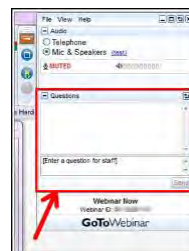


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---

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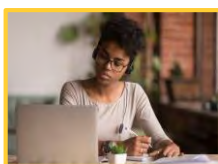
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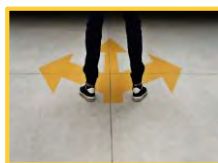
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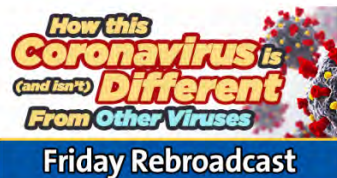
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- How the "novel" coronavirus, SARS-CoV-2 is related to the larger family of coronaviruses
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Tuesday, June 30, 2020 at 2-3pm ET  
Speakers: La'Trese Garrison, American Chemical Society / Thomas Holme, Journal of Chemical Education / Heather Weck, American Association of Chemistry Teachers  
Moderator: Dawn Del Carlo, ACS Division of Chemical Education

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- Ways remote education is advancing STEM education

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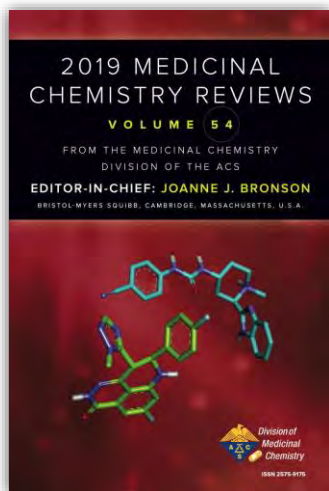
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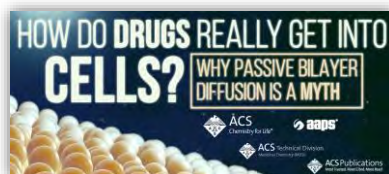
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# Enabling Technologies for Revealing Druggable Paths

## in RNA Biology

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### Enabling Technologies for Revealing Druggable Paths in RNA Biology



**Amanda Garner**  
Associate Professor, College of Pharmacy, Department of Medicinal Chemistry, University of Michigan



**Matt Disney**  
Full Professor, Department of Chemistry and Department of Neuroscience, The Scripps Research Institute

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## Enabling Technologies for Revealing Druggable Paths in RNA Biology

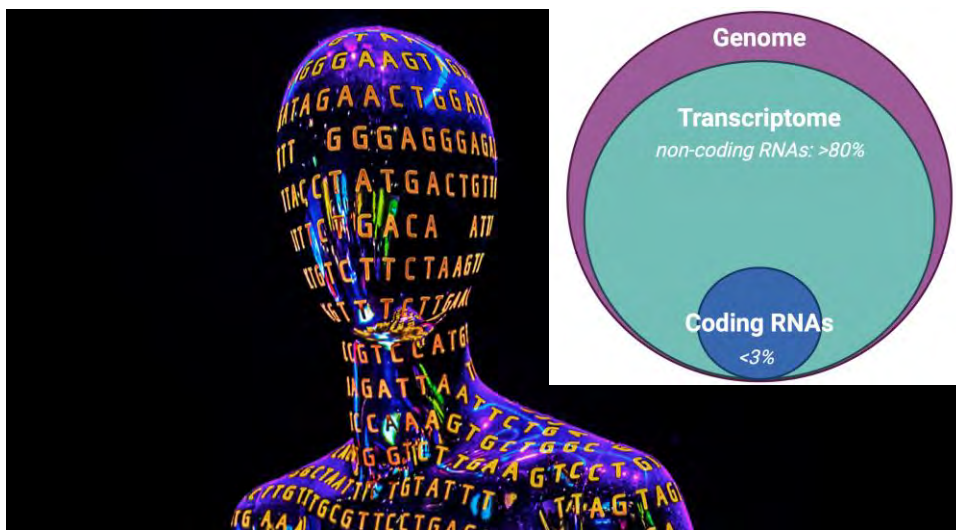
Amanda L. Garner, Ph.D.  
Associate Professor  
Department of Medicinal Chemistry  
University of Michigan

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### The Human Genome Project

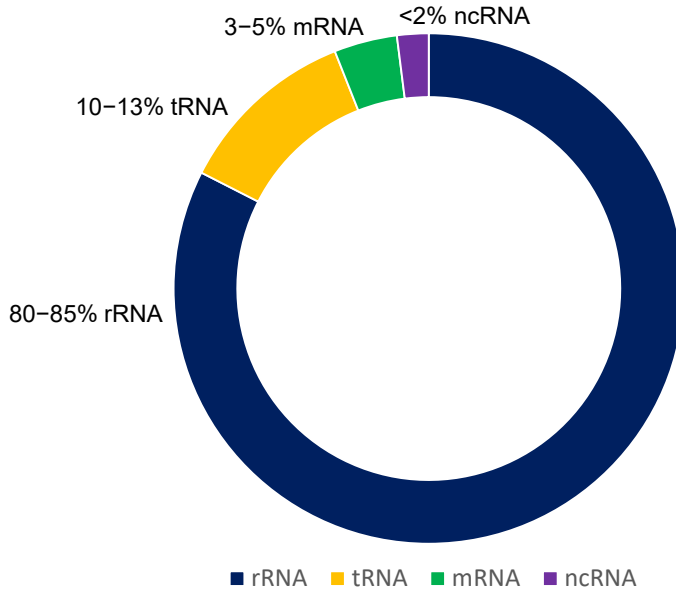
*Sequencing of the human genome promised many new drug targets:*



[https://web.ornl.gov/sci/techresources/Human\\_Genome/project/journals.shtml](https://web.ornl.gov/sci/techresources/Human_Genome/project/journals.shtml)



## The Landscape of Human RNAs



### ncRNAs:

- microRNA
- piRNA
- Y RNA
- snoRNA
- snRNA
- lncRNA



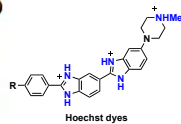
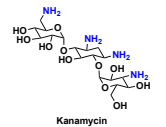
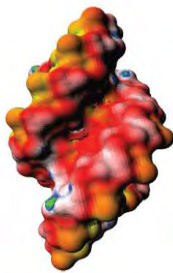
*replication*  
*transcription*  
*splicing*  
*translation*  
*RNA biogenesis*

EMBO Rep. 2001, 2, 986; Nat. Rev. Genet. 2014, 15, 423

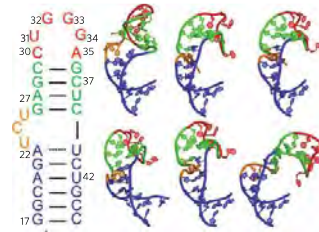


## Challenges of RNA-Targeted Drug Discovery

### Highly electronegative



### Highly dynamic



### RNA abundance

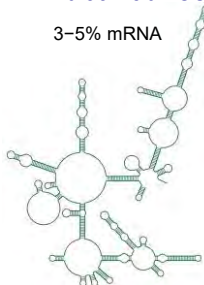
80–85% rRNA



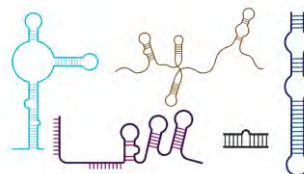
10–13% tRNA



3–5% mRNA



<2% ncRNA

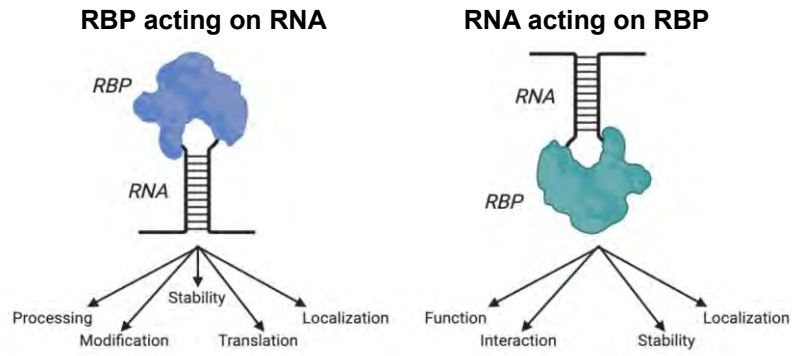


Fut. Med. Chem. 2019, 11, 2487



## Regulation of RNA Biology via RNA-Binding Proteins

*RNA-protein interactions (RPIs) play critical roles in regulating many aspects of RNA biology:*



**>1,500 RBPs have been identified to date and disruption of RPI networks have been linked to many human diseases**

*Nat. Rev. Genet.* **2014**, 15, 829; *Nat. Rev. Mol. Cell Biol.* **2015**, 16, 533; *Trends Cancer* **2017**, 3, 506; *Nat. Rev. Mol. Cell Biol.* **2018**, 19, 327; *Pharmacol. Ther.* **2019**, 203, 107390

### Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



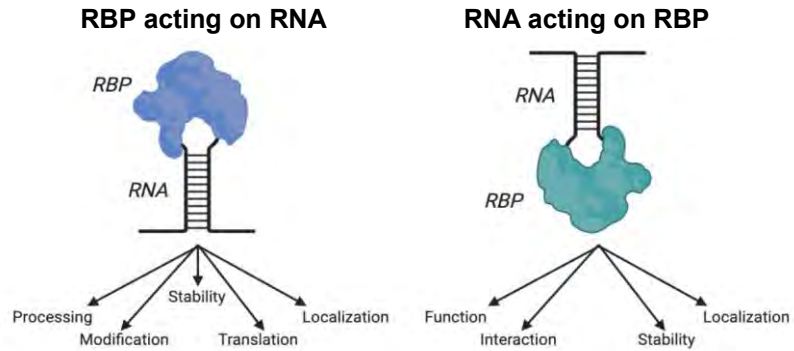
**Which of the following human proteins has been identified as an RNA-binding protein?** (Select all that apply)

- RNase H
- Fragile X Mental Retardation Protein (FMRP)
- GAPDH
- Cyclin A
- None of the above



## Regulation of RNA Biology via RNA-Binding Proteins

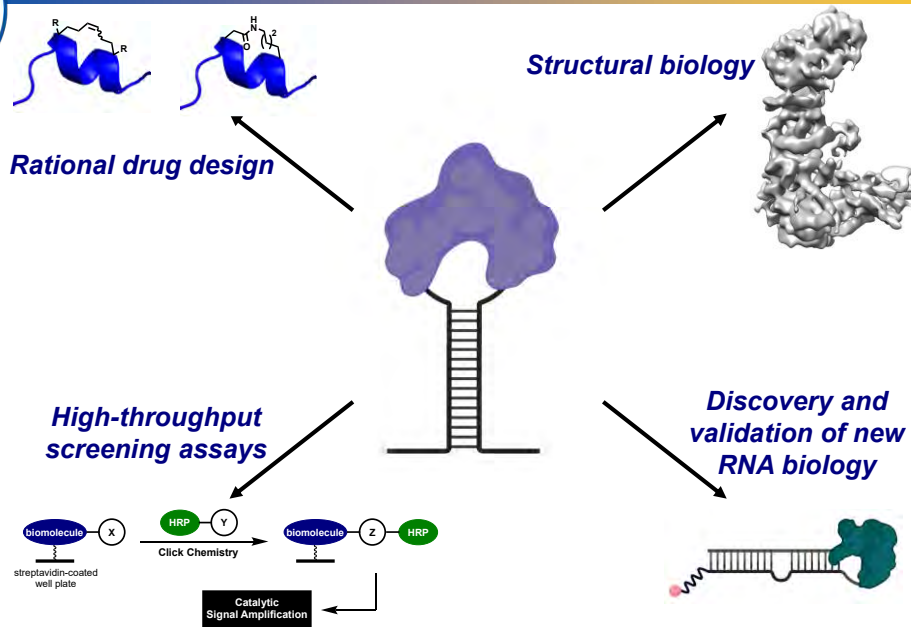
*RNA-protein interactions (RPIs) play critical roles in regulating many aspects of RNA biology:*



**HYPOTHESIS:**  
*Targeting RBPs is an alternative strategy for drugging RNA biology*



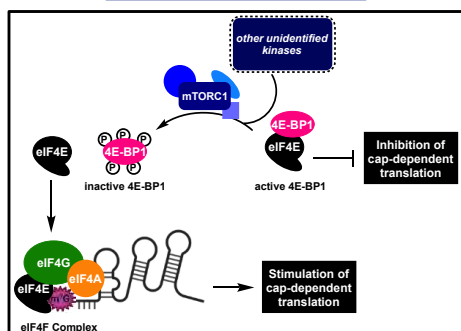
## A Multi-Faceted Approach for Studying RNA-Binding Proteins





## Garner Lab Research in Targeting Translational Control: From Coding to Non-Coding RNA Biology

### Cap-Dependent Translation Initiation



#### Assay Development:

*ACS Comb. Sci.* **2017**, 19, 763; *ChemBioChem* **2019**, 20, 40

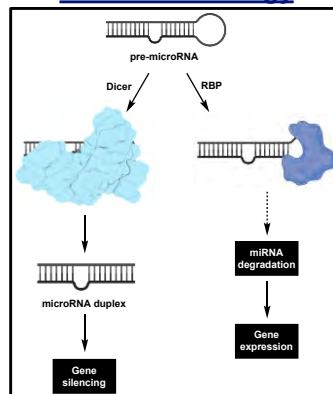
#### eIF4E-Targeted Inhibitors:

*Eur. J. Med. Chem.* **2019**, 166, 339; *J. Med. Chem.* **2019**, 62, 4967; *Org. Biomol. Chem.* **2019**, 17, 6414; *Eur. J. Med. Chem.* **2020**, submitted

#### 4E-BP1 Kinase Discovery:

*Cell Chem. Biol.* **2019**, 26, 980; *FEBS Lett.* **2020**, 594, 1307

### microRNA Biology



#### microRNA Maturation:

*Bioconj. Chem.* **2015**, 26, 19; *Chem. Commun.* **2016**, 52, 8267; *Top. Med. Chem.* **2018**, 27, 79; *SLAS Discovery* **2018**, 23, 47; *ACS Med. Chem. Lett.* **2019**, 10, 816; *Met. Enzymol.* **2019**, 623, 85

#### microRNA-Protein Interactions:

*ACS Med. Chem. Lett.* **2018**, 9, 517; *ACS Comb. Sci.* **2019**, 21, 522; *J. Biol. Chem.* **2019**, 294, 17188; *bioRxiv*



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## A Multi-Faceted Approach for Studying Pre-microRNA-Protein Interactions

**High-throughput  
screening assays**



Dan Lorenz



Sydney Rosenblum

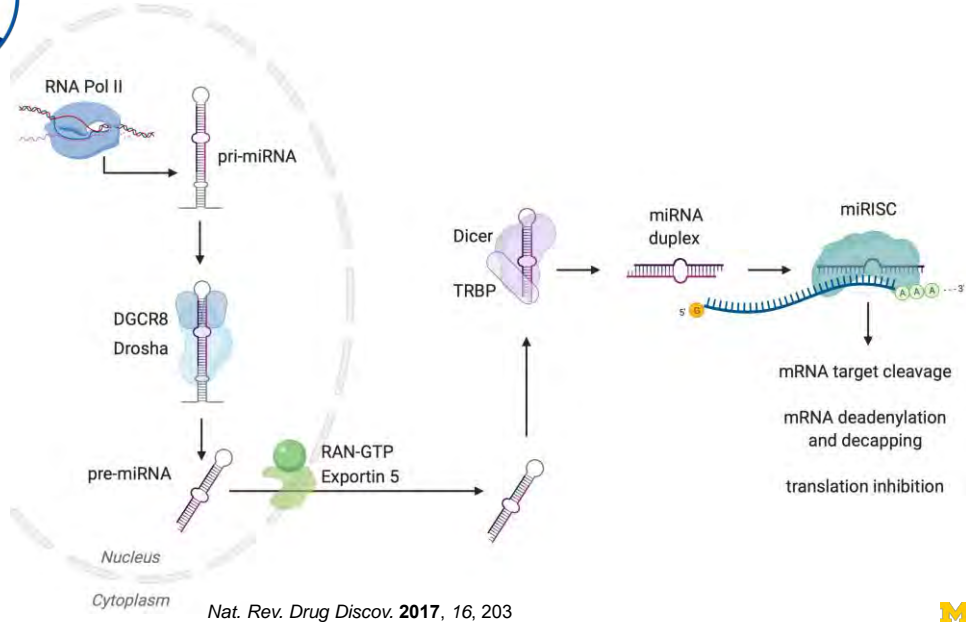
**Validation of new  
RNA-protein  
interactions**



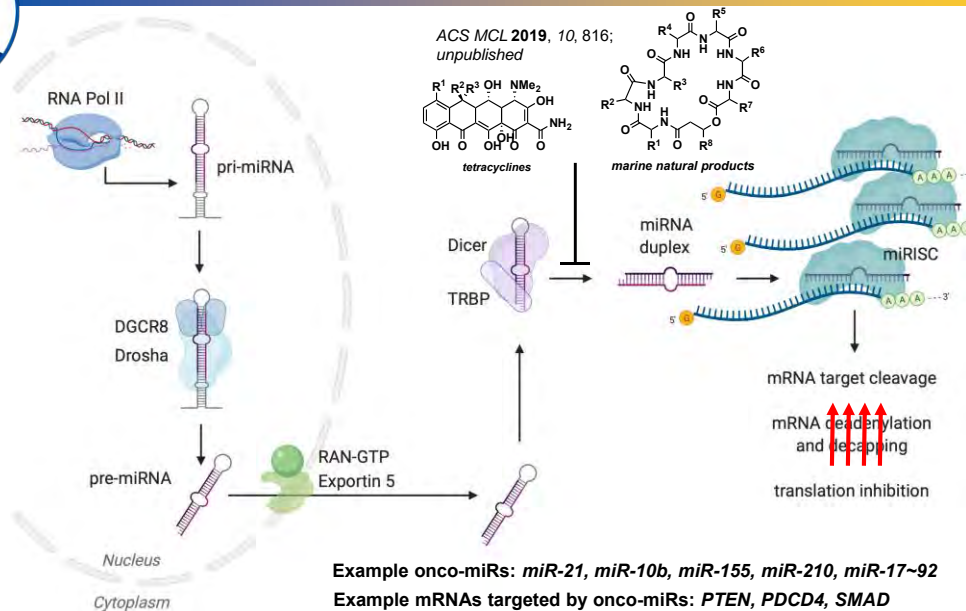
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## microRNA Biogenesis and Activity

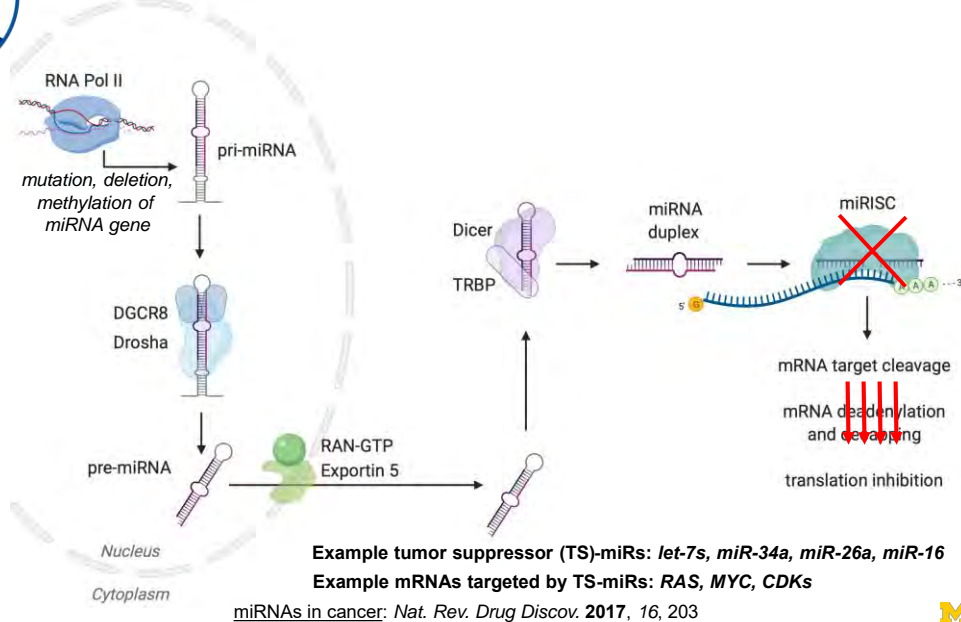


## Aberrant Regulation of microRNAs in Cancer

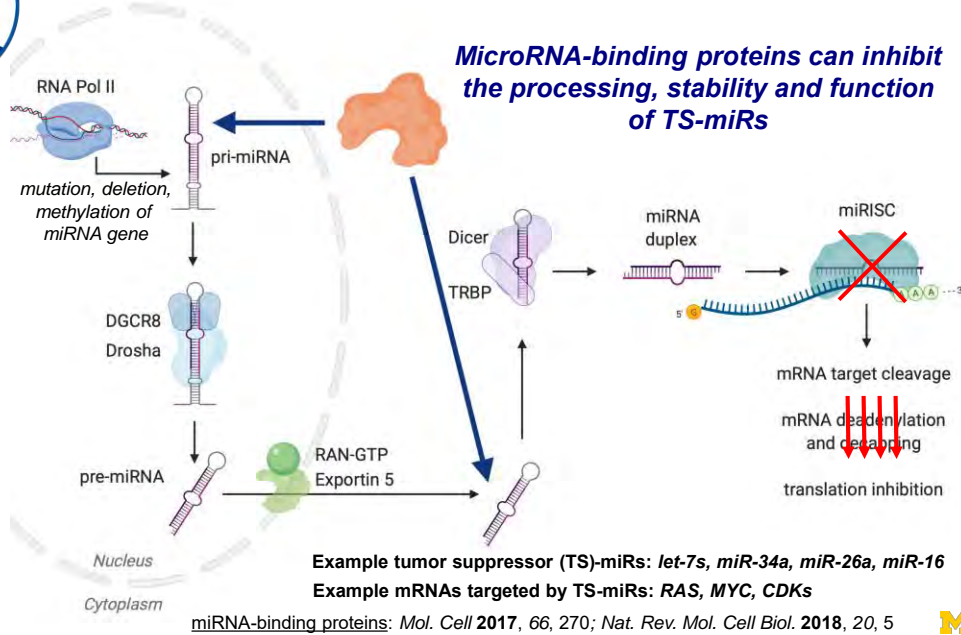




## Aberrant Regulation of microRNAs in Cancer



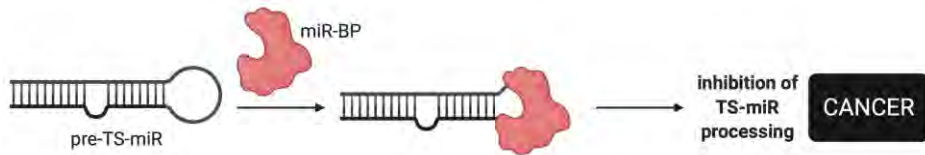
## Aberrant Regulation of microRNAs in Cancer





## Targeting microRNA-Protein Interactions for the Restoration of Tumor Suppressor microRNAs

*miRNA-binding proteins negatively regulate the maturation of TS-miRs:*

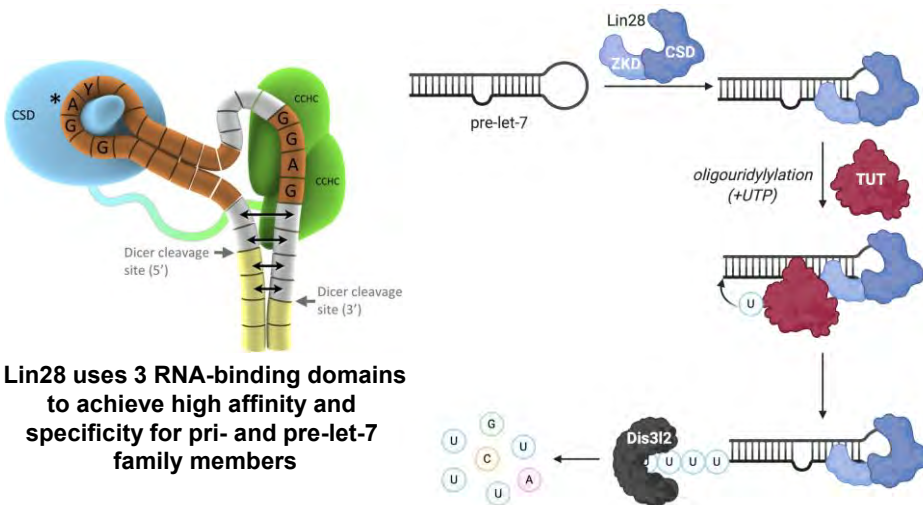


microRNA-binding proteins: *Nat. Rev. Cancer* **2011**, *11*, 644; *Nat. Rev. MCB* **2018**, *20*, 5



## Targeting microRNA-Protein Interactions for the Restoration of Tumor Suppressor microRNAs

*Lin28 is a negative regulator of the TS-miRs pre-let-7:*



let-7-Lin28: *Science* **2008**, *320*, 97; *Cell* **2011**, *147*, 1080; *RNA* **2013**, *19*, 613



## Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



Aside from pre-let-7 family members, how many other RNAs do you think Lin28 interacts with?

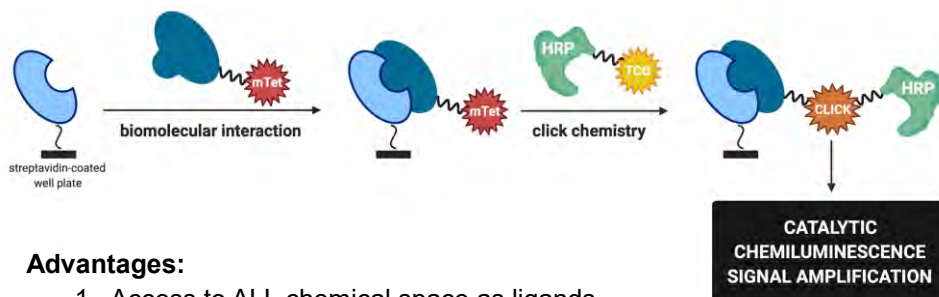
- 0
- 10
- 100
- 500
- Greater than 1,000

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### High-throughput Screening for the Discovery of Pre-let-7–Lin28 Interaction Inhibitors

#### *catalytic Enzyme-Linked Click Chemistry Assay (cat-ELCCA):*



#### Advantages:

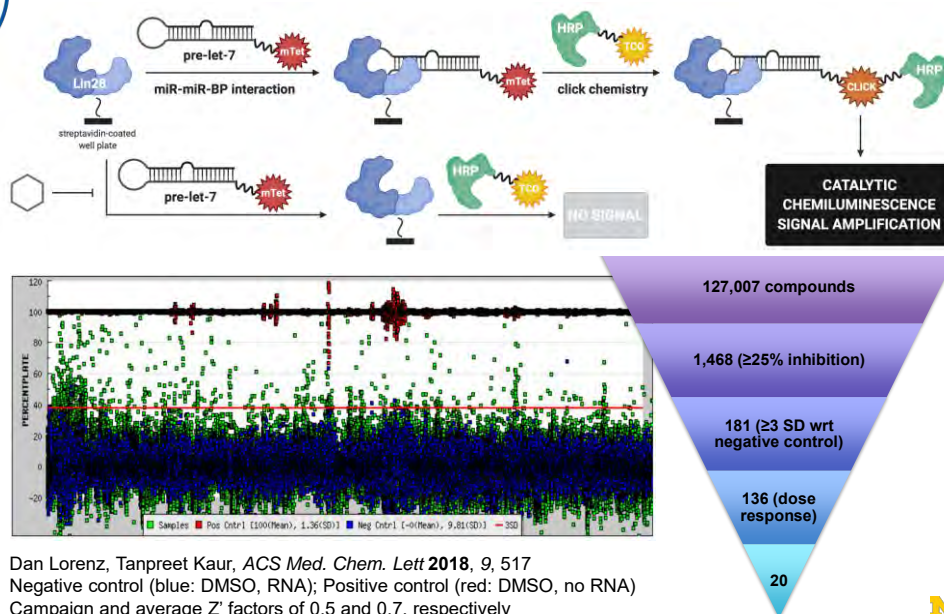
1. Access to ALL chemical space as ligands
2. Not subject to compound interference
3. Highly sensitivity due to catalytic signal amplification
4. All reagents are commercial or readily obtained: user friendly
5. No need for antibodies: widely applicable to any system

Garner and Janda: *Angew. Chem., Int. Ed.* **2010**, *49*, 9630; *Chem. Commun.* **2011**, *47*, 7512

Garner Lab: *Bioconj. Chem.* **2015**, *26*, 19; *Chem. Commun.* **2016**, *52*, 8267; *ACS Comb. Sci.* **2017**, *19*, 763; *Chem. Commun.* **2018**, *54*, 6531

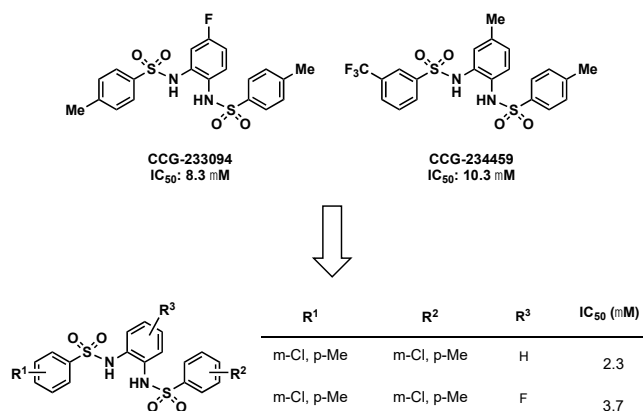


## High-throughput Screening for the Discovery of Pre-let-7-Lin28 Interaction Inhibitors



## High-throughput Screening for the Discovery of Pre-let-7-Lin28 Interaction Inhibitors

*N, N'-(1,2-Phenylene)dibenzenesulfonamides as Lin28 inhibitors:*

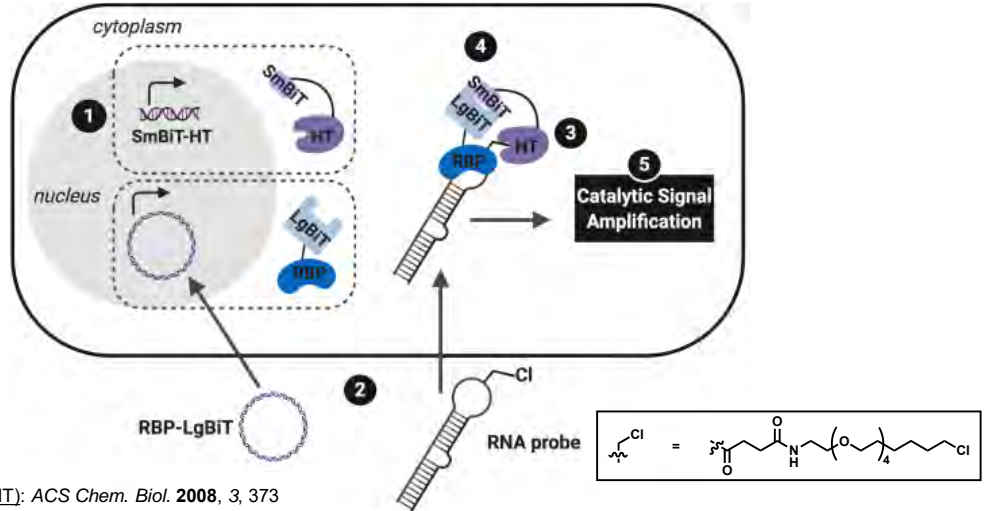


**Lin28A/B-binding ( $K_d \sim 300$  nM) small molecules with inhibitory activity against Lin28-pre-let-7 interactions**



## Live-Cell Assay Development for Detecting microRNA-Protein Interactions

### RNA interaction with Protein-mediated Complementation Assay (RiPCA): assay scheme

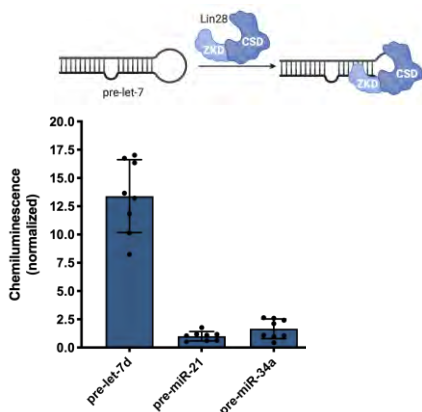


HaloTag (HT): *ACS Chem. Biol.* **2008**, *3*, 373  
 NanoBiT: *ACS Chem. Biol.* **2016**, *11*, 400  
 Sydney Rosenblum, Dan Lorenz, *bioRxiv* 2020



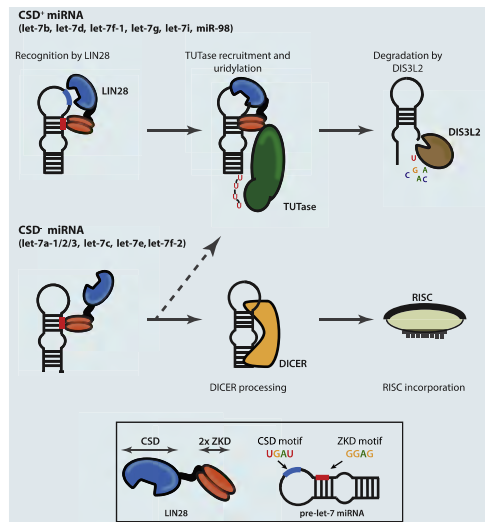
## Live-Cell Assay Development for Detecting microRNA-Protein Interactions

### RNA interaction with Protein-mediated Complementation Assay (RiPCA): specificity of detection



**Selective detection of CSD<sup>+</sup> pre-let-7s binding to Lin28**

Sydney Rosenblum, *bioRxiv* 2020

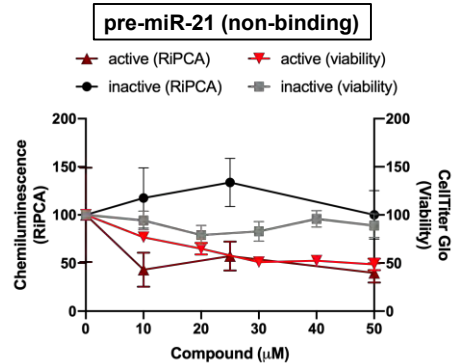
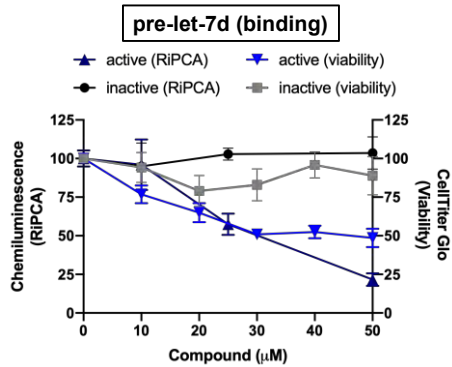
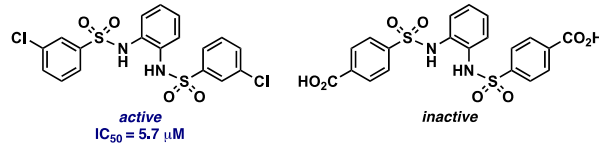


Let-7/Lin28: *Mol. Cell* **2018**, *71*, 271



## Live-Cell Assay Development for Detecting microRNA-Protein Interactions

### RNA interaction with Protein-mediated Complementation Assay (RiPCA): small molecule inhibitors

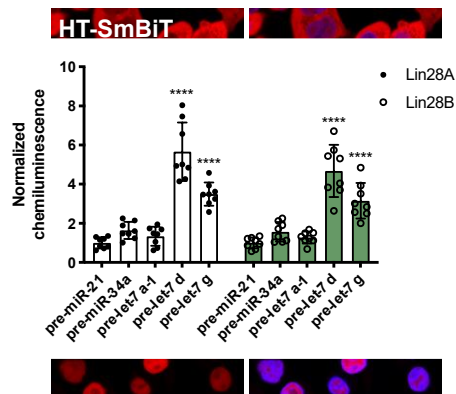
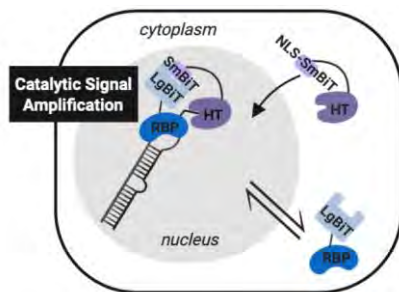


Sydney Rosenblum, unpublished results



## Live-Cell Assay Development for Detecting microRNA-Protein Interactions

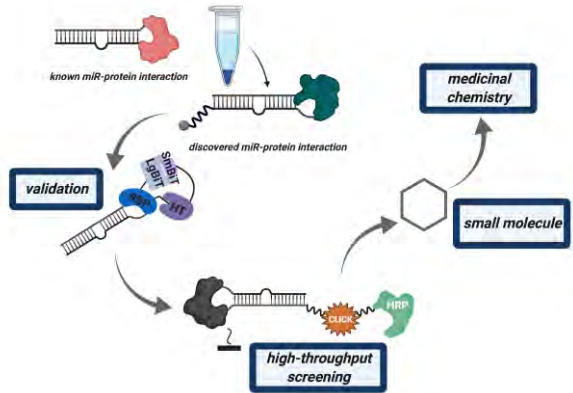
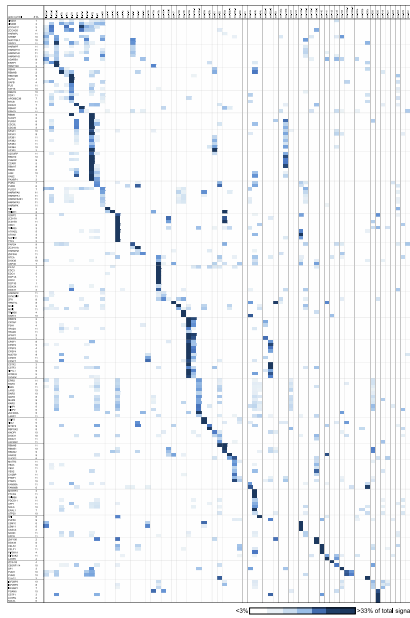
### Nucleus-Specific Live-Cell Assay for Detecting RNA-Protein Interactions: nuc-RiPCA



### Detection of pre-let-7-Lin28 interaction in the cytoplasm and nucleus

Sydney Rosenblum, Dan Lorenz, *bioRxiv* 2020

# A Pipeline for the Investigation of pre-miRNA-Protein Interactions as New Therapeutic Targets



Mol. Cell 2017, 66, 270

MEDICAL CHEMISTRY 41



miR-34a

SART3

A549

ta/CRAPome

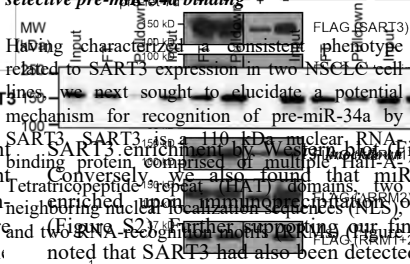
SART3

SART3

miR-34a

...lysisate complex... cells. In both A549 and H1299 parental cell lines, a substantial growth arrest in the G<sub>1</sub> phase was observed upon overexpression of SART3 (Figure 3B). In addition to cell cycle profiles, we analyzed and apoptosis and cellular senescence in these populations. Of 12 models, three showed significant growth arrest in A549 and H1299 parental cell lines. Western blot using an antibody for FLAG detection was found (data not shown). We first examined the N- and C-termini of high SART3 expression levels induces G<sub>1</sub> arrest in HEK293T full-length protein using an antibody via the miR-34a-CDK4/6 axis.

**D** C-terminal RNA recognition motifs give rise to selective pre-miR-34a binding

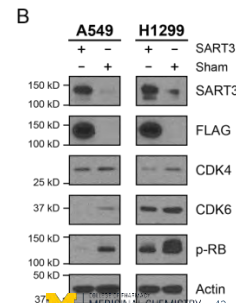


...specific contaminant over twenty different proteins. To identify high affinity proteins that were... as well as the... miR-34a... report, which identified this interaction across... cell lines (5). From these results,

## Validation of SART3 as a Protein and Maturation Regulator

...important for RNA recognition and binding (5,94). The NLS, which has been shown to play a role in pre-miRNA processing, ubiquitin-specific protease (Ubp1) recruitment, protein-protein interactions, and spliceosome recycling activity (69,71-73,77,78). The NLS allows SART3 to function as a nuclear protein, and the RRM1 and RRM2, although differing in sequence, are both thought to contribute to RNA recognition, binding, and splicing activity (72,73). Recognizing that each of these regions of SART3 has the capacity to be involved in miRNA regulation, we asked if any of these domains were crucial for binding to pre-miR-34a. To this end, we generated 3 FLAG constructs to express different variants of SART3, each containing deletions or truncations of one or more domains of the protein (Figure 4A). To assess the binding activity for each construct, we transiently transfected HEK293T cells with each plasmid and subsequently performed pre-miR-34a pull-down experiments as outlined in Figure 1A. Pre-miR-34a binding relative to pre-let-7d was then visualized by Western blot using an antibody for the FLAG epitope tag.

We first compared the N- and C-termini of SART3 to the full-length protein using an empty... We first compared the N- and C-termini of SART3 to the full-length protein using an empty... We first compared the N- and C-termini of SART3 to the full-length protein using an empty...

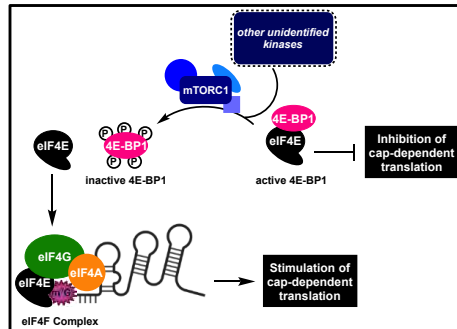


MEDICAL CHEMISTRY 42



## Garner Lab Research in Targeting Translational Control: From Coding to Non-Coding RNA Biology

### Cap-Dependent Translation Initiation

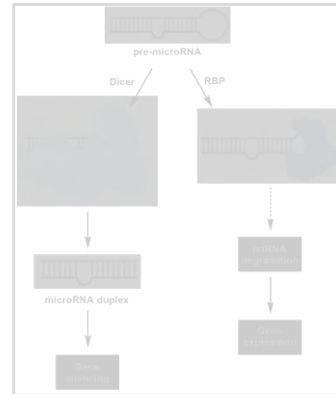


Assay Development:  
*ACS Comb. Sci.* **2017**, *19*, 763; *ChemBioChem* **2019**, *20*, 40

eIF4E-Targeted Inhibitors:  
*Eur. J. Med. Chem.* **2019**, *166*, 339; *J. Med. Chem.* **2019**, *62*, 4967;  
*Org. Biomol. Chem.* **2019**, *17*, 6414; *Eur. J. Med. Chem.* **2020**,  
submitted

4E-BP1 Kinase Discovery:  
*Cell Chem. Biol.* **2019**, *26*, 980; *FEBS Lett.* **2020**, *594*, 1307

### microRNA Biology



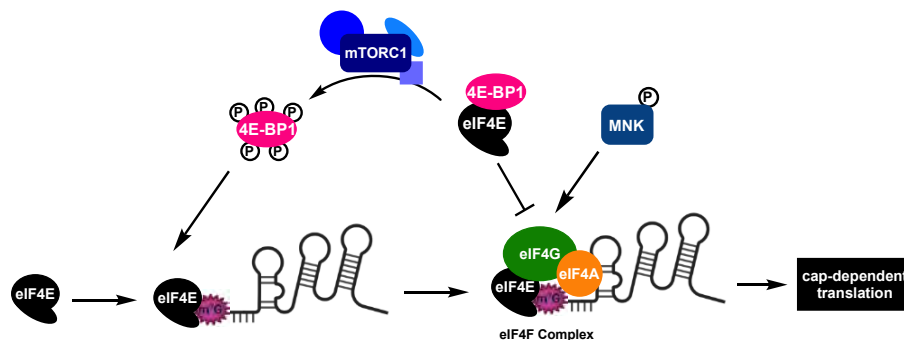
microRNA Maturation:  
*Bioconj. Chem.* **2015**, *26*, 19; *Chem. Commun.* **2016**, *52*, 8267; *Top. Med. Chem.* **2018**, *27*, 79; *SLAS Discovery* **2018**, *23*, 47; *ACS Med. Chem. Lett.* **2019**, *10*, 816; *Met. Enzymol.* **2019**, 623, 85

microRNA-Protein Interactions:  
*ACS Med. Chem. Lett.* **2018**, *9*, 517; *ACS Comb. Sci.* **2019**, *21*, 522; *J. Biol. Chem.* **2019**, *294*, 17188; *bioRxiv*



## eIF4E: An RBP Regulating Cap-Dependent Translation

*eIF4E is a translational oncogene:*



- **Cap-dependent transcripts** encode for **growth factors and oncogenes** (e.g. c-Myc, cyclin Ds, VEGF, ODC)
- **eIF4E** is the **rate-limiting initiation factor** and is **overexpressed in many human cancers** making it a **translational oncogene**

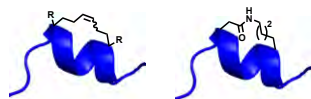
*Nat. Rev. Cancer* **2010**, *10*, 254





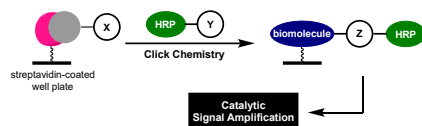
## A Multi-Prong Approach for Targeting eIF4E, an RBP Initiating Cap-Dependent Translation

### 4E-BP1 stapled peptides



*J. Med. Chem.* **2019**, *62*, 4967;  
*Org. Biomol. Chem.* **2019**, *17*, 6414;  
submitted

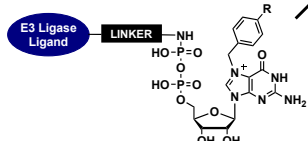
### High-throughput screening



ACS Comb. Sci. **2017**, *19*, 763

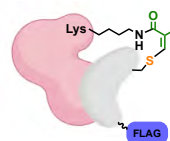
Catalytic  
Signal Amplification

### Cap analogues



*Eur. J. Med. Chem.* **2019**, *166*, 339

### Chemoproteomics



*Cell Chem. Biol.* **2019**, *26*, 980;  
*FEBS Lett.* **2020**, *594*, 1307

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## A Multi-Prong Approach for Targeting eIF4E, an RBP Initiating Cap-Dependent Translation

### 4E-BP1 stapled peptides



*J. Med. Chem.* **2019**, *62*, 4967;  
*Org. Biomol. Chem.* **2019**, *17*, 6414;  
submitted

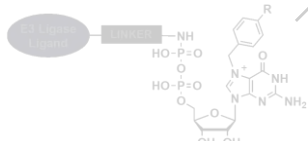
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*Eur. J. Med. Chem.* **2019**, *166*, 339

### Chemoproteomics



*Cell Chem. Biol.* **2019**, *26*, 980;  
*FEBS Lett.* **2020**, *594*, 1307

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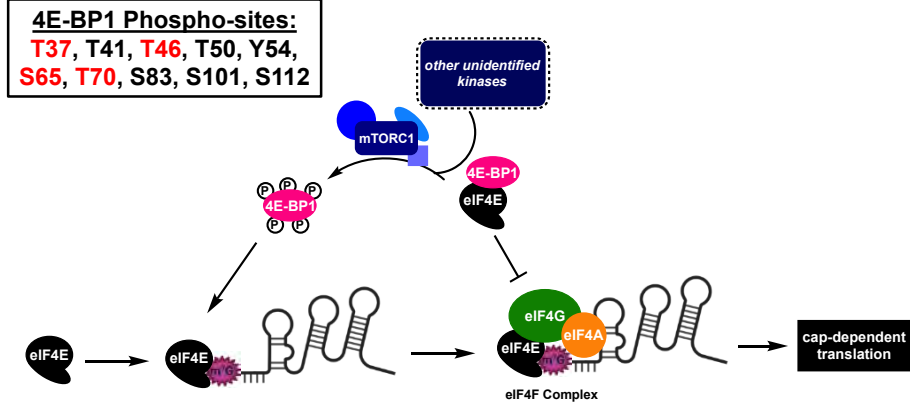


Dylan Mitchell



## 4E-BP1, the Guardian of eIF4E and Cap-Dependent Translation

Regulation of 4E-BP1 through phosphorylation and its complexities:



4E-BP1 phosphorylation and drug resistance: *Cancer Cell* **2010**, 17, 249; *PNAS* **2011**, 108, E699; *Nature* **2012**, 485, 55; *Cancer Res.* **2012**, 72, 6468; *Cell Cycle* **2012**, 11, 594; *Oncogene* **2013**, 33, 1367; *Oncogene* **2014**, 33, 1590; *J. Cell Sci.* **2014**, 127, 788

### Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



**Of the ~140,000 identified human phospho-sites, how many have been annotated to the kinase responsible for the phosphorylation event?**

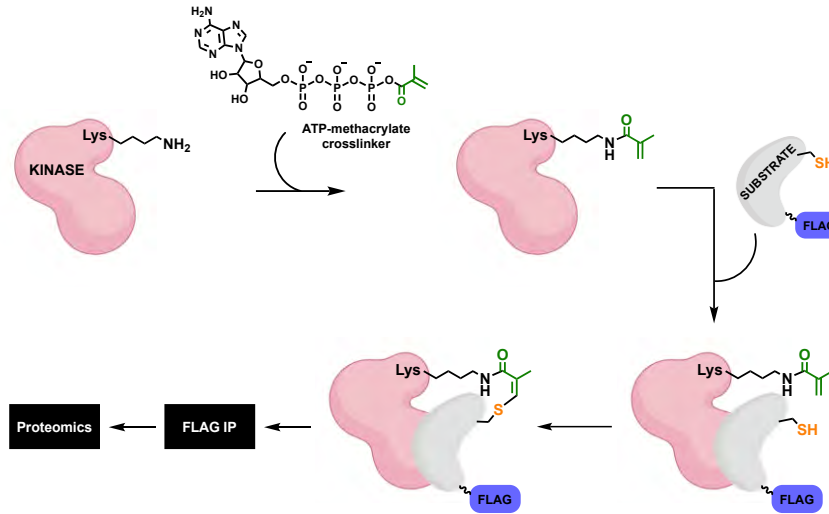
- ~10,000
- ~25,000
- ~50,000
- ~100,000
- ~140,000





# Chemoproteomic Approach to Identify Novel 4E-BP1 Kinases

## Phosphite-Accurate Kinase-Substrate X-linking Assay (PhAXA):



ATP crosslinker probe: *Chem. Biol.* **2014**, 21, 585

Previous generations of this approach: *JACS* **2004**, 126, 9160; *JACS* **2008**, 130, 17568



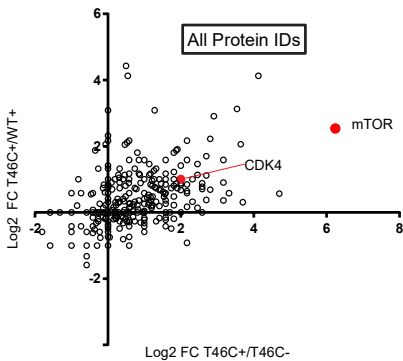
A

## PhAXA to Identify Novel 4E-BP1 Kinases

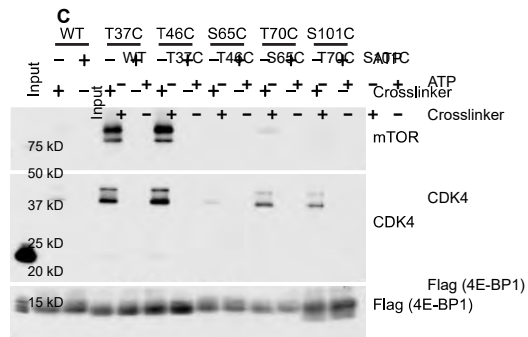
All Kinases Identified

Protein	WT +	WT -	Transfect		Serum Starve		Stimulation		Harvest	
			WT +	T46C -	WT +	T46C -	WT +	T46C -	WT +	T46C -
			FLAG-4E-BP1		(24 h)		+ ATP crosslinker			
			12	10	6.21	5.50	10.8	7.1	2.22	0.80
mTOR	12	0	74.5	6.21	6.21	5.50	10.8	7.1	2.22	0.80
CDK4	5.5	2.5	11	2	2.00	5.50	2.72	+/-0.63	2	+/-0.04
HEK293										
Erk2	3	3.5	6.5	6	2.17	1.08	2.86	+/-0.89	0.80	+/-0.13

B



C

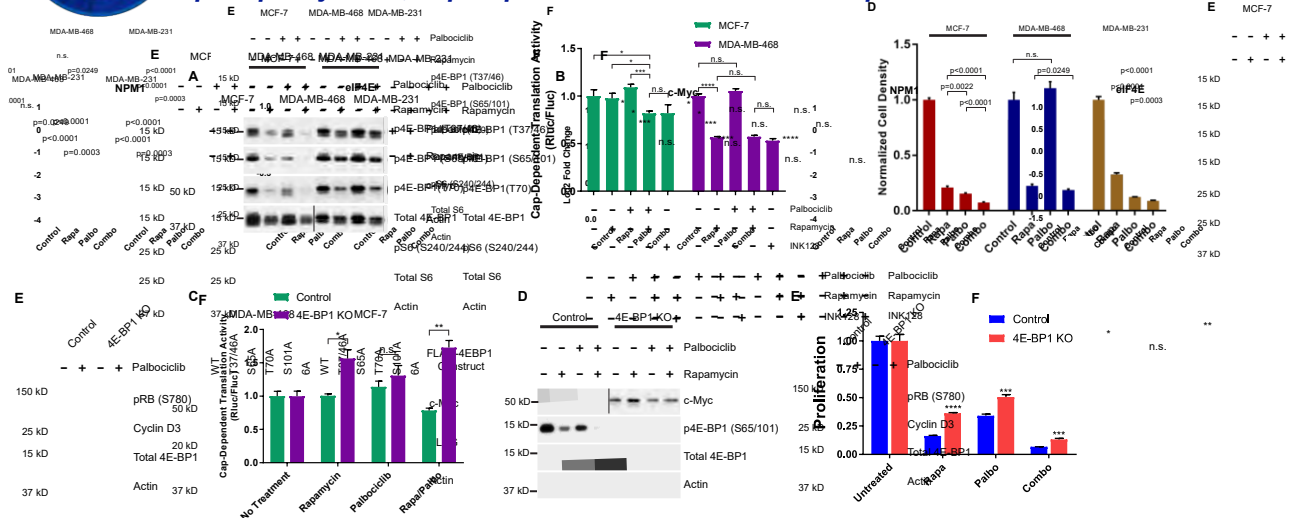


Dylan Mitchell, *Cell Chem. Biol.* **2019**, 26, 980



# PhAXA Identifies CDK4 as a Novel 4E-BP1 Kinase

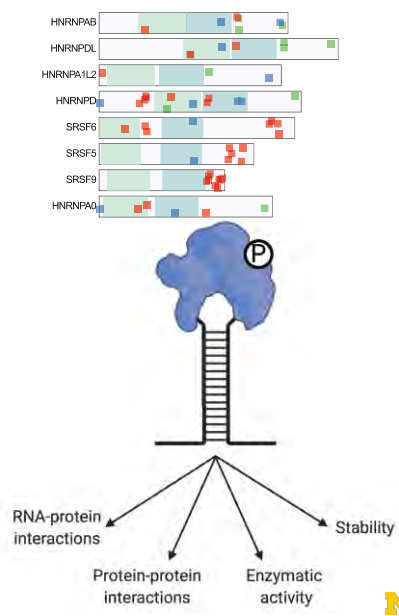
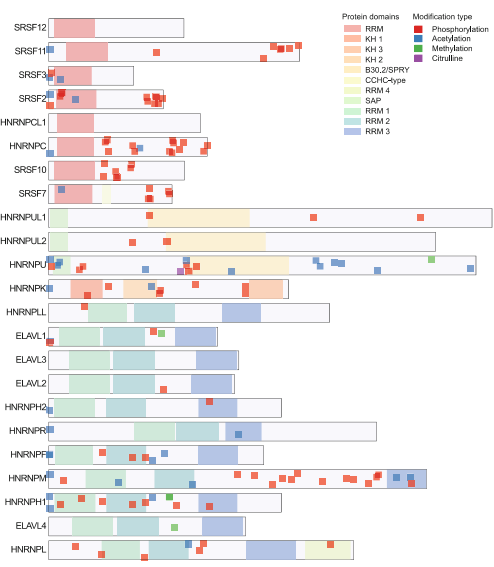
**Pharmacological inhibition of mTORC1 and CDK4 cooperate to antagonize 4E-BP1 phosphorylation, cap-dependent translation and cell proliferation:**



Cell Chem. Biol. 2019, 26, 980



# Future Work: Using PhAXA to Annotate Kinases Acting on Human RBPs

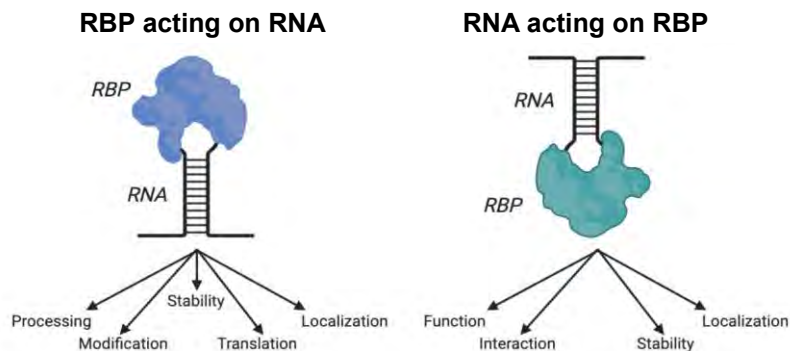


Adv. Exp. Med. Biol. 2016, 907, 297; Mol. Cell 2020, 78, 9



## Take-Aways from Today's Webinar

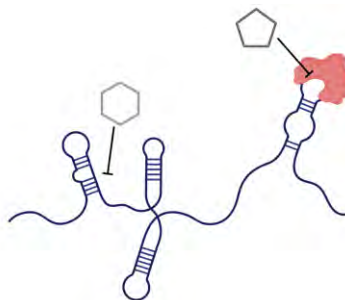
**RNA-protein interactions (RPIs) play critical roles in regulating many aspects of RNA and disease biology**



Many interdisciplinary approaches will be needed to reveal the druggability of these interactions and how to advance the field toward clinical applications



## Additional Resources on RBPs and Drugging RNA Biology



### Small molecules targeting RNA:

Matt Disney (Scripps), Amanda Hargrove (Duke), Thomas Hermann (UCSD), Jay Schneekloth (NCI), Gabriele Varani (UW), Steve Zimmerman (UIUC)

#### Select References:

Disney: *Drug Disc. Today* **2019**, 24, 2002;  
JACS **2019**, 141, 6776  
Al-Hashimi (Duke): *bioRxiv* 2020.05.02.074336  
Hargrove: *ACS Chem. Biol.* **2019**, 14, 2691  
Garner Ed.: *RNA Therapeutics 2017* in *Topics in Medicinal Chemistry*

### RNA-binding proteins:

Richard Gregory (Harvard), Michael Kharas (MSK), Gene Yeo (UCSD)

#### Select References:

Yeo: *Mol. Cell* **2020**, 78, 9  
Hentze: *Nat. Rev. MCB* **2018**, 19, 327  
Jankowsky: *Nat. Rev. MCB* **2015**, 19, 533  
Tuschl: *Nat. Rev. Genet.* **2014**, 15, 829

### RNA-modifying enzymes:

Chuan He (UChicago), Samie Jaffrey (Weill Cornell), Tony Kouzarides (Cambridge)

#### Select References:

Blackaby: *Med. Chem. Rev.* **2020**, upcoming!  
Kouzarides: *Nat. Rev. Cancer* **2020**, 20, 303  
He: *Cell* **2017**, 169, 1187

# Acknowledgments

## Contributing Researchers

### miRNA

Dan Lorenz  
Tanpreet Kaur  
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Sydney Rosenblum  
Jorge Sandoval  
Emily Sherman  
Rachel Torrez  
Yihao Zhuang

### eIF4E/4E-BP1

Emilio Cardenas  
Alyah Chmiel  
Erin Gallagher  
Oleta Johnson  
Arya Menon  
Lauren Mishra  
Dylan Mitchell  
James Song

## Collaborators

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Ashu Tripathi, David Sherman (UM NPDC)  
Melanie Ohi (UM LSI)  
Alexey Nesvizhskii and UM PRF  
Andrew Hsieh (Fred Hutchinson)  
Kirsten Deprey, Joshua Kritzer (Tufts)  
Qi Zhang (UNC)  
Alaji Bah, Julie Forman-Kay (Toronto)



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R01 GM135252



R01 CA202018



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Medical Research Trust



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T32 GM008353  
T32 GM008597

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T32 CA140044

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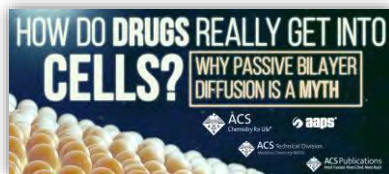
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Join Research Fellow Li Di of Pfizer as she discusses why design principles that increase passive permeability are effective approaches to increase oral bioavailability, enhance brain penetration, and reduce renal clearance. <https://www.acs.org/content/acs/en/acs-webinars/drug-discovery/passive-permeability.html>

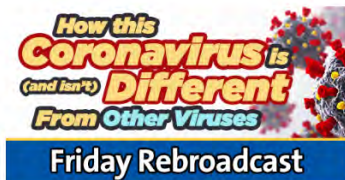


Join Douglas Kell, Research Chair in Systems Biology at the University of Liverpool to discover how drugs pass through cell membrane solely by hitchhiking on membrane transporters and why so-called "passive diffusion" through any bilayer in real cells is negligible. <https://www.acs.org/content/acs/en/acs-webinars/drug-discovery/so-lute-carriers.html>

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## Enabling Technologies for Revealing Druggable Paths in RNA Biology



**Amanda Garner**  
Associate Professor, College of Pharmacy, Department of Medicinal Chemistry, University of Michigan



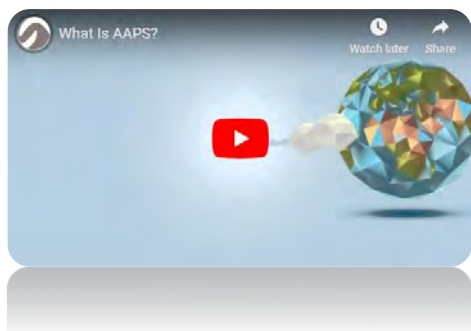
**Matt Disney**  
Full Professor, Department of Chemistry and Department of Neuroscience, The Scripps Research Institute

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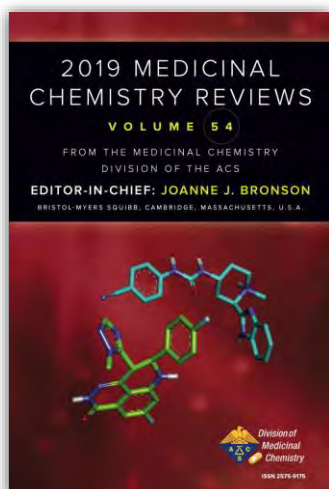
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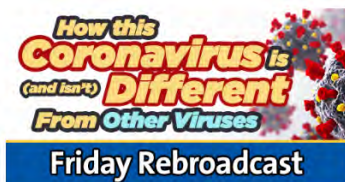
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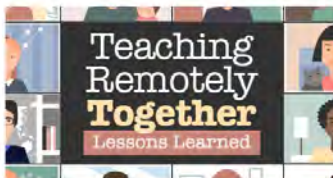
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