Harvard RNA Medicine Celebrates Fifth Anniversary!

Message from Director Frank Slack

This year marks our fifth anniversary and as I look back at the HIRM to reflect on our progress and why we did this, I am very proud to have been involved in launching and guiding this Harvard Initiative and especially proud to be a part of this amazing group of people. Harvard University has a large number of faculty doing amazing, world-class RNA research. In 2014, we wanted to bring together these leading RNA researchers from across the Harvard ecosystem to create the premier RNA Center in the country. Our mission then and now is to help our members to make and translate RNA discoveries into novel therapeutics and diagnostics. We have done this first by trying to provide a home for the broadly dispersed RNA community and to create a climate of learning and collaboration. Over the last five years, through our seminar series, research-in-progress talks, technology showcases, our annual RNA Medicine Symposium, and special educational seminars and classes, we have created a place for RNA investigators to connect with each other and stay abreast of the latest advances in RNA science.

We started a Pilot Grant Program to fund high risk research that could help solve some of the toughest barriers in RNA Medicine. We pushed the RNA community to put their heads together to come up with novel solutions by asking for proposals only from interdisciplinary teams of PIs. Our awardees in the “RNA Delivery” and “Immu-oncology” categories hail from across the Harvard ecosystem. So far, we have given out six awards (see below for this year’s winners).

To accelerate RNA research and medical applications further, we recently opened a state-of-the-art ncRNA Core Facility at BIDMC (see below) and plan to expand it by adding more cutting-edge technology in the future. In 2018, we also hired two bioinformatics faculty who focus their research on ncRNA (see below) and will head the Bioinformatics Unit of the Core Facility. With our three Core units, we are lowering the barriers to discovery in the RNA space and are excited to see which ncRNAs will emerge as new therapeutic and diagnostic translational targets in the near future.

To help our members translate emerging scientific breakthroughs from their labs to the clinic and industry and spin-off companies, we put together a Business Advisory Board (BAB) consisting of representatives from leading RNA industries, venture capital firms, and foundations. The BAB helps guide our member’s research...
direction and provides partnerships for commercializing their discoveries. Translating our member’s research into cures and diagnostics for diseases is our ultimate goal and we hope the BAB can help drive this process.

We will continue the activities of our Initiative next year and are planning to add new events like our first retreat on October 28th and are brainstorming new ideas to propel the Initiative further ahead in the coming years. This newsletter highlights our activities during the last year and how proud we are of our Members and their amazing work.

It is an honor to serve as director of the HIRM. Special thanks to our host, BIDMC for their support. To everyone who supports this important work, thank you for believing in the HIRM and for sharing our vision of changing Medicine for the better and making a positive difference in the world.

Frank Slack, PhD
Director, HMS Initiative for RNA Medicine
Shields Warren Mallinckrodt Professor, Departments of Pathology and Medicine, Harvard Medical School

New Bioinformatics Faculty

HIRM has recognized the essential role that data driven research has to play in delivery of translational interventions by recruiting and hiring two new faculty in bioinformatics.

There is an increasingly important role for biomedical data, buried within which lie the answers to the functions of non-coding genes, the role of pathways and networks, and even identification of the drugs and cures to diseases. Without the bioinformatics expertise to decipher these large datasets and to develop new methods of data analysis, the solutions in these datasets will be lost. The time for tremendous advances in RNA Medicine is quickly approaching, so the HIRM partnered with the BIDMC Cancer Center and Harvard Medical School to hire two bioinformatics faculty members with vigorous research programs focusing on non-coding RNAs (ncRNAs): Winston Hide, Associate Professor of Pathology and Ioannis Vlachos, Assistant Professor of Pathology. Both Dr. Hide and Dr. Vlachos joined the HIRM in July 2018 and since have set up the Bioinformatics Core Facility and their Research Labs. With highly complementary research programs in RNA systems medicine and non-coding RNA functional investigation using artificial intelligence (AI) and high throughput data, the two labs have already become a focus for novel research within the HIRM community. The team has recently been a key component for winning the recent HMS Dean’s pilot competition for Healthy Aging – bringing together the potential application of ncRNAs to improve resilience against Alzheimer’s disease.
Dr. Hide is implementing systems biology approaches to RNA medicine – connecting pathways that are involved with the etiology of complex diseases to their regulatory noncoding RNAs. This strategy can be used to build and implement systems that allow discovery and prioritization of key target genes and processes involved in cancer and drug resistance. Dr. Hide has worked with key industry partners such as Biogen to develop translational pipelines for target prioritization.

Dr. Hide performed his post-doctoral training at the University of Texas, Houston and Baylor College of Medicine. He gained industry experience in Silicon Valley at the MasPar Computer Corporation as director of genomics and founded the South African National Bioinformatics Institute where he co-authored the South African Government Biotechnology Strategy. He won the Oppenheimer Foundation Distinguished Sabbatical Research Fellowship in 2007.

Dr. Hide was elected into the Academy of Science of South Africa in 2007. He was also the first recipient of the “International Society for Computational Biology Award for Outstanding Achievement” — an award given in recognition of his work for the development of computational biology and bioinformatics in Africa.

Ioannis Vlachos, PhD., is an Assistant Professor of Pathology in Harvard Medical School and the Director of the Bioinformatics Unit of the Non-coding RNA Precision Diagnostics and Bioinformatics Core. He is also the Co-Director of the Bioinformatics Program at the Cancer Research Institute (CRI) and an Associated Faculty Member of the Harvard Stem Cell Institute.

Dr. Vlachos has continuously worked at the forefront of computational non-coding genome research, with a specific focus on non-coding RNAs such as microRNAs and long non-coding RNAs. The databases, models, and algorithms he has created empower researchers worldwide in decrypting ncRNA biogenesis, as well as in prioritizing ncRNAs as biomarkers or therapeutic targets. The systems and servers he has implemented are used by researchers in more than 55 countries worldwide, on all continents, excepting Antarctica. Many of these tools are considered as reference resources and have been deemed as “Expert Databases” in RNACentral and are official data sources in the Ensembl database. In parallel, he continues his research in machine learning and artificial intelligence, where he recently introduced Super Learning for the first time in a biomedical setting.

His research focuses on the effects of non-coding RNAs and non-coding variation on cancer initiation, progression and treatment, as well as immunosurveillance and immunoediting. Non-coding mutations and RNAs can be utilized as effective therapeutic targets or as biomarkers for diagnosis or patient stratification.
and management. The crosstalk between in silico, \textit{in vitro}, and \textit{in vivo} approaches, as well as between bench and bed-side have been central to Dr. Vlachos’ research. His long-term vision is to create the necessary methods and approaches that will enable the complete incorporation of the regulatory non-coding genome in personalized clinical decision making.

Non-coding RNA Precision Diagnostics and Therapeutics Core Facility Up and Running

The Harvard Initiative for RNA Medicine has launched a new, state-of-the-art Non-Coding RNA Precision Diagnostics and Therapeutics Core Facility to accelerate discovery of ncRNA diagnostics and therapeutics.

The ncRNA Core is the first core facility to offer a full range of integrated services for ncRNA investigators to decipher their RNA experiments and validate RNA function with the goal of developing powerful new cures and treatments for disease.

While ncRNAs are now known to be common and abundant, their detection and characterization requires specialized technologies for purification, imaging within tissues, and RNA sequencing. Highly specialized bioinformatics, computational software, and hardware are needed for whole genome/ncRNA transcriptome analysis and biomarker discovery, as well as for linking ncRNA targets with therapeutics. Specialized nucleic acid chemistry and biomedical engineering technologies are required to precisely deliver ncRNA drugs to diseased tissues.

On a fee for service basis, the facility offers comprehensive wet lab and dry lab services in detection, delivery, and bioinformatics. ncRNA biomarker and target identification is performed by sensitive and selective qRT PCR technology from MiRXES. The delivery of RNA via nanoparticle packaging both in vitro and in vivo is performed using the NanoAssembler Spark, Benchtop, and Blaze from Precision NanoSystems.

Co-directors Frank Slack, PhD. and Winston Hide, PhD. are excited about the possibilities.

“This combined range of services is not available anywhere else.” Says Slack “This core facility provides investigators not only the ability to identify new targets and biomarkers, but also ability to validate them as relevant to the disease they are studying. Our aim is eventually to go all the way to designing molecules that could lead to treatments – truly a concierge service unique among academic medical centers,”

Hide added, “For the first time, it’s possible to detect, create, test and action noncoding RNA within a seamless wet-lab/dry-lab environment. We have state of the art bioinformatics, and RNA technologies that are already helping our clients drive RNA medicine”

The new 1,393 square foot, self-contained lab facility is located in a building on BIDMC’s East Campus at 330 Brookline Avenue, Boston, adjacent to other research and clinical operations and easily accessible to
other major academic institutions as well as to biotech and pharmaceutical companies in Greater Boston.

The core is open for business and has already had many clients. If you are interested, please contact the ncRNA Core Facility to set up a consultation.

RNA MEDICINE 2019 Draws Record Attendance

Speakers and Moderators, left to right, Pier Paolo Pandolfi, Mano Manoharan, Eric Olson, George Church, Winston Hide, Mitch Guttman, Adrian Krainer, Erik Sontheimer, Richard Gregory, Frank Slack, Anna Krichevsky, Myriam Gorospe, Sandra Wolin, Suneet Agarwal.

Marking its fifth year, the annual non-coding RNA Symposium – sponsored by the Harvard Medical School Initiative for RNA Medicine (HIRM) and the Cancer Center at BIDMC – gave scientists both the chance to look back at the field’s explosive progress and to reflect on its potential to impact patient care in the future. With nearly 400 registrants, this year’s symposium was the best attended so far, nearly doubling the number of attendees present in 2015.

“Since the first RNA Medicine Symposium in 2015, we have witnessed the completion of multiple clinical trials in RNA medicine and the clinical approval of the first RNA interference drugs,” said HIRM Director Frank Slack, PhD, in his welcoming remarks. “The HIRM was founded on the belief that RNA medicine will fundamentally alter the way we treat disease and care for patients, and we are here today to celebrate RNA Medicine’s awesome power as we hear from some of the most prominent scientists and visionaries ever to
“At the Cancer Center at BIDMC, not only have we fully embraced the non-coding RNA revolution, but that revolution is now a core part of what we call ‘Ultra-Precision Medicine,’ ” added Pier Paolo Pandolfi, MD, PhD, Director of the Cancer Center at BIDMC. “By integrating RNA medicine with the Cancer Center’s other approaches to cancer research, we are able to engage the patient in a different journey – beyond offering them the usual diagnostics and standard of care. For selected patients seen in our Center, Ultra-Precision Medicine is now a reality.”

Long overshadowed by their better-known molecular cousin, DNA, non-coding RNA are now known to play a critical role in nearly all cellular processes by regulating gene expression. Over the past decade, scientists have demonstrated that changes in ncRNAs are associated with a range of human diseases, including cancer, and thus may serve as testable hallmarks, or biomarkers, for disease.

Symposium attendees heard from more than a dozen experts in this relatively new field, including Muthiah Manoharan, PhD, of Alnylam Pharmaceuticals, which now has two RNA-based therapies on the market, as well as Adrian R. Krainer, St. Giles Foundation Professor at Cold Spring Harbor Laboratory, whose work paved the way to the first FDA-approved RNA therapy for patients with spinal muscular atrophy.

“That was an amazing bench-to-bedside story he was able to tell,” said Slack, who is also the HMS Shields Warren-Mallinckrodt Professor of Medical Research at BIDMC. “We were really able to hear, for the first time this year, about the implantation of RNA medicine into patient care.”

While the U.S. FDA has approved a number of RNA-based therapies in recent years, none yet target cancer. Today, researchers at the Cancer Center at BIDMC and their colleagues are revealing the pathways by which ncRNAs drive tumor growth and resistance to cancer drugs. They’re also working to develop therapies that target dysregulated ncRNA to treat these very diseases By leveraging the power of ncRNAs to regulate gene expression, researchers have used them to suppress tumors in animal models.

These promising pre-clinical results are paving the way to the next wave of RNA medicine, in the clinic and in the lab. Eric Olsen, PhD, of UT Southwestern Medical Center described using RNA-guided CRISPR technology to repair the gene mutation causing Duchenne muscular dystrophy in a model organism. BIDMC’s own Winston Hide, PhD, Co-Director of the Cancer Research Institute’s Bioinformatics Program and the non-coding RNA core facility, discussed how taking a more systematic approach to identifying the networks and gene pathways implicated in disease can expedite the next generation of RNA therapies.

“Overall, the day featured a good mix of basic science, translational research and clinical science – which is exactly what our institution is trying to do at BIDMC,” said Slack. “It’s a very powerful indication of what’s to come.”

HIRM Awards Immuno-Oncology Pilot Grants

Immuno-oncology (IO) is therapy to stimulate our immune system to attack tumor cells. At the end of a normal immune response, say to viral attack, T-cells are instructed to “back off and retire” via interactions with repressive proteins on their surface, such as the PD-1 and PD-L1 proteins. Tumor cells sometimes aberrantly make these “checkpoint” proteins, repressing the immune response against themselves.
Mechanisms to block the production or action of the proteins by mAbs and vaccines can reawaken the immune system. There are multiple barriers to successful immunotherapy reflected in a ~25% response rate, plus some patients develop auto-immune toxicities. Non-coding RNAs (ncRNAs), such as microRNAs have been shown to directly regulate the immune system and immune checkpoint genes, while RNA is itself a potent stimulator of innate immune responses.

The goal of this year’s Pilot Grant Program was to fund innovative, inter-disciplinary projects attempting to harness or understand the link between ncRNAs and IO. HIRM received seven proposals from HIRM faculty at BIDMC, BCH, BWH, DFCI, and HSPH.

Contributions from HIRM donors and matching funds from the BIDMC Cancer Center funded three projects:

1) “Immunomodulatory Role of non-coding RNAs with a Personalized Leukemia Vaccine”
   David Avigan, MD, Frank Slack, PhD, Manoj Bhasin, PhD, Pier Paolo Pandolfi, MD, PhD, Dina Stroopinsky, PhD, and Jacalyn Rosenblatt, MD
   Beth Israel Deaconess Medical Center

2) “Deep Learning of Immunogenic Potential of Genomic Dark Matter: Neoepitope Formation from ncRNAs”
   Pier Paolo Pandolfi, MD, PhD, and Ioannis Vlachos, PhD
   Beth Israel Deaconess Medical Center

3) “Elucidating the Immunomodulatory Activities of LINC01133 in Basal-like Breast Cancer”
   Antoine Karnoub, PhD, Beth Israel Deaconess Medical Center, and Judy Lieberman, MD, PhD, Boston Children’s Hospital

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**SPARK: A Special Seminar on Commercializing Academic Discoveries in RNA Medicine**

On Tuesday, October 31, 2018, the HIRM co-hosted a special seminar with the BIDMC Technology Ventures Office, the Harvard University Office of Technology Development, and the Boston Children’s Hospital Technology and Innovation Development Office. Dr. Daria Mochly-Rosen, Founder and Co-Director of SPARK and The George D. Smith Professor in Translational Medicine, Stanford University School of Medicine, shared 12 years of knowledge on how to accelerate the bench to bedside translational process. Attendees learned the SPARK method of how to advance new biomedical research discoveries into promising new treatments for patients. SPARK is a unique partnership between university and industry experts which emphasizes new ways of thinking about bridging the gap between bench and bedside. It includes education, mentorship, and funding for promising product proposals and has now established a dozen academic institutions throughout the world. Our event drew a crowd of about 60 attendees who were able to consult with Dr. Mochly-Rosen and the SPARK team from Australia to consider setting up a SPARK-like program here.
HIRM Faculty Highlights

New Faculty: This year, we increased our membership to 35 by adding 8 new faculty:

- George Church, PhD, Robert Winthrop Professor of Genetics at Harvard Medical School and Professor of Health Sciences and Technology at Harvard and MIT
- Victoria D'Souza, PhD, Professor of Molecular and Cellular Biology at Harvard University
- Murugaiyan Gopal, PhD, Assistant Professor of Neurology, Harvard Medical School and BWH
- Winston Hide, PhD, Associate Professor of Pathology, Harvard Medical School and BIDMC
- Pavel Ivanov, PhD, Assistant Professor of Medicine, Harvard Medical School and BWH
- Jean-Pierre Kinet, MD, Professor of Immunology, Harvard University
- Pier Paolo Peruzzi, MD, PhD, Assistant Professor of Neurosurgery, Harvard Medical School and BWH
- Ioannis Vlachos, PhD, Assistant Professor of Pathology, Harvard Medical School and BIDMC

Faculty Member News

28-7 Therapeutics, founded by HIRM Faculty George Daley, Richard Gregory, and Frank Slack raised $85 million to fund a program in targeting RNA binding factors with known oncogenic functions.

Muru Gopal was selected as a recipient of 2019 AAI (American Association of Immunologists) Career in Immunology Fellowship which he will use to support a postdoctoral fellow working on microRNAs in neuroinflammation.

Richard Gregory became the first Stem Cell Biology Endowed Chair for Boston Children’s Hospital Department of Pediatrics (effective December 2018).

Richard Gregory and Frank Slack co-authored a paper in Nature examining the mechanisms for how N6-Methyladenosine (m6A) modification of mRNA regulates gene expression and found that METTL3, which catalyzes this process, actually promotes oncogene translation and tumorigenesis by circularizing the mRNA. They further showed that the interaction between METTL3 and the eukaryotic translation initiation factor 3 subunit h (eIF3h) is required for enhanced translation. These important findings uncover a mRNA looping mechanism of translation control and identify METTL3-eIF3h as a potential cancer therapeutic target.

Anna Krichevsky co-authored a groundbreaking paper in Acta Neuropathologica 2018 that provides the proof-of-principle that miR-132 replacement or supplementation in the brain may prevent or ameliorate Alzheimer’s Disease, Frontotemporal Dementia, and other neurodegenerative diseases. This study, based on an earlier discovery of miR-132 association with Alzheimer’s disease (AD), demonstrates that miR-132 is strongly neuroprotective in the context of AD. This work shows that miR-132, the most significantly downregulated microRNA in neurons in Alzheimer’s, lowers the levels of total, phosphorylated, acetylated, and cleaved forms of Tau that are implicated in tauopathies and that these and other effects are mediated by direct regulation of various Tau modifiers via multiple signaling pathways. The authors describe miR-132 as a master regulator of neuronal health indicating that miR-132 supplementation could be of therapeutic benefit for the treatment of Tau-associated neurodegenerative disorders. Dr. Krichevsky also published a comprehensive review in Nature Reviews Neurology 2018 about intercellular communication between the brain tumors and the cells of its microenvironment and a comprehensive overview of the molecular landscape of malignant gliomas in Neurotherapeutics 2019, exploring the most prominent molecular...
targets (protein-coding and regulatory RNA) that provide opportunities for the development of oligonucleotide therapeutics as a new class of drugs for brain tumors and other neurologic diseases.

**Carl Novina**’s lab previously identified a long non-coding RNA (lncRNA) called SLNCR and described its roles in altering gene expression and promoting melanoma invasion. To understand how this lncRNA functions at the molecular level and determine why more males than females die from melanomas, they published a follow-up study in *Cell Reports 2019* in which they show the androgen receptor (AR) and the transcription factor EGR1 bind to SLNCR and increase melanoma proliferation through coordinated transcriptional regulation of several growth-regulatory genes. This study suggests a new mechanism of action for the lncRNA SLNCR in melanoma proliferation: SLNCR recruits the androgen receptor AR directly to EGR1-bound genes, AR and SLNCR then appear to act as a transcriptional switch, inhibiting EGR1-mediated transcription of the tumor suppressor p21 to promote tumorigenesis. Because males express higher levels of AR than females, this novel model helps to explain why men have a higher incidence of melanomas compared with women and may lead to new therapeutic agents using non-coding RNAs.

**Carmelo Nucera** received the prestigious Van Meter Award which has been awarded since 1930 to a young investigator under age 45 for outstanding contributions to research on the thyroid gland or related subjects. For the presentation ceremony, Dr. Nucera spoke on “The role of a new thyroid-specific long non-coding RNA (lincRNA) in drug resistance and iodine metabolism in BRAFV600E thyroid cancer”. [https://www.thyroid.org/2018-van-meter-lectureship/](https://www.thyroid.org/2018-van-meter-lectureship/)

**Pier Paolo Pandolfi**’s latest research of PTEN, one of the most frequently mutated, deleted, down-regulated, or silenced tumor suppressor genes in human cancer, shows that a compound found in broccoli and other cruciferous vegetables, indole-3-carbinol (i3c), reactivates the function of PTEN. This exciting finding, published in the journal *Science*, was highlighted in [this article](https://www.nytimes.com/2018/03/05/science/pten-cancer.html) in the *New York Times*. In its active conformation, PTEN is a dimer at the plasma membrane. In this study, Dr. Pandolfi and his colleagues found that polyubiquitination of PTEN by the ubiquitin E3 ligase WWP1 suppressed its dimerization and tumor-suppressive functions. Further, they elucidated that WWP1 is transactivated by the MYC proto-oncogene and inhibited by i3c. These important findings identify the MYC- WWP- PTEN axis as an evolutionary conserved regulatory pathway and pave the way for a viable approach to “tumor suppressor reactivation” for cancer treatment.

**Pier Paolo Peruzzi**, the Principal Investigator of The Laboratory of Epigenetic Neurosurgery and RNA Therapies, was awarded a K08 grant from NIH in 2017. His lab has published a seminal manuscript titled “The functional synergism of microRNA clustering provides therapeutically relevant epigenetic interference in glioblastoma” in *Nature Communications 2019* which won the American Academy of Neurological Surgeons award in 2018 and the lab has since been invited to publish the protocol for the design, engineering and use of artificial microRNA clustering for gene therapy (Nat Protocols, 2019, and Journal of Visualized Experiments, 2019). The goal of this work was to provide a wider perspective for the use of microRNAs in cancer therapy. They describe a cluster of microRNAs (miR-124, miR-128 and miR-137) that target several transcriptional factors and when expressed in murine glioblastoma models, increase survival by 5-fold in combination with chemotherapy. They also demonstrated that transgenic microRNA clusters can diffuse as a group from cell to cell to affect tumors globally which makes this work even more translationally important.

The HIRM has come together with co-investigators Win Hide, Anna Krichevsky, Pier Paolo Pandolfi, Pier Paolo Peruzzi, and Ioannis Vlachos to use a novel computational/wet lab approach with PI Frank Slack in the Harvard Medical School’s Dean’s Pilot Award in Healthy Aging for “Systematic discovery and translation of novel neuroprotective non-coding RNAs modulating resilience to age-related cognitive decline".
Call for Membership Applications

The HMS Initiative for RNA Medicine welcomes applications for new members. Full and associate memberships are open to faculty members at Harvard-affiliated institutions who are contributing to the peer-reviewed literature in RNA biology/medicine (complete criteria available online or by request.) Junior faculty planning to conduct research in RNA are eligible for membership and are especially encouraged to apply. Prospective members should contact Jai Vartikar at jvartika@bidmc.harvard.edu.

Sponsorship Opportunities

The HMS Initiative for RNA Medicine welcomes inquiries from individuals and companies interested in supporting RNA medicine. Donations to the HIRM can be directed toward research or the overall operating costs for a particular event, including our annual Symposium. Please contact us for more information.

2018-2019 Donors

Without philanthropic support from our generous donors, we would not be able to do the work of the HIRM. We are grateful for all levels of contributions that we receive.

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