

# PATHWAYS



THE CAMPAIGN FOR  
UMASS MEDICAL SCHOOL

## UMMS RESEARCH STRATEGY OVERVIEW

**A summary to inform *Pathways of Promise*, The Campaign for UMass Medical School 2016**

The following document represents the research strategic priorities of UMass Medical School as articulated by a group of faculty and research administration leaders during the spring semester of 2016.

The process was led by Terence R. Flotte, MD, the *Celia and Isaac Haidak Professor in Medical Education*, executive deputy chancellor, provost and dean, School of Medicine.

Working groups were led by:

- Anthony Carruthers, PhD, dean, Graduate School of Biomedical Sciences
- Jean King, PhD, associate provost for biomedical science research
- Katherine F. Ruiz de Luzuriaga, MD, vice provost for clinical and translational science
- Brendan O’Leary, PhD, executive vice chancellor for innovation and business development

A group of 55 research leaders, chairs and directors met on June 6, 2016, for a day-long, facilitated retreat to prepare the following material for use by Chancellor Michael Collins, the Office of Advancement and their teams.

## OVERVIEW

### UMMS *Pathways of Promise* Research Vision 2020

The University of Massachusetts Medical School (UMMS) has a uniquely collaborative network of scientists and physicians who seek to unlock the mysteries of biology in order to change the course of history of disease. Two fundamental observations garnered from the past century of biomedical research will drive the central thematic priorities within the UMMS Research Vision 2020: (1) Family history passed down through **genes and the regulation of genes** underlie every form of human disease, and (2) abnormal regulation of the immune system, when activated to produce **inflammation**, is at the heart of most of the diseases that plague the planet today, including arthritis, heart disease, stroke, diabetes, obesity, liver disease, Alzheimer’s disease, Lou Gehrig’s disease (ALS) and many other neurologic and non-neurologic diseases.

These two threads, genetics and inflammation, carry forward through all four of the specific thematic areas that we aspire to address—areas that were selected because each builds upon unique existing strengths of the institution and takes advantage of opportunities that could be accelerated with the *Pathways of Promise* campaign. Specifically, we have identified opportunities in neuroscience (the NeuroNexus Initiative), RNA biology (the RNA Therapeutics Institute), Precision Medicine and Host Defense. In each of these areas of emphasis, the *Pathways of Promise* campaign could have dramatic impacts on our ability to truly change the course of disease throughout the world.

## Theme 1. NeuroNexus Initiative (NNI)

### Discussion leaders:

**Vivian Budnik**, PhD, the *Worcester Foundation for Biomedical Research Chair* and chair and professor of neurobiology

**Jean King**, PhD, associate provost for biomedical science research

**Robert H. Brown Jr.**, DPhil, MD, the *Leo P. and Theresa M. LaChance Chair in Medical Research* and chair and professor of neurology

**Doug Ziedonis**, MD, MPH, chair and professor of psychiatry

The NNI at UMMS builds on the institution's tremendous strengths to unlock the mysteries of the brain, from fundamental neurobiology to curative therapy for illnesses such as Lou Gehrig's disease (ALS) and Huntington's disease. It is an "institute without walls" featuring an interconnected consortium of researchers from various UMMS departments and programs within the traditional definitions of neuroscience, neurology and psychiatry, and in other key enabling areas of science, such as the biology of inflammation.

**Examples of opportunities** presented by the NeuroNexus Initiative at UMMS include:

- > **Program in Neuro-inflammation:** Our NNI researchers are illuminating new perspectives on "old" diseases, identifying how an over-active immune system can cause common human diseases of the brain, such as Alzheimer's disease, multiple sclerosis and autism. This program will bring together basic immunology researchers with neurobiologists, microbiome scientists, neurologists and other physician-scientists developing and testing cures based on this new insight.
- > **Program in Neuro-therapeutics:** This program will function within the Conquering Diseases Clinical Research Center at UMMS, providing the expert physicians, nurses and NIH-required regulatory infrastructure necessary to take gene therapies for brain and spinal cord diseases into the first human trials. Initial disease targets will include ALS, Huntington's disease, autism spectrum disorders, Fragile X syndrome and other orphan diseases that affect infants and children.
- > **Neurogenetics and development:** UMMS NNI researchers are striving to understand mankind's greatest mystery: the intricate workings of the human brain. Armed with the tools of genomics and ever more powerful imaging technology, basic neurobiologists seek to discover how the brain develops, matures, ages and experiences disease. The functions being studied include learning, memory, sensory integration, complex behavior, compulsion and addiction.

**Initiative to cure stroke:** This is a strategic alignment between experts in neurology, neurosurgery and radiology to deepen our understanding of the causes of stroke. This program will pioneer the use of new devices, drugs and molecular treatments for stroke patients and to help save the lives of more patients with this very common affliction.

UMass Medical School's **unique or distinguishing characteristics** in neuroscience include:

- A multidisciplinary team conducting the most advanced program in molecular therapy for Huntington's disease, under the direction of Neil Aronin, MD, professor of medicine, chief of endocrinology and metabolism in the Department of Medicine, and co-director of the UMMS Neurotherapeutics Institute.
- The world's leading ALS clinician and researcher, Robert H. Brown Jr., DPhil, MD, who discovered the first gene defect causing the inherited form of ALS and who is pioneering human gene therapy for this disease.
- One of the largest interdisciplinary communities of basic science researchers at any U.S. medical school using model organisms (fruit flies, roundworms and zebrafish), working in close collaboration with neurologists and neuroscientists.
- An outstanding program in innate immunity—the underlying mechanisms that drive immune defenses and inflammation, which is now known to be the primary offender in causing tissue damage in many common diseases, such as Alzheimer's disease and autism spectrum disorders.
- Notable expertise in the biology of the innate immune system of the brain, the microglia, led by Dori Schafer, PhD, assistant professor of neurobiology.

- The UMMS Center for Microbiome Research, led by Beth McCormick, PhD, vice chair and professor of microbiology and physiological systems, which seeks to understand how the microbiome affects the degree of inflammation within the brain.
- The UMMS RNA Therapeutics Institute, which consists of many of the world's best RNA biologists.
- A leading addiction research program that encompasses basic discovery, neuro-imaging and clinical care for patients with addiction to nicotine, opioids and other drugs.
- A multi-disciplinary team devoted to stroke research and care for patients with stroke and related diseases.
- An innovative Down syndrome research program, led by Jeanne Lawrence, PhD, chair and professor of cell & developmental biology, which draws parallels in the molecular disturbances in Down syndrome and in Alzheimer's disease.

## Theme 2. RNA Therapeutics Initiative (RTI)

### Discussion leaders:

**Phillip D. Zamore**, PhD, Howard Hughes Medical Institute Investigator, the *Gretchen Stone Cook Chair in Biomedical Sciences*, chair of the RNA Therapeutics Institute and professor of biochemistry & molecular pharmacology

**Melissa J. Moore**, PhD, former Howard Hughes Medical Institute Investigator, the *Eleanor Eustis Farrington Chair in Cancer Research* and professor of biochemistry & molecular pharmacology, and Chief Scientific Officer, Moderna Therapeutics.

The RTI at UMMS brings together the best RNA biology group in the world, including Zamore; Moore; 2006 Nobel laureate Craig Mello, PhD, Howard Hughes Medical Institute Investigator, the *Blais University Chair in Molecular Medicine* and professor of molecular medicine and cell & developmental biology—discoverer of RNA interference (RNAi); and Victor Ambros, PhD, the Silverman Chair in Natural Sciences and professor of molecular medicine, winner of the 2008 Lasker Award for Basic Medical Research and the 2015 Breakthrough Prize in Life Sciences—discoverer of microRNA, a form of RNAi present in all human cells and responsible for regulating genes.

Their discoveries of RNA-based gene regulation and gene editing have already revolutionized biology. They are now turning their attention to revolutionizing treatment for a host of diseases in which changes in gene function can be curative.

**Examples of opportunities** presented by the RTI at UMMS include:

- > **Master clinician researchers:** UMMS RTI researchers have discovered previously unknown pathways to turn genes off and on, and are striving to bring this incredible technology to the clinic. For each disease the RTI is approaching, such as Huntington's disease, ALS, pre-eclampsia and rare genetic diseases, we need master physicians and research nurses who are devoted to caring for the patients and performing the first human studies needed to prove the safety and effectiveness of these potential cures.
- > **“Bridge to Breakthroughs” Incubator:** Between the moment when a laboratory discovery is made and the first time it is used in a patient, a great deal of time, money and effort must be expended to overcome the regulatory requirements needed to get the potential therapy ready for the clinical setting. The “Bridge to Breakthroughs” incubator (BTBI) will greatly accelerate bringing the most promising therapies from the bench to the bedside.
- > **RNA biology of neurodegeneration and aging:** Aberrations of RNA biology are at the heart of a multitude of diseases that affect the brain, spinal cord and retina—most of which increase in prevalence with age. Examples include ALS, age-related macular degeneration, Alzheimer's disease and Parkinson's disease, among many others. This initiative will bring together physicians and researchers with these interests in order to unlock the mechanisms of these diseases and design curative new therapies.

UMass Medical School's **unique or distinguishing characteristics** in this area include:

- Multidisciplinary group of experts in RNA biology, gene therapy, gene editing (CRISPR), chemical drug design, structural biology with Cryo-EM and genetic neurologic and retinal diseases.
- The close collaboration between RNA therapeutics researchers and gene therapy researchers who have developed means for delivering RNA-based therapies to the brain, spinal cord and retina.
- Anastasia Khvorova, PhD, professor in the RTI, former CSO of Dharmacon and RXi.
- The RTI is now the only academic institute capable of synthesizing nucleic acid oligomers at the gram scale, which is required for pre-clinical trials in primates.
- The founding of start-up companies including:
  - o RXi, CRISPR Therapeutics (Dr. Craig Mello)
  - o Alnylam, Voyager Therapeutics (Dr. Phillip Zamore)
  - o Intellia (Dr. Erik Sontheimer)

### **Theme 3. Precision Medicine Initiative (PMI)**

#### **Discussion leaders:**

**Michael R. Green**, MD, PhD, Howard Hughes Medical Institute Investigator; the *Lambi and Sarah Adams Chair* in Genetic Research; director of the UMMS Cancer Center; and chair and professor of molecular, cell & cancer biology

**Katherine F. Ruiz de Luzuriaga**, MD, the *UMass Memorial Professor of Biomedical Research*, professor of molecular medicine, pediatrics and medicine, vice provost for clinical and translational science and global health, and director of the UMass Center for Clinical and Translational Science

The PMI at UMMS seeks to reap the benefits of decades of work on the fundamental molecular mechanisms of diseases to precisely target offending genes, proteins and pathways responsible for human disease. While some other institutions have used the PMI approach exclusively in the field of cancer, UMMS aspires to expand it to emerging public health burdens, such as addiction, complications of obesity and genetic diseases.

**Examples of opportunities** presented by the PMI include:

- > **Epigenetics of human diseases:** While much effort has focused on targeting defects in the primary sequences of DNA, epigenetics focuses on the study, and now treatment, of secondary modifications of DNA that regulate the functions of genes that may be inherited. Led by Dr. Green, our epigenetics researchers are discovering new medical treatments for defects that cause a range of diseases from early childhood developmental disorders to cancer.
- > **Precision addiction medicine:** The tragedy of the opioid epidemic, the ongoing toll of tobacco smoking and the threat of food addiction contributing to obesity are just a few examples of how addiction is burdening our health care system. Our researchers are initiating a range of studies from the molecular mechanisms of addiction to neuroimaging to patient care, allowing for precisely targeted therapies to move to clinical applications.
- > **Cardiometabolic Disease Initiative:** As obesity becomes a dominant problem in the U.S. and around the world, our researchers are conducting pioneering basic discovery and translational research to solve the problems of diseases caused by obesity. These include type 2 diabetes and heart disease, as well as non-alcoholic fatty liver disease (NAFLD), which represents the most common cause of serious liver disease in the U.S. This initiative will inform innovative precision solutions and cures based on our scientists' discoveries.
- > **Center for Microbiome Research:** A deeper understanding of the microbiome—the complex flora of microbes that inhabit our bodies and our environment—promises to be the key to future discoveries related to a range of diseases (from inflammatory bowel disease and autism to diabetes, cancer and antibiotic resistance), as well as to our understanding of how we maintain health and wellness. This center connects the work of basic scientists studying the microbiome (under the direction of Beth A. McCormick, PhD, professor and vice chair of microbiology and physiological systems, and co-founder of the Center for Microbiome Research) with that of physicians caring for patients with diseases linked to variations in the microbiome.

UMass Medical School's **unique or distinguishing characteristics** in this area include:

- We are an NIH-funded Clinical and Translational Science Award (CTSA) center (one of 60)
- Fully integrated clinical and research programs in diabetes and cardiovascular diseases
- Liver Institute, founded and led by Gyongyi Szabo, MD, PhD, the *Worcester Foundation for Biomedical Research Chair*, vice chair for research in the Department of Medicine, associate dean for clinical and translational science and professor of medicine, and includes the busiest liver transplant program in New England.
- Combined strengths in basic science, psychiatry, behavioral medicine and quantitative health sciences (including studies of health care disparities), which uniquely positions UMMS to incorporate social, behavioral and environmental determinants of health, and to ensure that we translate to all members of society who might benefit.

#### **Theme 4. Host Defense and Inflammation (HDI) Initiative**

##### **Discussion Leaders:**

**Kenneth L. Rock**, MD, chair and professor of pathology

**David Harlan**, MD, the *William and Doris Krupp Professor in Medicine* and director of the Diabetes Center of Excellence

**Ellen M. Gravallese**, MD, the *Myles J. McDonough Chair in Rheumatology* and professor of medicine

**Phillip D. Zamore**, PhD, Howard Hughes Medical Institute Investigator, the *Gretchen Stone Cook Chair in Biomedical Sciences*, chair of the RNA Therapeutics Institute and professor of biochemistry & molecular pharmacology

The HDI Initiative at UMMS builds on one of the fields in which our medical school has excelled since its inception. Immunology was initially known to be the key to transplantation, allergy and autoimmune diseases like type 1 diabetes and rheumatoid arthritis. It is now known that a number of common diseases, including atherosclerosis, stroke, heart attack, Alzheimer's disease, type 2 diabetes and autism, share inflammatory and immunologic mechanisms as the common cause of tissue damage. In addition, the cells and proteins of the immune system have the power to serve as the basis for therapies for a range of human diseases.

**Examples of opportunities** presented by the Host Defense and Inflammation Initiative at UMMS include:

- > **Human disease and immunology:** We are working to unlock the causes of and to design cures for a range of human diseases in which immunology plays a role by interfacing with a similar initiative in neurogenetics within the NeuroNexus Institute.
- > **Immuno-therapy Institute:** Using the mechanism of antibody-based therapies developed at MassBiologics (a leader in developing monoclonal antibodies to treat disease), we are developing T cell based therapies—including chimeric antigen receptor (CAR-T) cells—and vaccines for diseases like cancer, autoimmune diseases and infectious diseases that present risks to public health in the U.S.
- > **Drug design and resistance:** Designing small molecule inhibitors and biologics-based therapies to target host-factors and pathogens is a unique and highly integrated strength here, with expertise in small molecule screening; structure-based drug design using Cryo-EM and X-ray crystallography and anti-resistance strategies for cancer and infectious diseases.
- > **RNA-based defense against emerging mosquito-borne illnesses:** We are using innovative RNA-based technology (including gene drives) to understand how insects transmit diseases that affect global health and to potentially impede this transmission.

UMass Medical School's **unique or distinguishing characteristics** in this area include:

- An array of clinicians and researchers spanning the spectrum of immune biology, including innate immunity; T cell, B cell and NK cell immunity; and microbiome research.
- A world class program pioneered by Dale Greiner, PhD, the *Dr. Eileen L. Berman and Mr. Stanley I. Berman Foundation Chair in Biomedical Research* and professor of molecular medicine, for studying the human immune system in “humanized” mouse models of both normal host defense and immune-mediated diseases.
- Integrated programs in rheumatology and T1D, offering outstanding clinical care to patients by physicians who are themselves working on innovative discoveries into the role of the immune system in human diseases.
- Disease-specific programs in certain cancers for which UMMS researchers have distinct and unique expertise in designing immune-based therapies.
- Gene therapy Center, which will serve as a platform for CAR-T technology, programming the body’s immune system to attack cancer cells specifically.
- MassBiologics, the only nonprofit, FDA-licensed manufacturer of vaccines in the U.S., with capabilities for vaccine, monoclonal antibody and gene therapy vector production.