundred thousand cells in one tissue section gives us several levels of zoom, much like in Google Maps,” Li explains. “It allows us to zoom in and out of the “street views” — intracellular, cellular and multi-cell ensembles — to learn the patterns and interaction rules at each scale. It tells you how certain RNA molecules define this or that cell type, how these specific 10 cells assemble again and again to make up this working unit and how these units are coordinated to keep a liver or a kidney running. With today’s data we often see 80 million RNA molecules in over 100,000 cells, which lay out in a few hundreds of repeated functional units just like 100,000 houses in a hundred city blocks.”

Collaboration

For many years, Li has been deeply engaged in applying these advanced technologies in collaborative efforts with fellow CRB faculty Saher (Sue) Hammoud, Ph.D., and Professor of biomedical engineering Ariella Shikanov, Ph.D.

Hammoud is an associate professor of human genetics, obstetrics and gynecology, and urology. She has been studying how sperm develop in the testes, and Shikanov has been focused on how eggs mature in the ovaries. The team has been taking a closer look at the many cell types of the human reproductive system, including a recent study involving mapping and characterizing cells in the uterus and creating a “uterine cell atlas.”[2,3,4]

Li believes these kinds of interactions are tremendously helpful in breaking disciplinary barriers and over time manifest in highly effective collaborations. He says, “We like to think we have realized a dream, the ideal collaboration: biologists extracting the best value out of complex genomic data, while former physicists, mathematicians and engineers become genuinely interested in understanding living systems and solving applied problems.”

[2] N.D. Ulrich, A. Vargo, Q. Ma, Y. Shen, D. Bazzano, D.F. Hannum, S.J. Gurczynski, B.B. Moore, S. Schon, R. Lieberman, A. Shikanov, E.E. Marsh, A. Fazleabas, J.Z. Li, S.S. Hammoud, Cellular heterogeneity and dynamics of the human uterus in healthy premenopausal women, Proc. Natl. Acad. Sci. U.S.A. 121 (45) e2404775121, https://doi.org/10.1073/pnas.2404775121 (2024)

[3] https://www.michiganmedicine.org/health-lab/mapping-human-uterus-diverse-cells-interact-surprising-ways

[4] Andrea S. K. Jones et al. ,Cellular atlas of the human ovary using morphologically guided spatial transcriptomics and single-cell sequencing. Sci. Adv.10, eadm7506(2024). DOI:10.1126/sciadv.adm7506

Learning each other's language has been an important part of that synergy. Li shares, "I'm a computational scientist, and Sue is a biologist, so we were trained in different domains. I started out knowing nothing about how sperm develop in the testes; she knew nothing about programming and biostatistics. But after working together for nine years, I know more about reproductive biology than I ever imagined, and sometimes, when attending computational biology conferences, I could be mistaken for an M.D. Similarly, with my students, Sue sometimes started assigning them tasks after data review meetings before I had a chance to speak to them, because she understood so much about how to analyze data."

As a member of the BICC, Li was thrilled when in 2023, two computational colleagues, Josh Welch and Xiang Zhou, were among the five recipients of the prestigious Mid-career Biosciences Faculty Achievement Recognition Award (MBioFAR). With the third awardee, Kelly Bakulski, a genomic epidemiologist, it was the first time quantitative research was recognized so prominently by this award.

Joshua Welch, Ph.D., is an associate professor of computational medicine and bioinformatics, and an associate professor of electrical engineering and computer science, and fellow CRB faculty member Xiang Zhou, Ph.D., is a professor of biostatistics in the U-M School of Public Health.

Professor Jun Li at the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows induction ceremony, March 24, 2024. Photo courtesy of the American Institute for Medical and Biological Engineering (AIMBE).[5]

"Joshua is a computational biologist specializing in machine learning and AI for single-cell genomic and spatial transcriptomic datasets, and Xiang excels in developing statistical and computational methods for genetic and genomic studies," Li shares. "Their brilliance and their innovative, high-risk approach have been instrumental in maximizing the power of the new technologies at U-M."

A master class in crafting a unit of discovery

In the academic realm, Li emphasizes the importance of being mindful of the cultural distinctions of different disciplines — a philosophy he infuses into both research and education.

For Li, a turnkey approach — applying software tools as a generalist workflow — is detrimental to effective data analysis. "Close attention to each data set and careful controls are needed to pull the information out," Li explains. "An analysis plan must be customized to the mathematical structure of the data in hand and to the biological problem we want to solve. "In the end, we must feel as if we've all put our fingers in the crevasses of the data." He likes to say that no workflow can do mass production of data analysis, and the best one can do is mass customization of workflows.

Communication and daily interaction for several years are key components to moving a study forward for Li, who likens a collaboration to four people moving a heavy piece of furniture, each carrying one corner — "all must catch and lift," Li adds.

Li increasingly emphasizes to students the need to take a greater share of responsibility in interpreting data, "not over- or under-interpret," and to verify information rather than waiting for others.

"If you see nothing in the data, you need to go to the ends of the earth to ensure it's not a false negative. And if your story says there is something there, you need to apply all your passion and all the needed intellectual labor to make sure it's not a false positive. In the end, you always need to stop somewhere and have the humility to say, 'We're not completely sure, but the evidence is 70% hard. This is the best we can do.' To accurately say your degree of confidence and be transparent about how you came to that confidence are among the highest virtues in data science."

A good measure of scholarship is in the supplementary data — the layers upon layers of 'in-house' documentation. They are the foundation and "basement" of published research. Training students and colleagues to appreciate this pyramid of information remains a priority for Li.

"Ultimately, data themselves are mute." Li adds. "It's our awesome responsibility to say what the data may be saying, and it involves making algorithmic decisions based on both statistical skills and biological questions. That's the point of interdisciplinary work. It's a long journey, because it takes time to connect the systems of computing tools and information management with the systems of meaning in biology."

The researcher's way of life inevitably becomes the educator's way of thinking for Li. He champions a "whole-person, whole-career" approach to training computational biologists and bioinformaticians — not just giving them tools but the investigative passion to care about what they want to discover.

Scientific discovery is a rigorous yet rewarding journey for Li, and he waxes philosophical when discussing his approach. He shares, "Nils Bohr famously said, 'It is wrong to think that the task of physics is to find out how nature is. Physics concerns what we can say about nature.' Dr. Robert Oppenheimer, whom I sometimes cite in my talks, said, ' ... deep things in science are not found because they are useful; they are found because it was possible to find them.' And in his essay, Brain Metaphor and Brain Theory, published in 1990 at the dawn of the modern computer age, John G. Daugman said, 'Invariably the explanatory metaphors of a given era incorporate the devices and the spectacles of the day.' All talk about the constraints of one's particular time in history, how the limitation of one's understanding is rooted in the technological possibilities."

Li's views of education echo those of author Hannah Arendt in her book, The Crisis in Education. He

Jun Li instructing the next generation of scientists. Photo courtesy of Jun Li, Ph.D.

shares Arendt's statement: "'Education is the point at which we decide whether we love the world enough to assume responsibility for it, ... And education, too, is where we decide whether we love our children enough not to expel them from our world and leave them to their own devices, ... but to prepare them in advance for the task of renewing a common world.'"

Li notes that liberal education translates to its Latin root of "liberating" education. For Li, it's about liberating the next generation of scientists. "Scholarship is linked to pedagogy," says Li. "Students who we didn't train as deeply or whose behavioral mindset we didn't change sufficiently are also the ones who may be limited to making superficial contributions in the future.

"But those students who truly soaked in what we wanted to transmit are grown scientists. It's safe to hand the future of the world to them."

Learning how Dr. Jun Li weaves his life and his work into one seamless tapestry of scholarship and discovery — with an open mind, humble spirit and earnest diligence — is an enriching experience, a lesson expertly taught and most assuredly time well spent.

SCSAP SINGLE CELL SPATIAL ANALYSIS PROGRAM UNIVERSITY OF MICHIGAN

[5] https://medresearch.umich.edu/department-news/jun-li-inducted-2024-class-aimbe-college-fellows

Life Sciences Institute

The Life Sciences Institute at the University of Michigan exists to accelerate scientific possibilities in order to unleash new treatments, novel advances, and profound human impact. At this multidisciplinary institute, researchers from across the life sciences come together to explore biological processes, structures and functions at the finest scale and create impact on a global scale.

LIFE SCIENCES INSTITUTE
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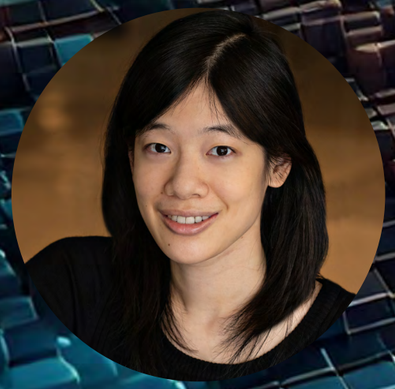
An Interdisciplinary Architect

Connie Wu, Ph.D.



Connie Wu, Ph.D., Research Assistant Professor, Life Sciences Institute, Assistant Professor of Biomedical Engineering, College of Engineering and Assistant Professor of Pharmaceutical Sciences, College of Pharmacy

Connie Wu, Ph.D., is a research assistant professor at the University of Michigan Life Sciences Institute (LSI) and assistant professor in biomedical engineering and pharmaceutical sciences.

She's also in the construction business. Buildings? Legos? No, RNA. RNA is a single-stranded nucleic acid found in all living cells that has structural similarities to DNA.

She engineers multifunctional, "all-in-one" RNA molecular scaffolds for therapeutic delivery and ultrasensitive single-molecule detection platforms to measure biomarkers for early disease diagnosis.

She also works on projects that combine these therapeutics and diagnostics sides of her lab.

In addition, she's an avid pianist, and finds that music stimulates the creative process, which in turn strengthens her work as a scientist.

It follows, then, that what initially attracted Connie Wu to the University of Michigan was LSI's interdisciplinary environment along with U-M's strengths not only in science and engineering but also in music and the arts. She found the ideal place to launch her independent career and, in 2023, became LSI's first joint recruit with the College of Engineering.[1]

Wu obtained her Bachelor of Science in Chemical Engineering from Yale University and Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology in the lab of Paula Hammond, Ph.D., while studying RNA therapeutic delivery.

She transitioned to diagnostics for her postdoctoral research in the lab of David Walt, Ph.D., at Brigham and Women's Hospital and the Wyss Institute at Harvard University.

At U-M, her research encompasses both of these fields — separately and together.

"On the diagnostics side of the lab, we're conducting ultrasensitive measurements of super low levels of proteins or other biomarkers of disease," explains Wu. "On the RNA side, we're involved in various therapeutic efforts."

Engineering RNA

RNA can fold into a three-dimensional object in myriad patterns.[2] The way RNA folds determines its molecular properties. Ergo, form equals function.

RNA is defined by its sequence of "letters" (its genetic code) and therefore can be synthesized very precisely. Wu and her team focus on building sophisticated RNA molecules and folding them into distinct structures that can perform multiple jobs. In one such project, they're using a polymeric form of RNA that consists of many repeat units to act as a structural scaffold.

Wu says, "We're thinking of how we can engineer the structure of the RNA to be multifunctional within a single framework: to activate multiple innate immune signaling pathways, exert translational or gene silencing capability, and act as a generic building block."

To accomplish these goals, Wu and her team engineer RNA to create stable and precise molecular structures.

The precision and stability allow Wu and her team to pattern specific spatial arrangements to present — that is, display or carry — specialized therapeutic molecules or agents on the RNA structure itself, similar to two pieces of a next-level 3-D jigsaw puzzle that fit together perfectly.

"This structurally secure RNA could then deliver whatever we want to the cells," explains Wu. "We could present molecules that can activate or be recognized by the immune system, which can be leveraged to develop vaccines against cancer and infectious diseases. We're working on ways to control and enhance this activation."

To deliver RNA safely and effectively into the body, RNA must first be packaged inside a delivery vehicle, usually a nanoparticle or lipid nanoparticle (LNP) such as those used in the mRNA COVID-19 vaccine, to protect it from degradation and ensure it reaches its intended destination.

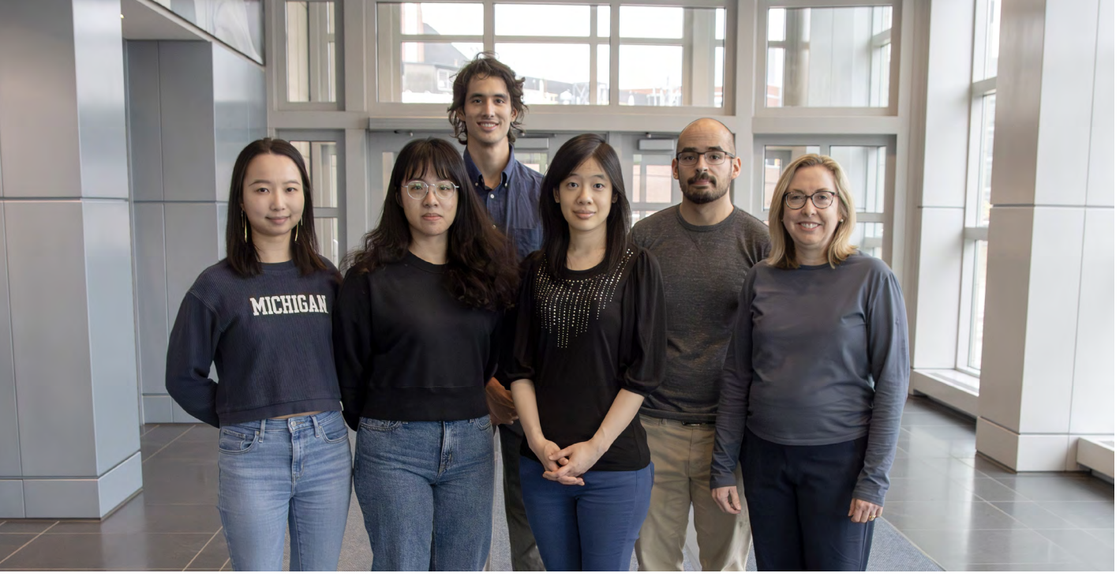
However, LNPs might cause undesired immune reactions or toxicity. So Wu asks, "Would it be possible to attach protective or targeting moieties — parts that have special functions — to the reinforced RNA superstructure in order to create a protective layer around it and reduce the risks associated with synthetic materials?

[1] https://www.lsi.umich.edu/news/2023-01/new-lsi-faculty-member-aims-develop-tools-span-discovery-science-and-clinical-research

[2] National Human Genome Research Institute https://www.genome.gov/genetics-glossary/RNA-Ribonucleic-Acid

Wu portrait image: Leisa Thompson Photography

Background: Image generated using Adobe Firefly



Connie Wu with members of the Wu Lab at the Life Sciences Institute. Photo: Rajani Arora, Life Sciences Institute Communications

“This sheath would ideally safeguard the RNA long enough to deliver it to target cells without the use of a delivery vehicle, eliminating the need for synthetic nanoparticle encapsulation and minimizing immunogenicity.”

Moreover, anything presented on the “outside” of the RNA molecule would be much more readily available. For example, ligands are biochemical “earrings” attached to pockets within the RNA that trigger a specific biological response and help stabilize the structure.

These custom adornments or handles would remain unencumbered to function more efficiently, improving how well molecules do their job and helping steer the RNA to its target.

The superhero of detection

As Wu continues to find ways to improve the effectiveness of RNA in various applications, she also focuses on diagnostics, expanding the ultrasensitive single-molecule detection platforms she pioneered during her postdoctoral training and developing further bioanalytical tools.

“These tools are much more sensitive than conventional detection methods and can measure extremely low levels of molecules,” explains Wu. “We can detect proteins at single-molecule resolution with minimal background. We count proteins one by one.”

Wu and her team target specific biomarker proteins found in the bloodstream, which are early indicators of certain types of cancers or predictors of treatment responses after diagnosis.

“The clinical significance of detection at this level cannot be underestimated,” Wu emphasizes. “It can be used to diagnose diseases like cancer early on in their development when there is not a large amount of biomarkers present in the body. Early detection is key to treatment success and survival outcomes.”

Wu uses the single-molecule detection platform to count single molecules, not study the properties of each, the kind of analysis conducted in the Single Molecule Analysis in Real-Time (SMART) Center for RNA Biomedicine (CRB) core facility. (For more on the CRB SMART Center, see the separate article, “Core Facilities,” in the “Center Report” section.)

Developing new ultrasensitive detection platforms and improving existing platforms remain her focus. However, Wu reveals, “It’s exciting to learn about new clinical applications for this technology within the U-M Medical School or Rogel Cancer Center and to make an impact on disease diagnosis.”

However, finding the right protein biomarker, particularly for cancer, continues to be a challenge. Protein biomarker technologies are not as advanced as nucleic acid detection technologies, and many cancer protein biomarkers also occur in individuals with benign conditions.

“It’s the chicken-egg scenario,” Wu explains. “We sometimes don’t know what we’re looking for, so we can’t measure what we don’t know is there. So we hypothesize. For example, if there is an overexpression of a certain protein in tumors, then we could hypothesize that it is released in the blood, and we go from there.”

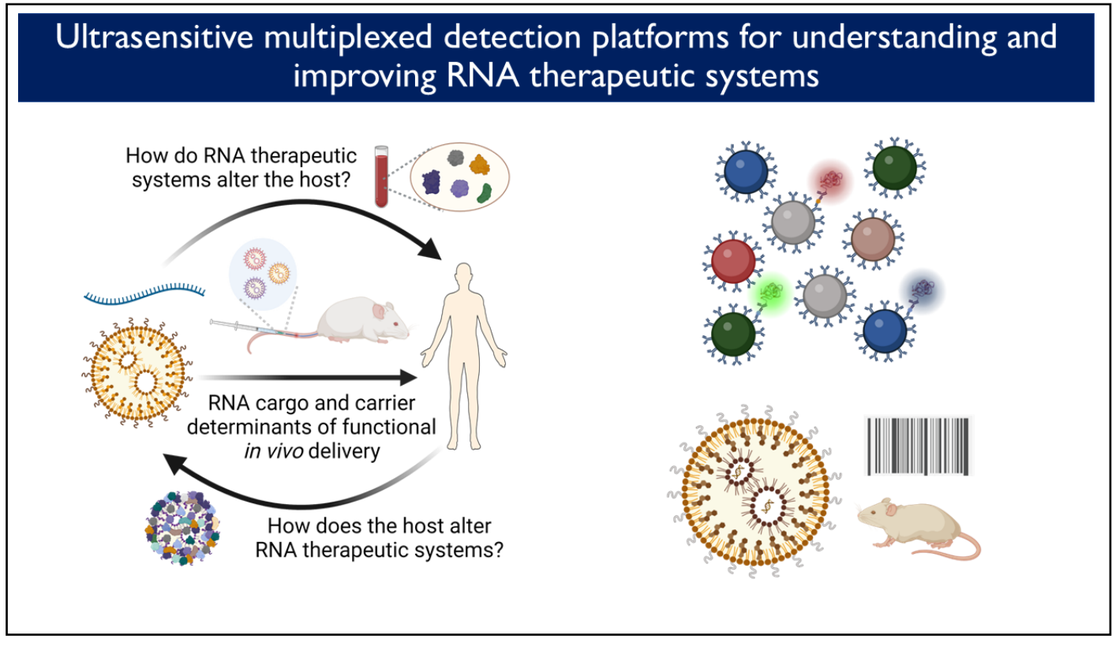
Multidimensional multitasking mice

In true engineering fashion, Wu has found a remarkable way to harness the full power of the ultrasensitive tool. And it’s animal friendly.

“We know we can measure very low levels of proteins or other biomarkers that can detect disease, but we can also apply these ultrasensitive measurement tools to characterize and screen different nanoparticle and mRNA delivery systems, and it integrates both sides of our lab,” she explains.

Generally speaking, the pipeline for a study of this kind begins with testing nanoparticles *in vitro*, that is, in cells in a dish, and then selecting several top-performing candidates and testing them in mice, *in vivo*. (See Figure 1.) However, what happens *in vitro* doesn’t correlate well with what happens in the body, which is much more complex.

Figure 1. Schematic showing ultrasensitive screening platform. Schematic courtesy of Connie Wu, Ph.D.



Wu adds, “We also face significant limitations with *in vivo* testing, as each system or nanoparticle formulation requires a separate mouse. Moreover, to adequately test various conditions, multiple mice are needed, which quickly scales to thousands of mice. It’s impractical.”

Wu came up with an innovative twist: test many delivery systems all in the same mouse.

Leveraging the single-molecule detection of low-abundance biomolecules, Wu aims to apply the ultrasensitive screening platform for a “pooled *in vivo* analysis” of mRNA therapeutic systems to understand what factors in the RNA and its carrier are crucial for successfully delivering the mRNA into living organisms.

“We inject a single mouse with many different nanoparticle formulations,” Wu explains. “Using our ultrasensitive detection tools, we read out from the blood which formulations go to which tissues and which function well *in vivo*. (See Figure 1 on page 43.)

“We’re measuring which of the delivery systems have the best function — translation, efficiency and/or target tissue accumulation — *in vivo*,” says Wu.

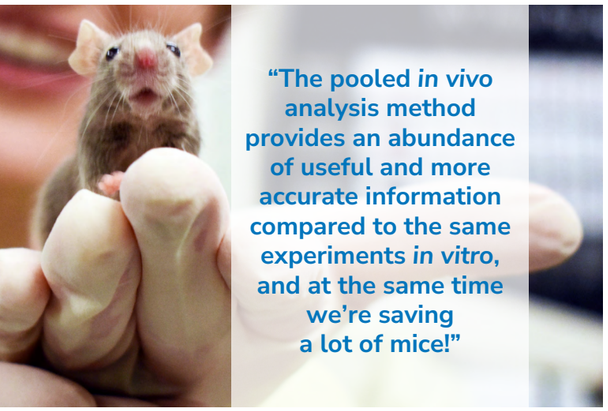


Photo: Amy Puffenberger, Animal Care & Use Program - University of Michigan

Collaborative research — a team U-M effort

Trained as a chemical engineer, Wu draws on her interdisciplinary background as well as current and potential collaborative partnerships with LSI colleagues and others across campus to fuel her research.

Janet Smith, Ph.D., CRB affiliate faculty and Strategic Advisory Board (SAB) member heads the Center for Structural Biology (CSB) at LSI. “They specialize in protein purification and could assist us with isolating specific proteins,” Wu says.[3]

Also “downstairs” at LSI sits the Center for Chemical Genomics (CCG), with which Wu anticipates partnering on large screening projects. “They have liquid-handling robots and large libraries of natural products and siRNAs [small interfering RNAs] and other resources — something we will very likely use in the future.”[4]

Wu is also an affiliate faculty member of the U-M Rogel Cancer Center. She recently published a paper in Cancer Discovery on the study of a multi-cancer blood biomarker — including ovarian cancer — and reached out to fellow CRB and Rogel Cancer Center faculty member Analisa DiFeo, Ph.D., to compare notes.[5]

DiFeo’s extensive work with ovarian cancer led to her discovery of a microRNA called miR-181a as a biomarker of the disease, and since early detection is critical to survival, she welcomed the opportunity to team up with Wu. (For more on DiFeo's work, see the separate article, “Why? But why? So, then … why?”)

In collaboration on a new project, Wu and DiFeo recently received a $376,835 grant from the U.S. Department of Defense. The award will fund their collective research on gynecological cancer biomarker detection and is backed by the Rogel Cancer Center’s Translational and Clinical Research (TACR) Program.[6]

[3] https://www.lsi.umich.edu/science/centers-technologies/center-structural-biology

[4] https://www.lsi.umich.edu/science/centers-technologies/center-chemical-genomics

[5] Taylor, M. S., Wu, C., Fridy, P. C., Zhang, S. J., Senussi, Y., Wolters, J. C., ... & Burns, K. H. (2023). Ultrasensitive detection of circulating LINE-1 ORF1p as a specific multicancer biomarker. Cancer discovery, 13(12), 2532-2547. https://doi.org/10.1158/2159-8290.cd-23-0313

[6] https://www.rogelcancercenter.org/research/programs/clinical-science-division/translational-and-clinical-research

Connie Wu speaking with a graduate student in the Wu Lab. Photo: Leisa Thompson, Michigan Photography, courtesy of Rajani Arora, Life Sciences Institute Communications.

TACR assists researchers dedicated to a bench-to-bedside approach, fostering scientific discoveries and transforming them into novel therapeutic treatments for patients with cancer.

Wu also teaches an undergraduate course on biomaterials; however, the majority of her time is spent on research, which is housed within the LSI, her research home.

“We’re currently the only engineering lab in LSI,” Wu reports. “The advantage is that we’re surrounded by a lot of people with different knowledge and skill sets at LSI.

“Sometimes we’re exploring something that might require expertise that our lab isn’t equipped to do, so it’s great to have the resources readily available within LSI to help us achieve our goals.

“Though there’s been little need to step out of the building so far, there are still so many resources available at U-M outside of LSI that I’ve yet to tap into, and I’m excited about forging new connections with the greater campus community.”

Life Sciences Institute

Leading the Discovery of Small-Molecule Miracles

Peter Toogood, Ph.D.

Peter Toogood, Ph.D., Michigan Drug Discovery Director and Research Associate Professor of Medicinal Chemistry, College of Pharmacy

I've often jokingly shared with my University of Michigan colleagues, *"You can't throw a stone here without hitting a Ph.D."* Little did I know that that idiom's connotative prophecy would come to fulfillment one partly cloudy October afternoon in Ann Arbor.

Peter Toogood, Ph.D., is the director of Michigan Drug Discovery (MDD) at the Life Sciences Institute (LSI) and research associate professor of medicinal chemistry at the College of Pharmacy. He orchestrates complex drug screening and drug discovery research projects consisting of layers upon layers of components, steps and processes that intersect with many centers, institutes and cores scattered throughout the U-M campus — from the biological sciences to medicinal chemistry to the Medical School, and seemingly everywhere in between.

And yes, he's a Ph.D.

Traveling north from the Chemistry Building on U-M's Central Campus, I crossed North University Avenue, marveling at yet another new angle of the Biological Sciences Building (BSB) as the intermittent sun played peek-a-boo with the rust-red ribbons of the faceted facade. My reverie was momentarily interrupted by catching a glimpse of — or what I thought was — a familiar face in the crowd up ahead.

"I know that guy," I said to myself. *"Or at least I think I do."*

My mental Rolodex flipped at light speed (Google it, ye of Gen X, Y, Z and above). In a split second, my mind's eye flashed through the archive of faculty, staff and students I've met in person and on Zoom, along with corresponding biographies I've perused during deep digital dives in a vain attempt to match a face with a name. *"Ok, he's coming from the direction of the LSI building"* ... putting two and two together ... and ... a quick inhale later ... click! A hit! " ... *it's Peter Toogood!"* ... a sigh ... *"I think."*

Though fairly confident, I nonetheless unabashedly stepped up and muttered, "Peter?" He stopped and smiled. I exhaled. "So sorry to bother you, but are you ... you are ... Peter Toogood?" He graciously affirmed as I fumblingly introduced ... and explained ... myself.

"How nice to run into you, I've been meaning to send you an email," I said. "I'm putting together the next issue of our annual magazine and spoke with Analisa DiFeo, who brought up your name as a principal collaborator on a project she's been working on."

He lit up. "Oh, yes, Analisa, of course," he said. "I'd be more than happy to speak to you about that project, although, I'm not sure I would have that much to say about RNA. I have no expertise in RNA — the molecule RNA — and that end of things."

DiFeo discovered a microRNA (miRNA) biomarker and teamed up with Toogood to screen small-molecule drugs that might target that microRNA. I emphasized that a story featuring his involvement in the joint project and his leadership position at MDD would complement her piece very well and also serve to exemplify this year's theme highlighting the power of collaborative RNA science.

"Oh, I see, I see ... wonderful!" he said. "Sure, I would love to speak with you, perhaps we could meet for coffee or breakfast, and we could have a nice chat. I'll look forward to your email!"

"Fantastic," I admitted to myself. "Great, well, so nice to meet you and I look forward to speaking with you."

As we parted ways, I thought, *"How lovely to meet in person. For coffee, breakfast. How civilized, that will be really nice. A three-dimensional experience. A remedy for a COVID-era hangover plagued by false-intimacy nausea and screen fatigue."*

But then fear and panic crept in. *"In person? Uh, oh! No Zoom recording to refer back to, what do I do, scribble down notes on a pad like Redford and Hoffman as Woodward and Bernstein in All the President's Men?"*

Peter Toogood, Ph.D., headshot photo: Leisa Thompson Photography
Background photo: Biological Sciences Building. Austin Thomason, Michigan Photography

Then I remembered. *"Voice memo. I can record it. Thank you, smartphone! Whew!"*

Fast-forward to one week later. Rinse, repeat. Another chance encounter, near the same spot, around the same time. *"What are the odds?"*

He smiled. "Still waiting for that email," he said.

"I know, I know, I am so sorry … ," I blurted. "Got waylaid with a couple of hard deadlines, and … "

He waved it off. "You know, after I thought about this further, there's much more I can tell you about projects we've worked on through MDD where we've targeted RNA."

"Oh, fantastic … that's great."

"Yes, so I really look forward to our conversation … and your email."

"Absolutely!"

Laptop. Email. Calendar. Meeting. Coffee slash breakfast. October 24, 2024. 9:00 AM. Maizie's Kitchen and Market. Central Campus. University of Michigan. Peter Toogood, Ph.D. "Score!"

DRUG DISCOVERY
UNIVERSITY OF MICHIGAN

Bagels and coffee in tow, we set up shop at a table in a somewhat sequestered section of the cafe, a subdued beehive replete with students immersed in laptops and overhead speakers subtly emitting 80s power ballads above the muted conversations. Recording in progress, I broke out my legal pad and began.

Paul Avedisian: Thanks so much for taking the time to meet with me.

Peter Toogood: My pleasure.

PA: So, during my interview with Analisa DiFeo, things really started to come together. The 2024 Nobel Prize for Physiology or Medicine was awarded for the discovery of microRNA, which is where her expertise lies, her Ph.D. student Grace McIntyre is involved in the drug-screening project, and she's connected to many other researcher-scientists, centers, institutes and cores at U-M including yourself and Michigan Drug Discovery, so that's the tie in. [For more on DiFeo's and McIntyre's work, see the separate articles, "Why? But why? So, then … why?" and "A Doctoral Journey."]

PT: Yes, it's a great intersection of many things, actually, and perfect timing. First of all, Analisa is terrific, and she's an excellent scientist. And secondly, she's such a great advocate for young people of science in so many ways.

PA: Yes, in her article I focus on her community outreach and the diverse makeup of her lab with middle and high school students coming in and how that influences everyone's way of thinking. She's so engaging.

PT: And she's so fun to work with …

PA: … and fun to talk to.

PT: Yes, yes. Do you know where she grew up?

PA: No, no.

PT: She grew up on the Amalfi Coast, it's one of the most gorgeous parts of Italy.

PA: Oh, wow!

PT: Yes. I jokingly asked her once, "Analisa, why are you here?" She said, "Well, I want to do science." Okay, I get it, but it's Amalfi! [Laughs]. If you ever get the chance to go, it's one of the most beautiful places I've ever been.

PA: Oh, my word, fascinating — adding that to my list! So, could you tell me a little bit more about Michigan Drug Discovery and your role as director?

PT: Yes, so let me paint a little picture of that. Michigan Drug Discovery lies within the Life Sciences Institute and was founded in 2012 as the Center for the Discovery of New Medicines.[1] There are essentially five drug discovery cores.[2]

PA: And what are those five cores?

PT: In many ways, Michigan Drug Discovery's origin is in what we now call the Center for Chemical Genomics [CCG], which evolved into its own research core at LSI where we conduct high-throughput compound screening.[3] Also at LSI, the Center for Structural Biology [CSB] has largely crystallography capabilities for solving structures of biological molecules, but we've also got deep expertise in cryo-electron microscopy [cryo-em] for structure determination.[4]

PA: Is that the Cryo-Electron Microscopy Core [Cryo-EM], one of the Biosciences Initiative [BSI] Scientific Research Initiative [SRI] programs?[5]

PT: Yes, it's also a core center at LSI but not one of the five drug discovery cores. The Natural Products Discovery Core [NPDC] at LSI works very closely with the screening core and houses 55,000 extracts of various microorganisms and other sources of natural products that we screen in the CCG.[6] Whatever hits we get are mixtures, and because they're just fractionated extracts, they've already been partially separated by a biophysical technique called chromatography. They're still mixtures, so we have to deconvolute anything that shows a biological activity that we're looking for. We then have to determine what the active component of that mixture is.

The Michigan League, at nearly a century old, is one of the most historic buildings on the campus of the University of Michigan and home of Maizie's Kitchen and Market. Photo: Marti Hwang, Michigan Photography.

PA: And that's all done within the Natural Products Discovery Core, which I believe is also a BSI program?

PT: Yes, exactly, and we have AI [artificial intelligence] tools and lots of capability for growing microorganisms at scale and purifying substances and structure determination of small molecules all within that core.

PA: So that's all within the Life Sciences Institute?

PT: Yes. Separately, in the College of Pharmacy, we have a team of medicinal chemists that make up the Vahlteich Medicinal Chemistry Core [VMCC]. The Pharmacokinetic and Mass Spectrometry Core [PMSC] specializes in tissue and blood pharmacokinetics, which tells us how the

[1] https://drugdiscovery.umich.edu/

[2] https://drugdiscovery.umich.edu/resources/cores-centers/

[3] https://www.lsi.umich.edu/science/centers-technologies/center-chemical-genomics

[4] https://www.lsi.umich.edu/science/centers-technologies/center-structural-biology

[5] https://www.lsi.umich.edu/science/centers-technologies/cryo-electron-microscopy

[6] https://www.lsi.umich.edu/science/centers-technologies/natural-products-discovery-core

Ivy painting the 1100 North University Building in vibrant autumn colors. Built in 1925 on the eastern side of the Diag on the University of Michigan's Central Campus, the building is located near the University Avenue crosswalk leading to the Biological Sciences Building. Photo: Paul Avedisian.

we're looking for translational projects that one can envision becoming full-fledged drug discovery operations that could be licensed out, form the basis of a startup company and put things in the clinic that we can ultimately test in human patients.

PA: And that's essentially the vision of Michigan Drug Discovery?

PT: Yes, and when I took over as director in 2020, the vast majority — I would say really exclusively all — of the money to support faculty through this program was being used to fund high-throughput screens, the kind of things we do in the Center for Chemical Genomics. But, we've expanded those capabilities.

PA: In what ways?

PT: We've enriched our compound collection with DNA-encoded libraries — billions of compounds in a single tube, each encoded by a piece of DNA. You incubate the whole mixture together with your target such as a protein or RNA, wash off all the stuff that doesn't stick, denature the target which elutes the stuff that did stick and decipher the structure of the molecule that bound simply by sequencing the DNA. Clever technology.

body interacts with the substance. So, none of the five cores report directly to me — they all operate independently — and my job is to try to coordinate those capabilities and resources and try to bring them to bear in a way that is fruitful and productive on projects that we deem worthy, if you will.[7,8]

PA: What are the steps of the project selection process and the criteria involved?

PT: We have a twice-yearly solicitation for research proposals, which are reviewed and selected based on four main criteria: Is this an unmet medical need? Is it commercially viable and what's the competitive landscape? Is it feasible and can MDD contribute? What's the level of commitment from the PI [principal investigator] and does their team have a plan? Primarily,

[7] https://pharmacy.umich.edu/vmcc

[8] https://pharmacy.umich.edu/pkcore

PA: Indeed.

PT: We also purchased libraries of compounds that had been selected specifically for having a higher probability of binding to RNA as a target — an RNA-focused library. We made that available specifically because we were starting to see a number of proposals from faculty who had RNA targets that they wanted to screen against.

PA: So, that's the genesis of the drug-screening collaboration with Analisa and Grace?

PT: Exactly, and I'll talk more about that in a moment.

PA: Got it.

PT: So, what I wanted to do — part of moving MDD forward — is to create a mechanism for funding more advanced projects. Say you run a screen and get a hit or a handful of hits. Now you have the basis for starting a medicinal chemistry campaign to try and optimize those compounds — make them bind better, improve

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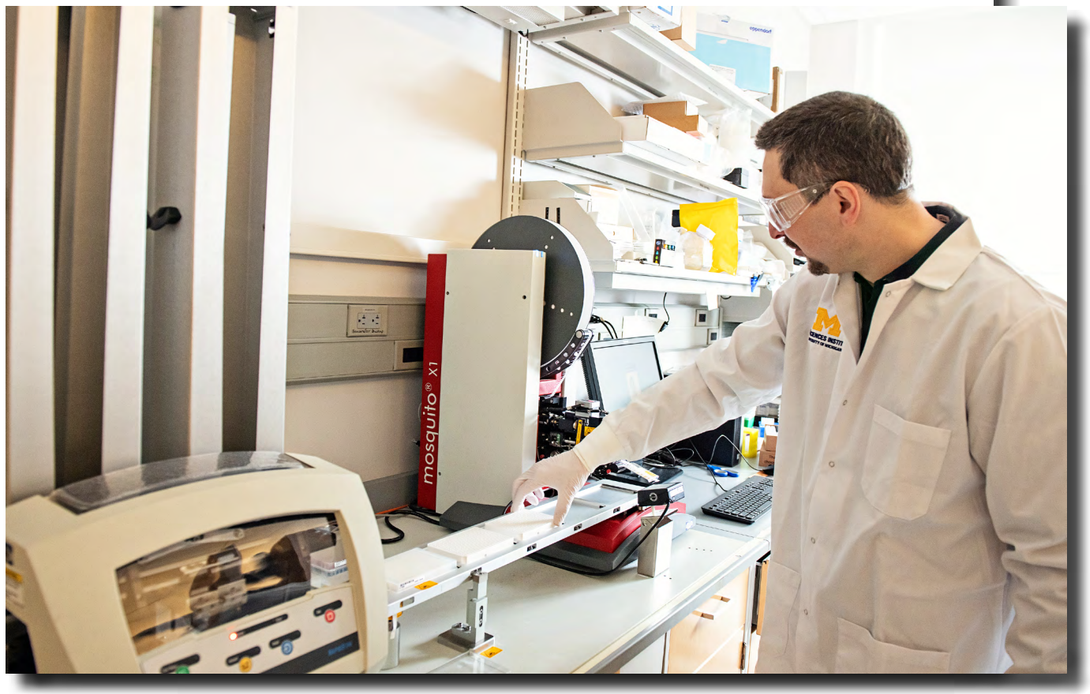
UNIVERSITY OF MICHIGAN

Andrew Alt, Ph.D., director of the Center for Chemical Genomics (CCG) at the Life Sciences Institute (LSI), conducting experiments. Photo: Leisa Thompson Photography.



their physical and ADME [absorption, distribution, metabolism and excretion] profile — so that you could administer them and test them in an animal model of a disease. So we created a sort of parallel pathway, which we very imaginatively call Project Grants. [Laughs] I do have to come up with a better name.

PA: [Laughs]

PT: Those are a bigger investment, more funds, and a two-year commitment with the proviso that they collaborate with us. We've done this with a couple of different projects, and we say we'll give you $200,000 over two years — a significant investment. We have monthly meetings and we're going to engage multiple cores in this work. So we can bring in the Vahlteich Medicinal Chemistry Core, the screening core at the Center for Chemical Genomics if it's applicable for running assays, the Center for Structural Biology, the Pharmacokinetic and Mass Spectrometry cores, et cetera. So now we're coordinating, getting people together, thinking about the same project, even if they only do it once a month, they're bringing their expertise to bear to address the key issues that need to be resolved to advance that project.

PA: Collaboration in its fullest form.

PT: Exactly, yes. So, that's worked reasonably well. I'll give you an example. One project started as a project on pain, targeting the opioid receptor, and pivoted midstream from looking for activators useful for treating pain to things that would down-regulate the activity of the receptor which are useful for blocking the effects of substances like fentanyl and heroin. That team just garnered a $3 million STTR [Small Business Technology Transfer] federal grant in collaboration with a [University of] Michigan spinout company called Eleven Therapeutics Corporation. So that's the kind of metric that we capture, and we say, "Look, this was successful. We put in $200,000, they secured a $3 million external grant, that's a win and exactly what we're trying to achieve." And then they can take it to the next level.[9,10]

PA: And would I be safe to assume that when you say "down-regulate" that might or would have something to do with RNA and/or the translational pathway?

PT: You would be, which brings us back to Analisa's project.

PA: Ah!

PT: Analisa applied for a grant to run a screen against a microRNA called miR-181 employing a very clever assay technology that they built in her lab, so we funded that. That engages the CCG folks like Laboratory Research Specialist Aaron Robida to work with, and in this case, Grace McIntyre, which they've been chiseling away at for multiple years. At this point, we always hope that these screens will be done in a year, but they almost never are.

PA: What are some of the reasons the timeline gets stretched out?

PT: It's a complex system because the microRNA is the result of multiple processing steps: the original transcription of DNA to RNA, processing to a primary RNA, a pre-miRNA, and then a microRNA. We knew we didn't want to inhibit the transcription, because that would probably be generally toxic. Originally, we thought we might be able to target the microRNA itself, but it turns out they're not really sufficiently well structured. They don't have a three-dimensional shape that's stable enough to put a small molecule into. What we're actually finding is that we have molecules that work somewhere along that processing pathway.

PA: And is that what Grace and Aaron have been focusing on?

PT: Yes. She's trying to figure out at a molecular level where they are working and what the target is exactly. Meanwhile, the compounds that came out of that screening look really attractive.

PA: Attractive?

[9] https://drugdiscovery.umich.edu/research-to-treat-pain-cancer-and-infection-gets-boost-from-michigan-drug-discovery/

[10] https://eleventx.com/

PT: That is a sort of med chem [medicinal chemistry] "squishy" term that you can't really define, but it's one of those I-know-it-when-I-see-it terms. Medicinal chemists build up an experience base, and I think every one of them would probably look at these compounds and say, "Yeah, I think that's an attractive starting point for a med chem campaign. We've got reasonable potency out the gate." There are things that we can change on a molecule — do chemistry on it — and anytime you can do chemistry, that gives you the opportunity to make changes that could improve the molecule, although it's no guarantee.

PA: So Analisa, Grace and their team provide additional targeting data, and then these "attractive" compounds can get modified further at VMCC?

PT: Yes, exactly. And if we can add molecular target information and then structural information to those molecules — what they bind to and how they bind with a crystal structure or cryo-em structure for example — that will help guide the kind of med chem changes that we need in order to make them more potent. Then we can address the question of how to deliver them and get them into an animal in a way they can be tested in a disease model.

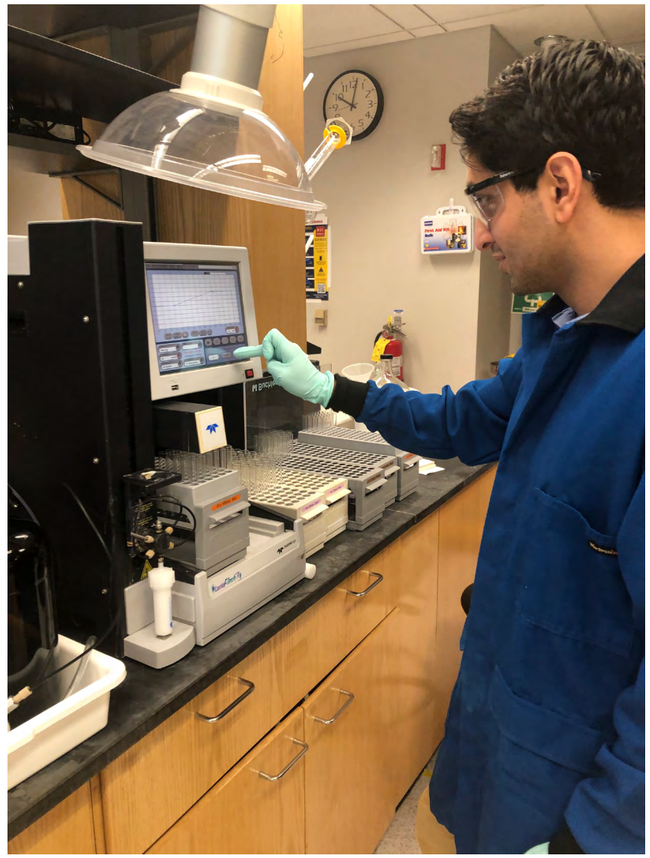
PA: That seems like a promising position to be in.

PT: It is, and we're just at the edge of starting that process. We've identified the compounds, and I made a few analogs, which are versions with slightly different compositions, that Grace tested. Now we've got a compound that's more potent than any of the hits she found from the screen, so we can move the needle in the right direction.

PA: You performed this — the chemistry — in your lab?

PT: Yes. Now, Analisa and Grace have asked us to design a biotinylated probe. Biotin is a small molecule that binds strongly to a protein called streptavidin, so you can use it like a fish hook. You put biotin on a molecule, and as long as that biotin doesn't disturb or alter the function of the molecule you started with, you can let that bind to its target. And then you fish it out with streptavidin, and the protein bound to it comes with it. And then you can ask, "What is the protein I just fished out?"

Seeking inhibitors of an RNA target that is important in ovarian cancer: a project at the Toogood Laboratory, University of Michigan. Photo courtesy of Peter Toogood, Ph.D.



PA: Fascinating.

PT: Yeah, fish it out, but with chemistry. That's kind of cool. We're going to give that a crack. It's been a fun project, and it's one that I would very much like to continue to be involved in.

PA: You mentioned the pain receptor study as a recipient of an MDD Project Grant, is Analisa's another?

PT: She's actually just at that stage now. We funded her as a screening project, and as I mentioned, identified chemical matter that is attractive and could provide the substrate for a med chem campaign. We've discussed applying, and maybe the next cycle we'll do that. The Mark Foundation [for Cancer Research] offers $1 million grants, and we're going to submit a letter of intent. If accepted, we can put in a full proposal next year and see if we can get a million dollars, which would be even better than getting an MDD grant. [Laughs][11]

PA: [Laughs] Wow, fascinating. So, Michelle Hastings and Peter Todd head up the center's RNA Therapeutics Initiative which focuses primarily on designing molecules made from RNA such as ASOs [antisense oligonucleotides] to act as personalized medicines. And your area of expertise is discovering small-molecule drugs, or chemical compounds, that could do the same thing — is that basically two sides of the same coin?

PT: Yes. It's all drug discovery. There are commonalities between them and they complement each other. I'm affiliated with the Center for RNA Biomedicine because there are multiple faculty with an interest in RNA as a target and using small molecules to modulate the function of that target. So that's the intersection. Just like we can target proteins, we can target nucleic acids like RNA with small molecules, so there is an overlap in that area.

PA: Got it, great. So you have Analisa's project …

PT: … yes, which has been a successful one so far — still early on — but an exciting project. We also have a project with Markos Koutmos in chemistry biophysics who's been looking at a riboswitch as a potential target for antibiotics. We've run a screen with him that's also been going quite well, but generating the RNA for these screens is challenging.

PA: How so?

PT: It's not a trivial exercise to get the RNA folded correctly and to then be able to use it in a screen. We've also worked with Amanda Garner on a different microRNA that turned out not to work. So in Annalisa's case, we screen the small molecules to see which ones bind to that RNA in intact cells with a very clever assay. So that's why that was successful.

PA: Interesting …

PT: … in Amanda's case, we did it with isolated RNA. Again, the challenge was largely around making the RNA in the first place. These RNAs don't fold very easily into the sort of three-dimensional structures that can provide nice pockets for small molecules to bind to. So we never really had a large amount, only screening a handful of compounds, about 300.

PA: And don't they degrade too?

PT: Yes, very easily.

[11] https://themarkfoundation.org/

PA: So that's another challenge.

PT: Yes. So, looking at the broader picture, although [University of] Michigan's not really known for drug discovery, we do have several drugs — not major drugs — but I believe nine products, a mix of therapeutics and vaccines — that have originated from the University of Michigan. We have five compounds currently in phase three clinical trials, another eight in phase two, and some earlier than that, any one of which, if it hits, could be a major success story and bring in significant revenues for the university. So we have a really robust, actually enviable pipeline of drugs — small-molecule therapeutics.

PA: Wow.

PT: Yeah. So it's a little bit of, "Watch this space." I think we're going to see some interesting, notable success stories in the near future. Other universities that have been fortunate in this space have been able to build buildings and create major institutes and things like that.

PA: Emily Kagey's article announcing your appointment as MDD director in 2020 pointed out that one of your goals was "to grow the university's impact on the local and state economy, by identifying opportunities and partners for licensing U-M discoveries and forming startup companies that can advance these discoveries through clinical development."[12]

PT: Yes. You know, it's the most important metric. Unfortunately, it takes 15 to 20 years on average for drug development, so I probably will be retired before it happens. [Laughs] What we really want to do is to connect the dots between discovery and implementation. Say, "Look, we funded this at the earliest stage, and now it's a drug!"

PA: That's very exciting, and I look forward to reading all about it! Well, thank you so, so much.

PT: Any time.

As Peter Toogood, Ph.D., departed the cafe for his next appointment, Journey's Don't Stop Believin' played overhead, providing the perfect soundtrack to accompany his infectious optimism. How appropriate. Serendipity. It's a bright future for drug discovery at the University of Michigan.

[12] Peter Toogood to direct Michigan Drug Discovery. Published January 6, 2020, Michigan Drug Discovery. Author: Emily Kagey, Communications Director, Life Sciences Institute. https://drugdiscovery.umich.edu/toogood-mdd-director/

Background photo: Ian Demsky, Life Sciences Institute. Inset photo edited by Stephanie King, Life Sciences Institute Images courtesy of Emily Kagey, Life Sciences Institute

Center Report

University of Michigan
Center for RNA Biomedicine

8
seminars with external speakers

2
core facilities

7
schools & colleges

41
departments

169
faculty members

1,102
members' publications

1
magazine

1
symposium with 6 keynote speakers

47
e-newsletters

By the Numbers

PEOPLE
169 RNA faculty members
Male: 68%; Female: 32%

ACROSS CAMPUS
Schools/colleges: 7
Departments: 41

LEADERSHIP
2 Co-Directors
2 RNA Therapeutics Directors
8 Executive Committee members
11 Strategic Advisory Board members
7 External Leadership Council members
8 Student and Postdoc Council members

RESEARCH FACILITIES
2 Research core facilities:
Bru-seq Lab and SMART Center

SCIENTIFIC PUBLICATIONS
1,102 total publications from all the faculty members

SEMINARS
8 external and internal speakers
20-30 in-person and 30-50 virtual participants in average attendance

SYMPOSIUM
1 Annual RNA Symposium with 6 keynote speakers

COMMUNICATION
1 annual magazine
47 newsletters

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From 7 schools and colleges across 41 departments

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Maria Castro, Neurosurgery, Medical School
Sriram Chandrasekaran, Biomedical Engineering, College of Engineering
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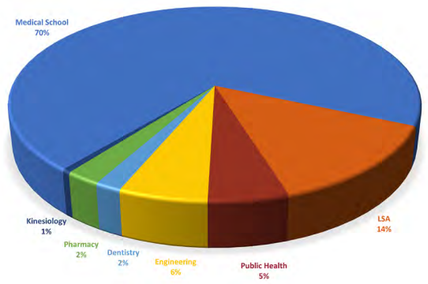
Saher Sue Hammoud, Human Genetics, Medical School
Phyllis Hanson, Biological Chemistry, Medical School
Michelle Hastings, Pharmacology, Medical School
Alfred O. Hero, Electrical Engineering and Computer Science, College of Engineering
Gerry Higgins, Computational Medicine and Bioinformatics, Medical School
Zhonggang Hou, Biological Chemistry, Medical School



Members' repartition across Schools and Colleges

Lori Isom, Pharmacology, Medical School
Shigeki Iwase, Human Genetics, Medical School
Matthew Iyer, Pathology, Medical School
Ursula Jakob, Molecular, Cellular & Developmental Biology, College of LSA
Paul Jenkins, Pharmacology, Medical School
Hui Jiang, Biostatistics, School of Public Health
Catherine Kaczorowski, Neurology, Medical School
Sundeep Kalantry, Human Genetics, Medical School
Hyun Min Kang, Biostatistics, School of Public Health
Sarah Kargbo-Hill, Molecular, Cellular and Developmental Biology, College of LSA
Sarah Keane, Chemistry and Biophysics, College of LSA
Evan Keller, Urology, Medical School
Tom Kerppola, Biological Chemistry, Medical School
Jeffrey Kidd, Human Genetics, Medical School
Anthony King, Psychiatry, Medical School
Jacob Kitzman, Human Genetics, Medical School
Markos Koutmos, Chemistry and Biophysics, College of LSA
Kristin Koutmou, Chemistry, College of LSA
Matthias Kretzler, Internal Medicine, Medical School
Chandan Kumar-Sinha, Pathology, Medical School
Steve Kunkel, Pathology, Medical School
Kenneth Kwan, Human Genetics, Medical School
Joerg Lahann, Chemical Engineering, College of Engineering
Adam Lauring, Microbiology & Immunology, Medical School
Cheng-Yu Lee, Internal Medicine, Medical School
Jun Hee Lee, Molecular & Integrative Physiology, Medical School
Jiahe Li, Biomedical Engineering, College of Engineering
Jun Li, Computational Medicine & Bioinformatics, Medical School
Yongqing Li, Surgery, Medical School
Jiandie Lin, Cell & Developmental Biology, Medical School
Jie Liu, Computational Medicine and Bioinformatics, Medical School
Mats Ljungman, Radiation Oncology, Medical School
Pedro Lowenstein, Cell & Developmental Biology, Medical School
Andrew Ludlow, Kinesiology, School of Kinesiology
Carey Lumeng, Molecular & Integrative Physiology, Medical School
Rahul Mannan, Pathology, Michigan Medicine
Anna Mapp, Chemistry, College of LSA
David Markovitz, Internal Medicine, Medical School
Hayley McLoughlin, Neurology, Medical School
Miriam Meisler, Human Genetics, Medical School
Daniela Mendonca, Dentistry, School of Dentistry
Gustavo Mendonca, Dentistry, School of Dentistry
Rajasree Menon, Computational Medicine and Bioinformatics, Medical School
Ryan Mills, Computational Medicine and Bioinformatics, Medical School
John Moldovan, Human Genetics, Medical School
Stephanie Moon, Human Genetics, Medical School
John Moran, Human Genetics, Medical School
Benjamin Murdock, Neurology, Medical School
Deepak Nagrath, Biomedical Engineering, College of Engineering
Sunitha Nagrath, Chemical Engineering, College of Engineering
Jayakrishnan Nandakumar, Molecular, Cellular & Developmental Biology, College of LSA
Nouri Neamati, Medicinal Chemistry, College of Pharmacy
Alexey Nesvizhskii, Bioinformatics, Medical School
Rachel Niederer, Biological Chemistry, Medical School
Erik Nielsen, Molecular, Cellular & Developmental Biology, Medical School
Roomi Nusrat, Internal Medicine, Medical School
Melanie Ohi, Cell & Developmental Biology, Medical School
Gilbert Omenn, Computational Medicine and Bioinformatics, Medical School
Akira Ono, Microbiology, Medical School
Edgar Otto, Internal Medicine, Medical School
Bruce Palfey, Biological Chemistry, Medical School
Stephen Parker, Computational Medicine and Bioinformatics, Medical School
Abhijit Parolia, Pathology, Medical School
Henry Paulson, Neurology, Medical School
Bambarendage (Pini) Perera, Environmental Health Sciences, School of Public Health
Alexandra Piotrowski-Daspit, Biomedical Engineering, College of Engineering
Sethuramasundaram (Sethu) Pitchiaya, Pathology, Medical School
John Prensner, Pediatrics and Biological Chemistry, Medical School
Jay Brito Querido, Biological Chemistry, Medical School
Indika Rajapakse, Computational Medicine and Bioinformatics, Medical School
Rajesh Rao, Ophthalmology & Visual Science, Medical School
Diane Robins*, Human Genetics, Medical School *Member Emerita
Anthony Rosenzweig, Internal Medicine, Medical School
Brandon Ruotolo, Chemistry, College of LSA
Russell Ryan, Pathology, Medical School
Maureen Sartor, Computational Medicine and Bioinformatics, Medical School
Laura Jean Scott, Biostatistics, School of Public Health
Jiaqi Shi, Pathology, Medical School
Lyle Simmons, Molecular, Cellular & Developmental Biology, College of LSA
Geoffrey Siwo, Learning Health Sciences, Medical School
Janet Smith, Biological Chemistry, Medical School
Cristiane Squarize, Dentistry, School of Dentistry
Jeanne Stuckey, Biological Chemistry, Medical School
Michael Sutton, Molecular & Integrative Physiology, Medical School
Andrew Tai, Internal Medicine, Medical School
Alice Telesnitsky, Microbiology and Immunology, Medical School
Muneesh Tewari, Internal Medicine, Medical School
Peter Todd, Neurology, Medical School
Peter Toogood, Medicinal Chemistry, College of Pharmacy
Raymond Trievel, Biological Chemistry, Medical School
Natalie Tronson, Psychology, College of LSA
Lam Cheung Tsoi, Computational Medicine & Bioinformatics, Medical School
David Turner, Biological Chemistry, Medical School
Sarah Veatch, Biophysics, College of LSA
John Voorhees, Biophysics, College of LSA
Nils G. Walter, Chemistry, College of LSA
Stanley Watson, Psychiatry, Medical School
Chase Weidmann, Biological Chemistry, Medical School
Xiaoquan (William) Wen, Biostatistics, School of Public Health
Max Wicha, Internal Medicine, Medical School
Andrzej Wierzbicki, Molecular, Cellular & Developmental Biology, College of LSA
Krista Wigginton, Civil & Environmental, College of Engineering
Ryan Wilcox, Internal Medicine, Medical School
Thomas Wilson, Pathology, Medical School
Trisha Wittkopp, Ecology & Evolutionary Biology, College of LSA
Connie Wu, Biomedical Engineering, College of Engineering
Swathi Yadlapalli, Cell and Developmental Biology, Medical School
Bing Ye, Cell & Developmental Biology, Medical School
Chengxin Zhang, Computational Medicine & Bioinformatics, Medical School
Jianzhi (George) Zhang, Ecology & Evolutionary Biology, College of LSA
Jifeng Zhang, Internal Medicine, Medical School
Yan Zhang, Biological Chemistry, Medical School
Yue Zhao, Computational Medicine & Bioinformatics, Medical School
Xiang Zhou, Biostatistics, School of Public Health
Guizhi (Julian) Zhu, Pharmaceutical Sciences, College of Pharmacy

Core Facilities

Two core facilities are affiliated with the Center for RNA Biomedicine, the Bru-seq Lab and the Single Molecule Analysis in Real-Time (SMART) Center.

The Bru-seq Lab

World wide web of Bru-seq

Mats Ljungman, Ph.D., Professor of Radiation Oncology and of Environmental Health, Medical School; Co-Director, Center for RNA Biomedicine

The Bru-seq lab helps internal and external research labs look under the hood to better understand mechanisms regulating gene expression. By capturing newly synthesized RNA and mapping it to the reference sequence, Bru-seq provides a genome-wide map of where in the genome transcription takes place.

Although only about 1% of the genome codes for proteins, about 20% of the genome of any cell line gives rise to RNA that Bru-seq can capture. The non-coding RNA is produced by transcription of sequences upstream and downstream of active genes as well as from enhancer elements that regulate genes.

In addition, many non-coding genes are located across the genome with very cell type-specific expression patterns. Bru-seq can also inform about splicing patterns of transcript isoforms and their lifespans using BruChase-seq.

The Bru-seq lab has served researchers in several countries around the world. In these collaborations, researchers perform the initial labeling of RNA using bromouridine and then ship cell samples on ice to the University of Michigan Bru-seq lab, where we capture the Bru-labeled RNA, sequence it and analyze genome-wide transcription.

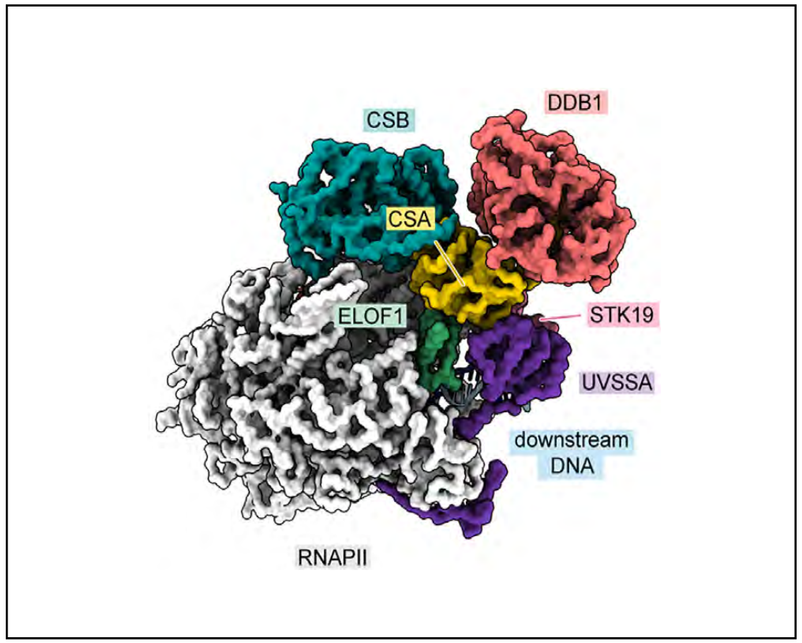
One research group that the Bru-seq lab has collaborated with for several years is the lab of Martijn Luijsterburg from Leiden University in the Netherlands. Martijn and his group have made seminal contributions to the study of how cells repair DNA damage.[1,2,3]

[1] Yana van der Weegen et al., ELOF1 is a transcription-coupled DNA repair factor that directs RNA polymerase II ubiquitylation, Nature Cell Biology, 23:595-607, 2021. https://doi.org/10.1038/s41556-021-00688-9

[2] Diana van den Heuvel et al., A CSB-PAF1C axis restores processive transcription elongation after DNA damage repair, Nature Communications, 12:1342, 2021. https://doi.org/10.1038/s41467-021-21520-w

[3] Diana van den Heuvel et al., STK19 facilitates the clearance of lesion-stalled RNAPII during transcription-coupled DNA repair. Cell. 2024 Dec 12;187(25):7107-7125.e25. https://doi.org/10.1016/j.cell.2024.10.018

Ljungman photo: Daryl Marshke, Michigan Photography, courtesy of Mats Ljungman, Ph.D.



Molecular structure of the transcription-coupled repair complex. Image courtesy of Mats Ljungman, Ph.D., the Bru-seq Lab.[4]

Transcription-coupled repair is an important pathway that promotes survival of cells exposed to DNA damage. This pathway helps cells recover RNA synthesis after DNA damage halts transcription.

Martijn's research group identified several novel factors involved in transcription-coupled repair, and with Bru-seq analyses at the Bru-seq lab, the group has shown that these factors were required for the transcriptional re-start after the removal of the transcription-blocking DNA lesions.

This fundamental research, aided by the Bru-seq lab, expands our understanding of how cells deal with environmental genotoxins and offers new opportunities for developing anti-cancer therapies targeting DNA repair in cancer cells.

Are you interested in trying Bru-seq for your project?
Please contact Michelle Paulsen at: tenbroek@med.umich.edu.

[4] Diana van den Heuvel et al., STK19 facilitates the clearance of lesion-stalled RNAPII during transcription-coupled DNA repair. Cell. 2024 Dec 12;187(25):7107-7125.e25. https://doi.org/10.1016/j.cell.2024.10.018. Publisher: Elsevier, ScienceDirect, Creative Commons license, https://creativecommons.org/licenses/by/4.0/

The Single Molecule Analysis in Real-Time (SMART) Center

The LUMICKS C-Trap® is here!

Nils G. Walter, Ph.D., Francis S. Collins Collegiate Professor of Chemistry, Biophysics and Biological Chemistry, Professor of Chemistry, Professor of Biophysics, College of Literature, Science, and the Arts; Co-Director, Center for RNA Biomedicine

The SMART (Single Molecule Analysis in Real-Time) Center, one of two shared-use core facilities of the Center for RNA Biomedicine (CRB) at the University of Michigan, provides university researchers with a variety of single-molecule detection and manipulation tools to track and analyze biomolecules with unprecedented detail.

It provides access to state-of-the-art instrumentation, including high-resolution fluorescent imaging such as TIRF (total internal reflection fluorescence) and smFISH (single-molecule fluorescence *in situ* hybridization); sequential single molecule localization like MERFISH (multiplexed error-robust fluorescence in situ hybridization) and STORM (stochastic optical reconstruction microscopy) super-resolution fluorescent imaging; atomic force microscopy (AFM) and fluorescence lifetime imaging as well as experienced support in experimental planning and analysis. SMART staff also pride themselves on their adaptability and responsiveness, often customizing instrumentation or developing new analysis tools to suit user needs.

Notably, they recently unveiled an exciting new addition to their equipment: the LUMICKS C-Trap®. This instrument, the result of a recent $1.6 million instrument grant from the National Institutes of Health (NIH), allows researchers to measure or exert extraordinarily small forces, in the force regime relevant to individual biomolecules, combined with simultaneous multicolor fluorescence imaging. The system boasts up to four optical traps, multicolor fluorescent imaging and super-resolution stimulated emission depletion (STED) imaging. The C-Trap® is an extremely user-friendly system with expansive capabilities, making this technology available to researchers across the university — including faculty members of the CRB — with thorough dedicated support from SMART staff.

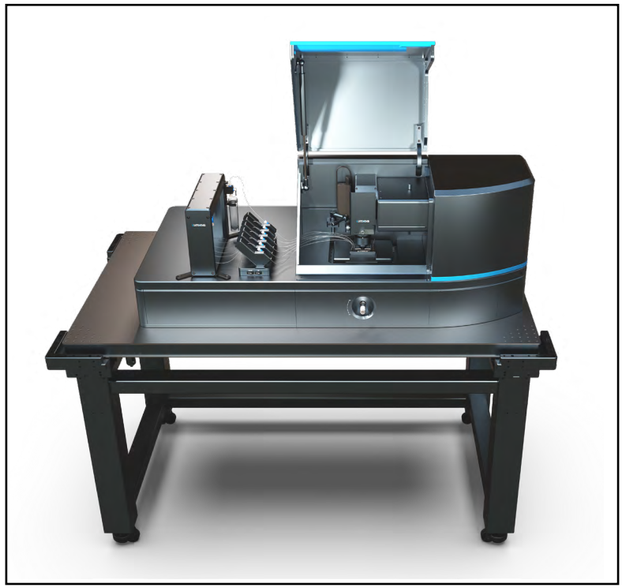
"The NIH award represents a $1.6 million enhancement of the initial U-M Biosciences Initiative $10.2 million investment in the Center for RNA Biomedicine and SMART Center," says Nils Walter, Ph.D., center director and primary author of the proposal.

Initiated by Walter, the instrument grant was submitted to the NIH in collaboration with scientists from the U-M, Michigan State University, Oakland University and the Van Andel Institute to serve as a local high-tech hub and resource. The funds will be allocated to purchase the equipment, and for delivery, installation, training and a five-year service contract.

SMART Center Manager Damon Hoff, Ph.D., says, "The C-Trap® is a commercial system that is not currently available anywhere else on campus or in the state of Michigan."

The C-Trap is equipped with four optical traps to observe the kinetic and mechanical work of molecules, giving it a lot of flexibility. Optical traps, or

Walter photo: Daryl Marshke, Michigan Photography, courtesy of Nils Walter, Ph.D.



The LUMICKS C-Trap® instrument with up to four optical traps, multicolor fluorescent imaging, and super-resolution (STED) imaging. Image courtesy of LUMICKS.

optical tweezers, work by holding in place or "trapping" microscopic glass or plastic spheres approximately one micrometer in size.

Investigators place or "stretch" the object they wish to study — proteins, RNA, DNA or protein droplets, for example — between these two "beads." This allows scientists to directly observe and measure the forces at play in the molecule(s) held between those two traps.

The C-Trap® is also equipped to perform multicolor fluorescence imaging of those molecules at the same time, to confirm their observational changes and dynamics, and includes super-resolution STED to give researchers a much clearer picture of how the molecules are behaving than with traditional fluorescence microscopy.

"With fluorescence imaging, scientists are normally limited to what they can see by what we call a diffraction limit of light, around 300 nanometers," says Hoff. "With STED super-resolution microscopy, scientists are able to see things much smaller, around 20 nanometers or so."

With regular fluorescence imaging, molecules lined up on a piece of RNA that are 100 nanometers apart would appear as a smear. With STED, scientists are able to resolve each individual molecule due to the much higher resolution. The objects you can see are now much smaller.

The C-Trap® will allow scientists to set up their experiments step by step and easily change solutions for a smooth, sequential flow, such as introducing a protein to see how it interacts. It also includes temperature control, to conduct experiments for any temperature-dependent biological process and measure activity under a variety of conditions such as room temperature, physiological temperature and so forth.

The LUMICKS installation and on-site training were recently completed, and the first projects are already underway, illustrating a variety of application types, including studies on protein-ligand binding force measurements, physics of nucleoprotein condensates, and cellular membrane tension-sensing.

SINGLE MOLECULE

Drs. Walter and Hoff are both excited to brainstorm with other researchers how this exciting new instrument could impact their projects.

For more information on the LUMICKS C-Trap®, or if you are interested in the SMART Center for your project, please contact Damon Hoff at hoffj@umich.edu.

Partnerships

Center for RNA Biomedicine Collaborative Partnerships

RNA Collaborative Seminar Series

The RNA Collaborative Seminar Series, initiated and led by the Center for RNA Biomedicine (CRB), is promoted by the RNA Society (website and Twitter/X). As of December 2024, it connected 30 RNA research centers and has hosted bi-weekly seminars with an average of 90 participants attending each seminar.

The RNA Collaborative is a grassroots effort led by a number of RNA research centers worldwide to provide an online seminar series during and beyond the institutional shutdown caused by COVID-19. The goal of the program is to promote and disseminate emerging RNA research and to establish and strengthen connections within the international RNA scientific community. Scientists are welcome to present all RNA-related research spanning from foundational discoveries to potential therapeutic applications. With the growth of the collaborative, seminars are now co-hosted between two institutions and entail one 60-minute event (each institute presents a 30-minute seminar with 1-2 speakers), four poster sessions with introductory lightning talks, or a combination of talks and poster sessions.

For more information on the RNA Collaborative Series and the RNA Society, visit https://www.rnasociety.org/rna-collaborative-seminar-series

THE SOCIETY FOR RNA THERAPEUTICS

RNA therapeutics have the potential to revolutionize the treatment of a wide range of medical conditions and improve the lives of patients across the globe. The Society for RNA Therapeutics (SRT) was founded with the goal of advancing RNA Therapeutics research, education, and technological advancements for the benefit of world health.

The SRT is a global network to support translational research and development of RNA therapeutics; establish standards for RNA manufacturing; create guidelines for clinical trials; facilitate public-private regulatory partnerships; promote accessibility of RNA therapeutics for all patients; offer public and professional education; create training guidelines; promote the interests of patients with diseases amenable to RNA therapies; and create clinical best practices.

For more information, visit https://srnat.org/

CYSTIC FIBROSIS FOUNDATION®

The mission of the Cystic Fibrosis Foundation is to cure cystic fibrosis (CF) and to provide all people with CF the opportunity to lead long, fulfilling lives by funding research and drug development, partnering with the CF community, and advancing high-quality, specialized care.

For more information, visit https://www.cff.org/

The work being done at the University of Michigan Center for RNA Biomedicine (CRB) helps progress the foundation's quest to cure cystic fibrosis. To apply for an award in cystic fibrosis research or professional training or development, review current and upcoming academic funding opportunities.

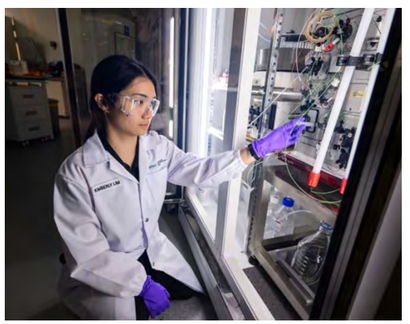
For more information, visit https://www.cff.org/researchers/academic-funding-opportunities

EDDC Experimental Drug Development Centre

The Experimental Drug Development Center (EDDC) in Singapore is excited to share our commitment with the University of Michigan Center of RNA Biomedicine (CRB) to innovate and excel in the pioneering field of small molecule-targeting RNA.

As a beacon of innovation in Singapore, EDDC is a nationally recognized entity for drug discovery and development, hosted by the prestigious Agency for Science, Technology & Research (A*STAR). Our mission is to translate discovery research into therapeutics through strategic collaboration and the pursuit of scientific excellence.

EDDC is dedicated to the mission of translating Singapore's extensive scientific knowledge into effective medicines. Our primary focus revolves around pioneering work in small-molecule targeting of RNA, representing a groundbreaking approach with significant implications across various diseases for therapeutic intervention. This mission underscores our commitment to address diseases with high unmet medical needs by expanding the druggable target space and targeting >90% of RNA in the human genome.



Chemical biology at EDDC.

We invite University of Michigan faculty members to explore with us the exciting field of translating RNA-driven diseases into therapeutic interventions. Collaboratively, we aim to develop small molecule drugs that target RNA through the integration of cutting-edge RNA discoveries from the U-M CRB and EDDC's innovative small molecule targeting RNA platform. Let us embark on a collaborative journey that not only explores new frontiers but also pushes the boundaries of drug discovery and development in the rapidly emerging field of RNA therapeutics.

We look forward to fostering a dynamic exchange of ideas and insights between our institutions and jointly contributing to the forefront of scientific and medical innovation.

To learn more, visit https://www.eddc.sg/

Photo courtesy of Wan Hsin Lim, Head of Chemical Biology and Therapeutics. Experimental Drug Development Centre

Events

2024-2025 RNA Innovation Seminar Series

The Center for RNA Biomedicine offers bi-weekly RNA Innovation Seminars that feature visiting professors, U-M faculty and students. The seminars cover a broad array of topics about RNA research and its application. In addition to learning about the latest research in the field, it is an opportunity to meet colleagues, network and foster collaborations.

For the 2024-2025 academic year, we offered 8 one-hour seminars, presented both in-person at the Biomedical Science Research Building (BSRB) and on Zoom. We gave our members the opportunity to meet individually with presenters to exchange ideas, share insights and explore possible partnerships.

We also hosted life sciences industry expert David R. Walt, Ph.D., for a special lecture, followed by an open-house breakfast, which offered members the opportunity to socialize with peers and connect with Dr. Walt.

Innovation Seminar Series and Special Lecture Speakers

David R. Walt, Ph.D., Hansjörg Wyss Professor of Bioinspired Engineering at Harvard Medical School, Professor of Pathology at Brigham and Women's Hospital and Harvard Medical School, "Why sensitivity matters for clinical diagnosis." (September 12, 2024)

Gregor Neuert, Ph.D., Associate Professor, Molecular Physiology and Biophysics, Biomedical Engineering and Pharmacology, Vanderbilt University, "Transcriptional stochasticity reveals multiple mechanisms of long non-coding RNA regulation." (September 23, 2024)

Joseph Yesselman, Ph.D., Assistant Professor, Chemistry, University of Nebraska, "High-throughput determination of RNA tertiary contact thermodynamics by quantitative DMS chemical mapping." (October 7, 2024)

Laura Scott, Ph.D., Research Professor, Biostatistics, University of Michigan School of Public Health, "Regulation of RNA levels in muscle and adipose tissues by sex and genetic variants." (October 21, 2024)

Nils G. Walter, Ph.D., Co-Director, Center for RNA Biomedicine, Francis S. Collins Collegiate Professor of Chemistry, Biophysics and Biological Chemistry, University of Michigan, "Single molecules come into focus: From bacterial riboswitches to mammalian cellular phase separation." (November 4, 2023)

Jennifer E. Phillips-Cremins, Ph.D., Associate Professor and Dean's Faculty Fellow, Bioengineering and Genetics, Penn Epigenetics, University of Pennsylvania, "The Science of Connections: Bridging chromatin folding, synaptic plasticity, and neurophysiology." (November 18, 2024)

Sundeep Kalantry, Ph.D., Professor, Human Genetics, University of Michigan Medical School, "Evolution of Mammalian Dosage Compensation." (February 17, 2025)

Connie Wu, Ph.D., Research Assistant Professor, Life Sciences Institute Assistant Professor, Biomedical Engineering, College of Engineering, University of Michigan. (April 28, 2025)

Drew Weissman, M.D., Ph.D., co-recipient of the 2023 Nobel Prize for Physiology or Medicine, speaking at the 2024 RNA Symposium.

Photo: Scott C. Soderberg, Michigan Photography

Annual RNA Symposium

Annual RNA Symposium

For the 2024 Symposium, “Unmasking the Power of RNA: From Structure to Medicine,” we were thrilled to welcome keynote speaker Drew Weissman, M.D., Ph.D., the co-recipient of the 2023 Nobel Prize for Physiology or Medicine.

Four other distinguished keynote speakers presented talks on various RNA topics: Victoria D’Souza, Ph.D., Harvard University; Brenton R. Graveley, Ph.D., University of Connecticut; Leemor Joshua-Tor, Ph.D., Cold Spring Harbor Laboratory and Peter Todd, M.D., Ph.D., University of Michigan. The event attracted an audience of over 500 participants, both in-person and virtual.

The 2024 Symposium also featured a poster session preceded by selected lightning talks, which served as a great opportunity for trainees to present their research to and network with a variety of leaders in the RNA field.

The 2025 RNA Symposium, “From Sequence to Solutions,” will be presented for the first time in partnership with the Society for RNA Therapeutics as their inaugural event. It will convene thought leaders and pioneering researchers in the field of RNA science and biomedicine over a three-day period.

Scheduled keynote speakers include John Cooke, M.D., Ph.D., Houston Methodist Hospital; Beverly L. Davidson, Ph.D., University of Pennsylvania; Adrian R. Krainer, Ph.D., Cold Spring Harbor Laboratory; Mats Ljungman, Ph.D., University of Michigan; Muthiah (Mano) Manoharan, Ph.D., Alnylam Pharmaceuticals and Anna Marie Pyle, Ph.D., Yale University.

The expanded format allows for more robust programming, featuring invited talks selected from abstract submissions, an evening poster session and a gala dinner. And thanks to the incredible support from our generous sponsors, we instituted a new scholarship opportunity available to junior researchers.

The MiSciWriters will blog about this symposium as they’ve done in past years. Blog posts will be uploaded and available to view at https://misciwriters.com/category/blog/

Please join us on March 6-8, 2025, for the 9th Annual RNA Symposium, to be held in the Kahn Auditorium at the Biomedical Science Research Building on the University of Michigan campus.

A 2025 Symposium detailed program is available at https://rna.umich.edu/events-navigation/2025-symposium/#program

Photos: Michigan Photography, Scott C. Soderberg

Center Hiring

Omar Salman, Ph.D.

Senior Consultant, Center for RNA Biomedicine

Omar obtained his Ph.D. in Chemical Engineering from The University of Illinois Urbana-Champaign in 1982. Omar worked for Pfizer in Kalamazoo, MI for 29+ years as a senior research advisor. He was the technical leader/subject matter expert (SME) in process development and scaleup for bioseparations, sterilization of active pharmaceutical ingredients, particle size reduction, and manufacturing of injectable sterile aqueous suspensions. Omar will support the design of a manufacturing line for RNA based lipid nanoparticles (LNP), purification, and aseptic filling of the final drug product for clinical trials under Current Good Laboratory Practices (cGLP) and/or Current Good Manufacturing Practice (cGMP).

Katelyn Lacy, Ph.D.

Managing Director, RNA Therapeutics

Katelyn joined the Center for RNA Biomedicine team to help develop RNA therapeutics at the University of Michigan and facilitate the design and initial testing of RNA medicines for pre-clinical research. Katelyn received her B.S. from the U-M in Cellular and Molecular Biology and went on to earn her Ph.D. in Molecular Biophysics at UT Southwestern Medical Center in the laboratory of Dr. Yunsun Nam where she became an expert in RNA/protein biochemistry and structural biology.

Her thesis work in mechanistic studies of RNA modification enzymes led her to a postdoctoral fellowship at Ionis Pharmaceuticals working with Dr. Stan Crooke and Dr. Frank Rigo as part of the Core Antisense Research group. There she focused on fundamental aspects of antisense oligonucleotide (ASO) function, from both the drug (ASOs) and the target (RNA) angles including the characterization of how naturally occurring RNA modifications affect ASO activity and evaluating structure activity relationships (SAR) of ASO chemical modifications on oligo activity and selectivity. She was promoted to a Senior Scientist at Ionis where she continued this work and investigated other modalities of RNA therapeutics evaluating them for further development.

Salman photo: Daryl Marshke, Michigan Photography. Lacy photo courtesy of Katelyn Lacy, Ph.D.

Giving

With your support for RNA research, we can help cure millions of people.

Photo: Michigan Medicine

Revolutionize Healthcare with Us

Fuel the Future of RNA Therapeutics

Imagine a world where the most challenging diseases are met with precise and personalized therapies. Thanks to extraordinary advancements in genome sequencing, this is no longer just a dream but a burgeoning reality.

RNA technology is the driving force behind this change, holding the key to treating even the rarest conditions.

This isn't a distant possibility; it's happening here and now in FDA-approved treatments. Tomorrow's cures are within reach today.

Photo: Michigan Medicine

Envision a transformed future in medicine.

Consider the difference we could make.

But we can't do it alone — your partnership is vital.

By equipping Michigan's foremost experts with cutting-edge RNA technology, we can accelerate the development of groundbreaking therapies.

Your support will help us secure the essential tools we need to tackle diseases ranging from rare genetic conditions to persistent illnesses.

And where better to advance this medical revolution than at the University of Michigan, a leader in research and innovation?

We have the expertise, the passion and an urgent mission.

Join us in making a profound impact with RNA Therapeutics at Michigan.

Thank you for your commitment to change.

UNIVERSITY OF MICHIGAN

Give Today

SCAN ME

For more information about how to support RNA research and the University of Michigan Center for RNA Biomedicine, please contact Maria Stieve (mstieve@umich.edu).

Photo: Eric Bronson, Michigan Photography

The Center for RNA Biomedicine is supported by generous funds provided by the University of Michigan Biosciences Initiative, University of Michigan Medical School Endowment for Basic Sciences, and the College of Literature, Science, and the Arts.

Thank you for your support!

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MICHIGAN MEDICINE

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Photo: Courtesy of Adrien Chauvier, Ph.D. Walter Lab
Back cover: 2024 RNA Symposium. Photo: Paul Avedisian

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