The mTOR-LARP1 axis and the anabolic reservoir of tumor cells: A new therapeutic target in colorectal cancer and beyond

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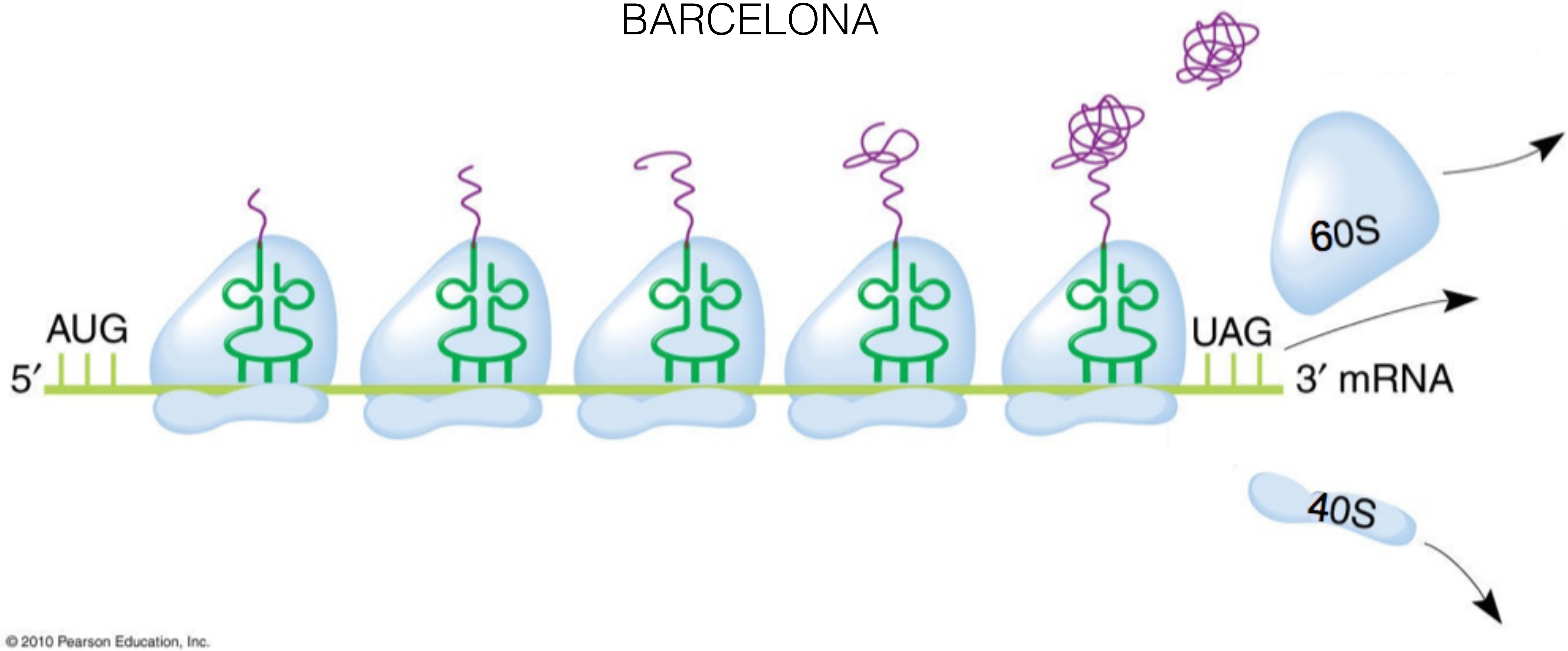
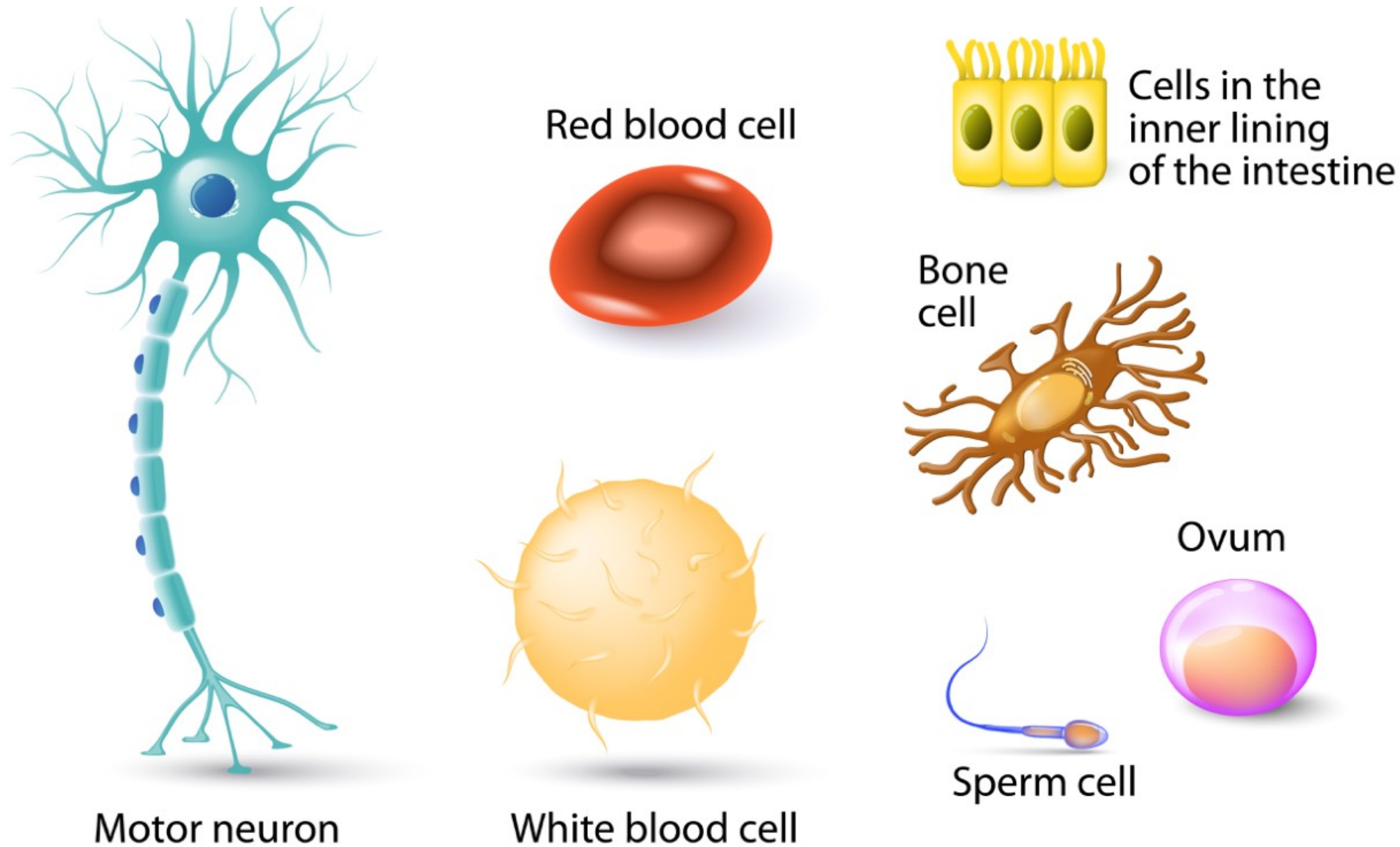


Homo sapiens

Gene Expression



The Mission of Biomedicine

UNIVERSITY OF Cincinnati

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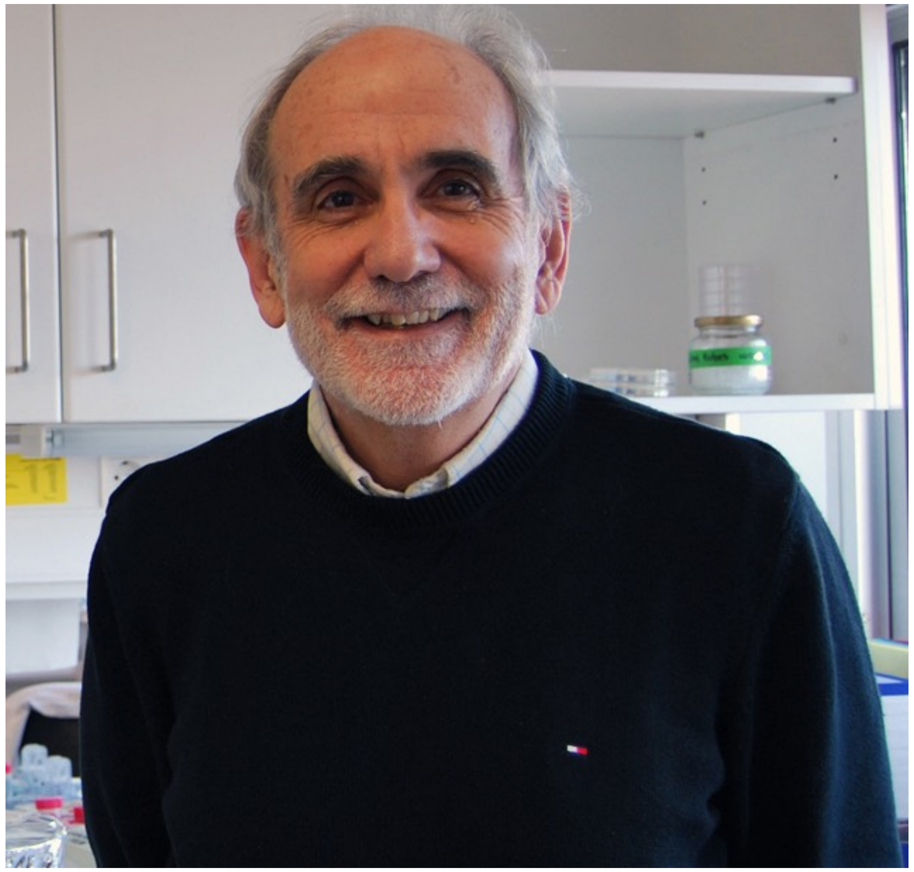
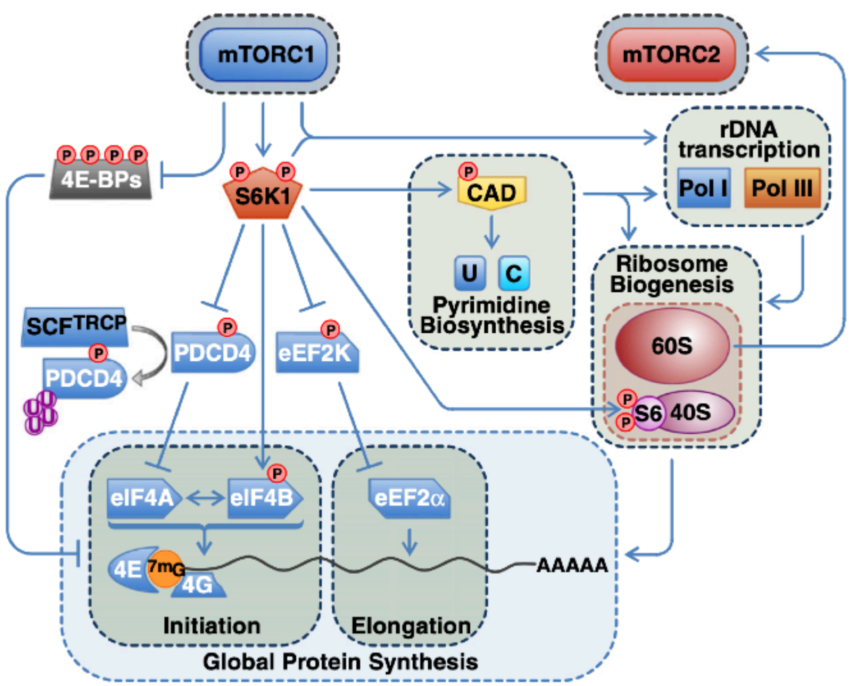




REPORT Science

Proliferation, But Not Growth, Blocked by Conditional Deletion of 40*S* Ribosomal Protein S6

Molecular Cell, Vol. 11, 1457–1466, June, 2003, Copyright ©2003 by Cell Press

Insulin Activation of Rheb, a Mediator of mTOR/S6K/4E-BP Signaling, Is Inhibited by TSC1 and 2

letters to nature

Absence of S6K1 protects against age- and diet-induced obesity while enhancing insulin sensitivity

Sung Hee Um[1], Francesca Frigerio[1], Mitsuhiro Watanabe[2], Frédéric Picard[2*], Manel Joaquin[1], Melanie Sticker[1], Stefano Fumagalli[1], Peter R. Allegrini[3], Sara C. Kozma[1*], Johan Auwerx[2] & George Thomas[1]

nature cell biology

Absence of nucleolar disruption after impairment of 40S ribosome biogenesis reveals an rpL11-translation-dependent mechanism of p53 induction

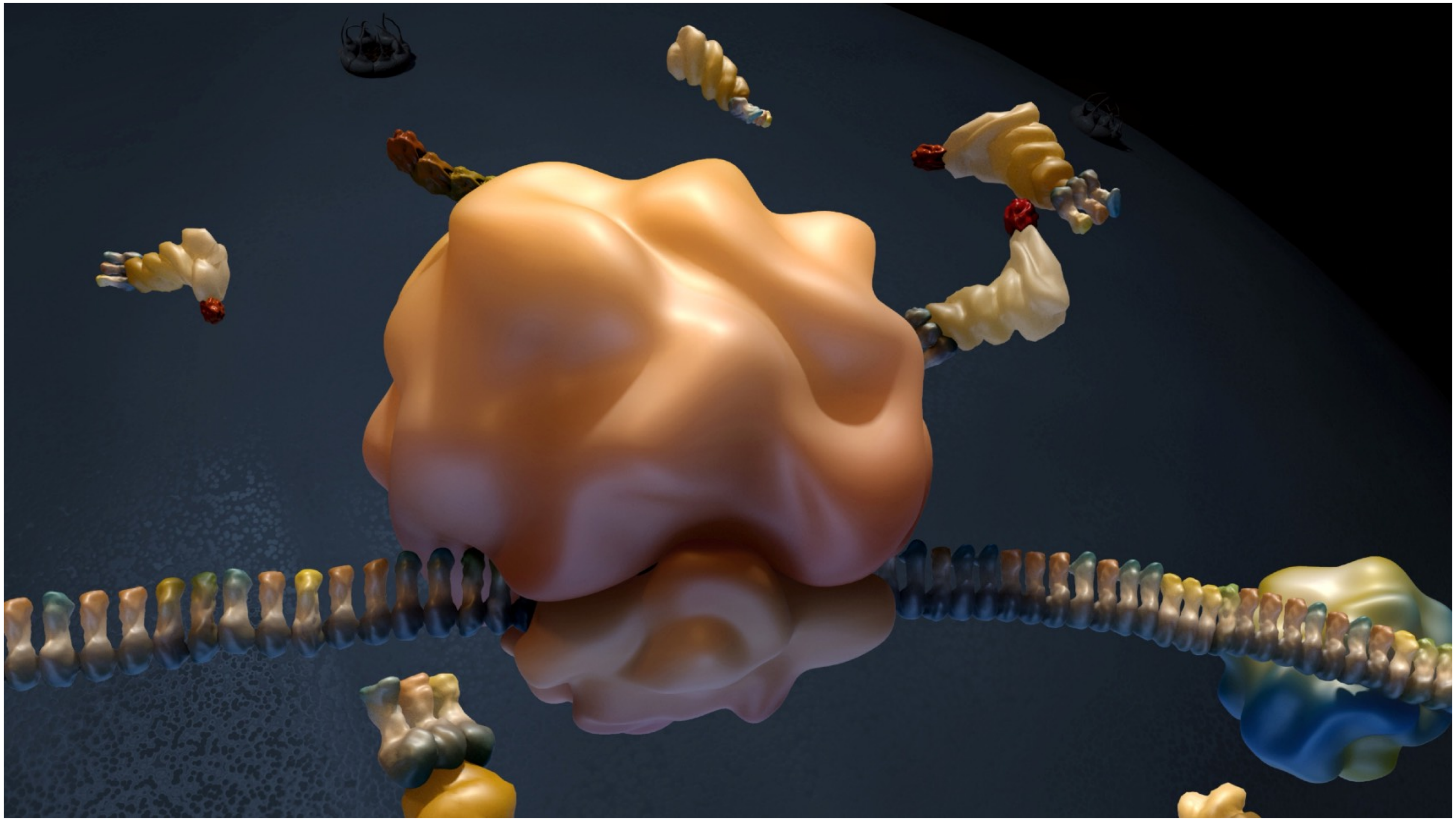
Stefano Fumagalli[1,8], Alessandro Di Cara[2], Arti Neb-Gulati[1], Francois Natt[3], Sandy Schwemberger[4], Jonathan Hall[3], George F. Babcock[4,5], Rosa Bernardi[6], Pier Paolo Pandolfi[7] and George Thomas[1,8]

Genes & Development

Suprainduction of p53 by disruption of 40S and 60S ribosome biogenesis leads to the activation of a novel G2/M checkpoint

Stefano Fumagalli,[1,2,5] Vasily V. Ivanenkov,[1] Teng Teng,[1,3] and George Thomas[1,4,5]

The Ribosome



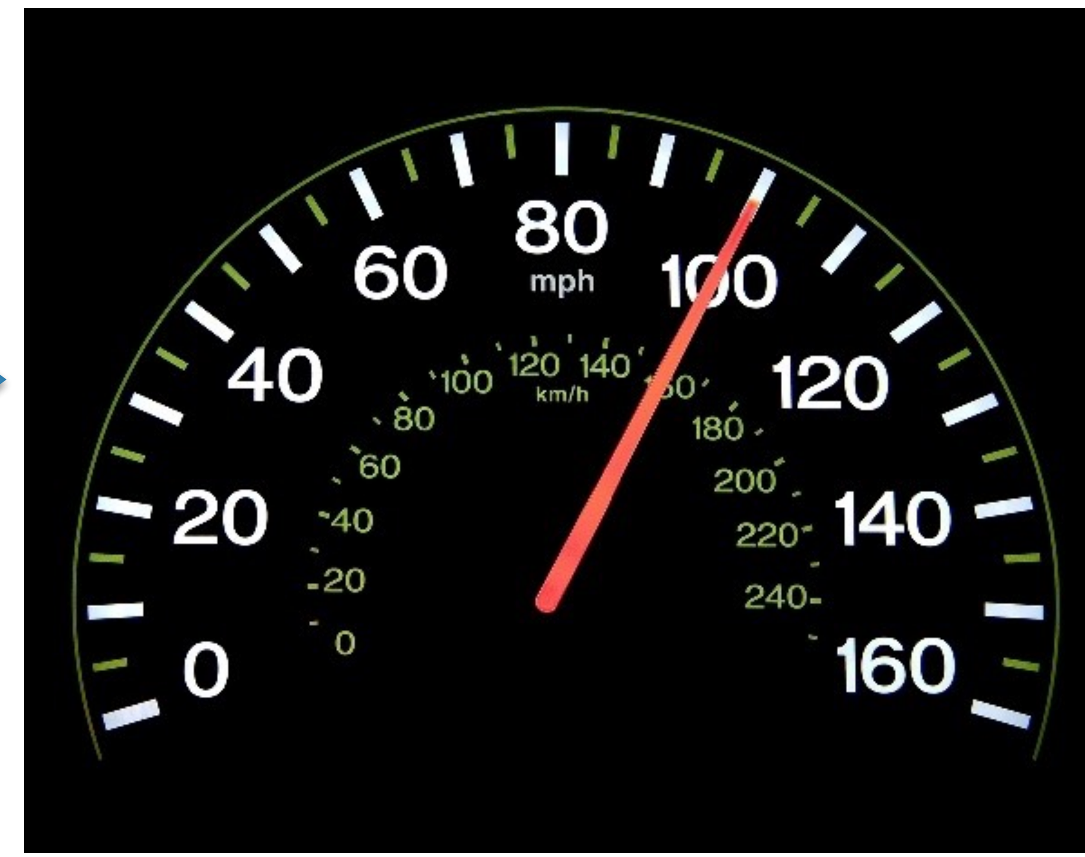
Protein Synthesis

Macrolides
Tetracyclins
Aminoglicosides
Chloramphenicol

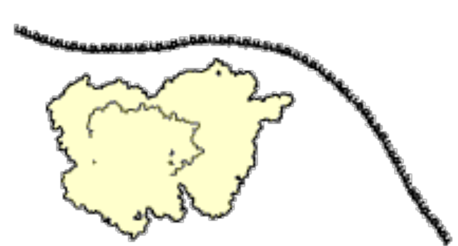
Protein Synthesis Rate

Ribosome Biogenesis

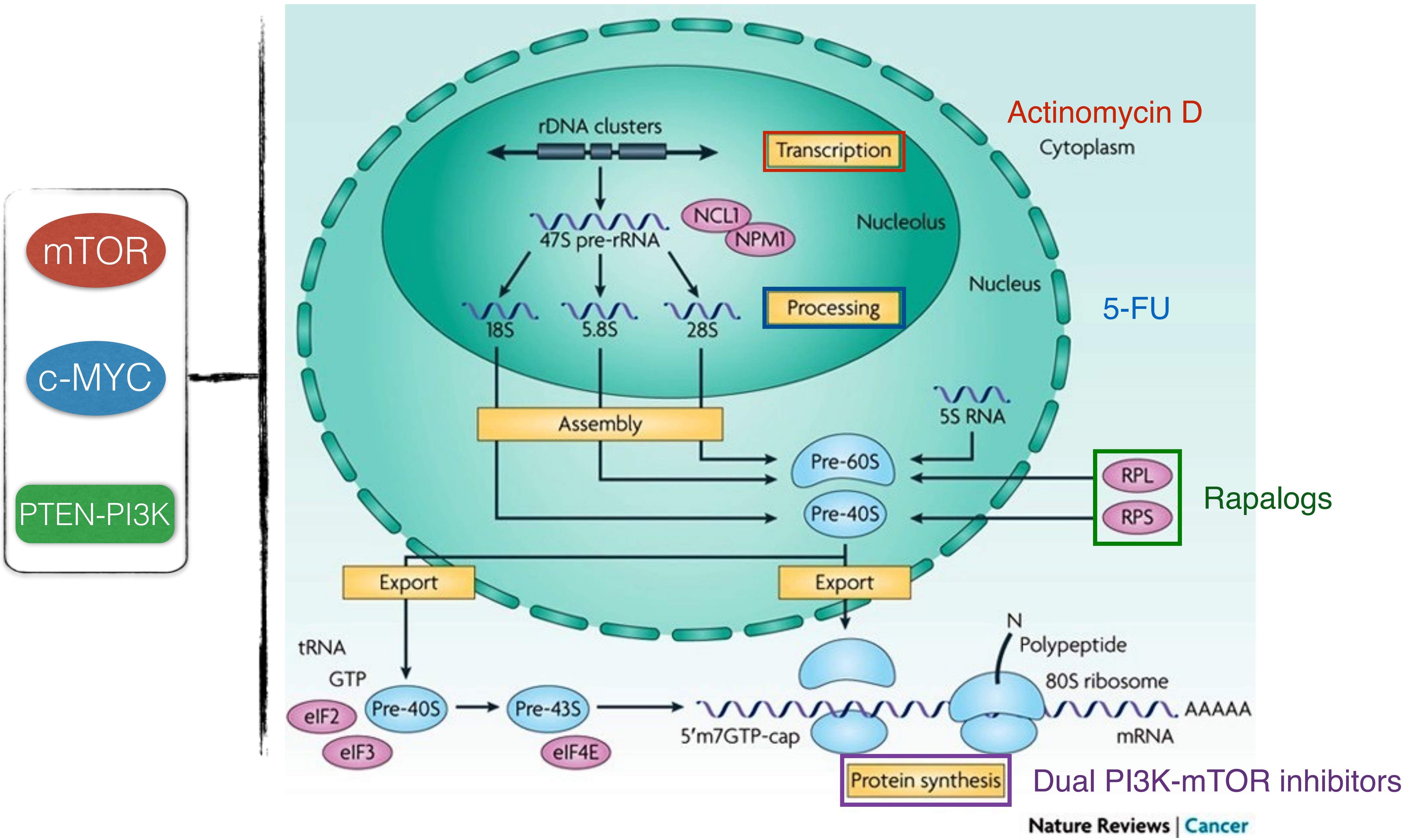
Protein Synthesis



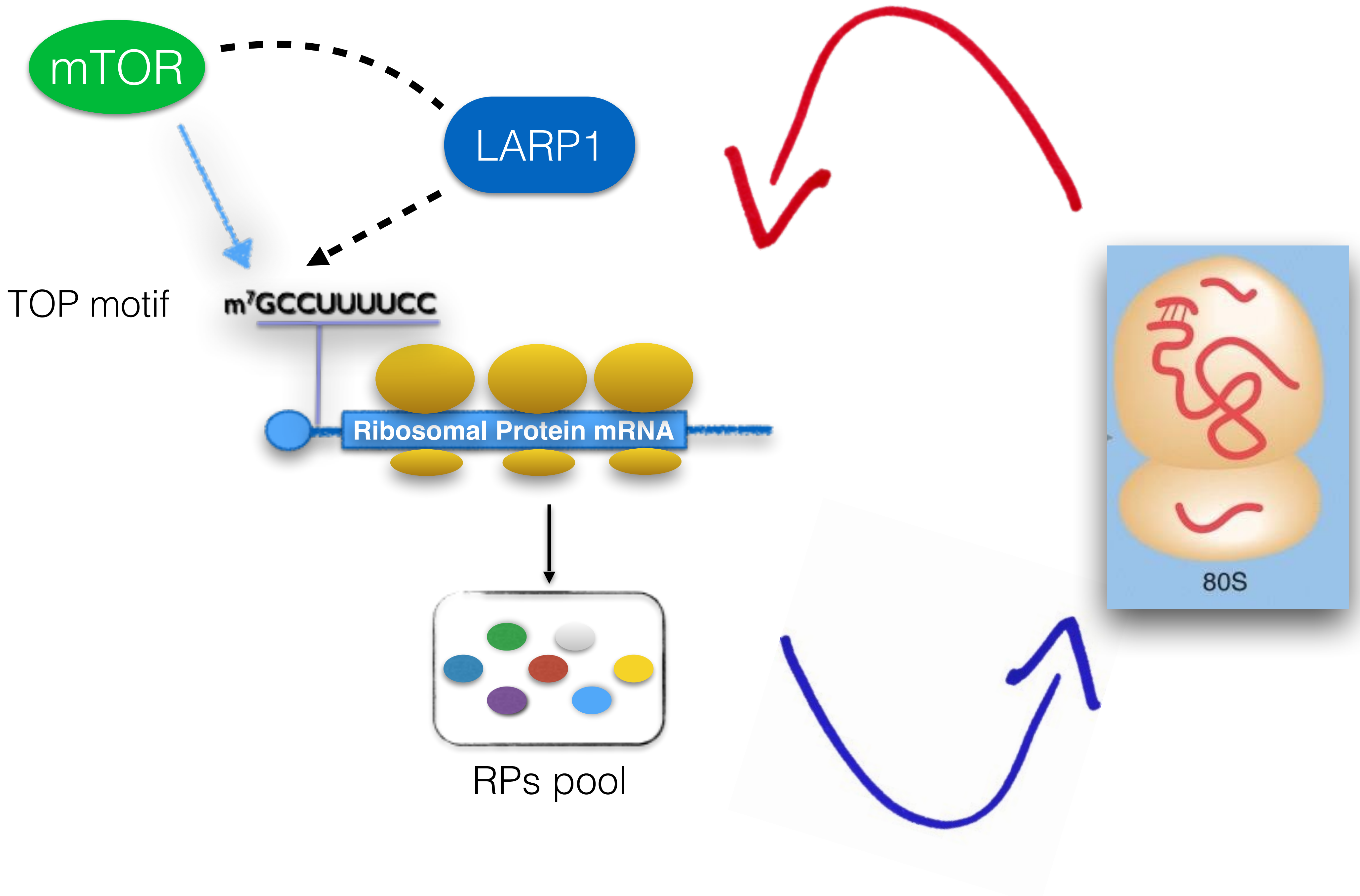
...Or NOT?



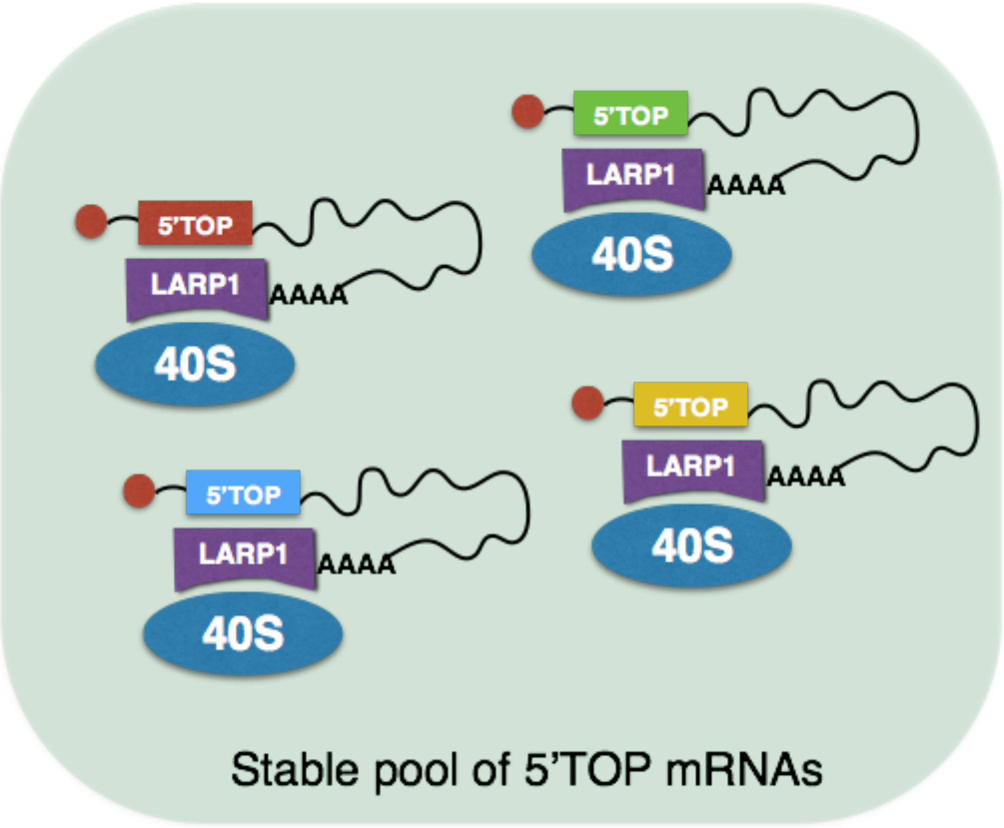
Ribosome Biogenesis



Ribosomal Proteins and mTOR

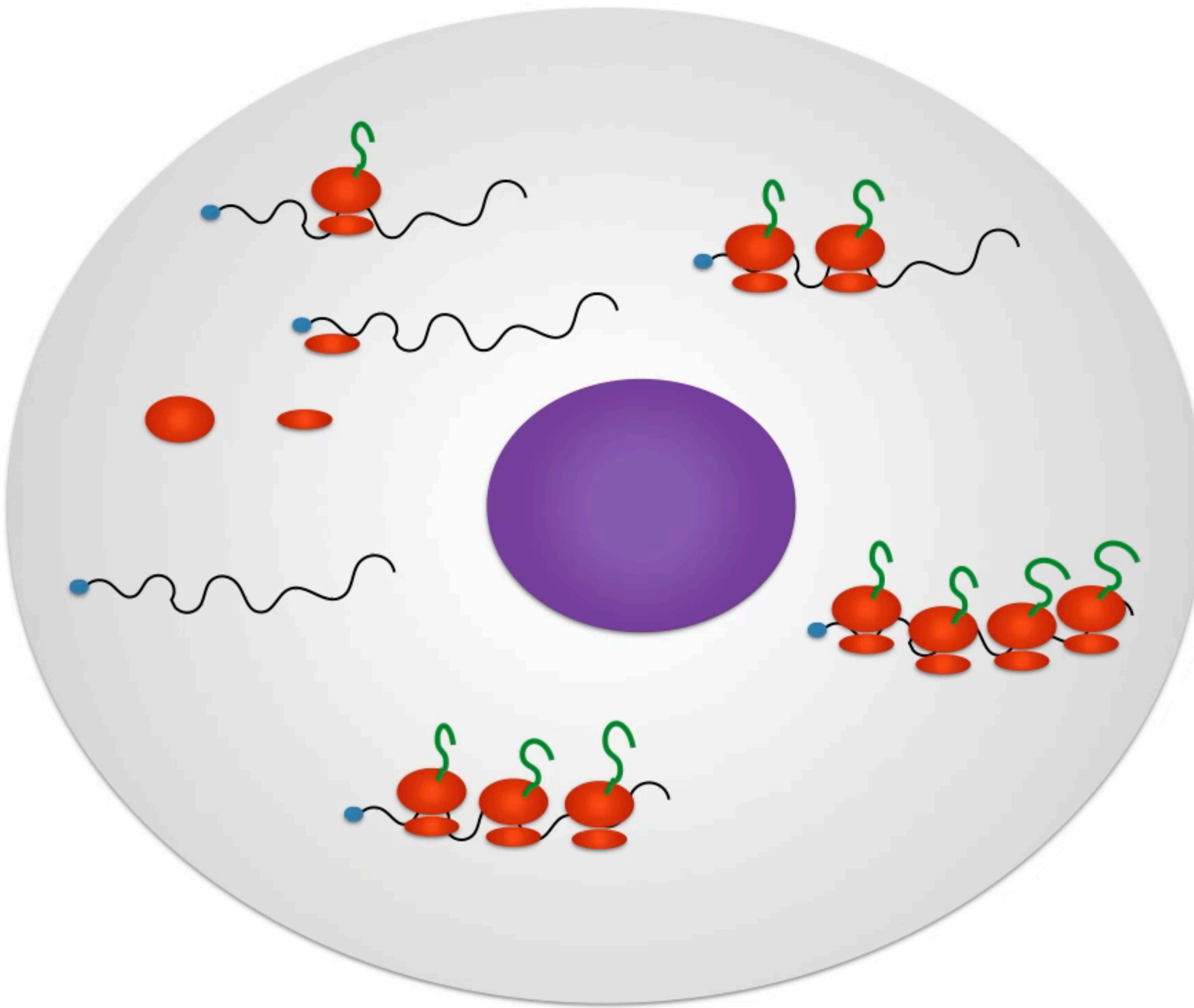


40S-LARP1-5'TOPs complex

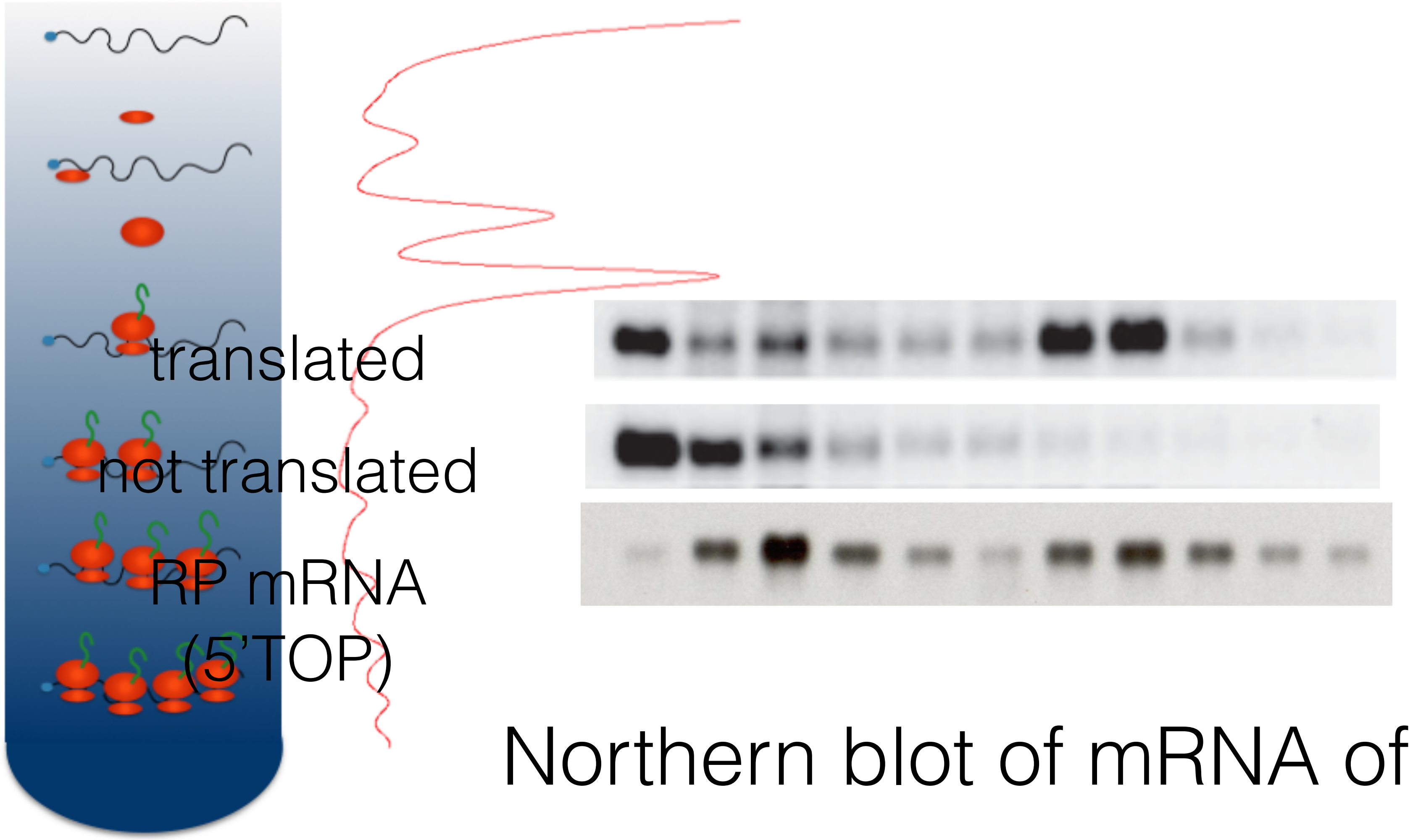


Gentilella et al., *Mol Cell* 2017

Polysome Profiling

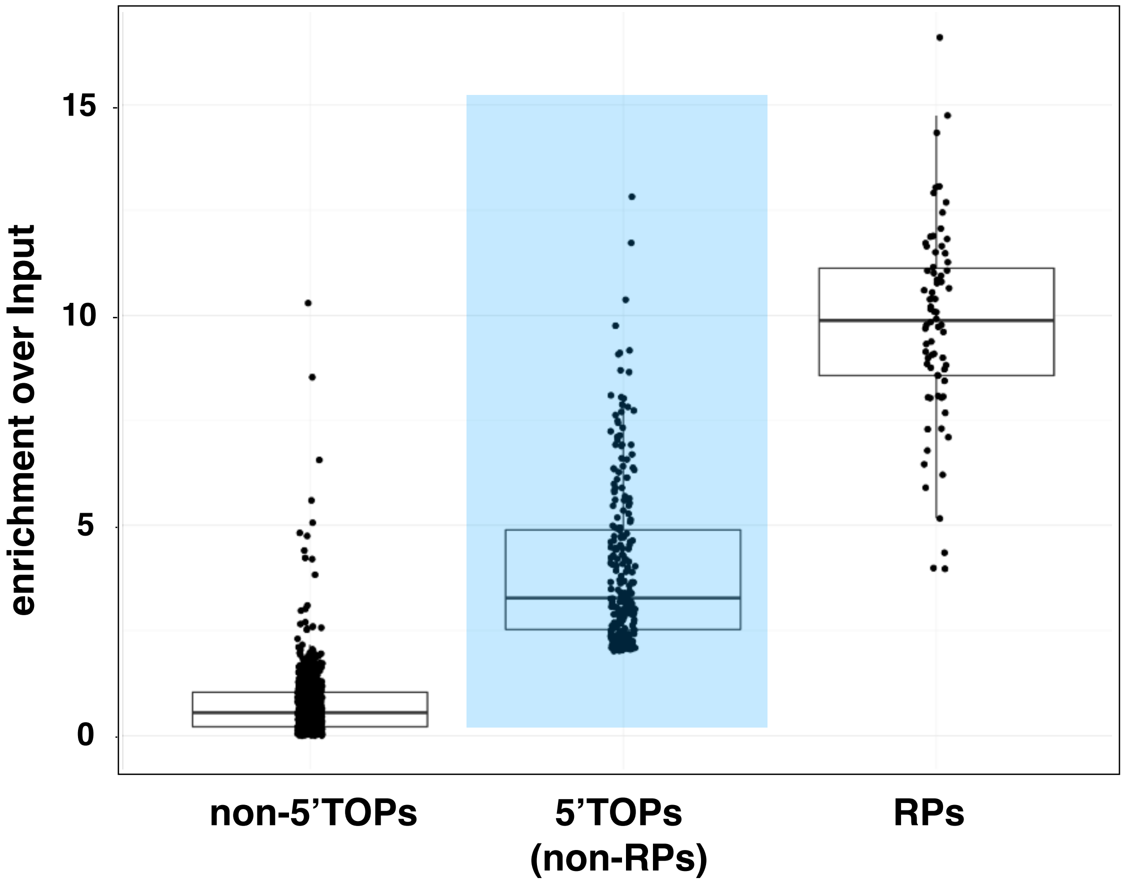


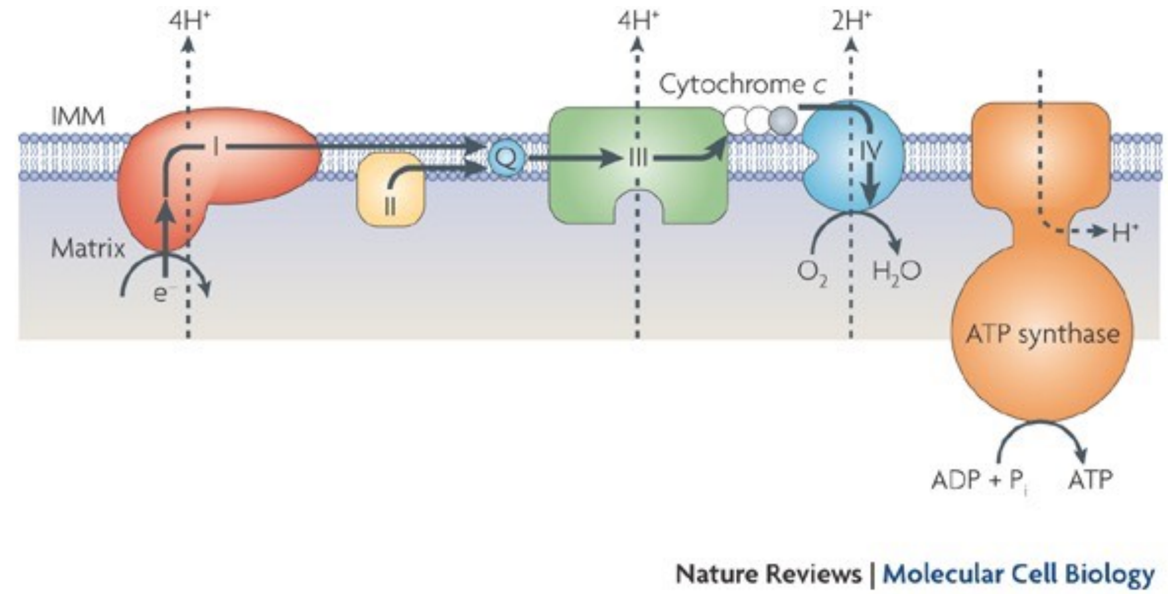
Polysome Profiling

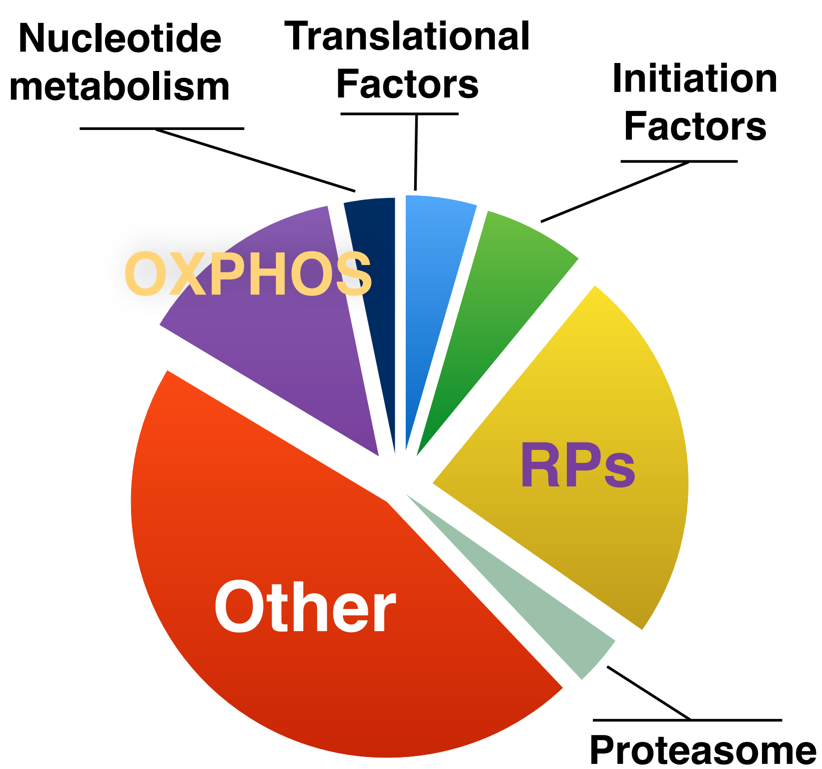


Northern blot of mRNA of interest

40S-LARP1-5'TOPs complex





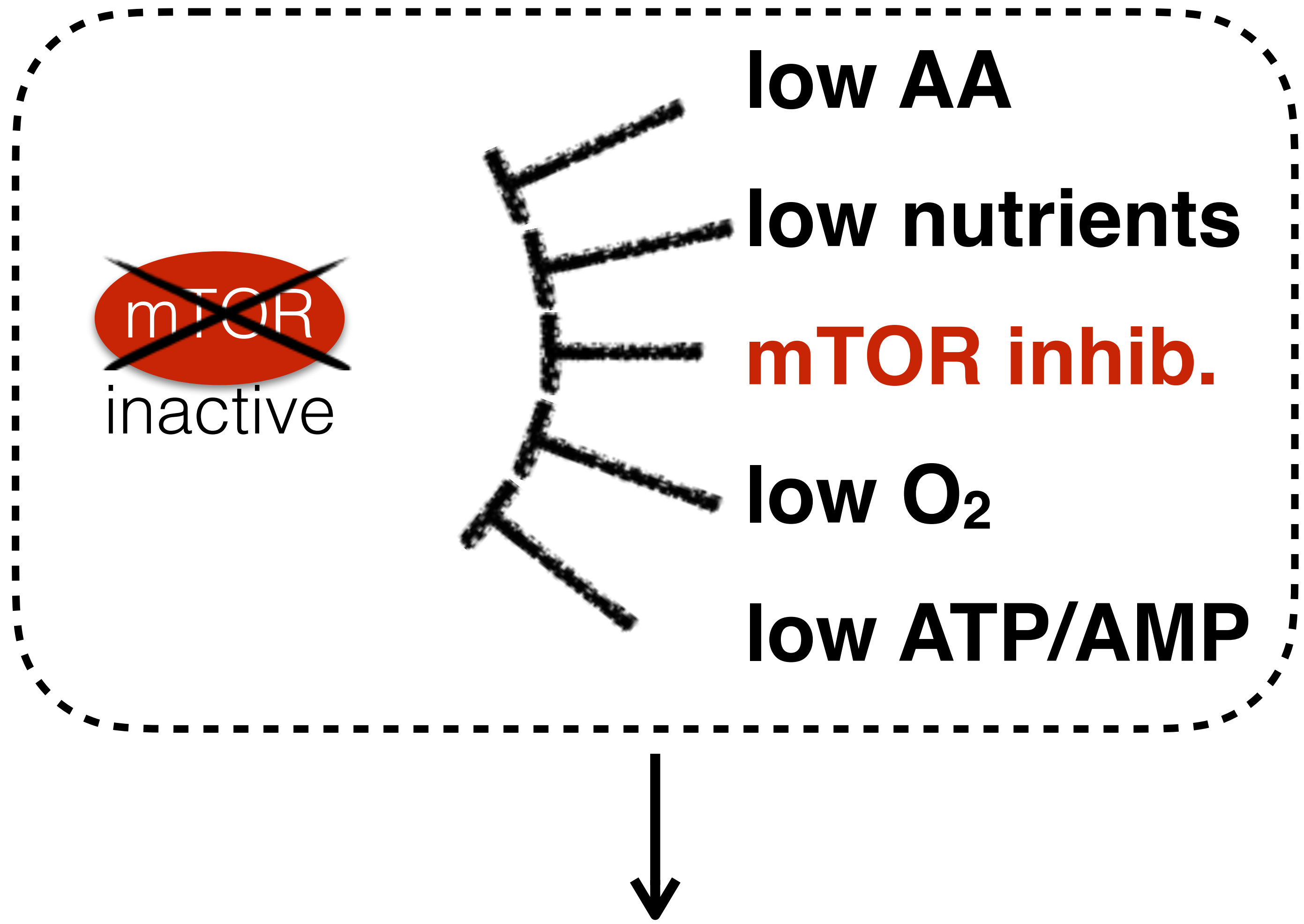


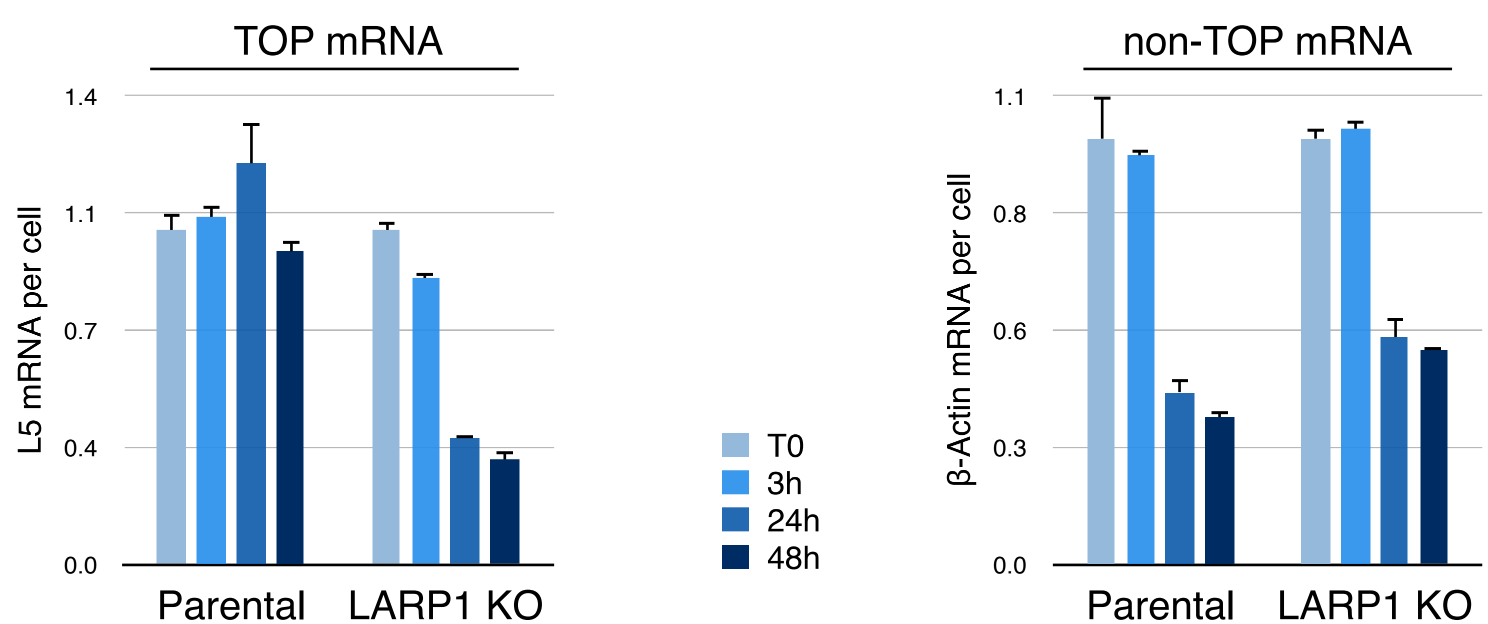
OXPHOS metabolism mRNAs

Complex V	Complex IV	Complex I	Complex III (bc1)	Other Complexes
ATP5I	COX6B1	NDUFB11	UQCRH	CYC1
ATP5B	COX8A	NDUFS4	UQCRQ	SDHB
ATP5D	COX7C	NDUFA4	UQCRB	TOMM7
ATP5G2	COX4I1	NDUFA3		TOMM22
ATP5L	COX5A	NDUFB9		TOMM20
ATP5E	COX5B	NDUFS5		TIMM8B
ATP5A1	COX6A1	NDUFS3		TIMM10
ATP5O	COX7A2	NDUFB4		TIMM13
ATP5J2	COX6C	NDUFS6		
ATP5F1	COX7A2L	NDUFA1		

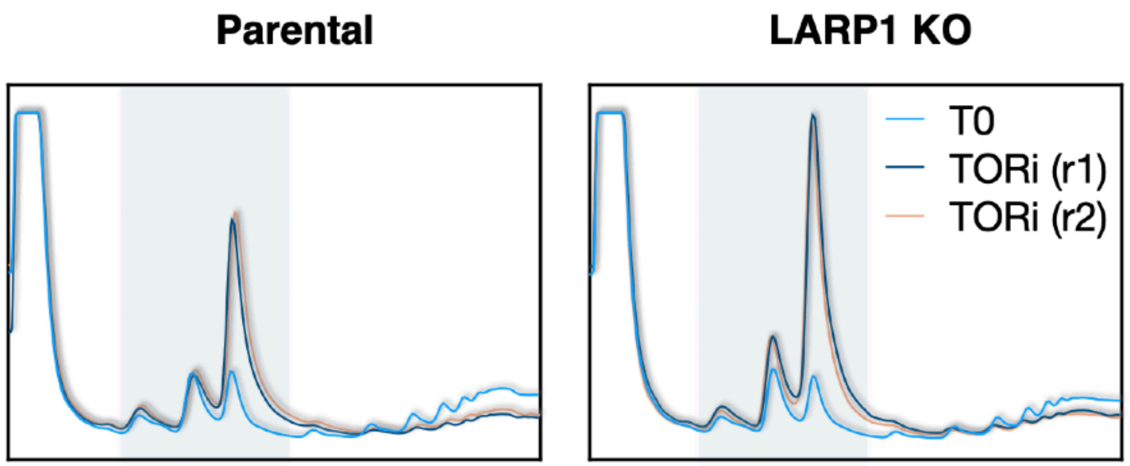
Gentilella et al., *Mol Cell* 2017

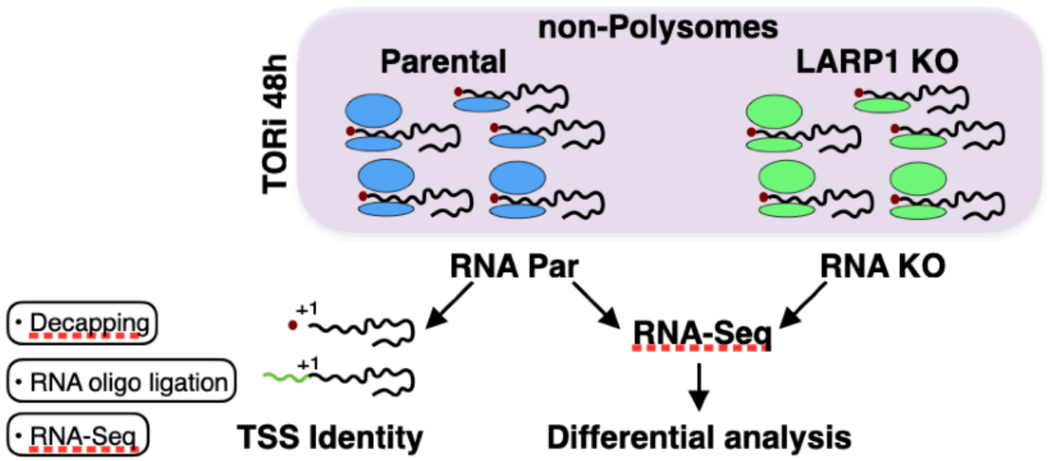
40S-LARP1-5’TOPs complex upon mTOR inhibition

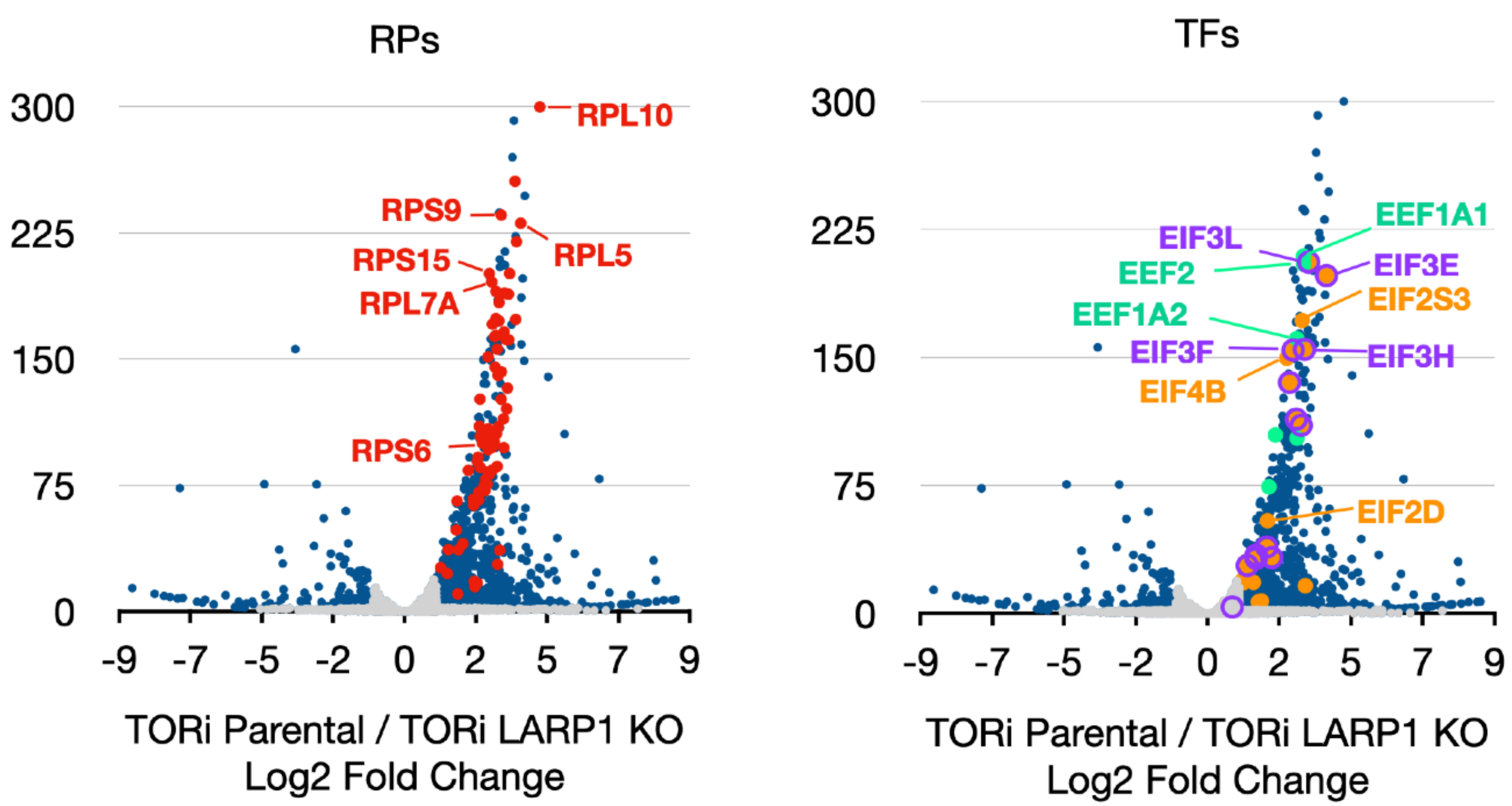




Translatome Protected by LARP1



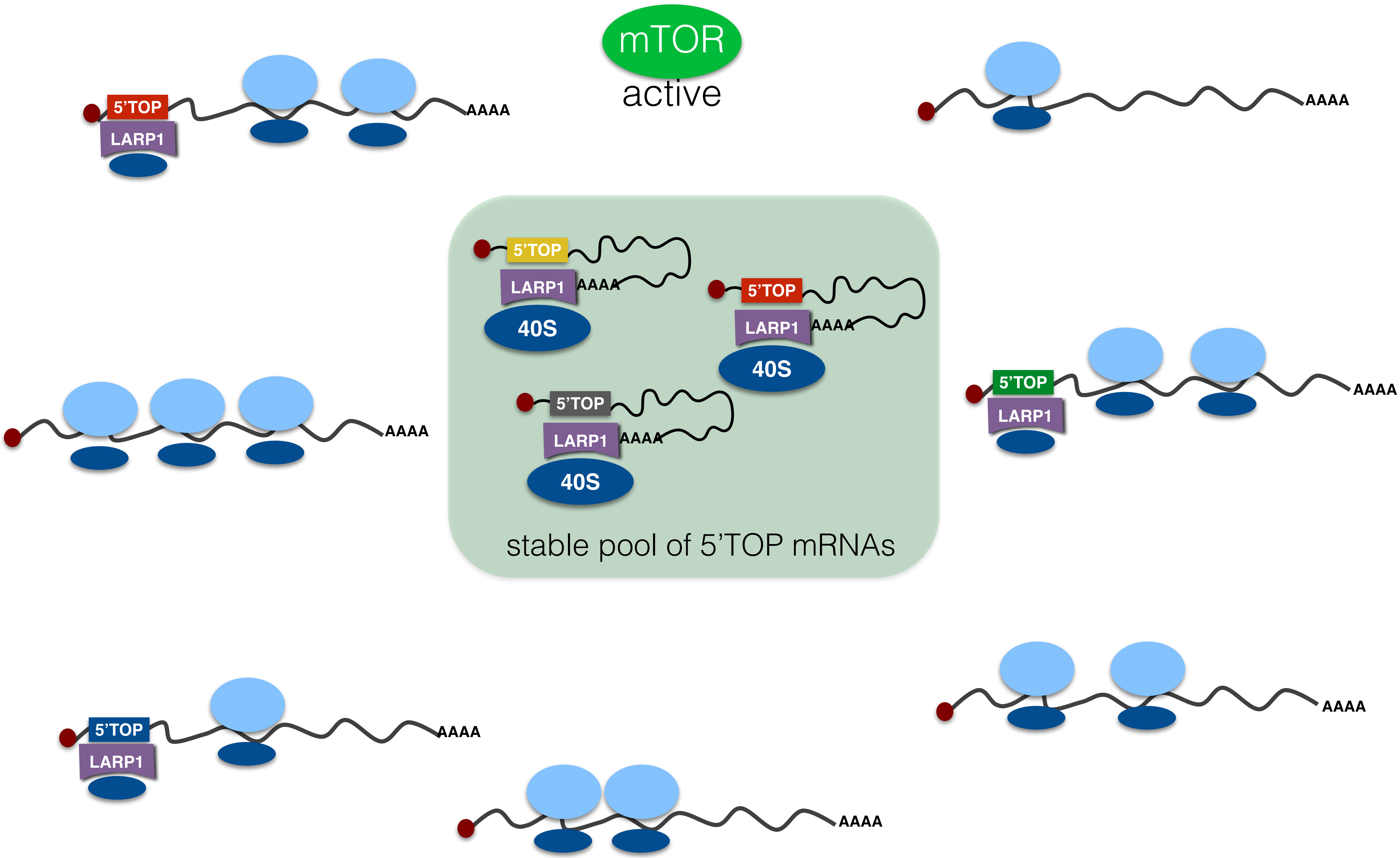




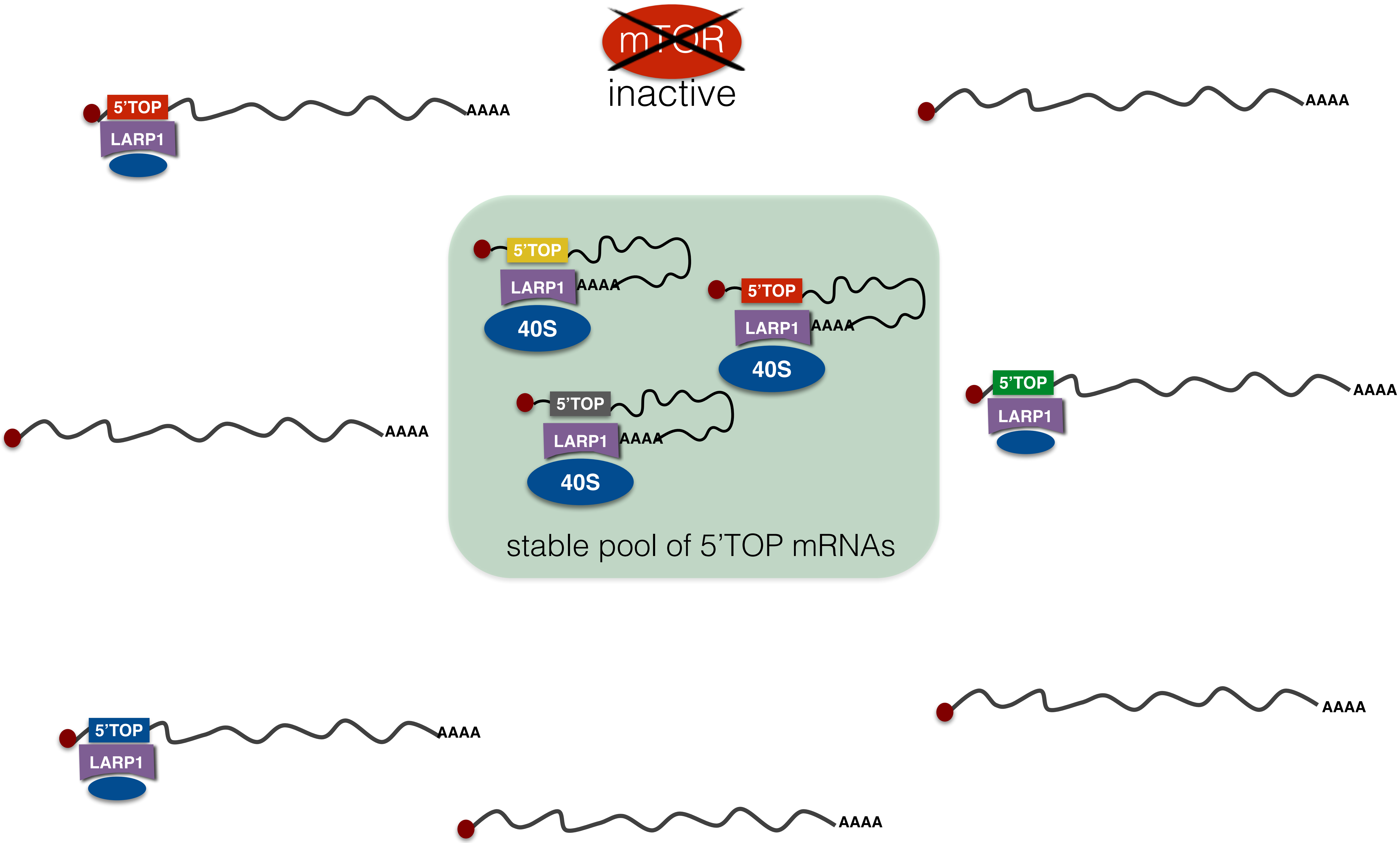
Ribosome Biogenesis and Protein synthesis

Fuentes et al., *Science Adv.* 2021

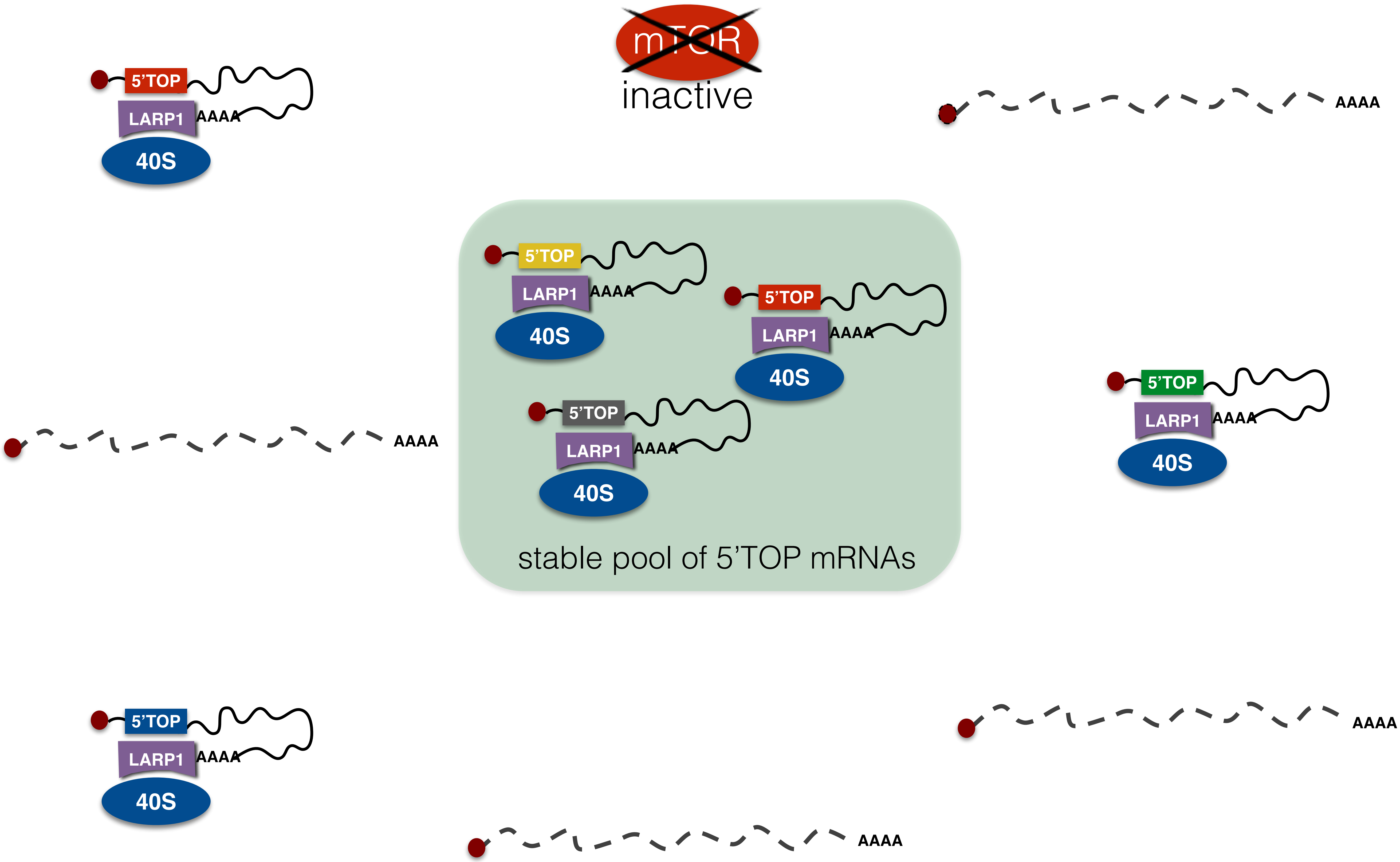
Working Model



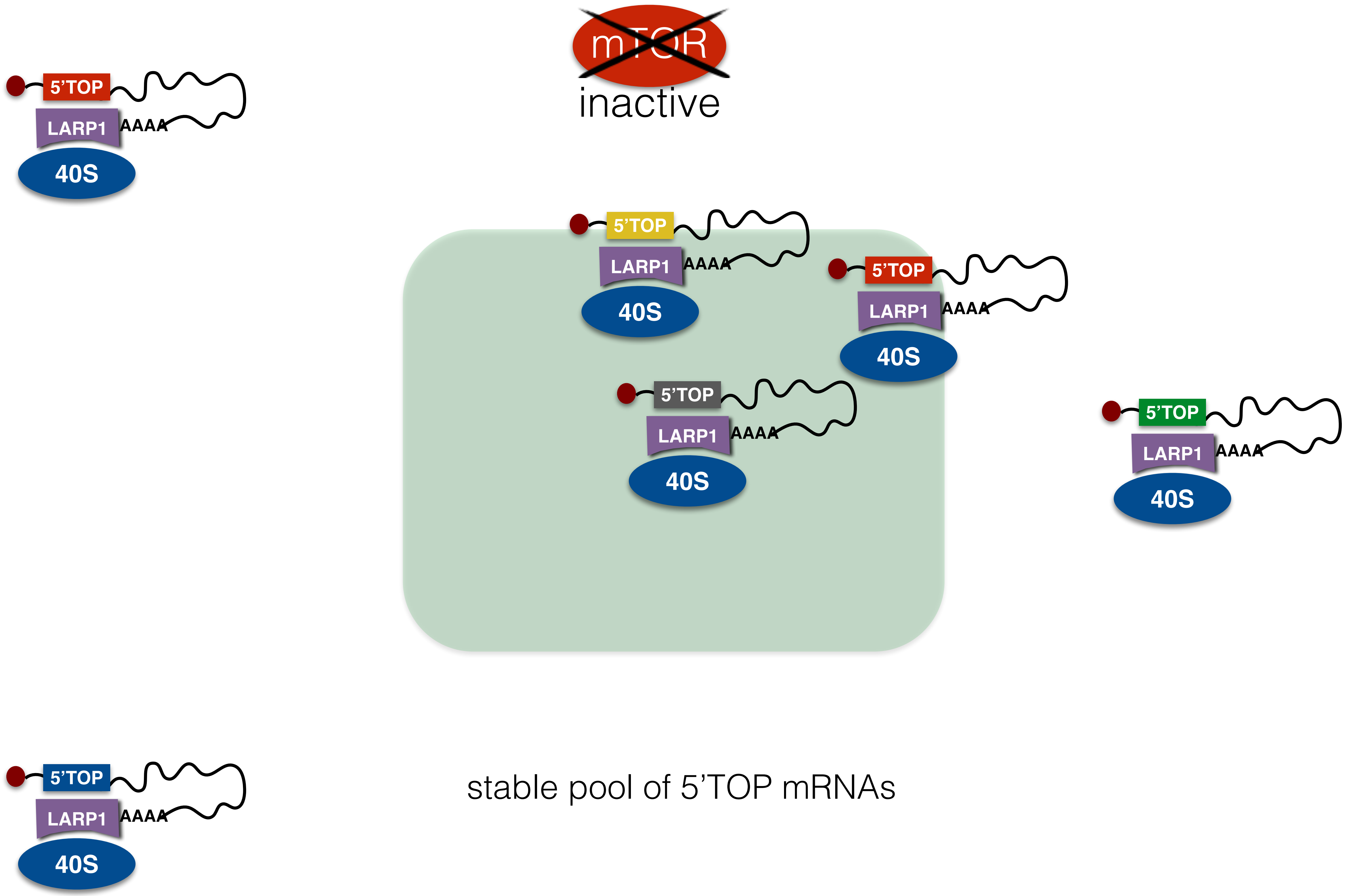
Working Model



Working Model

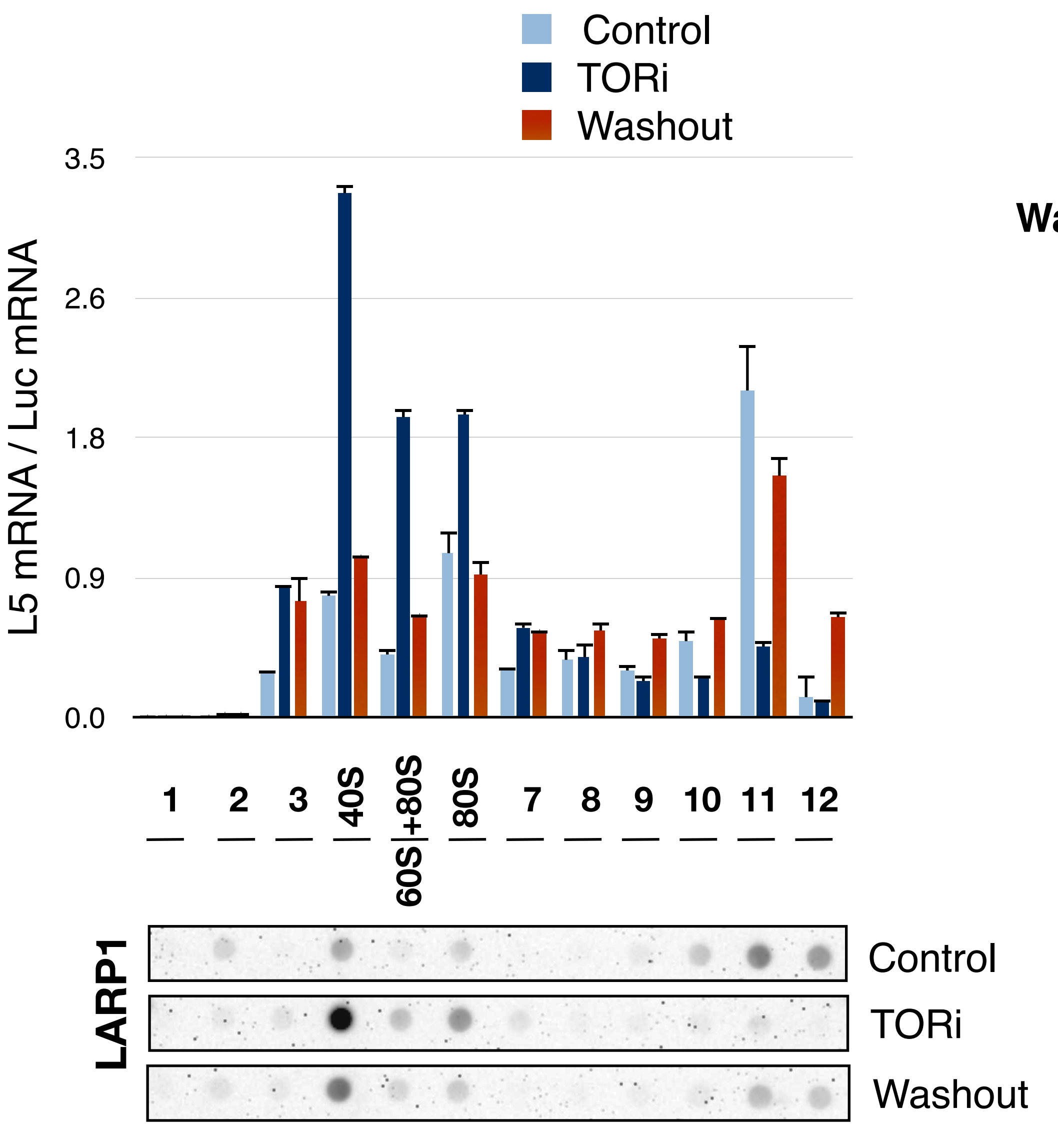


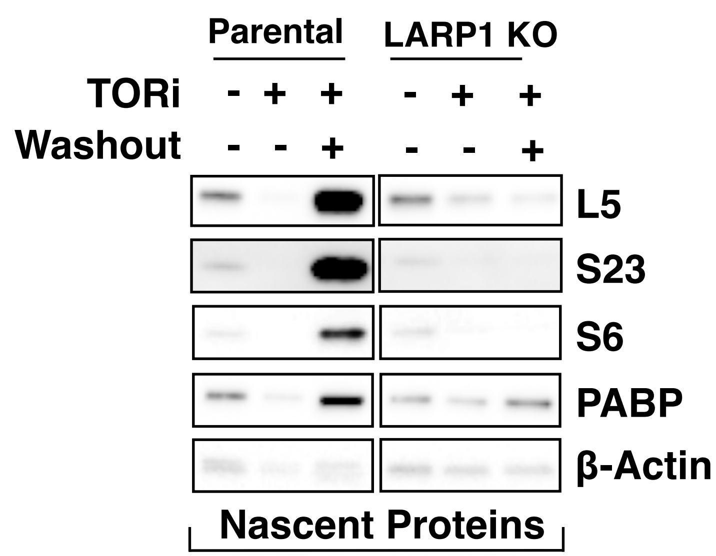
Working Model

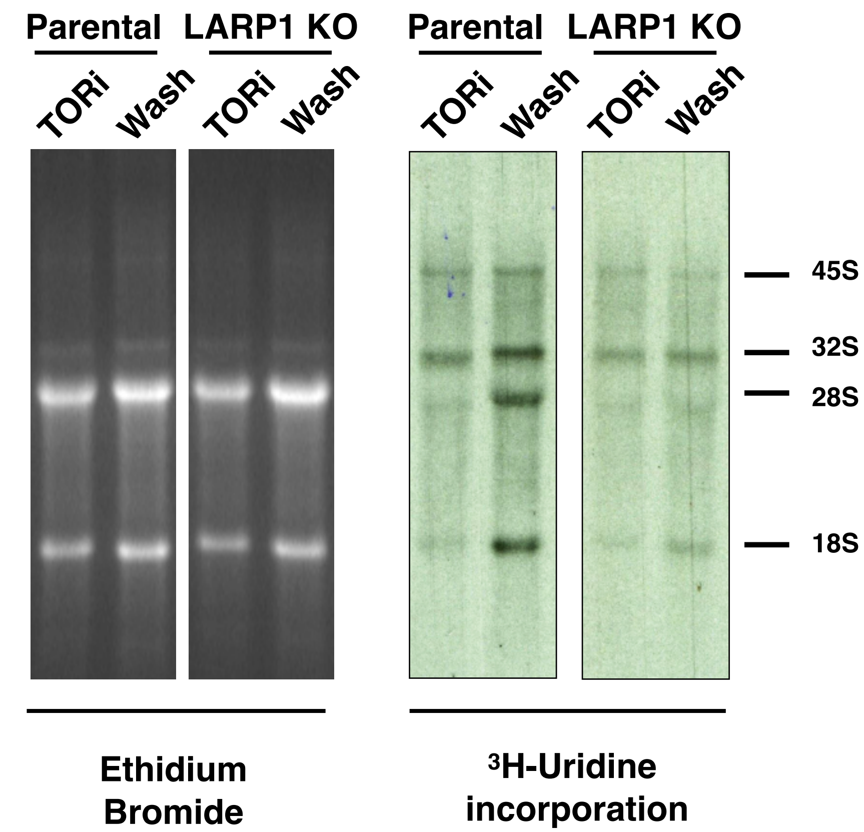


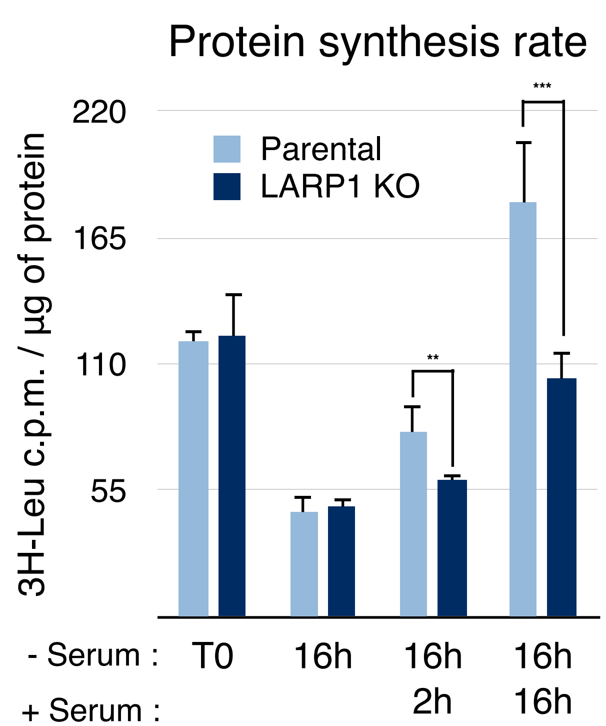
Utilizing the Protected Translatome

Growing cells → 48h TORi → TORi Washout (70 min)









Fuentes et al., *Science Adv.* 2021

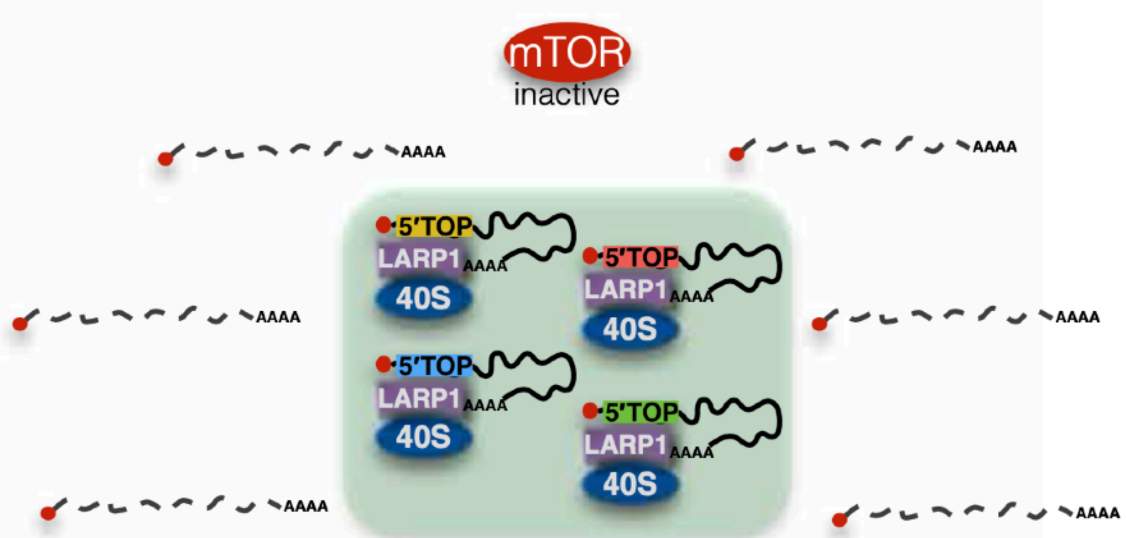
Issued Today

SCIENCE ADVANCES | RESEARCH ARTICLE

CELL BIOLOGY

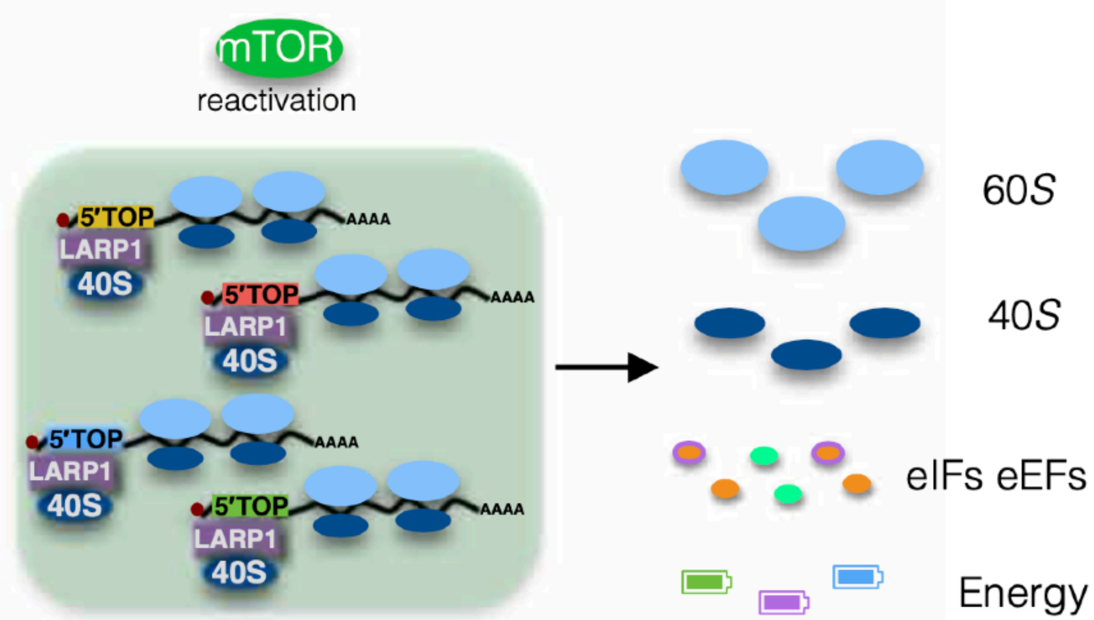
The 40*S*-LARP1 complex reprograms the cellular translatome upon mTOR inhibition to preserve the protein synthetic capacity

40S-LARP1–mediated transcripts selection upon mTOR inhibition



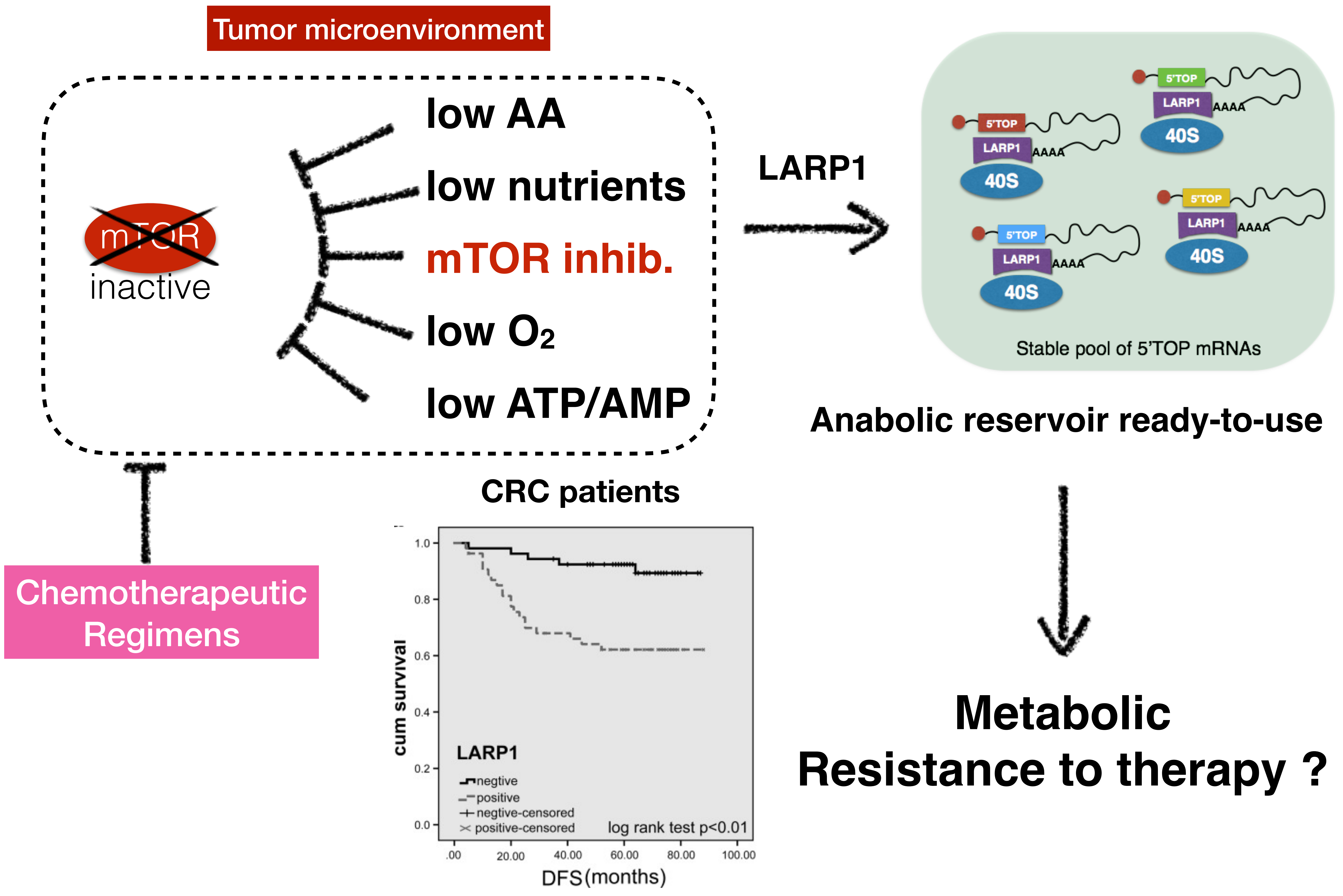
Preservation of ribosome biogenesis potential

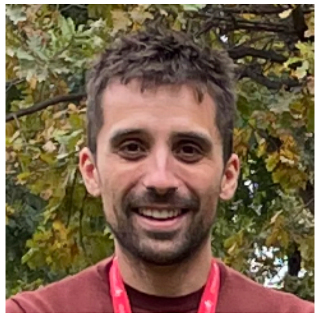
Translational reprogramming after mTOR reactivation



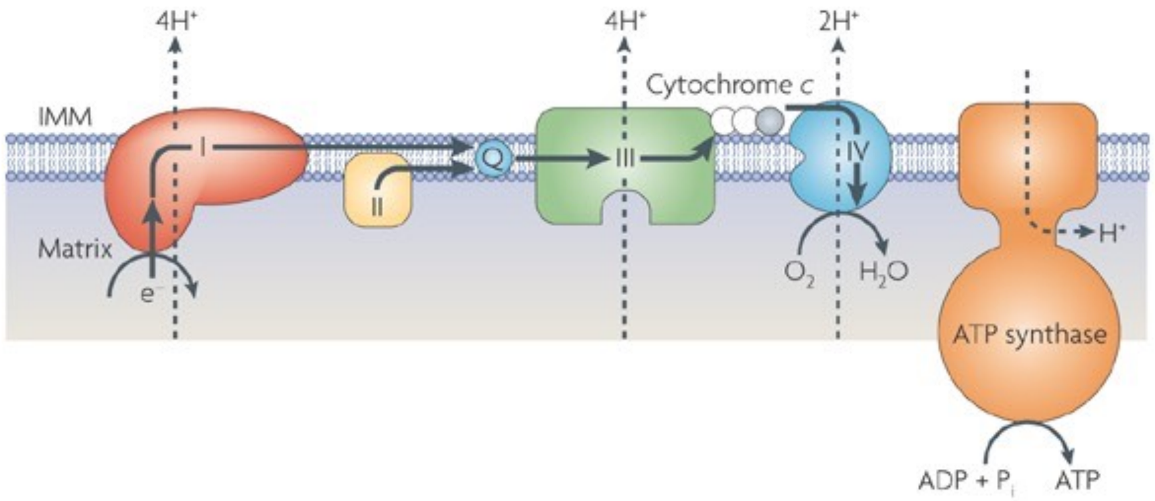
Fast reconstitution of protein synthetic capacity

40S-LARP1 complex in cancer





LARP1 and energetic production

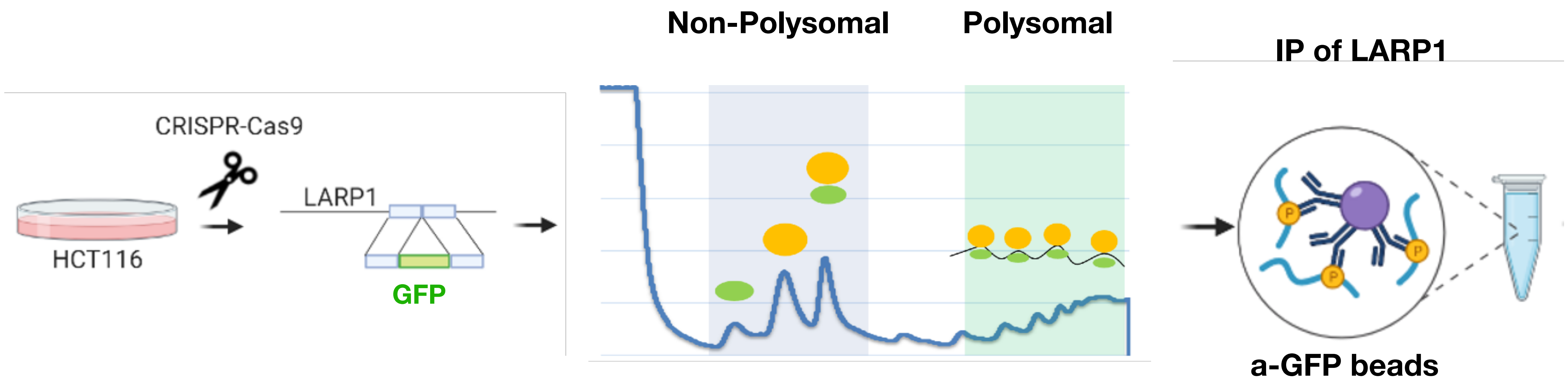


Nature Reviews | Molecular Cell Biology

OXPHOS metabolism mRNAs

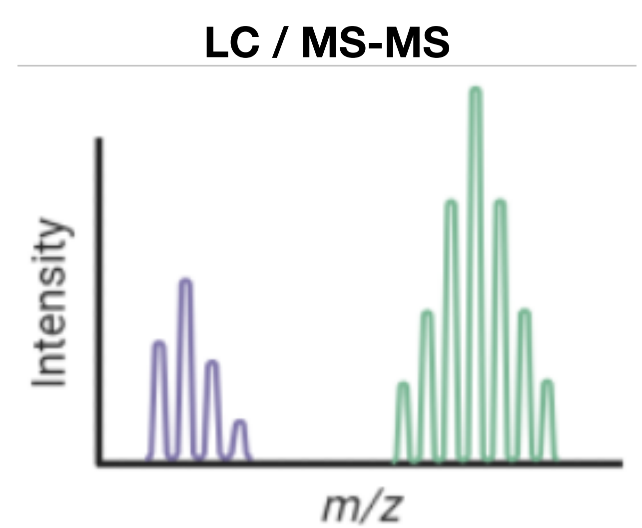
Complex V	Complex IV	Complex I	Complex III (bc1)	Other Complexes
ATP5I	COX6B1	NDUFB11	UQCRH	CYC1
ATP5B	COX8A	NDUFS4	UQCRQ	SDHB
ATP5D	COX7C	NDUFA4	UQCRB	TOMM7
ATP5G2	COX4I1	NDUFA3		TOMM22
ATP5L	COX5A	NDUFB9		TOMM20
ATP5E	COX5B	NDUFS5		TIMM8B
ATP5A1	COX6A1	NDUFS3		TIMM10
ATP5O	COX7A2	NDUFB4		TIMM13
ATP5J2	COX6C	NDUFS6		
ATP5F1	COX7A2L	NDUFA1		

What defines the 40S-LARP1 ribosomes?

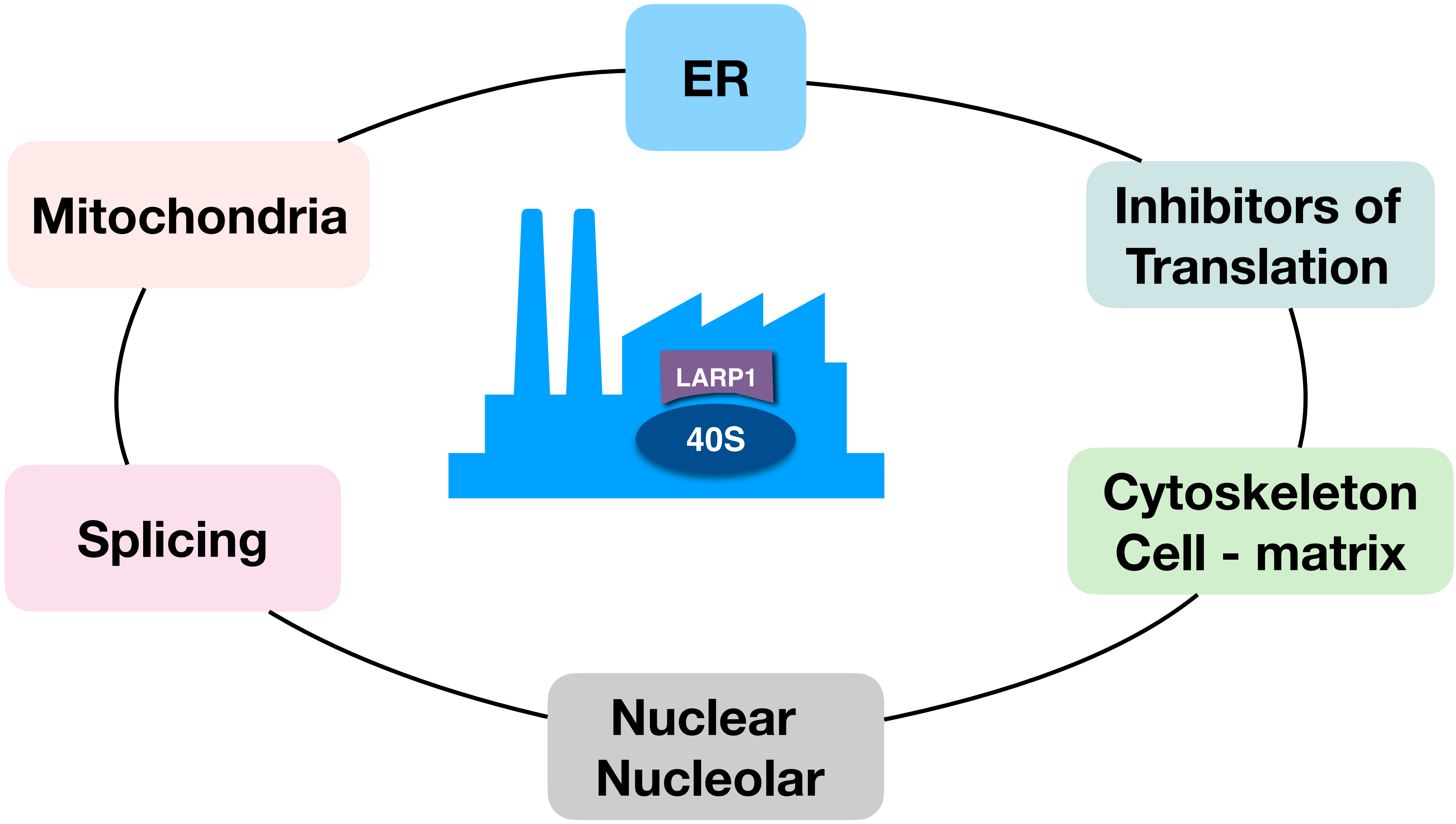


1. Growing
2. TORi
3. SS

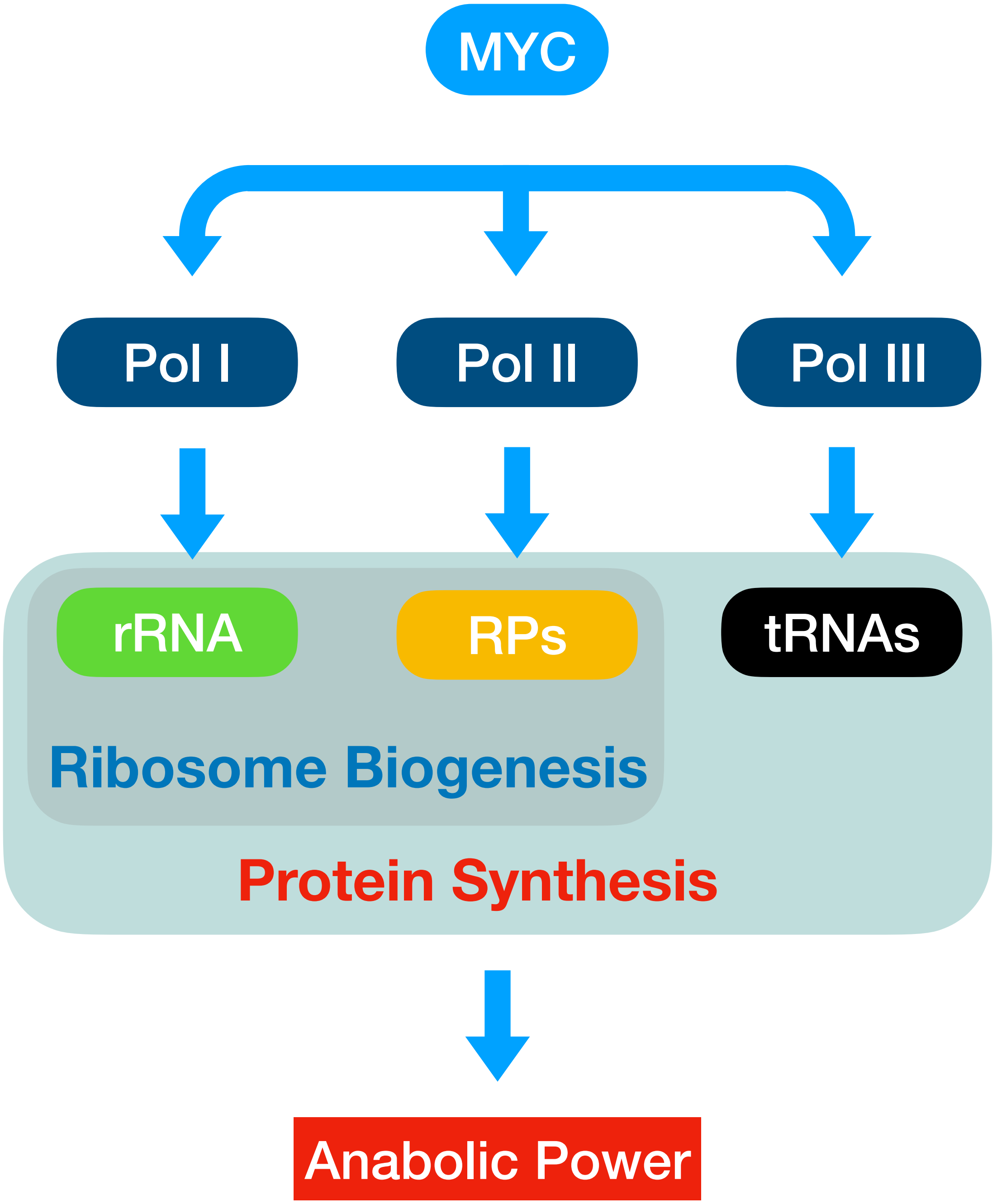
4. Growing



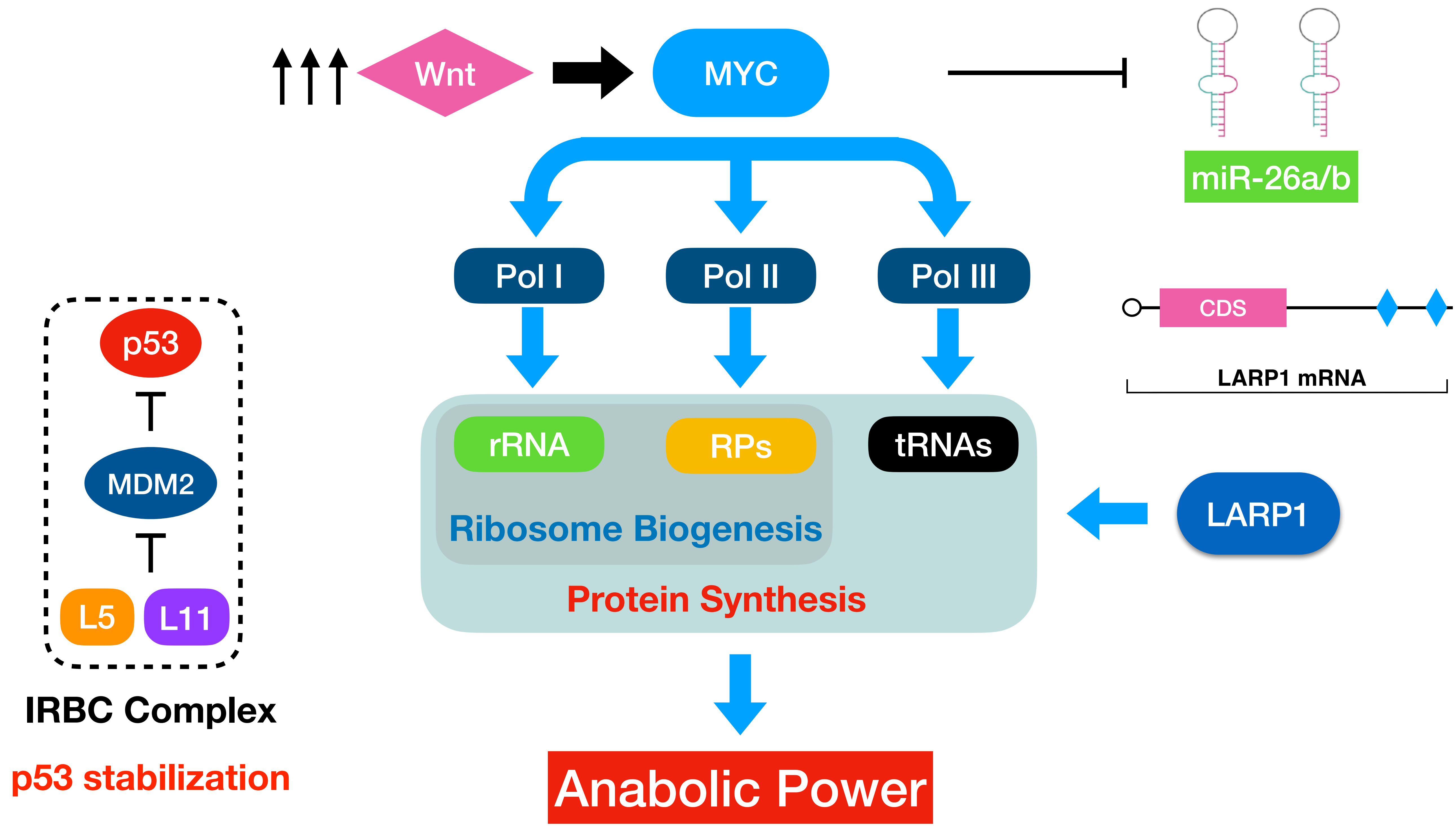
Are 40S-LARP1 ribosomes different in make up than 40S ?



c-MYC and Ribosome Biogenesis



Hyperactivation of Ribosome Biogenesis in CRC (CMS2-3)



Morcelle et al., Cancer Res. 2019

Pedro Fuentes
Joffrey Pelletier
Carolina Martinez
Flavia Iannizzotto
Pau Bosch
Albert Tauler

Virgina Diez-Obrero
Victor Moreno

Ramon Salazar

Santiago Ramon y Cajal
Marta Sese

Always looking for scientifically curious people !

agentilella@idibell.cat

To a Sailor With No Direction
No Wind is Favorable
(Seneca)

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