

# New kid on the (translation) block

Petr Těšina



National Institute  
of Virology and Bacteriology



Funded by  
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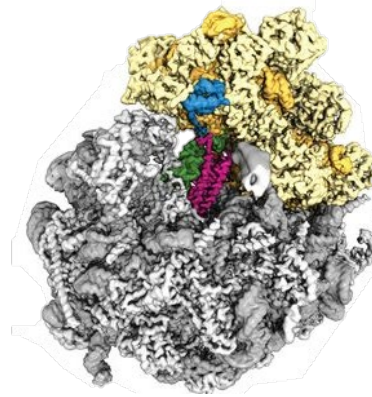
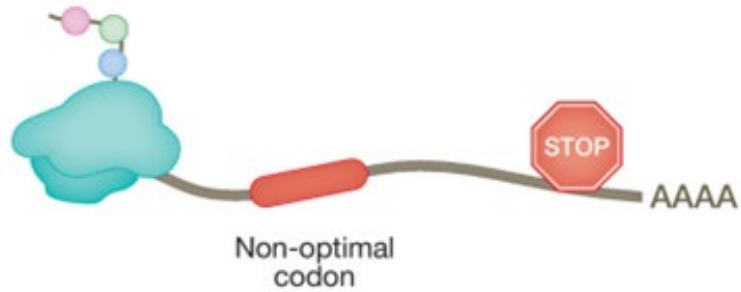
# About me

- PhD at IOCB Prague, group of Pavlína Řezáčová, Structural biology
- Postdoctoral experience in Gene Center Munich from 2016, AGs Halic and Beckmann
- Cryo-EM of co-translational surveillance processes
- PI position at CEITEC MU Brno (since July)



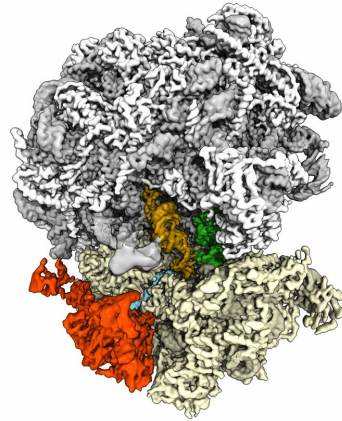
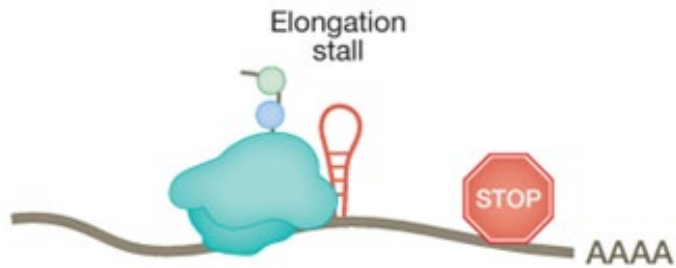
# Introduction – mRNA decay

## Codon optimality-mediated mRNA decay (COMD)



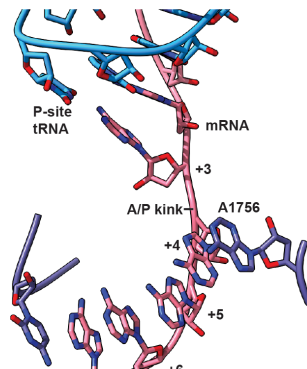
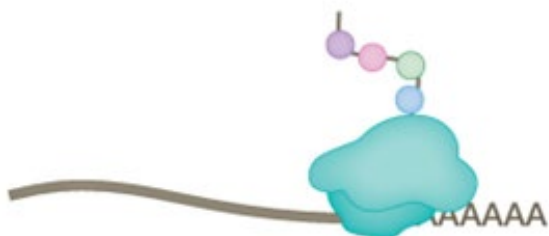
Buschauer R. et al., Science, 2020

## No-go mRNA decay (NGD)



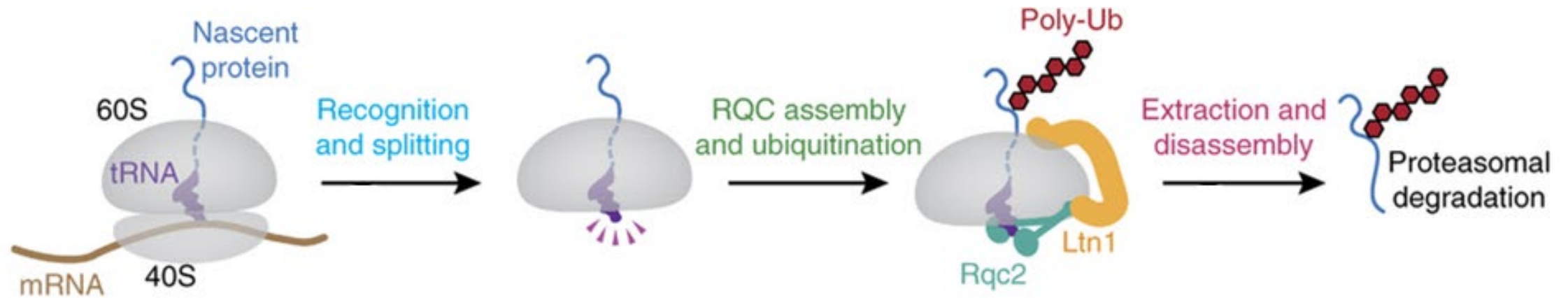
Tesina P. et al., NSMB, 2019

## Non-stop mRNA decay (NSD)



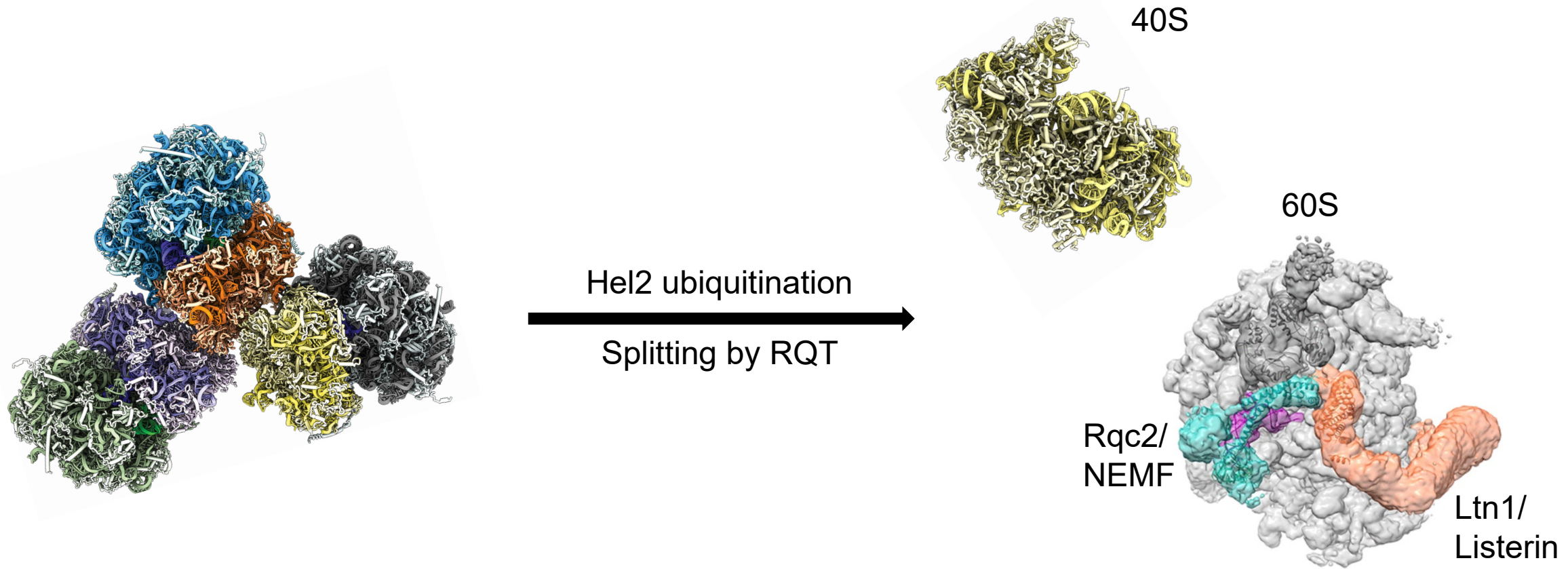
Tesina P. & Lessen L. et al., EMBO J, 2020

# Introduction: Ribosome-associated quality control (RQC)



- Ribosomal collision is the hallmark of problematic translation
- mRNA decay (NGD) + Ribosome-associated quality control (RQC)

# Introduction - RQC

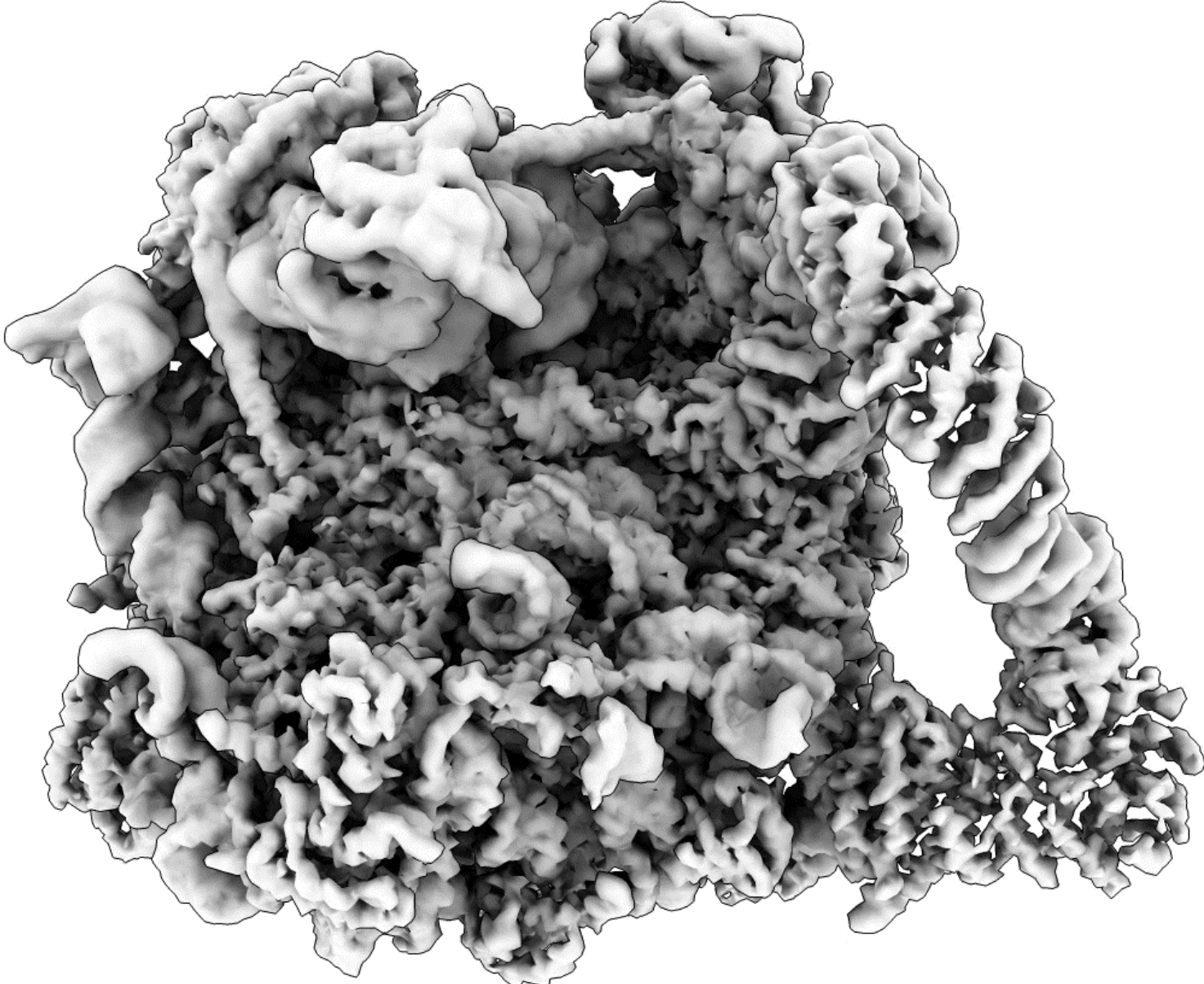


- RQC is conserved from bacteria to humans (C-terminal tails)
- How does Rqc2 govern peptide elongation cycle without 40S and mRNA?

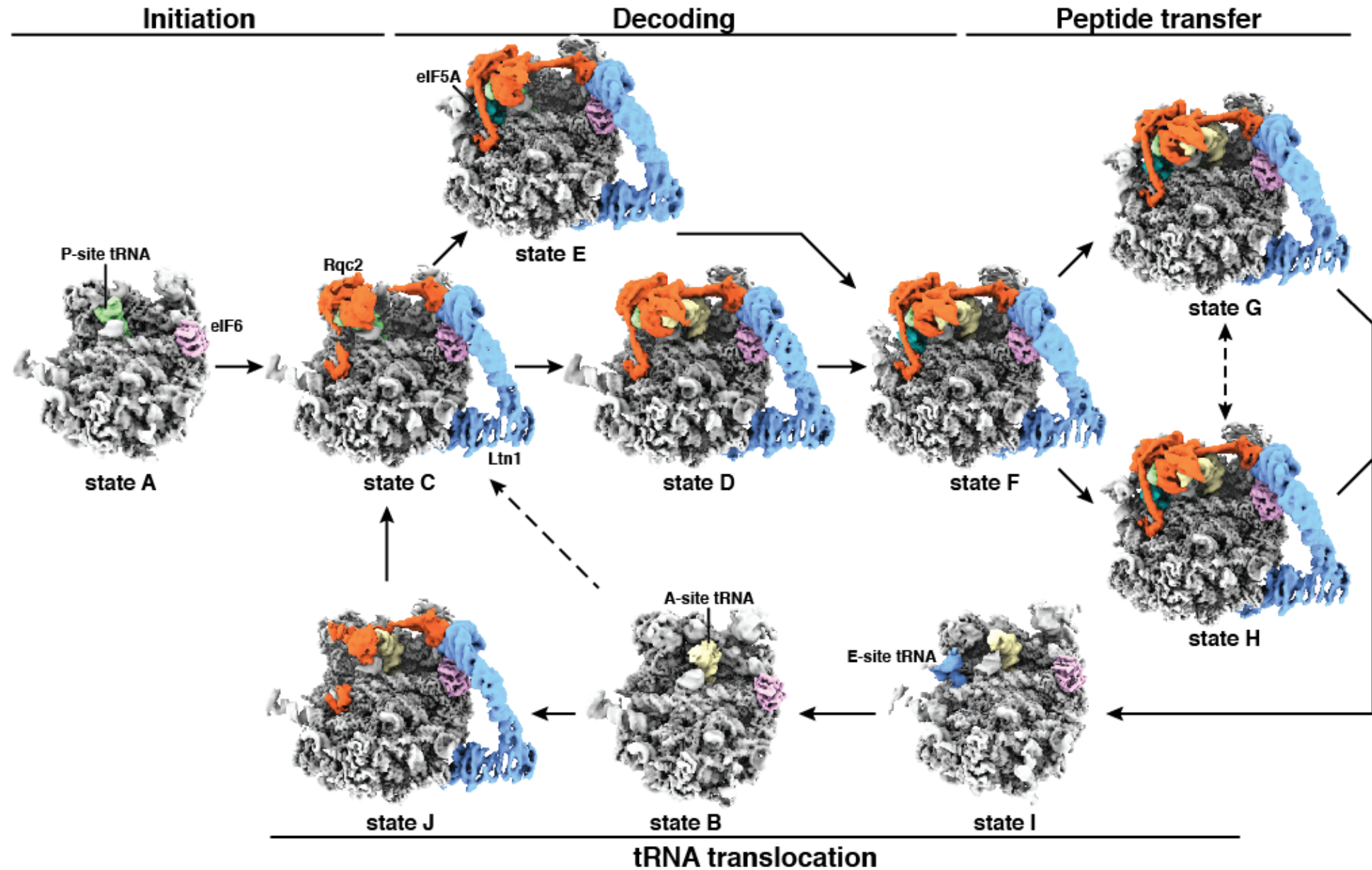


# Overview

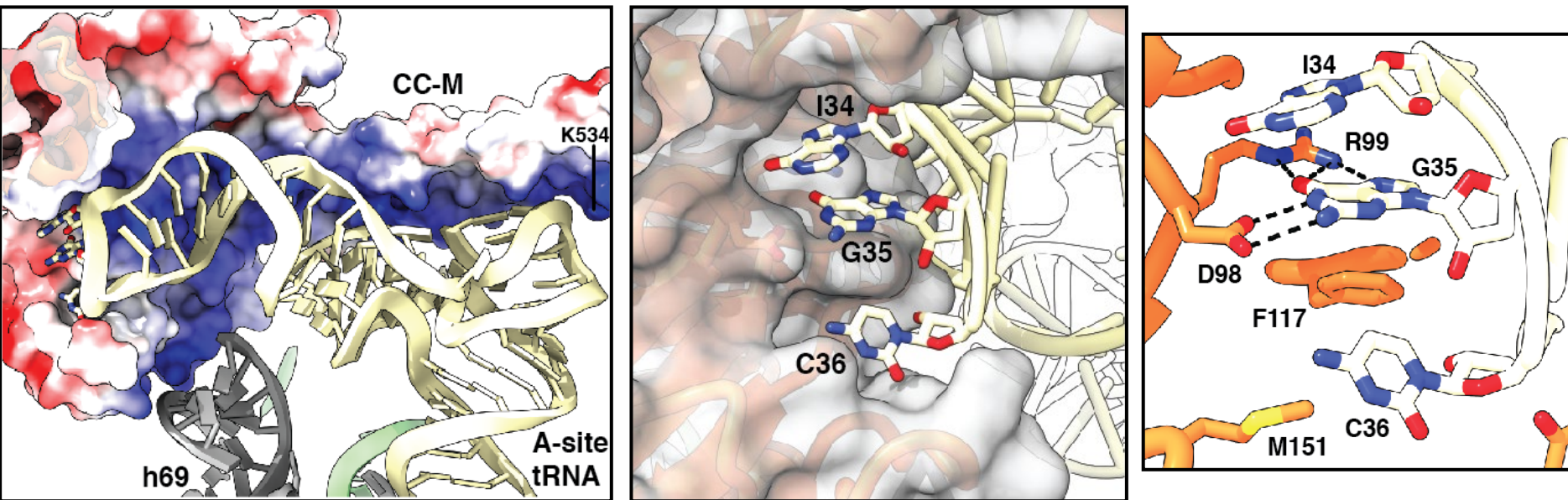
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# CAT tailing cycle



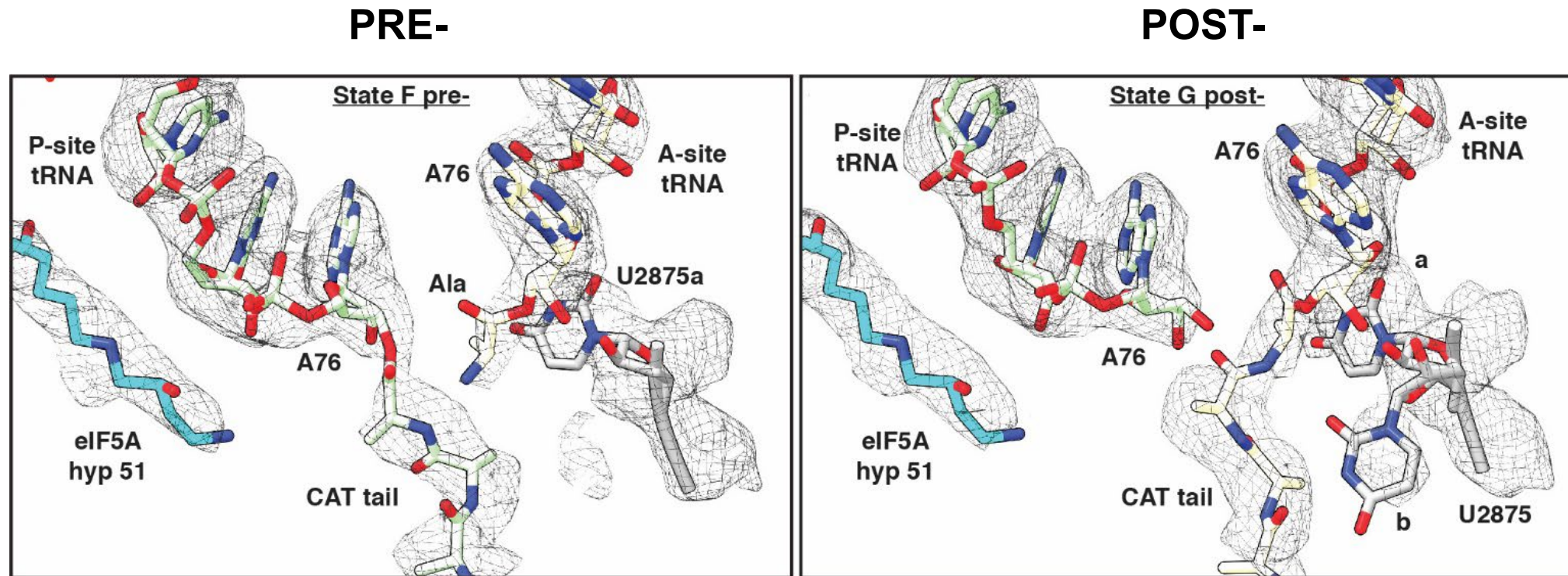
# Decoding



- Rqc2 structure selects for NGY anticodon, RCN in “codon language” - GCN = Ala; ACN = Thr

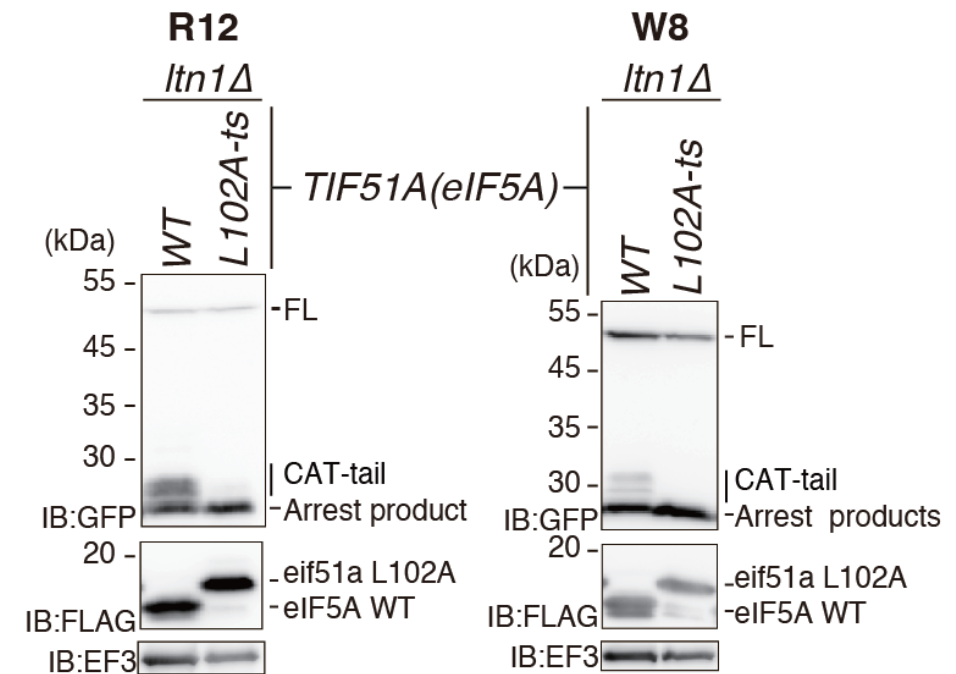
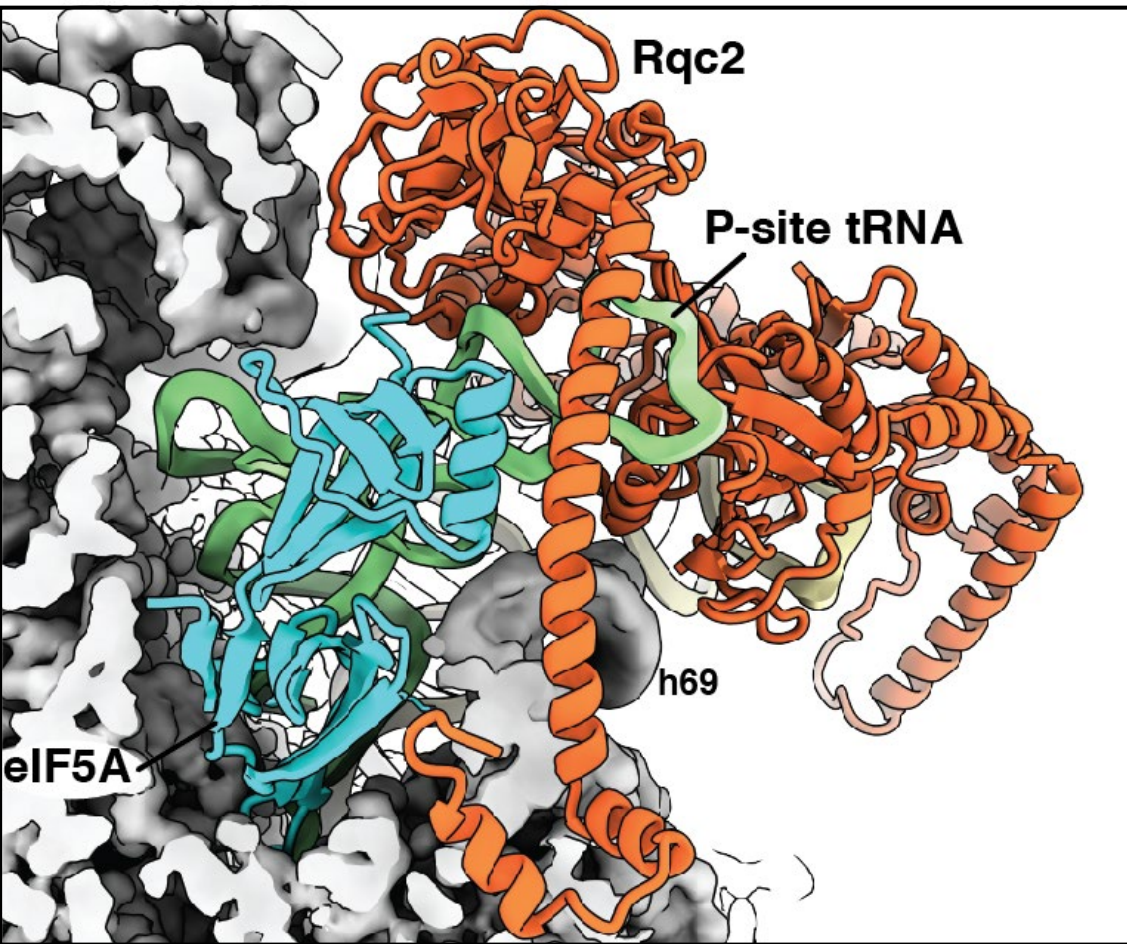


# Peptide transfer



- eIF5A present in all peptide transfer states

# eIF5A is a novel CAT tailing factor



- eIF5A is essential for CAT tailing

# Conclusions

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- eIF5A is a novel factor in eukaryotic CAT tailing
- Rqc2 governs initiation, decoding specificity and peptide transfer
- Rqc2 undergoes conformational rearrangement to allow for tRNA translocation
- Ltn1 exerts a broad range of movement to ubiquitinate a variety of degradation targets

**Molecular Cell**

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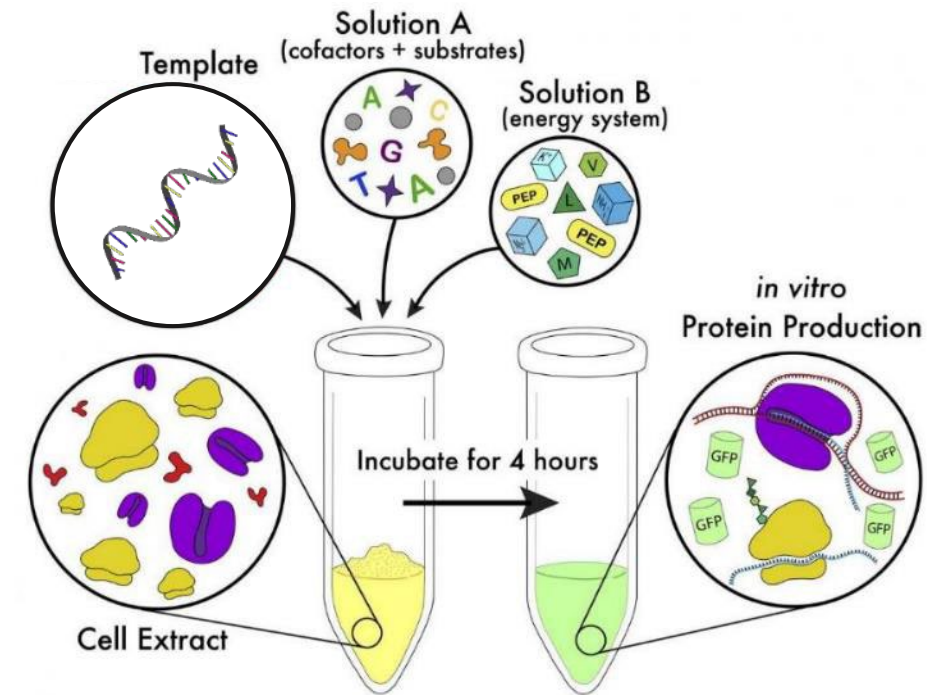
Article

## **Molecular basis of eIF5A-dependent CAT tailing in eukaryotic ribosome-associated quality control**

Petr Tesina,<sup>1,3,\*</sup> Shuhei Ebine,<sup>2,3</sup> Robert Buschauer,<sup>1,3</sup> Matthias Thoms,<sup>1</sup> Yoshitaka Matsuo,<sup>2</sup> Toshifumi Inada,<sup>2,\*</sup> and Roland Beckmann<sup>1,4,\*</sup>

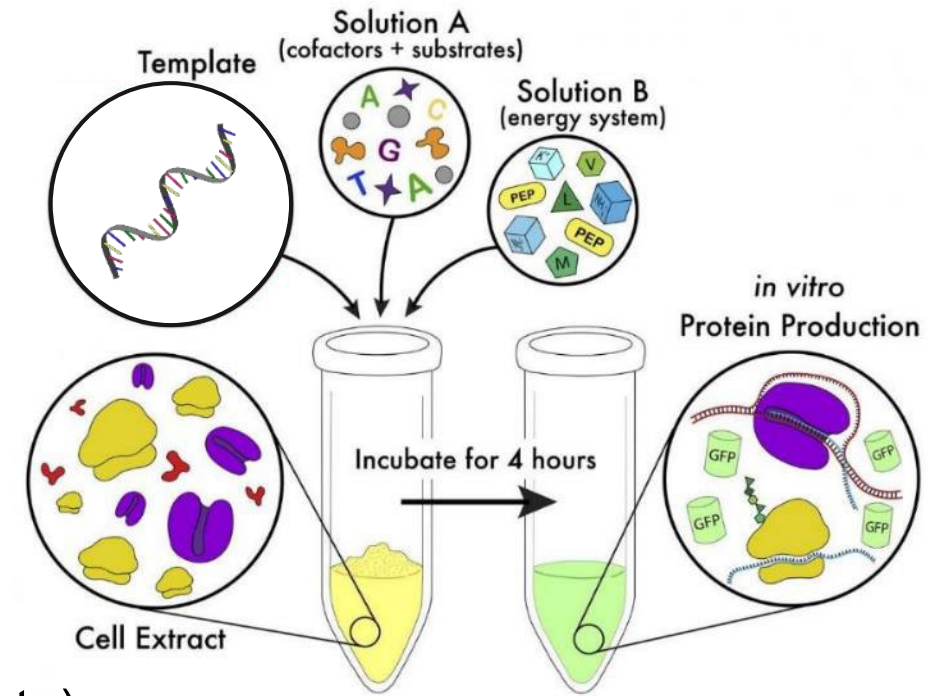
# Future plans: human host-pathogen interactions

- Mechanistic understanding by cryo-EM
- Challenges of the human system
- Key objective: unlock the potential of controlled *in vitro* translation in the human system.

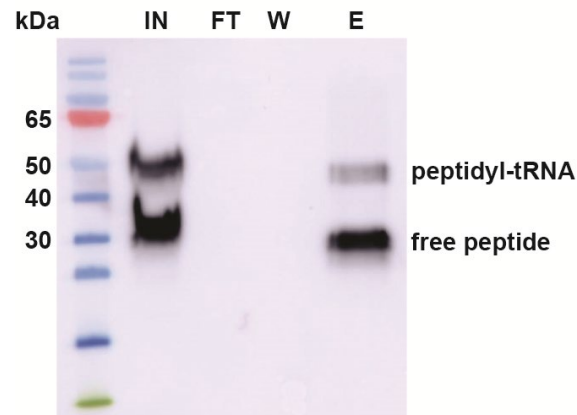
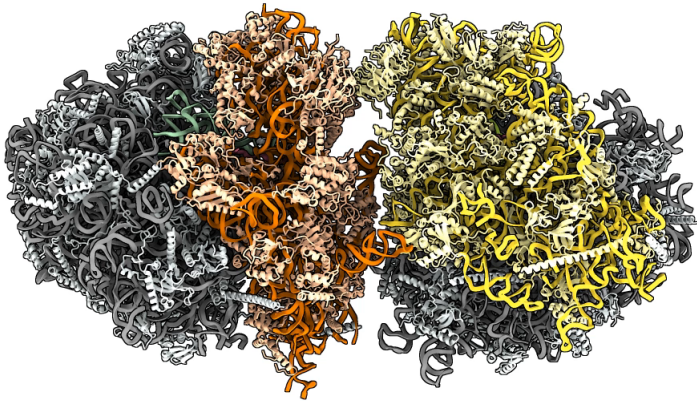


# Future plans: human host-pathogen interactions

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- Key objective: unlock the potential of controlled *in vitro* translation in the human system.



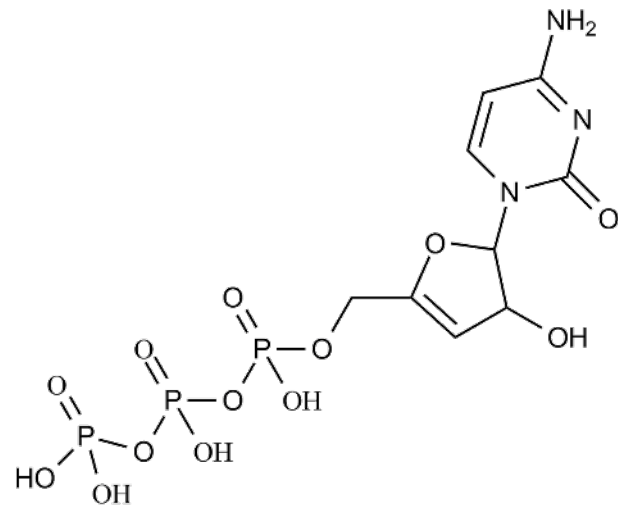
- Proof-of concept-study on human collided disomes (RQC substrate)



# RQC initiation in host-pathogen interaction

## Viperin and translation stalling

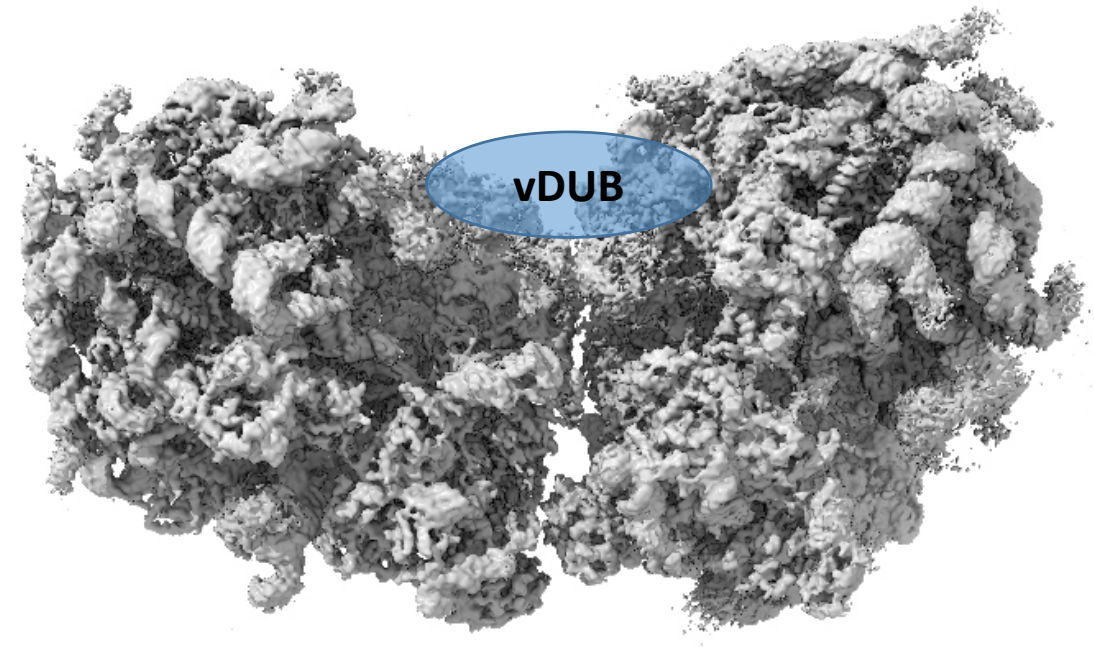
- The ddhCTP product inhibits viral RDRPs but not RNA Pol II, activation of ZAKα and GCN2
- Incorporation into mRNA and ribosome stalling?



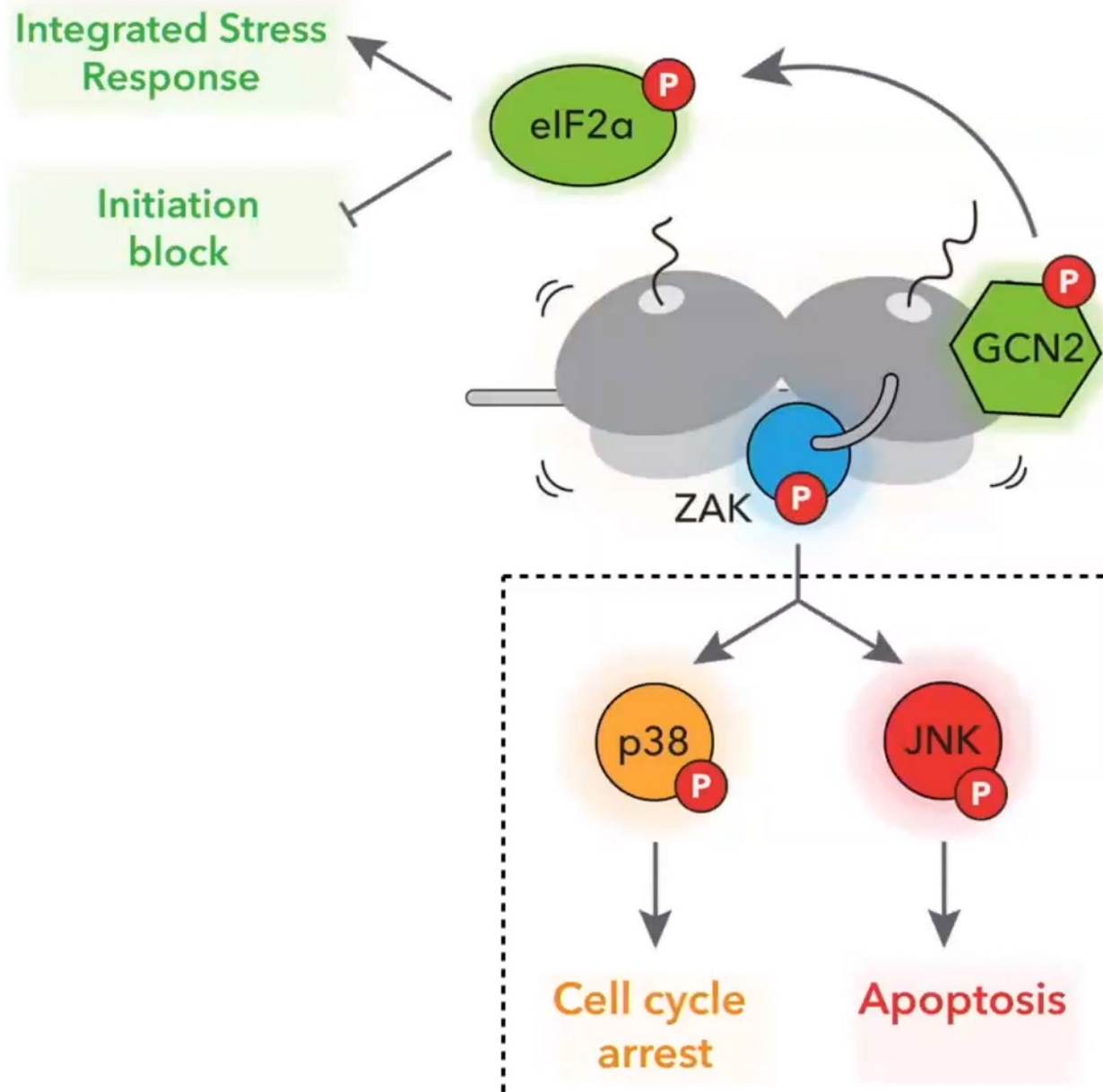
3'-Deoxy-3',4'-dideohydro-cytidine triphosphate

## EBV vDUB

- Counters ZNF598 activity



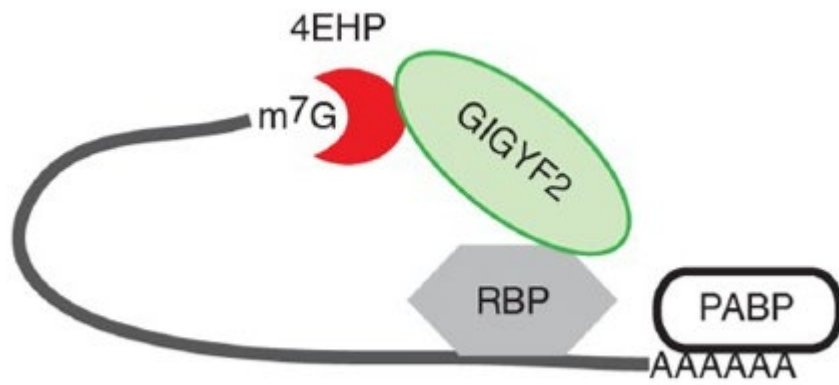
# ISR and RSR



# SARS-CoV-2 and translation control

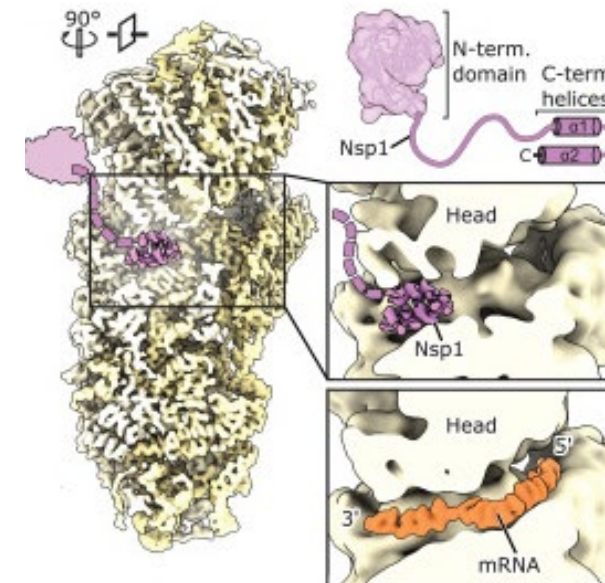
## NSP2 and interferone response inhibition

- NSP2 enhances binding of RQC pathway component GIGYF2 to cap-binding translation inhibitor 4EHP to inhibit interferone response
- Elusive connection to ribosome stalling



## NSP1 and viral protein translation

- NSP1 shuts down host translation by blocking mRNA entry channel
- How are the viral mRNAs translated? Role of the 5' leader sequence.





# Acknowledgements

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## The Beckmann lab

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Matthias Thoms

## The Inada lab

Prof. Toshifumi Inada  
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## The Jacquier lab

Prof. Alain Jacquier  
Micheline Fromont-Racine  
Abdelkader Namane

## The Green lab

Prof. Rachel Green  
Laura Lessen  
Collin Wu  
Allen Buskirk





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@petesoi1

# MUNI



## Tesina lab

### We are hiring!



Starting  
Grants



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