The RNomics Program

Frederick L. Tyson

Program Director, NIEHS

Ian Nova

Program Director, NHGRI

The RNomics Program

Concept Clearance: New Common Fund Program
TITLE: The RNomics Program

Objective:

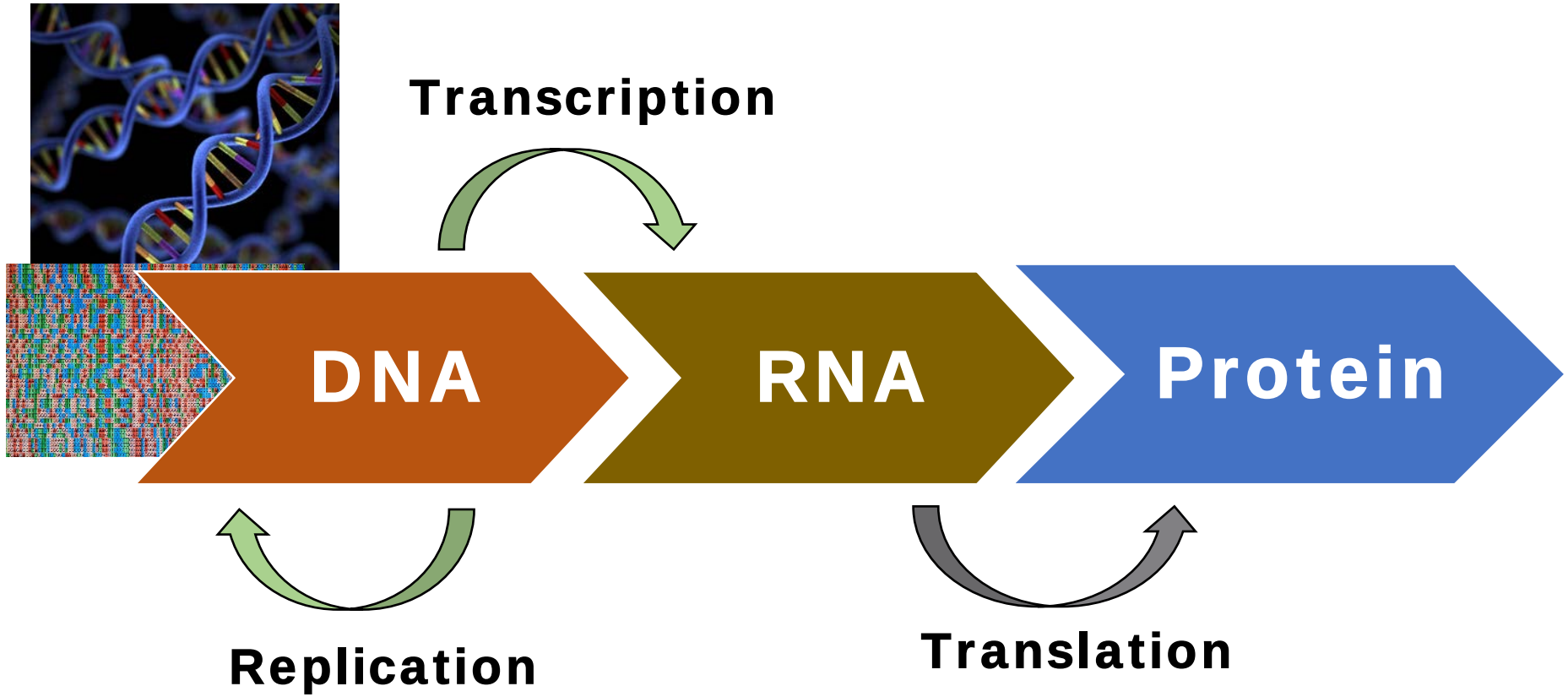
The RNomics Program will develop an essential toolkit for comprehensive characterization and measurement of the RNome, fostering a supportive infrastructure for groundbreaking research.

Funds Available and Anticipated Number of Awards: $30.25m per year for ~15 meritorious awards (contingent upon funding availability)

Program Duration: 5 years
Council Action: Vote for approval of the concept for The RNomics Program

Central Dogma

The flow of genetic information within a biological system

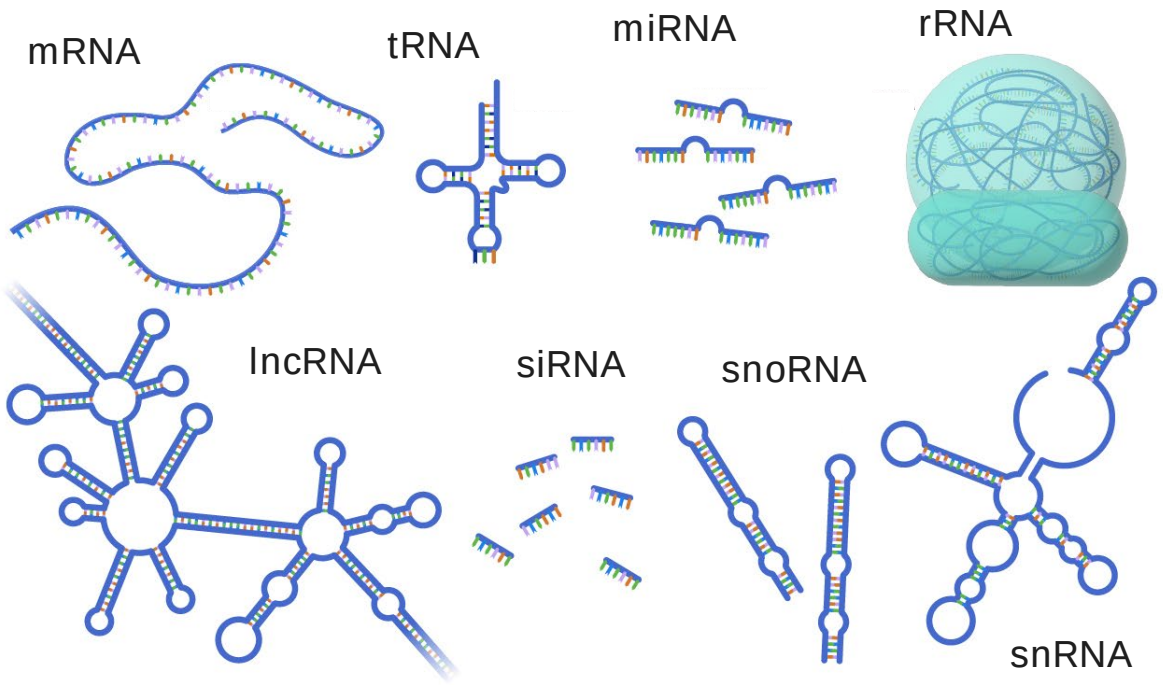


The RNome Challenge

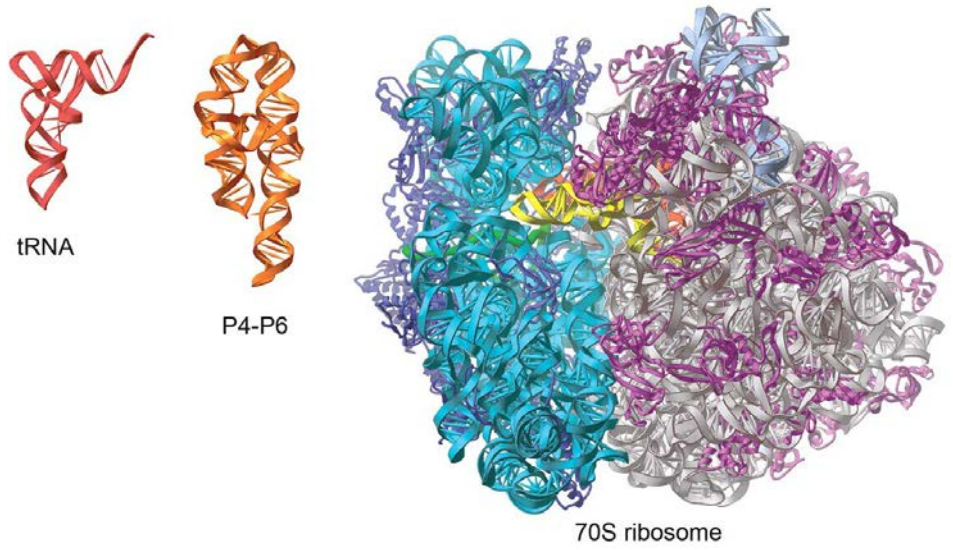
- The **RNome** is defined as the entire set of RNA molecules and modifications expressed in a cell, tissue or organism at a given time
- The diverse and complex functions of RNA are integral to human physiology; RNA changes give rise to disease and are influenced by environmental exposures
- We cannot currently measure the full RNome, as the tools, technologies, and methodologies for end-to-end sequencing of RNA and *all of its modifications* are insufficient
- There is no comprehensive, strategic effort or coordinated investment in the study, sequencing, and mapping of RNA with modifications

The Complexity of RNA

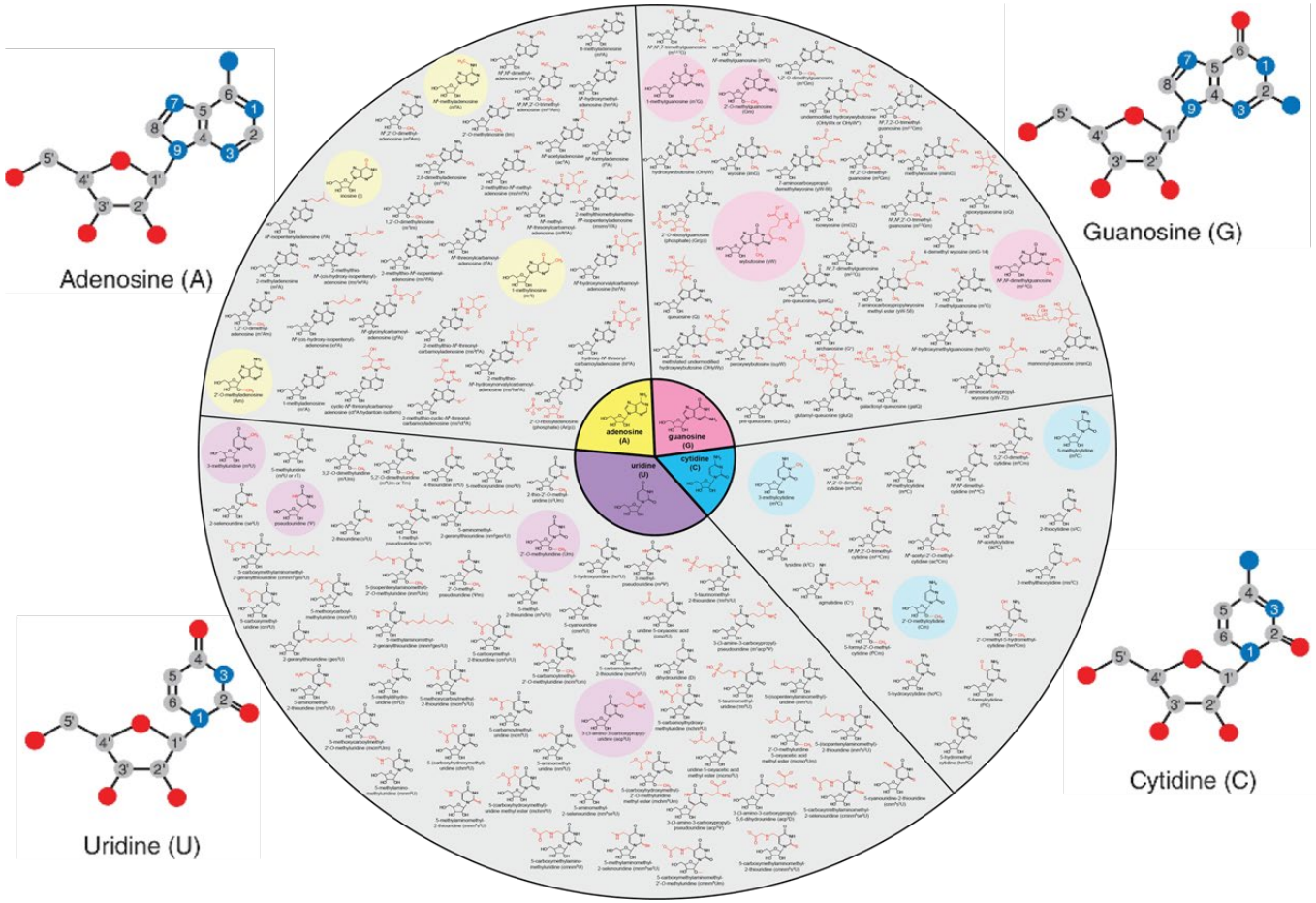
- Many types of RNA exist within the human body, and each serves a unique function (RNA encompasses more than vaccine development)
- This program is focused on understanding endogenous RNA



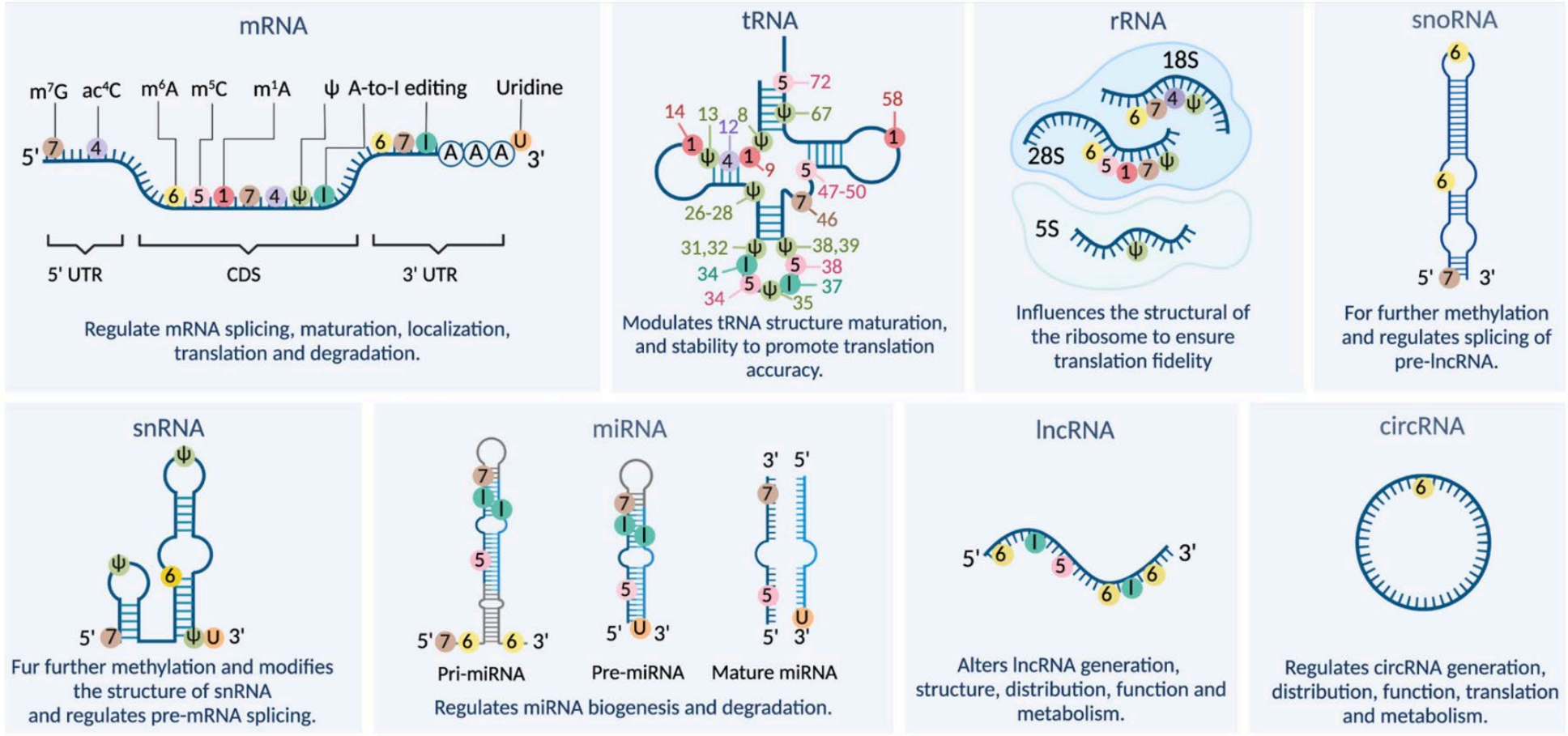
- RNAs fold into complex 3D structures based on their sequence



RNA Sequence: More Than AGCU

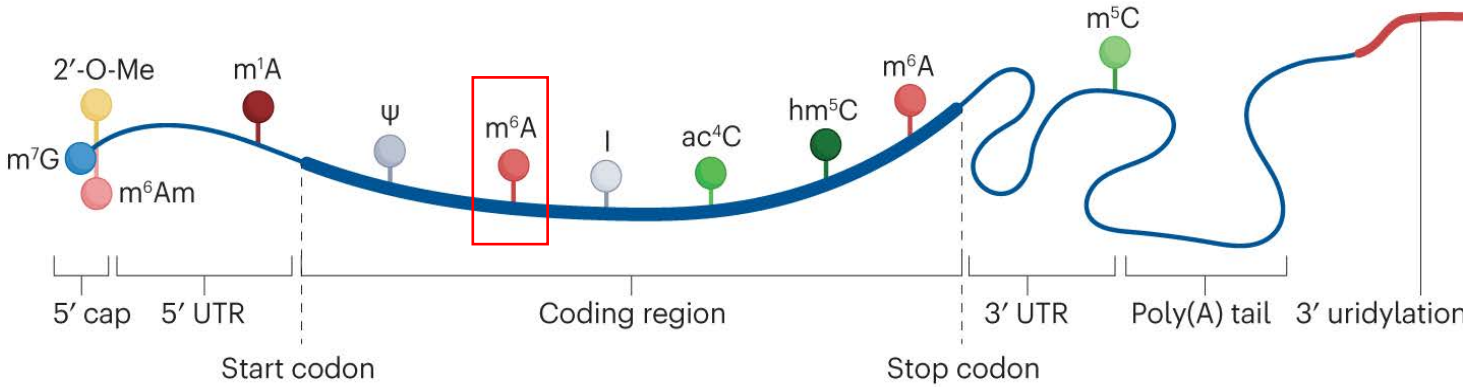


Modifications Impart Function Across RNA Types



Cui, et al, *Nature*, 2022

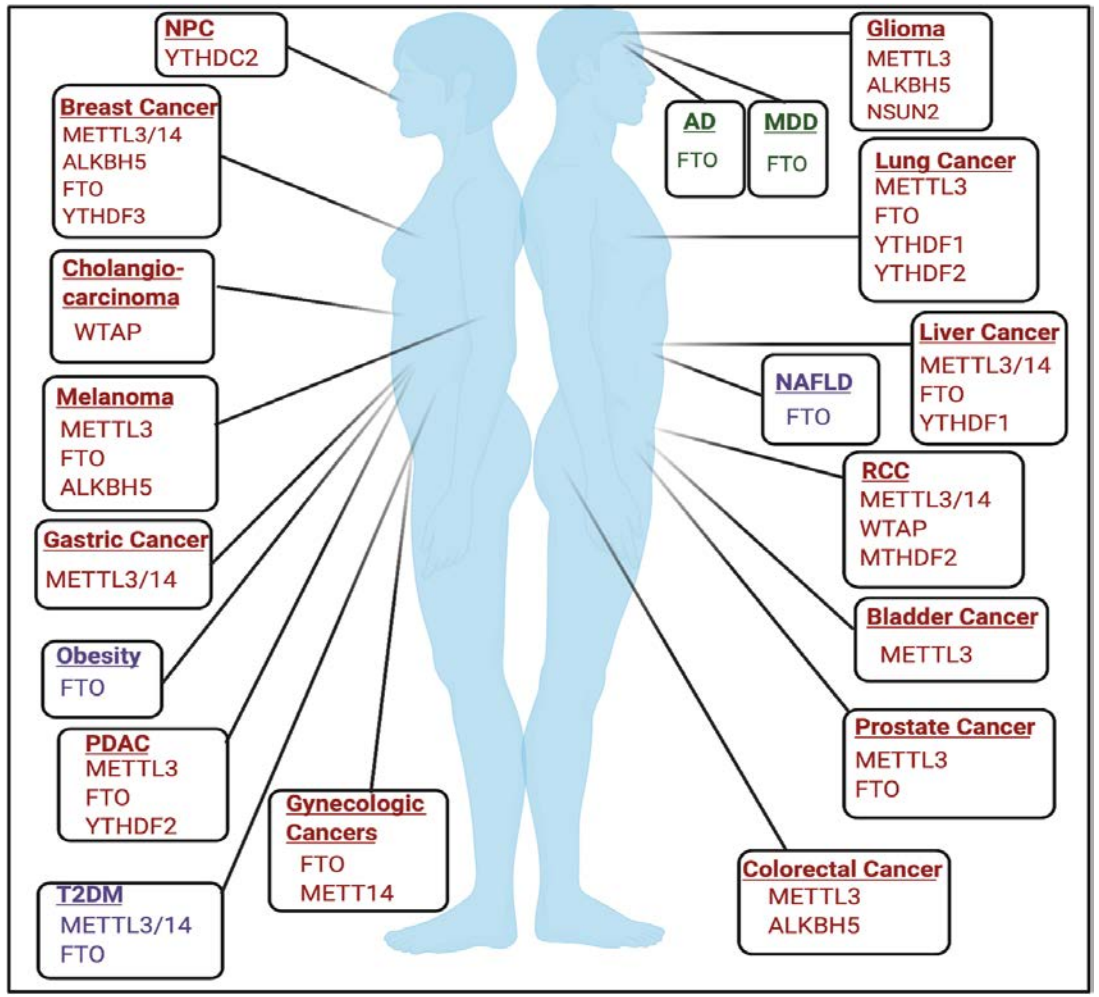
Base Modifications on mRNA



- A single type of RNA modification, **N6-methyladenosine (m6A)**, on mRNA affects expression, splicing, nuclear export, translation efficiency, RNA stability and miRNA processing

- Environmental exposures, such as arsenic, lead to aberrant m6A profiles that are associated with development and progression of skin cancers

RNA Modifications in Chronic Disease



Wilkinson, et al, *IJMS*, 2021

- Cancers
  - Lung
  - Breast
  - Prostate
  - Colorectal
- Metabolic Diseases
  - Obesity
  - Diabetes
  - NAFLD
- Aging
  - Neurodegenerative diseases
  - Cardiovascular diseases
  - Osteoporosis
  - Fertility decline
- Developmental Disorders
- Psychiatric Disorders

Major Limitations in RNA Analysis

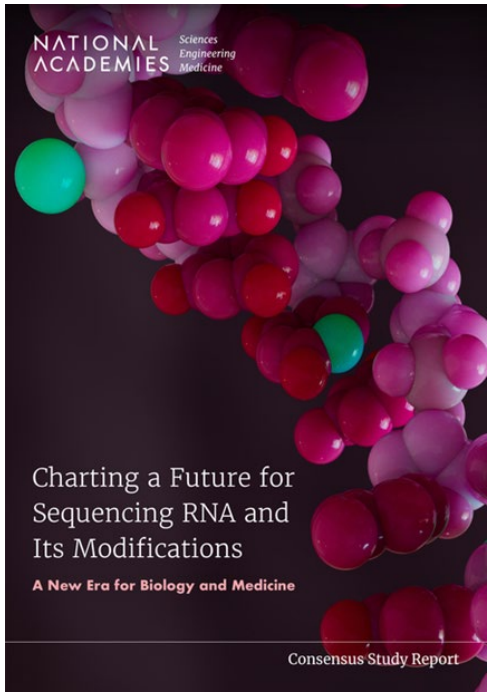
"RNA science stands at a critical crossroads"

Technology

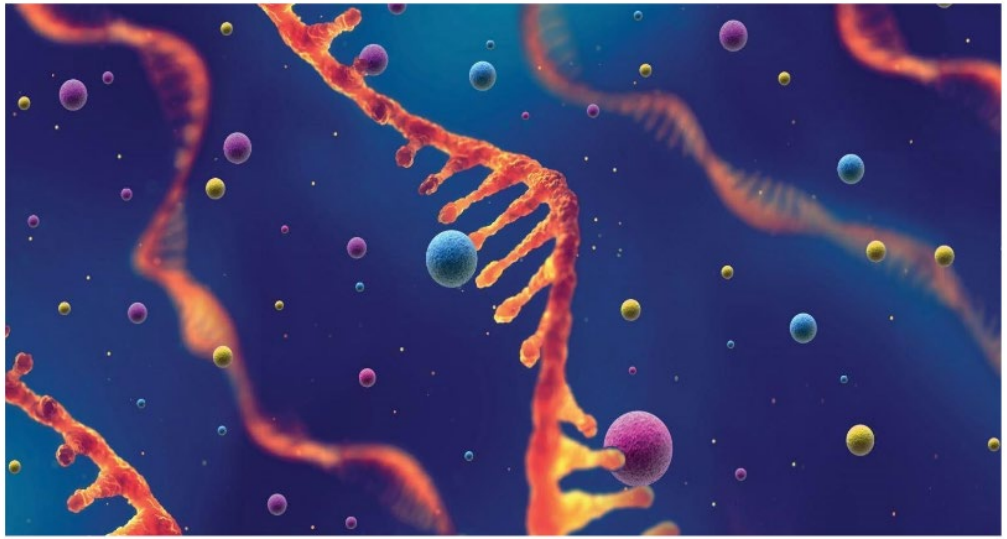
- Current technologies either sequence RNA indirectly as cDNA or directly with limited accuracy
- Methods to synthesize, manipulate, modify, and interrogate the functional role of RNA are underdeveloped compared to corresponding DNA tools

Data Standards

- Robust and consistent data standards and nomenclature for modification-inclusive RNA sequencing data do not exist
- Existing RNA databases are disparate and do not communicate

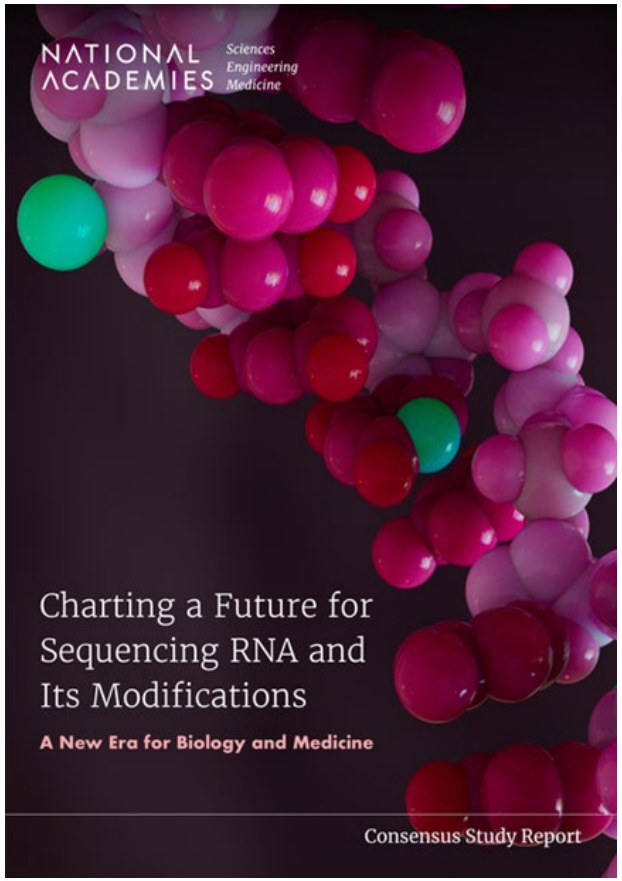


RNA Sequencing Planning Activities



Capturing RNA Sequence and Transcript Diversity, From Technology Innovation to Clinical Application

May 24 – May 26, 2022



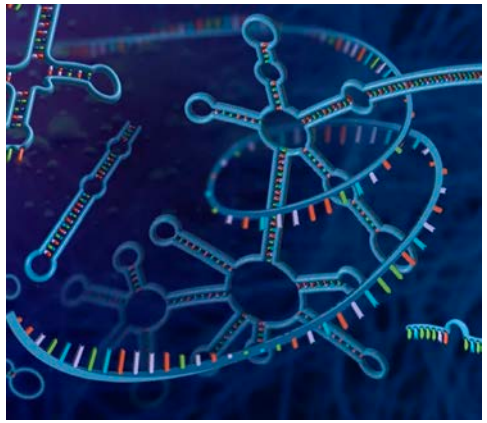
Guidance from the NASEM Report

The RNomics Program - Goal

Develop the essential toolkit to characterize and study the human RNome.

Transformative technologies that enable full sequencing of all cellular RNA

- Tools to understand the **functional role of RNA modifications**
- **Standards, and database resources** for modification-inclusive RNA sequencing
- First-of-their-kind **reference datasets and RNA-based clinical biomarkers**



Initiative 1: **RNA Sequencing Technology**

Initiative 2: **RNA Molecular and Computational Tools**

Initiative 3: **Molecular Standards**

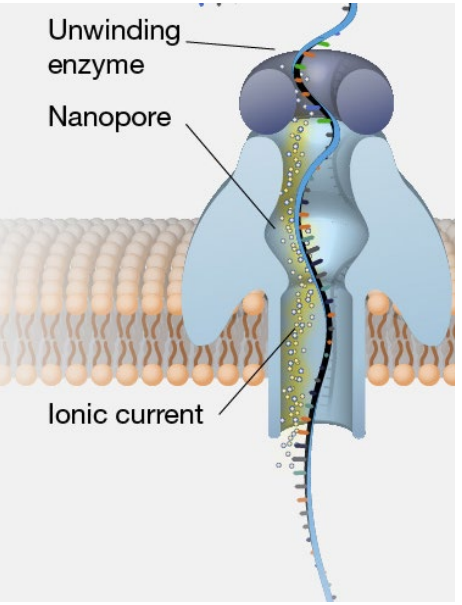
Initiative 4: **Coordinating Center for Benchmarking and Standardization**

Initiative 1: RNA Sequencing Technology

Critical gap: limits in comprehensive sequencing of RNA – where are the modifications?

Development of technologies and computational tools to enable end-to-end sequencing of RNA and all its modifications

- Emphasis on direct RNA sequencing technologies (full transcripts with many modifications)
- Refinement of existing technologies AND novel chemistries/ methodologies
- Transformative methods for improved sample preparation



Scope: $14M per year for 5 years (10–12 awards)

- High-risk, high-reward sequencing technology grants
- Collaborative RNA sequencing technology development centers

Initiative 2: RNA Molecular and Computational Tools

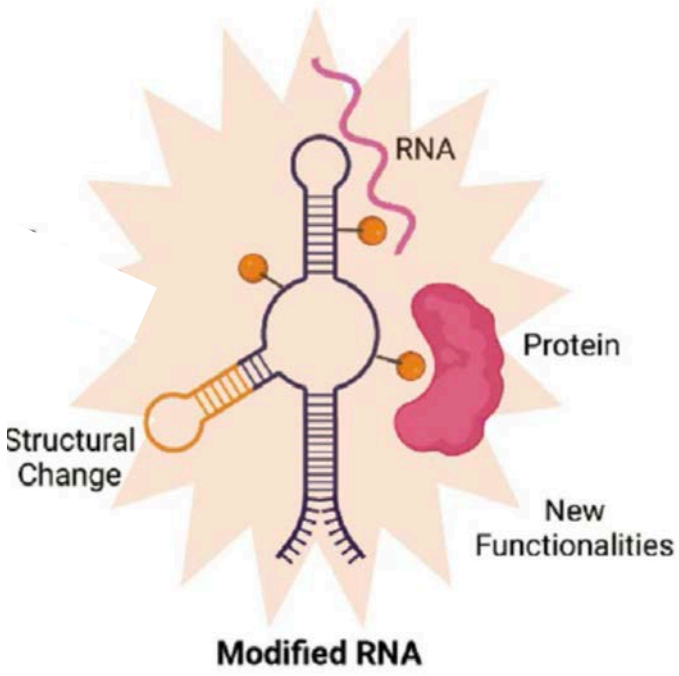
Critical gap: limited understanding of RNA function – what are the effects of modifications?

Development of molecular and computational technologies that enable functional analysis of RNA sequences with modifications

- Transformative methods in technology and data science for deciphering RNA function (structure, localization, interaction, dynamics, etc…)
- An improved suite of enzymatic tools (including RNA modification readers, writers, and erases, and RNA binding proteins)

Scope: $6M per year for 5 years (5–7 awards)

- High-risk, high-reward technology development grants
- Collaborative RNA molecular tool development centers



Initiative 3: RNomics Molecular Standards

Critical gap: lack of standard RNAs to test technologies – what is the ground - truth?

Production and distribution of synthetic RNA molecules, serving as a platform for development, cross-comparison and benchmarking of newly developed sequencers, base-callers, tools, and methodologies

- Standards of modified nucleosides (individual modified bases) for global RNA modification analysis
- Standards of RNA sequences with known, quantified, site-specific modifications: A suite of long RNAs representing various RNA types with many modifications within various sequence contexts
- Standards will ensure reproducibility across RNA technologies

Scope: $8M per year for year 1 ramping down to $4M per year by year 5 (3–4 awards)

Initiative 4: RNomics Coordinating Center

Critical gap: disparate datasets and unvetted technologies – which technology to use?

Establishment of a center to manage and harmonize technology development through standardization, benchmarking, and facilitation of data production

- Generate standard guidelines, nomenclature, and database requirements for modification-inclusive RNA sequencing data
- Benchmarking: create community challenges to cross-compare RNA technologies
- Coordinate data production: facilitate reference dataset selection and production
- Outreach: promote methods and create user guides for technology selection

Scope: $2M per year for year 1 ramping up to $7M per year by year 5 (1–2 awards)

Anticipated Impact

The tools and infrastructure developed within *The new Common Fund RNomics Program* and delivered to the scientific community will revolutionize RNA biology and jumpstart studies across NIH mission areas:

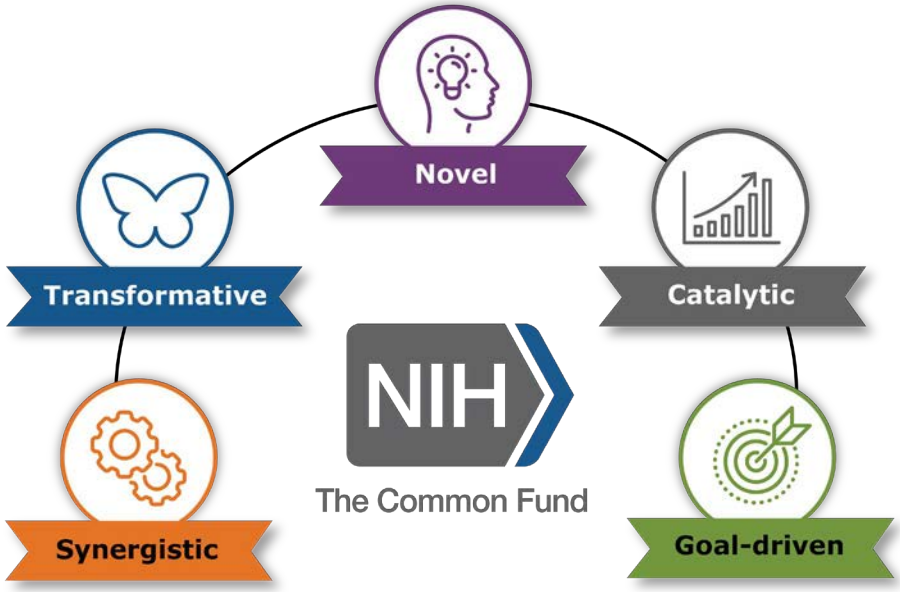
- Create a platform for generating comprehensive, tissue-specific RNomes and deciphering the mechanisms and overarching rules of RNA molecular physiology
- Discover RNA-based clinical biomarkers for diagnosis, prognosis, and treatment
- Drive development of RNA therapeutics and RNA-targeting drugs
- Monitor the effects of environmental exposure on biology and health

Alignment with Common Fund Criteria

Transformative, Catalytic, Goal-driven, Synergistic, Novel

Transformative: Overcoming tool limitations and standardization issues will dramatically enhance RNA analysis, opening new frontiers in all aspects of RNA biology

Catalytic: The development of critical standards, tools and models for RNA analysis will lay a robust foundation for future innovation and novel therapeutic development



Alignment with Common Fund Criteria

Transformative, Catalytic, Goal-driven, Synergistic, Novel

Goal-driven: Technology benchmarks and data generation, quality and consistency milestones will mark short and long terms project goals, ensuring innovations build upon each other and that a comprehensive and capable product is delivered at the culmination of the project

Synergistic: RNA plays a central role in biology with relevance to physiology, aging and disease that traverses NIH IC mission areas

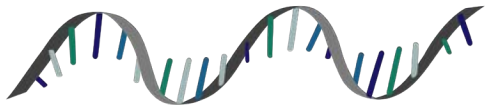
Novel: Uniting genomics, imaging, AI/ML offering NIH a unique opportunity to advance technologies and platforms for clinical, translational and basic research

Trans-NIH RNomics Group

Co-Chairs:
Rick Woychick, NIEHS
Lisa Chadwick, NHGRI

Coordinators
Fred Tyson, NIEHS
Ian Nova, NHGRI

Working Group:
Michelle Heacock, NIEHS
Kim McAllister, NIEHS
Leroy Worth, NIEHS
Maya Evanitsky, NIEHS
Ben Cubert, NHGRI



Stephanie Morris, NHGRI
Max Guo, NIA
Alison Yao, NIA
Stefan Maas, NCI
Kathleen Borgman, NIDA
John Satterlee, NIDA
Justin Zook, NIST
Conrad Mallia, NIAID
Rajeev Gautam, NIAID
Dimitrios Vatakis, NIGMS
Ken Chang, NCATS
Christine Happel, NCATS
Dominique Lorang-Leins, NIAAA

The RNomics Program

Develop the essential toolkit to characterize and study the human RNome.

Initiative 1: **RNA Sequencing Technology**

Initiative 2: **RNA Molecular and Computational Tools**

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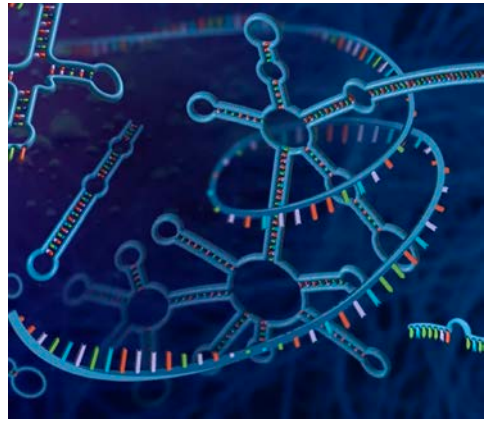
Impact

Understand and study the relationship between RNA biology and human health. Tools and infrastructure developed in this program could lead to:

- RNA-based clinical biomarkers
- RNA targeted therapeutics
- A better understanding of the environmental impact on molecular physiology



Council Action: Vote for Approval of the Concept “The RNomics Program”

commonfund.nih.gov

National Institutes of Health
Office of Strategic Coordination–The Common Fund