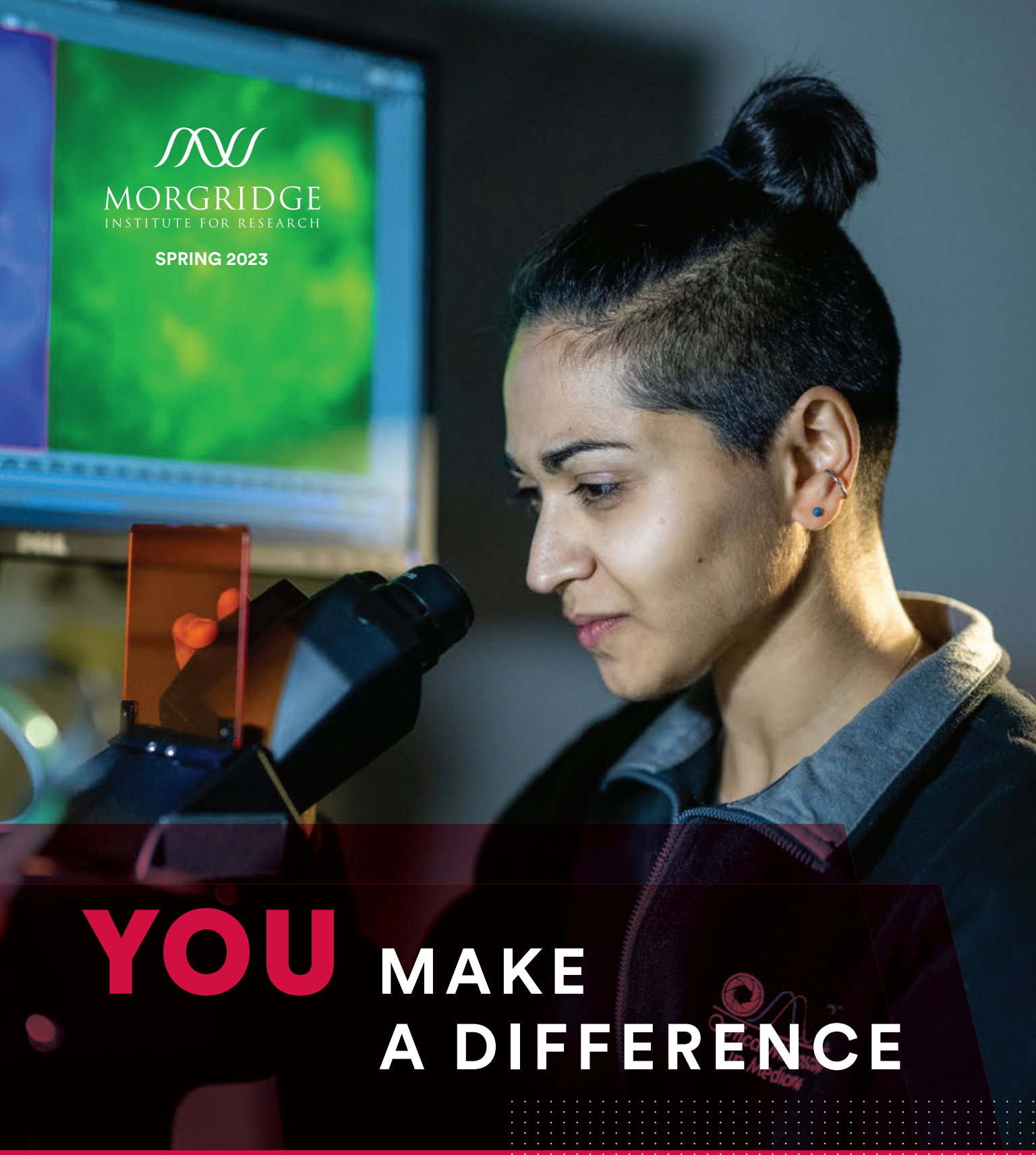


MORGRIDGE
INSTITUTE FOR RESEARCH

SPRING 2023

YOU MAKE A DIFFERENCE

INSIDE

A special report for supporters of the Morgridge Institute for Research

BRAD'S UPDATE

Spring is in the air and here at the Morgridge Institute, it is both the season of spring and new beginnings. You may notice a new design for this biannual newsletter, and I hope you enjoy the updated look and feel.

In just a few weeks, we will be congratulating and honoring the undergraduate and graduate students finishing their programs and moving on to the next chapters in their careers and lives.

We are also in the final stages of welcoming new outstanding scientists to the institute and expanding our life-changing programs in outreach and education. Both of these changes usher in the next chapter in the Morgridge Institute and are made possible by you.

We are all in a season of new beginnings. As a society, we continue to emerge from the COVID-19 pandemic. It's wonderful to see scientists, students, and collaborators navigating in-person, hybrid, and remote work to push science forward.

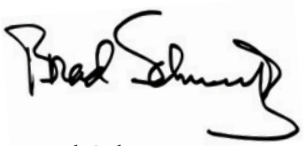
THANK YOU
Your ongoing support is a catalyst for science and discovery

We also remain steadfast in our support for raising up the next generation of scientists, like Danielle Desa, a postdoctoral fellow in the Melissa Skala Lab. Danielle, like many postdocs here, is an early-career researcher. And your support is vital to helping train and nurture the next generation of scientists.

In this report, you can learn more about the progress Morgridge scientists are making in many avenues of biomedical science and health. Fundamental research is a catalyzing force in discovery — and you can read about two avenues of exciting research: one continues our pathbreaking work to understand how viruses replicate — and stop them, and the other seeks to establish a new model animal (the Nile rat!) in diabetes research.

All of this work is made possible by YOU. Thank you for being part of our continued progress in science and discovery — and raising up the next generation.

I hope you enjoy this report. Thank you for helping scientists improve human health. We can't do this work without you.



Brad Schwartz, M.D.
Chief Executive Officer
Morgridge Institute for Research

P.S. What's on the cover? You'll see Danielle Desa, a postdoctoral research fellow, who is working on a project that combines microscopy and stem cells with the potential to deliver better heart disease therapies. Read more about Danielle on page 2.

Training the next generation of science leaders

DESA NAMED INAUGURAL MELITA F. GRUNOW POSTDOCTORAL FELLOW

Stem cells are a powerful tool to address cardiovascular disease, which is responsible for over 30 percent of all deaths worldwide.

Scientists are beginning to unlock their potential. Using human induced pluripotent stem cells, we can generate highly functional cardiomyocytes, the muscle cells responsible for the contraction of the heart.

Armed with these cells, scientists hope to model heart disease, screen drugs, and develop personalized patient therapies. However, the process of differentiating stem cells into mature cardiomyocytes is costly, labor-intensive, and highly variable.

And that's where Danielle Desa comes in. Desa was awarded the inaugural Melita F. Grunow Postdoctoral Fellowship, which funds early-career scientists.

She seeks to break new ground in optical imaging to monitor stem cell differentiation. Desa is mentored and supported by Melissa Skala, the Carol Skornicka Chair in Biomedical Imaging at Morgridge, and William Murphy, the Harvey D. Spangler Professor in the Department of Biomedical Engineering at UW–Madison.

Desa's project builds on the momentum of the Skala Lab's earlier work describing an imaging technique that can predict the efficiency of cardiomyocytes differentiation as a method of quality control.

For Desa, the goal is to make the entire process faster, cheaper, and more accessible. She is working to build and validate a cost-effective, user-friendly, high-throughput system using the intrinsic properties of cardiomyocytes. The hope is to determine when and how the stem cells differentiate and mature into heart muscle cells.

"The significance of Dr. Desa's postdoctoral research could be quite high," says Murphy. "Heart disease is the number one killer annually in the U.S., and scalable manufacturing of mature, functional human cardiomyocytes offers potential for a blockbuster new treatment."

The Skala Lab, and UW–Madison, were a natural fit for someone with Desa's background in biomedical engineering — here, she can leverage the optical prowess of the Skala Lab and the biomaterials expertise of the Murphy Lab.

She hopes to build a microscope with a smaller footprint that can be integrated with more widely available commercial microscopes, making it more accessible to research and industry.

"My personal interest has always been in microscopy," Desa says. "I think many people, especially on the biology side, just don't know exactly what they can do."

Desa's hope is that the system, paired with groups of stem cells from the Murphy Lab, will open up a new door to rapidly and noninvasively screen culture conditions and create new protocols for this evolving technology.

YOU'RE MAKING A DIFFERENCE

The Morgridge Institute for Research explores uncharted biomedical research. By asking the boldest questions and following the highest standards of quality research, we will improve human health.

And we can't do this important work without YOU. Our scientists count on donors like you to help improve human health — we can't thank you enough for your support.

When you give, you are:

Exploring Science, Fearlessly

You help scientists pursue fearless science. Morgridge scientists are fighting deadly diseases and disorders, unlocking the mysteries of biology, and driving the next advances in human health.

Changing Lives

Science is for everyone. Your gifts provide free science education and outreach programs for children and families, like the Summer Science Camp. Thank you for inspiring the next generation to explore science.

Learn more by visiting: morgridge.org/give

A stunningly detailed blueprint

Morgridge scientists reveal the complexity of how virsues replicate

RNA viruses, such as the coronavirus that causes COVID-19, are in a life-and-death race the moment they infect a cell.

These viruses have only minutes to establish their replication machinery inside the host cell before the genetic instructions contained in their vulnerable RNA genomes — which are more fragile than DNA — would be destroyed by cellular housekeeping.

If successful, the virus can go from just a few copies of its RNA genome to a half-million copies incorporated in new infectious particles in less than 12 hours. If not, the virus dies.

In new research published in the Proceedings of the National Academy of Sciences (PNAS), Morgridge scientists shed new light on these crucial early stages of virus infection and their control. The researchers developed new ways to release viral RNA replication complexes from cells and visualize them in sophisticated ways by cryo-electron microscopy (cryo-EM).

"This is a new chapter where we've been able to reach inside cells to capture and image in great detail even more intricate viral machinery that carries out the central events of viral replication," says Paul Ahlquist, director of the Institute's John and Jeanne Rowe Center for Virology and a University of Wisconsin–Madison professor.

Most microbe and host genes function in large protein complexes that operate as molecular machines. The structures of these critical assemblies, however, have largely been unknown.

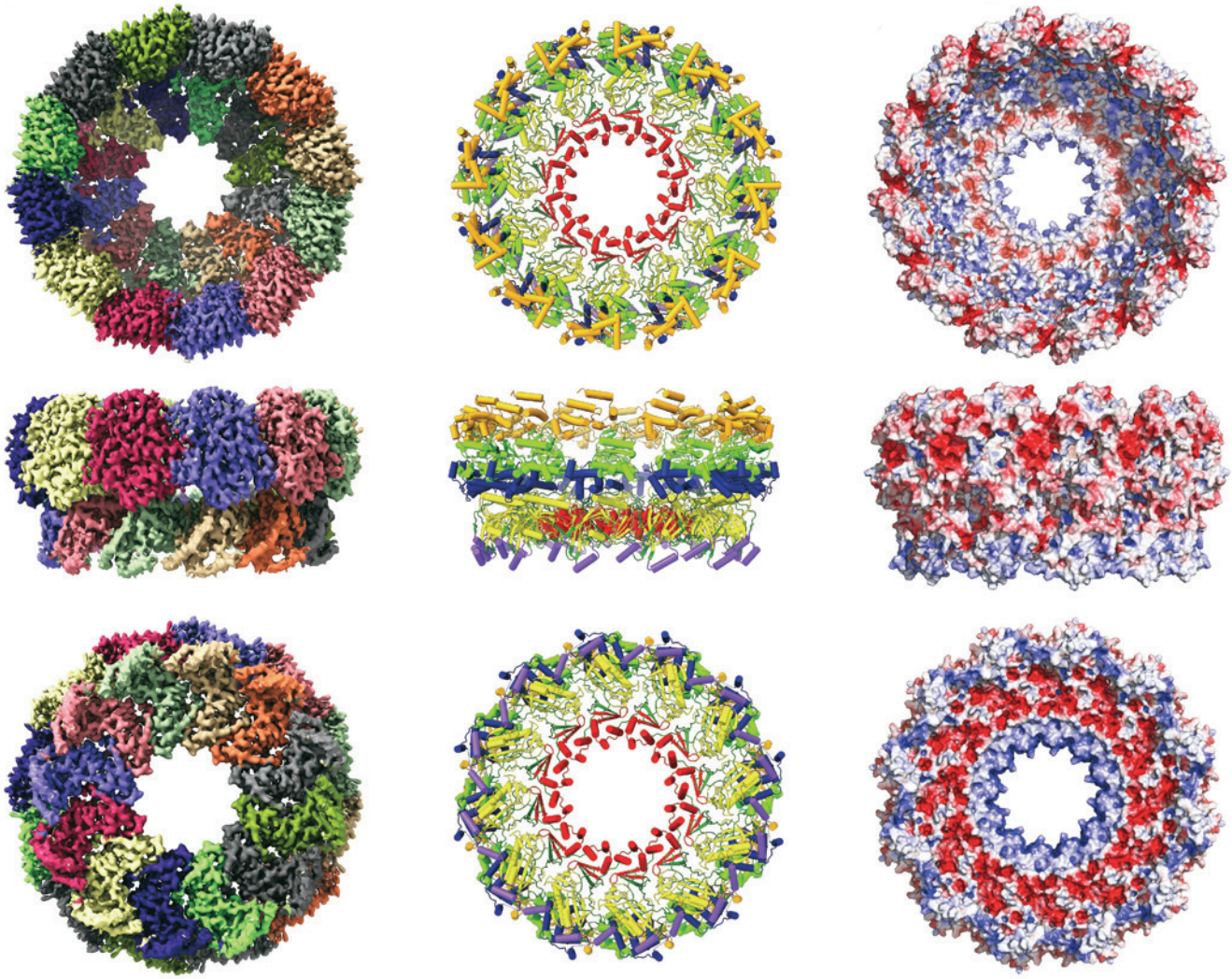
In 2017, the Ahlquist lab provided the first full imaging of a viral RNA replication complex and its striking organization. They found the parental viral genomic RNA "chromosome" tightly coiled within a narrow-necked vesicle. Around the opening of the vesicle is the RNA replication machinery in a previously unknown, 12-fold symmetric, ringed complex that they named the "crown."

Now, the team presents a further leap by revealing the intricate structure of this molecular crown and its component enzyme domains at atomic to near-atomic resolution.

"The first visualizations of the crown machinery by our lab in 2017 were like identifying the existence and general outline of a building," says first author Hong Zhan. "The new 2023 resolution is like showing fine details, such as the electrical wiring and door locks."

The team describes two stacked rings, each made up of 12 copies of viral replication protein with multiple domains, providing all functions required to synthesize new copies of the viral genomic RNA. However, the proteins in the upper and lower rings are in dramatically different conformations — perhaps operating in distinct ways in the different rings. Other features underscore that the crown is not static but a sophisticated, active machine that provides major functions for organizing many critical phases throughout infection.

"Just slowing down the assembly and function of RNA replication complexes is enough to kill these



In these diagrams, you can see segments of the single-particle cryo-EM proto-crown structure. The top, side, and bottom views of the crown include domains like the membrane association (purple), capping (yellow), and central ring (red) and a functionally unassigned region (dark green), among other domains.

viruses," Ahlquist says. "These new results provide a strong basis for finding new ways to do that."

Emerging results from the Morgridge group and other researchers indicate that the principles revealed by these studies are evolutionarily ancient, and that similar crown-like complexes are central to the replication of most, if not all, RNA viruses in this large class. This includes the COVID-19 SARS-CoV-2 coronavirus and many other pathogens.

Accordingly, the conserved underlying principles might serve as the basis for developing more powerful, broad-spectrum antiviral strategies that could inhibit infection by not just one but whole groups of viruses, Ahlquist says.

THANK YOU
You've made a difference for scientists, researchers, and students. Your donations provide critical resources that help scientists working on cutting-edge research.

Your life, your legacy

A legacy gift makes it possible for you, your loved ones, and the Morgridge Institute to all benefit. An estate gift is a powerful and meaningful way to honor your life and make a difference in science, outreach, and education.

Your generosity can help the next generation of scientists, researchers, and educators working at the forefront of science and medicine. You and your financial advisor can create a lasting impact. Legacy giving also provides a number of benefits for your financial, estate, and tax plans, and may result in substantial tax savings, especially on gifts of highly appreciated assets.

You and your family can direct all or a portion of your estate to the Morgridge Institute. In addition, we welcome the opportunity to create a fund named in your honor, or in recognition of a family member or person whom you seek to honor.

We're here to help. Let's inspire the next generation of scientists today — and improve human health together.

Contact Bill Swisher, Chief Development Officer, today.
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Learn more by visiting: morgridge.org/give

How donors like you make a difference

Bringing science to curious minds

Your support is vital to expanding science outreach and education in Wisconsin. Thank you for helping scientists and educators build partnerships with UW–Madison, our local community, and the state to bring the joy and wonders of science to children and families.

The Morgridge Institute inspires and engages society through its Discovery Connections science outreach programs. Programs are available in-person in Madison and on digital platforms, but many others are hosted at community centers, schools, libraries and museums throughout Wisconsin.

Your support allowed us the flexibility to try multiple electronic and digital approaches to find out what worked. Here are some vital statistics, accompanied by images from some of our signature programs.

IN A TYPICAL YEAR, WE WELCOME

700,000+ PEOPLE TO THE DISCOVERY BUILDING

THE WISCONSIN SCIENCE FESTIVAL HAS ATTRACTED 393,000+ STATEWIDE ATTENDEES SINCE 2011

80,000+
PEOPLE HAVE ATTENDED SATURDAY SCIENCE

WE HAVE ACTIVE PROGRAMMING IN AS MANY AS
44 COUNTIES
EACH YEAR

WE HAVE WORKED WITH
500+
FACULTY
ON PUBLIC ENGAGEMENT PROGRAMS

THE PHENOMENAL IMPACT OF THE SUMMER SCIENCE CAMP IN WISCONSIN

700+
HIGH SCHOOL STUDENTS

150+
TEACHERS

100+
HIGH SCHOOLS

Genome sequencing supports Nile rat animal model for diabetes research

Morgridge scientists help establish new avenues for research

Model organisms are essential for biomedical research and have enabled many important scientific discoveries. Now for the first time, researchers have assembled a high-quality reference genome for the Nile rat, a promising model organism for diabetes research.

The house mouse (Mus musculus) and Norway rat (Rattus norvegicus) are widely used in research due to their genetic similarities to humans.

But scientists at the Morgridge Institute and the University of California, Santa Barbara have now provided a high-quality reference genome assembly for the Nile rat, expanding its potential as a model organism.

Yury Bukhman is a computational biologist in the Stewart Computational Biology Group at the Morgridge Institute for Research.

"We need research tools that will enable us to do the same things with the Nile rat that we are used to doing with the lab mouse," says Yury Bukhman, a computational biologist in the Stewart Computational Biology Group at Morgridge and senior author on the project. "Having the reference genome is an advance toward that goal."

Bukhman, along with first author Huishi Toh, an assistant project scientist at UCSB, says the Nile rat serves as an alternative model in two research areas where lab mice and rats have limitations: type 2 diabetes and disorders associated with a disrupted circadian rhythm.

The Nile rat, which is more similar to voles, is diurnal — active during the daytime like humans. It also has more photoreceptors in its eye in comparison to nocturnal rodents, which makes it relevant for studying human retinal diseases, including diabetic retinopathy. In addition, the Nile rat's genetics reflect a diverse population, a factor that can help study the complex genetic factors contributing to disease.

The Nile rat genome was assembled by a large international collaboration working to create reference-quality genomes of all vertebrate species. But the technology to produce a complete and highly accurate genome sequence is still relatively new. Typically, to sequence a large genome, the DNA needs to be chopped into shorter lengths for sequencing. And the sequences are reassembled into longer contiguous sequences (contigs). Yet this approach tends to leave lots of gaps.

And that's where the Morgridge team got creative — they applied a variety of technologies to assemble longer contigs and join them together into scaffolds. Then, they fully resolved two copies of the genome — the one that the sequenced rat inherited from its mother and the one from its father.

"We don't have a 'smoking gun' at this point," says Bukhman, referring to a gene that may be responsible for diabetes. "You can always get a list of genes. But then, how do you know that they're really important in diabetes? That will take years and years of experimental work."

Now that the Nile rat has a high-quality reference genome, Bukhman and Toh hope that the species will become more widely used in biomedical research.

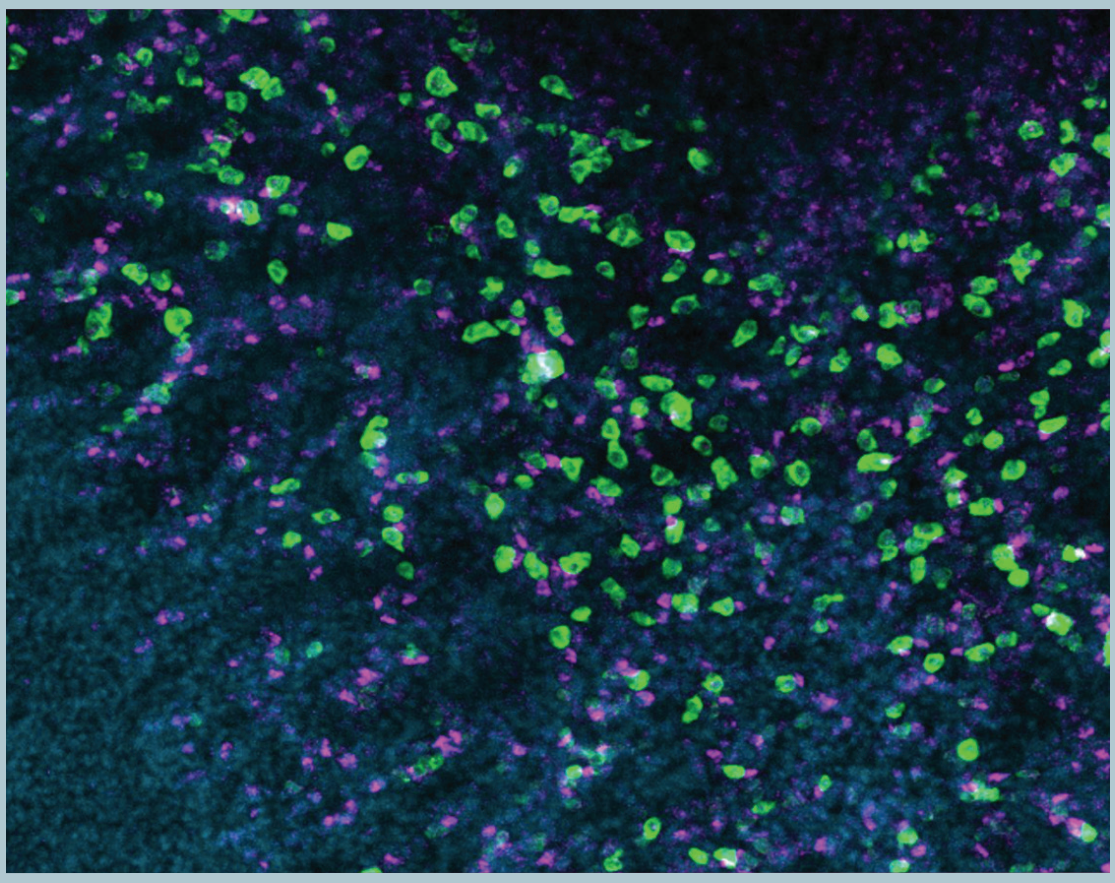
"People are resistant to using new animal models because it's a lot of money, a lot of effort, and a lot of risk," says Toh. "But we decided to take the unconventional route. In research, I think, to survive is to find different flavors, different trajectories. And we've removed some of that risk."

LOOKING CLOSER

Unlocking the secrets of regeneration

Morgridge scientists featured in *Wall Street Journal*

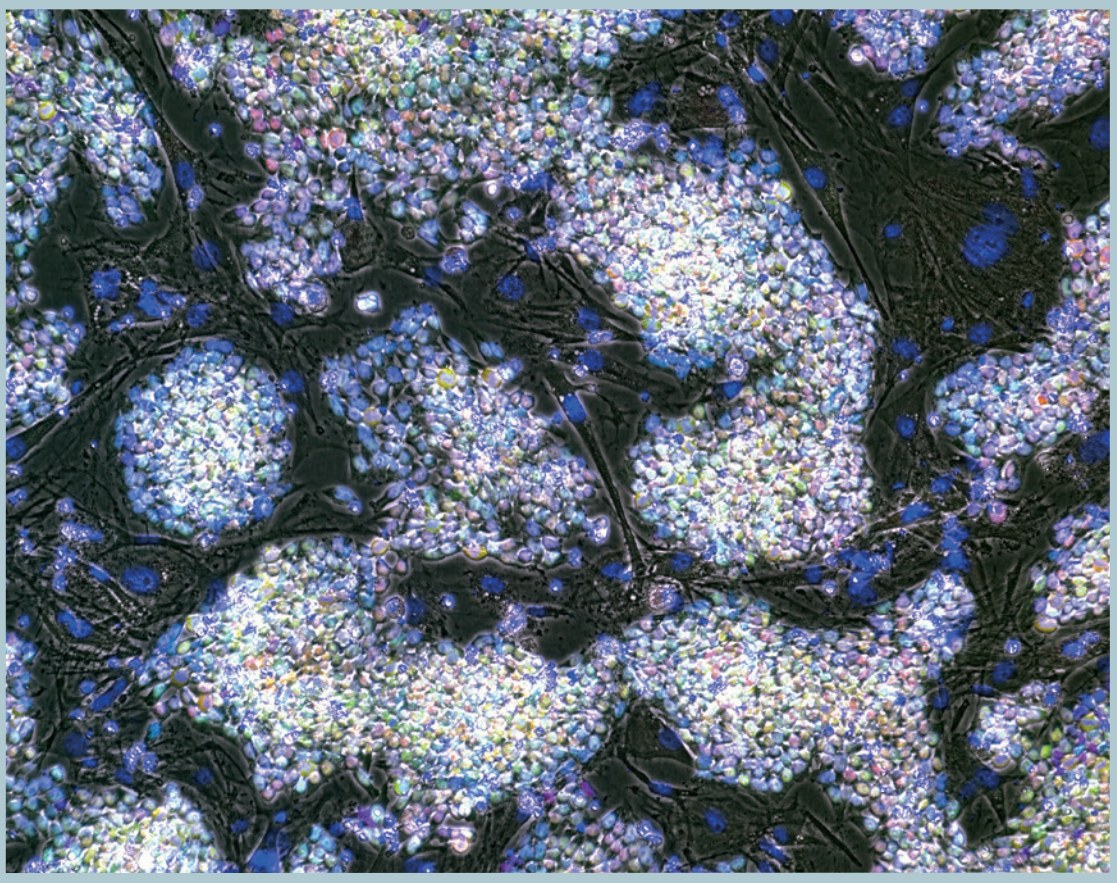
The work of Melanie Issigonis, a scientist in the Phil Newmark Lab, was recently featured in a Wall Street Journal photo essay that explores how many animals can regrow limbs and other body parts after injury. Her image shows stem cells — called neoblasts — that let the flatworm grow back lost organs including its reproductive system. Scientists are studying the flatworms yolk producing organs (glowing pink) and yolk cells (glowing green) to understand how the creatures bring back these complex organs.



Studying the development of dementia and Alzheimer's disease

Striking image reveals the intricacy of stem cells

A team of scientists including graduate student Julia Gambardella, Morgridge scientist John Maufort, and UW–Madison Professor Marina Emborg, were winners in the UW–Madison 2022 Cool Science Image Contest. Their work shows stem cells derived from the skin cells of a rhesus macaque monkey. The cells appear like multi-colored pearls atop spindly mouse cells that provide the stem cells with crucial support as they grow. Stem cells have the potential to become any type of cell in the body, but these are specifically destined to form brain cells to study the development of dementia and Alzheimer's disease.



“The Morgridge Institute is deliberately building a culture of support: to ask big questions and not being deterred by not immediately knowing what the answer is going to be.”

– PAUL AHLQUIST, DIRECTOR OF THE JOHN W. AND JEANNE M. ROWE CENTER FOR RESEARCH IN VIROLOGY

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