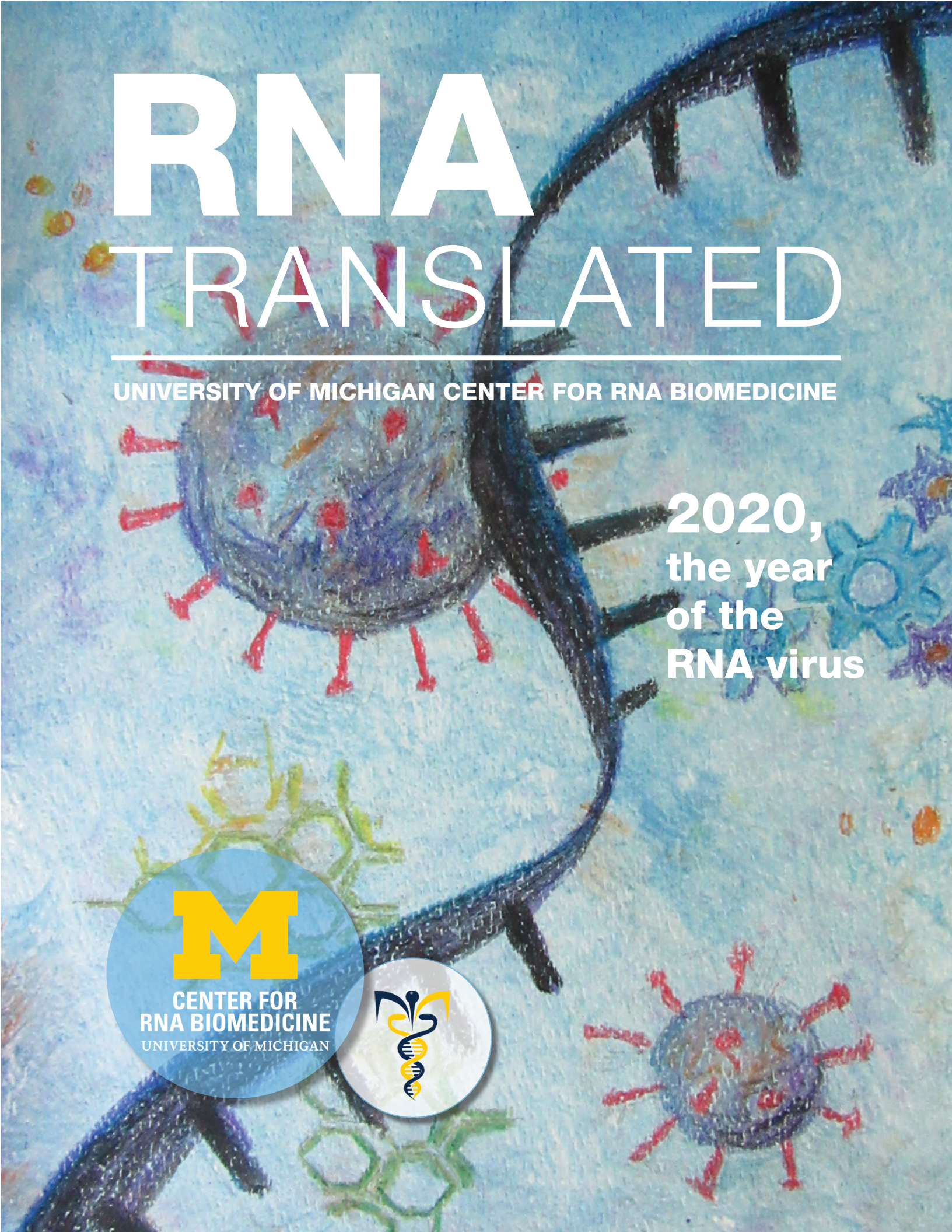
RNA
TRANSLATED
UNIVERSITY OF MICHIGAN CENTER FOR RNA BIOMEDICINE
2020,
the year
of the
RNA virus
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RNA Translated **is an annual publication of the University of Michigan Center for RNA Biomedicine**

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U-M CENTER FOR RNA BIOMEDICINE'S MISSION AND LEADERSHIP

The University of Michigan Center for RNA Biomedicine seeks to:

- **Promote and develop cross-disciplinary collaborations on RNA across campus.**
- **Mentor the next generation of RNA biomedical scientists.**
- **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 translational research to single cell and single molecule biophysics, 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.**

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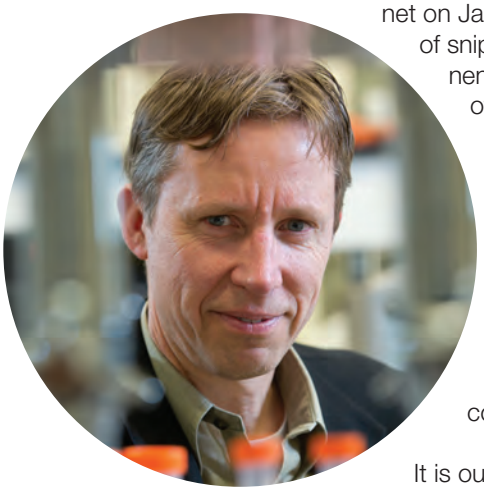

Mats Ljungman,
Professor of Radiation Oncology, Medical School

At the beginning of the year, few would have guessed where the next few months would lead us. If anything, the rapidly emerging COVID-19 pandemic has reminded us of two fundamentals: first, that RNA has awesome powers—as exemplified by the vicious replication of the single strand of RNA, now termed SARS-CoV-2, causing the viral disease. And, second, just how highly interconnected the entire world has become—as evident in the rapid spread of the virus across the globe, by sea, land and air. By now, at least three different RNA-based vaccines are in clinical trials, laying a foundation for our eventual rescue, empowered by the knowledge hard-earned by many RNA biomedical scientists over the last five decades.

An intuition that RNA may be powerful was first conceptualized in the 1960s as the RNA World Hypothesis by Carl Woese, Francis Crick (of Watson-Crick fame) and Leslie Orgel, proposing that the earliest life forms may have used RNA alone for the storage of their genetic information. In fact, we soon learned that RNA can also act as a catalyst, or enzyme, accelerating the chemical reactions needed for life. This insight solved the "chicken and egg" conundrum that proteins are good at being enzymes but bad at replicating genetic material, while DNA is the opposite – good at replicating but bad at being an enzyme; only RNA is the "jack of all trades" that can do both. Since then, we have learned that a large portion of the human genome codes for RNA, and we are just scratching the surface of understanding how all these RNA molecules govern health and disease. COVID-19 drives this point home.

Scientists are driven by the excitement of making discoveries about the world around us. Nowadays, this is best done in diverse teams that cover a broad selection of fields, since it is at the interfaces of the disciplines where a new discovery is most likely made. This is particularly true when rapid progress is needed to match a big problem, such as the COVID-19 outbreak. Once the genome sequence of SARS-CoV-2 was posted on the internet on January 12, 2020, scientists quickly developed tests for and made large quantities of snippets of the sequence; studied the structures of the virus and all of its components; developed ways to replicate the virus for further testing and screened libraries of small drug molecules for potential antiviral activity. The ultimate goal is to develop a safe and effective vaccine against the virus, and therapeutics based biomedical companies such as Moderna are among the first to run with the torch of developing RNA-based vaccines that show great promise in early clinical trials.

This inaugural issue of the *RNA Translated* magazine shines a light on the innovative research on SARS-CoV-2 and beyond taking place within the Center for RNA Biomedicine at the University of Michigan, highlights our two core facilities operating with the support by the Biosciences Initiative, and summarizes the Center's current activities to broadly promote and develop cross-disciplinary collaborations on RNA across campus.

It is our hope that by assembling this sketch of our collective scientific endeavors, we can give the broader audience a sense for the purpose and benefit of foundational research in RNA Biomedicine, a field only becoming more important as our knowledge of life biology expands. It takes a village to raise a child, so we gratefully acknowledge the contributions of many, including the members of our Executive Committee, the members of our Strategic Advisory Board, the Student Postdoc Council and our fantastic staff to the achievements highlighted in this Magazine.

Together, We Solve!

2020, the Year of the RNA Virus

As the world celebrated the coming New Year on December 31st, 2019, Wuhan Municipal Health Commission, China, reported a cluster of cases of pneumonia in Wuhan, Hubei Province. A new killer coronavirus was identified, spreading fast and devastating many, but little was known about it. On January 12, 2020, China publicly shared the sequence of SARS-CoV-2 genome, the virus behind the COVID-19 pandemic, launching one of the largest global scientific efforts in history.

SARS-CoV-2 is a positive-sense, single-stranded RNA virus. This means that its genetic material is coded in RNA—rather than in DNA—and that the virus multiplies by directly hijacking the protein synthesis mechanisms of host cells, killing them in the process. This also means that, literally overnight, RNA research became crucial to potentially saving millions of lives.

In response to the pandemic, many scientists from the University of Michigan (U-M) quickly pivoted their efforts toward the new virus, assembling a remarkable amount of knowledge and leveraging expertise and resources in the areas of bioscience, engineering, medicine, and epidemiology. Not surprisingly, many scientists with the U-M Center for RNA Biomedicine have found that their RNA research has direct relevance in the fight against COVID-19.

Accelerated by the power of collaboration that the Center nurtures, these projects have already produced publications, investigational therapies, and projects ripe for commercial licensing.

“There are many advantages to collaborations, and one of them is to tackle scientific challenges faster and in an efficient and coordinated manner,” says Nils Walter, Francis S. Collins Collegiate Professor of Chemistry, Biophysics, and Biological Chemistry, Co-Director of the Center for RNA Biomedicine. “The faster we establish collaborations, the faster we’ll understand the fundamentals of RNA virus biology that will lead to treatments and prevention, even through RNA itself as a drug, or drug target.”

Following the life-cycle of a virus, we present a few examples of the impact of RNA and bioscience research collaborations on tackling the COVID-19 pandemic and potential subsequent ones.

The virus must enter a host cell

If a virus cannot bind to a host cell surface, it cannot penetrate a cell, and it simply dies. Several teams of scientists at U-M have been focusing on ways to prevent the virus from connecting to a cellular surface.

"Sugar coating"

In 2015, a group led by infectious diseases specialists David Markovitz, M.D., Irwin Goldstein, Ph.D., and Hashim Al-Hashimi, Ph.D., a biochemist, published a study showing that a lectin from bananas, once engineered, could be used against HIV, the virus that causes AIDS.[1]

David Markovitz, M.D., Professor of Internal Medicine, Medical School

Some viruses have a carbohydrate called high-mannose on their surface. **"A lectin, a sugar-binding protein often obtained from plants, can work as an antiviral because it attaches to the high-mannose on the surface of the virus, coating the viral surface and preventing the virus from entering a human cell," explains Dr. Markovitz.** A specific lectin from bananas has been shown to be very effective against HIV, but it also triggers an uncontrolled immune reaction. Markovitz and his team demonstrated that a single mutation in the sugar-binding site on the banana lectin molecule could eliminate the unwanted inflammatory effects.

The next step was to test the engineered banana lectin against influenza in mice. The results, published in 2020,[2] show that animals who usually react very poorly to lectin do very well with this engineered lectin. This molecularly-engineered lectin worked against all influenza strains tested. It was also effective against HIV, hepatitis C, and Ebola.[3] With Jasper Chan at the University of Hong Kong, the team turned to coronaviruses, SARS, and MERS in particular, and found that both viruses were inhibited by the natural lectin when growing in cells.[4] When they gave this engineered lectin to animals in vivo, it was 100% effective against MERS when given prior to infection, but only 60% effective afterward. When the COVID-19 pandemic began, the investigators discovered that the lectin was also effective against SARS-CoV-2, both in the laboratory and in animals (manuscript in preparation).

The engineered banana lectin was also effective as a prophylactic when administered as drops into the nose of mice infected with influenza. Markovitz hopes to achieve similar results with nose drops against SARS-CoV-2. **"This modified lectin works with all influenza viruses and coronaviruses tested so far. It is a broad-spectrum drug that would be very good for a pandemic, but we're still far from human trials," concludes Dr. Markovitz.**

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Unlocking the cell: lessons from prostate cancer research

Arul Chinnaiyan, M.D., Ph.D.,
Howard Hughes Medical Institute Investigator, American Cancer Society Research Professor, and S.P. Hicks Endowed Professor of Pathology and Urology, Medical School

In the last few months, researchers have learned how SARS-CoV-2 uses cell type specific receptors to infect lung, gut, heart and kidney cells. SARS-CoV-2 enters a cell with the help of a protein called transmembrane serine protease 2, TMPRSS2 (pronounced "temp-press-two"). A receptor protein, ACE2, is like a key hole that opens up a cell once the virus inserts its "key," yet TMPRSS2 is needed to turn the knob and open the door. The combination of these two proteins is essential for SARS-CoV-2 to enter the cell where it reproduces.

TMPRSS2 is found in both men and women, but its production is influenced by testosterone, a male hormone. The more testosterone, the more TMPRSS2 is produced. If ACE2 is also present on the surface of a cell, then the conditions are perfect for SARS-CoV-2 to enter the cell, and this could explain why men are three times more likely to die from COVID-19 than women.

A team of scientists headed by prostate cancer researcher Arul Chinnaiyan, M.D., Ph.D., is studying this hypothesis, transferring knowledge about the production of TMPRSS2 from prostate cancer —where a fusion of this gene with the transcription factor ERG is involved in 50 to 60% of the cases— to the lungs of COVID-19 patients. Dr. Chinnaiyan considers that male hormones might play a role in COVID-19, and the team is testing for the co-existence of TMPRSS2 and ACE2 in the lungs. These scientists use phase contrast microscopy and single cell sequencing to study rare populations of cells, looking for the expression of the two genes on the membrane of a lung cell.

If their findings support the hypothesis, it would be possible to use an existing anti-androgen drug, for example enzalutamide, that lowers the levels of testosterone within 24 hours, keeping the production of TMPRSS2 very low, which would prevent the coronavirus from entering a host cell. This drug has been developed to treat prostate cancer and its use and potential are well known to doctors.

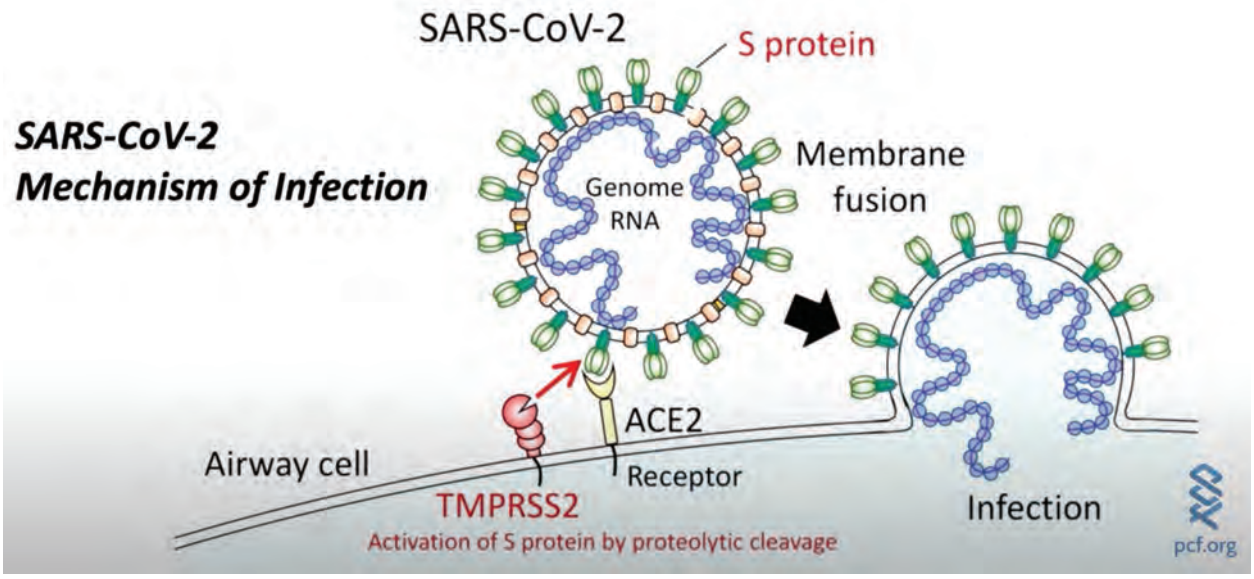


Figure courtesy of the Prostate Cancer Foundation

Several clinical trials across the country have been initiated to test this general hypothesis in patients infected with COVID-19. Perhaps the most noteworthy being the HITCH clinical trial funded by the Veteran's Administration (PI, Matt Rettig, UCLA/VA). Again, collaborations are proving crucial to advance biomedical science and its translation into therapies.

COVID-19 clues from kidney transcriptomics

Matthias Kretzler, M.D., Professor of Computational Medicine & Bioinformatics, and Professor of Internal Medicine, Medical School

Another example of how research from across RNA biomedicine yields potential solutions for COVID-19 comes from studying viral kidney damage. Since 2005, nephrologist Matthias Kretzler, M.D., and his team have collected and analyzed data from multiple cohorts of patients with kidney disease in Michigan, all over the USA, and the world, researching how HIV and BK virus infect the kidneys.

The team is currently using clinical data from these cohorts to identify specific kidney cells that selectively express SARS-CoV-2 receptors that might be targeted by the virus. With a better understanding of the molecular machinery that allows the virus to enter the cell, key molecular pathways can be identified that enable the coronavirus to infect cells, take over their metabolism, replicate, and eventually destroy them.

The molecular program encoded by cellular RNA, also known as the "transcriptome," can be measured in thousands of individual urinary kidney cells to define cell type-specific mechanisms of the kidney injury. The protocol was developed in 2019 as part of ongoing research in nephrotic syndrome. As urine can be easily obtained, the nephrology team could start this study even during the pandemic. This liquid "biopsy" provides a key window into how the virus damages kidney cells.

These existing data can be used to search for factors that increase virus receptors on cells. Patients with preexisting conditions such as diabetes, hypertension, autoimmune disease and organ transplantation are very susceptible to coronavirus infections. As the Michigan Medicine team has carefully studied the kidney transcriptomes in these diseases, research is underway to learn why the kidneys in these patients are so sensitive to viral damage.

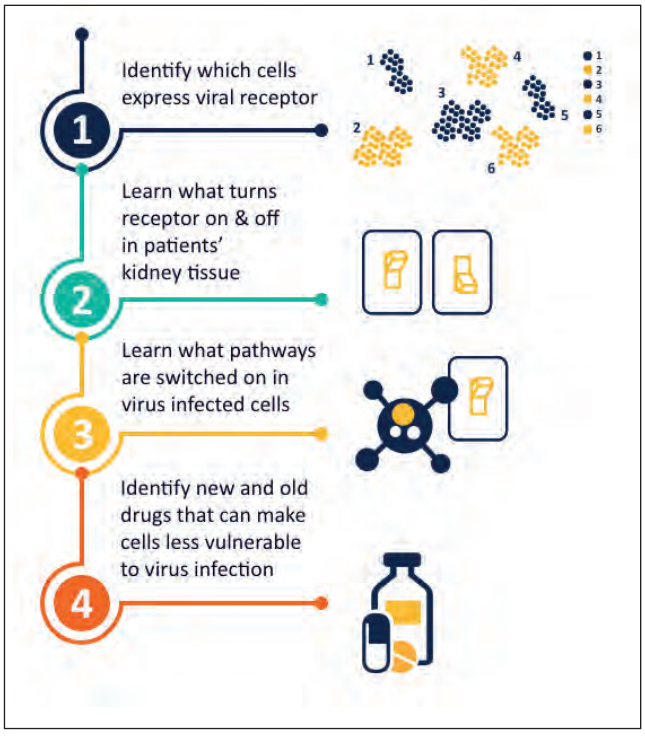


Figure courtesy of Dr. Kretzler's team

Dr. Kretzler's group is taking a two-pronged approach. From existing data, bioinformaticians are studying how the receptors are switched on and off in kidney development and diseases. In parallel, clinical nephrologists, molecular biologists,

kidney pathologists and computer scientists are studying patients with acute kidney injury from COVID-19 treated at Michigan Medicine.

In collaboration with the U-M Center for Drug Repurposing, Dr. Kretzler and collaborators are seeking medications that will modify the virus receptors in patients' cells to make them less susceptible to viral damage.

The large collections of kidney biopsy datasets coordinated by the Michigan team allow computer scientists to integrate and study these molecular and clinical data in multi-disciplinary research networks across the US, Europe and China. The research team's ability to rapidly shift research priorities, addressing the demands and challenges of this unprecedented COVID-19 pandemic, are a testament to the strength of data sharing and scientific collaboration.

Dr. Kretzler's work has benefited from the state-of-the-art University of Michigan core facilities which have rapidly responded to the challenge and are on standby to quickly process patient samples to generate the critical data needed from patients.

From the cell point of view

Andrew Tai, M.D., Ph.D., Associate Professor, Department of Internal Medicine and Department of Microbiology and Immunology, Medical School

Andrew Tai, M.D., Ph.D., is a cellular biologist who is interested in the impact of viruses on cell mechanisms. With collaborators from several U-M labs, he has been studying viruses for decades, in particular the host genes necessary for infection by several RNA viruses. Coming from a cell biology background, he has discovered cellular pathways required for replication of dengue and Zika viruses. The endoplasmic reticulum membrane protein complex (EMC) is known to assist the folding or membrane insertion of a number of membrane proteins. The EMC appears to be essential for efficient dengue and Zika infection but, curiously, not for hepatitis C, although these viruses are all classified within the group Flaviviridae.

Based on these similarities and others, could it be possible to identify host genes that are essential for several viruses to replicate in a cell? **"These early stages of infection are still very poorly understood," explains Dr. Tai. "It is technically hard to study how a virus establishes itself in the cell because only a very small number of viral genomes and proteins are present in the cell at this time."**

Instead of targeting specific viral proteins, Dr. Tai's team seeks to understand which cellular genes, proteins, and lipids have to be present in a cell to allow an array of different viruses to replicate. If one or several of these components could be inhibited, the hijacking viruses would not be able to replicate and propagate. Such broadly acting antivirals may also impose a higher genetic barrier for viral resistance than drugs that directly target virus-encoded molecules. His laboratory is also working on SARS-CoV-2, another RNA virus, by focusing on methods of studying viral replication that can be used at routine BSL2 biosafety levels.

Disrupting the copying mechanism

Vivian Cheung, M.D., Frederick G. L. Huetwell Professor of Pediatric Research, Research Professor, Life Sciences Institute, Professor of Pediatrics and Professor of Human Genetics, Medical School

For decades, Vivian Cheung, M.D., a pediatric geneticist with the U-M Life Sciences Institute, has studied a very rare disease, similar to Amyotrophic Lateral Sclerosis (ALS) but that manifests itself early in the teenage years and evolves very slowly. Named ALS4, this rare disease is caused by a mutation in a gene called senataxin, which is an RNA helicase that relaxes the RNA shape.

When information about SARS-CoV-2 was released, Dr. Cheung was very surprised: **"The RNA of the virus encodes a familiar protein, the one that I've studied for years in a very rare neurodegenerative disease. Here it was, in the RNA of the COVID-19 virus!"**

The coronavirus genome is much smaller than the human one. The virus has a genome of 30,000 nucleotides while humans have three billion. The virus makes fewer than 30 different proteins, while humans make 25–30,000 proteins. To be able to observe the similarity between a particular protein of the coronavirus (nsp12) and the protein that is mutated in ALS4 (senataxin) was extremely fortunate. Both nsp12 and senataxin are helicases that unwind RNA.

So why would a virus need this unusual protein? "**It turns out that this virus is particularly clever," explains Dr. Cheung. "When the virus gets into the human cell, its first job is to copy itself so it can spread. It needs to make many copies of its RNA. However, the RNA copying machineries of the virus need to differentiate between the viral and the human RNA. The virus RNA makes a unique folding pattern (a cloverleaf shape and a stem-loop). But then, the viral folded RNA needs to be relaxed by the helicase for all the machinery to copy it. This is where our excellent knowledge about this specific RNA helicase process comes in, so we can find ways to disrupt the virus copying process."**

This set of proteins and mechanisms are similar between all the coronaviruses that cause SARS, MERS, COVID-19, and a third of all common colds. Dr. Cheung and her team are now looking for a therapy that targets these shared properties of the viral replication process. This therapy would treat all existing coronavirus infections as well as any that emerge in the future.

The project team collaborates with investigators at the NIH National Institute of Allergy and Infectious Diseases and the National Institute of Neurological Diseases and Stroke. It is also partnering with a pharmaceutical company that specializes in RNA-based therapeutics.

Her team's ability to turn so quickly to this project makes clear the importance of the fundamental study of RNA. Their knowledge of the essential biology of RNA allowed them to step-up quickly to find solutions for an emerging pandemic.

RNA in the clover loop form. Drawing by Colleen McGarry

Our body fights back

Our immune system is made of two arms—the "innate" (non-specific) and "adaptive" (specific) immune responses. Both arms of the immune response are closely linked and work together whenever a germ or harmful substance triggers an immune response.

The innate immune response provides a general defense against harmful germs by recognizing molecular patterns expressed by a number of infectious agents. It combats infections using viral restriction factors, cytokines and immune cells such as natural killer cells and phagocytes that can battle the infection. The main job of the innate immune system is to rapidly fight infectious agents that enter the body. The adaptive arm of the immune response, sometimes called the cell mediated immune response, is generated by very specific recognition of small pieces (antigens) of the invading germ. The cells involved in this part of the response include antibody-producing B cells and killer T cells. Because the response is very specific and unique to each strain of germ the body is exposed to, the adaptive response takes longer to develop than the innate response.

Uncloaking the invader

Kathleen L. Collins, Ph.D., Professor of Internal Medicine, Professor of Microbiology and Immunology and Associate Dean for Physician Scientist Education and Training, Medical School

For decades, Kathleen Collins, Ph.D., an immunologist with Michigan Medicine, and her team have studied the major viral mechanisms of resistance to the innate and cell mediated immune (CMI) responses. Despite effective antiretroviral therapy, HIV evades eradication in a latent form that is not affected by currently available drug regimens.[5]

HIV is a retrovirus, which means that it copies its RNA into DNA and uses that DNA "copy" to incorporate viral genes into the DNA of the host cells. HIV evades the adaptive immune response and establishes infection by making viral proteins that counteract innate immune response.

Following initial infection, many HIV infected cells have short half-lives and die within days or months due to toxicity from the virus and direct killing by cells of the immune system—cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. But genes encoded by HIV allow some infected cells to evade killer T cells. Because of resistance to the innate and adaptive immune responses, HIV causes a chronic infection that cannot be cured by a natural immune response. Without treatment, HIV is devastating to the immune system, leading to acquired immunodeficiency syndrome (AIDS).

Certain enzymes—histone deacetylases (HDACs)—promote HIV latency. One possible therapy would be to target these enzymes to reverse the latency of HIV cells. Dr. Collins and collaborators have demonstrated that a targeted treatment with selective HDAC inhibitors induced more potent HIV latency reversal than broadly acting agents. The lab is also collaborating with Dr. David Sherman's lab at the University of Michigan Life Sciences Institute on a newly identified small molecule that sensitizes

5. Zaikos, T. D., Painter, M. M., Kettinger, N. T., Terry, V. H., & Collins, K. L. (2018). Class 1-Selective Histone Deacetylase (HDAC) Inhibitors Enhance HIV Latency Reversal while Preserving the Activity of HDAC Isoforms Necessary for Maximal HIV Gene Expression. Journal of Virology, 92(6). doi:10.1128/jvi.02110-17

virally infected cells to killing by T cells. A combined approach that reverses latency and sensitizes the infected cells to immune mediated killing could help clear the virally infected cells from the body.

Dr. Collins is exploring ways by which a possible cure for HIV could be applied towards SARS-CoV-2. Immune system evasion is a common tactic of RNA viruses, particularly the betacoronaviruses, including SARS-CoV, MERS, and SARS-CoV-2. A better understanding of how SARS-CoV-2 evades the immune response and causes severe disease will help with the development of specific therapies.

Innovations to treat and prevent infections by mutable and emerging viruses

Marilia Cascalho, M.D., Ph.D., leads Michigan Medicine's Transplant Biology program with Jeffrey L. Platt, M.D. A part of their research is focused on memory B cells that quickly produce antibodies to pathogens recognized from past infections. She is now working on antibody therapies for SARS-CoV-2, building on her extensive experience with organ transplants.

Marilia Cascalho, M.D., Ph.D., Associate Professor of Surgery Transplant and Associate Professor of Microbiology and Immunology, Medical School

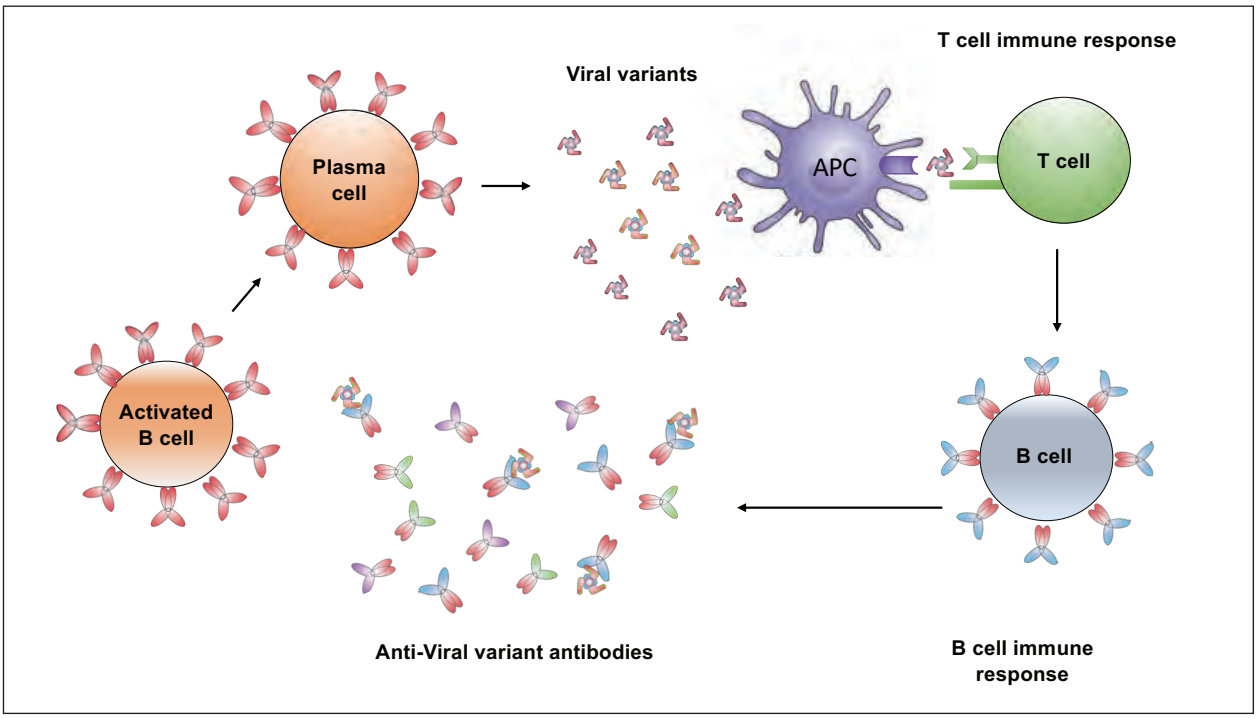
"When viruses mutate, the antibodies generated against the original virus can no longer bind to the new form of the virus," explains Dr. Cascalho. Viral proteins can vary from one strain to another. "This means that an effective vaccine or treatment will need to contain antigens from many different strains to respond to different versions of the viruses." Drs. Cascalho and Platt have developed techniques to engineer large quantities of antibodies that meet this need.

Monoclonal antibodies for mutable viruses

There are billions of B lymphocytes (B cells) in our body. B cells make antibodies that bind to the surface of foreign organisms, like viruses, marking them for destruction. There is perhaps about one in 100,000 B cells that makes the antibody capable of neutralizing a specific virus. B cells are also the only cells in the body that mutate their genes. These mutations are essential to make effective antibodies and to build immunological memory which protects us against repeated encounters with pathogens.

Currently, antibodies from the plasma of recovered COVID-19 patients are one of the most promising treatments for acute symptoms, but serum supply is limited. Engineering easily produced monoclonal antibodies is a logical solution, but it is very challenging to find the right antibody among the billion specific antibodies produced by our B cells. To maximize the odds and efficiently access blood from many patients infected with different strains of SARS-CoV-2, Drs. Cascalho and Platt have established a network of collaborations across the country including in California at UCLA, and at Henry Ford Hospital in Detroit.

They developed a novel technique to isolate the B cells that produce antibodies that can bind to the spike protein of SARS-CoV-2 (manuscript in preparation). They are also able to clone these antibodies to produce them in large quantities. The B cell isolation technique was first developed in the field of transplantation and is now adapted to produce antiviral antibodies for HIV, influenza, and COVID-19. This technique relies on the availability of natively expressed molecules, either at the surface of a virus, or expressed by cells mimicking natural infection.



This figure shows a schematic of the immune response to a mutable vaccine. Activated B cells mutate genes encoding viral antigens and become antibody secreting cells that also secrete mutated viral antigens. Mutated viral antigens in turn evoke specific cellular immunity that target mutated viral antigen "reservoirs." The mutable vaccine offers a solution to clearing viral reservoirs. Figure courtesy of Dr. Cascalho.

The team so far has isolated over 200 antibodies that can target coronaviruses and is now completing their testing for COVID-19. These monoclonal antibodies are relatively inexpensive to produce because they originated from COVID-19 patients' cells, and do not need to be "humanized" as if they were coming from another species like rabbits or mice.

Bringing engineered antibodies to the bedside requires production at large scale in specialized facilities where toxicity studies can be conducted to ensure safety. **"It was great to have U-M resources to start this research, and we now are ready to take it further. We'd love to have a relationship with a company that could take this work to the next step, and do the toxicity studies and establish safe conditions for human trials," says Dr. Cascalho.** She is currently searching for partners who can commercialize this antibody treatment for COVID-19 patients.

Mutable vaccine against mutable viruses

Scientists have attempted to create a "universal vaccine" for the influenza virus, targeting common strains of the virus. However, effective vaccines against every influenza viral strain still do not exist in part because mutations allow viruses to escape immunity generated in the course of infection or following vaccination against one or a few strains. Immunity helps to fuel virus evolution.

As an alternative to conventional vaccination, "we thought to co-opt the immunoglobulin somatic hypermutation machinery of B cells to mutate viral antigens and, in this way, immunize against antigenic variants generated in succession in vaccinated hosts," says Dr. Cascalho. Somatic hypermutation is the process by which the

immune system "improves" antibodies. In individual cells, a programmed mutation process creates slightly different versions of immunoglobulin. The hope is that by creating a vaccine that can instead mutate viral antigens using the immunoglobulin somatic hypermutation, B cells will be able to stay ahead of mutable viruses like HIV and influenza. "We found recently that the strategy is feasible in experimental animals where it evokes immunity against viral variants in anticipation of viral variation in the wild. We are anxious to test this novel strategy against mutable viruses like HIV and the coronaviruses," explains Dr. Cascalho. With Dr. Platt and collaborators, she patented this "mutable vaccine" concept. She is looking for pharmaceutical partners who can help move it forward.

"As scientists, it takes a lot of courage to pursue entirely novel ideas and models, and to think completely outside the box. But this is what we all so urgently need right now!" says Dr. Cascalho.

Antibody tests: sensitivity and selectivity

The adaptive immune system makes antibodies to selectively fight germs that the body has previously come into contact with. This is also known as an "acquired" or specific immune response.

Janet Smith, Ph.D., Margaret J Hunter Collegiate Professor in the Life Sciences, Professor of Biological Chemistry, Medical School, Research Professor, Life Sciences Institute, Associate Director, Department of Life Sciences Institute and Professor of Biophysics, College of Literature, Science, and the Arts

Antibody tests show whether one's immune system has reacted to a specific pathogen. If the test is positive, the individual must have been infected. However, one of the challenges with developing an antibody test for SARS-CoV-2 is to detect antibodies that are specific to this particular virus and not to any other one.

Biochemist Janet Smith, Ph.D., and collaborators from the U-M Life Science Institute Center for Structural Biology, a high-throughput protein laboratory for protein engineering, and protein purification facility for small- and large-scale protein production, have produced highly purified spike proteins of SARS-CoV-2 for an antibody test. The spike protein is a protein on the outside of the virus that interacts with host cell receptors. Smith's group has optimized the production of both the complete spike protein and the receptor-binding domain at the very tip of the spike. The proteins are used in antibody tests developed in the U-M Department of Epidemiology and validated in the Department of Pathology.

That receptor-binding domain is important in that it is the part of the spike that allows the virus to enter the host cells. It is also the portion of the spike that shows the greatest genetic variation from other coronaviruses, which is a key to developing highly specific antibody tests.

"Two main characteristics are most important for these tests," explains Smith. "The first is sensitivity, or how many antibodies must be present before the test can detect them. But much more important is selectivity —the test's ability to pick up only antibodies that would fight this specific coronavirus and not some other virus."

The U-M antibody tests have been evaluated with sera collected before the COVID-19 outbreak, to ensure the tests do not produce positive results in individuals never infected with SARS-CoV-2. Serum samples from patients who tested positive for COVID-19 by a molecular assay were also tested to confirm the sensitivity of the assay in the detection of antibodies in individuals recovering from infection. The antibody tests at U-M proved to be highly selective for SARS-CoV-2 and reliably sensitive. These tests are now being prepared for broader testing.

Drug repurposing and "cocktail therapy": attacking from multiple angles for an additive effect

Jonathan Sexton, Ph.D., Assistant Professor of Internal Medicine, Medical School and Assistant Professor of Medicinal Chemistry, College of Pharmacy

Knowing that it can take 10 years and billions of dollars to develop and bring a new drug to market, scientists are exhaustively surveying existing FDA approved drugs to treat COVID-19. **"This is the only way to respond as quickly as possible to the disease," explains Jonathan Sexton, Ph.D.,** one of the heads of the U-M Center for Drug Repurposing (UM-CDR) in a Michigan Minds podcast (April 8, 2020).

Following this approach, a repurposed drug showing beneficial effects against SARS-CoV-2 is already in clinical use. Remdesivir was originally developed against another single-stranded RNA virus, Ebola.

In early March 2020, Sexton and colleagues from the UM-CDR tested every FDA-approved drug in SARS-CoV-2 infected human cells and used artificial intelligence to analyze images of the cells. From this analysis, they identified compounds that could have effective antiviral properties for this new virus. With a total of 16 drugs in hand, they are adopting a "drug cocktail" methodology, similar to the one pioneered for HIV. Single agents like AZT had been deployed with marginal efficacy against HIV, but when used in combination with other drugs that inhibit viral replication, restore the immune functions, and reduce the transmissibility of the virus itself, the results were highly effective. Each drug within the cocktail has its own effect, and in combination, they create synergies that make them more potent, allowing lower dosing to minimize sideeffects. The combinatorial approach also diminishes the risk of acquired drug resistance from single-agent selective pressure.

Dr. Sexton and his collaborators have identified several FDA-approved drugs that have unexpected antiviral properties for SARS-CoV-2, including lactoferrin, ipratroprium (Atrovent), and domperidone.[6] Lactoferrin is made from a protein that exists in cow and human milk. It is very safe in humans, and is often added to baby formula. It prevents viral entry, stimulates an antiviral response in the host cell, and potentiates the efficacy of both remdesivir and hydroxychloroquine. Another drug is the Atrovent inhaler, a bronchodilator that relaxes muscles in the airways and increases air flow to the lungs. It not only helps with the respiratory symptoms of COVID-19, it also works as an antiviral. Not much used in the US, domperidone is usually prescribed to treat nausea and vomiting, and turns out to also be an antiviral. It would be particularly relevant when COVID-19 symptoms affect the gastrointestinal tract.

The U-M team is proposing a combination of existing drugs that can attack different viral mechanisms, at various stages to prevent SARS-CoV-2 from entering the host cell, inhibit viral replication, or dampen the cell stress response to the virus.

The next step for this research is to analyze thousands of patient records from the U-M Health System, as well as data mining millions of patient files in insurance company databases. This extensive study will establish safety and potential efficacy for the drugs the U-M team discovered, before engaging with human trials.

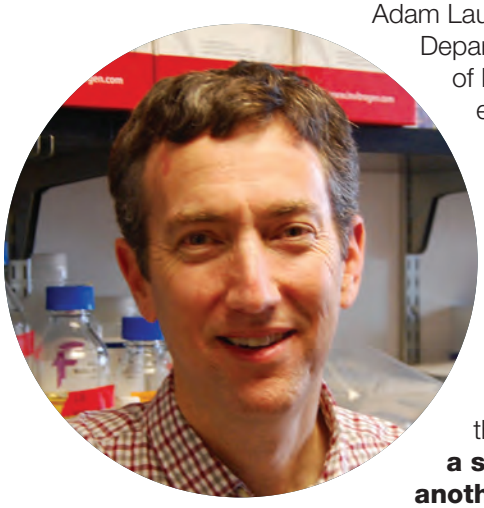
Drug repurposing requires a large array of skills, and, according to Sexton, "one of U-M's strongest points is the amazing collaboration.

6. Mirabelli, C., Wotring, J. W., Zhang, C. J., Mccarty, S. M., Fursmidt, R., Frum, T., . . . Sexton, J. Z. (2020). Morphological Cell Profiling of SARS-CoV-2 Infection Identifies Drug Repurposing Candidates for COVID-19. *bioRxiv* 2020.05.27.117184; doi:10.1101/2020.05.27.117184

It's the 'good old mid-West collegiality.' We have collaborators from the College of Pharmacy, the School of Public Health, gastroenterology and hepatology, microbiology, anesthesiology and more. We have this fantastic team that has really pulled together to move very quickly from the bench to the bed side. The idea started in March and we already have a plan for clinical application in September."

The team has also strong collaborations outside of U-M, and in particular with Michael Avidan at Washington University and the Crown Collaborative Network, funded by the Bill & Melinda Gates Foundation. Together they work on COVID-19 clinical trials around the world, including in South Africa where there is a strong infrastructure that was established for the HIV/AIDS pandemic.

Tracking viral spread through evolution



Adam Lauring, M.D., Ph.D., Associate Professor, Microbiology & Immunology, Medical School, and Co-Director of the University of Michigan Center for Infectious Disease Threats

Adam Lauring, M.D., Ph.D., a virologist in the Division of Infectious Diseases and the Department of Microbiology and Immunology, studies the genetics and evolution of RNA viruses. His goal is to identify new strategies to control infectious disease by understanding the evolutionary dynamics of the organisms.

Since 2012, he has collaborated with two epidemiologists from the School of Public Health, Arnold Monto, Ph.D., and Emily Martin, Ph.D., M.P.H., tracking respiratory infections throughout Michigan over the course of five flu seasons.[7]

They tested samples collected from the study to confirm influenza infection and identify subtypes, and then sequenced the viral genomes of the samples. By tracking flu variants, Lauring and his team were able to map the transmission dynamics of the flu in Michigan.[8] **"Mutations are like a signature that allows one to track a virus from one person to another. With this technique, we can understand how viruses are evolving in the 'real world,'" says Dr. Lauring. "We are able to draw a very detailed map of the influenza spread."**

Dr. Lauring and his colleagues are now transferring their expertise about the spread of the influenza virus to SARS-CoV-2. SARS-CoV-2 differs from influenza in a number of ways, and one important difference is in the rate of mutation. According to Darwin's theory of evolution, organisms benefit from and adopt the mutations that are adaptive while the deleterious ones die out. SARS-CoV-2 has approximately a 30,000-base genome, which is two to three times larger than the genome of most other RNA viruses. Scientists have also established that there is an inverse relationship between the length of a genome and its tolerated error rate, so that approximately one error is made per full replication event. The exceptional length of the coronavirus genome could explain why it is the only RNA virus equipped with a proofreading system, resulting in a mutation rate 10-fold lower than other RNA viruses.

Why, then, do RNA viruses still mutate so much? The oldest and most common explanation is that these mutations allow the virus to escape attacks from its host. Another explanation is that the virus works too fast and makes mistakes as it copies its genome.

"It's kind of intuitive, haste makes waste," explains Dr. Lauring. "The most important thing for a virus is to make more of itself, quickly. As a result, they make mistakes. For most RNA viruses, their polymerase (the protein that copies the RNA genome) does not have a proofreading system. The virus saves time and energy in order to reproduce faster, but makes mistakes. This is the case with poliovirus, for example."

Dr. Lauring describes viral mutations on two levels. At the molecular level, inside the cell, the polymerase makes mistakes, and the virus mutates. This is a biochemical mutation rate. At a population scale, mutations accumulate over time. This mutation

7. Monto AS, Malosh RE, Evans R, et al. Data resource profile: Household Influenza Vaccine Evaluation (HIVE) Study. *Int J Epidemiol.* 2019;48(4):1040-1040g. doi:10.1093/ije/dyz086
8. Mccrone, J. T., Woods, R. J., Martin, E. T., Malosh, R. E., Monto, A. S., & Lauring, A. S. (2018). Stochastic processes constrain the within and between host evolution of influenza virus. *ELife,* 7. doi:10.7554/elife.35962

rate depends not only on the biochemical rate, but also on other factors such as how many people are infected, and how the disease spreads. In this respect, the SARS-CoV-2 mutation rate is about half that of influenza, while its biochemical mutation rate is about 10-fold lower.

Dr. Lauring and his team are sequencing viruses from COVID-19 hospitalized patients and also in household cohorts in Southeast Michigan. As with their influenza work, they hope this will help them to define who infected whom and how the virus changes as it moves through communities. The results from the study will guide recommendations on how to prevent the spread of the corona virus within households, and how to live with a pandemic.

Advancing RNA research to combat COVID-19 and future pandemics

RNA viruses have been responsible for the major viral pandemics in recent history: Zika, SARS, MERS, Ebola, influenza, and now SARS-CoV-2. In a short time, we have witnessed the devastating impacts of a small RNA virus on human lives and the economy worldwide, highlighting the urgency of advancing RNA research to address the current pandemic and prepare for future threats.

There remain many unanswered questions about RNA viruses. For example, the genome of positive-sense RNA viruses has three different possibilities: it could be translated to make protein, it could be replicated by a polymerase to make more RNA molecules, or it could be packaged into viruses. But how is the fate of any individual RNA molecule decided? All of these areas require more investigation.

At the U-M Center for RNA Biomedicine, a community of over 150 RNA scientists collaborates to answer these foundational questions. All dedicated to excellence and passionate about the potential to revolutionize therapies, they share ideas that create synergies. The Center facilitates these scientific sparks and is an advocate for RNA research at U-M and beyond.

Due to the central role of RNA biology in COVID-19 and many other diseases with pandemic potential, the Center for RNA Biomedicine became an important linchpin to the newly created Michigan Center for Infectious Disease Threats (MCIDT). “RNA biology is very important to treat these infectious diseases so there are many topics MCIDT and the Center for RNA Biomedicine will synergize on,” says Dr. Lauring, Co-Director of the MCIDT.

Advanced technologies developed both at the U-M Center for RNA Biomedicine’s SMART Center and at the Bru-seq Lab are yielding answers to many of these questions. At the SMART Center, scientists are able to “see” RNA behaviors in real-time, in living cells. They can observe individual molecule behaviors rather than averages that mask the cell biology (see article p. 27). At the Bru-seq Lab, scientists can measure the rates of RNA activities inside cells (see article p. 22), and study the genetic code behind all cellular functions.

Cross-disciplinary and innovative RNA research is proving to be key to cure the current pandemic and the next ones.

What are viruses?

Over the years, there have been many debates about whether viruses should be considered living organisms or biological chemicals. These "creatures" keep fascinating and challenging scientists and anyone who comes to learn about them (see Dr. Moon and Dr. Keane's interviews, pages 38 and 40).

Biologists and botanists discovered viruses in the late 19th century, establishing virology as a new area of research. Since then, scientists from many fields have studied viruses, expanding and deepening the field of virology from the basic biology that looks at the interaction between the virus and its host environment to therapeutic interventions and applications. At the same time, new technologies have been developed that allow scientists to investigate the smallest scales (see articles on the SMART Center, page 27 and Bru-seq lab, page 22). All along, biomedicine and virology research have become more specialized and require a wide array of expertise that calls for collaborations with bioengineers, bioinformaticians and epidemiologists.

The infinitely small expands infinitely

Viruses have existed for millions of years, and are an integral part of all forms of life. There are billions of them, everywhere and in every living organism, plant, animal, and human. The polio virus, 30 nanometres (nm) across, is about 10,000 times smaller than a grain of salt. With a diameter of approximately 125 nm, SARS-CoV-2 is about 600 times smaller than the average diameter of a human hair. Most viruses are usually 100 times smaller than bacteria, yet if we were to align all the viruses of the planet Earth side by side, they would reach beyond the edges of our galaxy! SARS-CoV-2, approximately 125 nm, is 600 times smaller than the average diameter of a human hair, yet it can wreak havoc on the entire human body.

There are an estimated 380 trillion viruses in our body at any one time, while it is estimated that there are 30 trillion human cells in the average human body. Luckily, only a few of them can make us sick, and these pathogens are sometimes contracted through contacts with infected animals. These are called zoonotic diseases. COVID-19 is one such example, likely originating in bats.

Types and categories

There are many different types of viruses. Their genetic code comes either in the form of RNA or of DNA, but they all share two characteristics. First, they all are parasites, which means that they depend on the components of a host cell to replicate. Second, viruses mutate rapidly, which means that they change their genome and appearance. These two characteristics are essential to understanding the challenges associated with viral treatment and vaccine developments.

Viruses can be classified according to the way they replicate within a cell, their shapes, and their genetic structure (i.e., DNA versus RNA viruses). The largest group of viruses is characterized by a positive-sense single-stranded RNA genome, meaning that their RNA can be directly translated into a protein. This category includes many medically important viruses such as coronaviruses (SARS, MERS-CoV, SARS-CoV-2), flaviviruses (Yellow Fever, dengue, Zika, and hepatitis C), and picornaviruses (polio, norovirus). Other RNA viruses, such as Ebola and influenza, have a negative-sense genome that requires it to be first converted into a positive-sense RNA. Retroviruses, such as HIV, copy their RNA into DNA and use that DNA "copy" to infect host cells. They then use the cell's components to make additional viral particles. The retrovirus DNA can integrate into the genomic DNA of a host cell and hide there for a long time, possibly for millennia—in fact, 8% of the human genome derives from retroviruses that infected our ancestors.

Using this classification system, scientists can search for similarities and differences between viruses, and gain a better understanding of the fundamental biology of viruses and cell mechanisms. It also helps recognize scientific areas that are well understood and identify knowledge gaps.

Genome	Virus group	Viruses
Double-stranded DNA	Herpesviridae	Herpesviruses
	Papillovaviridae	Human papilloma virus
	Poxviridae	Smallpox
Positive-sense, single-stranded RNA	Coronaviridae	MERS, SARS-CoV, SARS-CoV-2
	Flaviviridae	Yellow Fever, Dengue, Zika, West Nile, hepatitis C
	Picornaviridae	Polio, norovirus, coxsackievirus
Negative-sense, single-stranded RNA	Filoviridae	Ebola
	Orthomyxoviridae	Influenza
Single-stranded RNA retroviruses	Retroviridae	HIV
Double-stranded RNA	Reoviridae	Rotavirus

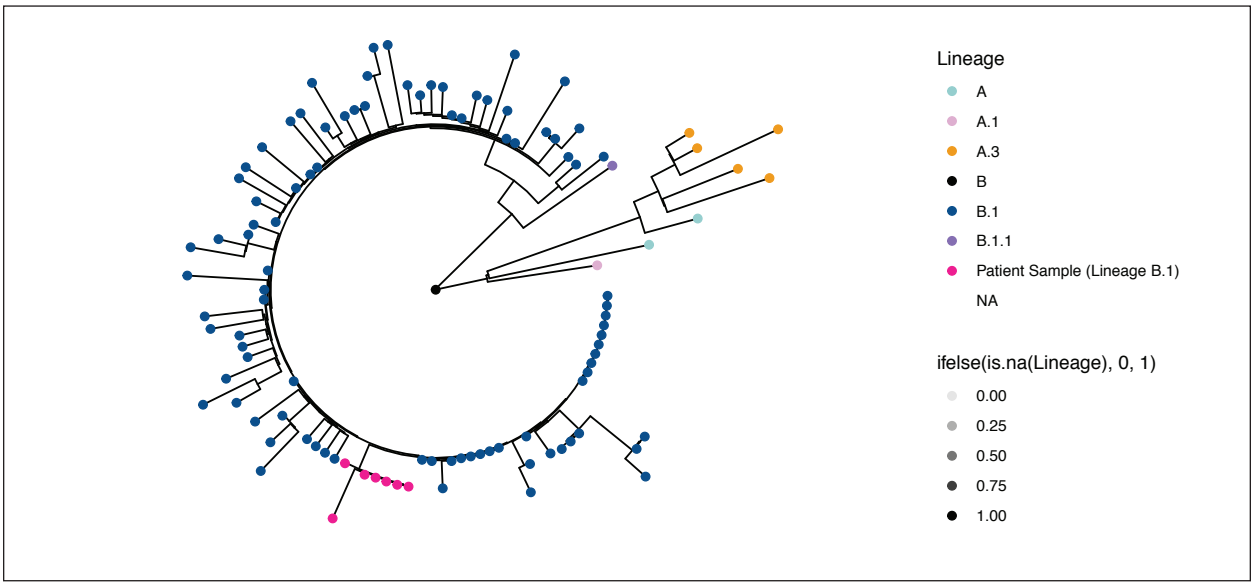
Table 1: Types of viruses according to their genetic structures with examples of medically important viruses

RNA viruses to test evolutionary theories

For decades, scientists have used the fast mutation capability of RNA viruses to test evolutionary theories. With just a few days or a few weeks of RNA virus replication in a lab, they can test theories about phenomena that usually take millions of years to happen.

Virologists are interested in evolutionary theories to understand the replication and propagation of viruses.

Evolutionary biologists have also used RNA viruses and their host cells like interacting ecosystems to model how one species can adapt to a new environment.



Phylogenetic tree that shows the relationship among SARS-CoV-2 viral sequences from U-M hospital, courtesy Dr. Lauring

Viruses and lab safety

Biosafety levels (BSL) are safety practices observed in labs in order to protect personnel as well as the environment and the community. The biosafety levels are defined from BSL1 to BSL4, four being the highest level and very rare. BSL3 is a lab where scientists can work safely on organisms that can cause serious or potentially lethal disease through inhalation. The U-M Medical School is equipped with BSL3 labs for in vitro research. Access is currently limited to projects related to COVID-19.

However, working in a BSL3 laboratory is time consuming and cumbersome, so efforts are underway to generate models of SARS-CoV-2 infection that can be safely used at lower biocontainment levels. Such models are incapable of producing infectious SARS-CoV-2 particles due to deletion of one or more viral proteins essential for virus production. These models would then be used at biosafety level 2 (BSL2), which is possible in most life science laboratories.

Can viruses be good for us?

"Fossil" viruses

In some cases, the genome of a virus is integrated into the genome of its host cell, where it can remain for a long time, "unnoticed." These are called endogenous viruses. If a viral integration happens in an egg or sperm cell, the bit of the virus genetic code is passed on from generation to generation. It becomes a sort of "molecular fossil." Endogenous retroviruses constitute about 8% of our entire genome.

Through mutations, the entire genome of a virus might be replaced in just a few hundred years. Endogenous viruses are slowly mutated until they are no longer viable, replicating viruses. This can take hundreds of thousands of years.

Since these pieces of viruses are living in the human body for so many years, and exist in such large numbers, could they play a role in normal human development? We know that it is the case with syncytin, a cell-cell fusion protein that is essential to the development of the placenta, and therefore to the evolution of mammals. Other examples confirm that endogenous viruses have shaped our immune system over time. Evidence suggests that, through mutations, endogenous viruses contribute to the plasticity and adaptability of our genome.

With trillions of viruses living in our bodies at all times, much is still to be discovered, but endogenous viruses are very likely to have played an important role in large scale evolution.

Viruses and bacteria, friends or enemies?

Some viruses can infect and replicate only in bacterial cells. Because these viruses destroy their bacterial host, they are called bacteriophages, or "phages" (from the Greek "devour"). They are ubiquitous in the environment and are recognized as the most abundant biological agent on earth. Phages are an important part of the human microbiome and are considered a critical mediator of genetic exchange between pathogenic and non-pathogenic bacteria.

Like all viruses, phages are very species-specific with regard to their hosts and usually only infect a single bacterial species, or even a single, specific strain within a species. For more than 100 years, research has attempted to use this phage property as a means to treat pathogenic bacterial infections in people and animals.

However, the interactions between viruses and bacteria remain an emerging research topic in infectious disease.

Gene therapy

Gene therapy is currently being developed to treat viral infections by inserting new genes that supercharge the cellular response against the virus. A lentivirus is used to perform the gene insertions.

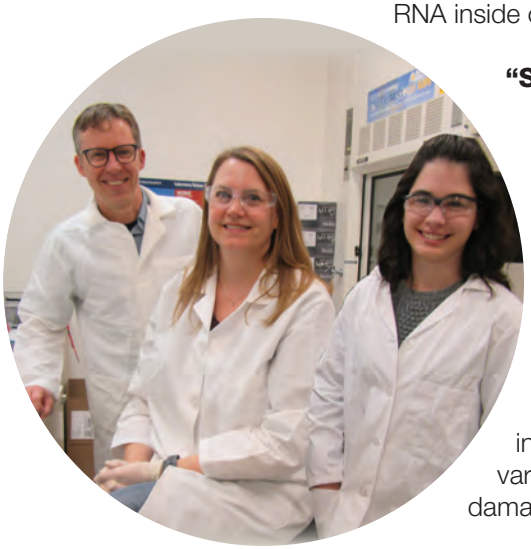
Using RNA vaccines to fight the RNA virus

RNA vaccines work by introducing an RNA sequence that encodes the antigen against which an immune response is sought. The body's own cells then take up and use this genetic material to produce the antigen. Potential features of this approach include the stimulation of long-term immune responses, high vaccine stability and relative ease of large-scale vaccine manufacture. Several RNA vaccines are in the research pipeline, although none are currently licensed for human use.

The COVID-19 pandemic may stimulate decades of foundational RNA research toward RNA vaccines: the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases, in partnership with the biotechnology company Moderna, launched a phase 3 clinical trial in July 2020 for an RNA vaccine against COVID-19. Pfizer/BioNTech and CureVac are also developing an RNA vaccine for COVID-19.

A "tsunami" of RNA data

Since 2013, the University of Michigan (U-M) Center for RNA Biomedicine Bru-seq Lab's experts have further advanced RNA sequencing techniques that allow them to investigate the complexity of RNA. In particular, the lab's team has developed Bru-seq and BruChase-seq techniques which record the production and degradation rates of RNA inside cells, bringing revolutionary insights into RNA functions.



Left to right: **Mats Ljungman,** Professor of Radiation Oncology and Environmental Health Sciences, Medical School, Director of the Bru-seq Lab, and Co-Director of the Center for RNA Biomedicine, **Michelle Paulsen,** Bru-seq Lab Manager, and **Hailey Blinkiewicz,** Research Lab Technician, in the Bru-seq Lab

"Scientific discoveries are in large part driven by technology advancements, and when next generation sequencing was made available, it became possible to simultaneously keep track of all the different RNAs present in cells." —Mats Ljungman

Following the Ljungman lab's first publication of the Bru-seq and BruChase-seq techniques in 2013,[1] the team has contributed its expertise to many studies, covering a wide range of topics from molecular mechanism of action of novel small molecule drugs and traditional chemo- and radiotherapy, transcriptional patterns in cancer cells, mechanisms of induction of chromosomal structural variations, replication timing, regulation of cellular responses to DNA damage, and inflammatory signals and viruses.

In only seven years, these studies have resulted in over 50 publications in high impact journals such as *Cell, Molecular Cell, Nature Genetics, Nature Communication, Science Translational Medicine, Genes and Development, eLife, Cancer Research,* and *Genome Research.*

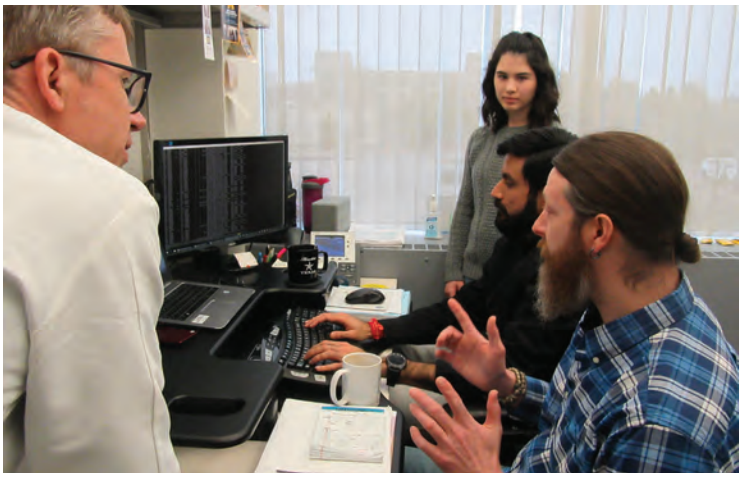
From studying all the RNAs to tracking production and degradation rates of each one of them

In the 1990's, sequencing was carried out one gene at a time. The results from the Human Genome Project (1990 to 2003) laid the foundation for the development of modern, large-scale sequencing techniques. One of them is RNA-seq, which reads and catalogs the abundance of all the RNAs present in cells.

Ljungman recognized that while being very useful, RNA-seq did not reveal the rates by which the different RNAs were being produced and degraded. To resolve this limitation, Ljungman's idea was to take a snapshot of the cell at the time of RNA production and then follow this RNA as it was further processed and eventually degraded. Ljungman first started exploring this idea in the early 2000's and further developed it in 2006 when the Lab began using the SuperArray PCR platform. This new technology allowed for the interrogation of 90 genes at a time, which was a considerable improvement over single-gene analysis, but it was still not quite powerful enough to routinely study the full picture.

[1] Michelle T. Paulsen, Artur Veloso, Jayendra Prasad, Karan Bedi, Emily A. Ljungman, Ya-Chun Tsan, Ching-Wei Chang, Brendan Tarrier, Joseph G. Washburn, Robert Lyons, Daniel R. Robinson, Chandan Kumar-Sinha, Thomas E. Wilson, and Mats Ljungman, Coordinated regulation of synthesis and stability of RNA during the acute TNF-induced proinflammatory response, *PNAS,* February 5, 2013 110 (6) 2240-2245; https://doi.org/10.1073/pnas.1219192110

In 2011, thanks to the University's investment in Illumina's next generation sequencing equipment, the Ljungman lab developed two very successful innovative techniques: Bru-seq and BruChase-seq. These techniques allowed them to investigate, simultaneously and in one single experiment, both the synthesis and the degradation rates of RNA from about 20,000 protein-coding genes and many thousands of non-coding genes. It was the first time that such analysis could be performed, opening the door to a broad array of novel investigations.



The Bru-seq Lab offers various computational analyses of Bru-seq data such as mapping, gene set enrichment analyses and visualization of the data on a custom Bru-seq browser.

Many collaborations

Following the 2013 publication of the Bru-seq and BruChase-seq techniques, the Ljungman lab received many U-M and external requests for Bru-seq collaborations, transforming the original lab into the Bru-seq Lab. The Lab's team has collaborated with over 50 U-M partners from different departments across campus. It has also partnered with two major pharmaceutical companies, and with over 20 research groups worldwide. "It has been very rewarding to be able to help investigators address their research questions with our Bru-seq tools," says Ljungman. "With these collaborations, we have been invited to take part in some extremely interesting studies that often result in high-impact publications. These participations also stimulate ideas that can lead to more innovative collaborative grants."

An example of such a collaboration is with Nouri Neamati, John G. Searle Professor of Medicinal Chemistry at the U-M College of Pharmacy. With the Bru-seq Lab team, the Neamati Lab has tested over one hundred novel small molecule drugs that they have developed. Using Bru-seq, they have identified many unexpected mechanisms of these compounds.

"We frequently use Bru-Seq to better elucidate the mechanism of action of a series of novel small-molecule compounds developed in my laboratory," says Neamati. "Digging through the tsunami of Bru-seq data is quite addictive and highly informative."

One of the most striking findings from this collaboration is a set of compounds that targets the protein folding machinery in cells, and also leads to reduced transcription of many critical DNA repair genes. Based on these findings, the teams showed that cancer cells are strongly sensitized by these compounds to DNA-damaging agents as well as to clinical PARP1 inhibitors.[2]

[2] Liu et al. 2019; Xu et al. 2019; Yang et al. 2019

Collaborations

20 outside U-M, in the USA or across the world

2 large pharmaceutical companies

Over 50 different groups of U-M

For another set of compounds, they have identified the nuclear RNA exosome as a molecular target, and are exploring these compounds as potential novel therapeutic drugs for cancer. Together, they have published 16 articles and have received four collaborative grants in which Bru-seq plays a big part.

The Bru-seq Lab also participates in the prestigious ENCODE project that emerged from the Human Genome Project. The ENCODE project is a public research consortium aimed at identifying all functional elements in the human and mouse genomes. In 2013, the Ljungman lab obtained funding from the National Human Genome Research Institute (NHGRI) for development of the Bru-seq suite of assays within the ENCODE 3 project. In 2017, the Bru-seq Lab became one of eight national mapping centers within the ENCODE 4 project, set to capture the nascent transcriptome as well as to provide RNA stability data and enhancer element identifications across human cell lines.

"We feel very fortunate and humble to be part of the ENCODE Consortium made up of remarkable investigators who have developed cornerstone genomic assays such as RNA-seq, ChIP-seq and Hi-C just to name a few. With our Bru-seq technologies, we add new data types that we hope will be useful to ENCODE and to the whole scientific community," adds Ljungman.

What does exactly happen at the Bru-seq Lab?

First bromouridine (the "Bru" in "Bru-seq") is added to a cell culture and gets incorporated into the RNA that is synthesized inside the cells. Then, the newly made (nascent) Bru-containing RNA is specifically captured with anti-Bru antibodies conjugated to magnetic beads. A bar-coded complementary DNA (cDNA) library is created and sent to the U-M Advanced Genomics Core where a state-of-the-art Nova-seq equipment sequences the libraries and collects the data. The U-M Core facility's equipment can run 250 of those samples at a time, in two to three days. The results are large data files of sequences that the Bru-seq Lab bioinformatics engineers map to the human or mouse genome.

2,000 samples sequences

~ 200 projects

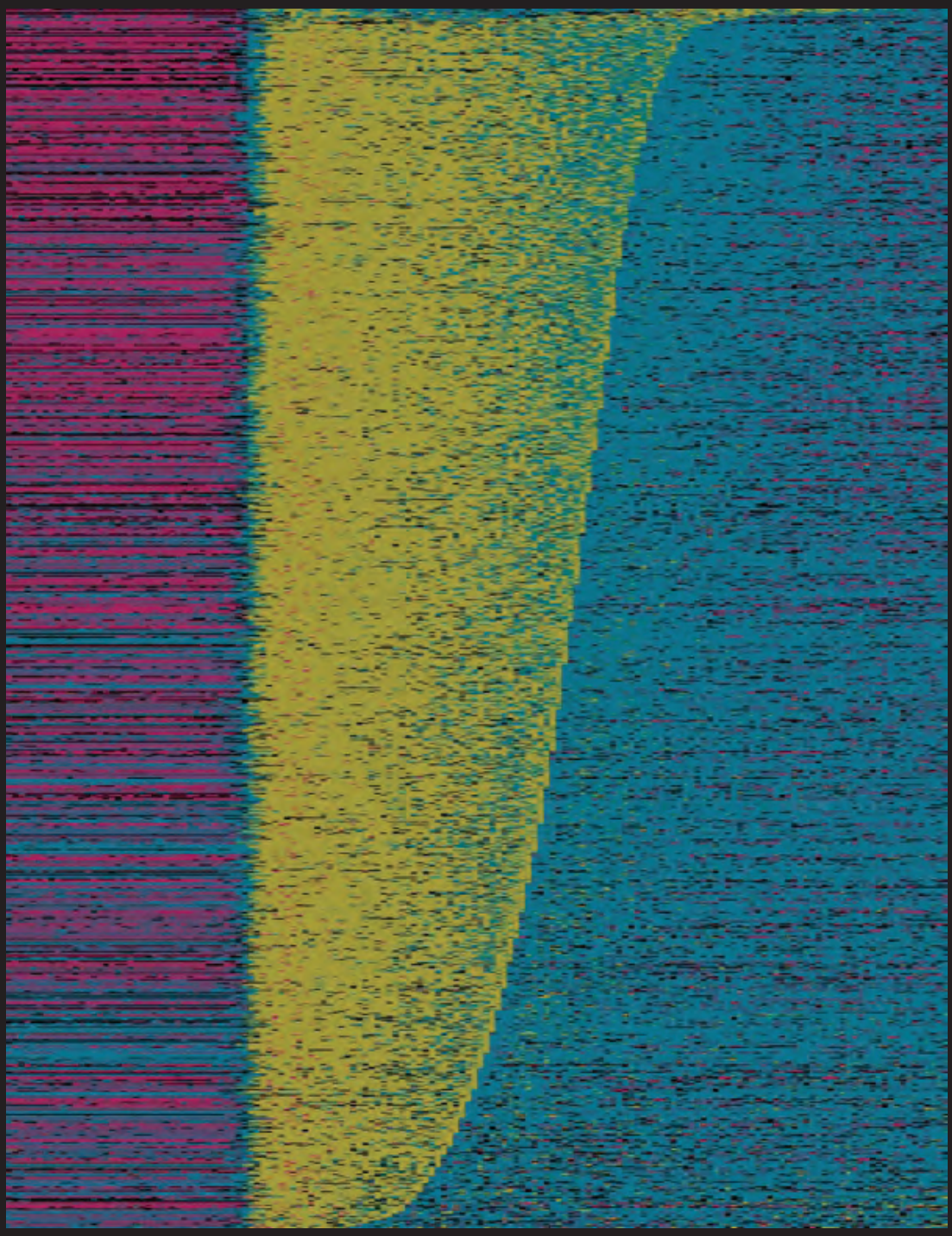
Over 50 publication contributions

Meet the RNA-seq team: Adenine, Guanine, Cytosine and Uracil

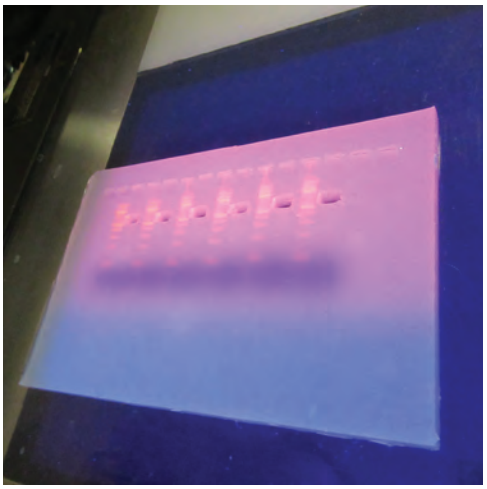
Imagine four different types of beads (nucleotides), and each bead has a name: Adenine ('A'), Guanine ('G'), Cytosine ('C') and Uracil ('U'). These beads join hands forming long strands (RNA) that align in a very specific order and form a sequence that is unique. The sequence constitutes a precise code, copied from the genomic DNA sequence, ready to carry out a specific mission.

These missions include carrying instructions from the nuclear genome to the cytoplasm for the assembly of proteins, creating structures that enable the cells to carry out certain functions, or directly regulating the activity of proteins and genes. Some RNAs are produced in large quantities all the time, while others are produced in response to specific environmental cues.

All of this happens at sub-microscopic scales, inside each living cell of any organism. So much can go wrong, leading to disease, but most of the time, it all goes right. The tremendous complexity of RNA processes excites scientific imagination and fuels explorations to develop innovative therapies for as yet incurable diseases.



Transcriptional elongation rates of some 3000 human genes ordered according to their elongation rate with fast elongation (top) and slow elongation bottom (from Veloso et al. *Genome Research*, 2015)



Michelle Paulsen, manager of the Bru-seq Lab, analyzes the quality of Bru-seq libraries on a stained gel.

Ljugman lab's website
sites.google.com/a/umich.edu/ljungman-lab/

The Bru-seq Lab has developed a robust mapping and analysis pipeline for genome-wide sequencing data sets. These data sets are stored in a comprehensive database that keeps track of raw and processed sequencing data as well as sample metadata. Tom Wilson, Professor of Pathology and Human Genetics in the Medical School and Faculty Director of the Advanced Genomics Core, has been instrumental in the development of the Bru-seq computational tools. Other key contributors have been Artur Veloso, Brian Magnuson, Ishwarya Venkata Narayanan, and Karan Bedi.

The technical and scientific excellence of the Bru-seq lab is demonstrated by its success. "The team is highly dedicated to providing good information and high-quality data. Many researchers are repeat customers, like Dr. Neamati, so we know they get useful data from our Bru-seq techniques," says Michelle Paulsen, Bru-seq Lab Manager who has been working with Ljungman in the development of the different Bru-seq techniques since their inception.

The University of Michigan maintains the Advanced Genomics Core facility to state-of-the-art standards with regular investments in new sequencing technologies. "This equipment places us at the cutting-edge of sequencing technology and expertise. As these technologies have been advancing, high quality, genome-wide Bru-seq data has also become more affordable," explains Paulsen. Capturing, processing and sequencing one sample costs approximately $500.

In addition to processing RNAs for sequencing, and data analysis and interpretation, the Bru-seq Lab team offers guidance and support for research design and execution to all of its collaborators.

Bru-seq Lab publication highlights

Flasch DA, Macia A, Sanchez L, Ljungman M, Heras SR, Garcia-Perez JL, Wilson TE, Moran JV. 2019. Genome-wide de novo L1 Retrotransposition Connects Endonuclease Activity with Replication. *Cell* 177: 837-851 e828.

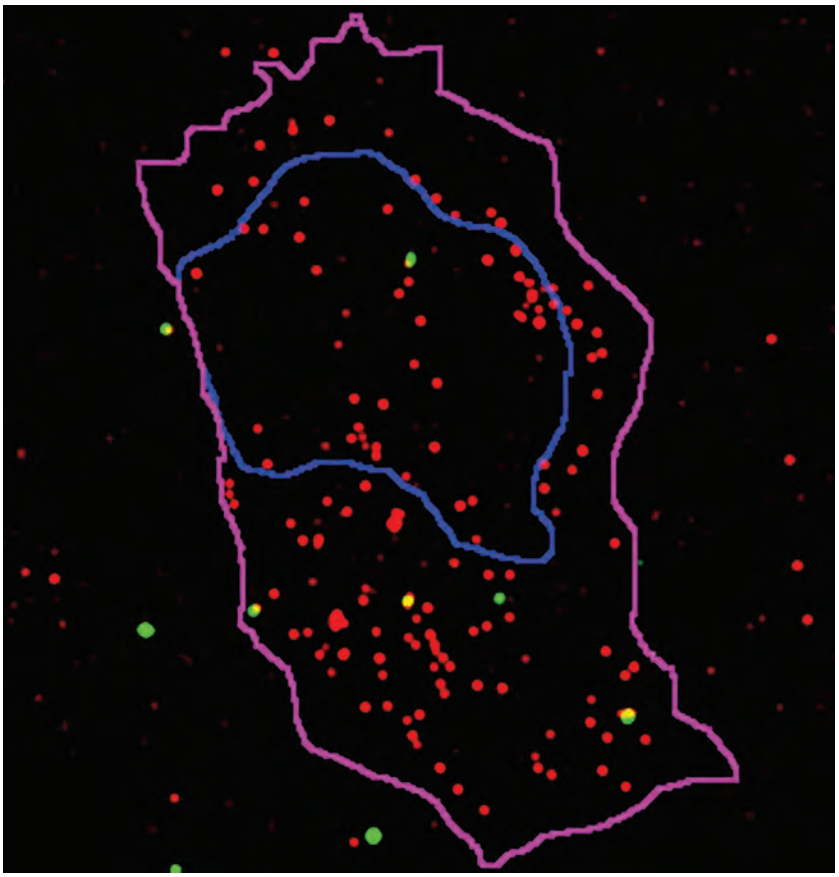
Liu Y, Ji W, Shergalis A, Xu J, Delaney AM, Calcaterra A, Pal A, Ljungman M, Neamati N, Rehemtulla A. 2019. Activation of the Unfolded Protein Response via Inhibition of Protein Disulfide Isomerase Decreases the Capacity for DNA Repair to Sensitize Glioblastoma to Radiotherapy. *Cancer Res* 79: 2923-2932.

Paulsen MT, Veloso A, Prasad J, Bedi K, Ljungman EA, Tsan YC, Chang CW, Tarrier B, Washburn JG, Lyons R et al. 2013. Coordinated regulation of synthesis and stability of RNA during the acute TNF-induced proinflammatory response. *Proc Natl Acad Sci* U S A 110: 2240-2245.

Sima J, Chakraborty A, Dileep V, Michalski M, Klein KN, Holcomb NP, Turner JL, Paulsen MT, Rivera-Mulia JC, Trevilla-Garcia C et al. 2019. Identifying cis Elements for Spatiotemporal Control of Mammalian DNA Replication. *Cell* 176: 816-830 e818.

Veloso A, Kirkconnell KS, Magnuson B, Biewen B, Paulsen MT, Wilson TE, Ljungman M. 2014. Rate of elongation by RNA polymerase II is associated with specific gene features and epigenetic modifications. *Genome Res* 24: 896-905.

Powerful developments: what SMART microscopy can show us



Red spots: miRNA-targeted mRNA
Green spots: processing bodies
Magenta: cell boundary
Blue: nuclear boundary

Image of a cell expressing messenger RNAs (red spots) that are repressed by gene regulatory microRNAs. While a majority of the mRNA molecules are spread across the nucleoplasm and cytoplasm, a small, but significant fraction of these messages localize at processing bodies (green spots, colocalization visible as yellow areas) for storage or degradation. The nuclear and cellular boundaries are outlined in blue and magenta respectively.

Sometimes, scientists have a feeling that a breakthrough is near, but to realize the discovery, they need to actually "see it." State-of-the-art technology supporting scientific leaps can have a tremendous impact.

A classic example of such a *Eureka!* moment comes from the field of genetic research when, in the 1950's, scientists could not make sense of the molecular organization of DNA. When James Watson and Francis Crick happened upon Rosalind Franklin's photo of a DNA diffraction image taken at unprecedented high resolution, the insight was immediate: DNA is structured as a double helix. This discovery unlocked the scientific understanding of the structure and function of genes in all living organisms.

A lot has happened since then, in both the fields of genetics and imaging, especially over the last 15 years. Since 2010, the pioneering University of Michigan (U-M) Single Molecule Analysis in Real-Time (SMART) Center has provided advanced imaging research support, with a focus on helping users achieve single-molecule and super-resolution imaging so that "seeing becomes believing." With leading-edge technology, intracellular activity can be understood at the scale of the underlying biology, based on the ability to watch individual biomolecules inside single cells, live, and in a real-time "feed."

In 2019, the SMART Center became one of the U-M Center for RNA Biomedicine's two research cores. **"Bringing people together on a sophisticated common-use instrument is one of the most effective ways to nurture groundbreaking collaborations, like a scientist's fancy 'water cooler,'" says SMART Center founder and Center for RNA Biomedicine's co-Director Nils G. Walter, Francis S. Collins Collegiate Professor of Chemistry, Biophysics & Biological Chemistry.**

"The whole is greater than the sum of its parts"

With single-molecule techniques, scientists can identify and observe distinct sub-populations of molecules and observe rare or transient events as they naturally occur in cells. The detailed image resolution shows states and behaviors of single molecules. These data allow scientists to construct a statistical picture of a group of individuals.

In comparison, traditional microscopy can only detect large numbers of molecules, and therefore results in averaged properties that often cancel out individuals and mask the biology.

Single-molecule imaging also enables an entirely new set of super-resolution microscopy approaches that use many small distinct dots of color to create images that overcome classic limitations and break into the nanometer scale dimensions of the biology of the cell (see Figure 1). This small-dot technique is comparable to Seurat's pointillism painting, the four-color CMYK printing process, or the three-color RGB sub-pixels of a flat screen TV.

These major advances allow scientists to directly observe how single molecules behave, localize, and interact. These leading-edge techniques vastly expand, challenge, and support our foundational knowledge about the idiosyncratic biology of individual cells.

J. Damon Hoff, Ph.D., SMART Center Manager

More than a lab

The SMART Center is a remarkable and highly forward-looking facility at the University of Michigan. For Stephanie Moon, Assistant Professor in Human Genetics at the Medical School and Faculty Scholar in the Center for RNA Biomedicine who joined the U-M RNA research community in January 2020 (see profile page 38), it was one of the decisive factors that brought her to Michigan. **"It is rare to have access to this type of advanced imaging facility," she explains.**

Such sophisticated tools require an expertise that biologists and other RNA scientists might not have. From its inception in 2010, the SMART Center has been set up to be more than a lab; it is a hub of expertise for single molecule studies. SMART Center Manager J. Damon Hoff, Ph.D., has worked in the field for almost 20 years and offers scientific consultations and recommendations on how to use the technology. He explains in detail what can be expected from these tools and fully supports all of the Center's users, from project inception to imaging collection, and with processing and interpreting the data.

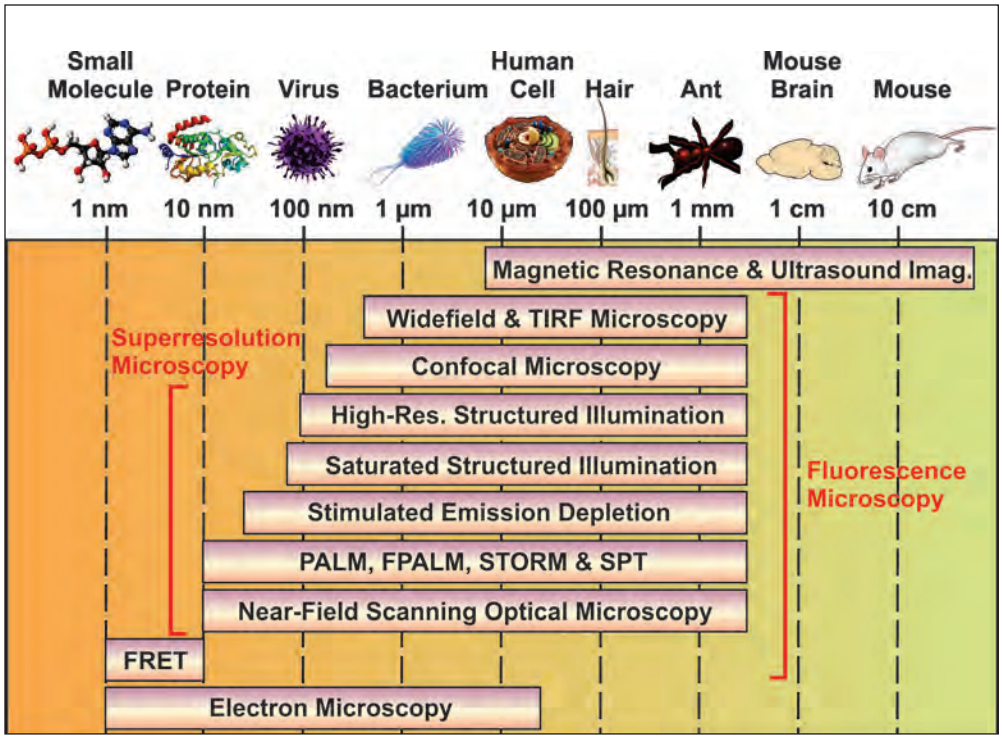


Figure 1: This table shows what is meant by "small," and which techniques are used to see at those sizes. Note that with single molecule imaging (e.g., STORM), it is becoming possible to bridge the resolution gap between fluorescent optical microscopy and electron microscopy.[1]

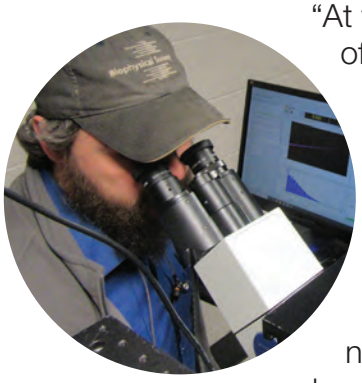
The results are impressive, with the SMART Center having contributed to dozens of publications since 2010, including in the prestigious journal *Nature.*

The SMART Center also serves as a training ground for the next generation of scientists. The facility hosts modules for four graduate courses and one undergraduate course each year.

Asked about the future of SMART, Hoff looks forward to extending its capabilities. **"A facility like ours needs to continue to offer leading-edge instruments and expertise, and that edge keeps advancing. To continue our mission of supporting state-of-the-art single molecule methods for both specialist and non-specialist researchers, we are actively seeking to increase the capabilities of all our instruments. Expanding STochastic Optical Reconstruction Microscopy (STORM) is a particularly high priority, with plans for more colors, faster imaging and more accurate localization within the cells."**

[1] In Bartke, R.M., Cameron, E.L., Cristie-David, A.S., Custer, T.C., Denies, M.S., Daher, M., Dhakal, S., Ghosh, S., Heinicke, L.A., Hoff, J.D., Hou, Q., Kahlscheuer, M.L., Karslake, J., Krieger, A.G., Li, J., Li, X., Lund, P.E., Vo, N.N., Park, J., Pitchiaya, S., Rai, V., Smith, D.J., Suddala, K.C., Wang, J., Widom, J.R. and Walter, N.G. (2015). Meeting report: SMART timing-principles of single molecule techniques course at the University of Michigan 2014. *Biopolymers* 103, 296-302. Figure reproduced with permission from the publisher.

From the Center's users



Robb Welty, Ph.D., Postdoctoral Research Fellow, Chemistry, College of Literature, Science, and the Arts

"At the most fundamental, RNA molecules are chains of interconnected atoms which interact (e.g., wrap around, thread through, or connect) with other pieces of cellular machinery. These interactions are predicated on the oscillations, vibrations or (simply put) wiggling of these molecules. Like symphonies emerge from vibrations of musical strings, life emerges from the motions of RNA. A special variety of RNA, called pre-mRNA, needs to contort its atoms in a special geometry to carefully remove sections of itself. If this 'gene splicing' goes awry it can cause diseases or even death. Fluorescence fluctuation spectroscopy at the SMART Center allows us to examine motions of single RNA 'strings' on the order of a million times a second. This peerless level of resolution enables me to examine the behavior of RNA that causes certain childhood genetic diseases."

— Robb Welty, Ph.D.

In this photo, Welty is working on a time-resolved confocal instrument, collecting Fluorescence Fluctuation Spectroscopy (FFS) data to measure Förster Resonance Energy Transfer (FRET) of some type of RNA one molecule at a time to get a distribution of the conformations present in cells.

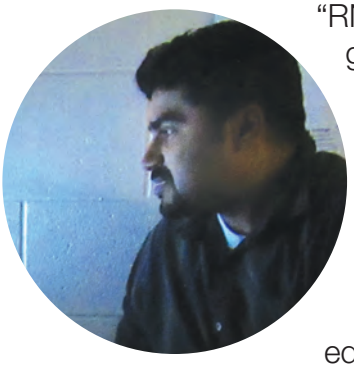
"A SMART day" by Damon Hoff, Ph.D.

SMART Center Manager

Read an article on a new technique
Settle in with my coffee to read a recent article about a novel method that puts a new spin on a single molecule technique. Today it's about applying machine learning to single molecule imaging. Jot down a few notes about how we might implement it and how it might impact current or future users.

Instrument maintenance
Image some fluorescent calibration standards. Keep the instrumentation is top condition. They've got to work!

Office hours
Meet with a potential user for a brainstorming session.



Sethu Pitchiaya, Ph.D., Research Investigator, Pathology, Medical School

"RNA localization is central to gene regulation and cellular function. With the SMART Center's state-of-the-art instrumentation, especially the single-particle tracking and single-molecule imaging technology, I'm able to visualize intracellular RNAs at unprecedented spatiotemporal resolution and understand mechanisms of RNA(-based) regulation."

—Sethu Pitchiaya, Ph.D.

"The SMART Center has provided us with its modular time-tagged fluorescence correlation spectroscopy instrument as a platform to develop a novel way of looking at diffusion and fluctuations on the sub-cellular scale. Because the instrument is not a black box but allows us access to hardware and raw data, we were, with the competent help of the SMART Center staff, able to implement our own data processing methods and extract information that is otherwise unobtainable. We are using this method to study the dynamics of the bacterial chromosome with high temporal and spatial resolution to answer basic questions about the mechanics of genetic regulation."

—Jens-Christian Meiners, Professor of Physics and Biophysics

The SMART ways of seeing

Three techniques are further explained on the SMART Center's webpage: tinyurl.com/SmartWaysOfSeeing.

1 | Single-molecule imaging to precisely localize particles

2 | Fluorescence fluctuation spectroscopy for diffusing molecules

3 | Force spectroscopy to measure molecular mechanical forces

SMART Center website
lsa.umich.edu/biophysics/resources/smart1.html

User complains about a laser that seems "weak."
A quick re-alignment and they are up and running again.

Train a new user on our Single Particle Tracker and collect some initial data as a proof of principle for their project
They'll be in again to take data under my observation before being cleared to use the instrument independently.

Meet with a SMART GSI
to go over an education module that she is developing to plug into future courses, or help introduce new or prospective users to single molecule image analysis.

Programming
a user needs a new Matlab module to help analyze some of their tracking data.

SMART Center publications highlights

Yang, G., Liu, C., Chen, S-H., Kassab, M.A., Hoff, J.D., Walter, N.G., Yu, X. (2018) Super-resolution imaging identifies PARP1 and the Ku complex acting as DNA double-strand break sensors. *Nucleic Acid Research.*

Michelini, F., Pitchiaya, S., Vitelli, V., Sharma, S., Gioia, U., Wang, Y., Cabrini, M., Iannelli, F., Pessina, F., Matti, V., Francia, S., Shivashankar, G.V., Walter, N.G., and d'Adda di Fagagna, F. (2017) DNA break-induced transcription of non-coding RNA is required for DNA damage response, *Nat. Cell Biol.*

Hodges, C., Kafle, R.P., Hoff, J.D., Meiners, J-C. (2018) Fluorescence Correlation Spectroscopy with Photobleaching Correction in Slowly Diffusing Systems, *Journal of Fluorescence*

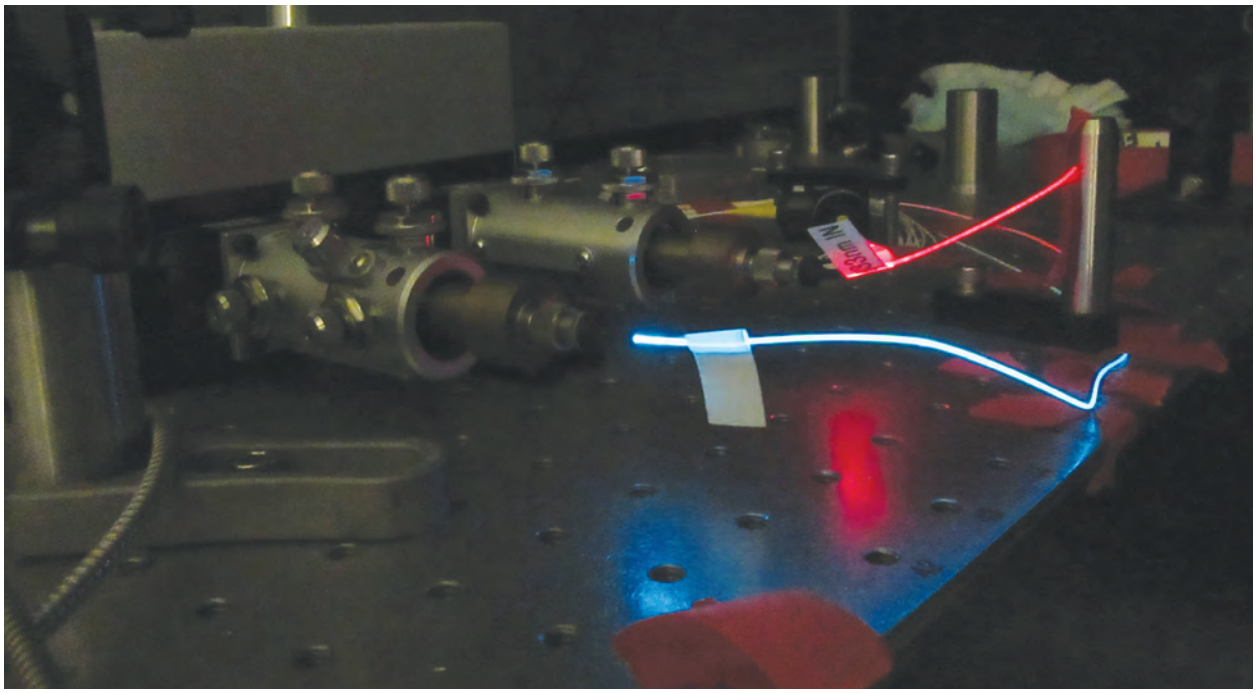
"Imagining" imaging in a SMART Center

In 2006, the University of Michigan organized a symposium that brought biology and nanotechnology experts together. During a panel discussion, these scientists imagined a center that would offer both advanced instrumentation and specialized training, and be a hub of expertise for single-molecule studies. The idea for a SMART Center was seeded.

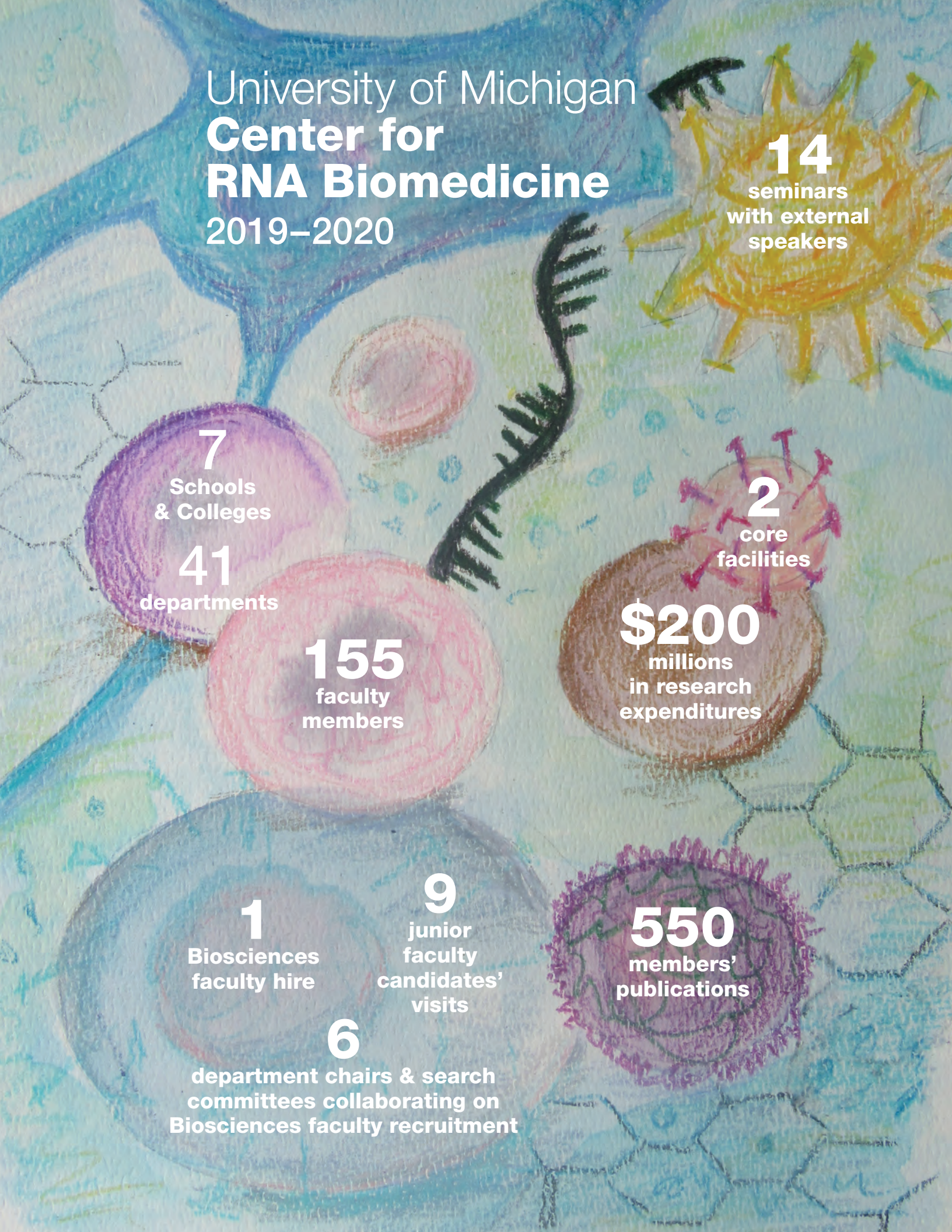
At its inception, the SMART Center was designed to support researchers in diverse aspects of single molecule studies, from experimental design through data acquisition and analysis.

An NSF MRI grant awarded in 2010 allowed the implementation of the SMART Center's vision. Since 2013, the SMART center has been supported by a combination of user fees and College subsidies.

Over the years, the SMART Center, hosted within the centrally localized College of LSA Chemistry building, has offered hands-on help to use state-of-the-art single molecule microscopes, and has trained more than a hundred users from dozens of labs across the U-M, including the College of LSA, the Medical School, and the College of Engineering.



Pulsed interleaved laser excitation (PIE) at the SMART Center allows two fluorescent colors to be measured "simultaneously," while totally eliminating crosstalk. A white-light pulsed laser source is split into two wavelengths (here, pale blue and red), which hit the sample just 25 nanoseconds apart. This very small delay between excitation of the two fluorophores is longer than typical fluorescent lifetimes (usually a few nanoseconds) but very fast compared to diffusion or conformational changes.


University of Michigan
Center for
RNA Biomedicine
2019–2020
14
seminars
with external
speakers
7
Schools
& Colleges
41
departments
155
faculty
members
2
core
facilities
$200
millions
in research
expenditures
1
Biosciences
faculty hire
9
junior
faculty
candidates'
visits
550
members'
publications
6
department chairs & search
committees collaborating on
Biosciences faculty recruitment

Center for RNA Biomedicine in Numbers

July 1, 2019–June 30, 2020

PEOPLE
155 RNA faculty members
Male: 70%
Female: 30%

ACROSS CAMPUS
Schools/colleges: 7
Departments: 41

LEADERSHIP
2 Co-Directors
9 Executive Committee members
12 Strategic Advisory Board members
17 Students and Postdocs Council members

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

FUNDING
RNA faculty are involved in raising about $200M/year in research expenditures.

3 *Grant Sprints* resulting in several internal and external grant applications

HIRING
1 Biosciences Faculty Hire
6 Department chairs & search committees collaborating on Biosciences faculty recruitment
9 Junior candidates brought to campus
1 Communication Manager

PUBLICATIONS
550 total publications from all the faculty members

SEMINARS
14 external speakers
45 persons in average attendance

SUPPORT FROM THE RNA SOCIETY
The U-M RNA Student & Postdoc Council was awarded an "RNA Salon Grant."

The "RNA Collaborative Seminar Series," initiated by the Center, is promoted by The RNA Society (website and Twitter). Until June, it connected 9 RNA research centers and hosted 5 bi-weekly seminars with about 150 participants each.

We invite you

To join us and our over 1,700 followers on Twitter (@umichrna).

To read our weekly newsletter, "The RNA Transcript," that reaches over 600 RNA fans, with an opening rate averaging 45%.

To visit our website, rna.umich.edu, that received over 7,600 users in the 2019–2020 academic year.

Some recent awards

Janet L. Smith, Ph.D.

Arul Chinnaiyan, M.D., Ph.D.

Sarah Keane, Ph.D.

Janet L. Smith, Professor of Biological Chemistry, Department of Biological Chemistry, College of LSA, and Margaret J. Hunter Collegiate Professor, Life Sciences Institute, and **Dr. Arul Chinnaiyan,** Investigator, Howard Hughes Medical Institute, and S.P. Hicks Endowed Professor of Pathology, Medical School, were elected **Members of the National Academy of Sciences.** They both are members of the Center for RNA Biomedicine Strategic Advisory Board.

Sarah Keane, William R. Roush Assistant Professor, Department of Chemistry and the Biophysics Program, College of LSA, is a **2020 Pew Scholar.** Keane is U-M's 15th scientist to receive this very prestigious award since its inauguration in 1985, and the first one since 2013. The 2020 scholars were chosen from nearly 200 applicants nominated by leading academic institutions and researchers across the US.

Stephanie Moon, Ph.D.

Nils G. Walter, Ph.D.

Martina Jerant

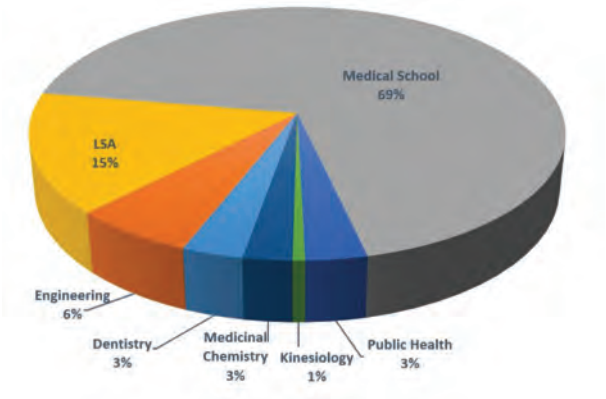
Stephanie Moon, Assistant Professor, Human Genetics, Medical School, and **Nils G. Walter,** receive a "Collaborative Pairs Pilot Project" Award from the Chan Zuckerberg Initiative. This prestigious award supports interdisciplinary collaborative approaches addressing key challenges in the biology of neurodegenerative diseases.

Martina Jerant, Center's Manager, received the U-M Staff Impact Award, from among 75 nominees.

U-M CENTER FOR RNA BIOMEDICINE

155 FACULTY MEMBERS

from 7 Schools and Colleges across 41 departments



Members' repartition across Schools and Colleges

Carlos Aguilar, Biomedical, College of Engineering
Huda Akil, Psychiatry, 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
Ebrahim Azizi, Internal Medicine, Medical School
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
Markus Bitzer, Internal Medicine, Medical School
Alan Boyle, Computational Medicine and Bioinformatics, Medical School
Charles Brooks, Chemistry and Biophysics, College of LSA
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
Matt Chapman, Molecular, Cellular, & Developmental Biology, College of LSA
Grace Chen, Internal Medicine, Medical School
Vivian Cheung, Pediatrics, Medical School
Lam Cheung Tsoi, Dermatology, Medical School
Arul Chinnaiyan, Pathology, Medical School
Michael Cianfrocco, Biological Chemistry, Medical School
Justin Colacino, Environmental Health Sciences, School of Public Health
Catherine Collins, Molecular, Cellular, & Developmental Biology, College of LSA
Kathleen Collins, Internal Medicine, Medical School
Analisa DiFeo, Pathology, Medical School
Yali Dou, Pathology, Medical School
Gregory Dressler, Pathology, Medical School
Monica Dus, Molecular, Cellular, & Developmental Biology, College of LSA
Eric Fearon, Internal Medicine, Medical School
Eva Feldman, Neurology, Medical School
Claudia Figueroa-Romero, Neurology, Medical School
Aaron Frank, Chemistry and Biophysics, College of LSA
Peter Freddolino, Biological Chemistry, Medical School
George Garcia, Medicinal Chemistry, College of Pharmacy
Amanda Garner, Medicinal Chemistry, College of Pharmacy
Scott Gitlin, Internal Medicine, Medical School
Thomas Glover, Human Genetics, Medical School
Daniel Goldman, Biological Chemistry, Medical School
Stephen Goutman, Neurology, Medical School
Yuanfang Guan, Computational Medicine & Bioinformatics, College of Engineering
Johann Gudjonsson, Dermatology, Medical School
Erdogan Gulari, Chemical Engineering, College of Engineering
Deborah Gumucio, Cell & Developmental Biology, Medical School
Gary Hammer, Internal Medicine, Medical School
Sue Hammoud, Human Genetics, Medical School
Alfred O. Hero, Electrical Engineering and Computer Science, College of Engineering
Gerry Higgins, Computational Medicine and Bioinformatics, Medical School
Shigeki Iwase, Human Genetics, Medical School
Ursula Jakob, Molecular, Cellular, & Developmental Biology, College of LSA
Paul Jenkins, Medicinal Chemistry, College of Pharmacy
Hui Jiang, Biostatistics, School of Public Health
Andrew Johnston, Dermatology, Medical School
Alon Kahana, Ophthalmology & Visual Science, 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
Steven King, Internal Medicine, Medical School
Jacob Kitzman, Human Genetics, Medical School
Raoul Kopelman, Chemistry, College of LSA
Markos Koutmos, Chemistry and Biophysics, College of LSA
Kristin Koutmou, Chemistry, College of LSA
Steven Kregel, Pathology, Medical School
Matthias Kretzler, Internal Medicine, Medical School
Chandan Kumar-Sinha, Pathology, Medical School
Steve Kunkel, Pathology, Medical School
Katsuo Kurabayashi, Mechanical Engineering, College of Engineering
Kenneth Kwan, Human Genetics, Medical School
Roland Kwok, Obstetrics and Gynecology, Medical School
Adam Lauring, Internal Medicine, Medical School
Jun Li, Human Genetics, Medical School
Yongqing Li, Surgery, Medical School
Jiandie Lin, Cell & Developmental Biology, Medical School
Jie Liu, Computational Medicine and Bioinformatics, Medical School
Mats Ljungman, Radiation Oncology, Medical School
Pedro Lowenstein, Neurosurgery, Medical School
Andrew Ludlow, Kinesiology, School of Kinesiology
Janine Maddock, Molecular, Cellular, & Developmental Biology, College of LSA
Anna Mapp, Chemistry, College of LSA
David Markovitz, Internal Medicine, Medical School
Richard McEachin, Biostatistics, School of Public Health
Miriam Meisler, Human Genetics, Medical School
Daniela Mendonca, Biologic and Materials Sciences & Prosthodontics, School of Dentistry
Gustavo Mendonca, Biologic and Materials Sciences & Prosthodontics, School of Dentistry
Rajasree Menon, Computational Medicine and Bioinformatics, Medical School
Ryan Mills, Computational Medicine and Bioinformatics, Medical School
Stephanie Moon, Human Genetics, Medical School
John Moran, Human Genetics, Medical School
Deepak Nagrath, Biomedical Engineering, College of Engineering
Sunitha Nagrath, Chemical Engineering, College of Engineering
Jayakrishnan Nandakumar, Molecular, Cellular, & Developmental Biology, College of LSA
Nouri Neamati, Medicinal Chemistry, College of Pharmacy
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
Ximena Paez-Colasante, Neurology, Medical School
Nallasivam Palanisamy, Pathology, Medical School
Bruce Palfey, Biological Chemistry, Medical School
Petros Papagerakis, Orthodontics & Pediatric Dentistry, School of Dentistry
Meeyoung Park, Neurology, Medical School
Stephen Parker, Computational Medicine and Bioinformatics, Medical School
Daniel Peltier, Pediatrics, Medical School
Brian Pierchala, Biologic and Materials Sciences & Prosthodontics, School of Dentistry
Sethu Pitchiaya, Pathology, Medical School
Ping Qiu, Internal Medicine, Medical School
Kaushik Ragunathan, Biological Chemistry, Medical School
Indika Rajapakse, Computational Medicine and Bioinformatics, Medical School
Diane Robins, Human Genetics, Medical School
Brandon Ruotolo, Chemistry, College of LSA
Russell Ryan, Pathology, Medical School
Maureen Sartor, Computational Medicine and Bioinformatics, Medical School
Santiago Schnell, Molecular & Integrative Physiology, Medical School
Laura Jean Scott, Biostatistics, School of Public Health
Audrey Seasholtz, Biological Chemistry, Medical School
Jiaqi Shi, Pathology, Medical School
Lyle Simmons, Molecular, Cellular, & Developmental Biology, College of LSA
Janet Smith, Biological Chemistry, Medical School
Ryan Spengler, Internal Medicine, Medical School
Cristiane Squarize, Periodontics & Oral Medicine, School of Dentistry
Jeanne Stuckey, Biological Chemistry, Medical School
Chitra Subramanian, Surgery, Medical School
Michael Sutton, Molecular & Integrative Physiology, Medical School
Andrew Tai, Internal Medicine, Medical School
Shuichi Takayama, Biomedical Engineering, College of Engineering
Alice Telesnitsky, Microbiology and Immunology, Medical School
Muneesh Tewari, Internal Medicine, Medical School
Peter Todd, Neurology, Medical School
Scott Tomlins, Pathology, Medical School
Raymond Trievel, Biological Chemistry, Medical School
David Turner, Biological Chemistry, Medical School
Michael Uhler, Biological Chemistry, Medical School
Sarah Veatch, Biophysics, College of LSA
John Voorhees, Dermatology, Medical School
Nils G. Walter, Chemistry, College of LSA
Lisha Wang, Pathology, Medical School
Stanley Watson, Psychiatry, Medical School
Max Wicha, Internal Medicine, Medical School
Andrzej Wierzbicki, Molecular, Cellular, & Developmental Biology, College of LSA
Thomas Wilson, Pathology, Medical School
Trisha Wittkopp, Ecology & Evolutionary Biology, College of LSA
Chao-Yie Yang, Internal Medicine, Medical School
Jianzhi Zhang, Ecology & Evolutionary Biology, College of LSA
Jifeng Zhang, Internal Medicine, Medical School
Xiang Zhou, Biostatistics, School of Public Health

Stephanie Moon's journey into science and back to Michigan

With grand-parents in Jackson, MI, **Stephanie Moon, Ph.D.,** affectionately remembers her summer visits there, splashing in the water with her brother and cousins: "There are a lot of good things about Michigan, summers are a lot of fun, and it's very beautiful." But what really brought her back to Michigan was the "welcoming RNA community and the possibility to pursue her research to make a contribution and help others."

Dr. Moon joined the University of Michigan (U-M) Department of Human Genetics in January 2020 as an Assistant Professor. She is the first—and so far only—faculty scholar hired into the U-M Center for RNA Biomedicine, and is a member of the U-M Biological Sciences Scholar Program. Dr. Moon has received numerous awards, and since at Michigan, she has already become the principal investigator on an NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation. She has also received a very competitive grant from the Chan Zuckerberg Initiative for a Collaborative Pairs Pilot Project.

At U-M, Dr. Moon will pursue the research she started as a post-doc with Roy Parker, Distinguished Professor, Department of Biochemistry, University of Colorado Boulder, about how RNA function and translation are affected when protein decay pathways are inhibited. Understanding the normal biology of RNA translation and localization to RNA-protein granules will contribute to our understanding of what happens in many neurodegenerative diseases. She will be using both the SMART Center (see page 27), and the next generation sequencing facilities (see page 22).

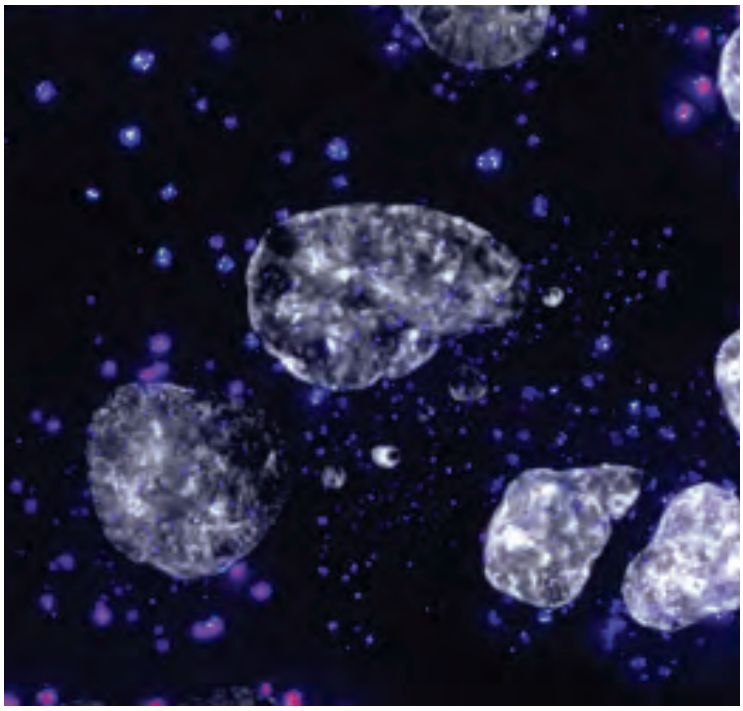
Dr. Moon was born and raised in small mountain towns in rural Colorado. She became interested in diseases very early on, asking many questions: "Why do we get chickenpox? Why does this virus give me a fever rather than something else?" She also knew someone with a rare disease, and found out that people with such diseases often struggle with finding a diagnosis and a treatment for their sickness. These challenges can be especially difficult for those living in rural communities.

Her path into science has also been inspired by both of her parents. Her mother went back to school to become a nurse, and had to navigate a challenging landscape to fulfill her desire to take care of people and become a professional, while working full time. "We often laugh together about how we both found something in healthcare, although her nursing is very practical and hands-on, while I'm way behind the scenes. Hopefully something we do in our lab will impact people in the future, but it's a long way down the path."

> **"We need to focus more our efforts to make a difference with rare diseases treatments."**

Her father studied biology and computer science in college, but he decided to follow another career, and became a cook at the Keystone Science School. Thanks to their employee discounts, Dr. Moon was able to participate in many of the School's science camps. "I think that this is why I wanted to become a scientist, because I was around a lot of them—environmental scientists, natural scientists, but I decided to go into molecular biology because I was always interested in diseases, and in helping others."

Growing up in a rural area, there were no colleges nor much knowledge about the educational system and how academia works. Dr. Moon found mentors who cared about her success and could give her specific pieces of advice. By the time Dr. Moon went to Colorado State University's Ph.D. graduate program, joining Professor Jeffrey Wilusz's lab, she knew that she wanted to study viruses, and was highly motivated to find out how diseases work to find cures.



The Moon lab is studying RNA (bright spots) localization in RNA-protein granules (blue) and RNA function in human cells during stress in healthy and disease conditions.

Dr. Wilusz was her first official PI mentor. "He taught me a lot about how to do science and how to choose interesting scientific problems. He also taught me how to persevere and to put a good work ethic into being at a lab," she explains. There, she also discovered that studying foundational virology can make an impact not only in the field of virology, but also in other areas of cell biology. In fact, historically, many important discoveries in molecular biology were done by virologists who studied how viruses co-opt cellular machinery to proliferate or hide in cells.

It is also there that Dr. Moon discovered academia and how it works. "I didn't know that when you join a lab, the research you can do has to be around a certain area, and is not as open-ended as I thought," she says. "Jeff guided me to study flaviviruses that are important global pathogens. This experience made me more flexible and broadened my interests into other areas of research. In fact, if we find something about, say Dengue viruses, chances are very high that it could be applied to many other viruses or completely different diseases."

When she first arrived in labs, she tried out several projects, and failed. "Many times in science, we try something and it doesn't work. Learning in science also means to learn to fail, and to keep trying." She is grateful for having the chance to try new things, and to have joined Roy Parkers's lab as a postdoc: "Roy encouraged me to work on important problems, be creative, and persevere".

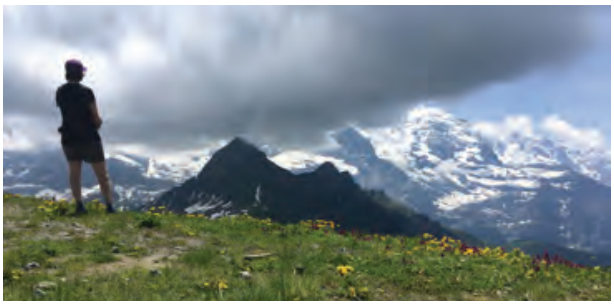
"Learning in science also means to learn to fail, and to keep trying."

In creating her own lab at U-M, Dr. Moon brings her experience with the discovery of the academic world. "I want to be a mentor who supports students from any background, remembering my experience as an outsider," she explains. "One challenge I've faced, perhaps related to being a woman in science, is acquiring more confidence about my expertise to be an effective member of the scientific community."

In her few months at U-M, she has already met many colleagues from her department and others, including from the Protein Folding Disease Initiative, and graduate students and post-docs from the RNA Journal Club organized by the Center for RNA Biomedicine. She is also supported by a launch committee, and a mentorship program. "There are so many people doing research in areas I'm interested in at U-M! I really feel at home here, and one of my goals is to be involved in many collaborations."

Dr. Moon's endless curiosity also applies to reading, hiking, traveling, and cooking. "Often the recipe ends up being a total disaster," she laughs, "but it's fun to do experiments in the kitchen too!"

She also learned Spanish during her undergraduate studies in Mexico, and was inspired by a friend to learn Vietnamese. "We have access to all of these free online learning tools, and it's fun to do something completely different. I love to learn about other cultures, and be able to experience things I had never considered before."



Dr. Moon enjoys the scenery, hiking in the Swiss Alps.

"Form follows function"

Sarah Keane, Ph.D., understands RNAs in three dimensions. She focuses on the structural biology of RNAs and how their molecular structures dictate their functions. "RNAs fold into complex three dimensional shapes, and these shapes can determine their functions," she explains. "In order to understand the mechanisms behind a function, we must first understand the structure that supports them."

Dr. Keane is a William R. Roush Assistant Professor in the Department of Chemistry and the Biophysics Program, College of LSA. She has been named a 2020 Pew Scholar, from nearly 200 applicants nominated by leading academic institutions and researchers across the United States. She is the 15th U-M scholar to win this very prestigious award since its inauguration in 1985, and the first one since 2013. She has also received an NSF Career award in July 2020, and an NIH grant.

Growing up in a family of scientists, Dr. Keane was exposed to science early on. Despite often teasing her parents, who are both psychologists, that they were not "real scientists," they offered her many opportunities to engage in science in summer camp programs throughout her childhood. When she was a senior in high school, a faculty member at UNC Greensboro hired her to enter data from heart rate recordings of children during baseline and social stress conditions. This was her first glimpse at working in a lab, and she never turned back.

Dr. Keane has always been drawn to both physics and chemistry, but "my brother took up physics, so I went into chemistry," she laughs. This rebellious decision was her entree into her academic journey, first studying inorganic and then organic synthesis at Furman University. As a graduate student at Indiana University in Bloomington, she switched her interest from organic chemistry to biological chemistry. There she worked with David Giedroc, Distinguished Professor and Lilly Chemistry Alumni Professor, Department of Chemistry, to characterize protein-protein and protein-RNA interactions that are important for coronavirus replication and transcription.

As a graduate student, she met Michael Summers, Professor, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County, in the fall of 2011. Summers had been invited by the chemistry graduate students to give a seminar, and during this visit, Keane had the opportunity to introduce herself and present her work. They had a productive conversation and, after completing her Ph.D. in 2012, she joined the Summers Lab as a postdoc, working on the RNA structural biology of HIV. She was grateful for the opportunity to interact with visiting speakers as a graduate student, and many of these interactions helped shape her career.

Dr. Keane's graduate research on coronaviruses was protein-centric. She viewed RNA as more of an accessory. "My focus was on how the nucleocapsid bound RNA and melted an RNA duplex. I had not given a lot of thought to functionality of the RNA," she explains. In Summers's Lab, she delved into studying large RNAs. "Dr. Summers's group was developing new methods for expanding the size of RNA that can be studied using Nuclear Magnetic Resonance (NMR) spectroscopy. Typically, the use of NMR was limited to small RNAs of 20-50 nucleotides. The RNAs I was studying were significantly larger. That was so inspiring to me! It's also something that not many labs were doing." This cutting-edge approach makes the structures of large, biologically-relevant RNAs accessible for study.

"I love viruses, and to move this research to the structural biology level is very fascinating."
—Sarah Keane, Ph.D.

Dr. Keane is very grateful for the mentors who have inspired and supported her throughout her career. "I still talk regularly to my graduate advisor David Giedroc and Mike Summers is mentor extraordinaire. In addition to the exciting science that was ongoing, a main reason that I wanted to work with Mike was because he has a great track record of mentoring, and in particular, mentoring women and minorities in science."

As a postdoc, Dr. Keane had the opportunity to work with many talented undergraduate students. This experience helped her to develop her own mentoring style for her lab. “You treat people with respect, you listen to their ideas, you make sure to have diverse perspectives. Most of all, you are accessible and encouraging. Students have to know that you are in their corner,” she recommends.

“You treat people with respect, you listen to their ideas, you make sure to have diverse perspectives. Most of all, you are accessible and encouraging. Students have to know that you are in their corner.”

Dr. Keane was attracted to the University of Michigan because of its renowned RNA research community. “There is a huge group of RNA scientists that are now more formally organized through the Center for RNA Biomedicine (CRB). I arrived in 2017, and Nils Walter, co-director of the CRB, talked about the vibrancy of the community and inter-connections between the College of LSA and the Medical School. The idea that my lab research could translate into something more clinically relevant is very exciting!”

Since then, Dr. Keane has discussed ideas and possible collaborations with Peter Todd’s Lab (Neurology, Medical School) and Amanda Garner’s group (College of Pharmacy). “It’s nice to just discuss scientific ideas and take them in directions we did not intend at first, even if we don’t have an actual project together yet.”

She also praises her outstanding colleagues in the departments of Chemistry and of Biophysics, and appreciates being part of both groups where she feels supported and valued. “I’ve got great colleagues here. I’ve found mentors, both formal and informal, who have given me advice, and helped me in challenging times. I’ve appreciated their continued commitment to my development as a scholar and scientist.”

Dr. Keane is well aware of work-life balance challenges. With her three young children, she enjoys making lava lamps with baking soda, oil and vinegar, growing rock crystals, and baking cookies and cakes. “Life can be hectic,” she says, and she appreciates the constant support and encouragement she receives from her husband.

Right: Solution structure of the HIV-1 packaging signal, determined by Dr. Keane while she was a postdoctoral fellow at UMBC. This region of the HIV genome directs the packaging of two copies of HIV genomic RNA into a new virus particle.

TOGETHER,

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

We invite you to join us in the fantastic journey into the world of RNA biology.

Much more research is needed—safe, innovative, and fast!

The COVID-19 pandemic, caused by an RNA virus, places RNA research at the forefront of all scientific priorities. It is most urgent to further understand the biology of the interactions between the human body and pathogens. This foundational knowledge is crucial to develop effective treatments and vaccines against COVID-19 and subsequent RNA virus diseases.

At the University of Michigan (U-M) Center for RNA Biomedicine, we believe and demonstrate that through scientific collaborations we gain a deeper understanding of the many roles RNA plays in cellular biology. Synergies between experts are also key to accelerate discoveries and innovations.

In this magazine we present how in response to COVID-19 members from the Center for RNA Biomedicine have constituted multiple cross-disciplinary teams within U-M to share and synergize their expertise. They have also engaged with many other institutions nationally and internationally, joining the global pandemic scientific effort.

The current SARS-CoV-2 research benefits from the knowledge that has been acquired over decades of studies of other viruses and of the fundamentals of biology, but COVID-19's devasting consequences are also revealing many knowledge gaps.

Looking forward, it is certain that the knowledge acquired about SARS-CoV-2 will bring insights not only into future viral pandemics, but also into many other therapeutic domains.

Why would you support the U-M Center for RNA Biomedicine?
Understanding RNA is highly challenging because it requires studying a wide range of processes and phenomena, from within single cells at nanometer scales to complex interactions between the 60 trillion cells of the human body. RNA research needs a broad group of experts from biology to engineering, computational science to medicine, to share ideas, data, and techniques to lay the foundations for the therapies of the future. RNA research also requires state-of-the-art equipment and highly sophisticated techniques.

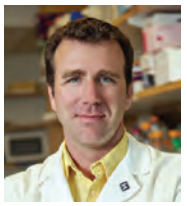
The mission of the U-M Center for RNA Biomedicine is to support the RNA scientific community with these multiple challenges. It is the largest academic RNA research center in the US. Together, our core members constitute a self-identified group of over 150 faculty scientists who lead cutting-edge investigations to under-

From our Members

"RNA science is a key to unravelling pathological mechanisms in neurological diseases."—Eva Feldman, M.D., Ph.D., F.A.A.N., Neurology

"RNA is the bridge between genome variation and molecular function that we are quickly crossing due to new technologies."—Ryan Mills, Ph.D., Human Genetics, Computational Medicine and Bioinformatics

"I see patients suffering from neurodegenerative diseases for which there is no cure. This is very difficult to know that there is no definitive treatment. We must keep advancing basic knowledge to end suffering."—Peter Todd, M.D., Ph.D., Neurology

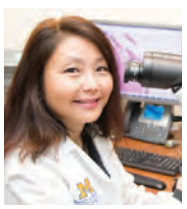


"No matter what disease we are studying, at the end of the day, it comes back to the RNA message."—Ashley Kalinski, Ph.D., Cell and Developmental Biology

"I see a very data-driven future for RNA Science —our sequencing capabilities are evolving rapidly and I am confident that there is much more to discover in all the data we are generating."—Marissa Cloutier, Ph.D. candidate, Human Genetics

"The future of RNA science lies in understanding how RNA regulates DNA."—Sundeep Kalantry, Ph.D., Human Genetics

"I can see RNA being at the center of biomedical research and one of the most critical components to understand and treat human diseases."—Jiaqi Shi, M.D., Ph.D., Pathology



Thank you!

The University of Michigan Center for RNA Biomedicine is the largest academic RNA research center in the US.

stand the basic biology of RNAs, at nano-molecular, cellular and organism levels. Their scientificfindings have the potential to translate into therapies for yet non-curable diseases.

Together, these faculty synergize their knowledge, skills and enthusiasm for scientific discoveries. The Center fosters their passion and supports their scientific inquiries by facilitating meetings, identifying funding opportunities, and organizing events.

Together, these faculty attract and train the next generation of scientists in innovative and rigorous thinking (see Drs. Moon and Keane's interviews, pages 38 and 40). They mentor students and colleagues to be leaders with strong passion and ethics. The Center includes a Student and Postdoc Council that reaches out to young scientists and contributes to their curriculum and extracurricular experience.

Together, our members experiment and practice novel techniques. They push the limits of leading-edge technology at the Center's two core facilities where they can further develop and test innovative concepts (see Bru-seq Lab and SMART Center articles, pages 22 and 27).

Together, we can help solve COVID-19, and future pandemics.

A young Center with broad connections

Established across seven Schools and Colleges of the University of Michigan, the Center for RNA Biomedicine is well integrated within the U-M, and has a remarkable track record both in funding and in attracting, training and retaining leaders in RNA research.

The Center and its outstanding faculty are well-recognized and renowned in the field of RNA research and biomedical sciences, nationally and internationally. Several of our faculty are elected members of the National Academy of Sciences and of other prestigious scientific societies.

Together, we can help solve COVID-19, and future pandemics.

In 2016, the U-M Center for RNA Biomedicine received initial seed funding from the U-M Taubman Institute under Dr. Eva Feldman's leadership. Four years later, the Center was awarded a Tier 1 Grant from U-M President M. Schlissel under the Biosciences Initiative for $10M over five years.

Our faculty raises an average of $200M per year in research expenditures from federal grants and Foundation awards.

Our students and postdocs are recruited by the best private biomedical firms as well as by highly-ranked public academic and research institutions.

U-M knows how to do research
The University is ranked the largest public research university in the US.

U-M's entire research expenditures are $1.62 billion, and about half of these are in the biosciences, with activity in medicine, pharmacy, dentistry, public health, nursing, engineering, kinesiology, biology, psychology, computer science, chemistry and physics.

For decades, the U-M has successfully encouraged and fostered cross-disciplinary collaborations, an approach to doing research that is required to innovate in biomedicine.

TOGETHER,

We can further advance RNA research at the University of Michigan. As a Center for RNA Biomedicine's supporter, you will be kept informed of the latest RNA research. **You will be offered opportunities to discuss RNA discoveries and investigations with our Center's members.**

We can continue to foster and promote the RNA scientific community and make a difference in this leading-edge field of investigation. As a supporter, **you will be offered the opportunity to network with our outstanding scientists.**

With your support, we can develop fellowship programs, events, and exceptional facilities.

For more information on how to join the fantastic journey into the world of RNA, and to consider how to engage with our scientific community, please contact Martina Jerant at mjerant@umich.edu.

UNIVERSITY OF MICHIGAN

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Qiagen sponsored our 2019–2020 seminar series.

THANK YOU FOR YOUR SUPPORT!

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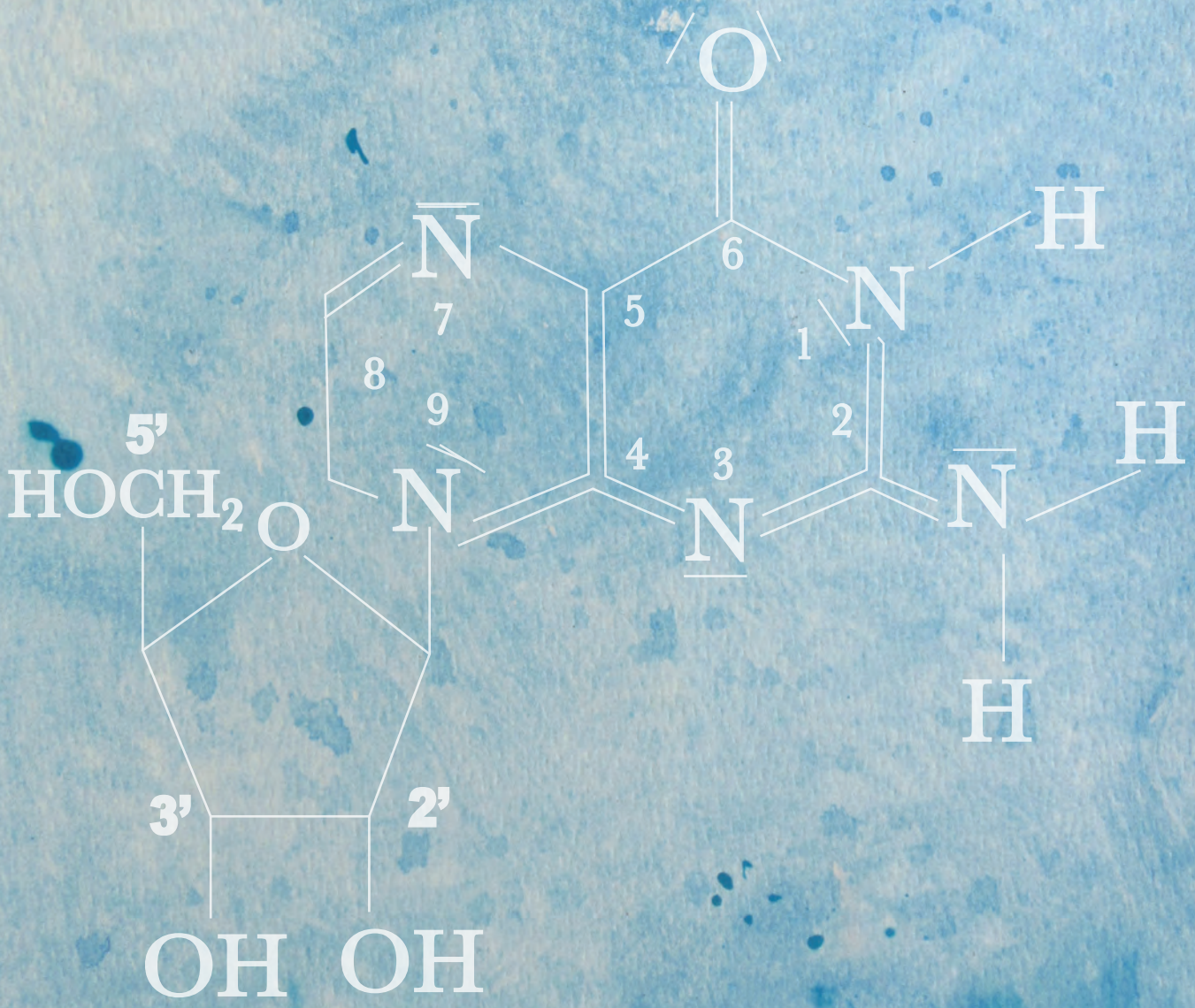
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