2024

RNA TRANSLATED

UNIVERSITY OF MICHIGAN CENTER FOR RNA BIOMEDICINE

M-RNA Therapeutics: Changing tomorrow's world of medicine, today

CENTER FOR RNA BIOMEDICINE
UNIVERSITY OF MICHIGAN

RNA Translated is an annual publication of the University of Michigan Center for RNA Biomedicine

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M-RNA Therapeutics Clinical Director

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

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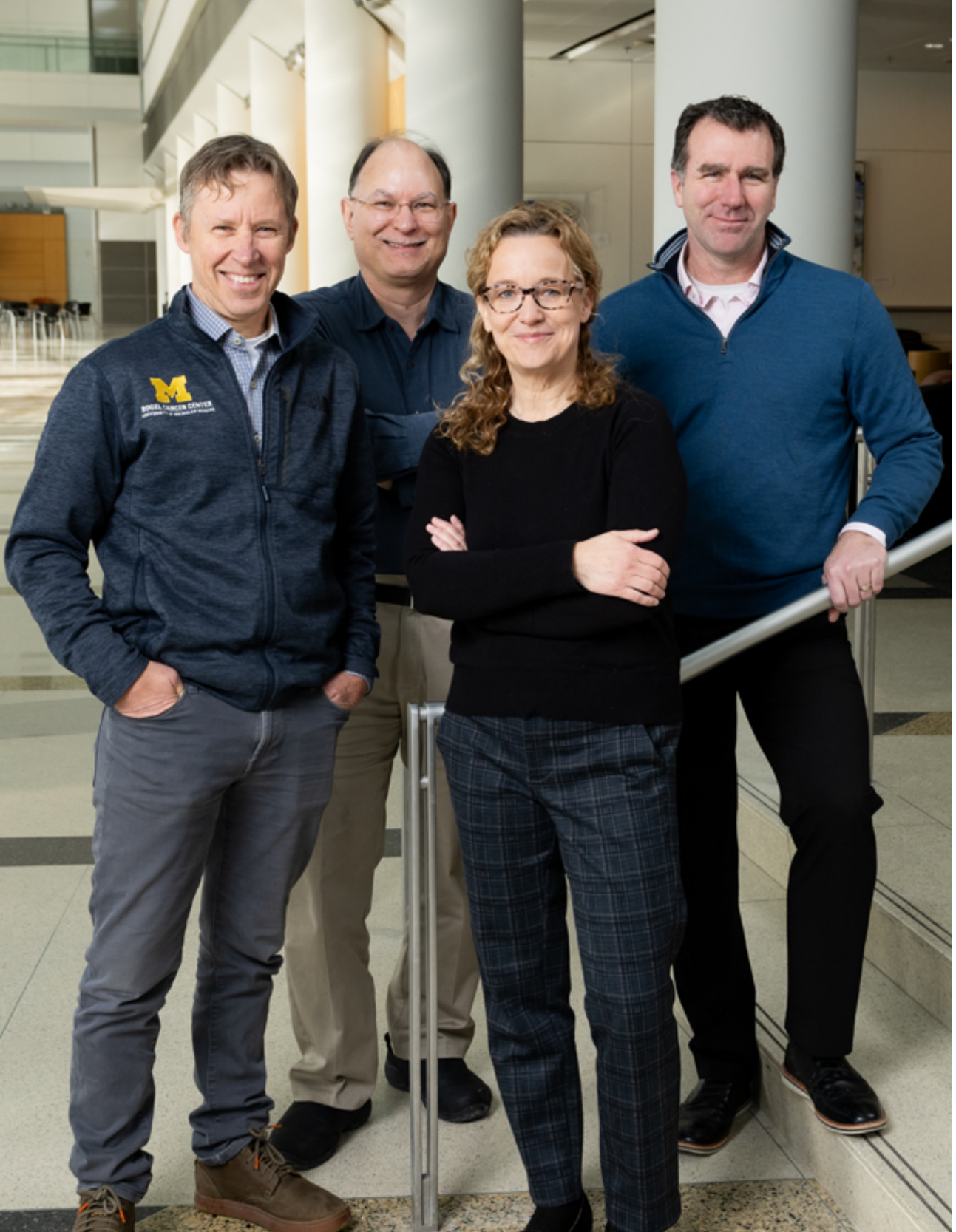
Huntington Sheldon Professor in Medical Discover, Professor of Molecular Biology and Genetics, Johns Hopkins School of Medicine

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.



Introduction

We are excited to unveil the newest, 2024 edition of RNA Translated, our annual magazine highlighting the cutting-edge advancements of RNA research at the University of Michigan. With the pandemic behind us — in significant part thanks to the whirlwind success of mRNA vaccines — the promise of RNA medicines at large is coming into greater relief.

The magazine dives right into our groundbreaking efforts to build a University of Michigan "M-RNA Therapeutics" initiative for "changing tomorrow's world of medicine, today." Our cover story sets the stage for a journey through the transformative power of RNA therapeutics, highlighting how these medicines are starting to turn dreams into reality.

Through the capstone recruitment of Professors Michelle Hastings and Peter Todd to our leadership team, we have the expertise to build a fast, efficient, and cost-effective pipeline from a patient's bedside to the research bench and back to the bedside. Join us on the scientific front with Hastings and the clinical front with Todd as they provide insights into how to bridge the divide between foundational and clinical research.

Our "Emerging Investigators" and "Established Explorers" segments introduce faculty shaping the future of RNA research at the University of Michigan. Curious about the basics? "RNA 101" takes you on a journey from transcription to translation, unraveling the core fundamentals of RNA therapeutics. The magazine also highlights the 2023 Nobel Prize in Physiology or Medicine to Katalin Karikó and Drew Weissman for their seminal work on mRNA vaccines, with Weissman presenting a keynote at our 2024 symposium.

Discover the influence of artificial intelligence on data and computational modeling for RNA therapeutics and delve into the collaborative efforts shaping the future of medicine. Our "Center Report" section presents essential stats, numbers, and core facilities driving our joint progress in M-RNA research. Stay informed about recent events and outreach activities, including seminars, our symposium, and film screening.

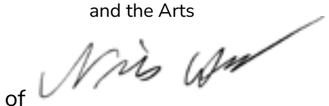
Meet the newest additions to our faculty, Rachel Niederer and Jay Querido, in the "Faculty Hiring" section. Finally, explore our "Giving" section to learn how you can contribute to advancing M-RNA therapeutics and making a lasting impact on the future of medicine.

We cordially invite you to immerse yourself in the dynamic world of M-RNA Therapeutics and witness the extraordinary contributions shaping the landscape of medicine at the University of Michigan.

It is truly a thrilling time for RNA!

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



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

Peter Todd, M.D., Ph.D., Chester and Anne Alecks Sackett Endowed Professor, Professor of Neurology, Associate Chair for Research, Department of Neurology and Medical Director, Neurology, Medical School

Photo opposite: Michigan Photography, Daryl Marshke

M-RNA Therapeutics

Turning the dream into reality: Changing tomorrow's world of medicine, today

Imagine you're a parent raising a child. Amelia enjoys running, playing, laughing, learning. It's her fifth birthday, and as she excitedly blows out all the candles on her cake, you notice that Amelia's eyes appear to be drifting from focus, ever so slightly. You glance over at your husband. He saw it too.

Or you're a single dad on a favorite hike along the beach with your eight-year-old ball of energy, Reynaldo. Suddenly you see his right leg collapse out from beneath him, causing him to stumble just a bit as you rush ahead to help him right himself.

Subtle observations like these, parents routinely log into the back of their mind and then dismiss just as readily. But then the backlog starts to build.

Further clues elevate into obvious warning signs — Amelia severely slurs her speech; Reynaldo develops seizures — dislodging the latent evidence into the realm of the conscious, leading to the inevitable visit to the family doctor for Reynaldo; the local clinic for Amelia. Specialists are sought out, and the arduous journey to seek answers begins.

Genetic disease experts diagnose each with Batten disease, a rare condition caused by a mutated gene, whose victims ultimately succumb to a series of progressively crippling symptoms very early in life. The prognosis: a healthy and happy childhood ripped from their lives. More questions than answers. And a death sentence within 10 years of diagnosis.

New therapeutics involving medicines derived from RNA molecules, along with traditional, small molecule medicines that directly target RNA, might be able to help Amelia and Reynaldo live a better, longer life by slowing the progression of the disease. But this option comes at the hefty price of $1 million to 10 million plus.

Hopeful, Reynaldo's father says he'll pay whatever it costs; money is no object. Heartbroken, Amelia's parents are confronted with the grim reality that they've reached a dead end.

RNA therapeutic development takes an inordinate amount of time primarily because pharmaceutical companies cannot pivot from a mass-production model. And time is a precious commodity. If the disease is too far advanced, the therapies are less effective.

The mRNA COVID vaccine was developed relatively quickly; however, it was essentially "one size fits all" — it could, and did, work for the general population. Not so with RNA therapeutics. Each afflicted individual has a different gene mutation than others with the same disease, so one therapy cannot work on the other.

And the clock is ticking for Amelia and Reynaldo. Reynaldo's father waits in earnest for a miracle medicine that may arrive too late to save his son, as he watches the disease further inflict its ravage on his little boy. And Amelia's parents, bereft of hope, see their little girl slowly descend into an uncertain future, savoring each precious moment they have left.

Science is on the cusp of being able to not only treat diseases such as Batten but also promise that anyone afflicted with a rare genetic disease will have an equal opportunity to get a medication made just for them, with the hope of thwarting or even preventing the development of an inevitably fatal disorder.

As a powerhouse public institution with an unequaled brain trust of world-renowned RNA experts, the University of Michigan is uniquely positioned to deliver on just such a promise.

The table is set: Scientists and physicians of the Center for RNA Biomedicine represent the largest, most diverse, and overall best-funded center in the U.S. — $200 million/year of the total $1.7 billion research and development (R&D) expenditure — and have feelers not just in RNA but in all fields of the biomedical endeavor; the U.S. News and World Report ranks Michigan Medicine among the best in the nation.

A complete pipeline, including a concerted community outreach effort and associated patient intake program, followed by a rapid development of treatment, is currently in development at Michigan, providing a solid beacon of hope to the Amelias and Reynaldos of the world.

But we're not there yet. This type of process takes the right kinds of facilities to manufacture these drugs on-site and tailor them for individual rare diseases. It takes the right kind of animal and lab testing and state-of-the-art toxicology services — all in-house — in order to bypass the time-consuming red tape that would beset a partnership with a major pharmaceutical company.

The overarching advantage of a public institution like the University of Michigan is equity. M-RNA Therapeutics can produce these medicines in a relatively short time, at cost, and make them available to all. And RNA-based medicines could be developed for Alzheimer's, amyotrophic lateral sclerosis, bipolar disorder, anxiety and depression, addiction, AIDS, Parkinson's, cancer, and so many more.

With your help, Amelia's parents would be afforded a way in and a medicine developed quickly that might stop Amelia's disease from taking a firmer hold. And Reynaldo's father could see his son's symptoms slowed considerably or even halted as a therapeutic is designed and delivered in as little as a few short months or even weeks.

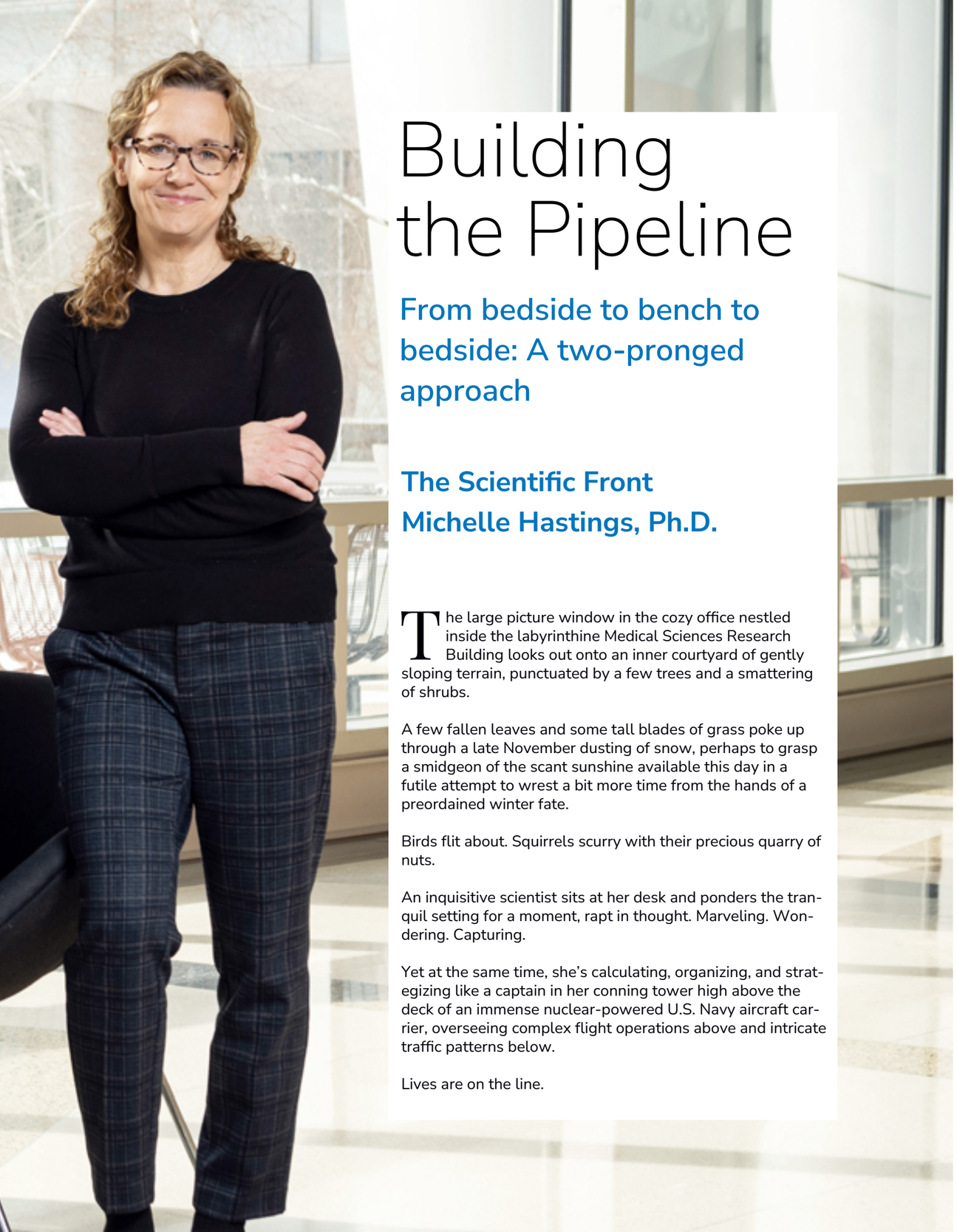
Housing a supersonic engine on the Michigan campus that could rapidly, cost-effectively, safely, and equitably develop, manufacture, and deliver medicines — a bench-to-bedside pipeline — would catapult the university past other prominent educational institutions currently in contention to outpace Michigan for a top-seeded place at the table to become a true leader in the RNA-based medical revolution surging throughout the nation and the world.

Instead of waiting at a bus stop for a bus that would never come, or worse yet pass them by, all patients with genetic diseases, no matter what their socioeconomic backgrounds, would be picked up and offered a door into a world of hope previously known only to a privileged few: genetic testing, diagnosing, treatment, and beyond.

Administered with the hope possibly to cure; delivered with the certainty of improving lives. That dream is soon to be a reality at Michigan.

With your help, we can build it.

And tomorrow ... ... becomes today.



Building the Pipeline

From bedside to bench to bedside: A two-pronged approach

The Scientific Front
Michelle Hastings, Ph.D.

The large picture window in the cozy office nestled inside the labyrinthine Medical Sciences Research Building looks out onto an inner courtyard of gently sloping terrain, punctuated by a few trees and a smattering of shrubs.

A few fallen leaves and some tall blades of grass poke up through a late November dusting of snow, perhaps to grasp a smidgeon of the scant sunshine available this day in a futile attempt to wrest a bit more time from the hands of a preordained winter fate.

Birds flit about. Squirrels scurry with their precious quarry of nuts.

An inquisitive scientist sits at her desk and ponders the tranquil setting for a moment, rapt in thought. Marveling. Wondering. Capturing.

Yet at the same time, she's calculating, organizing, and strategizing like a captain in her conning tower high above the deck of an immense nuclear-powered U.S. Navy aircraft carrier, overseeing complex flight operations above and intricate traffic patterns below.

Lives are on the line.

Michelle Hastings, Ph.D., Professor of Pharmacology, Pfizer Upjohn Research Professor of Pharmacology, arrived at Michigan in May of 2023 as the center's newly appointed Director of M-RNA Therapeutics. Her research focuses on understanding the genetic basis of disease and discovering therapeutics that target RNA splicing and maturation to alter gene expression. Her work has resulted in the discovery of antisense oligonucleotides (ASOs), with the potential to treat diseases such as cystic fibrosis, Usher syndrome, Alzheimer's, Parkinson's, and Batten disease.

An introspective, unassuming luminary uniquely gifted to lead one of the largest teams of RNA scientists in the world, her unequivocal care and compassion are equaled only by her vast warehouse of scientific knowledge and collective experience. Prodigy and pedigree.

"There are so many amazing investigators here — most I haven't even talked to yet — whose research could be developed into therapies, or translated in some way, to be beneficial to human health," Michelle reveals.

Her nerve center sanctuary is painted a beautiful blue, with accents of blue throughout — fabrics, ornaments — providing a comforting presence of endless sky, missing for many of Michigan's days, and no doubt indicative of Michelle's bright outlook on the future, and moreover, the possibilities the future holds for the modern medical miracle that is RNA therapeutics.

Spark of genetics

Michelle's interest is in not only the design and discovery phases of RNA therapeutics — her specialty — but also in navigating the long road of getting these discoveries into the clinic, clinical trials, and helping with intellectual property (IP) and licensing issues. She strives to ease bottlenecks to make the journey from bedside to bench to bedside a more streamlined, seamless process. The right person at the right time for such an ambitious undertaking.

Michelle completed her undergraduate degree in Biology at St. Olaf College in her native Minnesota, earned her Ph.D. in biology from Marquette University in Milwaukee, and trained as a postdoctoral fellow at Cold Spring Harbor Laboratory. Before coming to Michigan, Michelle was Professor and Director of the Center for Genetic Diseases at the Chicago Medical School, Rosalind Franklin University of Medicine and Science.

"I developed an interest in genetics at a very young age," Michelle relates. "In seventh grade, I joined a science club that had just formed at school. We had to do a science project, and I don't know how I came up with it, must've heard somewhere about breeding mice and what their offspring would look like. Today, if you want to work with mice there are lots of protocols and this never would have happened. But I went to the university and just asked them, 'Could I have a male black mouse and a female white mouse?' And they just gave them to me," she recalls humorously.

"They told me to place them in a warm, dark place, so I found a spot under the bathroom sink, and I worked out what coat color I expected them to be, but they didn't produce any pups. Maybe that's what catapulted me into science and a fascination with genetics — the drive — that first failed experiment."

From the captain's chair, Michelle sees the M-RNA Therapeutic initiative as helping bridge the gap between discoveries in the lab and patients who have a disease for whom an RNA therapeutic might be developed. In her RNA journal article, "RNA therapeutics," Michelle explains, "'RNA therapeutics' refers to a disease treatment or drug that utilizes RNA as a component. In

Photo opposite: Michigan Photography, Daryl Marshke

this context, RNA may be the direct target of a small-molecule drug or RNA itself may be the drug, designed to make or bind to a protein, or to mimic or target another RNA."[1]

The M-RNA Therapeutics pipeline is depicted in the graphic opposite and designed to resemble the common symbol for infinity. Every point along the continuum is dependent upon and a product of each adjacent point — a symbiotic relationship. And at any point along the pathway, one can return to or move on to any other point, representing the trial-and-error dynamic, checks and balances, and "Eureka!" moments that define a scientific environment.

So what's next...?

Michelle believes that Michigan can be a leader in a new way of treating disease and creating therapeutics from ground-breaking science. "We are already beginning to realize this vision on multiple fronts; we have started the engine and things are starting to move," she says. "We are on the threshold of our first successes, which will lead to more successes and faster advancement. With support from the university and by working together with our colleagues and with the community we serve locally and around the world, we will have an impact on the health outcomes of our society."

Michelle's work with rare pediatric neurological disorders caused by genetic variations found in only a handful of children is widely known. This work is made possible by the identification of the genetic cause of the child's disease by the child's physicians.

Unfortunately, for many children there's often little hope for finding a treatment to slow the progression of the disease. Parents reach out to Michelle for answers when they hear about her work using RNA-based therapeutic strategies to devise treatments for rare genetic diseases. In many cases, there are possibilities, hope. But currently, the path forward is still rough, unpaved.

Drug development projects cost millions of dollars — too much for finding medicines for a rare disease that only one person may have. However, RNA Therapeutics may make drug development affordable because the fundamental make-up of the drug molecules is all similar, no matter whether developed for common or rare diseases. Only the nucleic acid sequence changes as it is directed to a person's individual disease-causing mutation. Grouping the different types of RNA therapies together as a drug class, rather than as individual drugs, may allow people with rare diseases the hope of getting treatments and even cures.

Let's imagine a car. The main features on most cars are standardized, basically all the same. These features have been developed for cars

in general, and they make the car safer, more stable, reliable, et cetera. But, for people who live in harsher climates or with challenging road conditions, the tires on their car may need to be different, or specialized, to allow the car to drive better in snow, sand, or ice, for example.

Now, changing the tires on a car to have spikes or wider tread does not change the safety and functionality of the car; it just tailors it for optimal performance in a specific location or condition. Thus, rather than buying a new car, people can personalize their car to fit their specific driving needs at the relatively low cost of changing tires.

For RNA therapeutics, this concept of tailoring the basic RNA drug to a specific disease-causing mutation is akin to putting a different set of tires on a standard car to get it to go where you want it to go, in this case to a specific mutation. And it is this concept that should make development far less costly and thus has the potential to help so many more people.

Collaboration — where minds meet

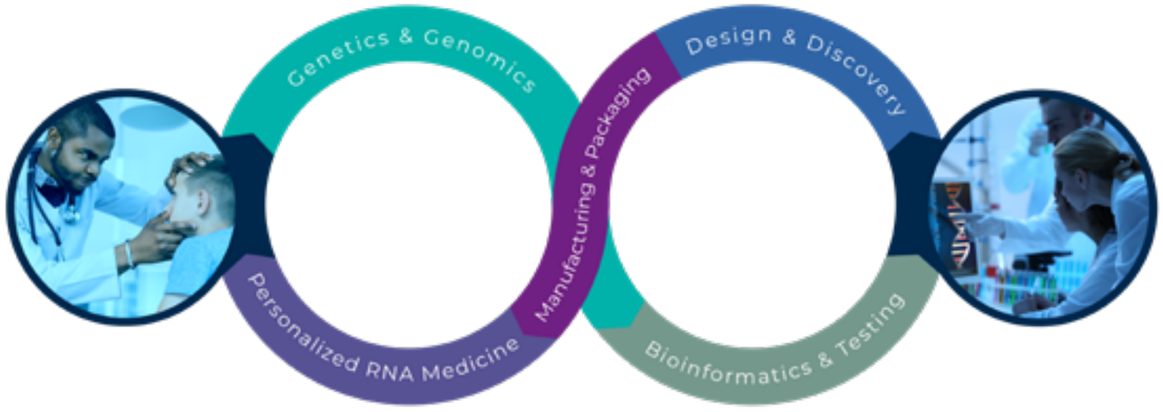
Rare genetic mutations might be able to be addressed through other treatments but may be best addressed — and perhaps most rapidly addressed – through this kind of personal, individualized therapy.

To conduct a project like this entirely at Michigan is possible. Some of the pieces are already in place and could expand; others could be easily brought in. Michelle comments, "There are experts here at all levels, from scientists and drug development specialists to genetic counselors and clinicians and others that, together, can feasibly develop a drug for a patient starting at diagnosis, going to the research bench, and bringing it back to the patient's bedside for treatment."

"The hope is that we can do it all here, have the infrastructure in place at Michigan," Michelle says. The kind of test case scenario she envisions could be templated for real cases in the future to serve as a road map for not only making the discoveries but also furthering development and initiating clinical trials.

One of the diseases that Michelle has been developing an RNA therapeutic treatment for is a rare form of Usher syndrome. One of the most debilitating symptoms of Usher syndrome is blindness. "My expertise is in designing and testing RNA-like molecules with therapeutic potential and modulating gene expression in a therapeutic manner," Michelle says. "I'm not necessarily a disease expert in all of the conditions we are working to devise treatment strategies for. So in developing a therapeutic for Usher, we need to team up with experts in the eye — and specifically, the retina — to help enable our discovery and development strategies and test our therapeutic candidates."

Enter Dr. Rajesh Rao, Leonard G. Miller Professor of Ophthalmology and Visual Sciences. Dr. Rao studies the pathogenesis of retinal disease and is a faculty member of the Center for RNA Biomedicine. A connection. An expert in the retina who works with organoids, artificially grown masses of cells that resemble an organ. (See separate article on Rajesh Rao, M.D., in the "Research Highlights Part I" section for more on organoids.)



"What he's doing is essential for advancing RNA therapeutics to the clinic for eye disease and is an example of the type of experts we need to work with to find treatments for other conditions," Michelle relates. "His research will help us understand the mechanisms of eye disease that could be targeted with RNA therapeutic

[1] RNA therapeutics, Michelle L. Hastings and Adrian R. Krainer, RNA, April 2023 29: 393-395, © 2023 Hastings and Krainer; Published by Cold Spring Harbor Laboratory Press for the RNA Society This article, published in RNA, is available under a Creative Commons License (Attribution-NonCommercial 4.0 International), as described at http://creativecommons.org/licenses/by-nc/4.0/. Article is online at http://www.rnajournal.org/cgi/doi/10.1261/rna.079626.123.

approaches. Partnering between specialists in RNA therapies and disease experts with retinal biology, for example, is an ideal way to find the best treatments."

"Those are the kinds of things that we have here at Michigan. There's no doubt that we can find the expertise here, with our network of researchers. It's this kind of coming together of different areas of expertise that's so important in developing the best treatment strategies."

The pot-holed road to the buildout

"There are still many barriers ahead to realize a vision of making therapeutics available for all," Michelle outlines. "But if something is effective and safe and powerful, it will eventually be realized. When I first started working with RNA as a therapeutic paradigm nearly 20 years ago, I had a hard time getting any funding to study the ideas because many people thought that the barriers to making an effective RNA-based drug were insurmountable. And yet 10 years later, an RNA drug became the first FDA-approved genetic treatment for the lethal pediatric neurodegenerative disease spinal muscular atrophy (SMA), capturing the attention of the world as its remarkable therapeutic effects were witnessed. Children that would not live beyond two years of age without the treatment are walking and thriving still to this day."

And then, in 2019, the world witnessed another RNA drug miracle, the COVID-19 vaccine, developed in months, saving countless people from the deadly virus. These events, along with a growing number of cases of RNA-like drugs rapidly and specifically developed to treat people with rare genetic diseases, have revolutionized the concept of drug development and opened the door to a future of personalized therapeutics tailored to one's individual genetic makeup.

As M-RNA Therapeutics Clinical Director Dr. Peter Todd also points out, a storehouse of RNA therapeutics "templates" could eliminate the need to start from scratch each time and speed the process of building customized medicines. "That's the hope," Michelle concurs. "Ideally, we could identify and create RNA-based approaches for treating disease before there is a person even diagnosed."

Making molecules to test in a lab and making a drug to deliver into humans are two very different things, the latter requiring much more stringent manufacturing protocols dictated by the FDA. Building on her research focus, Michelle sees the first, and perhaps most important, piece of the puzzle is a facility on campus that can make the necessary RNA molecules for the discovery and testing of potential therapeutics.

"We identify a causative genetic variation in a person's DNA," Michelle relays. "I or somebody else can devise a strategy to target and correct the effects of the genetic defect using an engineered RNA-based approach. We then make the molecules and get them to the researchers to test. That process gets you to that first level of discovery and enables scientists that have expert knowledge in a particular disease the means to potentially treat it. My aim is to facilitate this process and begin filling the pipeline with promising drug candidates."

Michelle speaking in front of friends and colleagues at her welcome reception event in May 2023. Photo courtesy of Michelle Hastings, Ph.D.

Cystic fibrosis

Another genetic disease Michelle works on is cystic fibrosis. Although there are effective medications helping people who have the most common disease-causing gene variants, about 6% of those afflicted with the disease have rare genetic variations that make them unresponsive to these medicines.

"While it might be ideal to find one drug that treats the six percent, it may be faster and more effective to design approaches for very specific genetic variants," Michelle notes. "But to do this effectively, we need a team approach, and for cystic fibrosis, we have an excellent one, right here at Michigan."

Alexandra Piotrowski-Daspit, Ph.D., Assistant Professor, Biomedical Engineering, and faculty member of the Center for RNA Biomedicine, is working on using nanoparticles for delivery to the lung, and Michelle envisions her therapeutic RNA molecules "hitching a ride" on these microscopic pack mules.

Rachel Niederer, Ph.D., Assistant Professor, Biological Chemistry, studies the largely unexplored area of genetic sequences that are in noncoding regions of the genome but can be manipulated to control the expression of genes. Michelle, Rachel, and Alexandra have just been awarded a multi-million dollar grant to design RNA-based medicines that could be used to treat cystic fibrosis patients with currently untreatable disease. "In close collaboration with other researchers, clinical scientists, and physicians at the Cystic Fibrosis Centers at Michigan, we hope to soon have therapies for people with the disease that currently have no disease-slowing treatment options," Michelle reports. (See separate articles on Alexandra Piotrowski-Daspit, Ph.D., in the "Research Highlights Part II" section; and Rachel Niederer, Ph.D., in the "Center Report" section.)

Time is not on our side

"Currently the only treatment for many people with genetic diseases is medications that treat their symptoms," Michelle states. "Treating the problem at its source — by modulating directly the expression of the gene that's been disrupted in the disease — may be a better solution, with the potential to be disease-altering treatments and even cures."

Hastings Lab members. Photo courtesy of Michelle Hastings, Ph.D.

There are still many challenges to overcome to achieve the full potential of these types of therapeutic approaches in personalized medicines; nonetheless, Michelle envisions a bright future for M-RNA therapeutics. Peter Todd, M.D., Ph.D., Clinical Director, sums it up best:

"Michelle brings an amazing expertise in both the development of these technologies and in their direct implementation in cases that she's been involved in. I think that she represents a really important leader of that scientific front, in that if she doesn't have the answer herself, she knows someone who would and helps us build that group that can provide us with the best possible answers."

A burst of sunlight illuminates the landscape outside her office window for a brief moment, glistening off pockets of earth and grass emerging through the melting snowpack in the arbor glen, perhaps portending that spring is soon on the way. The horizon boasts blue skies that promise smooth sailing ahead with Michelle Hastings, Ph.D., at the helm, leading the charge on the M-RNA Therapeutics scientific front.

Indeed, lives are on the line.

The Clinical Front
Peter Todd, M.D., Ph.D.

On the surface, Peter Todd, M.D., Ph.D., is a physician who sees patients and tries to find ways to improve their lives through medicines, therapies, surgery, or a combination of treatments. He's also a research scientist who's studying a field of medicine that would add to that arsenal of tools exponentially — RNA therapeutics.

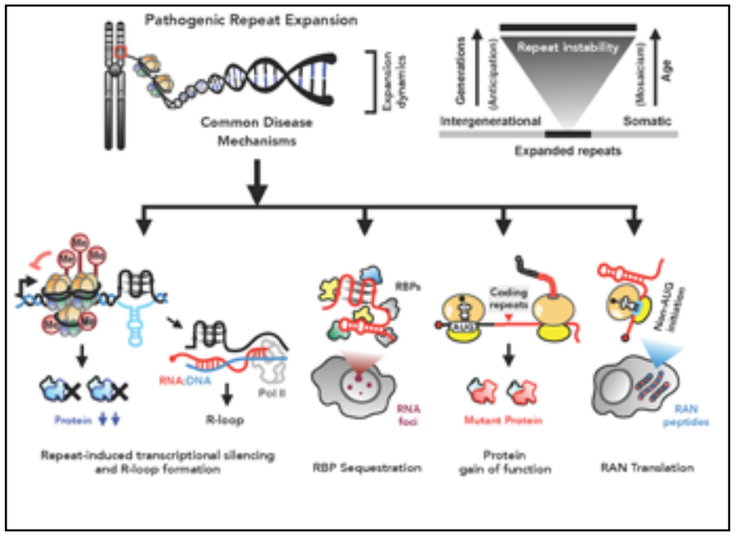
Underneath that exterior flows a deep river of understanding and extraordinary prescience that generates synergy. In his highly inventive mind, he's not only acutely aware of the power that RNA medicine holds to help improve the lives of patients suffering from neurologic and genetic diseases, but he's also cognizant of and pragmatic about what it's going to take to get us there.

As the new Clinical Director for M-RNA Therapeutics at the Center for RNA Biomedicine, he's laid out the roadmap of exactly how the RNA therapeutics engine build should happen, piece by piece: the components, the timeline, and ultimately, what it's going to look like.

A longstanding faculty and Executive Committee member of the Center for RNA Biomedicine, Peter came to Michigan in 2008, joined the Michigan faculty in 2010, was recently invested as the Chester and Anne Alecks Sackett Endowed Professor of Neurology, and is the Associate Chair for Research in the Department of Neurology.

His clinical work and research focus on the role of repetitive elements within the human genome and how expansions in a small number of these repeats cause inherited neurologic diseases, specifically Fragile X-associated disorders (including Fragile X Syndrome, FXTAS, and FXPOI), a group of progressive degenerative illnesses that cause problems with walking, tremors and dementia; amyotrophic lateral sclerosis (ALS); frontotemporal dementia; and cerebellar ataxia. He also founded the Program in Neurogenomic Medicine at Michigan to enhance the pace of diagnostics and therapeutic development for patients with inherited neurological disease.

"I think almost every scientist wants what they do to impact people," Peter reveals. "It's a dream of mine that something I do in my research lab will someday directly improve the care of a patient that I see."



Molecular mechanisms of nucleotide repeat expansion pathogenesis. Schematic courtesy of The Todd Lab.

Leading the charge on the M-RNA Therapeutics clinical front, Peter envisions a future when a patient who has a problem could walk into a Michigan Medicine Hospital, get a genetic diagnosis, and have a potential RNA therapy designed almost within the same day as well as delivered rapidly and safely within a few weeks.

"That's a theoretical possibility now, and the goal — the dream — is to make it a reality," Peter says. "But to drive the Ferrari, we first have to build the road."

The promise of RNA

RNA has the potential to change how we practice medicine. It's a highly modular molecule, a simple molecule, that can be adapted to do many different things. Peter uses the analogy of building a car to explain the significance. The same base chassis can become four separate car models just by putting different parts on top of it. RNA is a little bit like that, and that's what the real hope of RNA is, that this simple scaffolding can do a lot of different things.

"That modularity coupled with a deeper understanding of how we might turn a given gene up, turn it down, off, or on — customize it basically for each genetic disease just by changing its bases and structures — that's what's so exciting about it."

An additional boon to this kind of modularity is the potential to stockpile RNA "templates" that would serve as blueprints that could be adapted easily to a specific disease or individual.

Peter outlines that DNA carries a genetic code. During the process of gene expression, a long piece of RNA is produced from a large piece of DNA. That RNA then gets cut and pasted back together in myriad variations through a process known as splicing. Some gene mutations that cause disease trigger mis-splicing, to either include something that shouldn't be expressed or omit something that should.

He stresses that Director of M-RNA Therapeutics Michelle Hastings, Ph.D., has already designed ways to alter these splicing events — theoretically for every gene in the human genome. The hope then is that as each of these

Photo opposite: Michigan Photography, Daryl Marshke

pathways undergoes testing on biological samples in the lab, the repository of RNA templates will grow.

Peter surmises that as more and more of these tests are completed, computational models will eventually be able to calculate that the predicted effect will be the same as the actual effect.

“This will allow us to consolidate so that everything is computational. Then, the build itself to make the molecule can happen fairly quickly, and the odds of it working will be very high. Once we’re at that point, we can rapidly shrink the therapeutic odyssey for patients with rare diseases and genetic diseases.”

But we’re not there yet.

Timing is critical

The human genome was first sequenced in April 2003, representing a milestone in genetics research and allowing scientists the ability to identify which genes were responsible for both rare and common diseases.

For people with a rare or genetic disease, it’s often been a long road to get a final diagnosis. They usually don’t undergo advanced genetic testing until very late in the process and sometimes, not even then at all.

Once patients are diagnosed, clinicians can then see if there is already an FDA-approved drug for that diagnosis or a case study that offers other therapies, but in many of these cases, the disease is too far advanced for any of these drugs to have any effect.

The success of treatment therefore depends on when physicians meet their patients — the time in their disease process. What Peter and others have discovered in their research is that RNA therapeutics appear to be much more effective when they are introduced earlier in the disease cycle.

“Spinal muscular atrophy (SMA) is a horrible disease. Babies lose motor function at around six months of age — never sit, never stand — and eventually succumb at a very early age. When we administered these RNA therapies at that age — when they were already exhibiting symptoms — it didn’t “reverse” the process, but it extended their life and their motor problems got worse more slowly,” Peter explains.

“But when we gave [these MRA therapies] to babies who were diagnosed with the mutation at birth or within the first few weeks of life — before those motor symptoms manifested — those kids did really well. They could stand and walk, and they didn’t have the same degree of problems as the ones we treated later.”

Likewise, with neurologic diseases such as Parkinson’s or Alzheimer’s, the more advanced the disease, the more difficult it is for the healthy neurons to keep up. The brain does not grow back well. As more and more cells “fall to the dark side,” healthy neurons are required to take on a heavier workload, thus taxing the system.

“It’s like a phalanx of soldiers in a firing line,” Peter relates. “If you start losing all your sharpshooters, then everyone else along the line has to start working harder. So, if you can catch that diagnosis earlier, you have more of a fighting chance.”

The sequencing of the human genome allowed people to take proactive steps, such as getting more screenings if they found they carried a gene associated with colon cancer, for instance. A high-profile celebrity took a more aggressive approach and underwent a double mastectomy as a pre-emptive strike after discovering she carried both genes that factor into a high probability of developing breast cancer.

“We initially thought that the same principle would apply for neurologic diseases,” Peter states. “But we would need the proof of principle that we can impact these processes safely and effectively before we start giving things to people who have not yet manifested disease. The first rule of medicine is: Do no harm.”

The path forward

The first human genome cost billions of dollars to sequence. Today, the average cost for sequencing an individual’s genome is approximately $600.

Genetic testing. That’s where it begins.

The goal is to get a person into genetic testing faster and to share that data with RNA scientists who can properly assess if this is therapeutically targetable. “My idea is to have a ‘gene board,’” Peter proposes, “that would work much like a tumor board to make these kinds of judgment calls. A way to bring physicians and scientists together — a closed-loop system.”[1]

Meanwhile, cells can be collected from the patient — skin cells, blood cells — and converted into stem cells that can be used to grow human neurons in a dish.

While scientists were originally required to use human embryos to derive pluripotent human stem cells (cells capable of becoming any human cell type), advances in science now allow the reprogramming of almost any cell type into a stem cell-like state, called induced pluripotent stem cells or iPSCs. These pluripotent cells can then be turned back into the desired cell type. In the last ten 10 to 15 years, scientists also learned that they could bypass the middle stage and go straight from skin or blood cells to neurons.

Peter emphasizes, “We’re doing more and more of that, and we can grow these neurons in a period of just a few weeks. Even though the cells are not as robust as the iPSCs, the benefit lies in shortening the time window for therapeutic development. If we can create a human model of the patient we’re seeing in a dish — right in front of us — then we can use those cells to validate molecules as possible treatments to see what effect they have before being put into a person.”

Baby steps

At first, the process will be slow from a number of perspectives: regulatory, evaluation, production, safety, and so on. “I don’t think you can expect it to be a Ferrari right out of the gate,” Peter informs. “More like a John Deere tractor. We’re probably a decade from the Ferrari, but you’re not going to get anywhere without a road. And we’ve got a lot of road-building to do.”

Peter estimates that when a gene board reviews cases and asks the question, “Is this therapeu-

[1] Michigan Medicine tumor boards are composed of multidisciplinary teams of physicians, surgeons, medical oncologists, pathologists, radiologists, and other experts who meet to discuss patient cases and come up with innovative treatment options that could save lives.

tically targetable?" most of the time the answer is going to be "no." The percentage predicted for candidates deemed obviously fixable and for whom a therapy can be rapidly developed is probably somewhere less than 5%.

"But that's 5% more than we're doing now, and represents hundreds, thousands of individuals across the country that we could potentially help," Peter expounds.

"And as we build the ability to make better and better modular molecules, we will learn how to do it right and learn new ways to interfere with and correct problems. Through additional tools such as CRISPR [clustered regularly interspaced short palindromic repeats], protein replacement strategies, or small molecule drugs, we will build up our armamentarium so that the number of people for whom this pipeline yields a meaningful therapy climbs and climbs. Probably not up to 100%, but we must figure out the ways to intervene as fast as possible, as efficiently as possible, and for as many people as possible. That should be our long-term goal."

Peter wants to position Michigan as a leader in rare and genetic disease treatment. "If you've got a rare disease, you usually end up at the University of Michigan. You'll eventually find your way to one of our specialty clinics here," he says. "You come here for transplants, for the care and expertise you just can't get anywhere else."

However, the current playing field is not level, as access to this kind of treatment is granted only to a privileged few due to the astronomical costs associated with RNA therapeutic development.

"It's inequitable," Peter says. "We need to get to a space where your entry into these novel therapies is not about your socio-economic status. We must make sure the pipeline moves just as fast for everybody."

Michigan at the ready

With the expertise in RNA science and medicine at Michigan, Peter sees a way to streamline the intake process multifold. For instance, he wants to initiate a system that would more efficiently track how many of these rare and genetic cases are being attended to at Michigan Medicine — a searchable database to help healthcare professionals identify Michigan as an expert in treating a particular disease and therefore able to move quickly in therapeutic development.

He adds that not every therapy has to be built at Michigan through an in-house pathway. The Center for RNA Biomedicine cohort of scientists and physicians collaborate not only within the university but also with investigators outside of the university and with biomedical industry partners that are also actively pursuing mRNA-based therapeutic strategies.

That network strength positions Michigan to offer advice to patients and healthcare professionals who may be restricted geographically to put them into connection with experts nearer to where they are for clinical care. Peter adds, "We can let them know if there's an ongoing trial somewhere else for that condition; or if it's something we're doing clinical trials in, then we figure out a way to get them here."

It's clear to Peter that equitable access and cost control are key to the M-RNA Therapeutics pipeline and require finesse, diplomacy, and cooperation on many levels. Aside from a requisite buy-in from the Michigan School of Medicine, he foresees any number of possible successful scenarios: a complete in-house pipeline with on-site manufacturing capabilities; collaboration with venture capitalists; partnerships with private pharmaceutical companies; or any combination of the above.

"I'm very confident that given the breadth of expertise we have here at Michigan, we can build a group of people that for each case will allow us to assess what options we have and what would be the best approach. In many cases there may not be an answer yet, but in some cases, we can move forward and do some really great things."

Todd Lab members. Courtesy of Todd Lab.

Research Highlights Introduction

To provide a glimpse into this M-RNA therapeutics engine, we spoke to a core group of the Center for RNA Biomedicine faculty members who are deeply involved in not only the research side of RNA science (the Ph.D.s) but also the clinical side (the M.D.s).

Their combined experience and knowledge represent but a mere fraction of the wealth of expertise on hand at Michigan — a small sampling of the extensive depth and breadth of RNA scientific research currently being conducted.

Several breathe rarified air, possessing both a Ph.D. and an M.D., further underscoring the degree to which Michigan is more than poised and ready to meet the growing demands of the RNA therapeutic revolution.

You'll learn a little bit about their background, their current focus of research, where they see themselves fitting in within the M-RNA Therapeutics pipeline, what excites them most about where we're headed, and a whole host of other surprises.

We also asked them, "Why Michigan?" Overwhelmingly they responded, "Expertise and collaboration," emphasizing that the aggregate of talent at Michigan is like nowhere else, with endless opportunities to team up with colleagues, representing the strength of the collective.

To that end, we divided the cohort of investigators into two groups:

Emerging Investigators

Faculty of exceptional talent who've joined the University of Michigan within the past two years

Established Explorers

Long-standing faculty members of world-renowned status who've been with the University of Michigan for 10 to 30 years and beyond

These new recruits and stalwart scholars span the gamut of research — some share similar areas of focus but have widely disparate approaches; others study varied segments of a common subject. Yet, all have the same endgame: developing RNA-based or RNA-targeted therapeutics to help people with otherwise incurable diseases live better, longer, healthier lives.

It is important to note that the moniker for each group exists only for the purpose of identifying each group by length of tenure at the university, is in no way indicative of an individual's position in their professional academic career path, and should by no means diminish any amount of strength of expertise or number of years of experience.

In the following articles, you'll discover how each of these key players contributes an immeasurable amount of insight, knowledge, and findings from years and years of painstaking research that can be translated directly into RNA therapeutic development.

Peek in the window. Journey for a moment inside just one sliver of a vast new world that offers unimaginable possibilities and breathtaking discoveries.

Read their stories.

See for yourself.

RNA 101: The Journey from Transcription to Translation

DNA, RNA, genes, proteins, amino acids, enzymes, hormones… the list goes on. In this article, we'll attempt to explain in the simplest of terms the key role ribonucleic acid, or RNA, plays in all living things. Simply put, without it, we wouldn't exist. The process is much more involved, multifaceted, and complex than what we present; however, we'll stick to the basics.

DNA molecules are found inside the nucleus of a cell, and cells are what make up all the tissues of our bodies. These molecules carry genetic information called genes. Genes need to be "expressed" in order to make proteins, which are responsible for the structure and regulation of all the tissues and organs in the body.

Gene expression involves a two-step process: transcription and translation.

During transcription, genetic information from the DNA — the genetic code — is copied into messenger RNA (mRNA). This mRNA "transcript" then leaves the nucleus, enters the cytoplasm, and attaches to a ribosome.

Ribosomes are like little factories. They make proteins. They instruct transfer RNAs (tRNAs) to "read" the genetic code from the mRNA and to start synthesizing proteins.

Genetic information in the mRNA is conveyed using the nitrogenous (that is, containing nitrogen in chemical combination) bases of RNA: adenine, cytosine, guanine, and uracil, referred to by the letters A, C, G, and U, respectively. Each group of three of these bases makes up a codon.

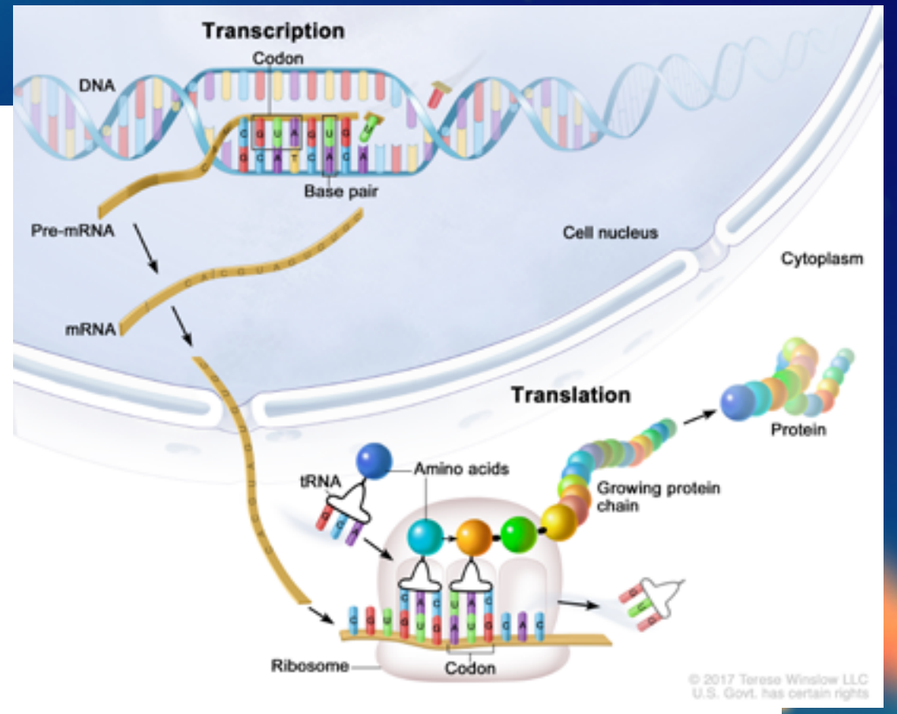
And tRNAs also have a triplet of bases at one end called an anticodon. The other end of tRNA attaches to a specific amino acid. Amino acids are the building blocks of proteins.

The tRNA then matches up with a complementary triplet base code on the mRNA, like a kind of molecular key that "unlocks" their cargo of amino acids, one after the other, in a multitude of triplet combinations.

The result is a chain of amino acids called a polypeptide or protein. Proteins then fold into distinct shapes based on and unique to their function.

The entire chain of events starts with a "launch code" consisting of three of the bases, adenine, uracil, and guanine, represented by the letters "AUG" — the initiation sequence. Hence, August 1st is known throughout the world as RNA Day. Incidentally, this miraculous process also involves a "stop code" that instructs the translation to cease.

Transcription and translation is how the genetic information is conveyed from DNA to RNA to protein. When the genetic information is incorrect, corrupted, or invalid, the trouble begins and manifests in malfunction or disease.



Schematic depicting the journey from transcription to translation. The top part of the image shows genetic information being copied into mRNA, leaving the nucleus and entering the cytoplasm. The bottom part of the image shows the mRNA attaching to a ribosome which instructs tRNA to "read" the genetic code and to start synthsizing proteins.

As you'll discover, the scientists highlighted in this publication, in concert with the entire faculty cohort at the University of Michigan Center for RNA Biomedicine, are investigating every inch and beyond along this amazing journey, from beginning to end, to find a way in — a method to intervene and correct the course when things go wrong.

Widely varied methodologies are the focus of much of their research: genetics and genomics (that is, finding which gene is responsible for carrying the faulty code); designing medicines made from RNA itself such as antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and mRNA vaccines; small molecule drugs (think aspirin, atorvastatin); and CRISPR-Cas9 (gene editing) technology.

They're even peering into non-coding RNAs (ncRNAs) — transcripts that don't translate into proteins — including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), so named because of their closed-loop as opposed to linear structure, which makes them more resistant to degrading.

These ncRNAs regulate a whole host of biological functions and likewise contribute to cancer and cardiovascular, neurological, and infectious diseases, presenting scientists with a myriad of new targets for potential RNA therapeutics.

It's a world of endless possibilities …

… and new discoveries are being made every day.

Research Highlights Part I

The Accidental Scientist, The Pioneer, The Shapeshifter, The Insightful Innovator

The Accidental Scientist

John Prensner, M.D., Ph.D.

Emerging Investigator

A day in the life of a principal investigator

When you have the distinct pleasure of meeting John Prensner, M.D., Ph.D., you will undoubtedly hear two words come up time and time again during your conversation: collaboration and interdisciplinary.

John Prensner, M.D., Ph.D., Assistant Professor of Pediatrics and Assistant Professor of Biological Chemistry, Medical School

Two words synonymous not only with his approach to work, but also with what lies at the very core of the entire University of Michigan research community ethos.

John earned both his M.D. and his Ph.D. from the University of Michigan, but his talents and interests guided him in a different direction early on in his career, which no doubt contributed immensely to his multi-dimensional, interdisciplinary approach to science and medicine.

After dabbling with — and rejecting — the idea of being a professional musician, John fell into English and literature after being locked out of courses in the Classics he yearned for his freshman year. However, reading criticisms of "Moby Dick" critics proved a venture much too deep.

John redirected his attention to history but found that reviewing diaries from victims of both world wars – albeit within the hallowed halls of the venerable Bodleian Library during study abroad at Oxford — invoked a similar gut reaction.

He'd always harbored a yen for chemistry, so he joined a chemistry lab. "I ruined reagents, snapped glass test tubes, and couldn't get reactions to work," he recalls. "I broke everything. Frankly, I don't know how they put up with me."

John liked the book science of chemistry, but not the lab science, so he resigned himself to the fact that maybe he just wasn't cut out to be a scientist.

That is, until he charted a new course for medical school at Michigan, where he zeroed in on cancer biology, which was to become his passion. An accident maybe; providence most assuredly.

Setting up camp

Fast forward: April 2023. John arrives in Ann Arbor and lays out stakes. Encouraged, moreover compelled, to return to Michigan to start his independent lab career, he shares, "Michigan is not only a large university with deep connections to clinical work as well as basic science research, but also a place where those two communities actually talk to each other."

The two-room molecular biology lab is rooted firmly adjacent to his office tucked deep within the core of the Pentagon-like Medical Sciences Research Building (MSRB) complex on the Michigan Medicine campus.

In one room, John and his team analyze and test living cells in Petri dishes *(in vitro)*, ergo a "wet" lab. Then, move to the next room and John is talking with computer coders, dissecting the nuances of genetic sequences, accordingly a "dry" lab.

Since it's relatively new, the Prensner Lab, though approved to do work in mouse models, has conducted living organism *(in vivo)* experiments only in conjunction with the Michigan Mouse Cores (see separate article, "Mouse Models").

Homing in on cancer and pediatrics

Prensner's research focuses on uncovering key factors of RNA translation that help to drive cancer, and in particular pediatric cancer. He first became interested in cancer biology during the early days of cancer genome profiling around the turn of the last century.

Throughout medical school, he saw what kinds of patient populations he might fit in with, and quickly narrowed in on his niche.

"I really appreciated working with kids. It was not only meaningful, but fun. Kids will color with you; they like to build Legos. Adults are fine, but rarely will they build Legos with you."

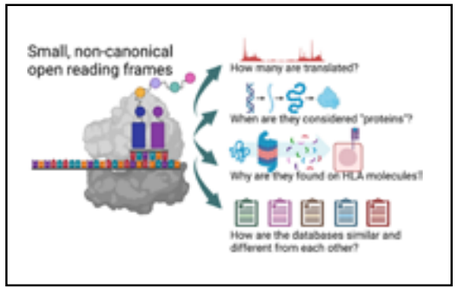
His unrivaled passion for science is outshone only by his earnest desire to use that science to help improve the lives of those suffering from an array of genetic diseases and cancer, particularly children, the most vulnerable of us all. "To clinical benefit," as he puts it.

His work entails identifying protein and microprotein targets within the nether regions of cancer cells, and developing new small molecule (for example, insulin, aspirin, antihistamines) drugs, or using existing small molecule drugs and RNA-based medicines already in use to treat other diseases, as a potential therapy.

Master of the dark proteome

In Prensner's quest to find the "ultimate disrupter" to the propagation of cancer cells in pediatric brain tumors, he's targeting an area of genomic investigation involving a hive of "worker bees" called noncanonical open reading frames (ORFs), which play a vital role in the regulation of RNA translation in the human genome. A domain oft referred to as "the dark proteome."

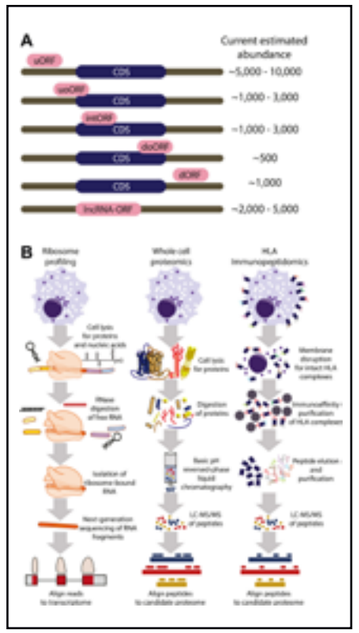
Unlike traditional mRNA sequencing (mRNA-seq) methods, which produce an approximate determination of how many RNA transcripts are present and what their structure is, Prensner's work relies on a next-generation, deep-sequencing-based tool known as ribosome profiling (Ribo-Seq), which allows Prensner and his team to identify ORFs, the select portions of RNA molecules that give rise to proteins — essentially coaxing the cell into giving up many more of its secrets.



This figure shows an overview of noncanonical ORF types and detection methods. Schematic courtesy of Prensner Lab.

Prensner hopes that this information will one day lead to improved RNA therapeutics for cancer and other diseases. However, one obstacle Prensner sees is that ribosome profiling in its current state is the "wild west" of RNA research, where few laws and regulations guide how researchers process their data. "Without clear metrics for this type of research," Prensner says, "scientists can potentially publish imprecise analyses due to a lack of best practices, which we actually already see happening in some instances."

Prensner headshot image courtesy of John Prensner, M.D., Ph.D.



This figure shows an overview of noncanonical ORF types and detection methods. Schematic courtesy of Prensner Lab.

To tackle this challenge head-on, Prensner harnessed an international team of RNA researchers and presented the results front and center in his paper, "What Can Ribo-Seq, Immunopeptidomics, and Proteomics Tell Us About the Noncanonical Proteome?," published recently in Molecular & Cellular Proteomics.[1] Working with experts in protein biology, RNA biology, and gene annotation, Prensner and the larger team codified a set of working principles that can be used to standardize how Ribo-Seq is used to find noncanonical ORFs.

Prensner and his fellow authors hope to create a roadmap for RNA researchers around the world that would lead them to perform more precise ribosome profiling and subsequently catapult this valuable tool to the top of the genomic arsenal.

Breakthrough in an aggressive pediatric brain cancer

In another research study focusing on the non-canonical ORF realm and recently published as an article in Molecular Cell, Prensner again teamed with an international contingent of investigators and discovered that a microprotein that derives from a gene called ASNSD1-uORF has a new role in cancer.

Prensner and his team found that this microprotein was essential for the survival of cancer cells in medulloblastoma, an aggressive childhood brain cancer and one of the most difficult to treat.[2]

Furthermore, the findings show the potential to use this microprotein to become a template that could target other types of genes for which finding therapies has proven difficult.

"We could place that microprotein within a molecular structure inside the cancer cells called the prefoldin-like complex, which begins operating as a unit. Then you can start exploring what kind of therapies might influence that unit as a whole."

Beyond that, this unit as a whole does a very specific thing in a cancer cell, which in the medical community is referred to as dyssynchrony. It dissociates (splits into different parts) the mechanisms cells use to produce RNA and protein. "It takes those fundamental biological processes and distorts them to its own end to breed cancer cells," Prensner states. "Is this therapeutically targetable?"

"Many of the proteins involved here are heavily involved in the cell cycle, which is itself a therapeutic target in many different contexts." The inference one could make is: Yes!

[1] What Can Ribo-Seq, Immunopeptidomics, and Proteomics Tell Us About the Noncanonical Proteome?, John R. Prensner, Jennifer G. Abelin, Leron W. Kok, Karl R. Clauser, Jonathan M. Mudge, Jorge Ruiz-Orera, Michal Bassani-Sternberg, Robert L. Moritz, Eric W. Deutsch, Sebastiaan van Heesch, Molecular & Cellular Proteomics, Volume 22, Issue 9, September 2023, 100631, DOI: 10.1016/j.mcpro.2023.100631, Publisher: Elsevier, Creative Common license, https://creativecommons.org/licenses/by/4.0/

[2] Translation of non-canonical open reading frames as a cancer cell survival mechanism in childhood medulloblastoma, Damon A. Hofman, Jorge Ruiz-Orera, Ian Yannuzzi, Rakesh Murugesan, Adam Brown, Karl R. Clauser, Alexandra L. Condurat, Jip T. van Dinter, Sem A.G. Engels, Amy Goodale, Jasper van der Lugt, Tanaz Abid, Li Wang, Kevin N. Zhou, Jayne Vogelzang, Keith L. Ligon, Timothy N. Phoenix, Jennifer A. Roth, David E. Root, Norbert Hubner, Todd R. Golub, Pratiti Bandopadhayay, Sebastiaan van Heesch, John R. Prensner, Molecular Cell, Volume 84, Issue 2, 18 January 2024, Pages 261-276.e18. DOI: 10.1016/j.molcel.2023.12.003

Two sides of the same gold coin

As an M.D. and a Ph.D., John Prensner represents an elite few whose amplitude of knowledge and expertise spans the entire spectrum from the lab to the clinic.

His degree path was in pediatric oncology. A three-year pediatrics residency was followed by a three-year hematology/oncology fellowship, then a roughly three-year period as a clinical instructor and postdoctoral fellow in the lab — cross-pollinating equally between the clinic and the lab during the clinical fellowship period. Bridging both worlds, John's widely interdisciplinary early career journey no doubt not only aided his ability to speak and understand a multitude of "languages" and assimilate easily to each new environment but also perhaps afforded him an inquisitive perspective to approach things from many distinct angles — aspects essential to critical thinking and scientific discovery.

John sees the big picture. It's an unencumbered view from 30,000 feet, evidenced by his succinct overview of the RNA therapeutics pipeline at Michigan:

"From a high level, therapeutics goals approach the topic from various angles — some closer to the clinic; some more upstream. Clinical studies of a new RNA-based or RNA-targeting medicine that's been tested in animal models and now in clinical trials lie closest to the clinic. Further upstream would be drugs that have already been approved for one treatment but are being considered to treat another disease. Still further upstream would be RNA medicines that have been developed and are being tested now on animal models. And farthest upstream would be the development of RNA medicines themselves."

This extraordinary scientist is unwittingly honored with yet another series of unofficial titles: number-one cheerleader, drum major, bell-ringer, and passionate advocate for the Center for RNA Biomedicine.

"I think science is a team sport. To take something from target to drug — single gene to therapy — you're looking at hundreds of people involved in the project, with highly variable expertise in chemistry, pharmacology, et cetera — areas outside my core knowledge. It's wonderful that there are new young faculty in the Center for RNA Biomedicine who are deeply expert in basic science and want to bring that to clinicians. That's where the collaborative aspect of science really shines forward."

Having started his attending position at the University of Michigan Hospital in 2024, John has begun seeing pediatric cancer patients at U-M, in addition to conducting pediatric cancer research. "It's so clarifying to speak with children and their families and learn about their experiences and what their needs are. It drives home our mission, gives purpose to what we do, and is a major inspiration for the research we hope to accomplish."

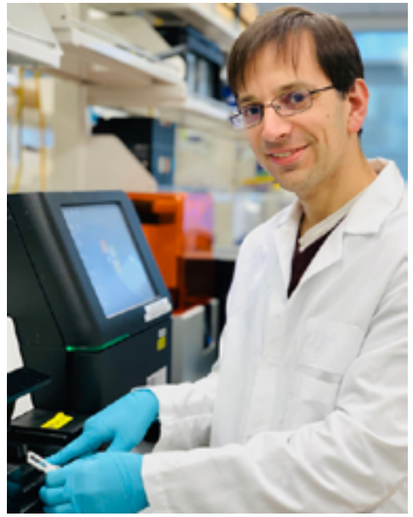


Image courtesy of John Prensner, M.D., Ph.D.

John's intel is immeasurably invaluable and a crucial component for the success of the development-to-delivery RNA therapeutics pipeline at Michigan. His innovative mindset makes John truly one of the most valuable new assets intrinsic to the core of scientists found at the Center for RNA Biomedicine and the kind of talent that sets Michigan apart.

"The center's focus on the creative, cutting-edge use of RNA therapeutics aligns well with my mission. I could even envision a possible merging with genome editing technologies, which are rapidly being developed at Michigan," John says. "I'm excited about what the future holds."

The Pioneer

Vivian Cheung, M.D.

Established Investigator

Vivian Cheung, M.D., Frederick G.L. Huetwell Professor, Department of Pediatrics, Division of Neurology; Professor, Department of Human Genetics; Research Professor, Life Sciences Institute

Vivian Cheung, M.D., is focused on finding out how RNA functions, why it needs to be "decorated" (i.e., chemically modified in myriad ways), and what the machinery for making the RNA is composed of to determine what kinds of therapeutics should be designed.

In a clinical setting, she travels regularly from Ann Arbor to Maryland to tend to children afflicted with motor neuron diseases, in particular a pediatric genetic disease similar to ALS, for her work with collaborators at the National Institutes of Health (NIH).

Then there's her day job, as she wittily puts it: sequencing of the entire human RNA, the goal of which is to create a reference point from which to build RNA therapeutic medicines faster and easier.[1] "It's just a little side project," she retorts. "It's my public service."

Vivian Cheung, M.D., Frederick G.L. Huetwell Professor, Department of Pediatrics, Division of Neurology; Professor, Department of Human Genetics; Research Professor, Life Sciences Institute, explains that RNA is more than just the letters G, U, A, and C. "If we give the body simply that, it will reject it," she states. "So RNA has decorations — more letters, maybe 50-60 — and we have to figure out the spelling."

Vivian uses the example of the U.S. Declaration of Independence. "If you only had the letters G, U, A, C," she explains, "you'd probably not be able to tell it was the Declaration of Independence. We need to find the entire sequence. We don't know what the spelling is of all the RNA, and we need to find it."

Vivian shared her idea with the National Academies of Sciences, Engineering, and Medicine, which organized a committee convened in December 2022 and meets regularly to write a consensus report that will include recommendations about how best to proceed with the project.[2]

The way drug development has worked for many years is to design chemicals that fit into a protein to stop that protein from working. Every protein has a unique shape, so it's difficult to find a way to inhibit the protein or activate the protein. "For RNA therapeutics, it's literally like Legos," she explains.

[1] Toward Sequencing and Mapping of RNA Modifications, National Academies of Sciences, Engineering, Medicine, https://www.nationalacademies.org/our-work/toward-sequencing-and-mapping-of-rna-modifications

[2] U-M researcher hopes to define the 'RNA alphabet' with support from new $2.3M grant, Michigan News, April 18, 2023. https://news.umich.edu/u-m-researcher-hopes-to-define-the-rna-alphabet-with-support-from-new-2-3m-grant/

Cheung headshot image courtesy of Vivian Cheung, M.D.

After a busy and productive day, RNome working group scientists joined Brown University and Warren Alpert Foundation leaders for dinner at the Brown Faculty Club. Photo by Adam Mastoon. Courtesy of Brown University.

"Once we figure out the spelling, have all the letters, the pieces, what shape it should be, we just put it all together. I think it will change the way that drug development will happen."

The Human RNome Project will be a massive undertaking and of a much larger magnitude than the Human Genome Project, which first sequenced human DNA in 2003. It's a collaborative effort, and Vivian is no stranger to taking the lead. "I went to the U.S. Congress to talk about RNA. I also organized the first Human RNome Working Group meeting in January in Rhode Island."[3]

Vivian also asked the NIH to put together a workshop based on the same idea.[4] She anticipated that the National Academies committee findings would be published

[3] In a 'transformative moment in medical research,' Human RNome Project launches at Brown, Phoebe Hall, Associate Director of Biomedical Communications, Division of Biology and Medicine, https://www.brown.edu/news/2024-02-08/human-rnome-project

[4] Capturing RNA Sequence and Transcript Diversity - From Technology Innovation to Clinical Application, https://www.niehs.nih.gov/news/events/pastmtg/2022/rnaworkshop2022

sometime in the first quarter of 2024, which would give her and the international consortium of scientists she's working with a clear roadmap forward.

It's difficult for Vivian to speculate how long the project will take. "The first step — figuring out the alphabet, computational structures, cells to sequence and technologies needed — should probably take us about three years or so," she reports. "In about five to 10 years I would hope we could have a draft sequence with the actual letters."

As a leading physician-scientist, Vivian is one of only 1.5% in the U.S. as of February 2022, down from 4.75% in the 1980s.[5] Her work in conjunction with the NIH allows her to see pediatric patients in the clinic and assess their conditions. She's given cells from these patients, which she can then turn into induced pluripotent stem cells in her lab and create different cell types to test whether the RNA therapeutics she develops will work on these human cells. (See separate article, "The Clinical Front, Peter Todd, M.D., Ph.D.," in the "Building the M-RNA Therapeutics Pipeline" section for more on induced pluripotent stem cells.)

She underscores how tremendously her work as a physician seeing patients in the clinic informs her research. "Being able to see the patient really helps me understand the issue," she relays. The NIH protocol covers all costs, which is a great advantage to the patient. She adds, "My commute is trivial compared to the benefit this gives to them."

"For example, we were studying the gene mutation that causes a neurodegenerative disease in children and found that the gene regulates a lot of other functions besides neurons," she relates. "About a month later, we saw a patient who had this mutation but also had other symptoms."

In the lab, Vivian and her colleagues discovered that the protein causing the neurodegenerative disease relaxes RNA, but it also increases the activity of a pathway called TGF-β — a pathway that oftentimes also increases in cancer.

Vivian recalls, "I wondered if other things that were going on may be telling us the patient may have a tumor. We were able to find the tumor and have it resected."

For Vivian, understanding the biology and being able to see the patient clinically allows her to put the two sides together. "The tumor was diagnosed early on so that no further therapy was needed," she reports. "Four, five years later, and the patient remains cancer-free."

Her work discovering the link between SARS CoV-2 and a pediatric neurodegenerative disease similar to ALS was featured in an article in the 2020 issue of RNA Translated, and she now has several RNA-based therapeutics developed from this study that she's testing on human cells.

[5] Utz PJ, Jain MK, Cheung VG, Kobilka BK, Lefkowitz R, Yamada T, Dzau VJ. Translating science to medicine: The case for physician-scientists. Sci Transl Med. 2022 Feb 16;14(632):eabg7852. https://doi.org/10.1126/scitranslmed.abg7852. Epub 2022 Feb 16. PMID: 35171650.

"We're still studying that helicase (i.e., an enzyme that helps 'unpack' DNA into RNA, like a chemical valet) which relaxes RNA, and since we have patients with mutations in that helicase, we are developing RNA medicine to silence that mutation," she reports. "We have some candidates we're testing in patient cells, control cells, motor neurons, and so on, and will hopefully get it to a point where it can be tested in the clinic."

Her project also produced an unexpected breakthrough when about a year ago Vivian and her team stumbled upon an RNA that they found controlled the regulation of a gene called APOE, identified 30 years ago as a susceptibility gene for Alzheimer's. "The control of that gene had been previously unknown," Vivian reports. "So we're hoping that this RNA can be used as a way for targeting Alzheimer's disease as a treatment."

This sets in place a continuum: childhood onset of a neurodegenerative disease to Alzheimer's later in life. It connects the dots, further fueling Vivian's research going forward.

She hopes to get these RNA candidate drugs in front of a pharmaceutical company to do the testing and manufacturing, and then get them into the arms of patients.

What's more, she would be authorized to deliver the medication that she discovered and designed directly into her pediatric patients — as an inoculation, for instance — truly personifying the full bedside-to-bench-to-bedside pipeline.

Vivian also envisions having a facility on campus to make the RNA medicine, to test it at a cell base level to make sure it really silences or activates the gene as needed, and to be able to rapidly deliver it to patients at a cost that people can afford.

In addition, Vivian would like to see a national effort to build an infrastructure that would support institutions like Michigan to make RNA medicines, and she outlined her views in a recent article in STAT News.[6]

"It's wonderful that we have a CRISPR-based treatment for sickle cell anemia, but the cost is still in the millions," she states. "It's unrealistic, so not everyone is going to be able to take advantage of it."

Vivian does not do animal testing. She conducts tests with yeast, technically a living thing, but closer to a bacterium than an animal. It's not sentient. It allows her to see how something might respond in a human body and also to see the evolutionary process. "If we see something in yeast that we also see in humans, that tells us that it's been preserved," she shares. "And yeast is much smaller and much easier to sequence."

It's just that kind of compassion — that tender mindset — that begets deep empathy. The tab for Vivian's medication alone to treat the symptoms of the rare disease that she studies amounts to approximately $20,000 a month.

"I think our goal as a public university is to find ways to make RNA therapeutics inexpensive and to be able to serve everyone and not just the few."

[6] How the government can help lower the price — not just the cost — of cutting-edge gene therapies, Vivian G. Cheung, M.D., Ph.D., STAT, November 1, 2023, https://www.statnews.com/2023/11/01/gene-therapy-rare-disease-cost-government-production/

The Shapeshifter

Guizhi (Julian) Zhu, Ph.D.

Emerging Explorer

Guizhi (Julian) Zhu, Ph.D., Ara Garo Paul Professor and Associate Professor of Pharmaceutical Sciences, College of Pharmacy

Guizhi (Julian) Zhu, Ara G. Paul Associate Professor of Pharmaceutical Science, received his doctoral degree from the University of Florida and completed postdoctoral studies at the National Institutes of Health in Bethesda, Maryland, focusing his research on nucleic acids — RNA and DNA — and their application in the tumor immunotherapy fields.

He took his first faculty position at Virginia Commonwealth University, where his interest in RNA and its use in vaccines for tumor immunotherapy and respiratory disease prevention grew.

Julian had always been aware that Michigan had one of the best pharmacy schools in the nation, having immersed himself in the robust volume of published literature produced by the faculty since graduate school, and he's thrilled with his recent faculty appointment.

"It's a lifetime opportunity for me," he relays. "It's something I never really dreamed of. I can work with my team and with collaborators around the campus to deepen and expand our study in RNA-related research."

One of those areas he's currently pursuing involves the shape of RNA, particularly circular RNA (circRNA), so named due to its circular structure, unlike conventional RNA, which has a more linear shape.

Because of their closed-ring structure, circRNAs are more stable and easier to store, making them excellent candidates for use in medicines such as therapeutics and vaccines.

"We can use circRNA in many different types of applications," Julian says. "The first is an mRNA-based application using circular-based mRNA. We design them to produce protein or peptide molecules that we hope can have some therapeutic function."

A circRNA can be designed as a tumor therapeutic vaccine to produce a protein or peptide identical to that of a cancerous tumor cell. This vaccine can essentially train the host's immune system to recognize the tumor's molecular identity, and then the trained immune system will recognize the tumor cells, attack, and kill them.

"For non-vaccine uses, we can design a circRNA to express a protein or peptide that can have another therapeutic function," Julian reports. "We're working on a project to use circRNA to express a functional protein to replace a dysfunctional protein in patients with genetic diseases, which we're now testing in animal models."

Julian's overarching idea is to deliver a message to human cells in the body so that they can produce a functional protein and bring that physiological function back to normal.

A similar approach Julian is exploring involves using circRNA to directly produce protein or peptide drugs in the body, essentially turning the body into its own molecular factory.

"Small molecule drugs, and even RNA-based medicines, break down quickly in the body, so patients need to take them regularly, or even daily," Julian reports. "Because circRNAs are more stable, the cells will continue to produce proteins or peptides for a longer period. So with this molecular factory, a patient might need to take the drug only once a week. That's a big advantage for the patient."

"We're also involved in a project to use circRNA as a guide RNA (gRNA) that can be used for gene editing," Julian says. "We've seen good results, and it seems to work better than the current established linear gRNA."

Pharmacokinetics is the study of how a substance such as a drug is distributed throughout the body during the drug's lifespan. Studying circRNAs in animal models, Julian has used small animals such as mice but explains that larger animals better resemble the pharmacokinetics of the human body. And different animal sizes have different profiles, which is also significant.

Julian explains, "An advantage of using larger animals is that for some disease models, larger animals can resemble the phenotype and pathology of human disease better than small animals. One drawback is the cost. They're more expensive to use. So it's common practice to use small animals, and more importantly, limit the use of animal models as much as possible."

The delivery of the RNA therapeutic molecules Julian designs has always been an integral part of his research — the "twin brother" of his research, as he calls it. "We have a few research projects to develop delivery approaches that could outperform current delivery systems that are not efficient," he adds.

In other applications, Julian is exploring ways to deliver RNA therapeutics that could target lung disease into the lungs safely and effectively. He states, "They could also be used to elicit a type of immunity called mucosal immunity to prevent respiratory infections such as COVID or flu."

Julian hopes to push his research further and further toward clinical translation. To that end, he's forged connections with colleagues throughout Michigan Medicine. "I've been working on a few projects with cardiovascular researcher Eugene Chen," he says, "and we've started collaborations with Dr. James Moon in pharmaceutical sciences."

Julian is also applying his research with circRNA to two current projects involving COVID-19 and flu. He notes, "The past few decades have seen incredible progress in the pharmaceutics field, particularly in our research area of RNA-related therapeutics."

"CircRNA has some very interesting properties and can be used as a broadly applicable platform to make existing RNA therapeutics work better and some experimental ones work. There's a tremendous opportunity to advance the entire field over the next few years."

Zhu headshot image courtesy of Guizhi (Julian) Zhu, Ph.D.

The Insightful Innovator

Rajesh Rao, M.D.

Established Investigator

Rajesh Rao, M.D., Leonard G. Miller Professor of Ophthalmology and Visual Sciences, Associate Professor of Ophthalmology and Visual Sciences, Associate Professor of Pathology and Associate Professor of Human Genetics, Medical School

Rajesh Rao, M.D., is a physician who sees patients with retinal problems regularly, treating them in the clinic and also performing retinal surgery. He's currently leading a first-in-human clinical trial on age-related macular degeneration (AMD), a retinal disease that can cause severe loss of eyesight, at University of Michigan Health Kellogg Eye Center.[1]

But that's not nearly the end of his story.

Dr. Rao is a scientist. A physician-scientist who has dedicated years of research studying the role of RNA in retinal development. Dr. Rao and his team are trying to find out why the retina does not develop properly, the mechanisms behind that, and to answer the larger question: How exactly is RNA involved in retinal development?

The methylation of RNA appears to be a smoking gun.

RNA methylation is a modification to RNA that happens during transcription and that regulates gene expression through modulating RNA metabolism as well as protein translation. A small "methyl group" (i.e., a chemical group) molecule is added to the RNA while it is being transcribed and helps determine that cell's function — think of it as another layer of gene regulation. Taken together, these chemically modified RNAs are known as the "epitranscriptome."

"The proteins that control RNA methylation are very important to properly make a tissue," Rao says. "Without RNA-methylating proteins, the retina is not properly made." Rao is studying the major RNA methylating enzyme, METTL3, as a key driver of retinal development.

In his lab at the Kellogg Eye Center, he and his team use pluripotent stem-cell-derived organoids to model certain diseases and better understand RNA methylation's influence on retinal formation.[2] The process involves collecting a patient's skin or blood cells, reprogramming them down into induced pluripotent stem

Opposite: Dr. Rajesh Rao's organoid research and first-in-human clinical trial for dry macular degeneration with neural stem cells was featured as a full page ad by Michigan Medicine in the official Rose Bowl Program.

[1] Finding new hope for people with vision loss. Michigan Medicine, Michigan Answers, December 7, 2022. https://www.michiganmedicine.org/michigan-answers/dr-raos-michigan-answer-finding-new-hope-people-vision-loss

[2] The modern term organoid refers to cells growing in a defined three-dimensional (3D) environment in vitro to form clusters of cells that self-organize and differentiate into functional cell types, recapitulating the structure and function of an organ *in vivo* (hence, also called "mini-organs"). Jensen KB, Little MH. Organoids are not organs: Sources of variation and misinformation in organoid biology. Stem Cell Reports. 2023 Jun 13;18(6):1255-1270. doi: 10.1016/j.stemcr.2023.05.009. PMID: 37315519; PMCID: PMC10277837.

Image courtesy of Rajesh Rao, M.D.

cells (iPSCs), then making them into retinal cells in a dish inside the lab. However, this methodology is not without its challenges. Rao admits, "They're very finicky. You have to coax them [iPSCs] very gently to make exactly the type of cells you want — in our case, retinal cells."

These organoids represent a phase of development in the retina and supply enough retinal cells that Rao and his team can study. "We study how METTL3 sits at the nexus of the epigenome (i.e., chemical modifications in chromatin, comprised of DNA and histones) and the epitranscriptome. When METTL3 is disturbed, changes to the epigenome and epitranscriptome occur that can lead to too much or too little of a protein. This can cause problems down the road, and the organ does not properly form," Dr. Rao says. It was through these organoid studies that he found that the methylation of RNA was vitally necessary for stem cells to become retinal organoids, and that's how he was able to zero in on that specific layer of regulation.

Dr. Rao adds, "Stem cells and their organoids are used to understand development, to model disease, to produce lost cell types in disease for cell therapy trials. Finding out how exactly METTL3 and RNA methylation are required for stem cells to make organoids will help us better apply scientific and medical applications of stem cells and organoids."

In addition to organoid studies, Dr. Rao is also currently working with the U-M Transgenic Animal Model Core to create a mouse line to further investigate RNA methylation in retinal development. Studying mouse eyes has some benefits since they share some key characteristics, but not all, with human eyes.

These "knockout" mouse models edit the genome by genetically removing the "business end" of METTL3, so that the gene gets transcribed, but the resulting protein cannot methylate RNA anymore. Dr. Rao explains, "In science, generally speaking, you don't know if something is a correlation or a cause. If we knock out a gene and something happens, then we would know it's a cause."

Dr. Rao is currently focused on mechanisms that are shared across individuals rather than mutations that are specific to one individual, for instance. He's looking at the general root of the problem first and intends to turn to individual genetic mutations further down the road.

"If we approach something from a perspective of focusing on a specific disease, it's important for us to know what the genetic mutation is," he says. "We'll want to get cells from persons and look at the changes in the genome of that person, such as DNA alterations, mutations, and copy number alterations."

Kellogg Eye Center, University of Michigan, Ann Arbor

For Dr. Rao, collaboration is essential to his work. He recently teamed with CRB Clinical Director Peter Todd, M.D., Ph.D., who helped him look at the RNA stability of the METTL3 gene. Dr. Rao also works closely with U-M Bioinformatics to help analyze the robust amount of data generated from his experiments. In addition, Dr. Rao holds joint appointments in Human Pathology and Human Genetics, which provide numerous opportunities to connect.

Outside of the RNA methylation project, Dr. Rao is also involved in a collaborative effort with a group of researchers at Ege University in Turkey as part of a $10,000 U-M Global REACH Partnership Development Grant. The study involves a child with Strømme Syndrome, an incredibly rare disease that causes issues with the brain, intestines, and eyes.

Dr. Rao and his team recently acquired skin cells from the patient — a year-long process — and reprogrammed them into iPSCs to study in a dish. They plan to grow them into retinal organoids to determine why a mutation in a specific gene, CENPF — an abundant gene in retinal development — disrupts this process and to understand the mechanisms at play in Strømme Syndrome. They are currently in the process of securing additional funding to assist them in continuing the project.

Before Dr. Rao specialized in the eye, he worked in neurology, specifically the brain. During the development of the neural tube, the same cells give rise to the brain, spinal cord, and retina. Strømme Syndrome patients also have problems with the brain, even more often than with the eye. Although his work currently focuses on the retina, he could provide valuable input as a member of the "gene board" Dr. Todd proposes, which would help identify candidates for whom an RNA therapeutic might be developed.

Dr. Rao remains optimistic about the open frontier that lies ahead but outlines the need to set the "ground rules" that govern RNA methylation-specific processes involved in eye formation. Those fundamental insights need to be made before translational efforts, such as therapeutics based on RNA methylation, can be applied. "A lot of people study the gene, a lot of people study the protein, and until recently due to attention garnered from the COVID-19 vaccine, RNA hasn't been as classically popular to study," he explains. "It's a less studied area of science, especially in the vision field.

Dr. Rao with his Ege University colleagues. From left: Esra Isik, Rao, Ferda Ozkinay, and Tahir Atik. Photo courtesy of Rajesh Rao, M.D.

"It's exciting to be in the early days in a field, exploring a layer that most people in vision science and blinding diseases aren't looking at, learning the fundamental rules, and gaining insight into the making of the eye, what RNA methylation controls, and what the implications might be. Will it be a biomarker for a diagnostic or key pathway for a disease for which a therapeutic might be developed? Right now, it's the 'Wild West' of ophthalmology."

Making Headlines

Nobel Prize Awarded to 2024 RNA Symposium Keynote Speaker Dr. Drew Weissman

The Nobel Prize medal

October 2, 2023 | Stockholm, Sweden

The Nobel Assembly at the Karolinska Institutet awarded the 2023 Nobel Prize in Physiology or Medicine jointly to Katalin Karikó and Drew Weissman.

Drew Weissman, M.D., Ph.D., will be featured as a keynote speaker at the Center for RNA Biomedicine's 8th annual RNA Symposium in March 2024 at the University of Michigan. He currently serves as the Director of the Penn Institute for RNA Innovation and is a leading physician and researcher at Penn Medicine.

The Nobel Committee recognized Dr. Weissman and Dr. Karikó for their groundbreaking research with dendritic cell inflammatory response to mRNA focused on how base modifications both reduced inflammatory responses and increased protein production, essentially paving the way for rapid development of base-modified mRNA vaccines to combat the SARS-CoV-2 virus that causes COVID-19.

Drew Weissman after receiving his Nobel Prize.

"The unexpectedly swift emergence of life-saving mRNA vaccines was based on many prior decades of dedication by a few visionary researchers, two of whom were honored today. This advent poises RNA therapeutics to rapidly realign the pharmaceutical and biotech industries and take over much of the current biologics market, justifying a Nobel Prize to be given now." — Nils Walter, Ph.D.

Katalin Karikó

Drew Weissman

Like many laureates before him, Drew Weissman signed a chair at the laureates' get-together at the Nobel Prize Museum in Stockholm.

Drew Weissman receiving his Nobel Prize from H.M. King Carl XVI Gustaf of Sweden at Konserthuset Stockholm.

Medicine laureate Katalin Karikó with her donation to the Nobel Prize Museum — her favorite pipette.

The implications of this historic bestowment of the Nobel Prize to RNA researchers are far-reaching. The endorsement not only underscores the significant contribution made by RNA discoveries on a global scale to greatly mitigate a raging epidemic but more than likely ensures that much-deserved attention and subsequent funding are directed toward RNA therapeutics — now more than ever poised to become the future in treating disease.

"The groundbreaking work by Drs. Kariko and Weissman is making the RNA therapeutic revolution in medicine possible. Walter Isaacson, the author of the book, 'The Code Breaker,' suggested that the CRISPR and RNA therapeutic revolution that we are now standing in front of will be a thousandfold more beneficial to mankind than the digital revolution. The Nobel committee in Stockholm appears to agree." — Mats Ljungman, Ph.D.

Research Highlights Part II

The Deliverer, The Brain

The Deliverer

Alexandra Piotrowski-Daspit, Ph.D.

Emerging Explorer

Alexandra Piotrowski-Daspit, Ph.D., Assistant Professor of Biomedical Engineering and Assistant Professor of Internal Medicine, Medical School

Alexandra Piotrowski-Daspit, Ph.D., Assistant Professor, Biomedical Engineering, Assistant Professor, Internal Medicine — Pulmonary and Critical Care Medicine Division, has an S.B. in Chemical-Biological Engineering and Biology from the Massachusetts Institute of Technology (MIT) and master's and Ph.D. degrees in Chemical and Biological Engineering from Princeton University. She also trained as a Postdoctoral Fellow in Biomedical Engineering at Yale University.

Alexandra is focused on engineering polymeric nanoparticles for nucleic acid delivery. In her research, she seeks to develop biodegradable and biocompatible materials that would be ideal delivery vehicles for RNA or other nucleic acid therapeutics to "hitch a ride" on.

"I think of them as protectors and guides of precious cargo," she says. Alexandra designs these nanoscopic messengers with two goals in mind: to protect the "cargo" from degradation, and to get the cargo to its intended destination without accumulating in any off-target locations.

To introduce these nanoparticles into the body — technically termed "delivery" — Alexandra is focused mostly on intravenous and systemic pathways, such as injecting them into a patient via a syringe into the vein, very much like getting blood drawn.

But she's also exploring another method, direct delivery to the lungs, by designing nanoparticles that are inhaled. In a recent study, she was part of a team that investigated the translational potential of inhalable platforms for messenger RNA (mRNA) therapeutics, with findings published in an article in Science Translational Medicine.[1]

"In the context of lung delivery, you'd want to develop a vehicle that has a tropism (i.e., an affinity) for the lung and specific cell types within the lung," she relates. "Diseases differ in their target cell types — epithelial cells, basal cells — so you have to factor that into the design."

Each delivery route into the body presents its own set of challenges, but overcoming barriers to delivery inside the body (*in vivo*) — such as the immune system and architecturally-based obstacles — adds another set of hurdles to jump. "It's a complex problem," she reports. "Once you get to the cell or cell type, you are confronted with an additional set of intracellular barriers.

"We want to understand what the structural-function relationships are that dictate how the polymer-based delivery vehicles behave in the body."

To do that, Alexandra and her team study polymer chemistry and nanoparticle characteristics to determine what the most influential factors are in guiding these vehicles inside the host. "We're also looking at the bigger picture," Alexandra adds. "We're always thinking of developing processes that will be easier to scale up to eventually get these therapeutics into patients."

The process from start to finish begins with Alexandra and her team manufacturing the polymer materials in-house, utilizing a space in her lab dedicated solely to that purpose. They formulate those into nanoparticles, administer them *in vivo* in research animals, then track where they go using fluorescent dye or a reporter nucleic acid.

"We're also building computational models," Alexandra shares. "We use the data from our biodistribution studies to better predict what design features are most important and what characteristics to tweak that will get us closer to our goal of delivering to a specific target tissue or cell type."

Alexandra sees advanced technology also playing an integral role in the process of optimizing delivery vehicles. "AI and machine learning could definitely be useful with this and all aspects of developing a therapeutic that goes from discovery to the clinic."

Another thrust of the Alexandra Piotrowski-Daspit Lab is creating "decoy" modulations and formulations to enhance the biodistribution of a nanoparticle that might be good at carrying the cargo but not so great at finding its target.

Alexandra's students in the lab. Image courtesy of Alexandra Piotrowski-Daspit, Ph.D.

The body has innate mechanisms such as phagocytes (i.e., cells that engulf or absorb bacteria, small cells, and particles) that consume foreign matter. "The idea is to prime the system to allow for more widespread delivery of a therapeutic nanoparticle," she says.

Like a magician who wields prestidigitation to misdirect an audience elsewhere whilst he performs his illusion, these decoys would distract and pre-occupy the phagocytes, allowing free passage for the therapeutic nanoparticles to continue on their mission to their target unperturbed.

Alexandra is also currently working on a project in collaboration with Rachel Niederer, Michelle Hastings, and Wren Michaels. The cohort was awarded

[1] Polymer nanoparticles deliver mRNA to the lung for mucosal vaccination, Suberi, Alexandra; Grun, Molly K.; Mao, Tianyang; Israelow, Benjamin; Reschke, Melanie; Grundler, Julian; Akhtar, Laiba; Lee, Teresa; Shin, Kwangsoo; Piotrowski-Daspit, Alexandra S.; Homer, Robert J.; Iwasaki, Akiko; Suh, Hee-Won; Saltzman, W. Mark, Science Translational Medicine, 16 Aug 2023, Vol 15, Issue 709, https://doi.org/10.1126/scitranslmed.abq0603

Piotrowski-Daspit headshot image courtesy of Alexandra Piotrowski-Daspit, Ph.D.

a $3 million Collaborative Research Grant from the Cystic Fibrosis Foundation to find RNA therapeutics for cystic fibrosis.

Cystic fibrosis mostly affects the lungs, but it also impacts the gastrointestinal tract as well, presenting a unique challenge for Alexandra and her team. “We are focused on designing nanoparticles that could ultimately target both areas,” she reports. “We’re setting our sights high to solve that problem, or at least contribute to solving that problem.”

Alexandra currently procures RNA therapeutics that are readily available from several companies to test in her delivery vehicles. For the cystic fibrosis project, Michelle Hastings would provide Alexandra with antisense oligonucleotides (ASO molecules) which Alexandra and her team would encapsulate in their nanoparticles.

“I’m looking forward to working with this great team of scientists that have complementary expertise to develop therapeutics for cystic fibrosis,” Alexandra says. “Michelle specializes in designing ASOs, so it’ll be our first time working with someone who knows how to optimize the cargo for maximum efficiency. She has also been a wonderful mentor to me personally!”

“Rachel can help us understand the factors that dictate the translational output of mRNA. Working with this highly skilled team of women is really a dream scenario.”

There are a lot of steps to scaling up the production of nanoparticles so that they can be administered safely in a clinical setting, the ultimate goal of Alexandra’s work. “We have many resources here at the university, including Innovation Partnerships right down the hall from our lab, that could provide eventual start-up incubator space for this kind of work if we are successful,” she shares.

“Everyone is so welcoming here. U-M is a great environment for the kind of interdisciplinary collaborations needed to solve complex problems like developing RNA therapeutics. It’s one of the things that attracted me to this institution when choosing where I wanted to pursue my faculty career. The College of Engineering and the Medical School are both strong. I’m a chemical engineer researching in the biomedical arena, so I’m excited to be at Michigan!”

CYSTIC FIBROSIS FOUNDATION®

The mission of the Cystic Fibrosis Foundation is to cure cystic fibrosis 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/

Cystic fibrosis is a rare, progressive, genetic disease that affects the lungs, pancreas, and other organs. The disease can affect people from any racial or ethnic group. The work being done at the University of Michigan Center for RNA Biomedicine helps progress the Foundation’s quest to cure CF. 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 www.cff.org/researchers/academic-funding-opportunities

The Brain

Maria Castro, Ph.D.

Established Investigator

Maria Castro’s office feels like command central, a den of deep, deep knowledge, stacked floor to ceiling with papers, books, publications, and all manner of interesting and intricate things. It bestows the impression of being inside the brain of a brilliant, benevolent master puppeteer.

Maria Castro., Ph.D., R. C. Schneider Collegiate Professor, Professor of Neurosurgery, Professor of Cell and Developmental Biology and Co-Director, Brain Tumor Research and Translational Neuro-Oncology Laboratories, Medical School

Maria Castro, Ph.D., Richard C. Schneider Collegiate Professor of Neurosurgery; Professor, Cell and Developmental Biology, sits comfortably surrounded by years and years of hard work on display for all to see, not tucked away neatly in some 1950s ferrous filing cabinet or dusky desk drawer. It’s homey. A cool mist humidifier is running. It’s not in the least bit intimidating but rather gives one the feeling of safety and security to be amidst such a bounty of accomplishments.

Maria and her research partner Pedro Lowenstein, M.D., Ph.D., Richard C. Schneider Collegiate Professor of Neurosurgery; Professor, Cell and Developmental Biology, work side-by-side in the Castro-Lowenstein Lab studying lower grade gliomas — cancers of the brain — and glioblastoma, a malignant and highly aggressive form of the brain tumor.

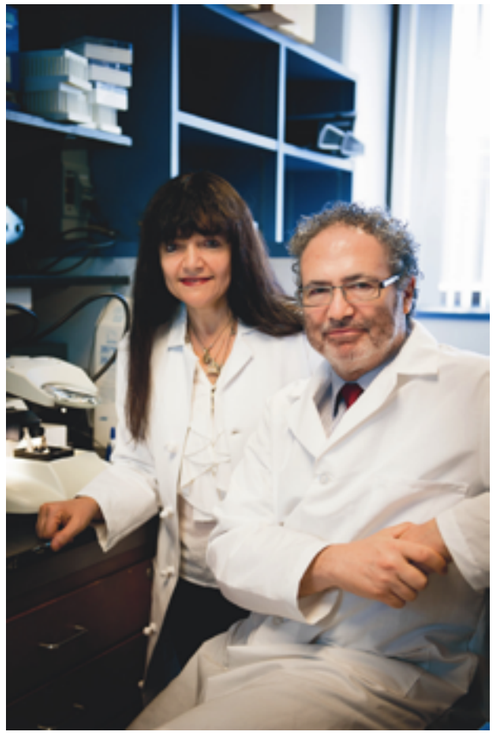
Brain cancer is heterogeneous, in that the disease in one patient is completely different in another patient, even though the symptoms may be the same. Furthermore, different areas of a tumor are very dissimilar to each other, which makes finding the right treatment a challenge.

Furthermore, tumors typically hijack the immune system, so the body doesn’t know there’s a foreign object there to attack. Maria and her team postulated that the immune system could be reprogrammed to attack cancer cells when they start to grow back.

Maria also found that brain tumors have a lot of networks, but some areas are “hubs” that seem to be very central and critical to their survival. Maria explains, “It’s like the London Tube or NYC subway. It’s a network of stations and hubs. If you remove a station, you can bypass it easily. But if you remove a hub, you obliterate the system.”

Maria and her colleagues discovered that if you target one of those hubs, you halt tumor progression. “We introduced a molecule of small interfering RNA (siRNA) that will block the RNA transcription factor machinery,” Maria reports. “We worked with another center member, Joerg Lahann, Ph.D., who packaged the siRNA in nanoparticles with homing mechanisms on their surfaces to enable them to home in on the correct target.”

Castro headshot image courtesy of Maria Castro, Ph.D.



Maria Castro, Ph.D., with Pedro Lowenstein, Ph.D., Richard Schneider Collegiate Professor, Assistant Chair, DEI in Research, Professor of Neurosurgery, Professor of Cell and Developmental Biology, Co-Director, Translational Neuro-Oncology Laboratories, Medical School

These nanoparticles were injected intravenously — a systemic delivery —and eventually made their way to the brain and the tumor to block that hub. The results were impressive. Tumor growth was blocked, and many animals were cured, but the real boon was that an immunological memory was elicited. Maria reports, "This was an astounding breakthrough!"

She adds, "The primary tumor often doesn't kill the patient. The neurosurgeon removes it. The patients are usually healthy for a year and a half to two years, but then the tumor grows back, often near to the site of the original tumor or even in other distant parts of the brain. So, the key is to train the immune system to recognize the tumor so that if the tumor starts to come back, the immune system will attack and kill those tumor cells."

"We delivered another tumor in mice on the other side of the brain from the original tumor, and the immune system — trained to recognize that tumor — eliminated it."

Animal models, mouse models in particular, play a large role in her research because of their competent immune system response, which is similar to that of a human and cannot be replicated in a dish, in organoids for example. You need a living host to test the immune reaction and responses. "We have a phenomenal animal model platform unique to our team," Maria relays. "We have requests from all over the world to distribute this model." (See "Rajesh Rao, M.D." in "Research Highlights Part I" for more on organoids.)

The animals are escorted with great care from their housing quarters to and from the Unit for Laboratory Animal Medicine (ULAM) by one of Maria's lab members who conduct some tests there. There are also some tests that they have to conduct in the ULAM. "All the experimental animals reside at ULAM. They do not live in the lab," Maria reports. "The animals are treated very ethically and humanely under very stringent guidelines." (See separate article, "Mouse Models.")

The team's success led to further research and the development of a combination gene therapy involving the immune-boosting component combined with a cytotoxic (i.e., cell poison or cancer-killing) agent, which proved to be effective and safe in animal models.

Generous funding from the National Institute for Neurological Disorders and Stroke, the National Cancer Institute, the National Institutes of Health, The Phase One Foundation, and others allowed Maria, Pedro Lowenstein and the whole team to progress to a first-in-human Phase 1 clinical trial conducted at the University of Michigan over a six-year period, and the results were published in an article in The Lancet Oncology in September 2023.[1] Maria and Pedro proved that the treatment was safe and that their hypothesis was correct. Two viral vectors (that is, virus vehicles) encoding for therapeutic genes killed cancer cells and extended patients' lives from three years in three patients to up to five years in one particular case, which is significant given the current life expectancy of 14 months.

The genetic therapy works in two parts. The first is a combination of a protein, HSV-1-TX, and Valtrex, an antiviral drug, which turned into a cytotoxic compound that killed actively dividing cancer cells. The second is the protein Flt3L, which summons the body's essential immune cells to the brain. So the therapeutic payloads piggyback on viruses whose disease-causing mechanisms have been disabled.

"We're very excited because the trial serves as a blueprint to greenlight the therapy for use in treating other diseases and other tumor types," Maria reports. "We're talking with pediatric neuro-oncologists about implementing a trial because a similar glioblastoma — also lethal — grows in children."

She's also exploring other siRNAs and combining other chemotherapeutic drugs, and recently talked with M-RNA Therapeutics Director Michelle Hastings, Ph.D., about how to deliver antisense oligonucleotide (ASOs) to the brain and develop an oligo-based platform to stop some of the growth pathways in the tumors. "We just don't know what's going to work best," Maria adds.

[1] Combined cytotoxic and immune-stimulatory gene therapy for primary adult high-grade glioma: a phase 1, first-in-human trial, Yoshie Umemura, Daniel Orringer, Larry Junck, Maria L Varela, Molly E J West, Syed M Faisal, Andrea Comba, Jason Heth, Oren Sagher, Denise Leung, Aaron Mammoser, Shawn Hervey-Jumper, Daniel Zamler, Viveka N Yadav, Patrick Dunn, Wajd Al-Holou, Todd Hollon, Michelle M Kim, Daniel R Wahl, Sandra Camelo-Piragua, Andrew P Lieberman, Sriram Venneti, Paul McKeever, Theodore Lawrence, Ryo Kurokawa, Karen Sagher, David Altshuler, Lili Zhao, Karin Muraszko, Maria G Castro, Pedro R Lowenstein, Lancet Oncol. 2023 Sep;24(9):1042-1052. DOI:https://doi.org/10.1016/S1470-2045(23)00347-9. Erratum in: Lancet Oncol. 2023 Oct;24(10):e405. PMID: 37657463.

Maria advocates for a multipronged approach to treating cancer and foresees an entire arsenal of different RNA molecules that might work together to combat the disease, similar to a cocktail of drugs prescribed to treat HIV infection.

"We also interrogate these tumors at the 'omics' level, so we know which pathways go up, which go down, and how the tumor cells are talking to the immune cells," Maria says. "So we could interfere with different pathways at the same time, one with siRNA, one with an ASO, or even an ASO that would modify the immune cells to go from immune-suppressing to immune-activating. There are a lot of possibilities."

Maria also sees the possibility of an mRNA vaccine being developed for glioblastoma. Once the tumor is removed, and the danger lies in the cells of cancer that remain on the periphery of that tumor, that's where the threat for regrowth is high. She relays, "With a vaccine, it would train the immune system to go after those cancer cells and get the immune system to destroy them, essentially curing the cancer.

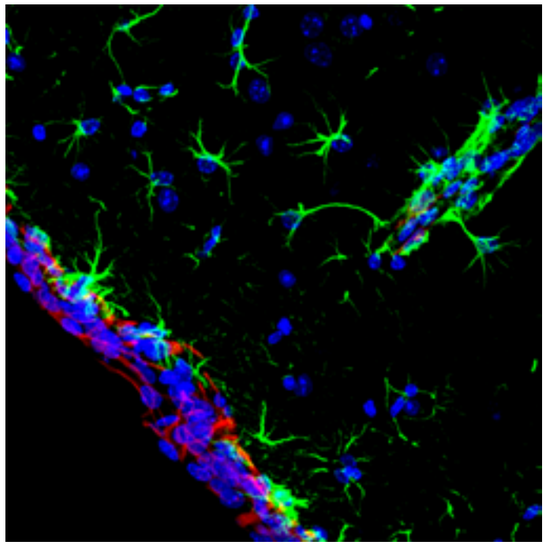


Image courtesy of Maria Castro, Ph.D., and the Castro-Lowenstein Lab.

"And if any new cancer cells show up in the future, the immune system would be triggered once again, and those recurrent cancer cells will be killed as well. We know which targets to develop vaccines against. So if there's someone within the center who has the technology, we could work together to develop RNA vaccines for brain cancer — that would be amazing!"

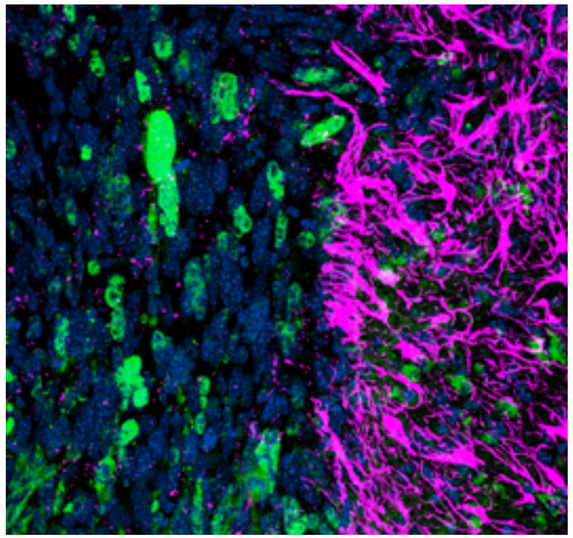


Image courtesy of Maria Castro, Ph.D., and the Castro-Lowenstein Lab.

For the next phase, Maria and her colleagues are thinking of using a combination of therapies. Cancer tamps down the immune system at areas called immune checkpoints. One area they're looking at is an immune checkpoint blockade approach in conjunction with their viral therapy to help unblock the immune system so that it will work much better.

Maria also developed a particular lower-grade glioma in animal models, which in human patients eventually turns into a glioblastoma, the stage-four aggressive cancer. The animal models uncovered that, just like in the human patients, two different glioma types manifested; one was aggressive, and the other was much slower growing. In patients, the aggressive GBM is fatal in two years, while patients with the less aggressive glioma can live up to 10 years.

Individuals who had the slower-growing, less aggressive type of cancer had a certain compound, G-CSF, that stimulates their immune system. "We found that it's the same substance given to chemotherapy and radiation therapy patients to help restore their immune systems," Maria states. "We discovered that if they gave that compound to the people with the more aggressive type, it slowed the growth of their brain cancer."

Maria discovered this by examining the RNAs that were being synthesized by these tumors. "We saw that a particular RNA was very high," she relates. "We looked at the protein the RNA makes, which was also very high. We looked at the mouse models, then at the human patients, and saw that the particular protein level was very high in the blood, and we had our target."

Maria, Pedro, and their team want to bring this new discovery to the clinic and are currently working on a multi-institutional grant including the University of California, Irvine; UCSD; UCLA; Harvard; and U-M to make that happen, hopefully within a year.

Maria explains the advantage of being at a university like Michigan with an integrated teaching hospital and being housed within the Department of Neurosurgery: "We get all the samples from any surgeries that are done on human patients — tissue from brain tumors, blood — and we can study them, study the immune cells, in the lab. We match what we find in the mouse models with what we find in the human patients, and then we can do the trials here as well. It's a powerful setup — the perfect storm."

Another benefit is that the pharmaceutical industry is not interested in pursuing therapies for glioblastoma since unlike lung or breast cancer, it is relatively rare, and therefore, in their eyes, not financially worthwhile. "It's a phenomenal niche for academia because big pharmaceuticals won't touch it, and you have little competition," Maria says.

Maria looks to the future with great optimism but cautions that we must relearn the art of interpersonal interactions, much of which was lost during the COVID-19 epidemic. "Things happen within a conversation," she affirms.

Maria sees tremendous potential for the Center for RNA Biomedicine. "It's the discovery part that really excites me!" she exclaims. "Why does this cancer want to grow back? It's like having a little black box. You don't know what it is, but you want to find out all about it. And finding ways to stop that from happening.

"Other members of the center are far more excited about the application part, and that's good, so it's important to share information and ideas — to get together. Great things are going to arise from these kinds of fluid interactions — the sky's the limit."

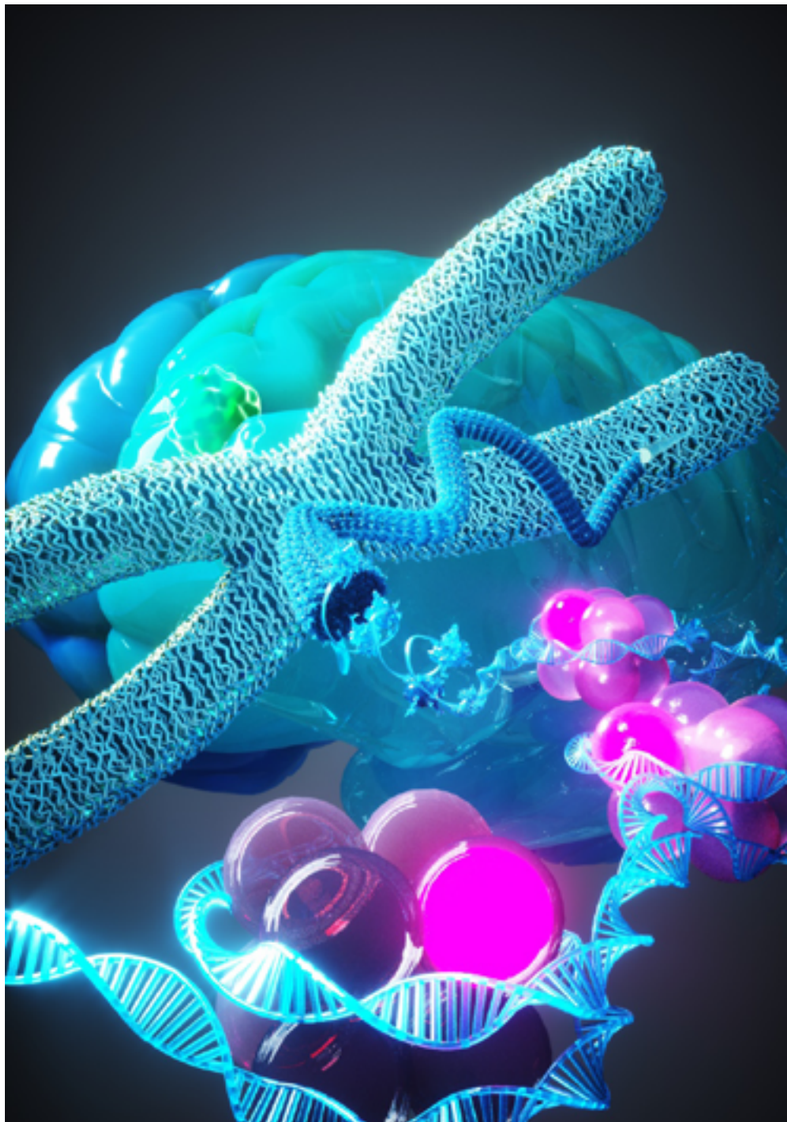


Image courtesy of Maria Castro, Ph.D., and the Castro-Lowenstein Lab.

PIs in the Spotlight

Dateline: 2023, The White House

President Joe Biden leads the applause for Huda Akil at a White House ceremony announcing her as a recipient of the National Medal of Science. (Photo by Ryan K. Morris and the National Science and Technology Medals Foundation)

Huda Akil, Ph.D.

Huda Akil, Ph.D., Research Professor, Michigan Neuroscience Institute, Gardner C. Quarton Distinguished University Professor of Neurosciences, Department of Psychiatry

October 24, 2023, the White House: In a formal ceremony presided over by President Biden, Huda Akil, Ph.D. — longstanding member of the Center for RNA Biomedicine faculty — is honored with the National Medal of Science Award, the nation's highest scientific honor.

Dr. Akil's research focuses on understanding the neurobiology of emotions, including pain, anxiety, depression, and substance abuse, and she is passionate about developing ways to potentially thwart symptom onset.

Identifying genetic and cell differences that could lead to a predisposition to substance abuse, for example, is at the heart of her research — a first step in developing a therapeutic medicine, such as that manufactured from RNA, to regulate expression of those identified markers and help minimize risk.

A true University of Michigan Pioneer!

Monica Dus, Ph.D.

Monica Dus, Ph.D., Associate Professor in the Department of Molecular, Cellular, and Developmental Biology, Michigan Neuroscience Institute

September 20, 2023, the White House: Center for RNA Biomedicine Faculty Member, Monica Dus, Ph.D., is selected as a 2023-2024 White House Fellow.

Founded in 1964, the White House Fellows program — one of the nation's most prestigious for public service — offers an opportunity for emerging leaders to work at the highest levels of federal government.

Dus' research centers on how dietary nutrients impact gene expression as well as the interaction of food, genes, and the brain and how this interaction influences health and disease.

Dus was placed with the Department of the Navy and sworn in by Secretary of the Navy Carols Del Toro, an alumnus of the program, and will serve for a year.

Congratulations, Monica!

Akil headshot image courtesy Huda Akil, Ph.D.
Dus headshot image courtesy Monica Dus, Ph.D.

Research Highlights Part III

The AI Architect, The Culture Broker, The Mathematician

The AI Architect

Geoffrey Siwo, Ph.D.
Emerging Explorer

Geoffrey Siwo, Ph.D., Research Assistant Professor, Department of Learning Health Sciences; Research Associate, Michigan Center for Global Health Equity

An AI architect in the making

Artificial Intelligence. AI. Two words and two initials that evoke fascination for some and horror for others. Is Cyberdyne Systems here? Is Skynet upon us? Should we expect the Terminator anytime soon? The Borg?

Before we start running for the hills, let's take a moment to break down this rapidly advancing technology, so omnipresent that it's practically taking over headlines of news outlets and subject lines of email inboxes each day. But are breadlines next?

Geoffrey Siwo, Ph.D., Research Assistant Professor, Department of Learning Health Sciences; Research Associate, Michigan Center for Global Health Equity, certainly doesn't think so. This warm, unassuming, philosophic scientist whose humble demeanor belies his supreme prowess in biological and computational sciences is a far cry from any icy robot with a vengeance.

He's a bio-computational architect, intent on making AI, machine learning, and deep learning work for us, not against us, and there's nothing artificial about that. So who better to help us understand the complexities from a 30,000-foot perspective on a tool poised to revolutionize medicine and in particular RNA therapeutics?

Dr. Siwo is also a member of the E-Health and Artificial Intelligence (e-HAIL) initiative at Michigan. The e-HAIL program was launched in 2021 with joint sponsorship from the College of Engineering and the Medical School and focuses on collaboration, grant development, and infrastructure to support a multi-disciplinary approach to innovations in e-health and artificial intelligence.

Geoffrey Siwo was born and raised in Kenya, in what he refers to as a low-resource setting. He did not own a computer, nor did his family.

His curiosity led him to formulate ideas early on. Geoffrey wanted to know what made things tick. "I found that unlike chemistry in non-living systems, which is dependent on reactions that occur under special conditions, biology was based on programmable molecules, in that biological processes are encoded by information in sequence-based molecules: RNA, DNA, and proteins," he remarks.

In the early 2000s, Geoffrey's initial journey into science focused on RNA and DNA. "One of the most exciting things about RNA, genetics, and biology is that biology has proven itself for over three billion years, and RNA has been a large part of that," he marvels. "RNA was one of the first biological molecules for living systems to emerge."

The Eureka! moment

As the first human genome was being sequenced, Geoffrey made a remarkable discovery of his own. He recalls, "I found that genetic material in our DNA, human DNA, that looks like viruses could be important for understanding diseases such as HIV, which is an RNA virus."

He shared his idea with a professor who told him it was brilliant, but he would need a very large lab and good funding to test his hypothesis, neither of which was available to him at the time.

Geoffrey said, "What if I could somehow do this on a computer, digitized in some way? Biology itself computes to do a vast array of things. Could I somehow transform this biological information into digitized parts?"

Moreover, he speculated that doing so could help solve problems much faster, much cheaper, and with much more accuracy because all of the research normally conducted in a dish could now take place inside a motherboard.

To test this theory, Geoffrey sought out a local Internet cafe — scrounging up the one-dollar-per-hour fee to use a computer and go online — and went to work. Day and night, he calculated, formulated, and searched the world's scientific repositories — the NIH's National Library of Medicine online resource, thousands of HIV RNA sequences from the Los Alamos National Laboratory — for data to synthesize and began creating computational models of biological information.

Geoffrey's arduous and painstaking work paid off. "In just a few months I got some exciting results that were accepted at the 2003 American Society for Microbiology's Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago," he relates, "but I couldn't afford to buy a plane ticket to go."

So thanks to the Internet — another piece of information technology — he sent an email to Dr. Anthony Fauci, then head of the National Institute of Allergy and Infectious Diseases, and shared his story. Dr. Fauci provided travel support for Geoffrey's trip to the United States, where he presented his findings to the amazement of the esteemed audience.

Siwo headshot image courtesy of Geoffrey Siwo, Ph.D.

Geoffrey garnered interest from some of the world's most prominent biological scientists in HIV research at the time because he was asking questions that had not been considered by most in the field about HIV and the human genome.

Digitizing biology

"Ten percent of the human genome contains DNA sequences that look like viral sequences. Biology is incredibly complex," Geoffrey explains. "So what if we could take biological problems and extract them into information problems at a speed, scale, and cost that you could never imagine?"

He became passionate about the intersection of AI and other computational technologies and therapeutics. Geoffrey reveals, "We can do it faster and cheaper because all of this biological data will be digitized. And the cost of computing keeps going down. The cost of representing the physical world in a digital space is continually going down.

"That convinced me in 2003 that the way to develop therapeutics in the future is to leverage information technologies as a platform — to take our therapeutic problems and convert them into information problems so that we can solve them using computational platforms."

He then began concentrating on modeling the immune system and other biological processes with machine learning and using systems thinking, trying to understand how that would help with designing vaccines and therapeutics for malaria — an area of study that would remain his focus throughout his Ph.D. degree program.

Dr. Siwo's current research includes using artificial intelligence and machine learning to address fundamental biology challenges in understanding the genetics of diseases and accelerating the development of RNA therapeutics that can be broadly accessible.

AI fuels the M-RNA Therapeutics engine

Taking this digital approach, he envisions accelerating the bedside-bench-bedside journey by having AI come into play at various stages along the way.

For example, in conducting fundamental research, AI can be used to identify genetic variants or mutations that underlie specific diseases. "For instance, in the case of cardiovascular disease, genetic studies in populations demonstrated that some versions of the gene PCSK9 were associated with lower risk for certain cardiovascular diseases," he relates.

"It's being translated in the clinic right now through the design of CRISPR-based RNA therapeutics that can target that particular gene. And that's possible because computational technologies allow us to do genome-association studies where we can find genetic variance that underlies a particular disease or modify the risk for better or worse."

Another potential application for AI is in designing the RNA therapeutics themselves. RNA and DNA are information molecules, in that they contain encoded messages. Since they are already information platforms, it's much easier to develop computational techniques using AI to design RNA/DNA molecules with a specific therapeutic goal. The FDA recently approved the first CRISPR-based RNA therapeutic to treat sickle cell anemia, marking a mere decade from the initial discovery of the CRISPR molecule to clinical application. Geoffrey adds, "It's incredible because this is the first time that the discovery of a new therapeutic modality in biology or chemistry has led to a new therapeutic in the clinic within a decade, so very fast."

Geoffrey's research also involves some aspects

Photo: Michigan Photography, Daryl Marshke, courtesy of Geoffrey Siwo, Ph.D.

of CRISPR and he sees AI playing a big part in helping design CRISPR molecules so that they have less off-target effects, thereby enhancing safety.

Practical applications of AI abound

He also foresees that AI will be a critical component in the manufacturing process of RNA therapeutics and in addressing the cost issue. "New chemical compounds or small molecule drugs require setting up new manufacturing processes and factories that may need to be customized," he outlines. "RNA therapeutics are programmable and therefore highly scalable, so you can use the same machinery to synthesize any kind of RNA or DNA sequence you design."

Another practical application for AI is in modeling protein structures. The human genome sequence is composed of four letters, AGCT, arranged in a myriad of combinations that produce RNA that is translated into proteins, all with a unique structure.

When working with biological samples, scientists who want to see the physical structure of a protein within a cell must go through an inordinately costly and time-consuming technique using crystallography. It can take months.

AI can accomplish the same result in hours or less because it can predict what shape that protein will take by using the digitized information found in the letters encoding the DNA and RNA.

In CRISPR-Cas9 technology, one hiccup is that it can sometimes target a gene that is similar to the specific area you want it to target since it's searching amongst six billion letters. Additionally, each person has a unique genome, so a CRISPR molecule that works on one person might not translate for another.

Geoffrey expounds, "One reason for this is that there are only a certain number of genome sequences available today, and 90% of them come from Caucasian individuals. African populations, for instance, are underrepresented. This can be improved by having more data."

"To have therapeutics that are equitable, we need to ensure that we have equitable representation of genetic data from different groups around the world."

AI can also aid in genome sequencing by helping to put the puzzle pieces together. Currently, genome sequencing machines produce pieces, segments, of DNA that scientists must assemble. In 2003, scientists still didn't know where many hanging pieces of the genome fit. The fully assembled human genome was realized only very recently in 2022.

In the M-RNA Therapeutics pipeline, Geoffrey sees AI as instrumental in speeding up the process of genome sequencing for a patient who walks into a clinic with a rare or genetic disease. "AI can help to assemble the sequences as images and make that information available to researchers more accurately and much faster so that the process of looking for targets and designing potential therapies can begin immediately."

Photo: Michigan Photography, Daryl Marshke, courtesy of Geoffrey Siwo, Ph.D.

Rogue genes and bull's-eye drugs

When a patient has a rare disease, it's oftentimes difficult to find the underlying gene responsible.

"Timothy Yu identified a unique mutation that had never been reported before in a girl named Mila afflicted with Batten disease.[1,2] He designed an antisense oligonucleotide (ASO), and the FDA granted permission to use the drug on Mila, and her symptoms improved dramatically. Unfortunately, the disease had gone on far too long, and Mila later passed away. But I think the same story can be replicated on a bigger scale."

Advances in the manufacturing of RNA therapeutics will make it possible to synthesize an RNA molecule designed for one person even in remote locations, for which AI will play an important part. Companies like BioNTech are working on building containers that they can ship to any part of the world to manufacture RNA therapeutics on-site. Moderna is building an RNA vaccine factory in Kenya.

"And that's where AI will help," Geoffrey reports. "Because it's information, a scientist could send an email with the sequence of the RNA therapeutic, and a scientist on the other side can have a machine manufacture it and deliver it to the patient.

"And a lot of the manufacturing will involve robotics mechanically synthesizing the therapeutics. This can all be done by an automated lab."

Humanitarian gatekeeper

Geoffrey is also using AI in another project to help design new forms of chemical molecules that look like nucleosides — the AGCT(U) in RNA/DNA, that hold potential as anti-viral molecules. "Beyond the AGCT(U), nature also creates some modified versions, hundreds of them," Geoffrey adds. "We need to explore beyond the AGCT(U) to make therapeutics that have desirable druglike properties.

"For a long while, mRNA vaccines were not successful because they induced a strong immune reaction in animals that could sometimes lead to death. Katalin Karikó and Drew Weissman found a special form of U (uracil), a nucleotide in RNA, that makes RNA in human cells to be non-immunogenic. They used this modification and introduced it in mRNA vaccines, and that way the vaccines could be tolerated in animals. They were awarded the Nobel Prize in Physiology or Medicine in 2023 for their discovery." (See "Making Headlines," page 40.)

What excites Geoffrey the most is the convergence of all this technology amongst a cross-disciplinary consortium. "AI has to be co-developed by engineers and biologists," he states. "AI has to be informed by biology. It's not purely data alone."

And those collaborations are between humans, not robots. Geoffrey Siwo is a scientist who adheres to a systems biology approach as opposed to reductionist biology. He sees the big picture, and that includes harnessing the latest technology and applying it to medicine and health to help people. Humans.

[1] Timothy Yu, M.D., Ph.D., Associate Professor of Pediatrics, Harvard Medical School; Attending Physician, Division of Genetics and Genomics, Boston Children's Hospital

[2] Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease, Jinkuk Kim, Ph.D., Chunguang Hu, M.D., Ph.D., Christelle Moufawad El Achkar, M.D., Lauren E. Black, Ph.D., Julie Douville, Ph.D., Austin Larson, M.D., Mary K. Pendergast, J.D., Sara F. Goldkind, M.D., Eunjung A. Lee, Ph.D., Ashley Kuniholm, B.S., Aubrie Soucy, B.A., Jai Vaze, B.A., Nandkishore R. Belur, M.S., Kristina Fredriksen, B.S., Iva Stojkovska, B.S., Alla Tsytsykova, Ph.D., Myriam Armant, Ph.D., Renata L. DiDonato, B.S., Jaejoon Choi, Ph.D., Laura Cornelissen, Ph.D., Luis M. Pereira, Ph.D., Erika F. Augustine, M.D., et al., 2019/10/09, New England Journal of Medicine, 1644-1652, 381, 17, 10.1056/NEJMoa181327931597037, DOI: 10.1056/NEJMoa1813279

Photo: Michigan Photography, Daryl Marshke, courtesy of Geoffrey Siwo, Ph.D.

So those who fear that a takeover of mankind by machine is imminent need not fret. The human element is not only necessary to unleash the full power of AI but also critical for its survival. No one understands that symbiosis better than Dr. Geoffrey Siwo, a compassionate scientist whose passionate advocacy for improving health and medicine equity throughout the world has no end.

The Culture Broker

Henrike Florusbosch, Ph.D.

All hail e-HAIL! University of Michigan E-Health & Artificial Intelligence (e-HAIL) Program Manager Henrike Florusbosch, Ph.D., the self-dubbed "culture broker" connecting and supporting researchers at the intersection of artificial intelligence and health.*

Housed within the expansive North Campus Research Complex at the University of Michigan, the e-HAIL initiative was launched in 2021 to bring together physicians and scientists from Michigan Medicine and the College of Engineering whose research aims to improve health using technology. Henrike's job is to get the right people in front of each other — *matchmakera academia supernova*, in scientific nomenclature.

A program manager at U-M runs the show, and Henrike Florusbosch is no exception. With the finesse of a magician and the authority of a lion tamer, Henrike focuses a great deal of her attention on supporting faculty researchers to help identify collaborators, write successful grant proposals, and source funding to do this kind of creative, innovative work.

"I call myself a culture broker because that's what I do. I bring people together from two different worlds and facilitate collaborations for grants and partnerships," she says. "My background is in anthropology, and I've spent the past two years learning about the research interests of many faculty working in this space, and that helps when I try to connect people. 'Oh, I think this person would be a good fit to connect with this other person for this grant application,' and so forth."

Make an appointment at e-HAIL; breathe rarefied air. It's highly recommended. Henrike will greet you with a level of hospitality that would rival that of a Les Clefs d'Or Concierge at The Ritz. She'll beckon you to enter a world of fascination, preparing your table for the cornucopia of technological marvels and medical wonders to come.

Though not a faculty member of the Center for RNA Biomedicine, Henrike is nonetheless a member of the center's chosen or extended family — one of a select group of key collaborators whose knowledge, experience, resources, and brainpower will most assuredly help accelerate the process of building the M-RNA therapeutics pipeline at Michigan.

* https://e-hail.umich.edu/

Photo top: Michigan Photography, Daryl Marshke, courtesy of Geoffrey Siwo, Ph.D.
Florusbosch headshot image courtesy Henrike Florusbosch, Ph.D.

The Mathematician

Indika Rajapakse, Ph.D.

Established Investigator

Indika Rajapakse, Ph.D., Professor of Computational Medicine and Bioinformatics, Medical School and Professor of Mathematics, College of Literature, Science, and the Arts

Who knew math could be so much fun?

Indika Rajapakse, Ph.D., that's who!

Fresh off an afternoon run, Indika arrives back outside his lab on the North Campus Research Complex agog that he might have missed our meeting. Far from it, yet he remains very concerned.

"Paul!" he exclaims. I reassure him that he's not in the least bit late and that we have plenty of time to talk. He exhales and erupts with delight. A smile that could light up a room beams to greet me.

Little did I know that over the course of the next hour, I'd be transported to another world and presented with my own private lesson from a gifted lecturer who left me not only mesmerized but ready to sign up for a U-M Ph.D. degree program in Computational Medicine & Bioinformatics.

"*I'll leave that to the professionals,*" I say to myself.

While conducting background research for this article, the first thing that stood out to me about Indika Rajapakse, Ph.D., Professor of Computational Medicine & Bioinformatics, Professor of Mathematics, was that he frequently quoted from world-famous science fiction author and mathematician Arthur C. Clarke throughout his lab's webpage.

"*Intriguing,*" I thought to myself. "*I wonder, what's the connection?*"

As the conversation commences, I soon learn that Arthur C. Clarke was the chancellor of the university that Indika attended in his native Sri Lanka and where Clarke lived the last half of his life. Clarke's futurist ideals represent the hope of things to come that Indika embraces with such childlike wonder when he imagines the infinite solutions that science holds to help improve the lives of people all around the world. "Serendipity," Indika regales.

He dives right in, like a kid who's discovered fishing for the first time. He wants to share what he knows, but even more interestingly, he wants to share what he doesn't know. His enthusiasm is infectious; his excitement buoying. I'm hooked and more than willing to go along for the ride.

"Questions," he explains. His philosophy. "Questions. The approach to scientific discovery must start with questions, not answers. That's paramount."

"Also, it must involve a critical level of thinking," he relates. Not just tackling a math problem with the brain of a mathematician but with the mind of a biologist, chemist, and engineer." "*He's all of those things,*" I interject in my head.

Rajapakse headshot image courtesy of Indika Rajapakse, Ph.D.

Indika with famed futurist Arthur C. Clarke. Courtesy of Indika Rajapakse, Ph.D.

"And you need an interdisciplinary approach to solve problems."

I heartily concur that a multifaceted perspective can be extremely rewarding and spark great ideas. I also share that I'm a novice when it comes to this branch of science, and admit to him, "My background is in geology. Earth processes, earth dynamics, which are for the most part macro in scale."

Not so his world, which resides in the nucleus of a cell — the domain of the human genome. And it's obvious he can't wait to take me there.

He launches right in, grabs his markers, and takes to the whiteboard.

Inside we go, into that realm where he's created a way to harness the transcription mechanisms of a human skin cell or blood cell, hijack them, and transform them into any other type of human cell using modified interfering RNA (RNAi) that removes something from the cell or modified mRNA that adds something to a cell.

His ultimate goal is to make them into potential weapons to fight cancer and other diseases — essentially recruiting cells to do his bidding like a bio-mathematical pied piper. Indika calls it cell reprogramming, and it lies at the heart of his groundbreaking work.

He explains that chromatin — a complex of DNA and proteins that form chromosomes — comprises two different types of "spring-like" structures, much like coiled land-line telephone cords: ones that are tightly coiled and ones that are more loosely coiled. These coils intersect with each other, sometimes closely. Where those junctures occur, you can remove that section, and they will essentially bind together into a new structure.

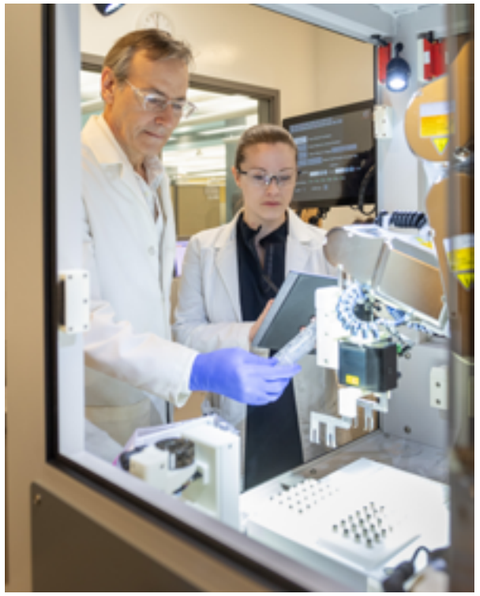
"A lot of people say form precedes the function, or form follows function," he relays. "I say the form *is* the function, and this is how we can reprogram a cell."

"Fascinating," I relay. "*I think there's more bioscience stuff coming,*" I say to myself. "*Buckle up.*"

"Inside the nucleus is like a universe. It is beautifully organized, and it's not just random," he marvels. "I'm interested in learning how that genome structure is changing over time."

What he invented — patented in 2020, in fact — he calls transcription factor data-guided control. It's an algorithm that he and a brilliant graduate student of his created that can predict what a cell will do and what kind of cell it will eventually become. Indika explains, "I know the initial condition of skin cells. Give me any targeted cell, and I will give you the recipe to tell you how to go to that target."

Indika has found a practical use for his discovery. In conjunction with the United States Air Force Office of Scientific Research, he used this algorithm to pinpoint the transcrip-



Inside the Rajapakse Lab, North Campus Research Complex, University of Michigan, Ann Arbor. Courtesy of Indika Rajapakse, Ph.D.

tion to a target that would reprogram skin cells to help wounds heal five times faster. He and his team are currently working on methods of delivery such as a spray application.

"Still, we are far from solving anything," he admits. Ever the scientist. "*What we don't know. Questions, not answers,*" I remind myself.

And then there's cancer. Currently, some cancer patients receive high doses of chemotherapy or radiation that essentially deplete the immune system, essentially destroying it. In order to assist the body in rebuilding the immune system, patients must undergo a bone marrow transplant, but that requires a donor with healthy tissue.

"The challenge becomes finding a compatible donor," he explains. "No one is going to match 100%, and you also get a lot of rejection, so there are a lot of issues. And it's even more difficult for people of African descent. Plus, they're not your cells, they're someone else's."

He wants to change that with his self-donor approach. "That's what I'm really passionate about!" he says.

Indika asks, "Now, what if there was a way to harvest, or grow your own bone marrow from your own skin cells?" Well, that's what he's working on now in the lab.

Indika wants to apply this technology to bone marrow transplants for cancer patients. Using a person's own skin cells to grow hematopoietic stem cells. Hematopoietic stem cells are the critical cell type in bone marrow, since they can make all immune cell types. "Then I don't need a donor. I am my own cure." He confesses, "I am so obsessed with going directly to hematopoietic stem cells from skin cells."

And he may just have the equipment he needs to do that. Prominently on display in his lab is what's called the BioAssemblyBot 400 (BAB) machine. Ebulliently he quotes Arthur C. Clarke, "Any sufficiently advanced technology is indistinguishable from magic." *How cool is this?* I think to myself. It's a 3-D biological printer. He wants to use this intricate machine to actually make not only the cells but the structure — the material that is bone marrow — the actual, tangible, living tissue.

That's his dream. *"And he'll do it,"* I convince myself.

I ask him what the obstacles are that stand in his way. "Time," he says. "Time to figure it out and perfect it."

Indika's other focus centers around reprogramming cancer cells to fight cancer. "With other diseases, you have many bad cells that are produced from one errant cell," he says. "With cancer, it's the opposite, you have many bad cancer cells, but they can all be destroyed by using the same reprogrammed cancer cell."

Indika poses, "What is the minimum required for a cancer cell to die? Can we identify a certain agent, or RNAi, modified mRNA, that only targets a cancer cell? Then this disturbance will cause the cancer cell to die. And it's one cure for all. That kind of mindset, that's how we need to think, and it's coming from engineering, from math, so we need to talk to each other a lot."

Indika reveals that he'll be on sabbatical starting in January 2024. He's using this time to work on another project: trying to create a "digital twin" for the human genome — essentially a digital version — of what's happening in reality, "in the dish."

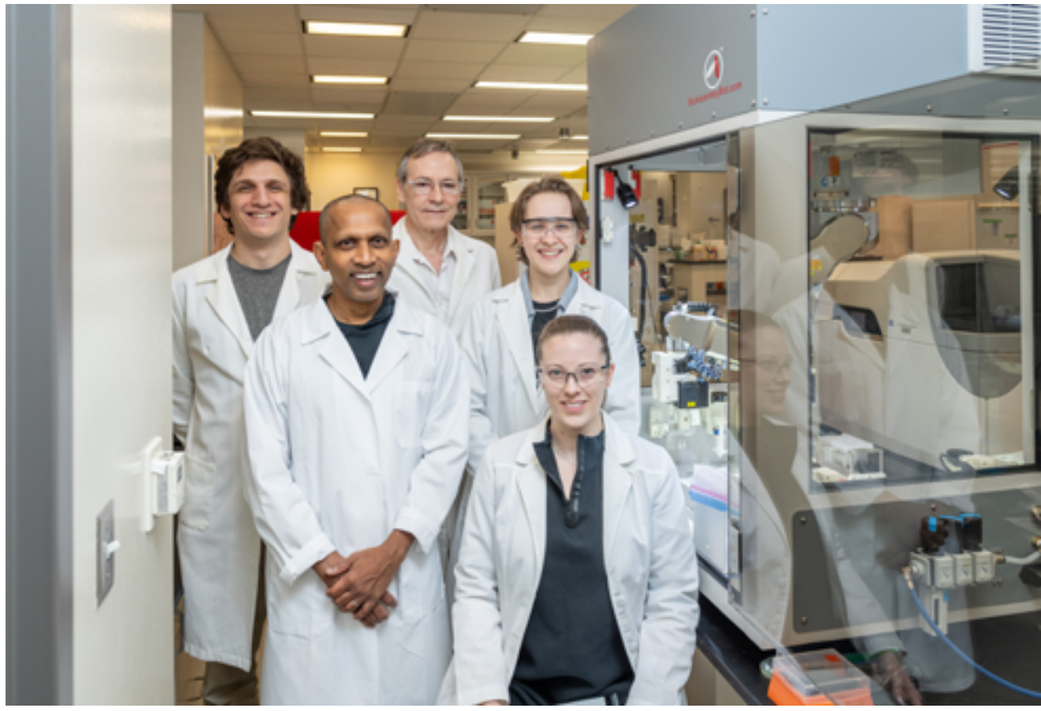
"Oh, is that all?" I sarcastically quip to myself.

In science, experimentation with biological materials — cells and tissues, in this case — all happens in a dish. "I want to manifest digitally what's going on in the dish," he states. "Then, you go through a lot of mathematical calculations and simulations using this digital twin a lot faster than with the actual sample."

"Did I detect a tinge of bittersweet melancholy?" I ask myself when Indika mentions going on his sabbatical. Perhaps he was pondering the prospect of traveling away from his home at the University of Michigan, for which he no doubt harbors no small amount of respect and adoration, in pursuit of a bounty of discoveries in ports real and unknown.

"Michigan is the best place. We have an amazing engineering school, an amazing medical school, and amazing math and physics. It's amazingly interdisciplinary. We can challenge each other here. That's why I love teaching. I have so many different students studying so many different subjects asking lots of questions — it really challenges me."

"A scientist whose enthusiasm for learning and knowledge is so infectious, you just might need an mRNA vaccine," I say to myself in awe and deference.



Indika with Rajapakse Lab members. Courtesy of Indika Rajapakse, Ph.D.

Mouse Models

And no, we're not talking about a statuesque rodent parading down the runway in Milan wearing the latest designer fashion.

Many of the researchers we spoke to mentioned mouse models, or animal models in general, as being an integral part of their research. Before new medicines or therapies are used on humans, they must first be tested on animals — a necessary step in scientific research.

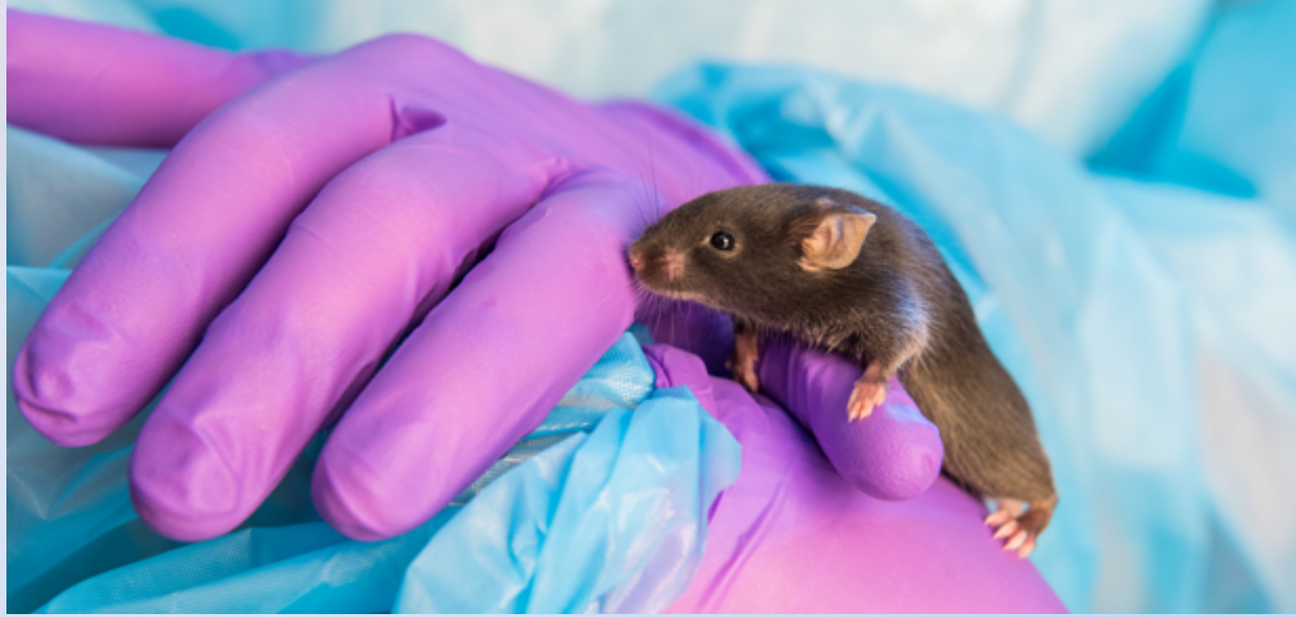
But, the universal aim among these scientists — and in fact, every scientist at Michigan — is to maximize use of *in vitro* testing, that is, testing outside of an animal, in an effort to minimize the degree of *in vivo* testing, or testing in a living animal.

This no doubt brings up questions and concerns from not only animal rights advocates but also anyone who harbors even the slightest degree of critter compassion. Is this kind of testing really necessary? How are the animals treated? What steps are taken to mitigate pain and suffering? And so on.

We reached out to the Unit for Laboratory Animal Medicine, part of the Animal Care and Use Program at the University of Michigan and one of the nation's oldest and most recognized programs training laboratory animal veterinarians, to help answer these questions and more.

The following article outlines the extent to which the university goes to safeguard these animals — stringent treatment guidelines, controls in place to ensure their well-being — and the ethics involved therein.

I went to the animal fair,
The birds and the beasts were there ...



The Humble Laboratory Mouse: An Oft-Overlooked but Essential Ally in Biomedical Research

At first glance, it may seem that mice and humans don't share much in common. Beyond the obvious differences in certain physical characteristics, including habitat, mice have a much faster aging process — the average mouse, living in a controlled research environment with access to food, water, housing, enrichment, and routine veterinary care, has a lifespan of one to three years. Mice also have a far shorter gestation period and typically have multiple litters each year.

Though these surface-level attributes present a clear delineation between the lived experiences of a mouse and a human, they offer an unparalleled opportunity to explore myriad diseases and treatments over the course of a living organism's entire life. When coupled with the fact that mice and rats share approximately 95% of their genes with humans, it is easy to see why the humble mouse — an often-unwelcome pest of a houseguest — is an essential ally to biomedical researchers at the University of Michigan (U-M) and beyond who are pursuing scientific advancements to improve collective mammalian health.

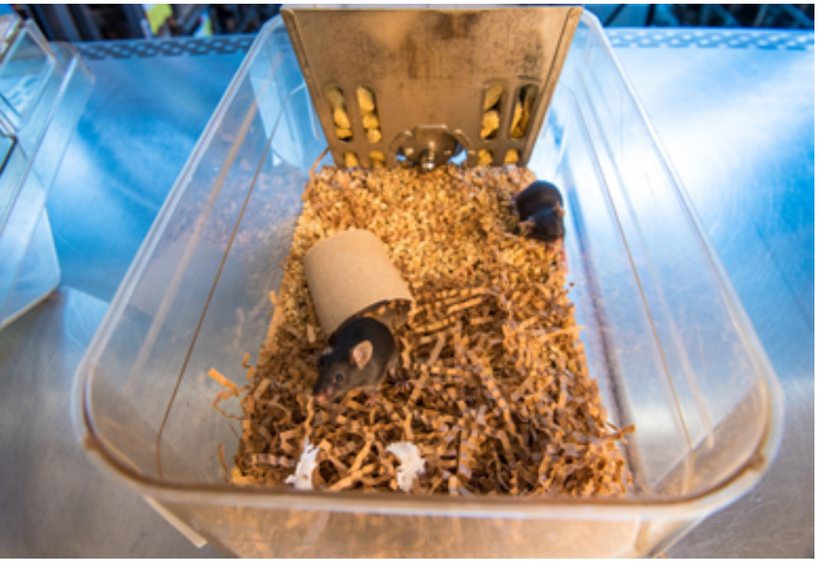
Ensuring Animal Welfare

Good science and good animal welfare are symbiotic. The rules and regulations that protect animals in research in the United States are considered some of the most stringent in the world. The U-M also has many policies and controls in place to safeguard animal well-being and monitor all projects that involve the use of animals.

Before a U-M researcher can begin a study with animals, a detailed description of the project and its intended purpose must be reviewed and approved by the U-M's Institutional Animal Care & Use Committee (IACUC).* This committee reviews the goals, objectives, and benefits of the proposed study to ensure that it has appropriate scientific merit (i.e., the project will benefit human or animal health).

* animalcare.umich.edu/iacuc

Cover photo and top image: Austin Thomason, Michigan Photography - University of Michigan



Consistent with a set of international standards known as the 3Rs — Reduce, Refine, and Replace — the IACUC also assesses each study based on the following criteria:

- Has the number of animals being used been **reduced** to the minimum necessary for the study?
- Can animals be **replaced** with less sentient or non-animal models wherever possible?
- Have all practices been **refined** to provide the best animal welfare possible?

Once approved, projects are monitored via an extensive compliance ecosystem of various university, federal, funding-sponsor-specific, and independent accrediting bodies who are responsible for making sure that the research adheres to the highest national and professional animal welfare standards. In tandem, animals receive around-the-clock medical care from highly trained, licensed veterinarians and veterinary technicians with specialized training in laboratory animal medicine.

The research environment is meticulously controlled to maximize the animals' lived experience and minimize potential study variables, which includes the provision of food, water, and clean enclosures; appropriately lighted and well-ventilated housing; detailed analgesic regimens/procedures to reduce any pain or discomfort; and species-specific socialization and enrichment.

Contributing to Scientific Advancements

At the University of Michigan, mice, rats, and various species of fish comprise over 99% of all animals involved in scientific research. These projects span a wide variety of fields — medicine, dentistry, engineering, natural resources and the environment, public health, and kinesiology — **including many notable contributions from faculty affiliated with U-M's Center for RNA Biomedicine:**

- **Lori Isom, Ph.D.** — Dr. Isom's laboratory uses transgenic mouse lines to study the mechanisms of pediatric epileptic encephalopathy, sudden unexpected death in epilepsy, and cardiac arrhythmia linked to mutations in voltage-gated sodium channel genes. In a recent publication in Brain, the lab detailed how an antisense oligonucleotide (ASO) drug repaired defective brain cell signals in mice with Dravet syndrome, a severe genetic epilepsy.[1]

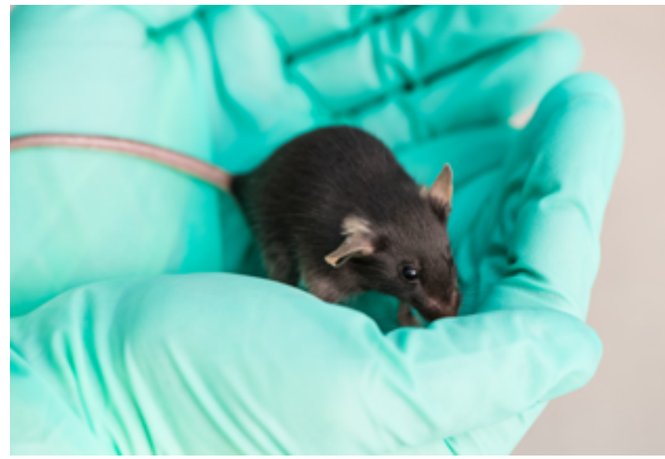
[1] ASO restores excitability, GABA signalling and sodium current density in a model of Dravet syndrome, Yukun Yuan, Luis Lopez-Santiago, Nicholas Denomme, Chunling Chen, Heather A O'Malley, Samantha L Hodges, Sophina Ji, Zhou Han, Anne Christiansen, Lori L Isom, Brain, 2023; awad349, https://doi.org/10.1093/brain/awad349

Image credit: Austin Thomason, Michigan Photography - University of Michigan

- **Huda Akil, Ph.D.** — In October 2023, Dr. Akil was awarded the National Medal of Science for her work to uncover the genetic underpinnings of emotions, depression, pain, and addiction in brain biology.[2] Her 50+ year career has included several animal studies that have been used to help pinpoint the genetic markers of addiction, which may ultimately lead to more targeted treatment strategies for substance use disorders.[3]

- **Maria Castro, Ph.D., & Pedro Lowenstein, M.D., Ph.D.** — Drs. Castro and Lowenstein have developed novel, world-renowned rodent models of malignant brain cancer using *in vivo* gene transfer technologies. Their research has made significant contributions to the study and understanding of gliomas, including a gene therapy for brain tumors that has shown promising early results in its first human patient clinical trial.[4]

As evidenced by only a few of the groundbreaking studies above, it is difficult to overstate the essential role that animals — especially mice and rats — play in advancing biomedical research. From a peanut allergy vaccine to treatments for metastatic breast cancer and pediatric brain tumors, one needn't look far for an opportunity to thank the humble laboratory mouse for improving the collective health outcomes of human and animal patients alike.



[2] U-M neuroscientist Huda Akil, Ph.D., wins National Medal of Science, Kara Gavin, Michigan Medicine News Release, University of Michigan, michmed.org/Kq2AJ

[3] Study Pinpoints Genetic Markers That Influence Addiction, Kara Gavin, Michigan Medicine Health Lab, University of Michigan, michmed.org/MM3GR

[4] Gene therapy for brain tumor shows promising early results in humans, Anna Megdell, Michigan Medicine Health Lab, University of Michigan, michmed.org/2VWqQ

Top image: Amy Puffenberger, Animal Care & Use Program, University of Michigan
Image right: Austin Thomason, Michigan Photography, University of Michigan

By the Numbers

PEOPLE
170 RNA faculty members
Male: 69%; Female: 31%

ACROSS CAMPUS
Schools/colleges: 7
Departments: 41

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

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

SCIENTIFIC PUBLICATIONS
1,155 total publications from all the faculty members

SEMINARS
16 external and internal speakers
60 participants in average attendance

SYMPOSIUM
1 Annual RNA Symposium with 5 keynote speakers

COMMUNICATION
1 annual magazine
47 newsletters

We invite you:

To join us and over 3,392 followers on X (Twitter) @umichrna, connect with us on LinkedIn @ umichrna, and subscribe to our YouTube channel @umichrna.

To visit our website, rna.umich.edu, that received over 27,000 users during the academic year.

To read our weekly newsletter, "The RNA Transcript," that reaches over 1,000 RNA fans, with an opening rate averaging 52%.

Subscribe at rna.umich.edu/email-sign-up/

U-M Center for RNA Biomedicine

170 Faculty Members

From 7 schools and colleges across 41 departments

Carlos Aguilar, Biomedical, College of Engineering
Huda Akil, Neurosciences Institute, Medical School
Benjamin Allen, Cell & Developmental Biology, Medical School
Joshi Alumkal, Internal Medicine, Medical School
Anthony Antonellis, Human Genetics, Medical School
Brian Athey, Computational Medicine and Bioinformatics, Medical School
Sara Aton, Molecular, Cellular, & Developmental Biology, College of LSA
Ryan Bailey, Chemistry, College of LSA
James Bardwell, Molecular, Cellular & Developmental Biology, College of LSA
Sami Barmada, Neurology, Medical School
Scott Barolo, Cell & Developmental Biology, Medical School
Stuart A. Batterman, Environmental Health Sciences, School of Public Health
Allison Chelsa Billi, Dermatology, Medical School
Markus Bitzer, Internal Medicine, Medical School
Alan Boyle, Computational Medicine and Bioinformatics, Medical School
Charles Brooks, Chemistry and Biophysics, College of LSA
Charles Burant, Internal Medicine, Medical School
Margit Burmeister, Computational Medicine and Bioinformatics, Medical School
Mark A. Burns, Chemical Engineering, College of Engineering
Laura Buttitta, Molecular, Cellular, & Developmental Biology, College of LSA
Dawen Cai, Cell & Developmental Biology, Medical School
Sally Camper, Human Genetics, Medical School
Maria Castro, Neurosurgery, Medical School
Sriram Chandrasekaran, Biomedical Engineering, College of Engineering
Matt Chapman, Molecular, Cellular, & Developmental Biology, College of LSA
Grace Chen, Internal Medicine, Medical School
Vivian Cheung, Pediatrics, Medical School
Arul Chinnaiyan, Pathology, Medical School
Michael Cianfrocco, Biological Chemistry, Medical School
Justin Colacino, Environmental Health Sciences, School of Public Health
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Analisa DiFeo, Pathology, Medical School
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James Elder, Molecular Genetic Dermatology, Medical School
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Eva Feldman, Neurology, Medical School
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Amanda Garner, Medicinal Chemistry, College of Pharmacy
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Yuanfang Guan, Computational Medicine & Bioinformatics, Medical School
Johann Gudjonsson, Dermatology, Medical School
Gary Hammer, Internal Medicine, Medical School
Saher Sue Hammoud, Human Genetics, Medical School
Michelle Hastings, Pharmacology, Medical School
Alfred O. Hero, Electrical Engineering and Computer Science, College of Engineering

Members' repartition across Schools and Colleges

Gerry Higgins, Computational Medicine and Bioinformatics, Medical School
Zhonggang Hou, Biological Chemistry, Medical School
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 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
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Adam Lauring, Microbiology & Immunology, Medical School
Cheng-Yu Lee, Internal Medicine, Medical School
Jun Hee Lee, Molecular & Integrative Physiology, Medical School
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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
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John Moran, Human Genetics, Medical School
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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
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Abhijit Parolia, Pathology, Medical School
Henry Paulson, Neurology, Medical School
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Sethuramasundaram (Sethu) Pitchiaya, Pathology, Medical School
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Jay Brito Querido, Biological Chemistry, Medical School
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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
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

The Bru-seq Lab provides services to university research groups as well as through external collaborations with academic or industry partners. The Bru-seq suite of techniques was developed in the lab of Dr. Mats Ljungman to interrogate the transcriptome in cells in new ways.

Sign for the airport at which all Bru-seq samples are coming in… can you guess which one? Hint: it's Brussels, Belgium!

By incubating cells in bromouridine for a short time, nascent RNA is labeled, and by using anti-BrdU antibodies, the nascent RNA is specifically captured and then deep-sequenced. This provides a picture of ongoing transcription genome-wide in cells. The turnover of RNA can also be assessed by including a "chase" for any desired period after the bromouridine labeling.

The Bru-seq suite of techniques was developed as part of ENCODE 3, an initiative from the NIH to map regulatory elements throughout the genomes of human and mouse cells. In ENCODE 4 the Ljungman lab acted as one of eight "mapping centers" generating large amounts of transcriptome data across 16 human cell lines.

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

The Managing Director of the Bru-seq Lab, Michelle Paulsen, grew over 10 billion cells in the lab for the Bru-seq experiments and to supply cell samples to the other seven mapping centers. The ENCODE 4 project has constituted a large portion of the samples processed through the Bru-seq lab over the past several years, but also several U-M groups have obtained Bru-seq data, as have international labs and Pfizer and Genentech. Here are some data on the volumes of samples processed in the Bru-seq Lab in the last 3 years:

2021: 412
2022: 165
2023: 334
2024: 108 through February 7, 2024

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

The license plate of one of Mats Ljungman's Bru-seq lab members, the "Bruseqer."

Ljungman headshot image: Michigan Photography, Dylan Marshke, courtesy of Mats Ljungman, Ph.D.

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

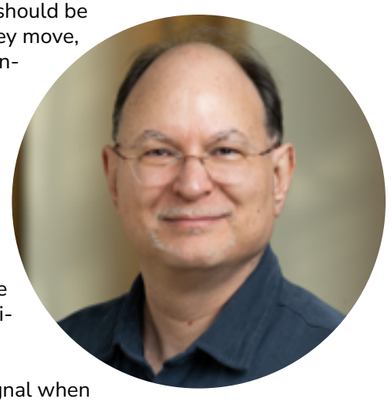
Damon Hoff, Ph.D., manages one of the two Core Facilities at the Center for RNA Biomedicine: the Single Molecule Analysis in Real-Time, or SMART, Center. Part scientist, part manager, part administrator, part technician, Damon helms a tight ship, navigating smoothly to provide specialized imaging and other analyses on myriad research projects for a variety of internal and external clients, not the least of which are members of the Center for RNA Biomedicine.

The SMART Center is a National Science Foundation-seeded, shared-use facility providing university researchers with single molecule detection and manipulation tools to track and analyze biomolecules with unprecedented detail. It provides access to state-of-the-art instrumentation, including single molecule spectroscopy and imaging, laser tweezers, and atomic force microscopy (AFM) as well as experienced support in experimental planning and analysis.

So what does this mean for RNA researchers? The SMART Center provides exciting methods to explore transcriptomics, the complete set of all the RNA molecules (called transcripts) expressed in a cell, tissue, or organism. Essentially, the SMART Center assists investigators with seeing in real time what theory says should be there, such as locations of different types of RNA within a cell, how they move, change shape, interact with other biomolecules, clump, where they transcribe their associated protein, and so forth.

Some of the types of methods provided by the SMART Center are showcased in a recent paper on nanoengines co-authored by Nils Walter, Ph.D., Co-Director of the Center for RNA Biomedicine and SMART Center Director, that was recently published in Nature Nanotechnology.[1] Nils utilized not only the fluorescent imaging capabilities of the center, but more importantly, the atomic force microscopy instrument, which uses a probe, allowing investigators to see what these tiny structures look like on a scale much smaller than can even theoretically be seen with fluorescence.

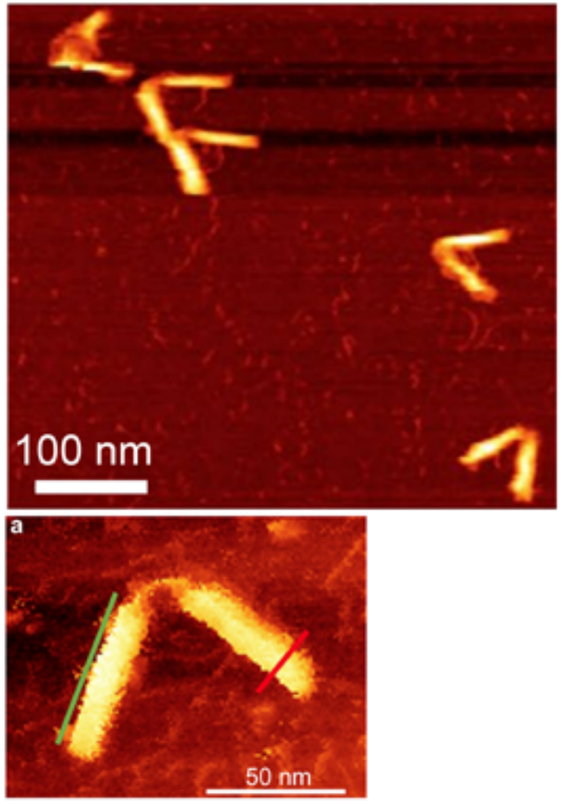
The nanoengines in Nils' study were designed to emit a fluorescent signal when an attached RNA polymerizing protein was active, but researchers had been having a problem seeing the expected signal and didn't know exactly what was causing the problem. Damon relays, "By ,using the AFM, we could actually see that [the nanoengines] looked like little 'V's. And I'm not talking about some downstream effect, we could actually see what each one looks like."



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

[1] A rhythmically pulsing leaf-spring DNA-origami nanoengine that drives a passive follower, Mathias Centola, Erik Poppleton, Sujay Ray, Martin Centola, Robb Welty, Julián Valero, Nils G. Walter, Petr Šulc & Michael Famulok, Nature Nanotechnology volume 19, pages226–236 (2024), https://doi.org/10.1038/s41565-023-01516-x

Walter headshot image: Michigan Photography, Dylan Marshke, courtesy of Nils Walter, Ph.D.



AFM images (scale bars added) that were taken at SMART showing "V"-shaped engines. Adapted from Centola et al., 2023. Courtesy of SMART Center.

Damon and colleagues found that these "V"-shaped nanoengines were clustering together, rendering them inoperative. The ability to directly see the molecules' structure allowed the team to adjust the conditions so that the molecules were in the right configuration, and voilà! "Nils said that the kind of imaging done with the AFM was critical to developing the right assay conditions to do this kind of work," Damon reports.

Updated from the SMART Center

Spatial -omic imaging, such as MERFISH sequential single-molecule localization (where MERFISH is short for multiplexed error-robust fluorescence *in situ* hybridization), is up and running and is a great resource for transcriptomics. Using this family of techniques, researchers can simultaneously image the location of an enormous variety of types of RNA molecules, visualizing exactly where and when the various components of the cell's protein machinery are being produced. Cells or tissues are imaged while a series of different fluorescent reporter molecules are introduced. The unique barcode system of the probe molecules allows for the identification of thousands of types of RNA from only a handful of fluorescent images. This instrumentation similarly allows for the sequential imaging of many different labeled biomolecules, such as antibody-tagged proteins, using sequential buffer and fluorescent label exchange.

As researchers publish new analysis methods that are relevant to the instruments in the SMART Center, Damon and his team are continually implementing new analysis code to interpret their data.

Damon reports that the SMART Center is looking forward to investing in new instrumentation and equipment to improve its capabilities. Damon continually modifies equipment to meet the needs of specific users, such as adding different optics, or different configurations of the light path, and so forth. For example, new lasers and cameras were recently purchased to allow for better and faster imaging.

If you are interested in the SMART Center for your project, please contact Damon Hoff at hoffj@umich.edu.

Collaboration

Center for RNA Biomedicine Collaborative Partnerships

RNA Collaborative Seminar Series

The "RNA Collaborative Seminar Series," initiated and led by the Center for RNA Biomedicine, is promoted by the RNA Society (website and Twitter). As of June 2023, it connected 26 RNA research centers and has hosted bi-weekly seminars with about 100 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. Host centers can choose to present an hour-long seminar, two 30-minute seminars, four poster sessions with introductory lightning talks, or a combination of talks and poster sessions.

For more information, 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/

The mission of the Cystic Fibrosis Foundation is to cure cystic fibrosis 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 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.

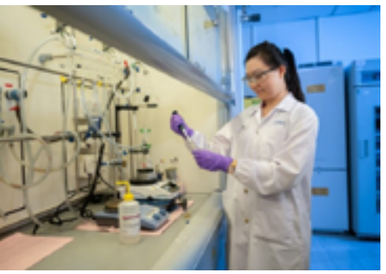
For more information, visit https://www.cff.org/researchers/academic-funding-opportunities

The Experimental Drug Development Center (EDDC) in Singapore is excited to share our commitment with the University of Michigan Center of RNA Biomedicine 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 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.

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 Center of RNA Biomedicine 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/

Worth Repeating

"Since its beginning, our interdisciplinary medical research landscape has produced breakthroughs, new technologies, and innumerable world-class researchers and doctors. The Center for RNA Biomedicine builds on this long legacy, using the building blocks of life itself to make strides at the frontiers of biomedicine. The center's M-RNA Therapeutics initiative shows the potential for a profound impact on human health when we combine top-tier medical facilities, unparalleled scholarship, and a culture of collaboration."

— Laurie McCauley, D.D.S., Ph.D., Provost and Executive Vice President for Academic Affairs, University of Michigan

"The M-RNA Therapeutics Initiative is a tremendous opportunity for the University of Michigan to become the top destination for patients afflicted with rare and genetic diseases seeking treatment. As a public university, there's huge potential for U-M to impact the health and lives of people positively and equitably throughout the state, the country, and even the world. This unique, life-saving capability will support job creation, attract companies, and grow the burgeoning biopharmaceutical industry already firmly positioned in the state, and we look forward to working together to make this a reality."

— Mark Ignash, CFCM, GWCCM
Interim Executive Director, Michigan Defense Center and
Senior Sector Development Director & Defense Advisor, Market Development
Michigan Economic Development Corporation | State of Michigan

"Through new faculty recruitments and engagement and support of a large cadre of existing U-M faculty, the RNA Biomedicine initiative has positioned U-M for major impact in advancing new RNA therapeutics approaches for the treatment of cancer, neurological and neurodegenerative diseases, and other conditions. It will be exciting to follow the innovative science and therapies that will emerge from U-M in the upcoming period."

— Eric R. 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

"The Center for RNA Biomedicine truly exemplifies our university-wide vision for serving the world through research and discovery. Since its inception in 2016, the center has played a critical role in developing and implementing support mechanisms to help accelerate innovation across disciplines."

— Lisa A. Prosser, Ph.D., Associate Vice President for
Research-Health Sciences, Office of the Vice President for Research

Events and Outreach

2023-2024 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 2023-2024 academic year, we offered 16 one-hour seminars, presented both in-person at the Biomedical Science Research Building (BSRB) and on Zoom. Our members were also given the opportunity to meet individually with presenters to exchange ideas, share insights, and explore possible partnerships.

Speakers

Graham Erwin, Ph.D., Stanford Cancer Institute Postdoctoral Fellow, Department of Genetics, Stanford University, "Discovering and Targeting Repeat Expansions in Human Disease" (September 11, 2023)

Jeffrey Barrick, Ph.D., Associate Professor, Molecular Biosciences, University of Texas Austin, "Turning Bugs into Features: Engineering and Evolving Insect Symbiont-Mediated RNA Interference" (September 25, 2023)

Guizhi (Julian) Zhu, Ph.D., Ara G. Paul Associate Professor of Pharmaceutical Science, University of Michigan, "Engineer and Deliver Nucleic Acid Immunotherapeutics and Vaccines – a Focus on Small Circular mRNA (circRNA) Vaccines" (October 9, 2023)

Susan Gottesman, Ph.D., Chief, Laboratory of Molecular Biology, NIH/NCI Distinguished Investigator "Bacterial Small RNAs: Regulatory Circuits, On & Off Switches & Quality Control" (October 23, 2023)

Irina Artsimovitch, Ph.D., Arts & Sciences Distinguished Professor, Department of Microbiology, The Ohio State University, "Locking Rho Up" (November 6, 2023)

George Lisi, Ph.D., Thomas J. & Alice M. Tisch Assistant Professor, Department of Molecular Biology, Cell Biology & Biochemistry, Brown University, "The Invisible Dance of CRISPR-Cas9 through Molecular Space and Time" (November 20, 2023)

Andy Berglund, Ph.D., Empire Professor of Innovation, Director of RNA Institute, University at Albany, "Mis-splicing in Repeat Expansion Diseases and Development of Potential Therapeutics" (December 4, 2023)

Anthony Rosenzweig, M.D., Professor of Internal Medicine, Director of the MM Institute of Heart & Brain Health, University of Michigan, "Noncoding RNA Targets in Heart Failure" (January 22, 2024)

Sarah Woodson, Ph.D., T.C. Jenkins Professor of Biophysics, Johns Hopkins University, "How Chaperones Help RNAs Choose the Right Partner" (February 5, 2024)

Joan Steitz, Ph.D., Sterling Professor of Molecular Biophysics and Biochemistry, Yale University, "RNA-RNA Base Pairing: Key to Unlock the Functions of Many Noncoding RNAs" (February 19, 2024)

Evgeny Nudler, Ph.D., Julie Wilson Anderson Professor of Biochemistry, Department of Biochemistry & Molecular Pharmacology, New York University (March 18, 2024)

Shuying Sun, Ph.D., Associate Professor, Department of Physiology, Brain Science Institute, Johns Hopkins University School of Medicine (April 1, 2024)

Connie Wu, Ph.D., Assistant Professor, Biomedical Engineering, College of Engineering, Research Assistant Professor, Life Sciences Institute, University of Michigan (April 15, 2024)

Catherina Kaczorowski, Ph.D., Elinor Levine Professor of Dementia Research, Professor of Neurology, University of Michigan Medical School (May 6, 2024)

Jeannie Lee, Ph.D., The Philip A. Sharp Endowed Chair in Molecular Biology, Professor of Genetics & Pathology, Harvard University (May 20, 2024)

Alexandra Piotrowski-Daspit, Ph.D., Assistant Professor, Biomedical Engineering, Assistant Professor, Internal Medicine – Pulmonary & Critical Care Medicine Division, University of Michigan (June 3, 2024)

Photos: Michigan Photography, Austin Thomason

Annual RNA Symposium

Since our last issue, the 2022 Symposium, “Towards our Future of RNA Therapeutics,” was held on Friday, March 25, 2022, and featured a welcome by then-University of Michigan President Mary Sue Coleman. Attendance was marked at 400, both in-person and virtually.

The 2023 Symposium, “From Molecules to Medicine,” took place on Friday, March 24, 2023, for an in-person and virtual combined audience of 347. Opening remarks and a special introduction were delivered by University of Michigan President Santa J. Ono, Ph.D.

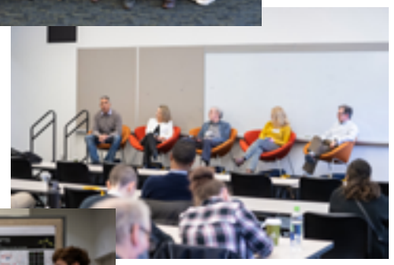
For the 2024 Symposium, “Unmasking the Power of RNA: From Structure to Medicine,” we are thrilled to feature keynote speaker Drew Weissman, M.D., Ph.D., the 2023 recipient of the Nobel Prize for Physiology or Medicine.

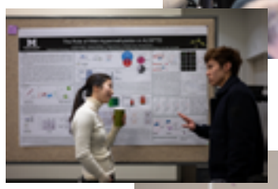
Four other distinguished keynote speakers will be presenting talks on various RNA topics: Victoria D’Souza, Ph.D., Harvard University; Leemor Joshua-Tor, Ph.D., Cold Spring Harbor Laboratory; Brenton R. Graveley, Ph.D., University of Connecticut; Peter Todd, M.D., Ph.D., University of Michigan.

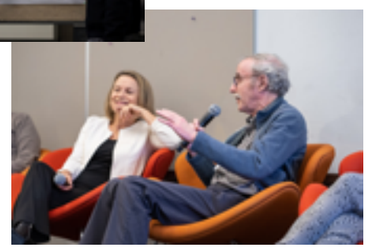
This 2024 Symposium will also feature a poster session preceded by selected lightning talks, which serve as a great opportunity for trainees to present their research to and network with a variety of leaders in the RNA field.

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 8, 2024, for the 8th Annual RNA Symposium, to be held in the Kahn Auditorium at the Biomedical Science Research Building on the University of Michigan campus. A 2024 Symposium detailed program is available at https://rna.umich.edu/2024-symposium/program/







Photos: Michigan Photography, Austin Thomason

Film Screening and Panel Discussion

Michigan Theater Foundation

On September 27, 2023, the Center for RNA Biomedicine, together with Michigan Medicine, presented a special screening of the film “Awakenings” at the historic Michigan Theater. The presentation was preceded by a panel discussion and Q&A session with Michigan experts specializing in neurology and the development of RNA therapeutics for neurologic disease.

Directed by Penny Marshall and starring Robin Williams and Robert De Niro, the film follows the victims of an encephalitis epidemic many years ago who were rendered catatonic ever since and explores how a new drug offers hope and the prospect of reviving them.

The screening was preceded by a one-hour Q&A panel discussion with Center for RNA Biomedicine neurology and neurologic disease experts Michelle Hastings, Ph.D.; Maria G. Castro, Ph.D.; Christiane Wobus, Ph.D.; Henry Paulson, M.D., Ph.D.; Peter Todd, M.D., Ph.D.; and moderated by Nils G. Walter, Ph.D.

The annual event was co-sponsored by Michigan Medicine and the Michigan Theater Foundation. In 2022, the Center for RNA Biomedicine presented the 25th anniversary of the theatrical release of “Gattaca,” a science fiction film that addresses the potential complications of a world in which genetic information can be rapidly analyzed and manipulated, which was also preceded by a panel discussion. Since the movie’s release, many of the tools anticipated by the film have become a reality, and some aspects of the genetic selection processes proposed are used in reproductive clinical practice today.

Bottom photos: Paul Avedisian

Grant Sprints

Ready … set … Grant Sprints!

On July 19, 2023, the leadership team along with Center for RNA Biomedicine (CRB) Executive Committee faculty members Laura Scott, Ph.D., Sundeep Kalantry, Ph.D., and Yan Zhang, Ph.D., met to brainstorm under the guided hand of former CRB Program Manager Martina Jerant, currently Program Manager for the U-M Weiser Center for Prostate Cancer.

Martina and CRB Program Manager Maria Stieve led the group in exercises designed to unlock innovative thinking for writing grant proposals that are more efficient, effective, and fun.

Grant Sprints facilitates the concept, ideation, and writing process while delivering strong grant proposals and helps faculty reconnect with their passion and feel again the excitement of collaborations and discovery.

“Grant Sprints are a great way to get faculty members to step out of the comfort of their usual writing processes. This method of creative problem-solving is a great way to jump-start the creation of new ideas and approaches to the problems they are trying to solve.”
— Maria Stieve, Program Manager, Center for RNA Biomedicine

Photos: Paul Avedisian

Faculty Hiring

The University of Michigan recognizes that RNA research is an important field and wishes to further expand and strengthen its research expertise and capability to train the next generation of RNA scientists.

In 2019, the University of Michigan Biosciences Initiative charged the Center for RNA Biomedicine with the mission to hire five tenure-track faculty in collaboration with various departments of the university as part of its $10.2 million grant.

Our first recruitment cycle led to the successful hiring of Stephanie Moon, Ph.D., Assistant Professor of Human Genetics, who started on January 1, 2020, followed by Chase Weidmann, Ph.D., Assistant Professor in the Department of Biological Chemistry of the Medical School, who joined us on September 1, 2021.

The second phase commenced in 2022 with the hiring of RNA Faculty Scholar Jay Brito Querido, Ph.D., named a Biological Sciences Scholar by the University of Michigan Medical School and member of the University of Michigan Rogel Cancer Center. Rachel Niederer, Ph.D., Assistant Professor of Biological Chemistry and member of the University of Michigan Rogel Cancer Center, rounds out the team as the fourth Assistant Professor hired. They both started on September 1, 2022.

The fifth and final faculty hire was Michelle Hastings, Ph.D., Professor of Pharmacology, Pfizer Upjohn Research Professor of Pharmacology, who joined us in May 2023 as Director of M-RNA Therapeutics.

We are thrilled to be able to hire scientists who share and practice our values of scientific excellence and collaboration as well as diversity, equity, and inclusion.

Jay Brito Querido, Ph.D.

Faculty Scholar, Center for RNA Biomedicine

Jay Brito Querido, Ph.D., Assistant Professor, Biological Chemistry, U-M Medical School; Research Assistant Professor, Life Sciences Institute, received his Ph.D. from the University of Strasbourg in France. For postdoctoral studies, he moved to Cambridge, the United Kingdom, to join the lab of Venkatraman “Venki” Ramakrishnan, who in 2009 received the Nobel Prize in Chemistry for his discovery of the structure and function of the ribosome, the machine that decodes mRNA into proteins.

“Proteins are the building blocks of our cells, and the ribosome is the cellular machine that decodes the genetic information to make every single protein in our body,” Jay explains. “Without the ribosome, genetic information is useless.”
As a postdoc in Venki’s lab, Jay was trying to understand how RNA translation

starts. As a part of that, he published a paper on the first high-resolution structure of the human translational initiation complex. “Because of that paper,” Jay relays, “I was one of the scientists that the RNA Society features each month in the field of RNA biology and was contacted by the Center for RNA Biomedicine at Michigan to give a seminar.”

It was well-known to Jay that Michigan housed an extensive RNA research community, so after his presentation, a conversation was initiated, which led to him applying for his current position.

Jay arrived on campus in September 2022 and began setting up his lab in earnest. With his research involving the mechanisms of translation initiation well underway, he wanted to expand into the relatively unknown area of aberrant initiation.

Similar to Dr. Peter Todd’s study of abnormal repeat sequences, Jay’s current focus is on how repeat sequences in mRNA can support aberrant translation initiation that generates toxic proteins. These toxic proteins can aggregate in the brains of affected individuals and have been found to be associated with neurological disorders such as frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS).

“Normal translation starts when the ribosome encounters the start codon ‘AUG,’” Jay explains. “Some mRNAs have repeated sequences on them. Mutations that expand the repeat sequence in the mRNA support non-AUG translation. For reasons unknown, some of those expanded repeats will trigger the ribosome to become trapped, or ‘locked up,’ and start translation even before it encounters the AUG.” (See “RNA 101: The Journey from Transcription to Translation” on page 28.)

“It starts decoding and generates proteins in a kind of a chain reaction with many repeats on them, building up these aggregates in the brains of patients with ALS and FTD. We still don’t understand the mechanism behind this aberrant translation, and that’s what I’m trying to find out in my lab.”

To do that, he uses a method called cryo-electron microscopy, which freezes samples so fast that he can preserve his biological samples in their native state as vitreous ice, unlike other methods that will form crystal ice that can interfere with the electron beam.

He hopes to find out what’s at play to trap the ribosome. “Maybe it’s not only the mRNA, but you need different proteins that trigger this to happen,” Jay says. “But if we find the factors that are only involved in this process, then we can use that to develop a small compound that could block those abnormal translations and develop a new therapeutic to treat those neurological diseases.”

Short repeats in the genome are normal. The problem lies in the length of those repeats. The ribosome can process the shorter repeats, but when they become a certain length — expanded repeats — they will jam the ribosome, much like trying to feed too much paper into a shredder — it freezes up.

Jay speaking at the 2023 RNA Symposium

Jay is also studying how circular mRNAs, which are naturally present in cells, recruit the ribosome to start translation. “The mRNA vaccines currently use linear mRNA, which degrades rapidly, requiring boosters,” he explains. “I believe future mRNA vaccines will be circular mRNA vaccines, which will have a much longer period of life and production of protein.”

Jay is collaborating with fellow Center faculty member Dr. Guizhi (Julian) Zhu, who also studies circular RNAs. He points out that “with Peter Todd, we both are interested in repeat disorder, but both use completely different systems. Rachel Niederer and I both want to understand how translation starts, but she uses a genetic approach, and I use a structural approach.

The Center for RNA Biomedicine supports such a strong culture of collaboration, and I look forward to making new connections and working together.”

Querido headshot imagecourtesy Jay Brito Querido, Ph.D.

Rachel Niederer, Ph.D.

Faculty Scholar, Center for RNA Biomedicine

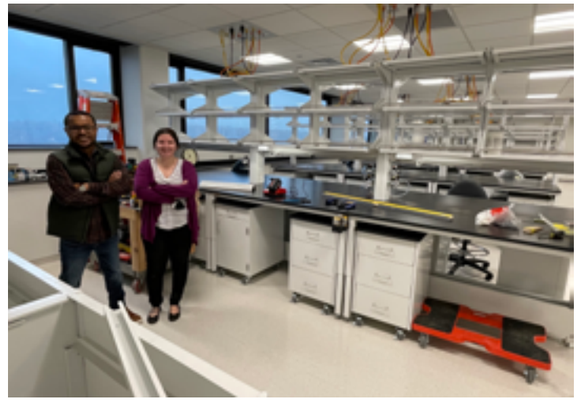
Rachel Niederer, Ph.D., Assistant Professor of Biological Chemistry, already knew that the Center for RNA Biomedicine was a well-established cohort of scientists when in 2020 she participated in a workshop sponsored by NextProf Science, a U-M program that assists postdoctoral trainees committed to diversity who are considering a career in academia.

She used that time to gather a lot more information about the center and the faculty scholar hiring initiative in particular. “As soon as I saw the ad for the assistant professorship posted, that was one of the first applications I submitted!” she says. So began the process which culminated in her appointment in September 2022.

Rachel attended high school in Wyoming — a befitting location since both her parents are geophysicists — and completed her undergraduate degree at the University of Maryland and her graduate degree at Johns Hopkins University. She started postdoctoral work with COVID-19 vaccine pioneer and RNA Innovative Seminar speaker Dr. Melissa Moore at the University of Massachusetts Medical School. Her term was short-lived as Melissa closed her lab to become Chief Scientific Officer of Moderna in 2016. Fortunately, Rachel was then able to join Dr. Wendy Gilbert’s lab at Yale. “In the end, I feel very lucky that I got the opportunity to work with two of my favorite RNA scientists during my postdoc,” she says.

Upon arriving at Michigan, Rachel began setting up her own lab, which can pose challenges to first-timers; however, the opportunity to share space with fellow faculty scholar Dr. Jay Brito Querido proved beneficial in several ways. “Since our research areas are very similar, we are able to share a lot of the same equipment, and our students interact with one another frequently, so we’ve been able to establish a cooperative community,” Rachel states.

The two labs get together regularly to watch the RNA Innovative Seminar series virtually, which provides a great opportunity for collaboration. Rachel also finds it highly rewarding to work alongside Jay and assistant professors and fellow faculty scholars Dr. Chase Weidmann and Dr. Stephanie Moon, further deepening connections.



Rachel Niederer with fellow Faculty Scholar Jay Brito Querido in their shared lab space. Courtesy of Rachel Niederer.

Niederer headshot image courtesy Rachel Niederer, Ph.D.

Rachel's lab members enjoy relaxing excursions. Courtesy of Rachel Niederer.

Rachel's appointment resides within the U-M Medical School, so her teaching responsibilities are not particularly heavy, though instructing undergraduate students is something she enjoys. "I'm really excited to be teaching seven lectures for a course this semester that started in January 2024. I did quite a bit of teaching in graduate school, and it can be a lot of work, but it's refreshing to interact with students at the beginning of their scientific journey. It's revitalizing."

Her research focuses on identifying the regulatory features involved in the translation process of mRNA, finding out how cellular machinery reads mRNA, and how that program is executed.

"We're interested in a number of pieces of that process, including identifying all the components and features, and figuring out how they work," she says. "These are the very processes that tend to go awry — cells making the wrong protein, or too much or too little protein — which manifest in disease. So if we can understand these signals a little bit better, we can design better interventions and therapeutics."

The meteoric rise of mRNA vaccines has catapulted RNA science into the spotlight, and is of particular relevance to Rachel's area of expertise. "The regulatory features of mRNA vaccines differ from one company to the next, so it's obvious they're thinking a lot about how to leverage the tools and systems that cells have already evolved to make a protein do what you want it to do," Rachel explains.

Rachel's goals encompass two major aims: growing the number of regulatory features that can impact protein synthesis, and figuring out how they work. Some features are used differently in a cancer cell than they are in a healthy cell, and some are used differently in the brain than they are in the liver.

"Once you've identified the feature, there's still quite a bit to learn about exactly how it's executed, or at least well enough to try to figure out what kind of therapeutic interventions or targets are available," Rachel reveals. "So there's a lot of work to do, but it's a very exciting time."

During the translation process, mRNA decodes genes into proteins, but there are also two areas located at the beginning and at the end of the mRNA molecule strand that do not translate into proteins. This noncoding, or untranslated, region represents a new frontier of RNA science and is where Rachel and her team are concentrating their efforts.

"One of the greatest things about being at Michigan is that there are people here working on these same things and even on a more granular level," Rachel notes. "And then being in an environment where we can share each other's discoveries of chemical decorations, for instance, or identification of a new modification, is really great — it's a rich tapestry of possibilities."

Rachel believes that Michigan's strength lies in its breadth of expertise, complemented by the willingness of fellow scientists to help out in a collaborative manner. "I like to follow the science and conduct a lot of curiosity-driven research, and it's nice to feel empowered to do that knowing that Michigan has the resources that enable us to accomplish our goals."

Before coming to Michigan, Rachel was intrigued with the possibility of using ASOs to treat cystic fibrosis (CF). She attended a conference for CF where she met Michelle Hastings and Alexandra Piotrowski-Daspit, with whom she now works on a collaborative grant project funded by the Cystic Fibrosis Foundation. "I study the mechanistic biology, Alexandra the delivery, and Michelle the molecule design," Rachel says. "It's a great example of this kind of collaboration."

"It's an exciting time to be an RNA biologist. There are a lot of possibilities!"

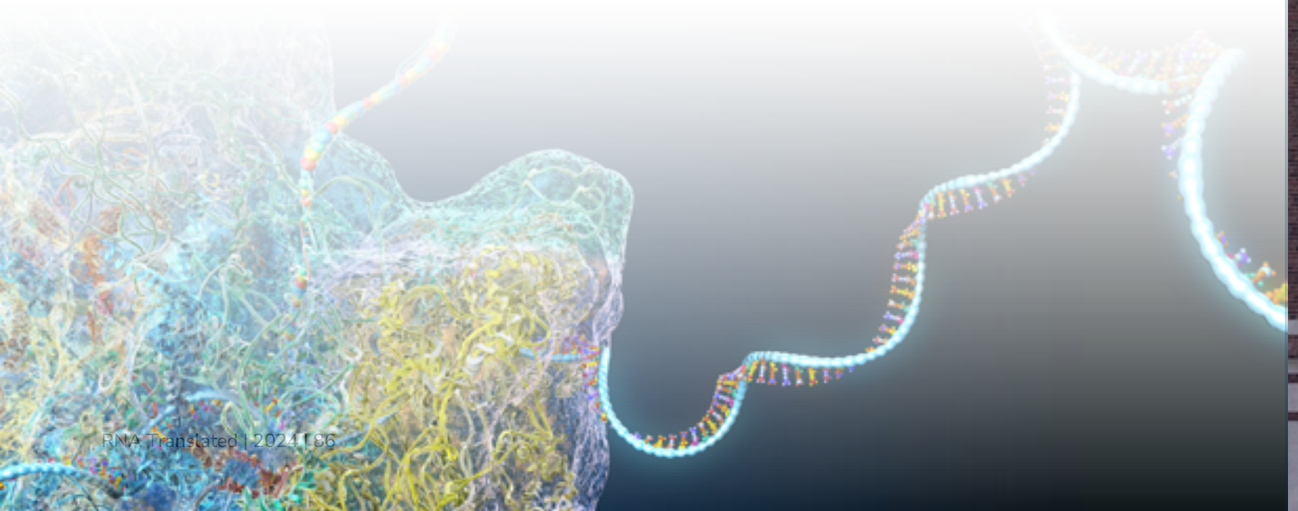
Help change the world of medicine

Support M-RNA Therapeutics

Humanity is at a pivotal moment in medical breakthroughs. Since the first instance of sequencing the entire human genome over two decades ago, rapid advancements in this technology have led to the creation of medical tools that can interface with and alter the genome.

These therapies, nearly all of which contain RNA as a player and component, can then be used to treat some of the rarest diseases facing our population.

No, this isn't a science fiction novel — this is an adaptation of existing technology that's currently being used in FDA-approved applications. The cure could exist today.



Imagine how that changes the landscape of medicine.

Imagine how that could change lives.

But we need your help.

Providing the use of this technology to the experts at Michigan is the first step in making this possibility a reality.

Your support will allow us to purchase the equipment that facilitates the creation of treatments for diseases both rare and chronic.

And where better than a world-class institution and medical facility like Michigan?

We have the personnel, the expertise, and most pressingly, the need.

Join us in the life-changing next step of bringing M-RNA Therapeutics to Michigan.

Thank You.

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Give Today

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

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Thank you for your support!

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