Pre-Application Webinar

RNA Modifications Driving Oncogenesis

(RNAMoDO), RFA-CA-24-029

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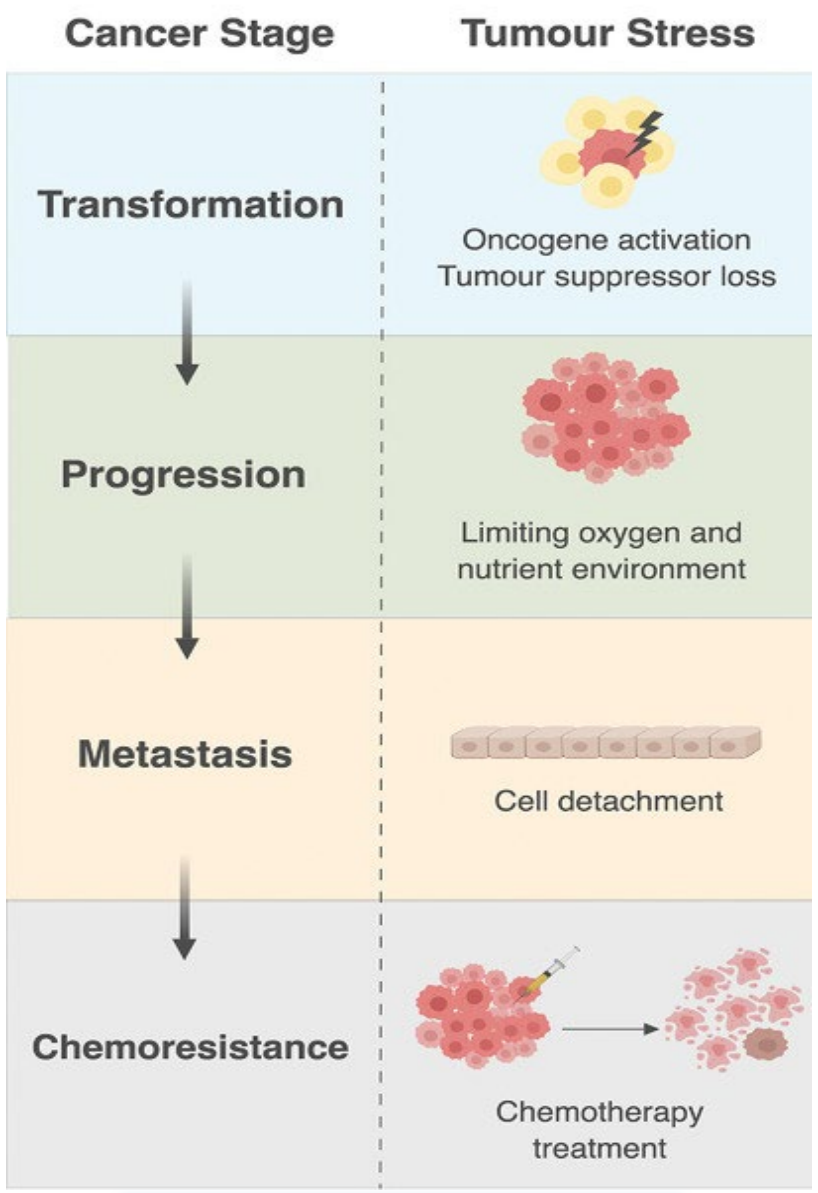
NIH NATIONAL CANCER INSTITUTE



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

Program Goal

Mechanistic research on RNA modifications driving oncogenesis through translational reprogramming

Precancerous and tumor cells face various stress situations

↓

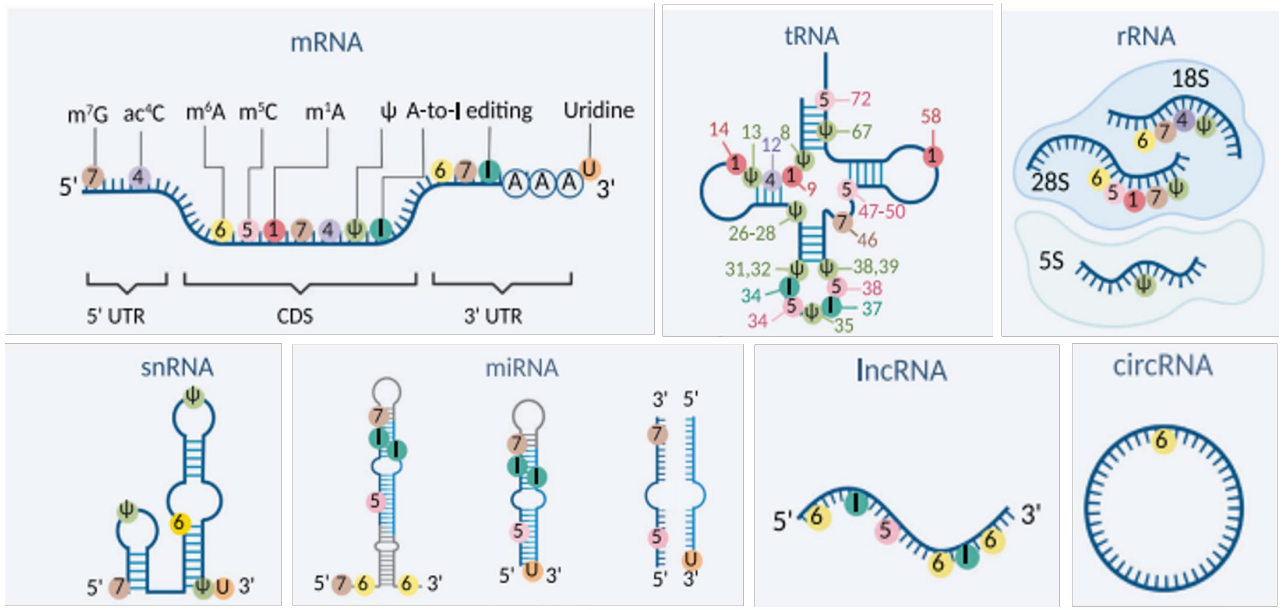
Translational reprogramming enables rapid adaptation to stress

↓

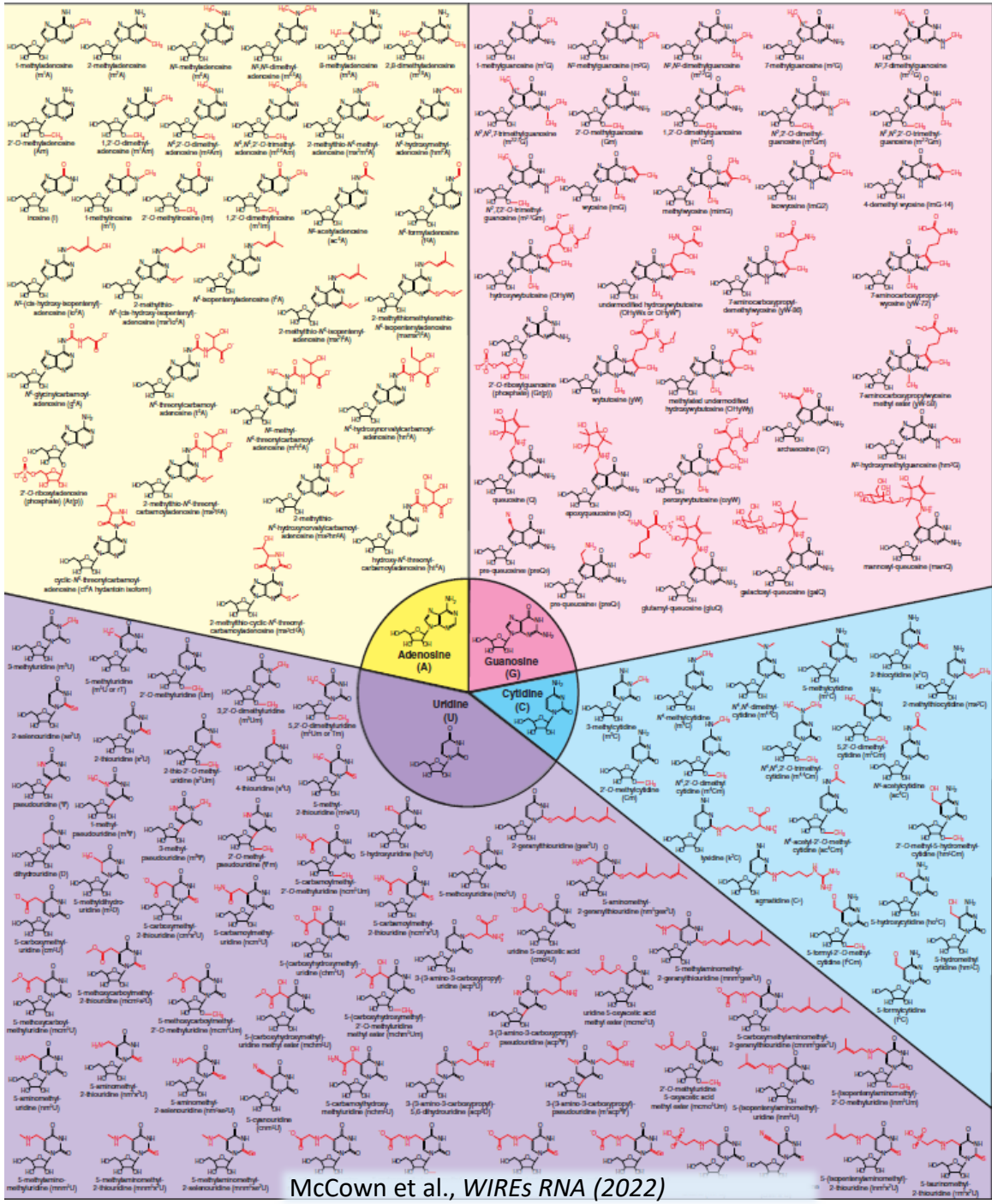
Dynamic RNA modification emerges as key mechanism to reprogram translation

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 —

- Most transcripts (tRNA, rRNA, mRNA, ncRNA) are modified
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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

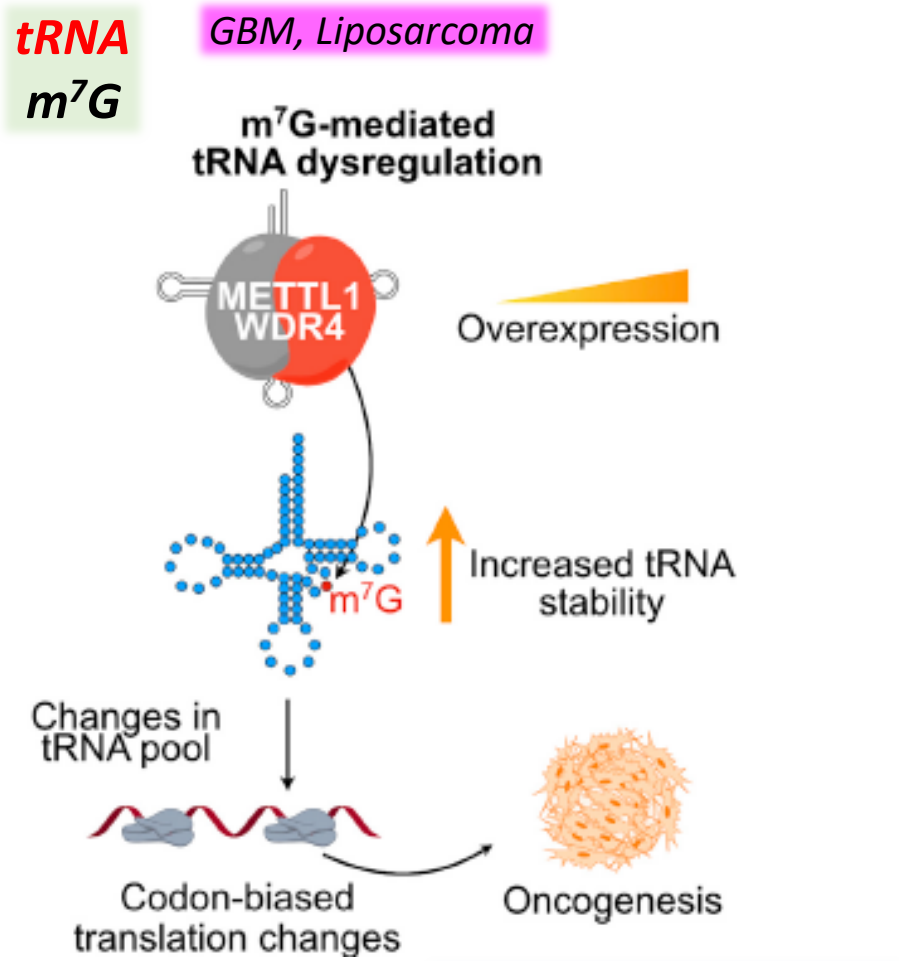
(only displaying partial list; see publication for full table)

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)

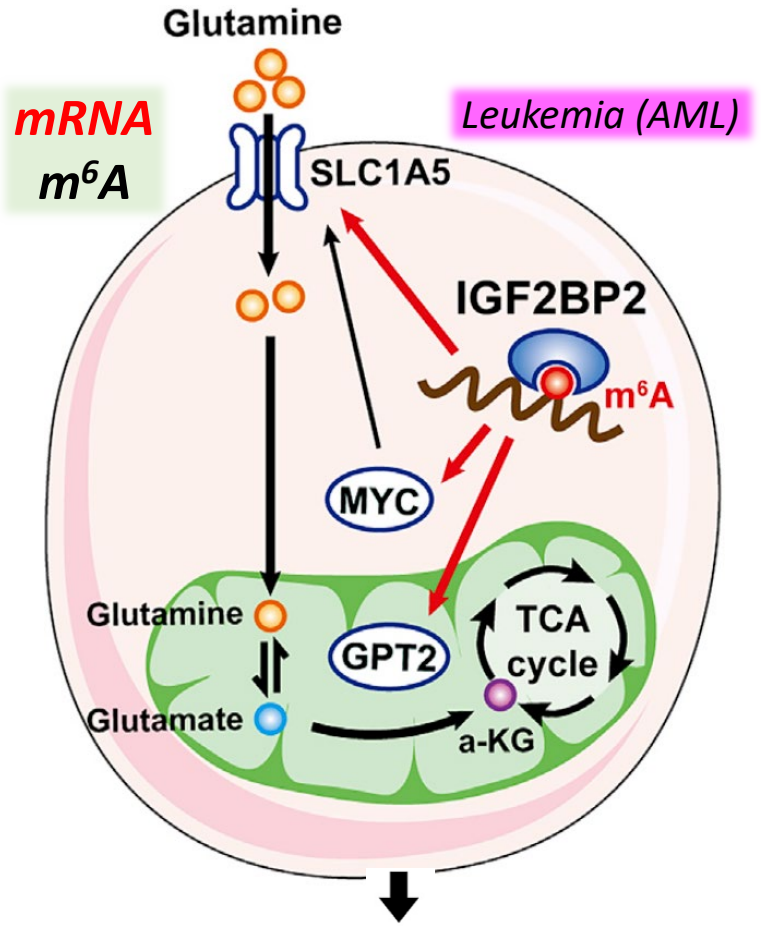
cBioPortal for Cancer Genomics based on TCGA PanCancer Atlas Studies (10,967 samples). Cancer type and frequencies are listed in tumors with >200 samples available and with the frequency >3.75%.

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

RNA Modifications Drive Translational Reprogramming in Cancer

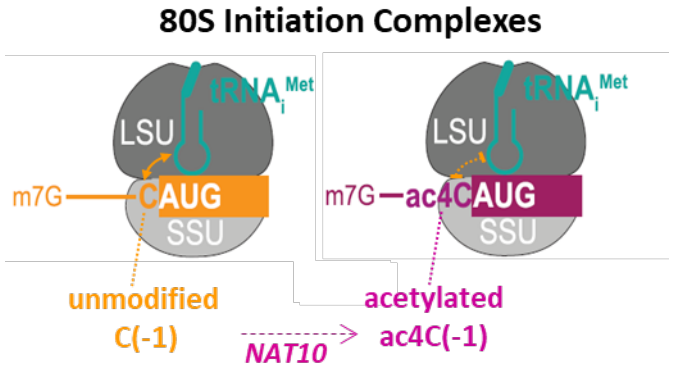


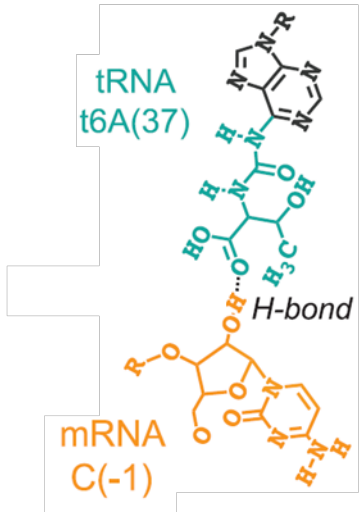
Orellana et al., *Mol Cell*, Aug 2021
Dai et al., *Mol Cell*, Aug 2021



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?

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,
  - 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

RNA Modifications Driving Oncogenesis (RNAMoDO)
Special Review Criteria (1):

Significance:

- How likely will the proposed studies reveal important mechanisms or concepts concerning how RNA modifications and/or their related machineries (writers, erasers, readers) impact translational reprogramming in cancer?

- How well does the application take into account the possible impact of interactions between RNA modifications across modification types and/or RNA species?

RNA Modifications Driving Oncogenesis (RNAMoDO)
Special Review Criteria (2):

Investigator:

- How well does the expertise of the investigative team cover RNA biology and modification, translational regulation and cancer research?

- How well does the application demonstrate that it will foster strong collaboration and interaction between the participating investigators

RNA Modifications Driving Oncogenesis (RNAMoDO)
Special Review Criteria (3):

Approach:

- How likely can the proposed approach further our understanding of the cellular and/or molecular mechanisms by which RNA modifications drive oncogenesis through translational regulation?
- How well does the approach describe a strategy to explore potential interactions between modifications within or across RNA molecules?
- How well presented is the premise for the investigation of interactions between modifications, while taking into account that this area of investigation may not yet be supported by substantial preliminary data?
- How well does the proposed analysis of RNA modifications across modification types and/or RNA species include considerations for data harmonization, integration and sharing?

FAQ:

Submission deadline: Single submission date **Nov 4** for all

(the 'continuing submission' policy does not apply, and no late submissions allowed)

U01 application format: Same components and page limits as R01; single project

Review: Special Emphasis Panel specific for this RFA (→ *please submit LOI by Oct 5*)

Budget: cap of $650,000 DC/y;
set aside 8% DC in years 2-5 for future collaborations;
budget travel to attend annual program meeting

Thank you!

Questions?