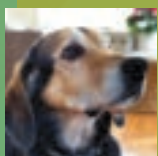


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Therapeutic revolution

two decades in the making

story on page 8



17 Genome's
best friend



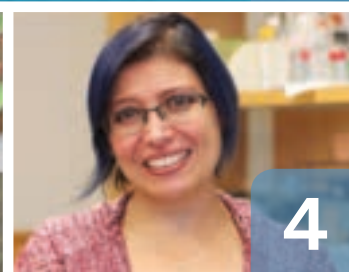
20 Championing
community
health



24 Nurses take
on opioid crisis

The University of Massachusetts Medical School is the commonwealth's first and only public academic health sciences center, home to three graduate schools. Our mission is to advance the health and well-being of the people of the commonwealth and the world through pioneering education, research and health care delivery with our clinical partner, UMass Memorial Health Care.





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Institute reinforces commitment to rare diseases

In 1983, Congress defined a rare disease as one that affects fewer than 200,000 people. Also known as orphan diseases, they often don't receive the attention or funds that diseases afflicting larger numbers of people do. But collectively, rare diseases affect an estimated 25 to 30 million people.

"They can often feel hopeless when they're seeking treatment or looking to connect with researchers who share their drive for a cure," said UMass Medical School Chancellor Michael F. Collins.

UMass Medical School is now offering hope to these individuals. The Li Weibo (李卫波) Institute for Rare Diseases Research, supported by a \$10 million endowment gift from the Li Weibo Charitable Foundation in China, is home to UMMS faculty whose expertise has led to profound discoveries related to diseases such as ALS, cystic fibrosis, Canavan disease, Rett syndrome, Huntington's disease, fragile X syndrome, CDKL5 disorder and others. The new institute builds on the school's already substantial accomplishments in gene therapy, RNA biology and RNAi technology to accelerate the development of novel therapeutics for a host of disorders.

"Our scientists and physician-investigators have long been committed to discovering life-changing treatments and cures for these diseases," said Chancellor Collins. "This generous gift from the Li Weibo Charitable Foundation will allow us to expand on our discoveries, bringing research support and hope for people around the world."

The \$10 million gift is one of the largest charitable donations to UMass Medical School in its history. Additionally, Li Weibo is contributing \$750,000 to establish an annual scholarship for up to five doctoral students in the Graduate School of Biomedical Sciences.

The institute is led by Guangping Gao, PhD, the Penelope Booth Rockwell Professor in Biomedical



Guangping Gao, PhD, (left) and Michael Green, MD, PhD, are co-directors of the institute.

Research, professor of microbiology & physiological systems and director of the Horae Gene Therapy Center & Vector Core at UMass Medical School, and Michael Green, MD, PhD, Howard Hughes Medical Institute investigator, the *Lambi and Sarah Adams Chair of Genetic Research*, and chair and professor of molecular, cell & cancer biology. The establishment of the institute was announced in late 2017, and to date, 42 faculty members have become members.

In May, an additional gift from the Li Weibo Charitable Foundation was received to establish a new endowed

chair at UMass Medical School that will support research initiatives that advance the fundamental understanding of human biological systems and offer new and innovative pathways to treat human disease. Zhiping Weng, PhD, professor of biochemistry & molecular pharmacology and director of the Program in Bioinformatics & Integrative Biology, is the inaugural chair holder.

For more information about the Li Weibo (李卫波) Institute for Rare Diseases Research, visit www.umassmed.edu/rare-disease-research. □



Zhiping Weng, PhD, (center) is the inaugural holder of the Li Weibo Chair in Biomedical Research. She is pictured with Chancellor Michael F. Collins (left) and Li Weibo (right).

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Nick Todisco (below) received a lifesaving dose of equine tetanus antitoxin manufactured by MassBiologics in 1946. Last year, MassBiologics celebrated its centennial anniversary as a federally licensed manufacturer and distributor of biologic products.

Reflections on a life saved

In 1946, when Nick Todisco was 16 years old, he almost died from a small cut he got while playing hockey on Jordan Pond in Shrewsbury. Todisco developed lockjaw as a result of a tetanus infection and was hospitalized in serious condition. But thanks to what was at the time a novel and newly available treatment, he lived to enlist in the Marines and fought in the Korean War. He married and raised four children. And lived to be an 87-year-old grandfather of 11, thanks in part to MassBiologics of UMass Medical School.

Todisco was the fortunate recipient of equine tetanus antitoxin, which MassBiologics had developed and manufactured at its Jamaica Plain laboratories. A lifesaving dose was rushed to Shrewsbury and Todisco quickly recovered and resumed a normal, productive life.

"The guy lived his life. With the second chance that he was given, he lived his life to the fullest," recalled his son, Nick Jr. "He was my Little League manager, my Babe Ruth manager and coached me all the way up. He learned how to scuba dive and he got his pilot's license. If you were his friend, you never had a better friend. He was kind and had a tremendous heart for people that he loved."

"Nick's story exemplifies the day-to-day mission of MassBiologics—to create medicine for better lives," said Mark Klempner, MD, executive vice chancellor for MassBiologics and professor of medicine. "The treatment that Nick got in the 1940s was not widely available then. MassBiologics was on the forefront of developing safer, human tetanus immune globulin, which became today's standard treatment. Millions of lives have been saved



as a result of the research, development and manufacturing of vaccines and biological medicines from MassBiologics."

Last year, MassBiologics celebrated the 100th anniversary of being federally licensed as a manufacturer and distributor of biologic products. Since 1917, it has manufactured millions of doses of life-saving treatments and vaccines for numerous diseases and infections, and is the single largest manufacturer of the diphtheria/tetanus vaccine in the country.

Today MassBiologics is the only nonprofit, FDA-licensed vaccine manufacturing facility in the United States. Since becoming affiliated with UMass Medical School in 1997, MassBiologics has expanded its research and manufacturing mission to combat diseases globally, including rabies, *clostridium difficile* infection, diphtheria, Parkinson's and Lyme disease.

Also last year, MassBiologics and the Serum Institute of India announced the launch of Rabishield, a rabies monoclonal antibody they developed in partnership. While rabies is rare in the United States, worldwide it kills more than 50,000 people a year and an estimated 20,000 people die every year in India alone because they lack access to the treatment. Rabishield will help close the gaps in rabies prevention and is expected to significantly reduce the rabies mortality rate in India.

"Rabishield will go a long way toward dramatically reducing rabies deaths," said Chancellor Michael F. Collins. "We are proud to have partnered with the Serum Institute of India to make treatment available and gratified by the global public health impact of the commonwealth's only public medical school." □



Teresita Padilla-Benavides, PhD, (center) received the 2017 SACNAS Outstanding Research and Professional Mentor Award for her record of encouraging underrepresented minority students to pursue advanced degrees in science. Left and right, students and mentors attend the 2018 SACNAS New England Regional Conference hosted by the SACNAS-UMMS student chapter.

Fostering the next generation of scientists

Society for the Advancement of Chicanos and Native Americans in Science aims to increase diversity and inclusion of minorities in science and health

For MD/PhD candidate Aurian García-González, the national Society for the Advancement of Chicanos and Native Americans in Science (SACNAS) played a critical role in career choice. The Puerto Rico native said she knew she wanted to go into medicine, but it was not until she received scholarships from the organization to attend national conferences, where she worked with physician-scientists from around the world, that she decided to pursue that path.

"As an undergraduate, I was very fortunate to be awarded travel scholarships to attend and present at two SACNAS national meetings," said García-González, who studies in the lab of Marian Walhout, PhD, the *Maroun Semaan Chair in Biomedical Research*, professor of molecular medicine and co-director of the Program in Systems Biology. "At that point, I realized the importance of national professional organizations like SACNAS in fostering the next generation of scientists."

Last year, with support from Teresita Padilla-Benavides, PhD, instructor in biochemistry & molecular pharmacology, García-González and PhD candidates Daniel Hidalgo and Raziel Rojas-Rodríguez

established a SACNAS student chapter at the medical school.

"Having the opportunity to create the SACNAS student chapter at UMass Medical School has allowed us to contribute to the institutional mission of promoting and empowering underrepresented groups," said Dr. Padilla-Benavides, faculty co-advisor of the chapter with Jaime Rivera, PhD, associate professor of pediatrics.

The national SACNAS organization was established in 1973 to foster the success of Chicano/Hispanic and Native American scientists in attaining advanced degrees and careers and positions of leadership in science, technology, engineering and math (STEM) disciplines.

In the year since its inception, the SACNAS-UMMS student chapter has received a national award, hosted the 2018 Northeast Regional Conference and established itself as one of the more active chapters nationally.

At UMMS, the chapter's goals are: to provide a platform for students to connect with role models for mentorship and professional development opportunities; to engage the community and increase awareness of the importance

of biomedical research; to help mentor and recruit the next generation of STEM professionals; and to support city and institutional diversity initiatives.

In keeping with its goals, the chapter received a UMMS public service grant and quickly implemented *Ciencia y Salud entre amigos* (health and science among friends), a public seminar program through which members of the medical school community share their knowledge with the general public.

"These public talks are a great way for us to foster discussions about what we are doing as researchers at UMMS and how what we do relates to the well-being of the community at large," said Pamela Cote-Hammarlof, a PhD candidate in the lab of Daniel Bolon, PhD, professor of biochemistry & molecular pharmacology.

"We're scientists and part of our job is to train, to educate and to contribute to society to make the world a better place. I think we just don't want to only show science, we want to show how scientists can be advocates for social change through education," said Padilla-Benavides. □

45th Commencement honors Huda Zoghbi



JOHN GILLOOLY, PEI

At its 45th Commencement exercises on June 3, UMass Medical School honored groundbreaking physician-scientist Huda Y. Zoghbi, MD, of Baylor College of Medicine, who delivered the keynote address. Dr. Zoghbi is pictured here with Terence R. Flotte, MD, the *Celia and Isaac Haidak Professor of Medical Education*, executive deputy chancellor, provost and dean of the School of Medicine; UMass President Marty Meehan; and UMass Medical School Chancellor Michael F. Collins.

Nursing leader Marion E. Broome, PhD, RN, FAAN, of Duke University; and Cyrus S. Poonawalla, PhD, founder, chairman and managing director of the Serum Institute of India, the world's largest vaccine manufacturer, also received honorary degrees.

This year saw the presentation of 193 degrees, including three honorary degrees. There were 105 Doctor of Medicine degrees awarded, one Master of Science in clinical investigation, 60 Doctor of Philosophy degrees in the biomedical sciences, seven MD/PhDs, and, in nursing, two Master of Science degrees, two post-master's certificates, two PhDs and 11 Doctor of Nursing Practice degrees. Jacqueline Monteiro Pires, right, was among the graduates to earn a Doctor of Medicine degree.



Veterans at UMass Medical School embrace next chapter of service

While their paths to a career in medicine are as varied as any, there's a common thread connecting three UMMS students: a desire to turn the lessons from their military service toward the field of medicine.

As a U.S. Army combat medic and paratrooper serving in Afghanistan, Johnny Jarnagin experienced the privilege of being called "Doc."

Jarnagin enlisted in 2007 and trained as a combat medic before attending airborne school to become a paratrooper. In 2009, he was deployed to Afghanistan for 12 months, where he conducted more than 300 missions, many in coordination with local Army and police forces.

"My time as a combat medic stoked my interest in medicine, especially my time in Afghanistan, where at times I was the only medic responsible for the health and welfare of scores of men," said Jarnagin, who earned his undergrad degree from UMass Boston. "These men entrusted their lives to me and even opened up to me about their ailments outside of the physical. One of the highest honors for a medic is to be addressed by your men as 'Doc;' I can still recall the first time they called me Doc and it will always remain in my consciousness as I continue this journey in medicine.

"I want to ensure that our veterans and future generations of veterans are able to have access to the best health care possible," he said.

Likewise, when U.S. Army 2nd Lieutenant Maria Navarro earns her medical degree, she, too, will focus on fellow soldiers.

"I love soldiers and I cannot think of a better way to serve those who don't think twice about placing their boots on the ground in defense of our way of life, than to assume responsibility for a soldier's care and the care of a soldier's loved ones," said Navarro.



Maria Navarro, William Selkirk and Johnny Jarnagin (left to right) chose to pursue careers in medicine in part because of their experiences in the military and their continuing desire to be of service.

"I love soldiers and I cannot think of a better way to serve those who don't think twice about placing their boots on the ground in defense of our way of life, than to assume responsibility for a soldier's care and the care of a soldier's loved ones." Lt. Maria Navarro

Navarro was born in Brazil and moved to Brockton with her family 18 years ago. She graduated from the United States Military Academy at West Point as a second lieutenant in the medical services branch, with a major in life sciences.

William Selkirk is a veteran of the U.S. Marines. It was through his service as a paramedic, after his military service, that he became interested in medicine.

Selkirk served in the Marines from 2002 to 2006, as a presidential guard with Marine Security Company - Camp David. He served as a section commander of a platoon of Marines responsible for the safety and security of President George W. Bush while he visited Camp David. After completing his service in 2006,

Selkirk joined the South Hadley fire department as an on-call firefighter, eventually training to become a full-time firefighter/EMT. He attended Greenfield Community College and earned his paramedic license and later earned his undergraduate degree at Emmanuel College.

"While working as a firefighter and paramedic, I was only able to impact my patients' lives through short encounters, and I began to realize that I wanted to play a larger role in my patients' well-being, and it was at this time I made the decision that I wanted to pursue a career as a physician," said Selkirk, who lives in Natick.

Jarnagin and Selkirk are members of the SOM class of 2020; Navarro will graduate in 2021. [□](#)



The New England Newborn Screening Program uses the same specimen—usually collected when the baby is between 24 and 48 hours old—to test for 32 disorders as part of routine screening. Each of the cards (inset) contains blood droplets from a single infant.

New England Newborn Screening Program continues research and development

Four new medical conditions joined a list of more than 30 disorders that Massachusetts newborns can be tested for by UMass Medical School's New England Newborn Screening Program. Screens are now available for two lysosomal storage diseases, Pompe disease and mucopolysaccharidosis type I, as well as X-linked adrenoleukodystrophy and spinal muscular atrophy.

The conditions were added to the voluntary newborn screening panel, which is offered to all babies born in Massachusetts. The commonwealth mandates that all babies are tested for 32 conditions on the routine newborn screening panel; the number of voluntary tests now totals eight.

The New England Newborn Screening Program, part of UMass Medical School's Commonwealth Medicine division, operates the Massachusetts newborn screening

program on behalf of the Massachusetts Department of Public Health. DPH defines the conditions to be screened for on both the mandated and voluntary panels.

All testing is performed on the same specimen, usually collected in the hospital when the baby is between 24 to 48 hours old.

The addition of these new tests was one of the factors for the New England Newborn Screening Program's relocation in 2017 from the Hinton State Laboratory Institute in Jamaica Plain to the UMass Medicine Science Park, adjacent to UMass Medical School's Worcester campus. In addition to increasing the number of tandem mass spectrometers and real-time polymerase chain reaction instruments for the laboratory, instrumentation and capabilities for genetic sequencing were added to meet the analytical needs for detecting the added conditions. □



Therapeutic revolution

two decades in the making

When you're dying, you'll try anything.

That's what Rick Schrader thought when he heard about a potentially lifesaving but experimental drug for the disease that was quickly killing him.

The disease is called hereditary ATTR amyloidosis. It's a progressive, fatal disease that runs in families. Children watch grandparents die. Then a parent, aunt or uncle is stricken. If this is your family, you've got a 50-50 chance of carrying the destructive gene.



It typically attacks the heart and nervous system with a cruelty that obliterates hope. Research has revealed a clear picture of the disease. The faulty gene is known. The way it harms the body is known. But it was beyond the reach of science to stop the disease.

That all changed on Aug. 10, when the U.S. Food and Drug Administration approved patisiran (pronounced pah-tee sa-ran), a life-saving therapy for some 50,000 people worldwide with hereditary ATTR amyloidosis. It is the first of a new class of medications that will treat many heretofore untreatable diseases. And a ray of hope for patients like Schrader. (Read more about him on page 15)

Developed by Alnylam Pharmaceuticals in Cambridge, patisiran (which will be sold under the name Onpattro) is based on the science that flowed from laboratory discoveries in the 1990s by Craig Mello, PhD, Howard Hughes Medical Institute Investigator, the *Blais University Chair in Molecular Medicine*, distinguished professor of RNA therapeutics and professor of molecular medicine, and others of how a common laboratory research organism, the tiny worm called *C. elegans*, reacted in genetic studies. Those observations set Dr. Mello on a path of discovery at the University of Massachusetts Medical School that ultimately uncovered an ancient

mechanism of gene regulation called RNA interference (RNAi) and opened a line of inquiry that would earn Mello and a collaborator, Andrew Fire, PhD, now at Stanford University, the 2006 Nobel Prize in Medicine or Physiology.

Much like the discovery of penicillin launched the era of antibiotics and transformed human health, Dr. Fire and Mello's discovery of RNAi revealed a new layer of biology and launched development of radically new approaches to treat disease. The discovery revealed that cells in nearly every organism use RNA-guided search mechanisms to silence a target gene. This discovery enabled researchers to exploit this natural mechanism by programming it with any search query they wish, in order to target a specific gene.

For the many illnesses in which damaged genes create toxic proteins that cause disease, using a gene-specific guide RNA to silence those harmful genes can be a treatment. That's what patisiran does for hereditary ATTR amyloidosis. RNAi-based medicines are expected to have the capacity to treat a vast array of diseases known to be caused by the products of faulty genes, including cancer, ALS, Huntington's and hemophilia.

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"This is an incredible moment," Mello said. "These findings demonstrate the power of treating disease at the genetic level. The potency and duration of effect in humans rivals what we saw in the worm, and frankly the clinical findings from this first-generation RNAi drug already surpass what we would have dreamed possible just 10 years ago."

"The opportunity to take groundbreaking science and develop it into a transformative medicine is almost a once in a lifetime opportunity," said John Maraganore, CEO of Alnylam. "This has been quite a journey. It started with a very powerful piece of science, the seminal work done by Mello and Fire, and we are pleased to be a part of that story. We've had our ups and downs, but the science always was in front of us, and it was always promising, so we never gave up."

The mutated gene at the root of hereditary ATTR amyloidosis is active mostly in the liver, where it causes production of a faulty protein. The healthy version of that protein carries hormones through the bloodstream and vitamin A through the nervous system. It deposits the cargo where needed, then degrades and is recycled. In the disease state, the faulty protein has the wrong shape and doesn't degrade. It's released from the liver and builds up in areas of the body, clogging the works, damaging tissues.

Patisiran is a "Trojan horse" therapy, Maraganore said. The drug is infused intravenously into the bloodstream, flows into the liver and presents itself as nanoparticles that liver cells are happy to take up as part of their normal filtering function. Once inside the liver cells, however, the nanoparticles burst open and release their weapons: small RNA molecules specifically designed to block production of the faulty protein.

The Phase 3 clinical trial of patisiran enrolled 225 patients with hereditary ATTR amyloidosis whose disease had progressed to the point that physicians estimated they had less than two years to live. Participants in the clinical trial received IV infusions every three weeks for 18 months. The results, reported in the fall of 2017, were stunning. The faulty protein was blocked. Most patients had a reduction in nerve damage, greater muscle strength and improved ability to walk. Schrader, who was treated after the FDA allowed for compassionate use of the drug, is among the patients who experienced these remarkable results.

Discovery

Mello is often asked about the big moment, the "Eureka!" flash of discovery, when he realized what RNAi was all about. In truth, that's not how it happened. The line of inquiry that led to RNAi was more like stepping off a familiar trail to explore a path in a thick patch of woods. You had hiked that trail for years, but never noticed the path, and that seemed strange. So, you take a few steps. Then a few more. You begin to see things that make no sense, but you keep going because you're intrigued by the

The drug is infused intravenously into the bloodstream, flows into the liver and presents itself as nanoparticles that liver cells are happy to take up as part of their normal filtering function. Once inside the liver cells, however, the nanoparticles burst open and release their weapons.

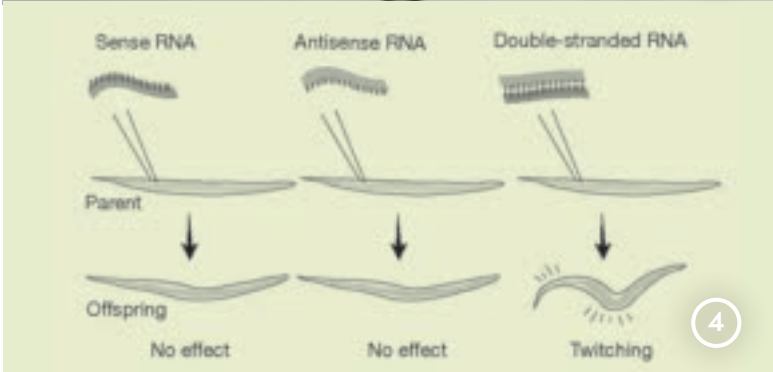
mystery. Eventually you come to a clearing and find an amazing undiscovered city.

Mello first saw the opening to that path in 1995, less than a year after he joined the faculty at UMass Medical School. Mello researches the molecular biology of cells that pass on genes to the next generation. Researchers call this the "germline," and he is fascinated by how it maintains itself and the ability to produce a single cell, the egg, that grows into an adult organism. He explores this fundamental process, shared by all animals, in the soil-dwelling *C. elegans*. Mello refers to this tiny worm as "the real Nobel prize winner."

In 1995, whole genome sequences were not available. So, most of the DNA in *C. elegans*, like most human DNA at the time, was unknown territory. To study genes, researchers worked for months, if not years, trying to figure out the function of one gene. The process was trial and error, often laborious. Researchers would use crude chemical means to try to stop a gene from doing its job, by creating DNA changes called mutations, then observe any changes in the development or behavior of the organism. Once a mutated gene causes a visible change, like blocking a worm's ability to forage properly, then the gold standard follow-up test is to put back a working copy of the gene and see if that "rescues" the worm—in this case, if the worm is able to forage properly again, once the working gene is inserted.

Working under a microscope, scientists had to inject the DNA into the gonad of the 1 millimeter-long worm. Mello and Fire, working independently at first and then collaboratively, were among the first to succeed in this painstaking process of introducing DNA back into the worm. They quickly shared their techniques with the small but well-connected community of "worm labs" across academia. In that worm world were Su Guo, PhD, and Ken Kemphues, PhD, at Cornell University, who, in the mid-1990s, were trying to prove they had identified the function of a particular worm gene, but couldn't add back a working copy of that gene using the DNA injection method. So as something of a last resort, Dr. Guo turned to RNA.

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1. Craig Mello and Barry Greene of Alnylam participate in the panel discussion "RNAi: From Lab Experiment to FDA Review" at the Xconomy What's Hot in Boston Biotech conference in May 2018.
2. At the UMass Medical School celebration of the Nobel Prize in 2006, Craig Mello is greeted by Phillip Zamore.
3. Staining appears around the mouth area of *C. elegans*, where muscle RNA was not targeted by RNA interference, while reduced or nonexistent staining along the body wall shows the inactivation of muscle genes through RNAi.
4. From an illustration by Annika Rahl, ©The Nobel Committee for Physiology or Medicine
5. Andrew Fire speaks at a press conference on Oct 2, 2006.
6. Phillip Zamore offers the opening remarks at the inaugural RNA therapeutics symposium at UMass Medical School, held in June 2018.



Similar to DNA, RNA molecules are structured like a ladder. When RNA molecules are reading genes from the DNA ladder, they make complementary copies of the gene for use by the protein building factories of the cell. Guo's hope was to intervene in that RNA part of the process, to show they had properly identified her target gene's function. She injected half of the RNA ladder, or a single strand of RNA aimed at the gene. Her approach worked so well that the potency of a single strand of RNA as a research tool quickly got the attention of others, including Mello.

Mello was astounded to discover two remarkable things about the response of the worms to the RNA injection. First, almost unbelievably, Mello could silence a gene in the worm's eggs just by injecting the single RNA strand into the head or gut of the animal. The silencing was spreading between tissues. Second, the RNA silencing effect could be transmitted to offspring for several generations. It was as if a child was born with the same tattoo her grandfather had. Nothing known in biology at the time could explain it. This was the turning point that forced Mello to step off the well-worn research trail and explore the new path. Mello and his lab concluded that the worms were mounting a heretofore unknown, highly specific and amplified silencing response, triggered by the RNA injections. They named it RNA interference, RNAi, without the slightest clue to the underlying mechanism.

Having gotten to know each other through worm meetings and by reading each other's publications over the years, Mello and Fire were already collaborating on other matters at this time, so they began brainstorming about the mechanism of RNAi. Since the silencing

response was specific to a target gene, it had to involve blocking production of that gene's protein. But what was the trigger? Since the effect was amplified (tissue to tissue and across generations) Mello preferred the idea that either half of the RNA ladder molecule could initiate amplification and that an enzyme must copy the RNA (just as DNA is copied when cells divide). Fire proposed an alternative: that a small amount of double-stranded RNA (the full ladder) in the injection mixture could be the factor triggering the effect. The RNA preparation methods used at the time invariably resulted in small amounts of both RNA strands that could coalesce. Fire reasoned that the worm's physiology could mistake these double-stranded RNA molecules for an invading virus, some of which are naturally RNA-based. This rudimentary immune response to fight the virus would actually silence the targeted gene and spread throughout the tissues to protect the animal. Fire's idea panned out. Virtually any known worm gene targeted by double-stranded RNA injection was silenced. Even feeding worms the double-stranded RNA was sufficient for silencing. Mello and Fire described these findings in a 1998 *Nature* paper now known as the seminal work that launched the RNAi field.

Mello needed to know more; he wanted to know how this process was working. Mello and co-workers turned to searching for mutant worms that were resistant to RNAi. The next year, they published a study showing one worm gene in particular was required for the double-stranded RNA response in worms. What made the finding so important was that this gene had related genes found in all complex organisms—from petunias to humans—so it was well conserved across many species. This same study also showed that a related genetic mechanism was

From groundbreaking science to transformative medicine

Napoli and Jorgensen report on an attempt to make deep purple petunias by adding additional copies of the color-causing gene. Instead, the gene's expression was dramatically reduced, resulting in white or variegated petunias, not purple.

1990



Craig Mello



Andrew Fire



1995

Mello and Fire are among the first to succeed at the painstaking process of reintroducing a working copy of a gene back into a worm.

1995

Guo and Kemphues at Cornell turn to antisense RNA instead of DNA as an experimental technique when trying to demonstrate they had identified the function of a particular gene. But inexplicably, sense RNA also silenced the gene.

involved in controlling tiny virus-like genetic elements that can hop from place to place in the genomes of worms, a key aspect of evolutionary change. For Mello, making these genetic discoveries in worms, findings which were present in all animals and plants on Earth, meant that RNAi was basic biology. That was the moment of understanding. That's when Mello felt like he'd stepped from that winding path into a clearing and saw the lost city. The implications were clear. Cells must use RNA-guided search mechanisms to control gene expression. And by using the biology of RNAi, researchers could program those search engines to study gene function and to find and silence harmful genes.

That same year, Phillip Zamore, PhD, was a postdoctoral researcher working in David Bartel's lab at the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology. The 1998 Fire-Mello paper hit like a thunderbolt, Zamore said; its potential as a breakthrough application for controlling genes was immediately clear.

Dr. Zamore, now an Investigator of the Howard Hughes Medical Institute, the *Gretchen Stone Cook Chair of Biomedical Sciences*, and chair and professor of RNA therapeutics at UMass Medical School, is a biochemist whose passion is exploring the molecular mechanisms of basic biology. He joined the UMass Medical School

faculty that fall, where he's since made major discoveries that advanced the RNAi field; he is one of the founders of Alnylam.

One of the most common ways that researchers, their students and their postdoctoral fellows understand new developments in the field is by presenting interesting scientific papers for discussion at journal club meetings;

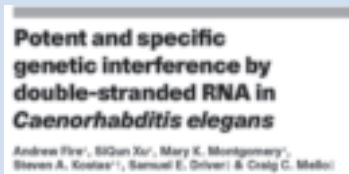
Zamore decided to present the Mello paper at a journal club meeting at the Whitehead, to put the matter of RNAi on the table for the whole lab to consider. Coincidentally, a postdoctoral colleague in the lab, Thomas Tuschl, PhD, was scheduled to present his ideas for how to study RNAi at the same meeting. Dr. Tuschl's goal was to

figure out the biochemical processes involved in the RNAi phenomenon that Mello and Fire had explained in living organisms. Tuschl was planning to work in another species of worm, but Zamore suggested using extracts from fruit fly cells. The pair agreed to work together and began with Zamore's plan.

They developed an experimental system using compounds from fruit fly embryos and targeted a well-known fly gene called luciferase, which produces a glowing protein (the same one that makes fireflies glow). First, they prepared a biochemical soup that enabled the luciferase gene to be read and send a message to make

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Mello and Fire began brainstorming about the mechanism of RNAi. Since the silencing response was specific to a target gene, it had to involve blocking production of that gene's protein. But what was the trigger?



1998

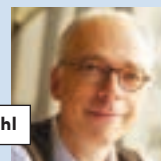
Mello and Fire publish findings in a 1998 *Nature* paper now known as the seminal work that launched the RNAi field, establishing that double-stranded RNA—a contaminant in earlier experiments—triggers RNA interference.

Zamore and Tuschl collaborate to understand the biochemical processes involved in the RNAi phenomenon that Mello and Fire identified.

1998



Phillip Zamore



Thomas Tuschl

1999

Tuschl, Zamore, Lehmann, Bartel and Sharp publish the results of research that allowed them to isolate the RNAi process to a test tube.

PHOTO: ROCKEFELLER UNIVERSITY

the glowing protein. Then they synthesized a double-stranded RNA molecule that matched the luciferase gene sequence. All this was combined in a test tube to see if the double-stranded RNA would stop the gene from creating a message to make the glowing protein. The experiment worked the first time. The gene was silenced. And the direction of Zamore's career changed in that same moment.

"We knew—from that first line of data—that we had RNAi in a test tube," he said. "And once we had a cell-free extract to study it, we could do classical biochemistry to start picking the RNAi process apart."

Zamore and colleagues published the results of the RNAi test tube system in 1999. The following year, Zamore was the lead author on a landmark paper in *Cell* that documented his discovery of a cellular process in which double-stranded RNA was chopped up into small fragments, 21 to 23 bases long, which then became guides for specific RNAi machinery in cells, including mammalian cells. It was a breakthrough for many reasons. The 1999 paper and a subsequent publication in 2000, showing that RNAi worked in fruit fly cells, blew open the field of RNAi. RNA interference was not only conserved across species, it could be defined as a series of biochemical processes.

To cure a disease

"RNAi was a godsend," said Phillip Sharp, PhD, Institute Professor at MIT, who won the Nobel Prize in 1993 for discovering gene splicing. Dr. Sharp was a mentor, along with David Bartel, PhD, to Zamore and Tuschl in those early days of RNAi research. "It was immediately clear that this was important. Everyone could replicate it. And it wasn't that it worked one time out of 10, it worked

every time. Its impact on research is unparalleled. It has dominated mammalian cell research since 2000."

They all understood the need to commercialize the technology. A generation earlier, Sharp had been one of the co-founders of biotech giant Biogen, which helped lead the global biotechnology revolution by commercializing the process of using living cells to make medicines like monoclonal antibodies. So, Sharp, Zamore, Tuschl and Bartel formed Alnylam. "We knew this was promising, but we had to answer the key question: Could it work in a patient? And you aren't going to answer that question until you test in a patient, and the only way to get enough money to go into the patient, is to start a commercial company," Sharp said.

The four Alnylam founders—and their investors—knew that RNAi-based drug development would be a sea change from conventional drug development. It would be a rational process, based on the sequence of genes and RNA molecules; not a massive task of trial and error, screening millions of chemical compounds trying to find one that hit a target. Equally important, the approach would leverage natural biologic processes in which RNAi machinery and other RNA-guided processes control gene expression and defend cells against invading viruses.

"The idea seemed so patently obvious to us, that if it worked in worms, and it worked in flies, then of course it would work in humans," Zamore said. "What we were saying to the broader research community is that this is a fundamental pathway that traces its origins to the last common ancestor of plants, fungi and animals. It's really, really ancient, and that's the key. Unless humans mysteriously dropped the pathway, there is no reason to think it wouldn't work."

continues on page 16

Zamore is lead author on a landmark paper in *Cell* that proved double-stranded RNA is chopped up into 'small interfering RNAs'—the specific determinant for RNAi.



2000



2002

Sharp, Zamore, Tuschl and Bartel form Alnylam Pharmaceuticals to explore RNAi-based drug development.

Mello and Fire receive the Nobel Prize in Physiology or Medicine for their discovery of RNAi.

2006



'When you're dying, you'll try anything'

Rick Schrader's father didn't know what killed him. Now Schrader thinks he does, because he's fighting the same battle.

"It started with some tingling in my hands and feet. At first, I thought it was just part of getting older," Schrader said. "Then my whole world came crashing down."

It was January of 2017. Schrader was 62 years old. A native of Buffalo, N.Y., who has lived in Virginia since 1987, Schrader worked hard and he played hard. "I'd been selling software for 30 years, making a great living. I was coaching and refereeing hockey, playing softball and golf; my life was 100 miles an hour. Then, all of a sudden, I'm falling down, getting weak, can't walk 50 feet without a walker," Schrader said. "It was insanity."

Schrader's wife is a nurse. She started researching his condition and reached out to a neurologist at the University of Maryland Medical Center. "They ran all kinds of tests, and nothing showed. Everyone was just guessing, while I was getting worse, quickly," Schrader said.

Eventually Schrader's medical team contacted Michael Polydefkis, MD, at Johns Hopkins, one of the physicians who enrolled patients in the Phase 3 clinical trial of patisiran, a revolutionary new kind of drug (see main story, page 8). Genetic testing confirmed what Dr. Polydefkis suspected after examining Schrader — he has a mutated gene that causes hereditary ATTR amyloidosis.

A rare disease affecting about 50,000 people worldwide, hereditary ATTR amyloidosis develops when the mutated gene produces a faulty protein that builds up throughout the body, causing nerve numbness and pain, or heart failure—or both. Patisiran blocks production of the defective protein.

By the time Schrader saw Polydefkis, the Phase 3 clinical trial of patisiran was closed. The early results from patients in the Phase 2



trial were so positive, however, that Alnylam, the drug's manufacturer, got FDA approval to provide patisiran to people outside of the trials, if those patients met certain criteria. Under an FDA waiver called "expanded use," the goal is to make potentially life-saving drugs available to people who have no other options.

"Dr. Polydefkis explained it all to me; that there were no promises and it was still considered experimental," Schrader said. "But I couldn't jump in fast enough. When you're dying, you'll try anything."

He began the same patisiran treatment regimen used in the clinical trial, an intravenous infusion every three weeks. He noticed an impact very quickly. "The therapy stopped the progression," Schrader said. "I'm not getting worse and I feel a little stronger. My family says I look better. And this past month, my taste buds started to come back out of nowhere, which is great, because I used to live to eat, but this disease hits your taste buds, so I couldn't taste a thing."

Schrader's father died eight years ago after suffering a rapid onset of neuropathy and a resulting decline in health. Even after a number of tests, doctors in Buffalo were unable to

diagnose his father's fatal illness, but Schrader and Polydefkis suspect that hereditary ATTR amyloidosis was the cause. There's a 50-50 chance that parents with the deadly gene will pass it on to their children.

Schrader and his wife have two adult children, an adopted son and a biological daughter. They have four grandchildren. "My daughter has been tested, and she's negative," Schrader said. "Thankfully, for my immediate family, this ends with me."

Still, Schrader's thoughts extend beyond his family, to others who may be suffering with unexplained symptoms like his. "I'd tell them to learn about this disease, and to get tested, because there is hope," he said. "I am very fortunate to be surrounded by a lot of expertise and caring people. They have given me hope, and I can't thank them enough."

Schrader said his immediate goal is to continue building strength and be around to watch his eldest grandchild graduate from college. "I've been through all the phases of anger and depression, all the 'why me?' stuff," he said. "Now I realize my life is altered and I am trying to focus on what I can do, not what I can't do, and set some goals for what I want to do with the rest of my life." □

RICH RIGGINS

The major technical challenge was how to get RNA molecules synthesized in a lab to survive in a patient's blood stream and enter the targeted cells to do their gene-silencing work. RNA is a fragile molecule that is quickly degraded in the bloodstream or within a cell. The scientific team at Alnylam worked for more than a decade, at a cost of more than \$1 billion, to develop technology that protects RNA molecules while circulating in the blood, and allows them, as in the case of patisiran, to enter liver cells and release their payloads effectively. As a result, Alnylam has several other RNAi-based programs in development for hemophilia, hypercholesterolemia, acute hepatic porphyria and primary hyperoxaluria—all conditions that can be treated in the liver.

"We have conquered delivery to the liver, so now we are like fishermen in a great school of fish, who will fish out as many great medical opportunities as we can," Maraganore said. "Now that our technology is in this reproducible, modular stage, where we can load the system with any RNA sequence we want, the ability to go from one program to the next is quite simple."

While Alnylam leads the way with the first approved RNAi-based drug and a robust pipeline of other RNAi therapeutics close to the clinic, other companies around the world are working to develop novel treatments using RNAi or the rapidly emerging related technologies that have RNA-guided elements.

Nobel investments

By the fall of 2006, UMass Medical School's research enterprise was already significant, with strengths in cell and molecular biology, HIV, infectious disease

and diabetes research, among other programs.

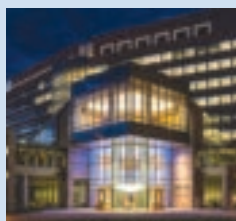
The recognition of a Nobel Prize, of course, elevated the school's profile. The following spring, leadership at the medical school transitioned to Michael F. Collins, MD, as chancellor and Terence R. Flotte, MD, as dean. Both knew the importance of furthering RNA research. "I think what was unusual in this instance was the Nobel Prize came so early. It was just eight years after they first published, and that speaks to the landmark nature of the discovery," Chancellor Collins said. "When Terry and I got here, the environment was pretty incredible, and we said, 'Let's take advantage of this moment.'"

Working closely with Mello, Zamore and other faculty, Collins and Flotte crafted an ambitious plan to build a major new research complex on campus and to fill it with people capable of advancing the field. Their aim was to meld basic science and clinical translational research in RNA biology, gene therapy and related areas to give the world a better understanding of what was possible.

With support of then-Gov. Deval Patrick and the Massachusetts legislature, UMass Medical School received funding toward the construction of the Albert Sherman Center, which now houses the RNA Therapeutics Institute and a new Gene Therapy Center.

"I feel a responsibility to find the resources to let basic scientists go where the science leads them, because we never know where the next discovery will come from," Collins said. "That said, when we do see a discovery that can impact patients' lives, we have to invest in it. So, I believe strongly that basic science and clinical translational work need to be coupled." □

—Michael Cohen



2008

UMMS receives funding to construct the Albert Sherman Center, which now houses the RNA Therapeutics Institute and a new Gene Therapy Center.

Phase 3 clinical trial of patisiran enrolled 225 patients with hereditary ATTR amyloidosis whose disease had progressed to the point that physicians estimated they had less than two years to live.

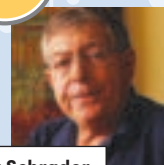
2016

2017

Results of patisiran clinical trial are "stunning." The faulty protein causing hereditary ATTR amyloidosis was blocked and most patients had greater muscle strength and improved ability to walk.

FDA approves patisiran, a life-saving therapy for 50,000 people with hereditary ATTR amyloidosis. It is the first of a new class of medications based on the science that flowed from laboratory discoveries at UMMS.

2018



Rick Schrader

see his story on page 15

A photograph of a woman with grey hair, wearing a blue and white patterned shirt, leaning over two dogs. One dog is a golden retriever with its mouth open, and the other is a black dog. The background is a grassy area.

Genome's best friend

New information on the genetic origins of disease comes from a surprising source

It's a new breed of research at UMass Medical School. Dog owners across the country are enrolling in a "citizen science" project to enable genome-wide association studies of cancers and compulsive behavioral disorders that affect both canines and humans. Scientific research was once considered a scientists-only discipline; citizen science, first popularized in astronomy, where volunteers pore over photos of distant regions of the galaxy for previously unknown objects, is now becoming an integral part of biomedical research.



JULIANA SOHN

"Our whole approach with Darwin's Dogs and the new cancer study is all based on a relationship with pet owners who care about their dogs," Karlsson said. "We want to make sure that our research not only helps us better understand human disease, but also has a benefit for dogs as well." Elinor Karlsson, PhD

The UMMS project, originally launched as "Darwin's Dogs," was started in 2015 by Elinor Karlsson, PhD, assistant professor of molecular medicine in the Program in Bioinformatics and Integrative Biology, who studies large data sets of genetic information searching for patterns associated with specific diseases. Dr. Karlsson has focused on the genetics of dogs for several years and was one of the authors of a landmark 2005 paper published in *Nature* that reported the first completely sequenced dog genome.

"We have believed for a long time that dogs can be an important model for studying the genetics of complex diseases like cancer and anxiety disorders, where there are many different genes involved and where the environment matters," Karlsson said. "Even though we've known this for a while, it's been difficult to go further because our sample sizes have not been large enough. So, Darwin's Dogs really began as a way to make dog genetics work by reaching out to dog owners and involving them to expand the scale of our data."

More than 19,000 dogs are currently enrolled in the study; their owners have answered 2.2 million questions about their dogs' physical attributes and behaviors. The questions are grouped into 21 online surveys, covering topics such as eating habits, home environment,

communication, play, interaction with people and reaction to stimuli, among others. Once dog owners complete the surveys, they qualify to submit a sample of their pet's DNA using a saliva collection kit they receive by mail. "People are giving us fantastic information," Karlsson said. "People really do understand their dogs and they are eager to participate."

It is precisely the close relationship dog owners have with their pets that makes domesticated dogs such a potentially powerful research model, Karlsson said. Humans and dogs have lived together in close quarters for thousands of years, so their evolution was shaped by similar environments. Present-day dogs and owners are exposed to similar environmental risks that could cause some cancers. So, the pairing of canine DNA data and human observations can yield a uniquely rich set of information to be mined.

As the dog DNA database grows, Karlsson's team will use advanced analytical tools to compare the genomes of thousands of dogs, who, for example, exhibit compulsive behavioral problems like excessive chewing on objects, or fear-based conditions such as separation anxiety or panic during thunderstorms, and search for patterns of genes involved in those conditions. Since previous work by Karlsson and others has shown that the human and canine genomes

have broad similarity, knowledge gleaned by studying dog genetics should help inform human biology.

Participation in Darwin's Dogs is free and open to all dog owners, with the genetic sequencing paid for by research grant funding. In return for answering the survey questions and submitting the DNA samples, pet owners eventually will be given their dogs' genetic information with some analysis of their breed ancestry. Because of the surprisingly large and surprisingly fervent response, the return of genetic results for any one dog, however, will take time. "We know that some people who have submitted samples are frustrated with us, with good reason, because it's taking a long time to get their dog's DNA sequenced," Karlsson said. "This project has been far more successful than we ever imagined, so funding to pay for the DNA sequencing is a big issue."

This surfeit of canine DNA suggested an alternate route as well: "Darwin's Ark," announced in 2018, gives dog owners the option of submitting their canine's DNA for research purposes, or purchasing sequencing results if they're mostly, or more immediately, interested in their pet's genetic heritage.

So far, the project has sequenced the genomes of nearly 1,000 dogs. The canine genome has approximately 2.4 billion bits of information, so analyzing that data

Jan and Dave Weaver
of Westminister, Mass.,
with their Leonbergers
(left to right) Faith, Jingle, Joy
and Velcro. The lone male
among the four, Velcro is
enrolled in Darwin's Dogs.



for patterns or associations across populations of dog breeds is a massive computational task requiring advanced algorithms and software systems.

To begin testing analytical frameworks, Kathleen Morrill, a graduate student in the Karlsson lab, has run some proof of concept genome-wide association studies for physical traits including height and coat color. "Those initial studies worked really well," Morrill said. "We found the same genes that had been identified before in the literature, and we also found some new ones, so that was exciting and showed us our approach is working."

Morrill expects the dog DNA database will soon be large enough to begin mining for associations with behavioral disorders. If those tests find potential genetic targets of interest, Morrill will then probe deeper into the biology of those genes with lab experiments using cultured neurons. "My interest is in anxiety disorders, and how working with dogs can help us understand human diseases," she said.

While the Darwin's Dogs recruitment process continues, the Karlsson lab is diving deeper into canine cancer with a new, three-year grant from the National Cancer Institute. The study began in April and will focus on pet dogs being treated for several cancers that are known to be similar to human cancers. Blood samples will be collected while the dogs are in clinic receiving chemotherapy. The samples will be examined using a new technology

called liquid biopsy developed at the Broad Institute at MIT, where Karlsson also serves as the director of the Vertebrate Genomics groups.

"The liquid biopsy technology captures tumor DNA circulating in the blood, so we hope to sequence the tumor without getting a physical tumor biopsy, which would be amazing," Karlsson said. "Getting physical biopsies is invasive, handling the samples is hard and recruiting people to participate is difficult. With just a blood sample, it will be much easier and we hope to dramatically expand the scale of cancer studies."

Karlsson's team will build a software system to analyze canine cancer DNA and compare it with human cancer data compiled by The Cancer Genome Atlas and the International Cancer Genome Consortium Data Repository, which collectively hold cancer genome data from 31,000 patients.

The initial canine blood sample collections will be done in collaboration with the Cummings School of Veterinary Medicine at Tufts University. The project will then broaden to recruit pet owners

nationwide to use an online research portal and a smartphone application custom-built to collect information about their dogs' history and clinical data during cancer treatment. "This is where the citizen science model comes into play again," Karlsson said. "We hope to get dog owners across the country to work with the veterinarians and participate in this study."

With a large enough cancer DNA data set, Karlsson said she hopes to identify genetic patterns that put dogs at higher risk, and better understand the genetic mutations that drive canine cancers. Given the overlap with human cancers, she hopes the work will uncover new science that enables development of better treatments for both dogs and people.

"Our whole approach with Darwin's Dogs and the new cancer study is all based on a relationship with pet owners who care about their dogs," Karlsson said. "We want to make sure that our research not only helps us better understand human disease, but also has a benefit for dogs as well." □ —Michael Cohen

Championing

community health from within

New medical degree track emphasizes population-based health and causes of health disparities in urban and rural communities

For as long as he can remember, Springfield native Kevin White has dreamed of a career in health care, envisioning himself following in the footsteps of his mother and grandmother. White was raised with a deep appreciation of the care both women provided to patients over the years in their work as certified nursing assistants. He remembers being captivated by the pages of his mother's many medical textbooks scattered about the house as she studied to become a medical assistant and, later, a respiratory therapist.

"I've always liked science and helping people. I feel it's in my nature because that's who my mom is. I realized, as I got older, that being a physician would be an ideal path for me," said White, a second-year student in the School of Medicine at UMass Medical School.

As much as White cherished the example set by his loved ones, there was one mentor missing from his community.

"Growing up, I saw very few physicians who were like me," said White, who is African-American. "I want to be that person that youths like me can look up to and know they can also achieve great heights, like becoming a doctor."

White is one of 22 students in the inaugural class of a new UMMS medical degree track, Population-based Urban and Rural Community Health, or PURCH, based at a new regional campus called UMass Medical School-Baystate in Springfield. PURCH will prepare doctors to address the needs of and advocate for underserved populations of both cities like Springfield and the rural towns of Western Massachusetts. The program, a partnership between Baystate Health and UMass Medical School now in its second year, teaches students to think comprehensively about population health and the causes of health disparities by understanding patients' perspectives and how their communities impact their health. The curriculum emphasizes ways to practice medicine in diverse urban and rural communities and expects students to be both leaders and collaborators on the health care team and advocates in the community.

In the first two years of the program, students conduct the majority of their studies at the Worcester campus, but travel to the UMMS-Baystate campus on Main Street

in Springfield every other week for a full day of classes. In Springfield, they are taught and mentored by faculty from UMMS-Baystate. As is becoming more important in medical school studies around the nation, students are also taught by local community members, many of whom work for human services agencies and nonprofit groups, and others who simply heard about the program and want to help shape the next generation of doctors. These community members are PURCH community faculty who help teach about their experiences, many as newly trained standardized patients who help students learn, practice and perfect their clinical interviewing skills. The standardized patients play an integral role in teaching students what matters from a patient perspective.

In the final two years of the program, PURCH students will spend most of their time in Western Massachusetts, where, like their student peers in Worcester, they will obtain core clinical experiences in both inpatient and outpatient settings.

For White, who was born at Baystate Medical Center, the PURCH program will help him to become the doctor he wants to be, and to have a greater impact on the community for which he cares so much.

"Growing up in an urban environment, I've always had a kind heart for the city," he said. "Now, I'm realizing that by being a medical student learning in the community

continues on page 22



Laura Schwartz, Kevin White, Amanda Whitehouse and Poornima Manikantan are second-year students in the Population-based Urban and Rural Community Health medical degree track at UMass Medical School.

where I grew up, I can actually have more of a say in some of the things that are going to help this community be healthier. I want to serve the minority population and to help with health disparities. That's important to me."

The architects of the PURCH program designed it to generally follow the same curriculum as the traditional MD track, but PURCH is augmented by the emphasis on population health, patient-centered community-based care, and innovative, immersive learning experiences.

"We want to bring a different approach to teaching some of the topics of a traditional medical school education, and do it in a way that might resonate a little deeper amid these populations," said Kevin Hinchey, MD,

of the Springfield homeless shelters, we learned to take a social history by listening to people there who had volunteered to speak to us about their experiences with homelessness.

"I will never forget that experience and how it emphasized the crucial role that housing insecurity plays in health."

Rebecca Blanchard, PhD, assistant dean for education at UMMS-Baystate, said that's exactly what she and colleagues had in mind when they developed the PURCH program.

"It is not about teaching the principles that make you a good doctor; we do that, of course. It's about wrestling with these principles and reflecting on them and working with them constantly, as the scaffolding, to learn what you need to know to be a doctor," said Dr. Blanchard. "It's not about having a session on bias. It's about having a threaded, reflective opportunity to think about how biases can affect the care you provide as a physician. It's about understanding the connection between the patient care that is provided in the clinic and the future patient care that these doctors will be able to give in the community."

"PURCH is really about the fundamental understanding of these bigger issues that come into play in the doctor-patient relationship—advocacy and policy, public health and housing and transportation—it's this understanding that those things are as much a part of your patient relationship as getting the story of that patient. Bringing those things into the conversation is what makes PURCH different."

Amanda Whitehouse taught in Teach for America in Camden, N.J., where 42 percent of the population lives below the poverty line, prior to applying to the PURCH program. She was looking for a way to fuse medicine and education as a way to address the inequalities she saw in Camden.

"Camden was an incredibly challenging, but rewarding, experience," said Whitehouse, a member of the PURCH class. "The banner at the entrance of our school in Camden was, 'Demography should not equal destiny.' The idea of the zip code in which you were born dictating the rest of your life is problematic. I think being in Camden made me realize the importance of the need for efforts to be multifaceted—health, education, food security, housing stability, access to employment—which is why I felt comfortable going into medicine as a way to address the inequalities I witnessed."

"When I was applying to medical school, I thought PURCH really addressed much of what I hope to incorporate into my future practice. There is so much outside of the doctor's office that impacts a person's health, which is so much a part of better health outcomes."

Poornima Manikantan, a PURCH student from Longmeadow—and the daughter of two physicians—said the first year of the program has already helped her better relate to patients.

"When I was applying to medical school, I thought PURCH really addressed much of what I hope to incorporate into my future practice. There is so much outside of the doctor's office that impacts a person's health, which is so much a part of better health outcomes." Amanda Whitehouse

senior associate dean for education at UMMS-Baystate. "We want students to recognize their biases and stimulate their compassion and empathy."

For their doctoring and clinical skills class, half the students conducted their first patient interviews at a Friends of the Homeless shelter in Springfield; the others did so at the Hampden County jail in Ludlow.

"At the homeless shelter, we met a diabetic who kept candy bars by his bed because they aren't perishable and they have a lot of calories," Dr. Hinchey said. "Now we know he's going to come to my office in two days with high blood sugar and we are going to say he needs medicine to treat it. But our students learned that if he actually had access to good food, he might not have diabetes to begin with."

The arrival of a patient at the jail shackled at his wrists and ankles left a lasting impression on students.

"This encounter challenged the students to examine their conception of what an 'inmate' was. People are people and they need us to be compassionate to them. These experiences are helping students truly understand the social determinants of health," Hinchey said.

"Having the opportunity to learn about what health care is like for people who are in jail or prison was unique; it really helped us learn about the systematic public health effect of inequalities and lack of access to resources in a very poignant way," said Laura Schwartz of Framingham, who applied for the PURCH program because of her desire to address social determinants of health. "At one



PURCH students (left to right) Afua Nti, Prith Roychowdhury, Anushay Mistry and Juliana Dixon



PURCH student Tatiana Petrovick listens in class.



Harry Hoar III, MD, assistant professor of pediatrics at UMMS-Baystate, teaches a class of PURCH students in Springfield.

...by 2030 there may be a shortage of 40,000 to 100,000 physicians
Association of American Medical Colleges' Center for Workforce Studies

"Thinking about socioeconomic factors and cultural factors has really been emphasized in the program and that has been helpful in being able to connect with people and to better understand what is important to them," she said.

According to the latest report from the Association of American Medical Colleges' Center for Workforce Studies, by 2030 there may be a shortage of 40,000 to 100,000 physicians.

"Massachusetts will not be spared," said Chancellor Michael F. Collins. "We have aging demographics and a geographic maldistribution of both generalist physicians and those who provide specialty care. At UMass Medical School, we have a special responsibility to train the physician workforce to take care of the people in this state. We are working to decrease this shortage and this partnership helps address this issue effectively."

To create more opportunities for future physicians and in response to the shortage of primary care physicians nationwide, UMMS has increased the number of students it accepts each year for its medical degree program to 162.

"I believe we're unique in offering, through the PURCH track, both urban and rural primary care practice opportunities, which is reflective of the physician health care needs in the western part of Massachusetts," said Terence R. Flotte, MD, the *Celia and Isaac Haidak Professor of Medical Education*, executive deputy chancellor, provost and dean of the School of Medicine.

"We know that in medicine, where you train is, quite

likely, also the place where you will practice. Many of the students in the PURCH track who come to Baystate for their clinical experience will, we hope, also choose to train in this area and thus, have a much greater likelihood of practicing here."

"Health care is undergoing a paradigm change—physicians are expected to manage the health of their entire population of patients, providing a continuum of care from prevention to disease management," said Chancellor Collins. "Doctors must shift their focus from a single patient to the community, and develop a deeper understanding of the interwoven social and environmental factors that contribute to health disparities. PURCH is an innovative approach to teaching that."

The program represents the best of UMass Medical School and will serve as a model for new medical education pathways, said Melissa Fischer, MD, MEd, professor of medicine, associate dean for undergraduate medical education and associate dean for curriculum innovation at UMMS.

"This partnership is a manifestation of UMass Medical School's strength in primary care education and cutting edge research and in population-based and individualized medicine," Dr. Fischer said. "We are highly committed to being the state's medical school and committed to Central and Western Massachusetts. So when we were looking to grow our medical education program, it was only natural to look to our partners at Baystate to help us develop this program." □

—Lisa M. Larson



Graduate School of Nursing takes on the opioid crisis

Opioid Safe-prescribing Training Immersion 'a national model' for health care providers at the frontline

Should a family nurse practitioner prescribe additional opioid medication for a suburban mom who says she is still experiencing pain from a recent operation? Why wouldn't a critical care nurse practitioner in the emergency department prescribe opioids for a man who broke his arm in a car accident? How can a psychiatric nurse practitioner help a hospitalized overdose victim find the road to recovery?

These real life scenarios confront health care providers at the front line of the opioid epidemic every day, in every health care setting.

But until 2016, specialized training for health professions students in pain management, safe prescribing, and preventing and treating opioid use disorder was not widely or consistently available. In 2016, UMass Medical School answered the call from Gov. Charlie Baker to all Massachusetts medical schools to identify core competencies and best practices for safe opioid prescribing. Faculty from both the Graduate School of Nursing and the School of Medicine were instrumental in creating the Opioid Safe-prescribing Training Immersion (OSTI), which students are now putting to use in clinical practice across the commonwealth.

"Addiction is everywhere, and our students will encounter it wherever they work," said Jill Terrien, PhD, ANP-BC, associate professor of nursing and the nursing lead for OSTI development. "It is crucial for students to know the best practices for prescribing, as well as preventing misuse of opioids, identifying when patients have a problem and knowing resources to get help and treatment."

The Graduate School of Nursing was the first nursing school in the state to incorporate safe opioid prescribing into its curriculum. Opioid conscious training is now part of medical student and resident physician training across the curriculum.

Called a national model by Massachusetts Department of Public Health Commissioner Monica Bharel, MD, MPH, the OSTI features a series of simulated clinical encounters with standardized patients, who are actors specially trained to portray a diverse array of patients. The OSTI consists of five simulations representing the range of pain management needs frontline health care providers typically encounter in their day-to-day clinical practice. Each of the five OSTI simulations helps students develop specific skills for pain management and preventing and treating opioid use disorder. Following the simulations, students meet with patients and families in recovery to hear their stories, ask questions and reflect on what they've learned.

"Asking about bias and about how they will incorporate the day's experience into their future practice is very powerful and emotional for students," said Dr. Terrien. "As we have found, the opioid crisis has touched many of our lives personally."

Margaret Donovan, DNP, a family nurse practitioner at a primary care



Clockwise from top right: students participating in the OSTI read a description of the scenario they are about to witness; the OSTI instructor demonstrates how to deliver nasal naloxone; a standardized patient 'recovering' from an opioid overdose talks with a student playing the role of a care provider.

"It is crucial for students to know the best practices for prescribing, as well as preventing misuse of opioids, identifying when patients have a problem and knowing resources to get help and treatment." Jill Terrien, PhD, ANP-BC

clinic, was part of the first cohort of GSN students required to complete OSTI prior to graduation. Donovan, who earned her Master of Nursing and her Doctor of Nursing Practice degrees at the GSN, was motivated by losing a friend to addiction, as well as seeing a gap in clinical care, to make the opioid crisis the topic of her doctoral capstone requirement. Her project employed opioid safe prescribing training to improve prescribing at a rural community health center.

"Using the tools that are taught in the OSTI helps inform conversations with patients with chronic pain, those already taking opioid medications and patients who are requesting opioids," said Dr. Donovan, who says such conversations arise a couple of times a week in her own practice. "The most impactful part was working with standardized patients to practice

having these real conversations."

Terrien and colleagues have been disseminating OSTI nationwide, publishing papers in peer-reviewed journals and presenting at nursing education conferences. Their efforts have been featured nationally by Hearst Television and the Associated Press.

"The faculty have gone above and beyond to ensure all of our learners become safe prescribers," said GSN Dean Joan Vitello, PhD, RN. Dr. Vitello was the only academic nursing representative invited to serve on the Governor's special commission on the professional training of students who may prescribe controlled substances. "We are proud that UMass Medical School has taken the lead in providing interprofessional training for our nurse practitioner and medical students as a means of combatting the opioid crisis." □

—Sandra Gray

PATHWAYS *of* PROMISE

NEW DISCOVERIES. NEW METHODS. NEW PATHWAYS.

THE CAMPAIGN FOR UMASS MEDICAL SCHOOL

Help us clear the path

With an overall goal of \$250 million, the *Pathways of Promise* campaign will support the endeavors of our community across three vital areas.

Pursuing these priorities will significantly enhance our ability to develop life-changing medicines and train the leading physicians, scientists and nurses of tomorrow.

\$185M

Research

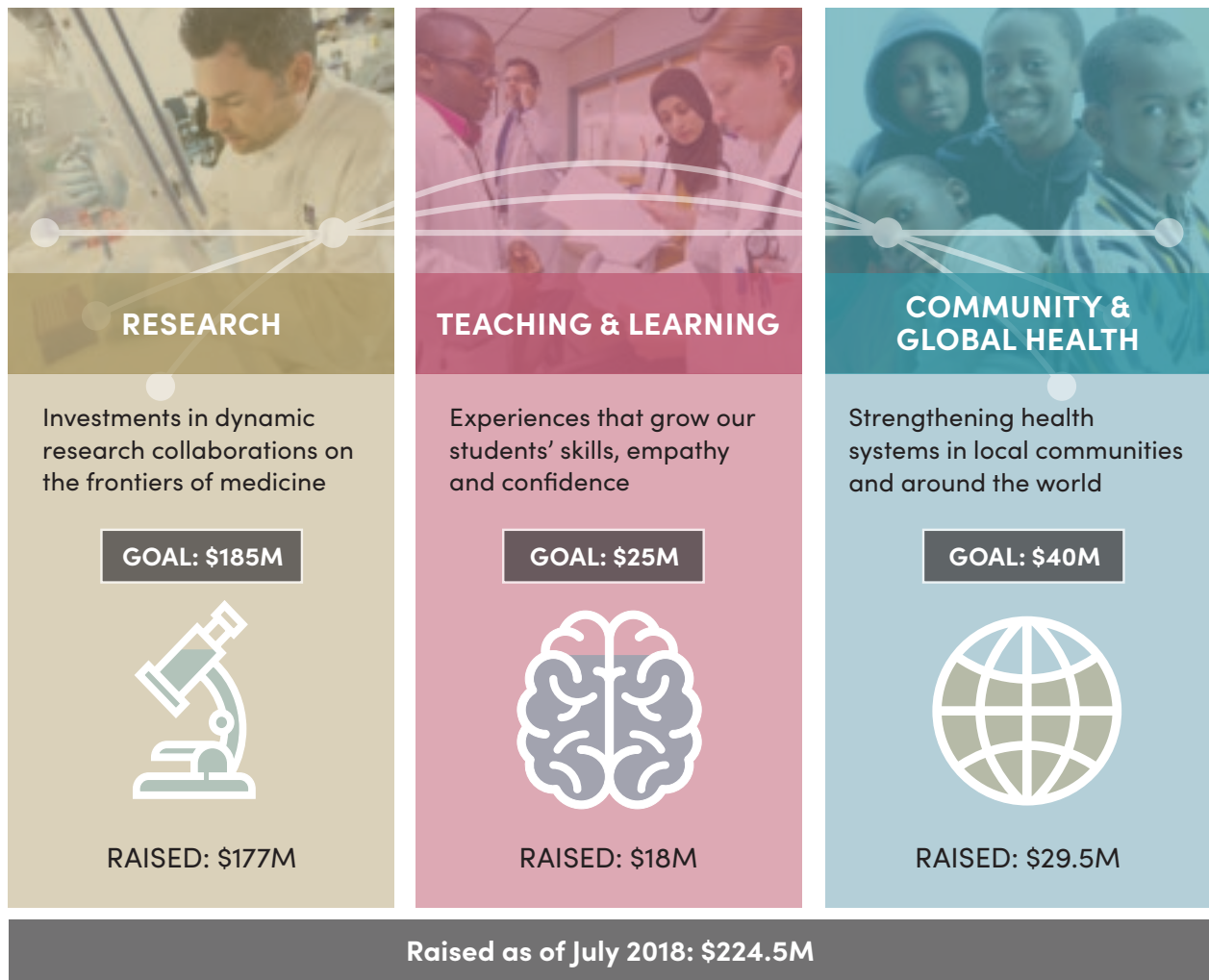
\$25M

Teaching & Learning

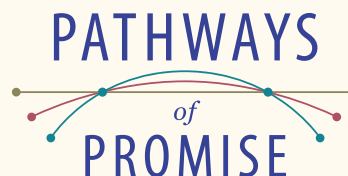
\$40M

Community & Global Health

Our comprehensive campaign celebrates and advances the mission of this unique institution. We will invest in outstanding scholars, physicians and scientists working to resolve daunting challenges of human disease through dynamic research and incisive discovery. We will increase our capacity to educate tomorrow's medical, science and nursing leaders by enhancing our curriculum and expanding technologies. And we will build upon our legacy of achievement with new partnerships and programs focused on community and global health.



The Pathways of Promise campaign represents an unprecedented opportunity to celebrate and strengthen the power of UMass Medical School. Our circle of support includes faculty and alumni, visionaries and private-sector partners. It comprises a diverse array of individuals who believe—as we do—in the mission of creating a better, healthier future for us all. We hope you will join us.



If you would like to learn more about the campaign or speak with someone about making a gift, please contact the Office of Advancement at 508-856-5520 or send email to giving@umassmed.edu.

Every day one of our students, alums or professors does something extraordinary in the world. Recently we have seen the launch of a UMass Medical School-developed treatment for rabies that will save thousands of lives in India; started a clinical trial to test the safety of a new type of vaccine for HIV/AIDS; and welcomed back students and faculty from their work at a medical clinic in a batey—a migrant worker camp in the sugarcane fields of the Dominican Republic—that is a teaching site for students in our International Medicine Interest Group. We are deeply proud of the extraordinary impact that members of our community have on health and social issues around the world.

But I want to tell you about something much closer to home—almost within sight of our Lake Avenue campus, in fact—because the depth of our commitment to the communities in which we live and work hopefully will encourage you.

For more than 20 years, UMass Medical School's Worcester Pipeline Collaborative has partnered with public schools in some of the most economically challenged neighborhoods in Worcester in an effort to increase opportunities for students from backgrounds that remain underrepresented in medicine, nursing and biomedical research. In the last decade alone, more than 6,000 students in the North Quadrant have joined in mentoring, job-shadowing, tutoring, internships and intensive summer study programs that open our doors to students like Jonathan Quang, whose participation in Pipeline programs took him from North High to our Health Sciences Preparation Program, all the way through UMass Medical School. Jon (SOM '18) is now an emergency medicine resident whose success is both a part of the answer to the physician shortage in underserved communities and a shining example that where you are from does not have to limit how far you can go.

As needs grow, so, too, does our commitment. UMass Medical School supports a food pantry in a local high school; filled and handed out 700 backpacks with first-day-of-school supplies for students at Union Hill and Rice Square schools; and donated clothes washers and dryers to address a hidden barrier to learning that keeps some students from their full potential. Next, we will begin the



FAITH NINIVAGGI

Michael F. Collins, MD, Chancellor and Senior Vice President for the Health Sciences.

We are deeply proud of the extraordinary impact that members of our community have on health and social issues around the world.

Classroom Enrichment Grant program to help teachers whose students need a little extra. The generous support of the Remillard Family Community Service Fund—bolstered by nearly \$60,000 in charitable donations by our students, faculty and staff—helps these schools keep their focus on learning.

I hope you share our pride in witnessing the undeniable impact of UMass Medical School around the globe and right here in Worcester, where we know that regardless of your circumstances, the sky is the limit. □



@umassmed

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Readers are invited to comment on the contents of the magazine, via email to ummscommunications@umassmed.edu; please include "*@umassmed* magazine" in the subject line.

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UMass Medical School launches *Voices of UMassMed* podcast

UMass Medical School has launched *Voices of UMassMed*, a podcast series sharing the always interesting and sometimes amazing stories behind the pioneering work that takes place here every day.

The first podcast debuted in August, featuring an interview with Chancellor Michael

F. Collins. The series seeks to provide rich discussions with UMMS faculty so that listeners have the opportunity to learn about who they are and to highlight their ongoing contributions to science, medicine, education and public service.

A new podcast is released about every two weeks.

Recent topics include the Ebola crisis, addressing the needs for palliative care and caring for mothers with perinatal depression. Podcasts are available for listening at: www.umassmed.edu/news/voices. You can also subscribe to *Voices of UMassMed* on SoundCloud.

Voices
OF UMASSMED



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