Project Proposal: A "Focused Research Organization" to Develop RNA Sequencing Technologies

RNA therapeutics are gaining popularity since they are cheap and easy to make, but sequencing technologies today rely on converting RNA back to cDNA, which collapses information on the more than 150 different chemically modified bases for RNA into just four bases. To address this knowledge gap, this project aims to develop direct sequencing tools specifically for RNA including chemical modifications in order to enable the complete sequencing of RNA bases and improve RNA therapeutics.

Problem Statement

RNA encodes regulatory information that directs cellular functions. This dynamic information is written in four canonical bases, each of which can be chemically modified to create more than 150 different bases. Today, sequences of RNA are mostly obtained by converting RNA back to cDNA which is then sequenced; in that process of reverse transcription, all the modifications on RNA are lost. This knowledge gap significantly weakens our understanding and treatment of human diseases.

Project Concept

As a Focused Research Organization, this project will recruit an interdisciplinary team to develop a low-cost tabletop device that can sequence RNA, including chemical modifications, as accurately as we sequence DNA, and make this product available to researchers at large. We propose to 1) improve high-resolution imaging technologies, 2) develop single-cell mass spectrometry for RNA sequencing, and 3) advance nanopore technology to enhance their accuracy and resolution. Ultimately, the imaging technology will be coupled with the mass spectrometry or nanopore technology to extract full-length RNA transcripts from subcellular locations and then sequence them. In parallel, we will develop algorithms to deconvolute data and build data displays to quantitatively reflect the locations of RNA transcripts and their sequences with all modifications.

What is a Focused Research Organization?

Focused Research Organizations (FROs) are time-limited mission-focused research teams organized like a startup to tackle a specific mid-scale science or technology challenge. FRO projects seek to produce transformative new tools, technologies, processes, or datasets that serve as public goods, creating new capabilities for the research community with the goal of accelerating scientific and technological progress more broadly. Crucially, FRO projects are those that often fall between the cracks left by existing research funding sources due to conflicting incentives, processes, mission, or culture. There are likely a large range of project concepts for which agencies could leverage FRO-style entities to achieve their mission and advance scientific progress.

This project is suited for a FRO-style approach because academia is too siloed to support the kind of large-scale, interdisciplinary research project that this would require, and companies that

currently provide DNA-based RNA sequencing tools have no motivation to innovate beyond tweaks to the current methods.

How This Project Will Benefit Scientific Progress

The development of direct RNA sequencing technologies with all chemical modifications will enable the execution of the Human RNome Project, which is anticipated to result from the the National Academies of Sciences, Engineering and Medicine Report (NASEM) on RNA Sequencing. A similar NASEM report resulted in the creation of the Human Genome Project. The Human RNome Project aims to identify all the possible chemical modifications of RNA and create a true sequence of RNA, *i.e.* the RNome. Direct RNA sequencing technologies will also enable scientists to sequence the complete genome of RNA viruses, such as SARS-CoV-2, the hepatitis C virus, and influenza viruses and accelerate the development of new RNA therapeutics for these viruses and other diseases.

Key Contacts

Authors Vivian Cheung, University of Michigan, Life Sciences Institute, vgcheung@umich.edu
George Langford, Syracuse University

Referrers Matt Hourihan, Federation of American Scientists, mhourihan@fas.org
Alice Wu, Federation of American Scientists, awu@fas.org