RNA as an Engine of Synergy and Excellence at the University of Michigan

Co-PIs: *Nils G. Walter (LS&A) & Mats Ljungman (Medicine)*

Administrative Coordinator: *Martina Jerant*

Executive Committee: *Peter Freddolino, Sundeep Kalantry, Stephen Parker, Peter Todd (Medicine); Amanda Garner (Pharmacy); Jayakrishnan Nandakumar (LSA)*

Strategic Advisory Board: *Arul Chinnaiyan, Eva Feldman, Gil Omenn, Hank Paulson, Janet Smith, Max Wicha (Medicine); Mark Burns (Engineering); Charles Brooks, Charles Doering (LS&A)*

Executive Summary

Revolutionary discoveries in biomedicine have now revealed that ribonucleic acid, or RNA, is critical for most aspects of human health and that its misregulation is responsible for many diseases. The known range of cellular RNAs has recently expanded to include short and long non-coding RNAs whose functions in human physiology are still only beginning to be discovered, but are already understood to profoundly impact all cellular processes, from stem cell differentiation to cancer. These revelations provide an unprecedented opportunity to invest in advanced studies of RNA as a gateway to precision medicines. Emerging in parallel are revolutionary new technologies for RNA analysis, ranging from single molecule microscopy and next-generation sequencing to genome editing, ushering in a bountiful era of both discovery research and medical translation in RNA biomedicine that is about to go "viral" (Walter, 2015). In response to these opportunities, a grassroots effort of nationwide unmatched proportions – involving ~150 faculty from across campus – has started to empower the University of Michigan (UM) with a dominating position in the biosciences by forming the nascent Center for RNA Biomedicine (CRB, http://www.umichrna.org). We now propose to unleash the enthusiasm, energy and synergy of this movement to help push the UM to the forefront nationally through a comprehensive Biosciences Scientific Research Initiative in RNA, enacting linchpin hires and establishing innovative campus-wide resources.

After its inaugural symposium on March 25, 2016, with keynote talks from two Nobel laureates of the RNA field, the CRB launched with a mission portending that of the Biosciences Initiative itself:

- Promote and develop cross-disciplinary collaborations on RNA across campus
- Mentor the next generation of RNA biomedical scientists
- Enrich the UM's intellectual and training environment in the biosciences
- Leverage and promote the strengths of the UM RNA community, ranging from translational research to single cell and single molecule biophysics, and across RNA mediated diseases such as cancer, neurodegeneration and viral infection
- Provide a central organizational structure to help recruit and develop common resources, including collaborative research grants, shared equipment, and faculty

In pursuit of this mission, we now propose a linchpin hiring plan: 5 World-class faculty (at least one Full Professor) will be recruited into our shared infrastructure that will support these hires, in turn benefitting all Center-affiliated groups. The following research areas are recommended for recruiting, with the aim to strengthen important, currently underserved areas of expertise in the proposed units (appointments could be split as appropriate); some potential candidates include the keynote speakers of our symposia (http://www.umichrna.org/rna-research-at-michigan):

1. **Cryo-electron microscopy or tomography of RNA nanomachines** | LSI/Biological Chemistry/Biophysics/MCDB
2. **RNA structure modeling *in vivo*** | Chemistry/Biophysics/DCMB
3. **RNA protein interaction profiling** | Biological Chemistry/MCDB
4. **RNA drug targeting or as medicine** | MedChem/Pharmacology
5. ***In vivo* analysis of long non-coding RNA function** | MCDB/Human Genetics/CDB

Our linchpin hires will aim to synergize with multiple other bioscience-related hires, proposals and initiatives, such as those on protein misfolding pathologies, neuroscience, opioid addiction, innate immunity, cancer, the microbiome, etc. This is possible since RNA is a field that arguably touches on all areas of the natural sciences, medicine, business, law, and even philosophy (as RNA-guided genome editing raises ethical concerns).

We will complement these coordinated, synergistic hires by building on UM-grown expertise in education and scholarship, establishing the following innovative resources and making them as widely accessible as possible:

An RNA Graduate Fellows Program: Fellowships will be awarded on a competitive basis to top 1st-year and 2nd-year graduate students working in any CRB group; in addition, students can apply for a Rackham certificate in RNA Biosciences. The ultimate goal is to build the necessary track record and momentum towards a successful federal (NIH or NSF) training grant application.

An innovative "R-Cubed" pilot grant mechanism: Upon discovery of a novel disease-associated non-coding RNA by a UM faculty member (they need not initially be a CRB member), an expert "RNA Rapid Response" ("R-Cubed") team is quickly and competitively solicited, assembled and empowered with $100,000 pilot funds for one year (renewable for a second year) to delineate its mechanism. The ultimate goal is for the team to acquire the necessary data and build momentum towards a successful federal (NIH or NSF) project grant application (which in turn will ensure the CRB's long-term sustainability).

Micro-Pilot Subsidies: Micro-grants of $1,000 will be competitively, yet readily disbursed to defray facilities costs of two or more collaborators across units seeking to generate preliminary data for a joint research grant application. Such costs may include those for RNA-sequencing or imaging modalities that are likely to provide a go/no-go decision for further studies or produce preliminary data for a joint grant application.

CRISPR Genome Editing Core: A centralized facility will be established to set up robust platforms for the kind of mammalian genome engineering that facilitates research on fundamental biological and disease problems, including trafficking, nuclear organization, neuroscience and cancer. A rate-limiting step in these research endeavors is often the need to implement a CRISPR editing platform that creates incisive reporter, knockout or mutated cell lines in relevant endogenous gene loci. The core will be led by a senior scientist with extensive experience in CRISPR gene editing, stem cell and induced pluripotent stem cell culturing, and cell biology. The services provided will entail consultation, hands-on experimental guidance, product delivery and evaluation.

Nascent RNA Bru-seq Core: This UM-developed technology will be made available to researchers seeking to assess transcriptional and post-transcriptional regulation in living cells. The core will be an extension of the ENCODE Bru-seq Mapping Center established at the NCRC and will provide assay development consultation, experimental service and data analysis, and further develop the technology toward single-cell sensitivity.

Single RNA Molecule Imaging Core: Housed within the existing Single Molecule Analysis in Real-Time (SMART) Center (https://lsa.umich.edu/biophysics/resources/smart1.html), a centralized facility will be established to set up robust imaging assays for single RNA molecules and their accompanying protein pathway partners. Both live and fixed cell imaging support will be offered by a senior scientist with extensive experience in single molecule fluorescence imaging, including consultation and hands-on experimental guidance.

We envision that these investments will propel the UM to the forefront of the RNA Biosciences in the nation, with tremendous promise for discovering the next RNA-based breakthrough biology and technology right here on campus.

Long-term sustainability

Funds beyond the period of Biosciences Initiative support will come from a mix of overhead return from research grants, direct support on project and training grants, core recharge fees, and UM Office of Research funds.

Reference

Walter, N.G. (2015). Going viral: riding the RNA wave to discovery. RNA *21*, 756-757.