The RNomics Program

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

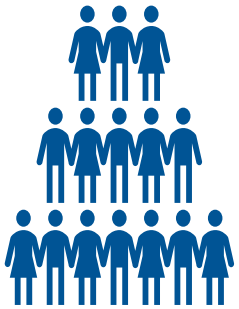
»COMMON FUND = Catalyzing Discovery

COMMON FUND= Uncommon Approaches + Research + Solutions

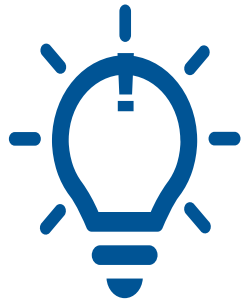
- Substantial investments in time-limited, *ambitious goal-driven* programs
- *Significantly change trajectory* of biomedical research

Accelerate Emerging Science

Remove Research Roadblocks



Enhance Research Workforce



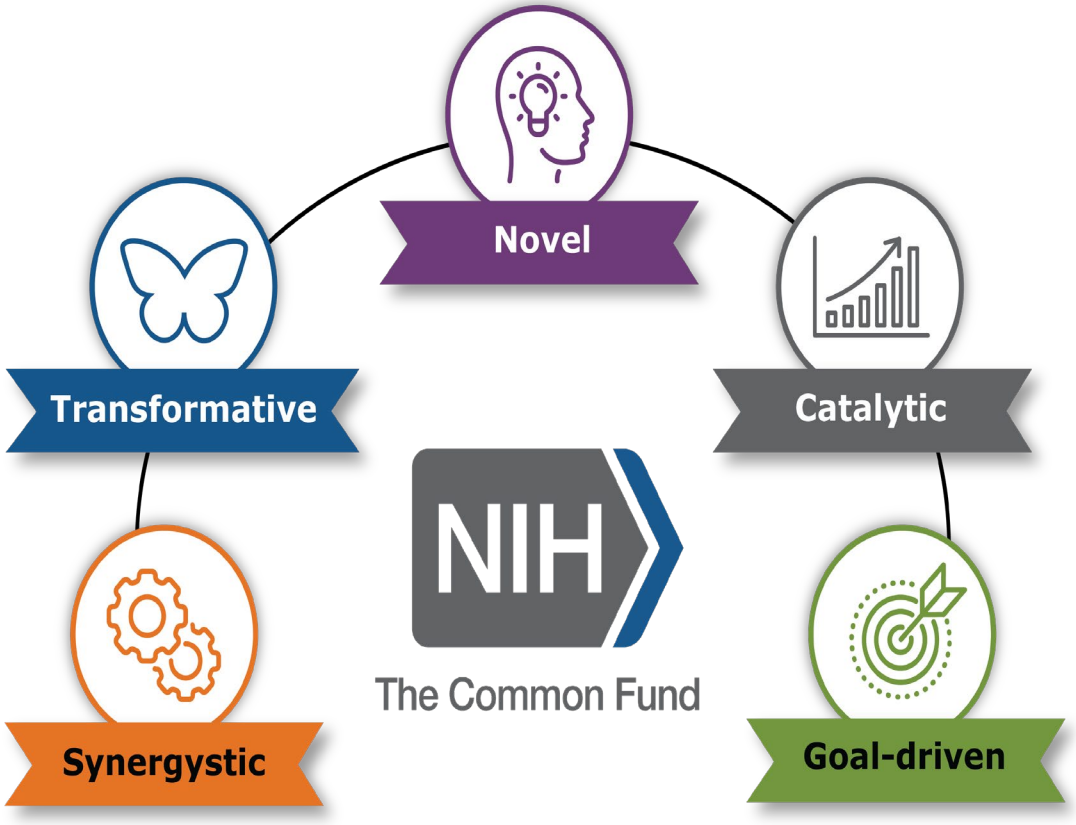
Support High-risk, High-reward Science

The NIH Common Fund

COMMON FUND= Uncommon Approaches + Research + Solutions

Mission

- Support bold scientific programs that **catalyze discovery** across all biomedical and behavioral research.
- Investigators and multiple NIH Institutes, Centers, and Offices **collaborate on innovative research**
- **Address high priority challenges** for the NIH
- Make **broader impact** in the scientific community

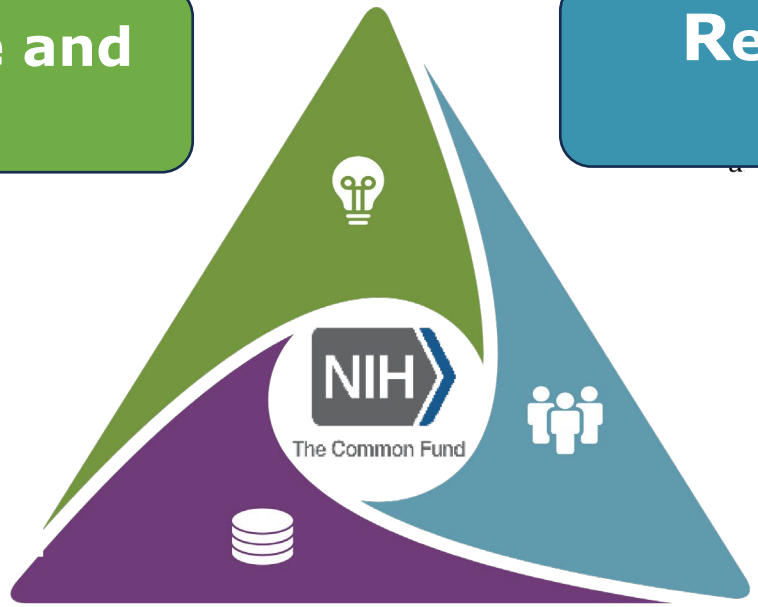


Common Fund Program Areas

Transformational Science and Discovery (TSD)

Transform Scientific Knowledge

- Create paths to discovery
- Establish new scientific principles, models, and research resources



Re-Engineering the Research Enterprise (RRE)

Transform Biomedical and Behavioral Research

- Make robust research workforce
  - Contribute new perspectives and ideas
    - to discovery
    - transform research into prevention and therapies
    - share findings broadly

Catalytic Data Resources (CDR)

Accelerate Research Through Data Resources

- Manage and develop data for scientific discoveries

The Common Fund

Common Fund Program Criteria

TRANSFORMATIVE
- Exceptionally high and broad impact in biomedical/behavioral research

CATALYTIC
- Time-limited investments capitalizing on *new scientific knowledge or breakthroughs to accelerate and enable* research

GOAL-DRIVEN
- Defined goals for specific deliverables

SYNERGISTIC
- Advance multiple NIH ICO missions; accelerates research relevant to multiple diseases/conditions

NOVEL
- Innovative solutions to specific scientific challenges

Ad hoc Dec 2025 Council of Councils
OSC–Common Fund Presentation

- **Concept Clearance: RNomics Program**
  Presenter(s): Frederick Tyson, Ph.D. (NIEHS) and Ian Nova, Ph.D. (NHGRI)

  - *Establish an RNomics program with four initiatives to advance technology development, create more expansive molecular and computational tools, develop standards, and coordinate data resources and benchmarking*

  - *Impact: Will span from the development of new clinical biomarkers to understand RNA modifications in human health and disease*

The RNomics Program

Revised 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

How we addressed reviewers' comments

Council members stated concerns about the feasibility of the program as presented, specifically related to:

- The timing and potential interdependency of the proposed initiatives
- The broad scope of the program
- Concerns about the high-risk nature of some of the proposed initiatives

To address these concerns in this presentation, we are:

- Providing more detailed information about each of the initiatives proposed, including additional context to the current state of the field and the tools/technologies that represent the starting point for development
- Clarifying the milestones, scope, and goals of each initiative
- Discussing in more depth the timing and interaction between the proposed initiatives

We have integrated these changes throughout the slides and believe this presents a comprehensive package for the council to consider.

How we addressed reviewers' comments

Concern: Applicability across broad area of science meeting the "synergistic" requirement for Common Fund programs

- Additional background on the relevance of RNA science, and how achieving the goals of this program will impact research across all NIH mission areas

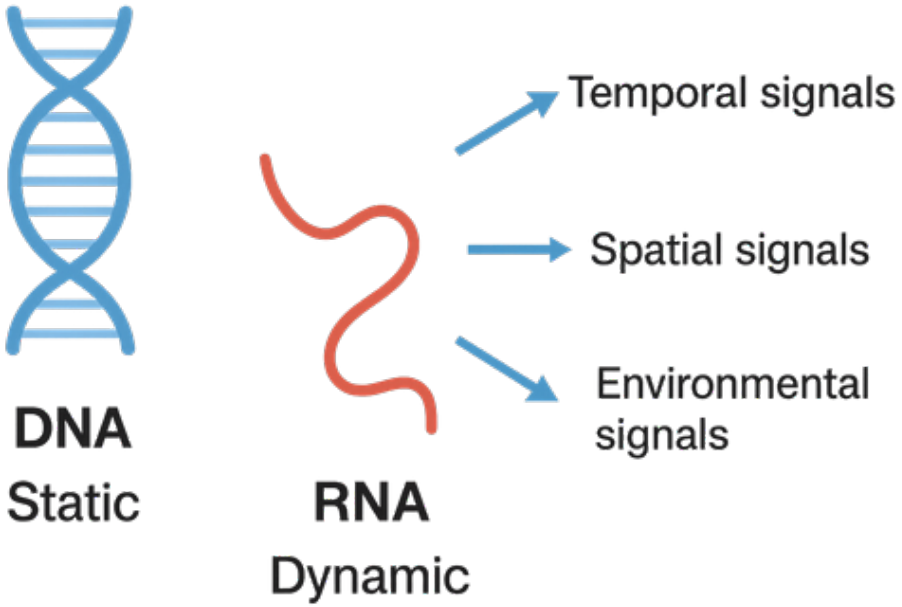
Concern: The need for this research and high-risk nature of the proposed initiatives

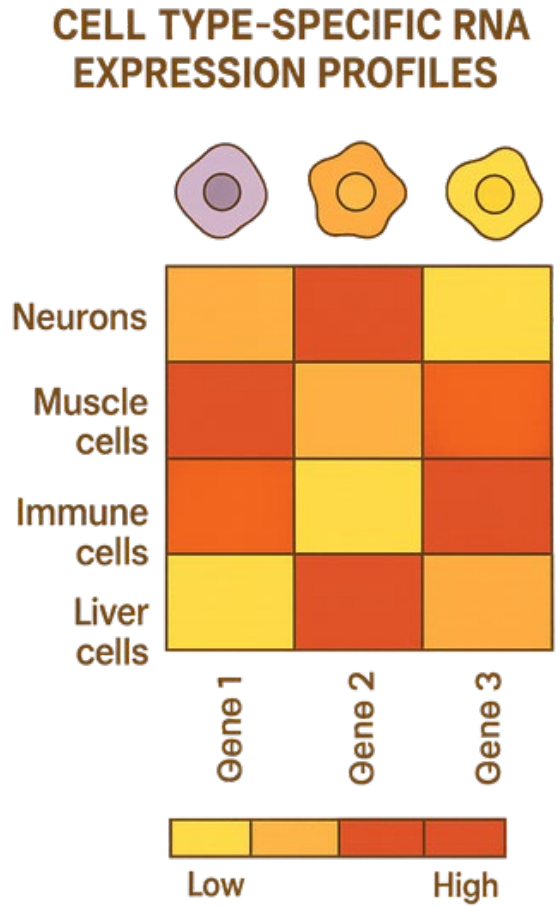
- More details highlighting how the specific elements of the program are designed in direct response and alignment to the NASEM report recommendations
- Description of how initiative 1 (RNA sequencing technology) balances risk and reward by capitalizing on existing innovation

Concern: Interdependency of proposed initiatives

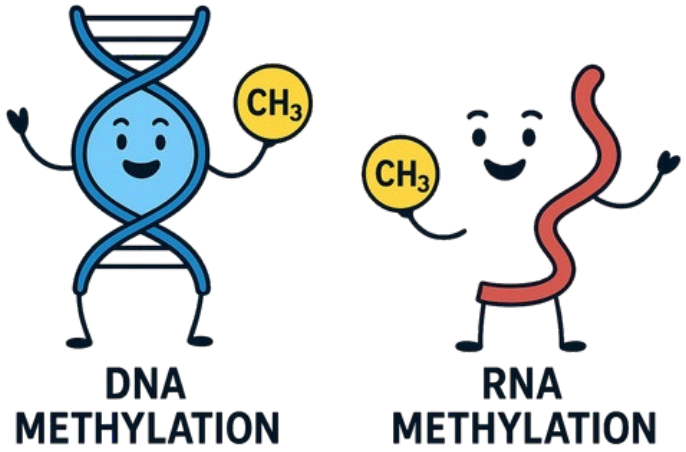
- Descriptions of why initiative 2 (molecular tools) does not depend on the success and output from initiative 1
- Description of why initiative 3 (molecular standards) does not need to be completed for initiative 1 to begin and succeed, and how the two initiatives can progress concurrently

What is RNA & why do we care about it?





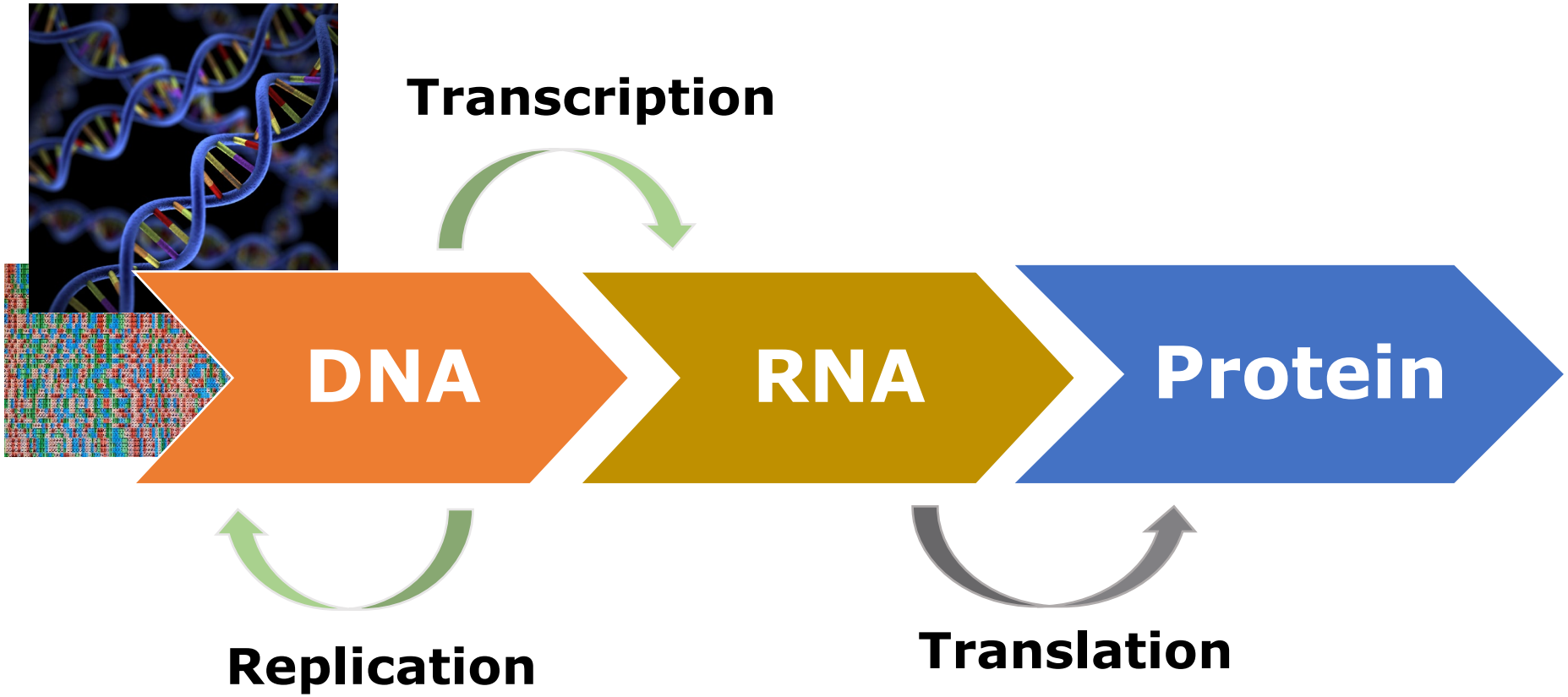
RNA Epigenetics



NIH NIEHS
NIH NHGRI
NIH NATIONAL CANCER INSTITUTE
NIH NIAID
NIH National Institute on Drug Abuse
NIH NIA

Central Dogma

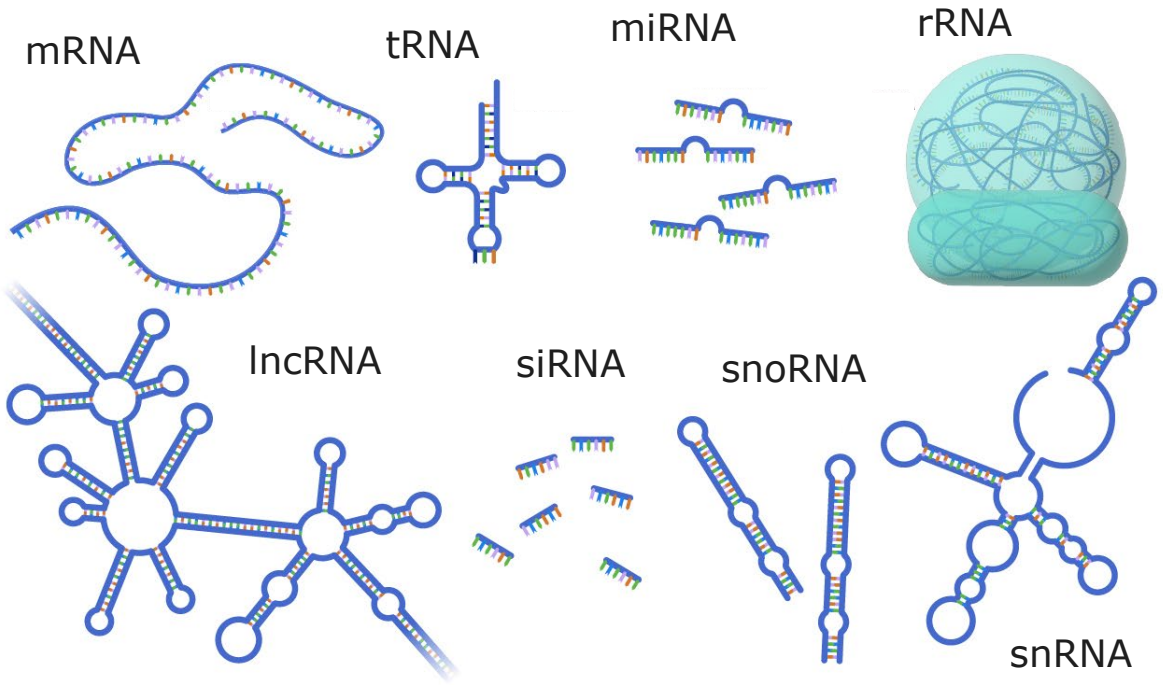
The flow of genetic information within a biological system



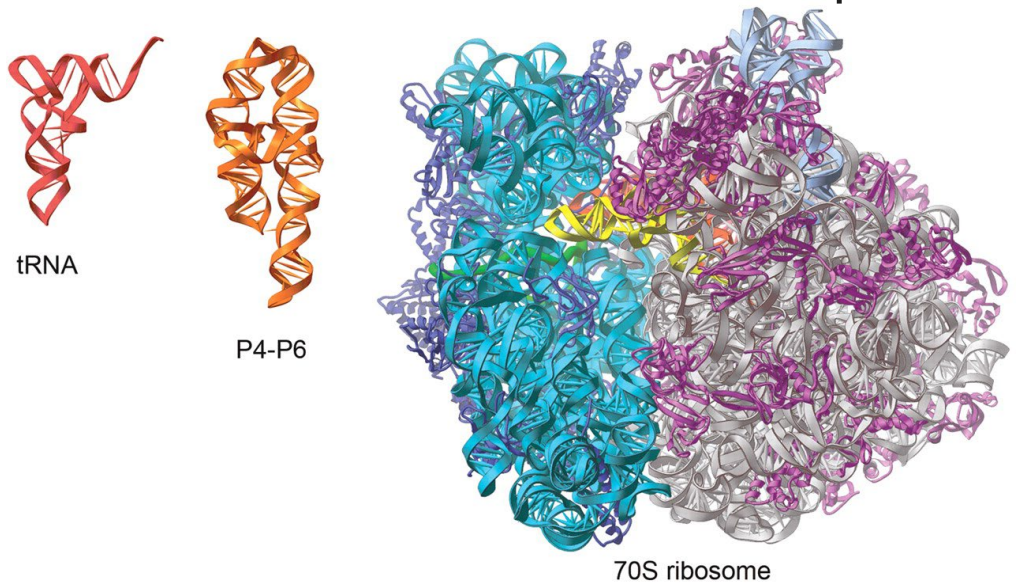
The Complexity of RNA

- Many types of RNA exist within the human body, and each serves a unique function (RNA encompasses more than vaccine development)

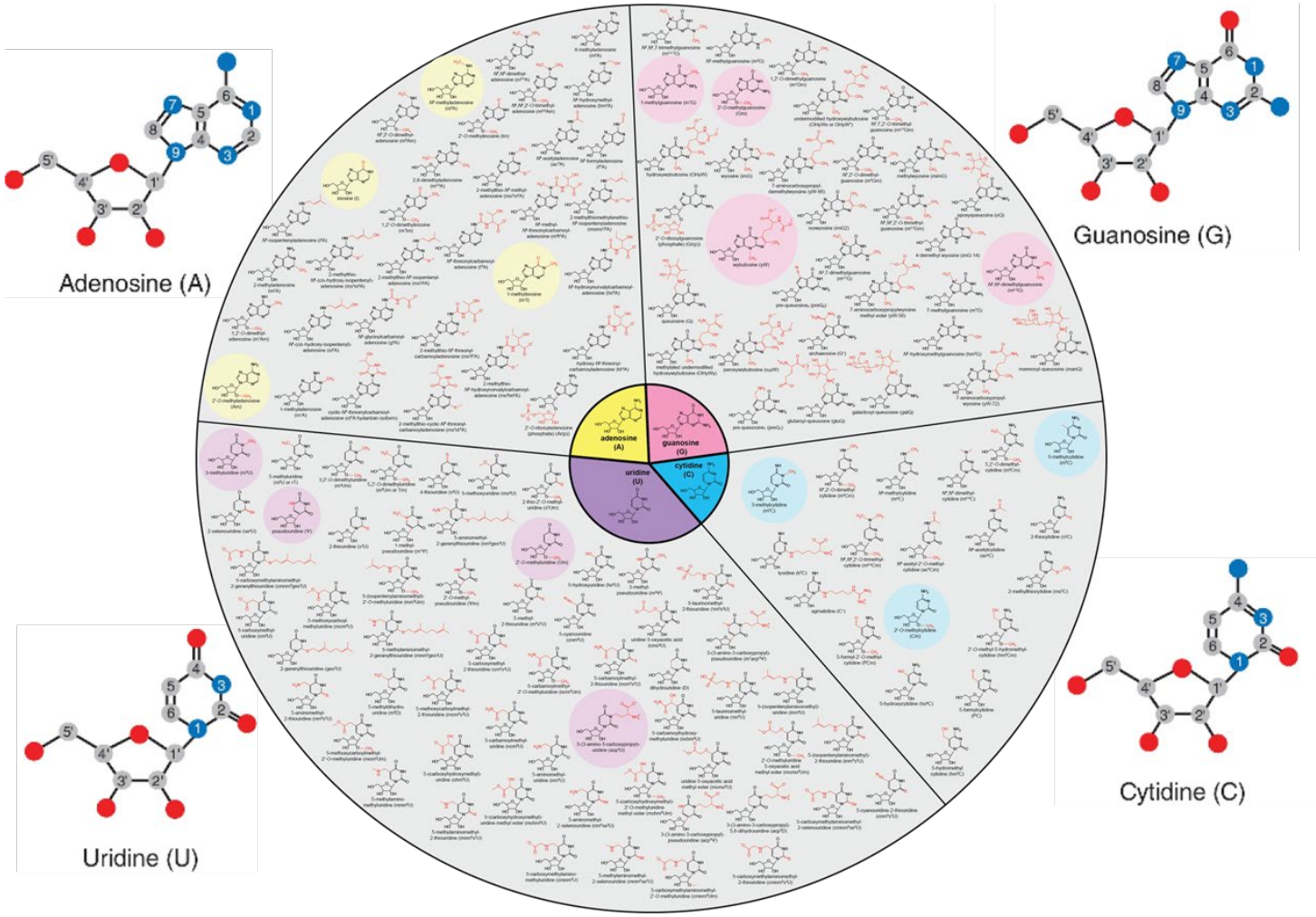
- This program is focused on understanding endogenous RNA



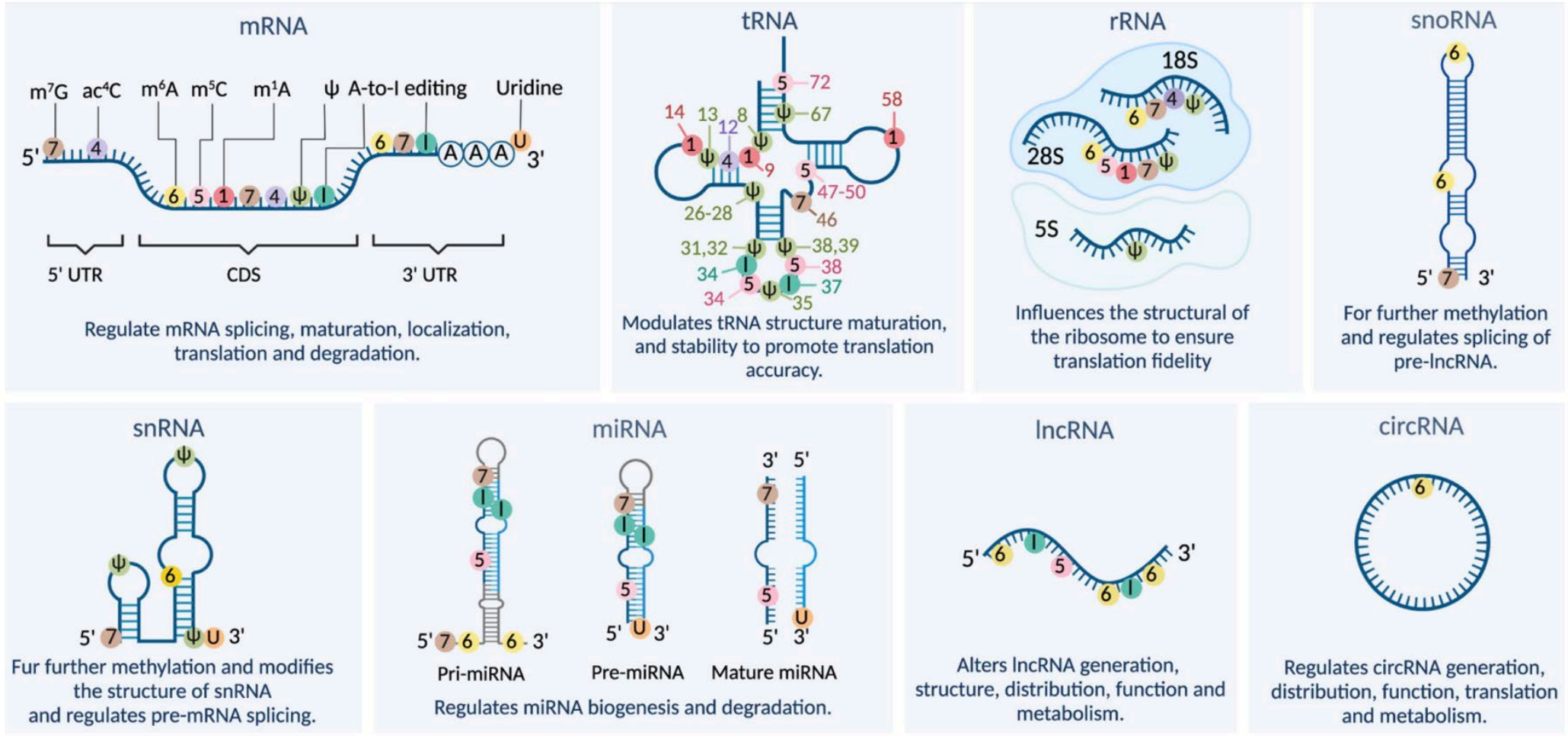
- RNAs fold into complex 3D structures based on their sequence



RNA Sequence: More Than AGCU

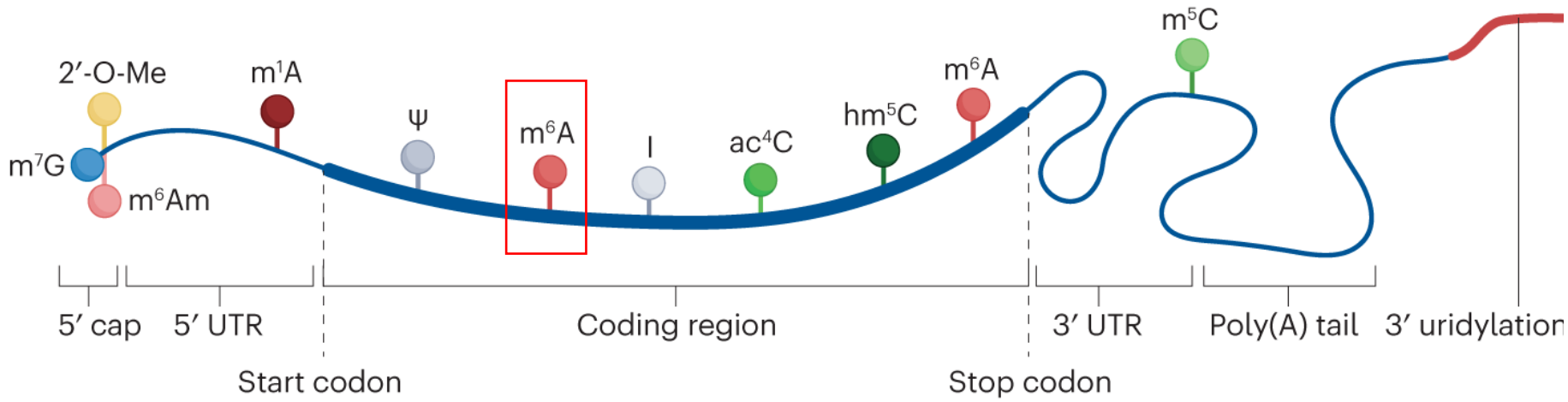


Modifications Impart Function Across RNA Types



Cui, et al, *Nature*, 2022

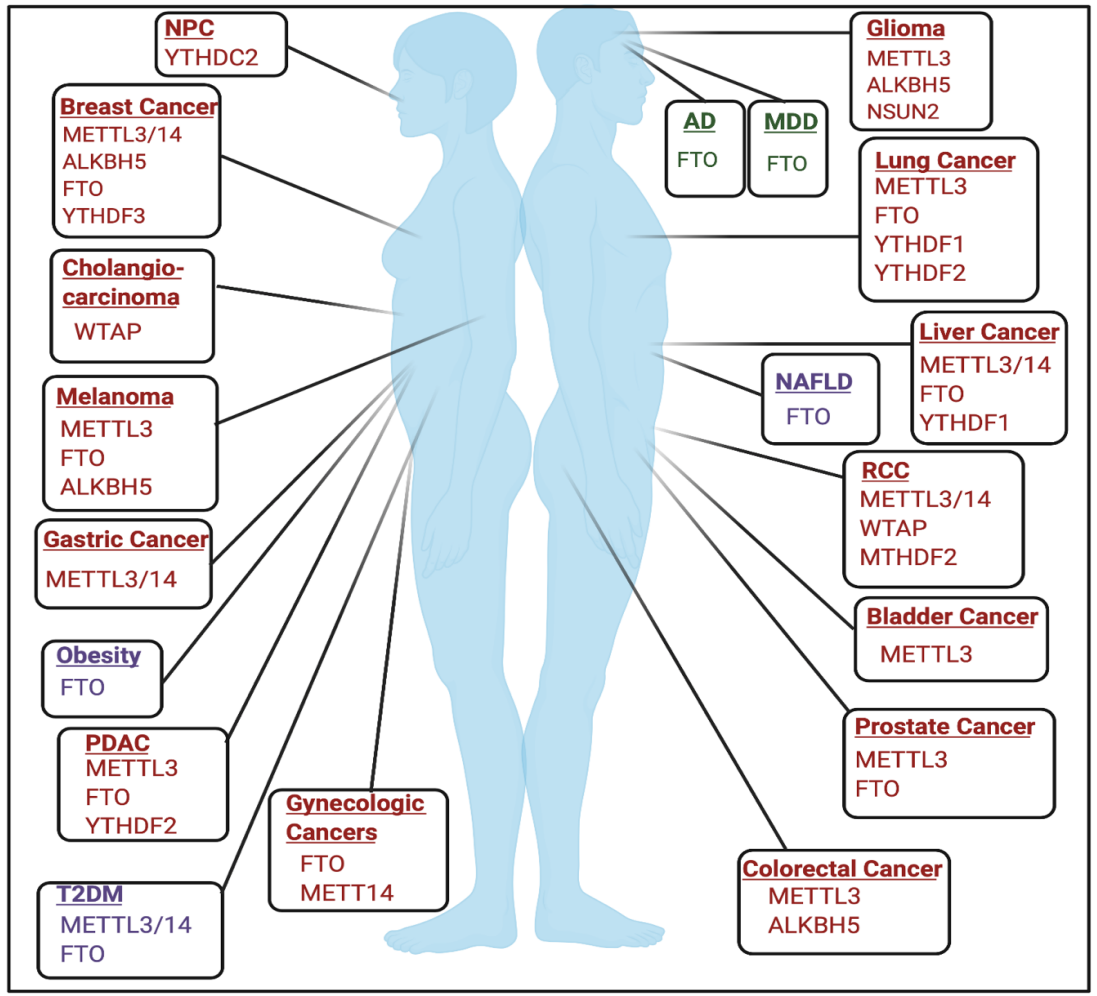
Base Modifications on mRNA



- 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



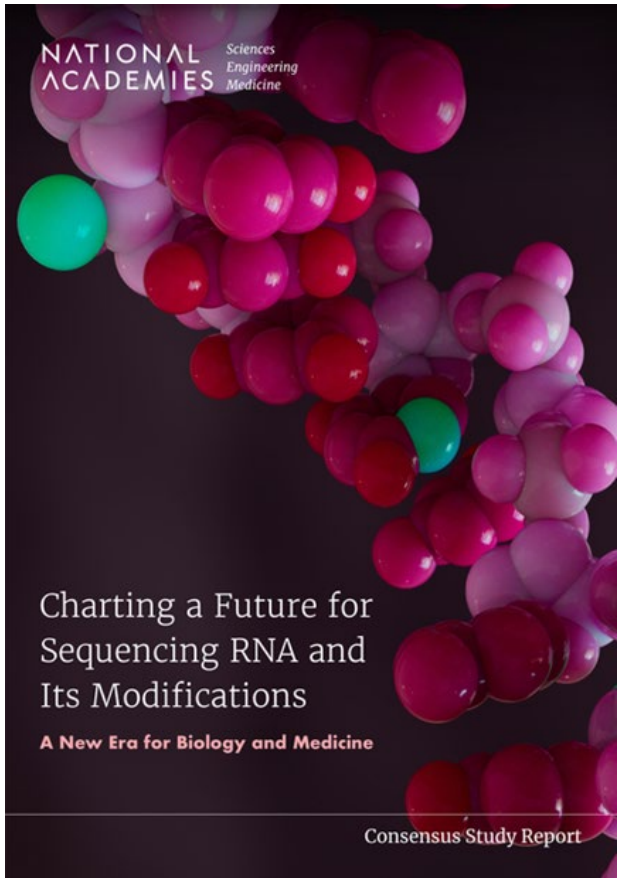
Wilkinson, et al, *IJMS*, 2021

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

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

RNA Sequencing Planning Activities



- NIEHS and NHGRI along with Warren Alpert Foundation commissioned the NASEM Consensus Report
- NASEM recruited leading RNA scientists to review the state of the science with regard to direct RNA sequencing efforts
- The Report highlighted current limitations and set forth a 15 year plan to overcome these identified limitations

Major Limitations in RNA Analysis

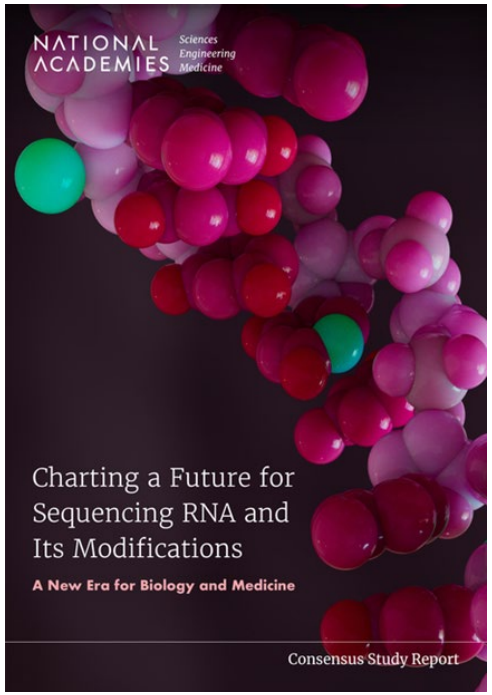
"RNA science stands at a critical crossroads"

Technology

- Current technologies either sequence RNA indirectly as cDNA or directly with limited accuracy
- Nanopore, LC-MS/MS, Enzymatic approaches currently being developed
- 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



The RNomics Program - Goal

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

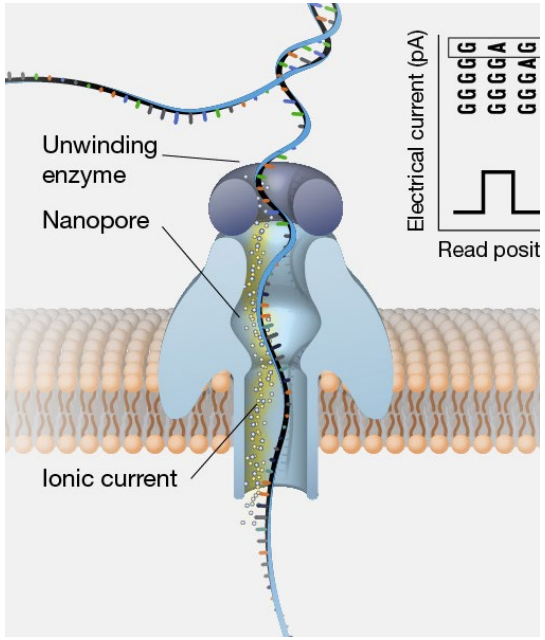
- **Transformative technologies** that enable full sequencing of RNA
- Tools to understand the **functional role of RNA modifications**
- **Standards, and data resources** for modification-inclusive RNA sequencing
- First-of-their-kind **reference datasets and RNA-based clinical biomarkers**

Technology development prioritized before reference dataset generation, providing the scientific community with **well-vetted**, **generalizable** tools to analyze any RNA sample of their interest

Initiative 1: RNA Sequencing Technology

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

Propel development of technologies and computational tools to enable end-to-end sequencing of RNA and its modifications



- Improve sensitivity, specificity, and throughput of current tech (nanopore, mass spec)
- Explore emerging methods for sequencing to enhance capabilities (ZMWGs, nanopore chemistries, etc…)

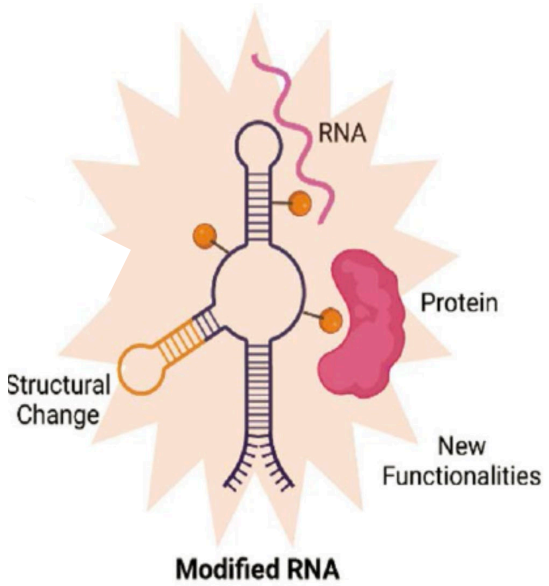
Scope: $14M per year for 5 years (10-12 awards)

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

Initiative 2: RNA Molecular & 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



- Combination of imaging, labelling, sequencing (cDNA-based or direct), and data science methods
- An improved suite of enzymatic tools for RNA analysis

Goal: support tech that generates information from sequencing data or compliments/ adds to sequencing data interpretation

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

Initiative 3: RNomics Molecular Standards

Critical gap: "pressing need for standards in order for the field to progress" -NASEM….. what is the ground - truth?

Production and distribution of synthetic RNA for development, cross-comparison and benchmarking of newly developed sequencers and base-callers

- Deliver first set of standards in Y1 of program
- Use sequencing results and progress to inform further production and distribution
- Availability to both tech developers in program AND wider RNA biology community (partner with NIST for validation and distribution)

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?

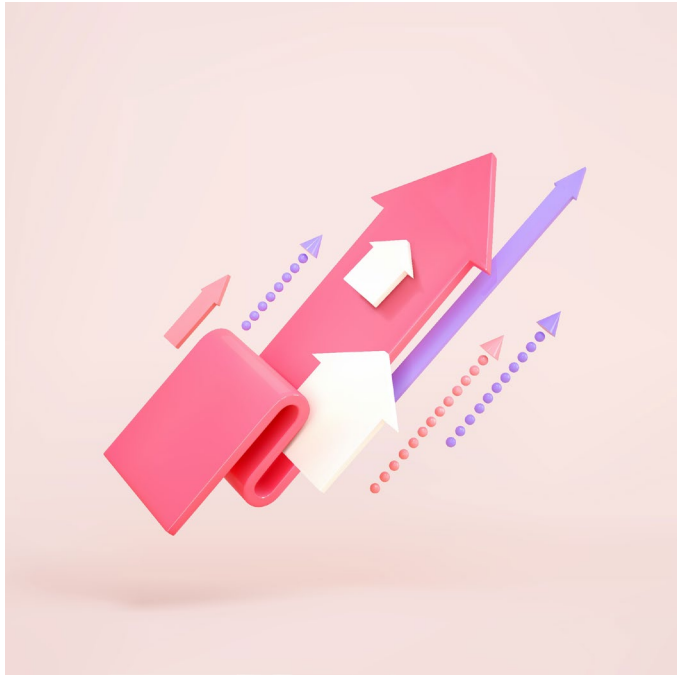
Establishment of a center to manage and harmonize technology development through standardization, benchmarking, and facilitation of data production

- 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

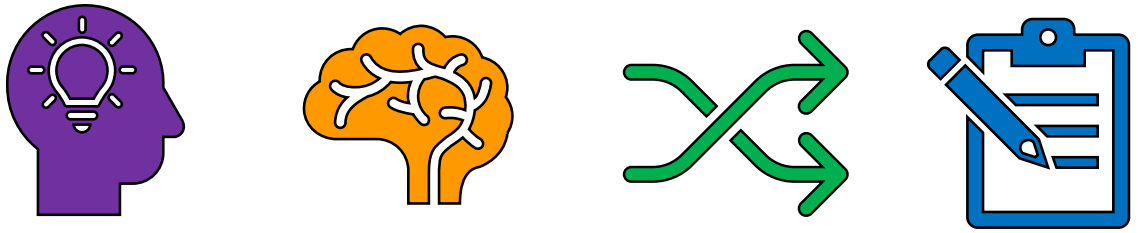
Scope: $2M per year for year 1 ramping up to $7M per year by year 5 (1-2 awards)

Maximizing Impact, Balancing Risk and Reward

- Balance of high-risk, high reward projects with projects further along in development that need refinement, coordination
- Mix of individual tech development projects and collaborative centers
- Milestone based-projects, phased awards
- A supportive, collaborative infrastructure that centralizes the field
- Provide the connective tissue in a field hamstrung by lack of coordination and guidelines
- Milestones/ goals in technology, data, and outreach products



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:

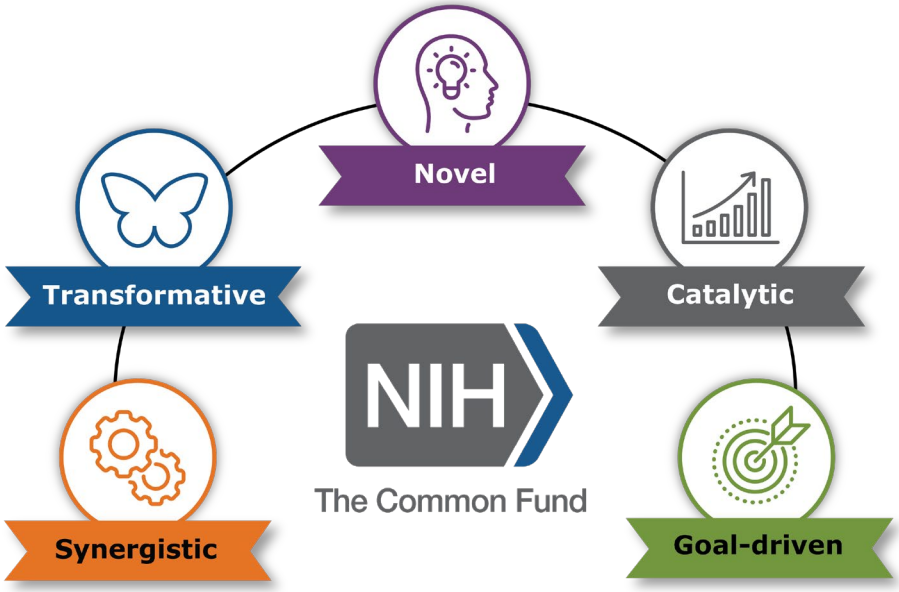
- **Create** a platform for generating comprehensive, tissue-specific RNomes and deciphering the mechanisms and overarching rules of RNA molecular physiology
- **Discover** RNA-based clinical biomarkers for diagnosis, prognosis, and treatment
- **Drive** development of RNA therapeutics and RNA-targeting 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

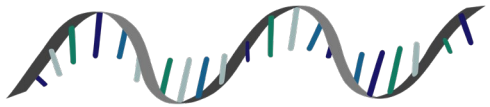
Novel: Uniting genomics, imaging, AI/ML offering NIH a unique opportunity to advance technologies and platforms for clinical, translational and basic research

Trans-NIH RNomics Group

Co-Chairs:
Kyle Walsh, 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
Jessica Elder, NIEHS
Ben Cubert, NHGRI



Stephanie Morris, NHGRI
Max Guo, NIA
Alison Yao, NIA
Stefan Maas, NCI
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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

Council Action: Vote for Approval of the Revised Concept "The RNomics Program"

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