SCIENCE MEETS LIFE

Mechanisms in C9orf72 linked ALS and FTLD.

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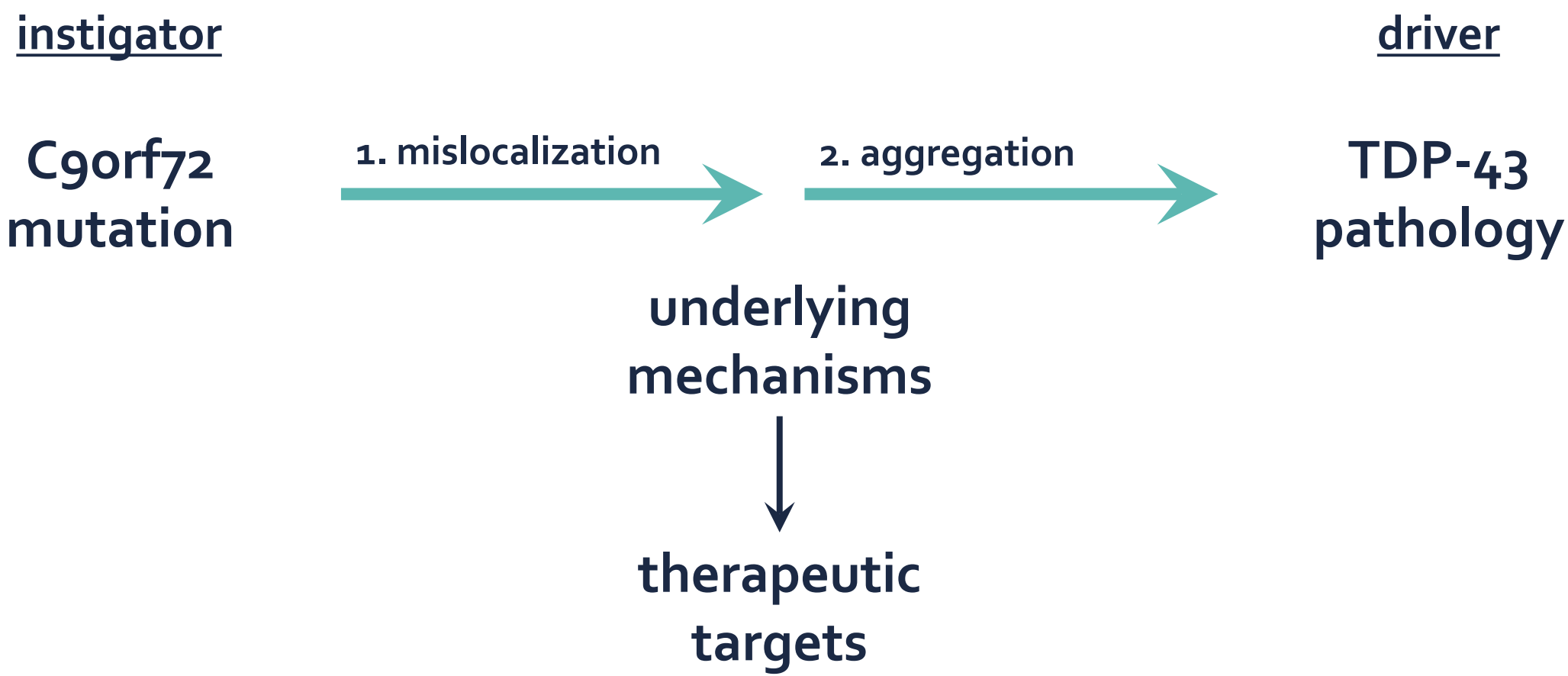
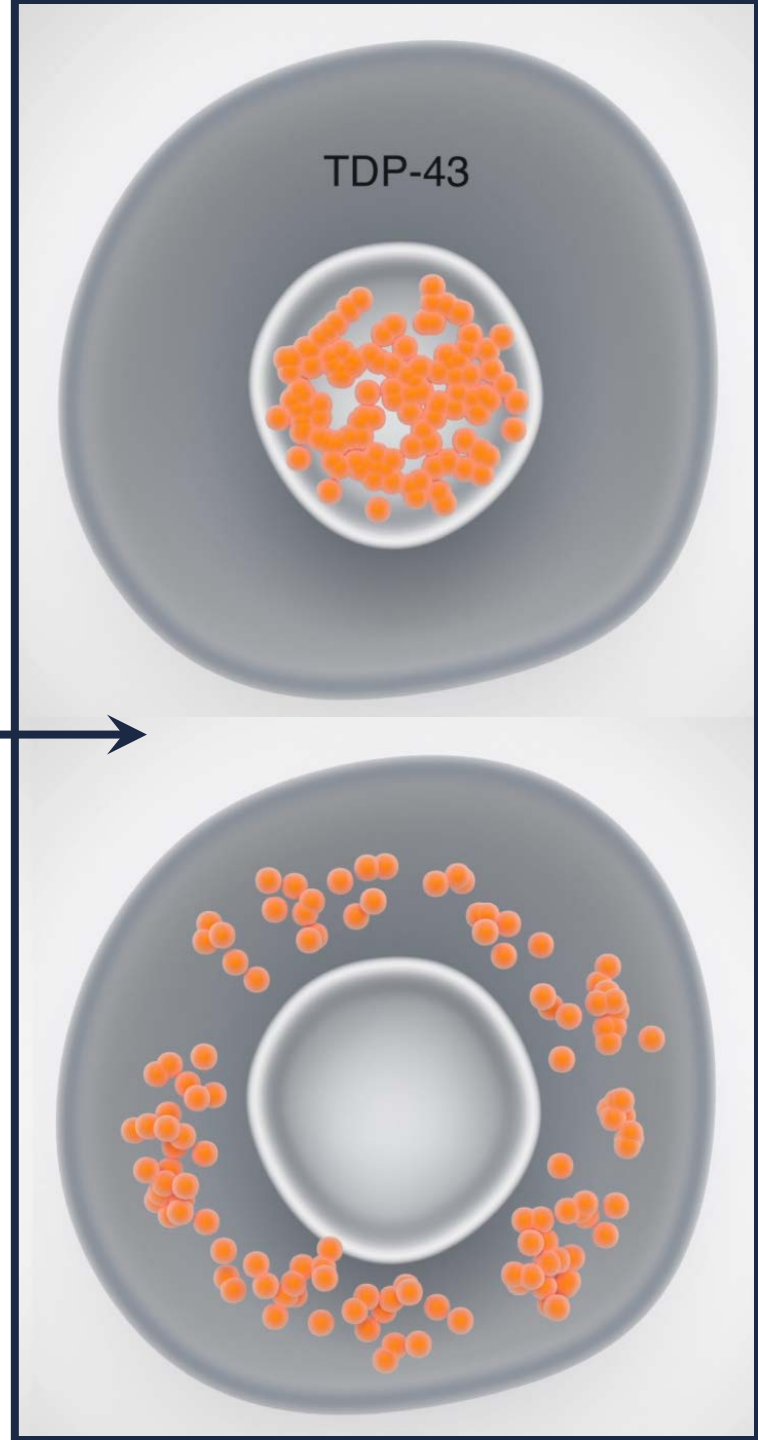
VIB

Understanding the initial steps of ALS



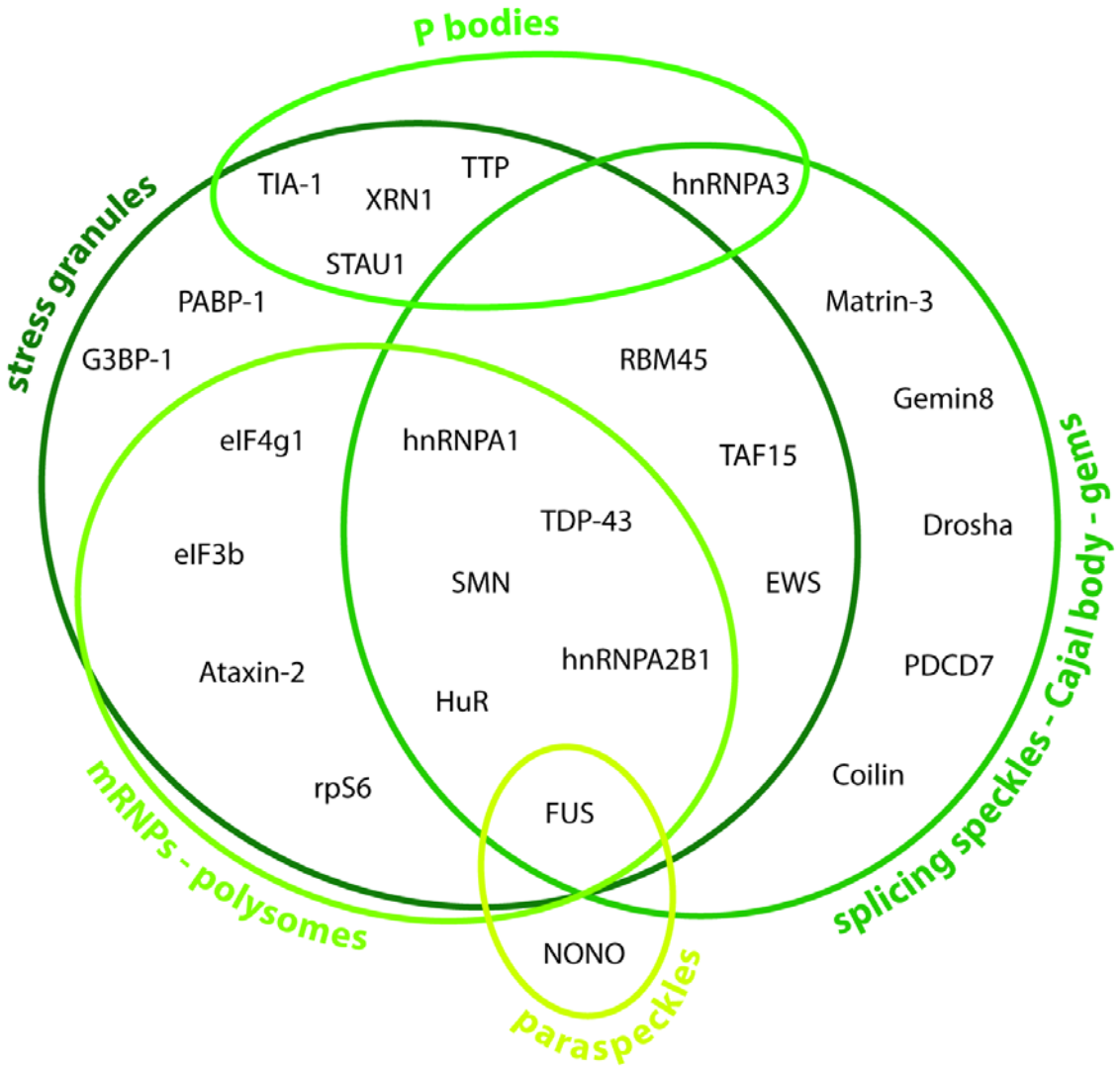
Arginine-rich DPRs perturb nucleocytoplasmic transport

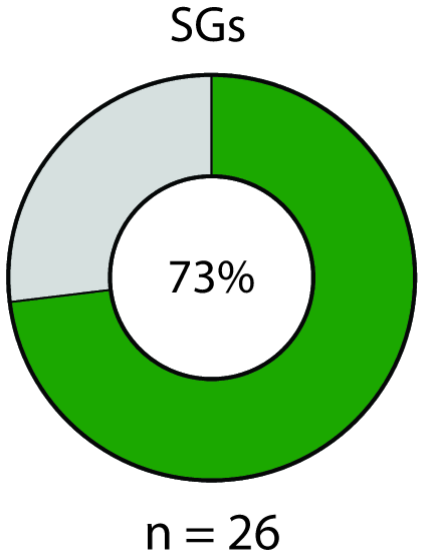
- yeast and fly genetic screens point at nucleocytoplasmic transport
- evidence for transport defects in models and patient material

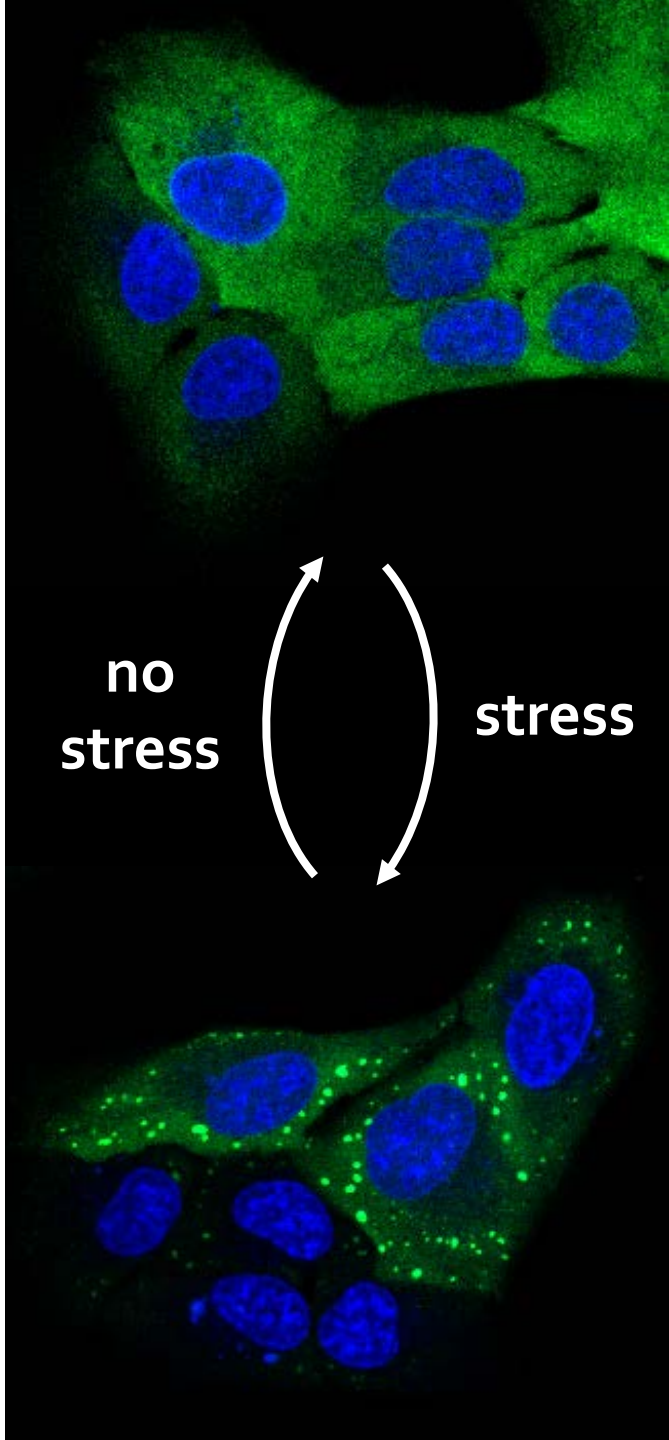


Boeynaems & Bogaert et al., *Sci Rep* (2016)
Boeynaems et al., *Acta Neuropath* (2016)
Jovicic et al., *Nat Neurosci* (2015)

Stress granules in ALS

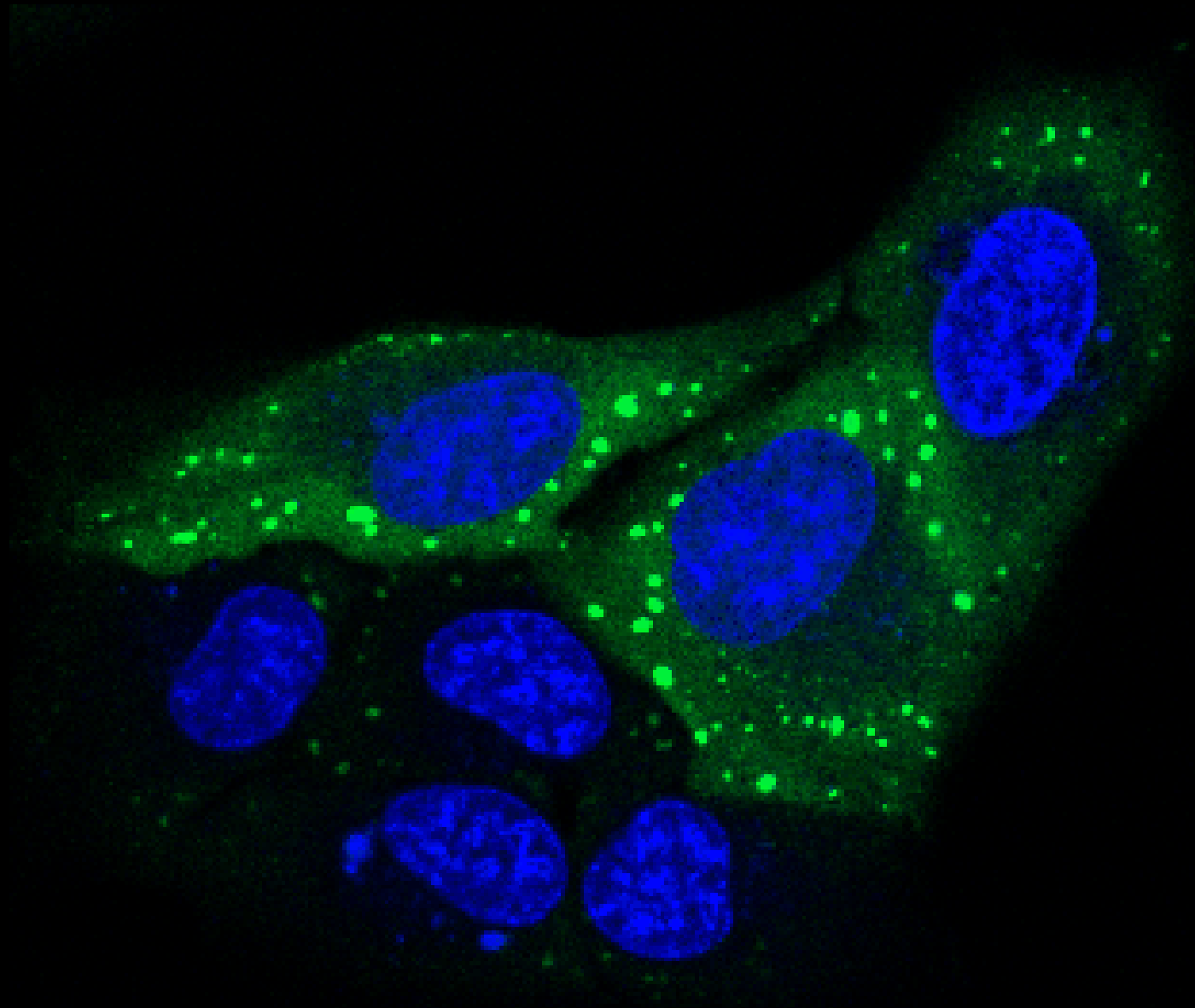






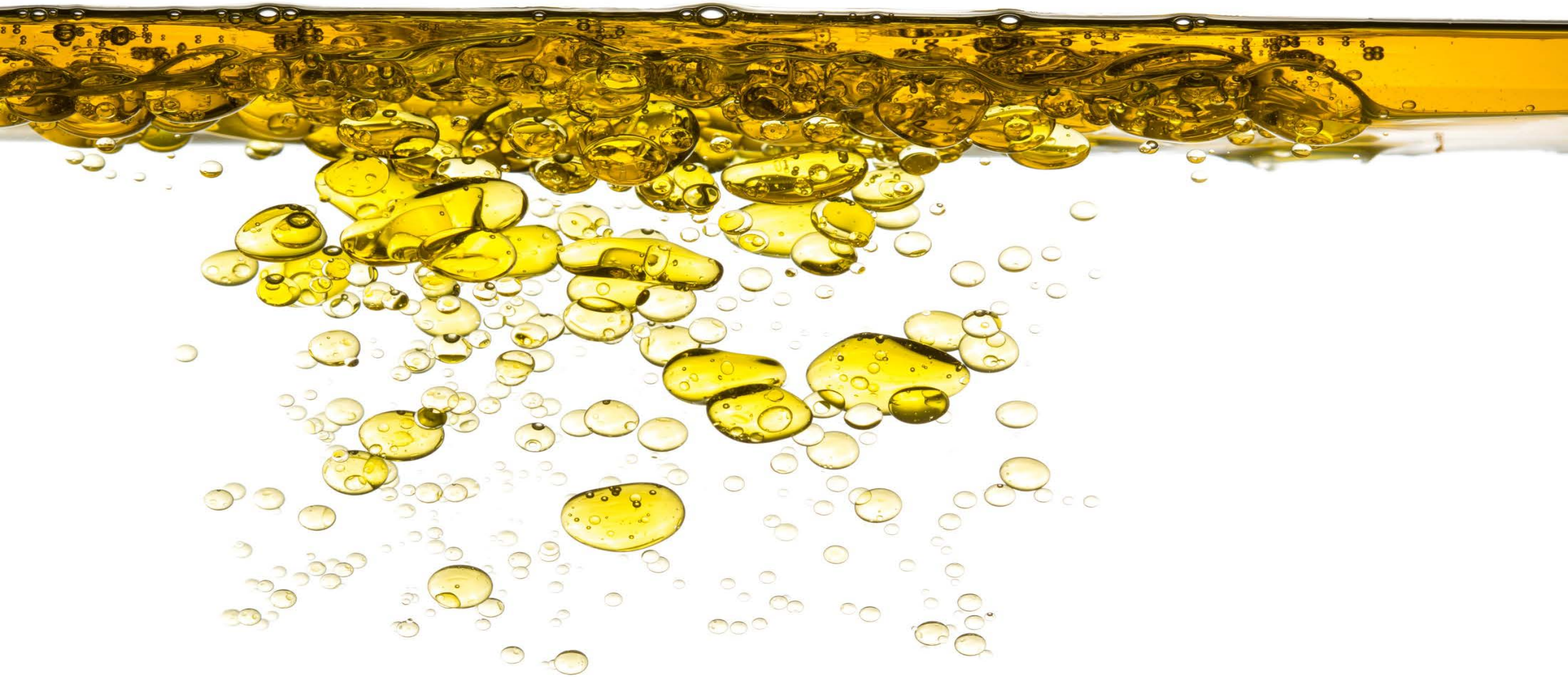
Boeynaems et al., *Acta Neuropath* (2016)

Stress granules are dynamic compartments



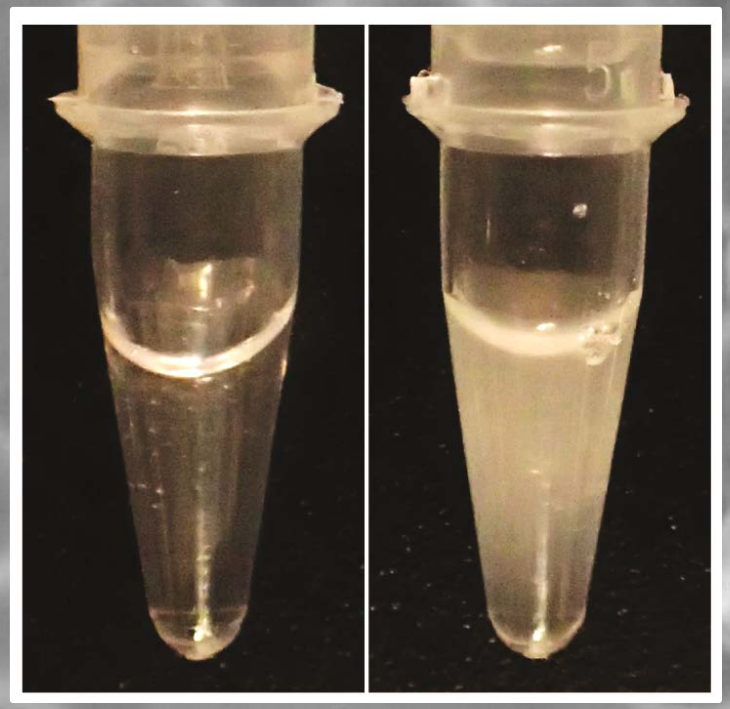
nucleus
G3BP1-GFP
speed 100x

Liquid-liquid phase separation (LLPS)



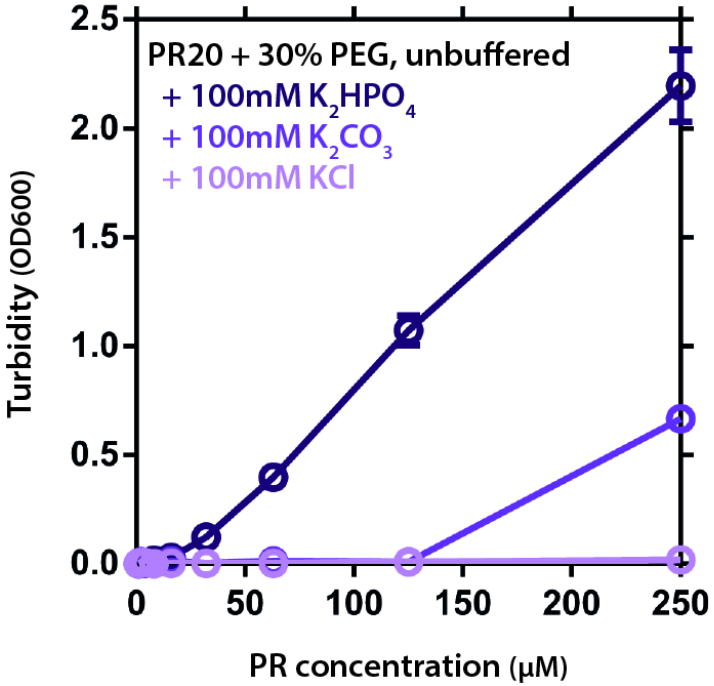
Arginine-rich DPRs undergo LLPS

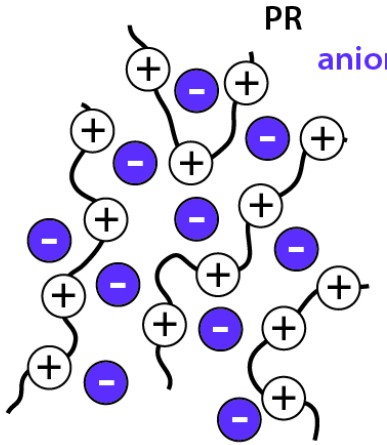
PR30 + PEG



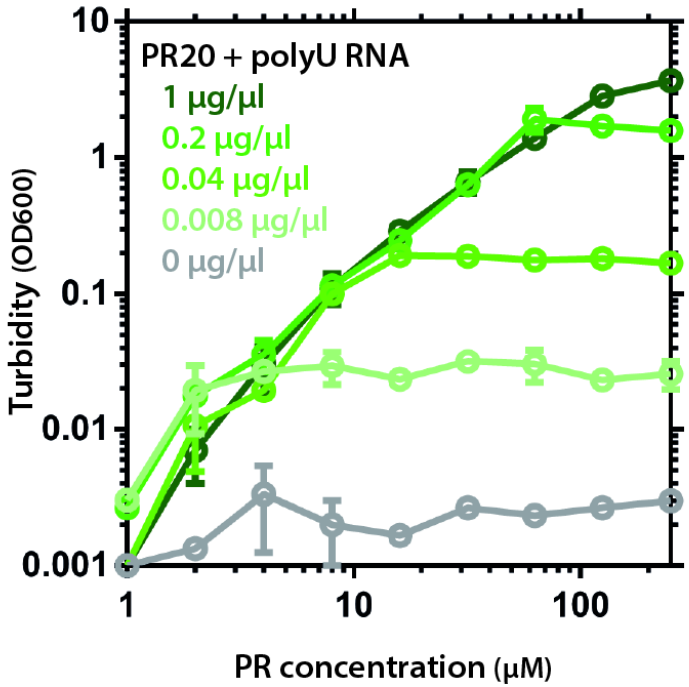
PR20 LLPS is dependent on counteranions

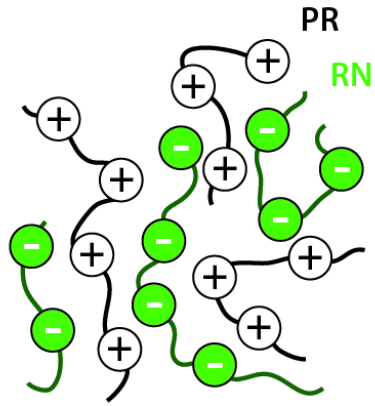
inorganic salt





RNA

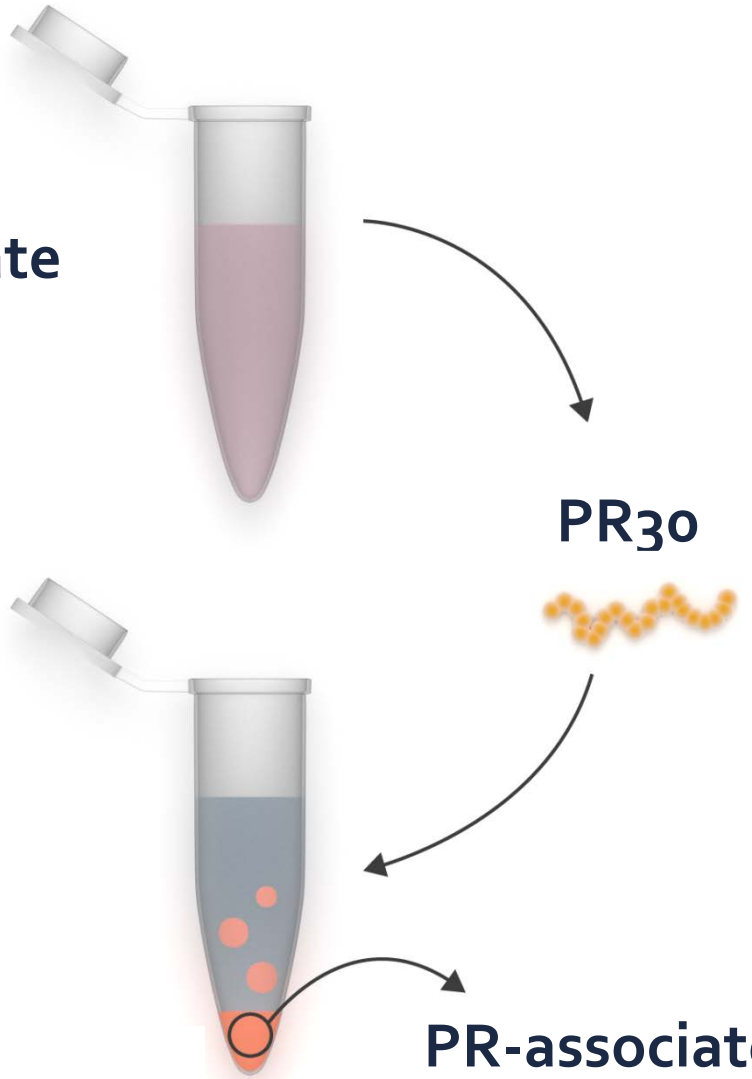




Boeynaems et al., *Mol Cell* (2017)

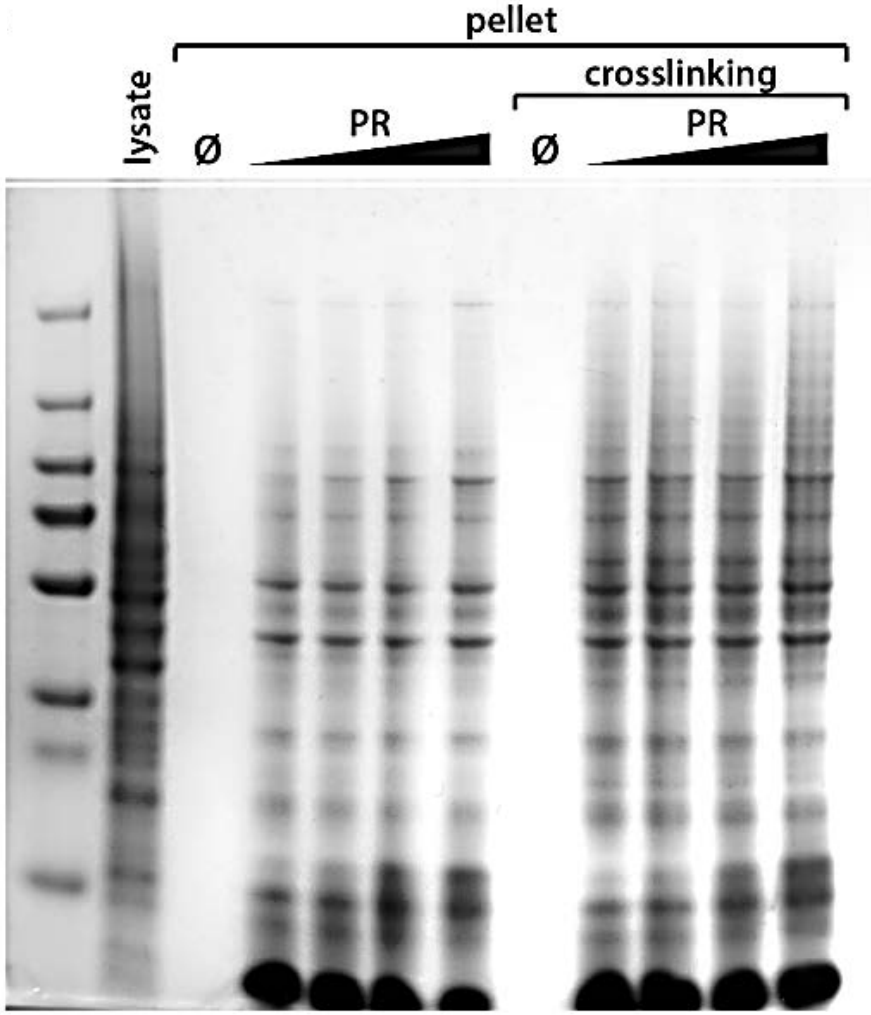
PR30 precipitates specific cellular proteins

Soluble cell lysate

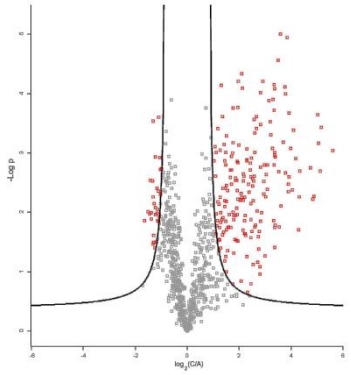


PR30

PR-associated proteins

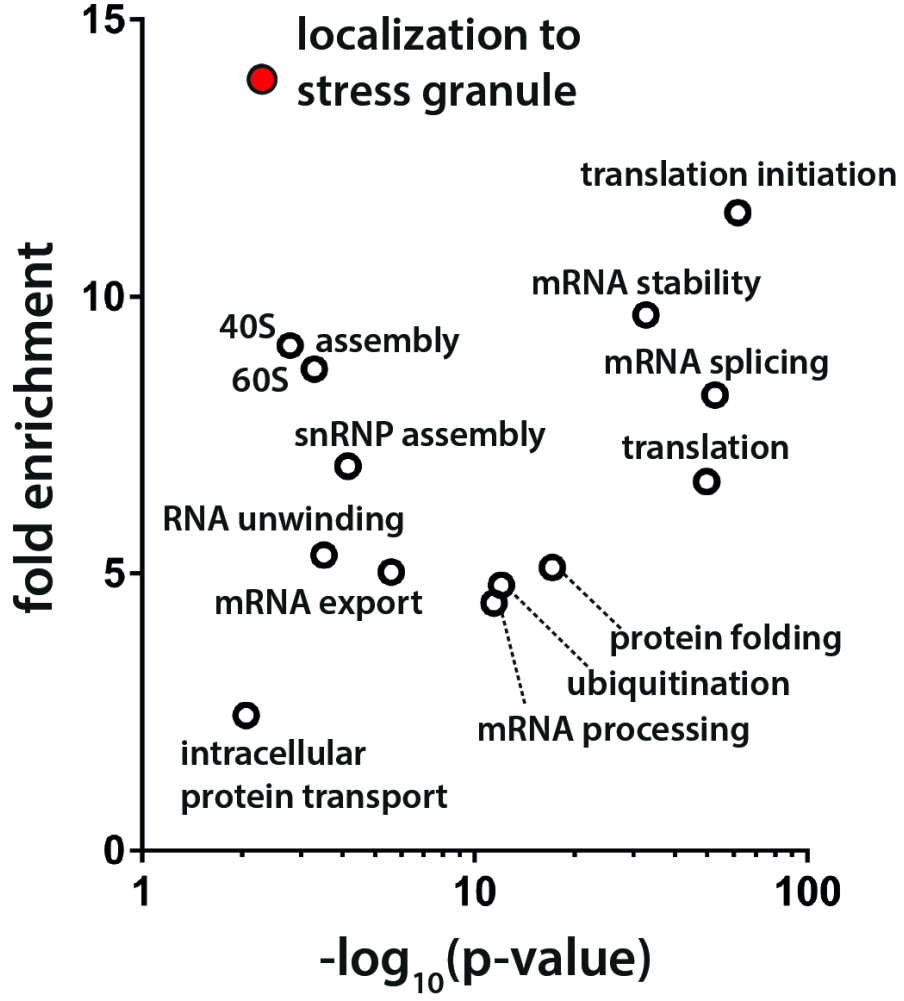


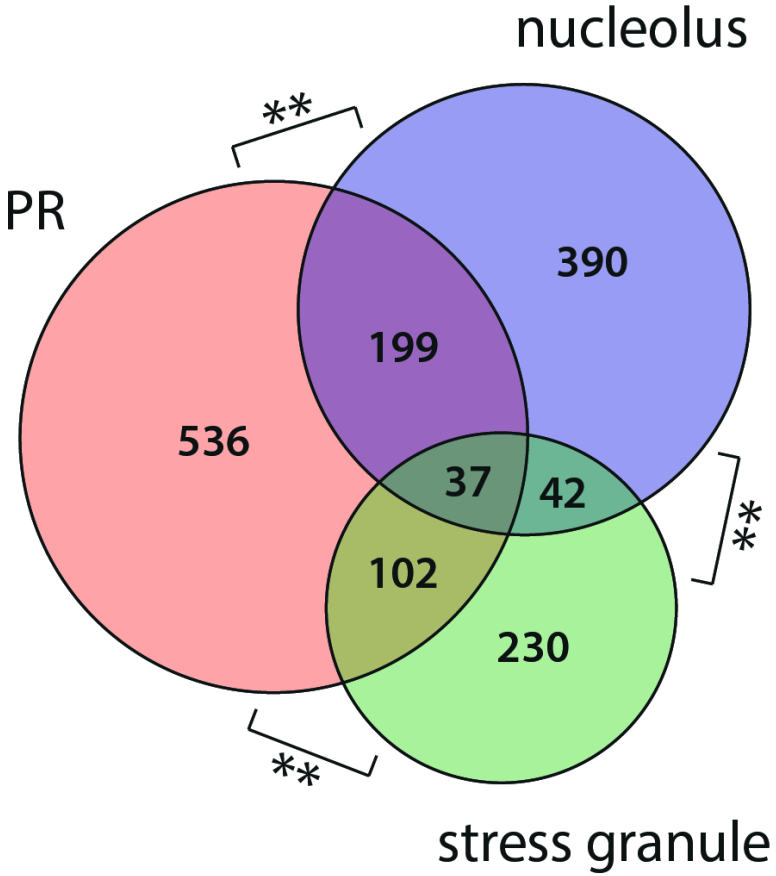
PR30 precipitates stress granule proteins



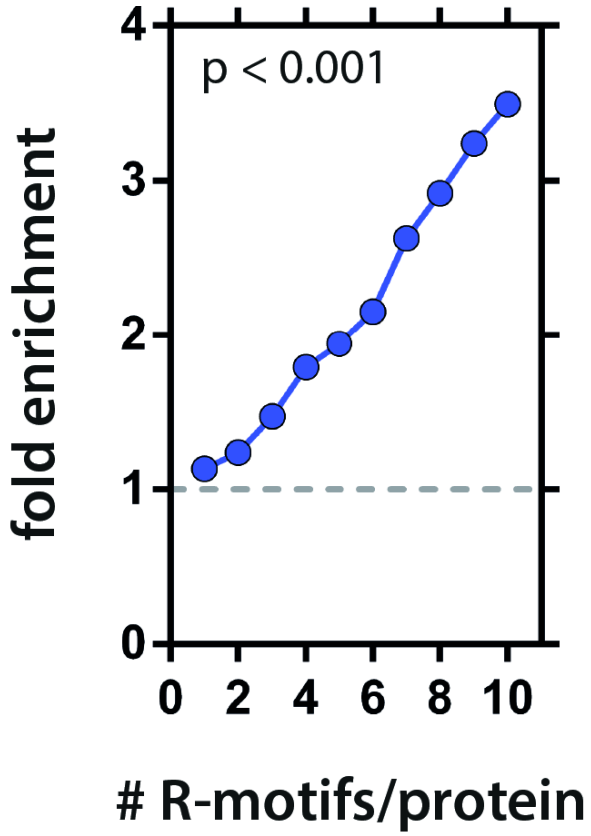
874 proteins

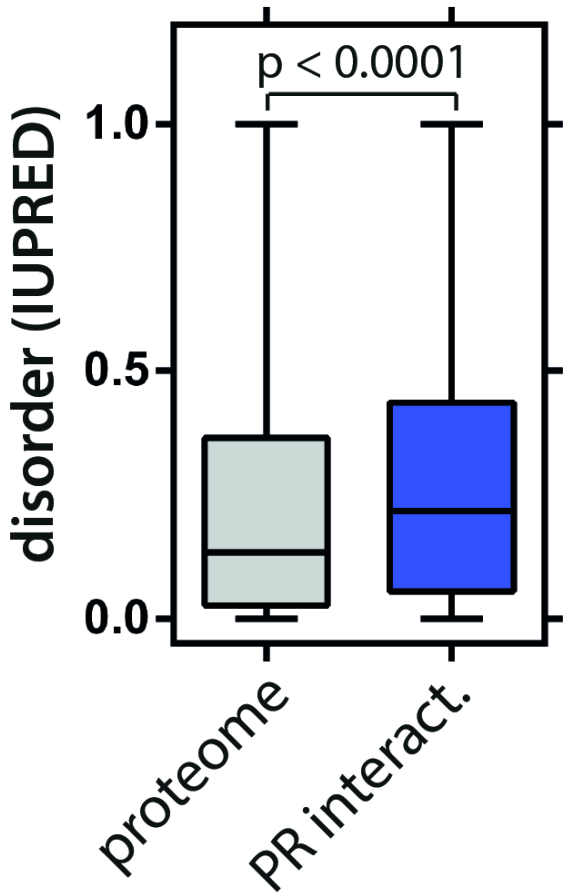
enrichment analyses

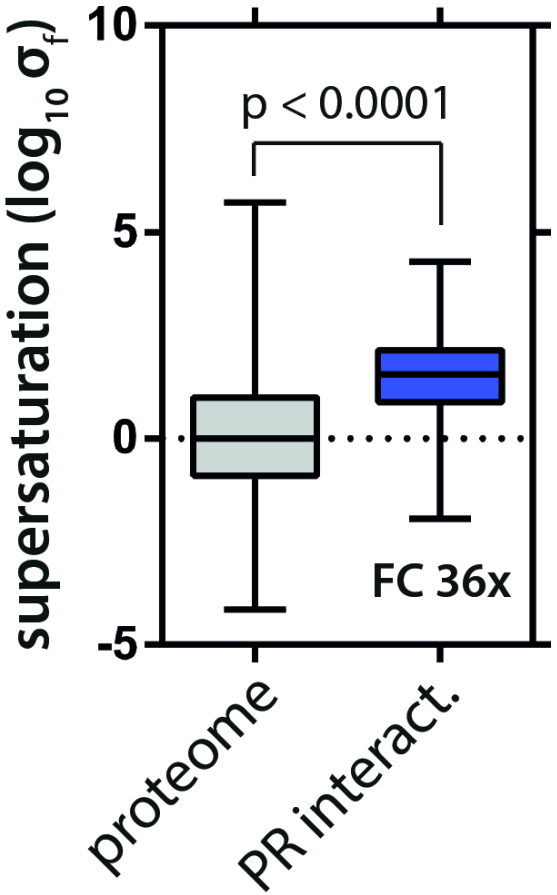




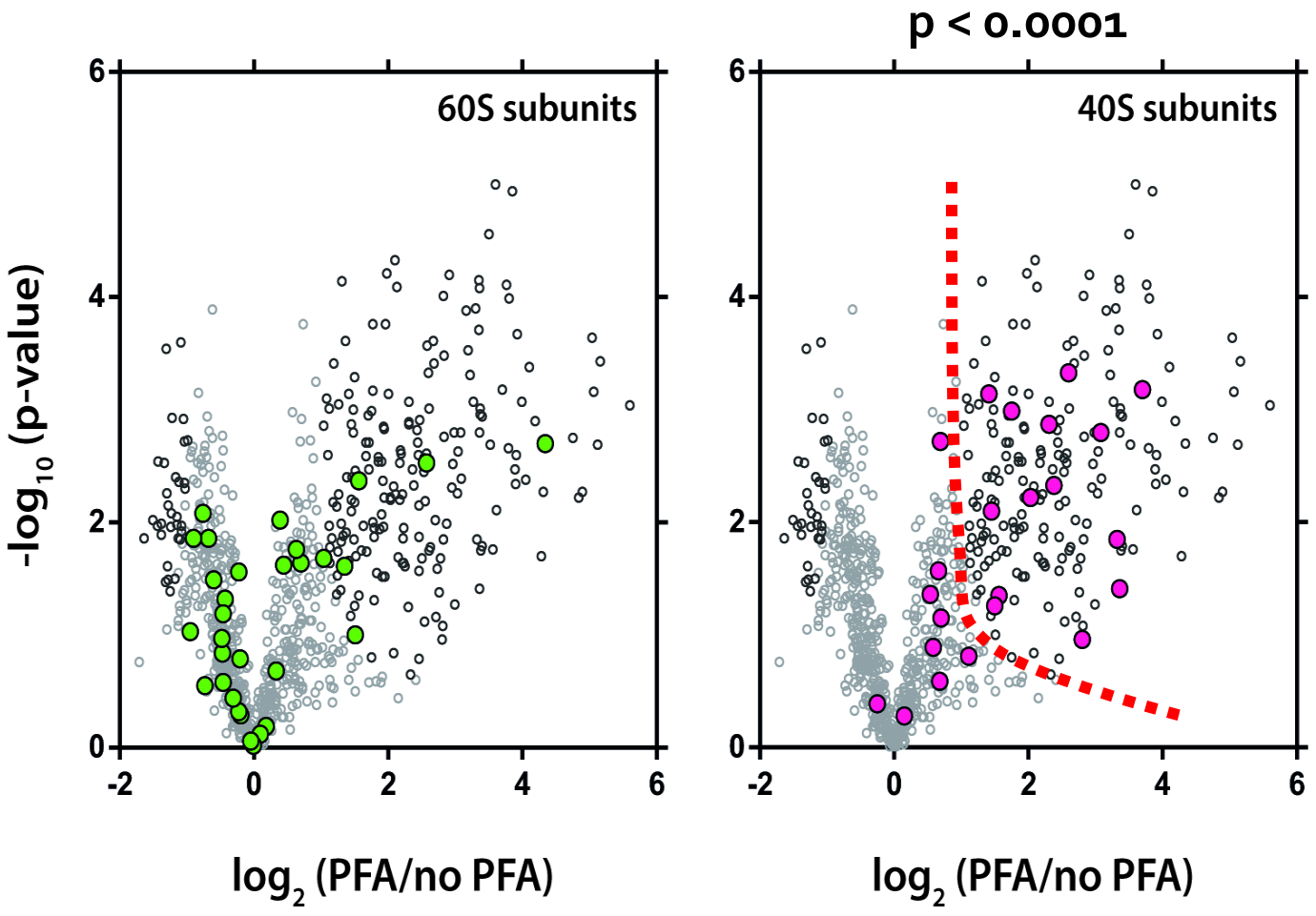
PR30 precipitates arginine-rich, disordered and aggregation-prone proteins





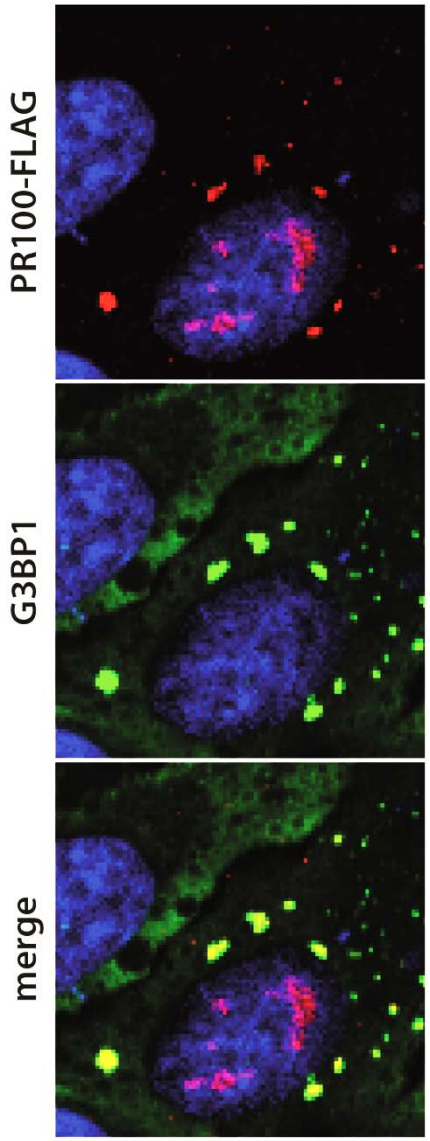


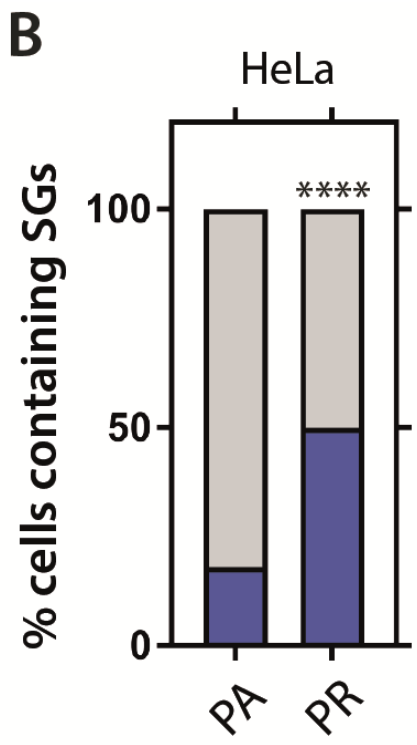
PFA crosslinking enriches specific proteins

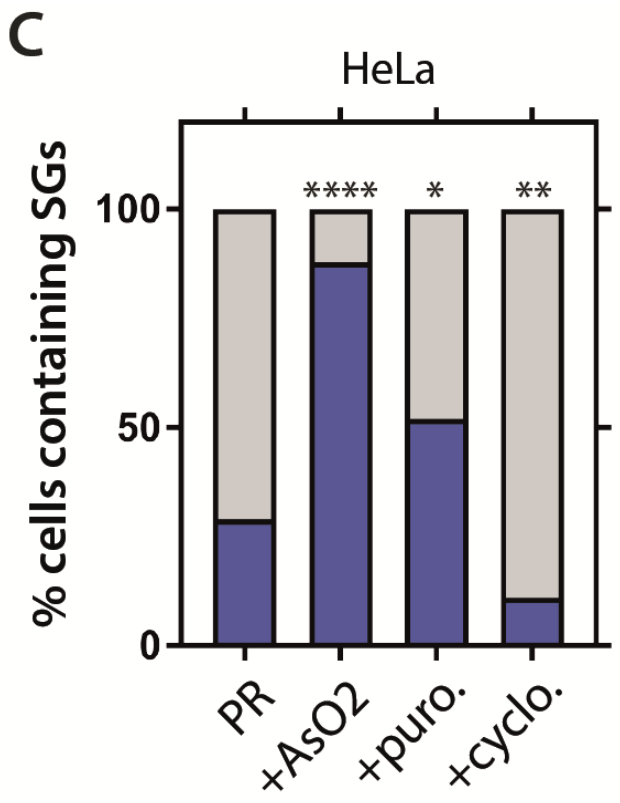


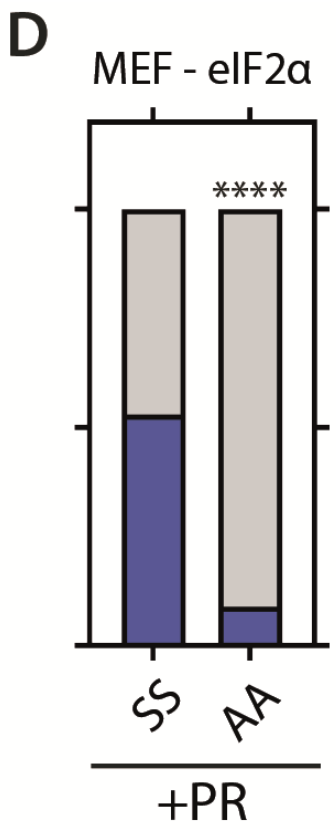
- stable core vs liquid shell
- cellular stress granules enrich 40S but not 60S

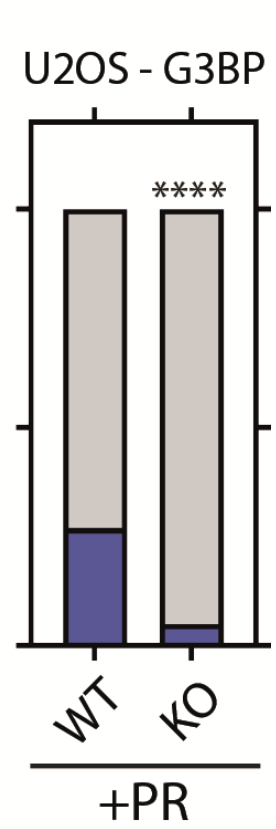
PR induces stress granules through eIF2α





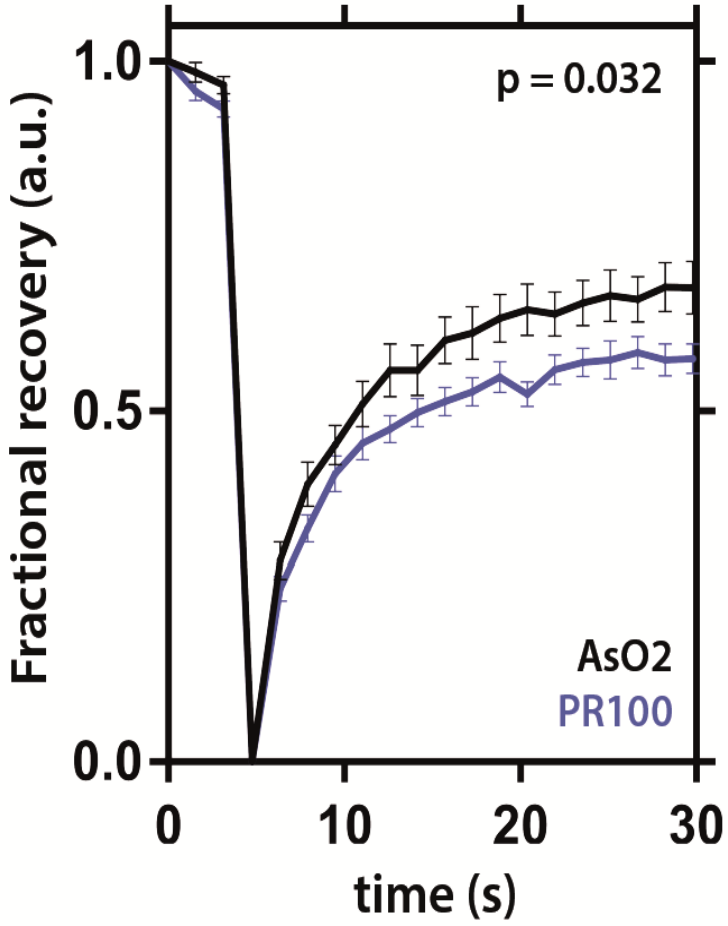




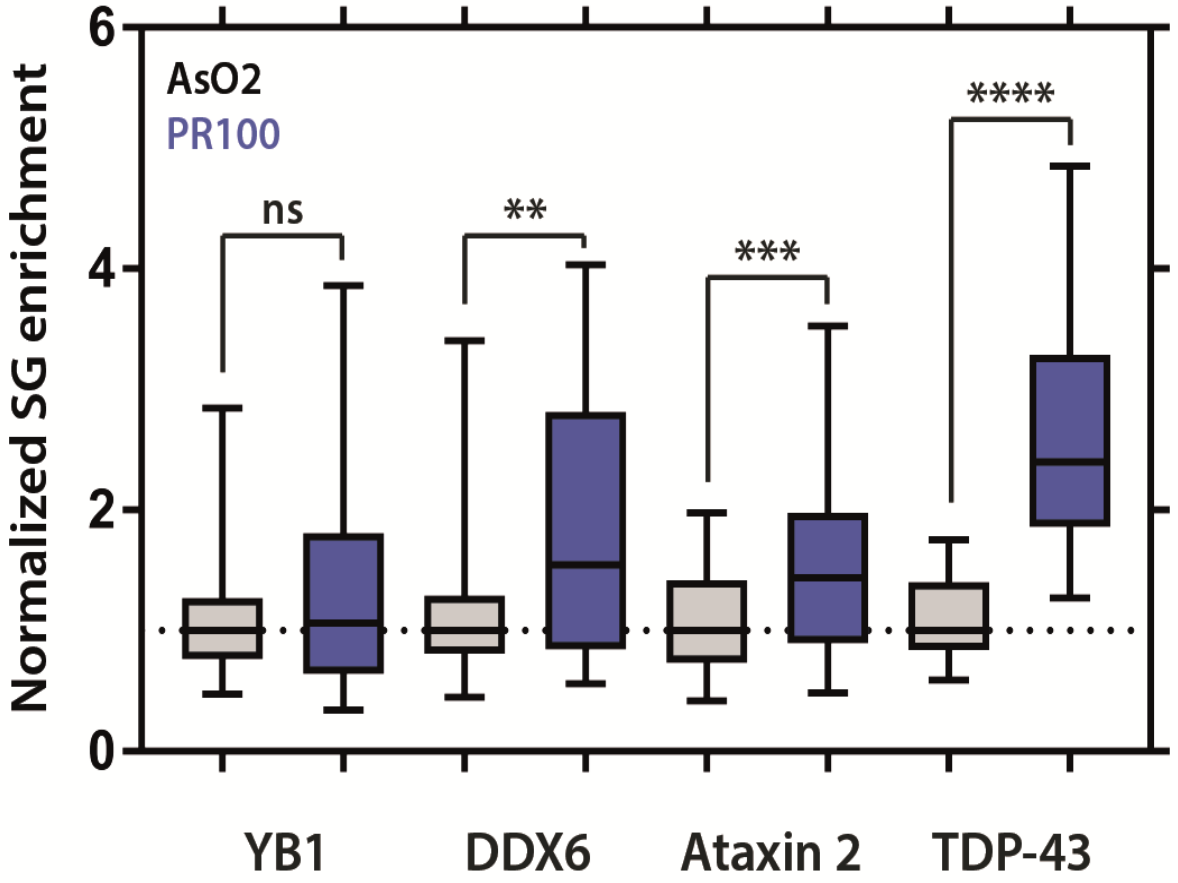


PR perturbs stress granule dynamics and content

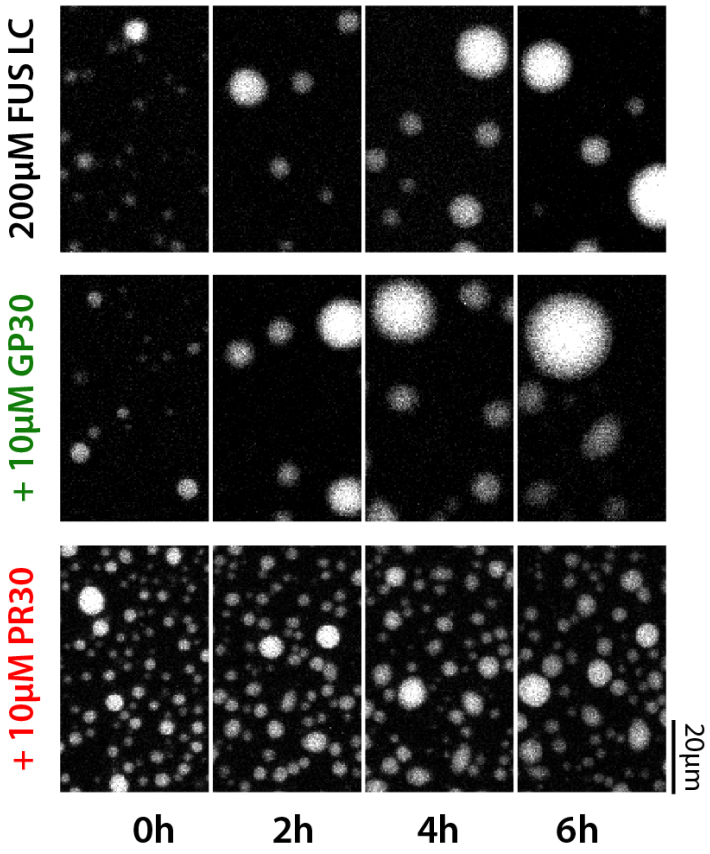
FRAP



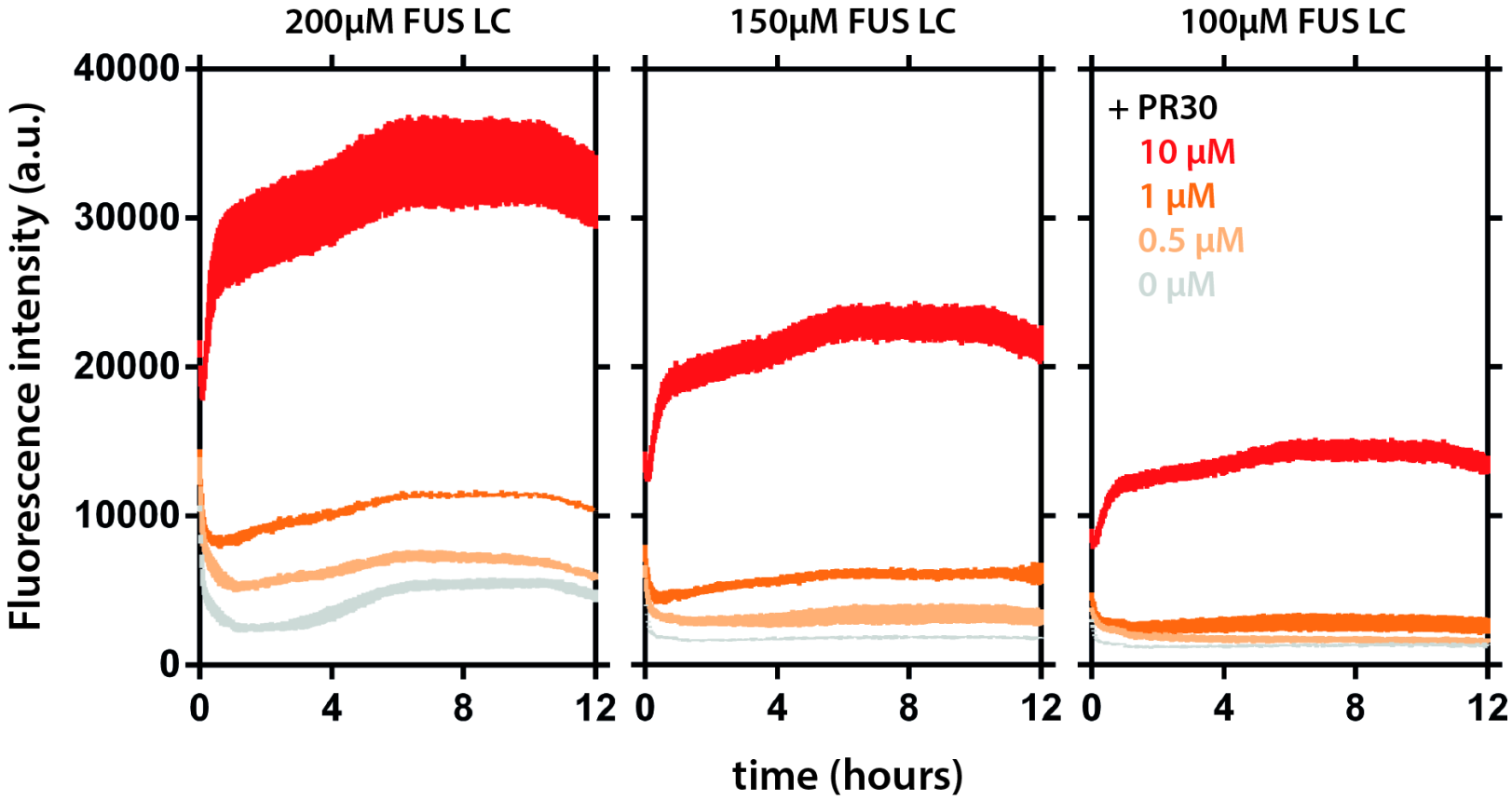
protein enrichment



PR promotes liquid-to-solid switch for other ALS proteins



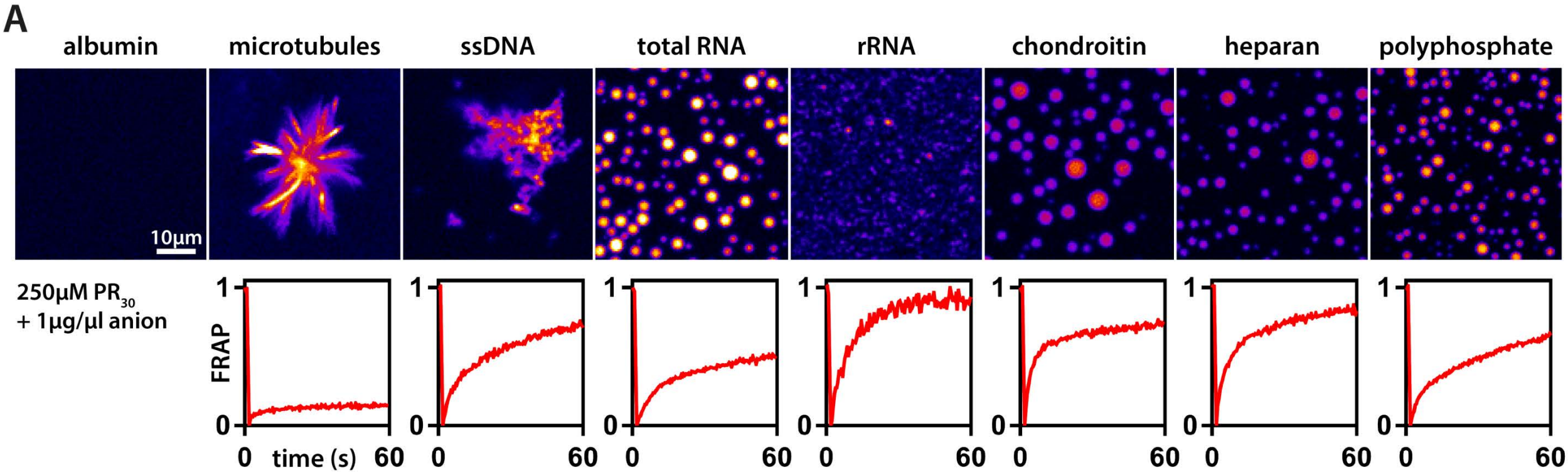
ThT fluorescence



Conclusions:

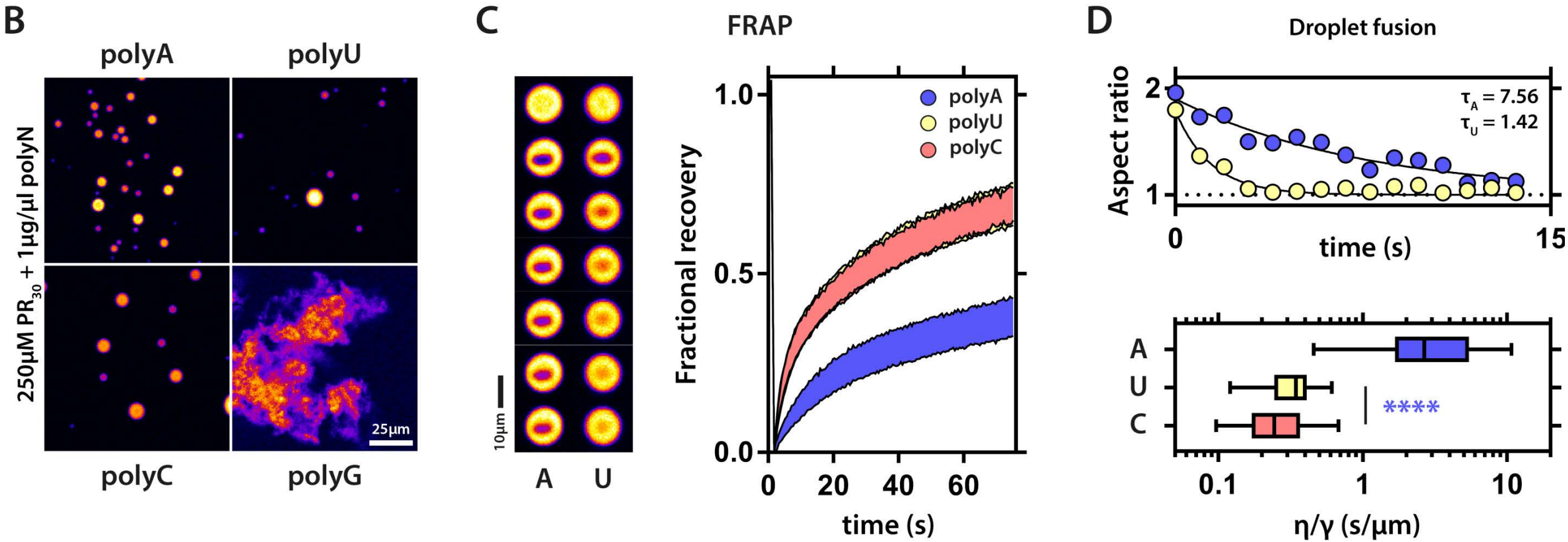
- strong role for arginine residues in liquid and solid phase separation
- PR induced SG assembly requires eIF2α phosphorylation
- PR promotes liquid-to-solid switch of ALS proteins

Nucleator alters material state of PR granules



(unpublished results)

Nucleator alters material state of PR granules



(unpublished results)

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