RNA Modifications Driving Oncogenesis

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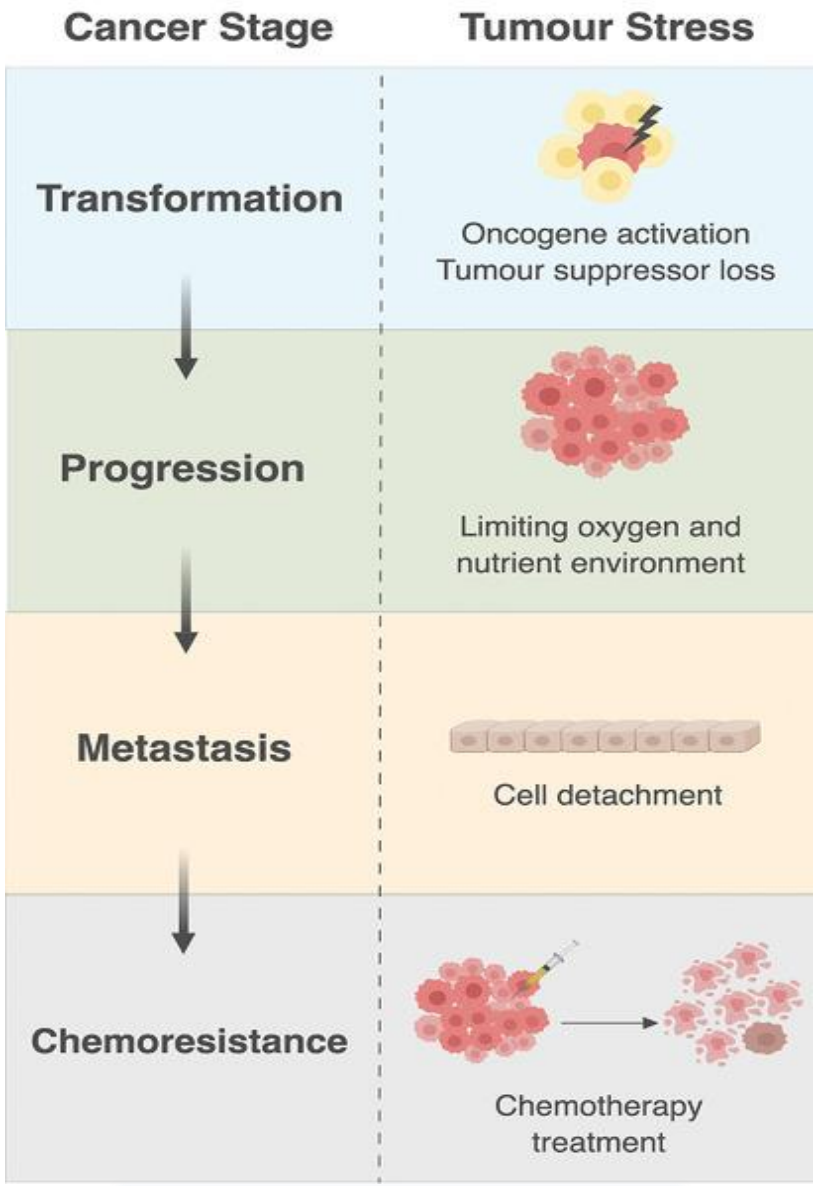
NIH NATIONAL CANCER INSTITUTE

Concept Goal



Madden et al., *Biology of the Cell (2018)*

Mechanistic research on RNA modifications driving oncogenesis through translational reprogramming

Precancerous and tumor cells face various stress situations

↓

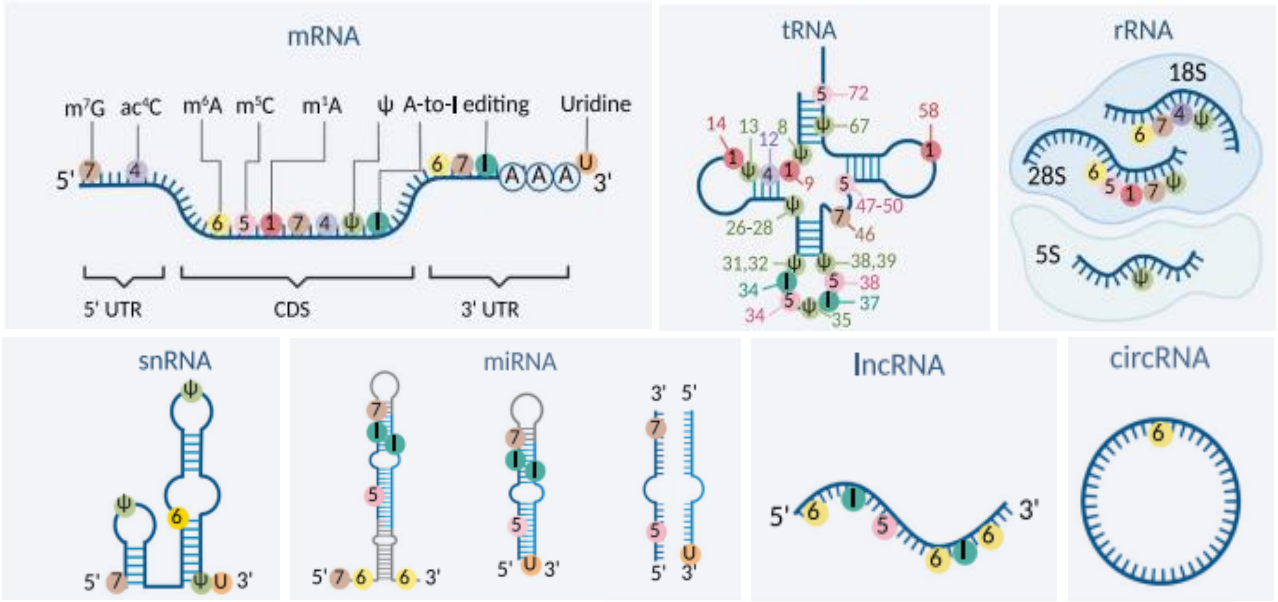
Translational reprogramming enables rapid adaptation to stress

↓

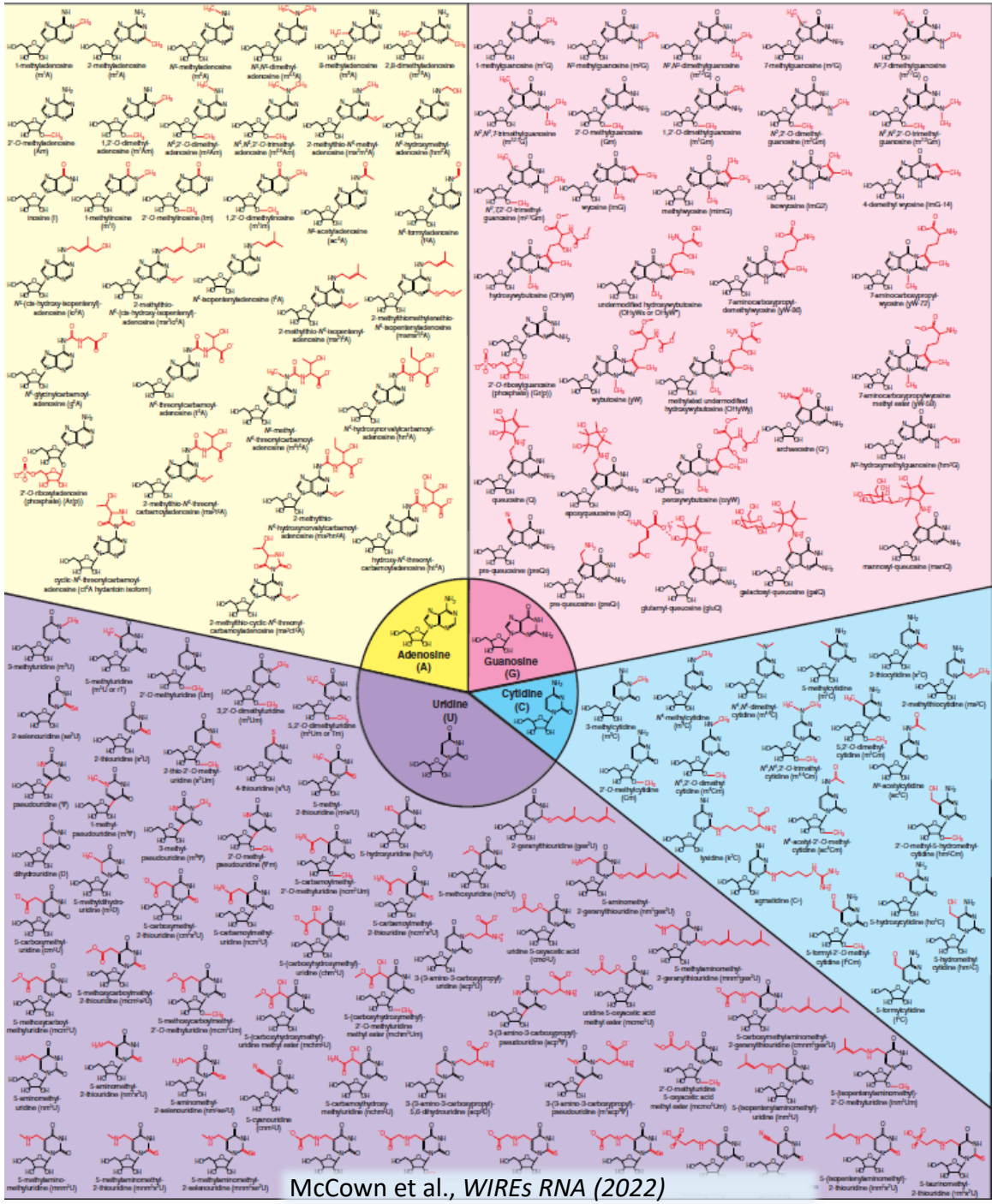
Dynamic RNA modification emerges as key mechanism to reprogram translation

RNA Modifications —

- Most transcripts (tRNA, rRNA, mRNA, ncRNA) are modified
- >170 modification types in eukaryotes (~100 in human) with methylation, deamination, and pseudouridylation most frequent
- Impact on RNA structure, stability, metabolism, transport, localization, translation, and other functional properties



Ma et al., *Signal Transduct Target Ther. (2022)*



McCown et al., *WIREs RNA (2022)*

RNA Modifications —

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— in Cancer Biology

- Aberrant modifications in specific RNAs can drive cancer development and progression
- Modification states can serve as diagnostic, prognostic, or therapeutic markers
- Hyper- or hypoactivity of the machinery introducing, removing, or recognizing modifications can drive cancer development, progression, and adaptation to therapy

Table 1. Overview of genetic alterations within RNA modifier protein coding genes

(only displaying partial list; see publication for full table)

Gene	RNA modification	Type	RNA target	Genomic alteration	Cancer type (frequency %)
HAKAI	m^6A	Writer	mRNA	Mutations	UCEC[b] (3.87)
KIAA1429 (VIRMA)	m^6A	Writer	mRNA	Amplification	BLCA (6.33), BRCA (9.41), PRAD (8.1), LIHC (7.26), OV (6.51)
METTL14	m^6A	Writer	mRNA	Mutations	UCEC (4.16)
METTL3	m^6A	Writer	mRNA, ncRNA	Mutations	BLCA (4.38)
ALKBH5	m^6A	Eraser	mRNA	Amplification	SARC (8.63)
IGF2BP2	m^6A	Reader	mRNA	Amplification	LSCC (33.86), OV (17.98), CSCC (13.8), HNSC (13.77)
NPM1	m^6A, 2-O-M	Regulator, writer	mRNA, tRNA, snRNA, rRNA	Amplification	KIRC (6.85)
				Mutations	AML (27)
RRP8	m^1A	Writer	rRNA	Mutations	UCEC (5.29)
TRMT10C	m^1A	Writer	mt-tRNA	Amplification	LSCC (6.37), CSCC (4.71)
NSUN1 (NOP2)	m^5C	Writer	rRNA	Amplification	OV (5.65), BLGG (4.86)
				Mutations	SKCM (5.18)
NSUN2 (TRM4)	m^5C	Writer	mRNA, tRNA	Amplification	LSCC (11.91), LUAD (9.19), BLCA (7.79), OV (6.85), CSCC (4.78)
ADAR1	A-I	Writer	mRNA, tRNA, miRNA	Amplification	LIHC (10.48), LUAD (8.66), BRCA (8.21), BLCA (4.14), OVC (3.94)
				Mutations	SKCM (4.05), UCEC (5.86)
DKC1	Ψ	Writer	mRNA	Mutations	UCEC (4.73)
CMTR2	2-O-M	Writer	mRNA, snRNA	Mutations	UCEC (6.05), LUAD (5.48), SKCM (5.63)
TRIT1	i6A	Writer	tRNA	Amplification	OV (8.22), BLCA (6.33)
NUDT16	$m^7Gpp(pN)$	Eraser	mRNA	Amplification	LSCC (6.37), CSCC (5.72)
ALKBH8	mchm5U	Writer	tRNA	mutations	UCEC (3.78)
TRMT12 (TYW2)	o2yW	Writer	tRNA	Amplification	OV (25.68), BRCA (12.36), LIHC (10.75), STAD (7.73), UCEC (4.16), BLCA (5.6), PRAD (7.49), HNSC (7.27), LUAD (5.48)

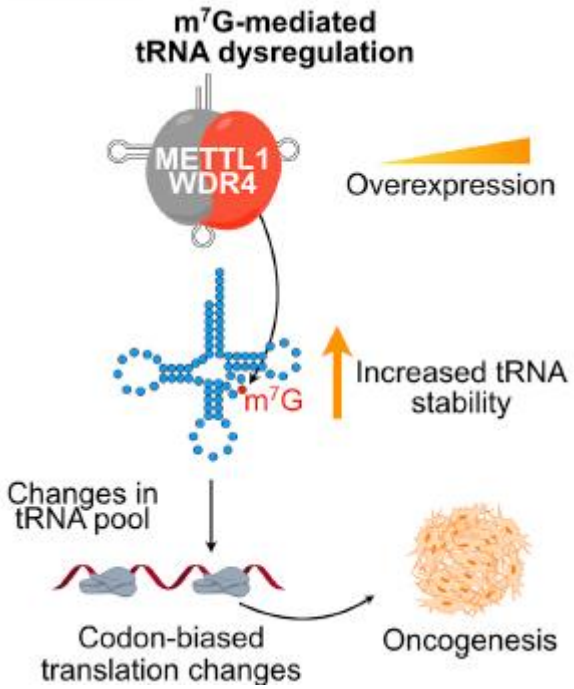
cBioPortal for Cancer Genomics based on TCGA PanCancer Atlas Studies (10,967 samples). Cancer type and frequencies are listed in tumors with >200 samples available and with the frequency >3.75%.

Orsolic et al., *Trends in Genetics (2023)*

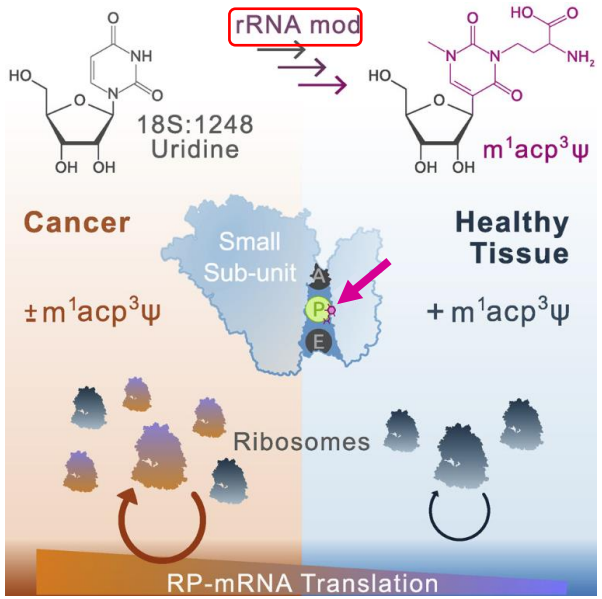
RNA Modifications Drive Translational Reprogramming in Cancer

tRNA
m^7G

GBM, Liposarcoma

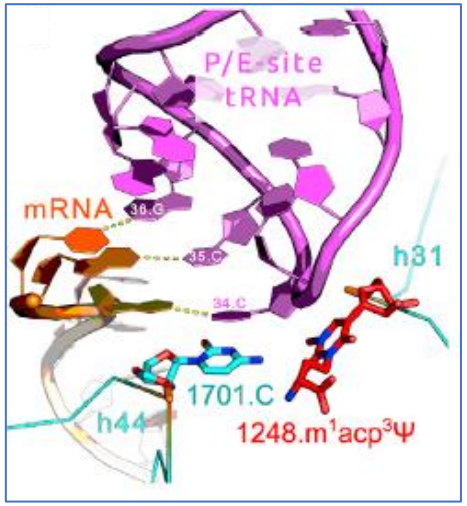


Orellana et al., *Mol Cell*, Aug 2021
Dai et al., *Mol Cell*, Aug 2021



rRNA
$m^1acp^3\psi$

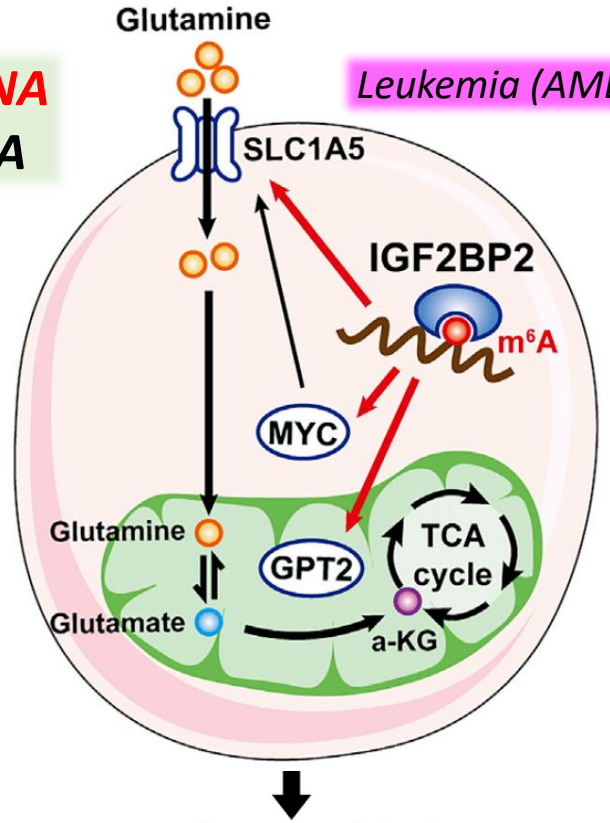
Colon Cancer



Babaian et al.,
Cell Reports,
May 2020

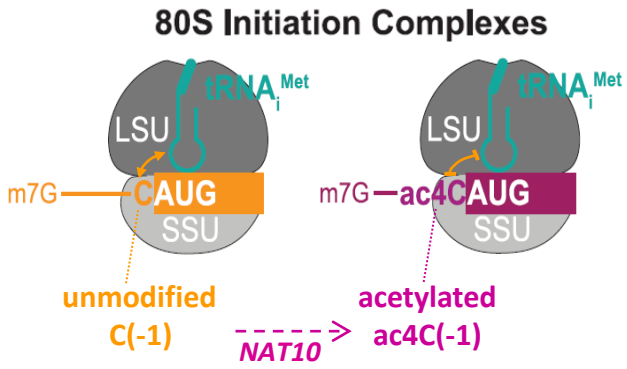
mRNA
m^6A

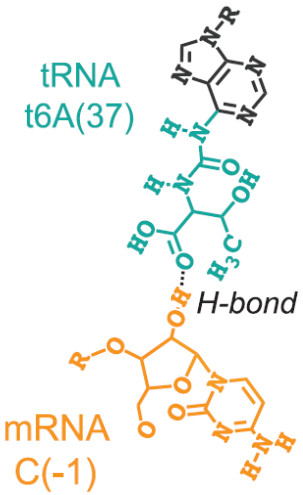
Leukemia (AML)



Weng et al., *Cancer Cell*, Dec 2022

Fundamental Questions and Gaps





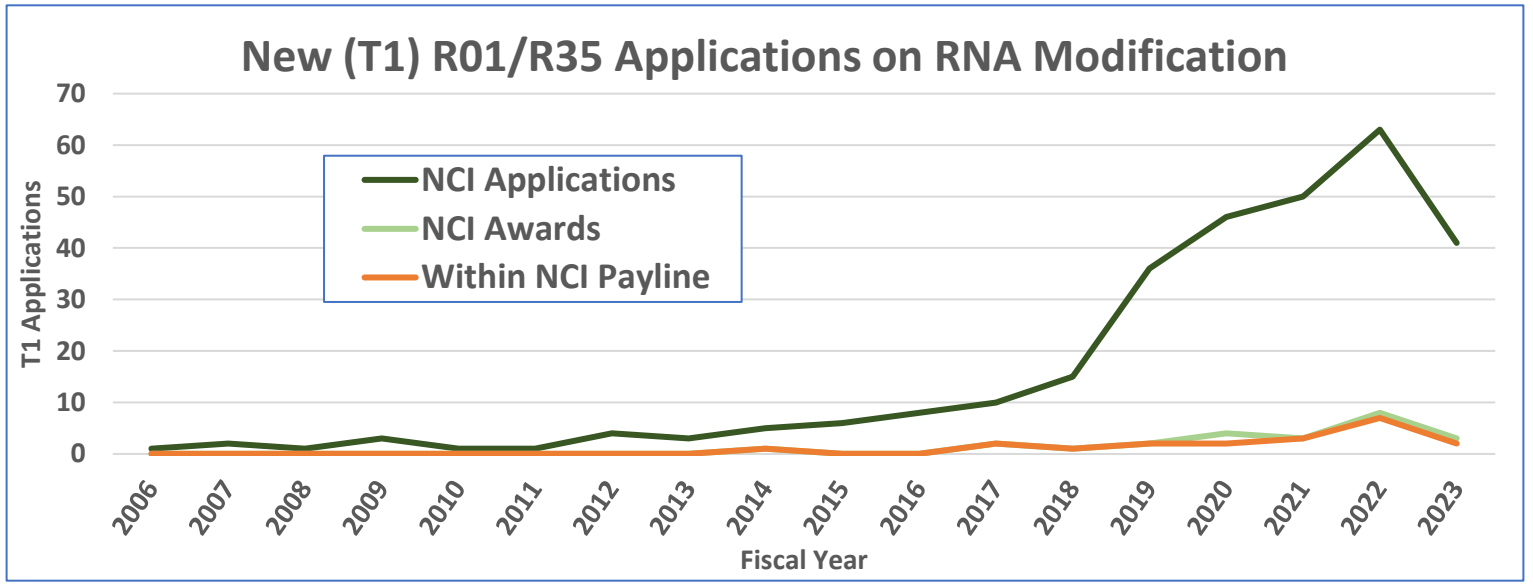
Arango et al., *Mol Cell*, Aug 2022

- How do different m/r/tRNA modifications lead to selective translation during oncogenesis?
- How do precancerous and tumor cells use dynamic changes in RNA modification to adapt to stress?
- How do RNA modifications contribute to ribosome heterogeneity in cancer initiation and progression?
- **How do intra- and inter-molecular interactions between different RNA modifications during translation affect oncogenic processes?**
- What are the dynamics of RNA modification levels and loads during oncogenesis?
- Do RNA modification changes in cancer create targetable vulnerabilities?
- What are the roles of RNA modifications in the formation of tRNA fragments?

Recent and Ongoing Activities in Support of and Aligning with the Initiative:

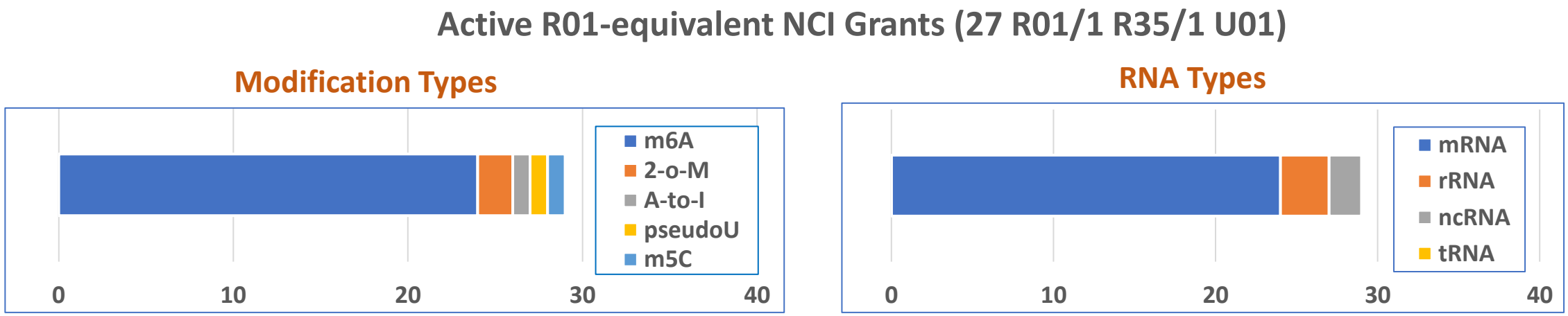
- NCI workshop on '*RNA Epitranscriptomics in Cancer*' (Sept 2020)
- NSF/NHGRI '*RNA tools*' funding opportunity (2023)
- National Academies Consensus Study (2023)
  '*Toward Sequencing and Mapping of RNA Modifications*'
- NOSI for R03/R21 exploratory and technology development projects (2022, 2023)
  '*RNA Modifications in Cancer Biology*' (NOT-CA-22-003/NOT-CA-23-060)

NCI Grant Applications/Awards



iSearch string: {mm=2} +RNA FTO METTL? ALKBH5 YTHDF? YTHDC? modification "RNA methylation" epitranscriptomic~2 m6A "(m6A)" m1A m7G "2-O-M" cm5U ncm5U mam5U mam5s2U m5C 5mC 5hmC "A to I editing" "A-I" "C to U editing" pseudourid "C to U" -"DNA modification"*

The NCI Portfolio of RNA Modification Grants is Small and Narrow



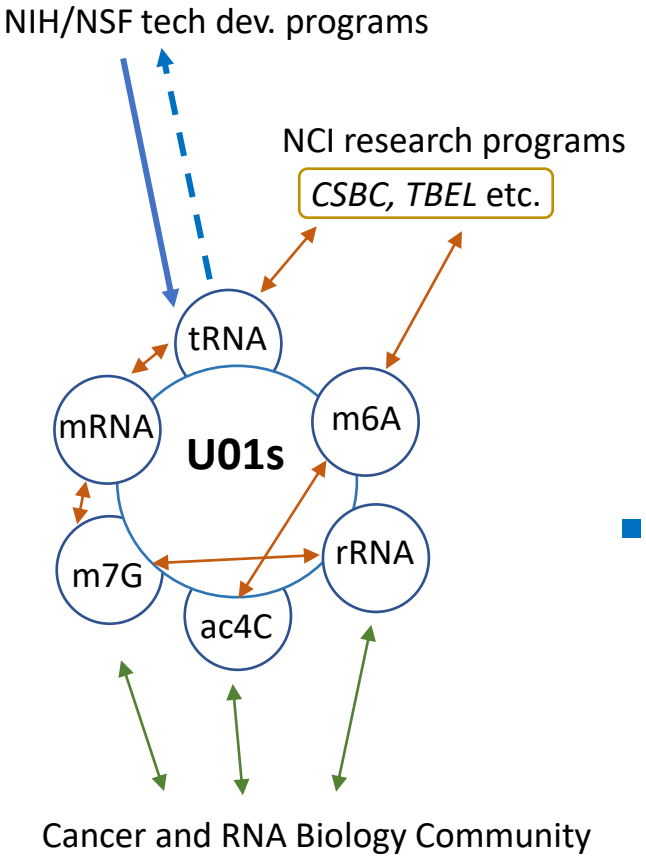
- Of 29 NCI awards, only **3** fully (+ 4 in part) investigate the impact on translational regulation in cancer
- No funded project on tRNA modification
- No grant investigates the interplay between RNA modifications

In comparison: there are **>200** funded R01-type NCI grants on DNA epigenetics, despite the much smaller number of DNA modification types

RNA Modifications Driving Oncogenesis (RNAMoDO) Program Goals:

- Promote mechanistic investigations into t/m/rRNA modifications and their interactions driving oncogenesis through translational reprogramming
- Decrease fragmentation and siloing regarding modification types and RNA species
- Attract top RNA modification researchers to cancer biology and vice versa
- Foster collaborative research on interactions between modifications
- Build on and integrate exploratory research (NOSI) and tech development (NSF/NAS)
- Link to DCB/NCI/NIH programs and advance the goals of the National Cancer Plan (especially: '*Develop Effective Treatments*' (#3) and '*Maximize Data Utility*' (#7))
- Promote outreach and the training of the next generation of researchers (*junior PIs in MPI teams and collaborations, involvement of trainees in projects, meetings and working groups*)

RNA Modifications Driving Oncogenesis (RNAMoDO) U01 RFA



- Multi or single PI **U01 projects** covering essential expertise in m/t/rRNA modifications, translational regulation, and cancer biology
  - Cohesive program that drives mechanistic research in the field
  - Each project investigates the interplay between m/t/rRNA modifications (*otherwise non-responsive*)
  - Collaborative network of interactive projects (including restricted funds for cross-project collaborations)
  - Community approach to sharing of knowledge, tools, data, and problem solving

- **NCI Staff**
  - program management and oversight,
  - maximize collaboration,
  - prioritize program composition,
  - organize annual meeting and working groups,
  - link network with NCI resources and NCI research programs

5 U01 awards, each $650k DC;
$4.9 Mio TC/y set-aside; $24.5 Mio over five years

Program Evaluation Principles

- Level of collaboration and integration within and between U01 grant projects across RNA and modification types.
- Publications of key research data.
- Development and sharing of models, tools, and resources to address challenging questions in this nascent field.
- Effective participation and discussion of progress at annual RNAMoDO investigator meetings and in working groups.
- Participation in the development of new studies with the larger scientific community.
- Active participation in national and international conferences.

Thank you!

BSA sub-committee

Drs. Jennifer Grandis, Michelle Le Beau, Sylvia Plevritis

QUESTIONS?