

Defective protein complex assembly and ER stress as the proximal cause and key to therapeutics for Usher syndrome

- Bernardo Blanco-Sánchez
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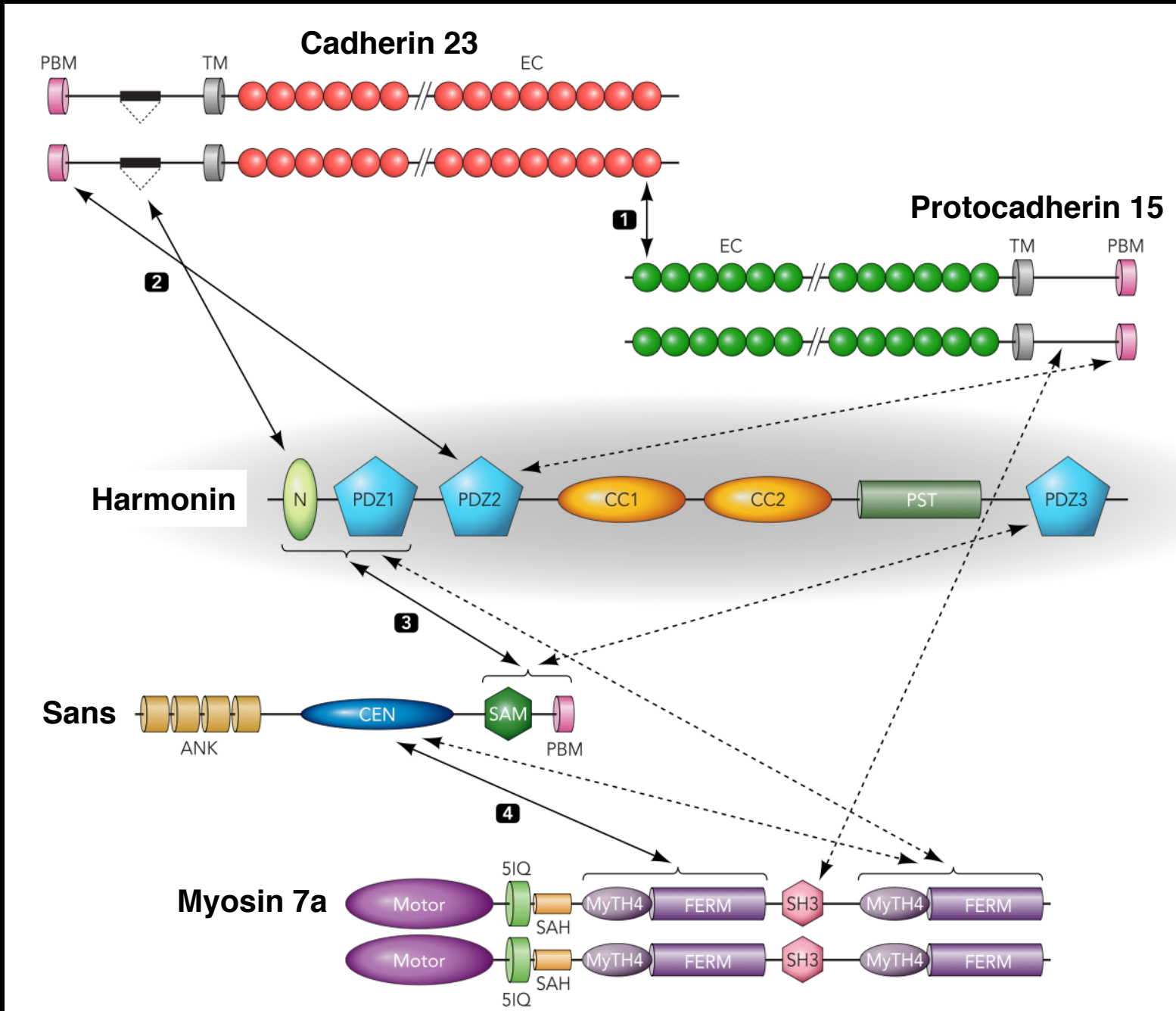


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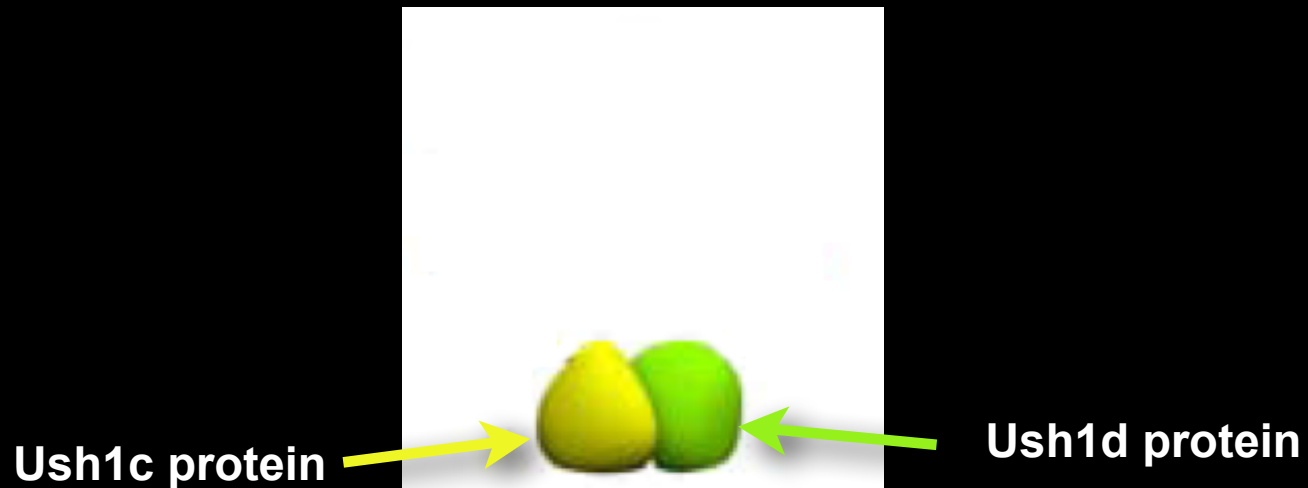


- **Usher protein complexes preassemble at the ER**
- **Usher mutations cause ER stress and cell death**
- **Treating ER stress to save cells from death**

Usher proteins form a multimolecular complex

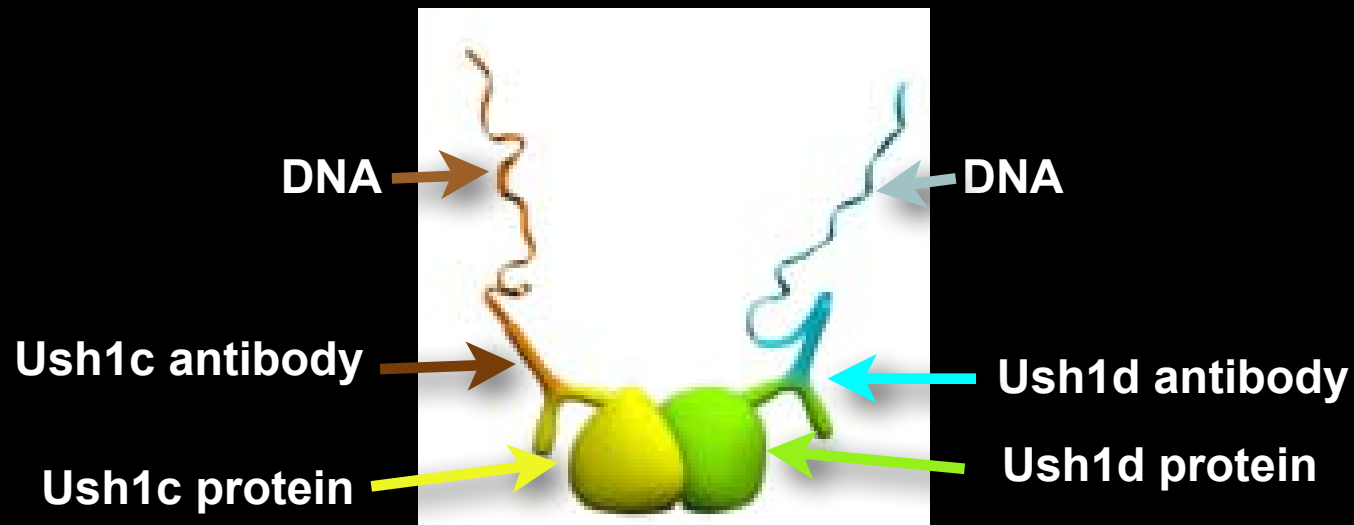


Usher protein interactions



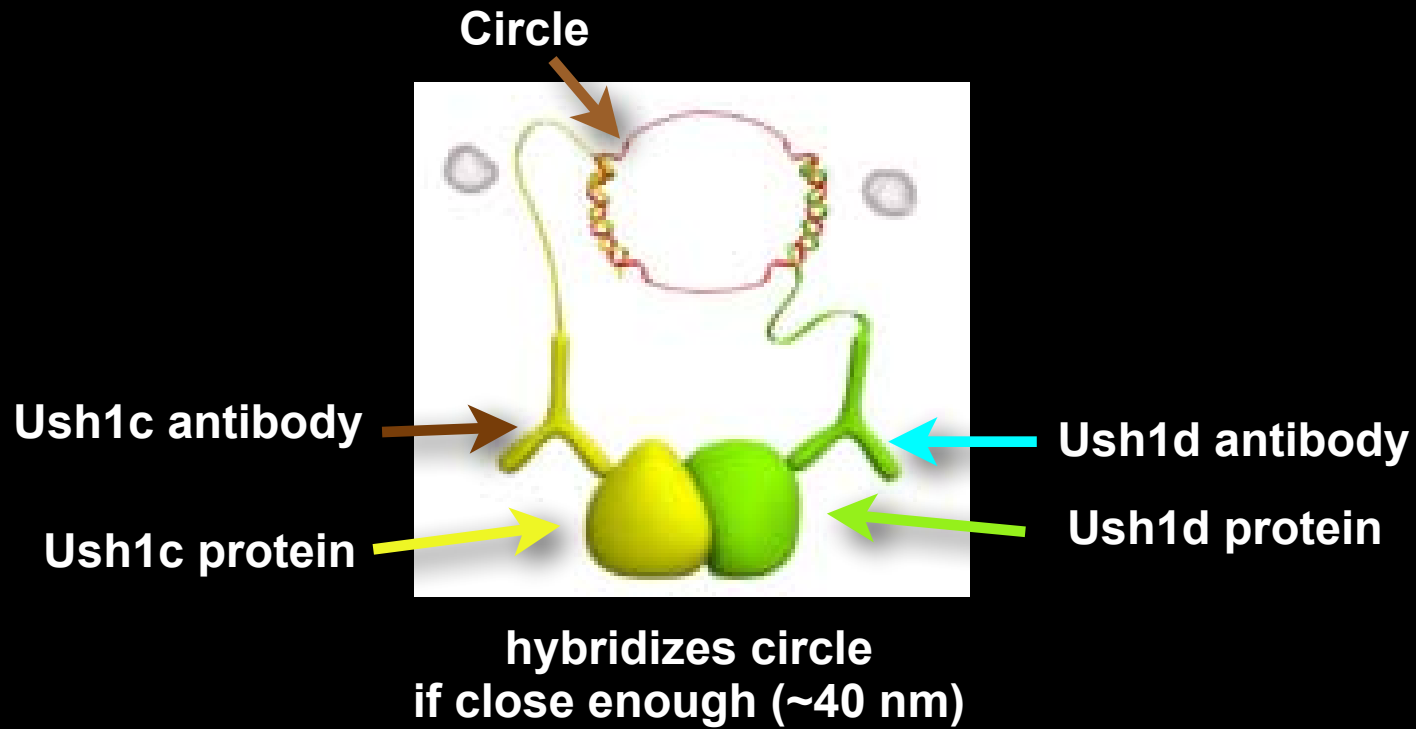
Part of Usher protein complex

in situ hybridization probes

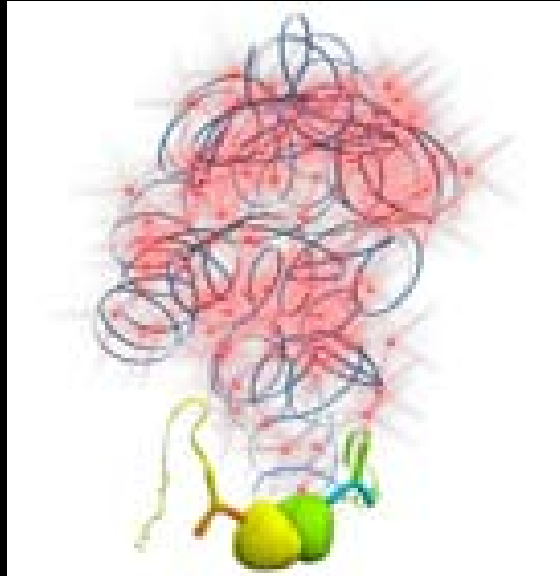


probes generated by
conjugating DNA to antibodies

Proximity ligation *in vivo*



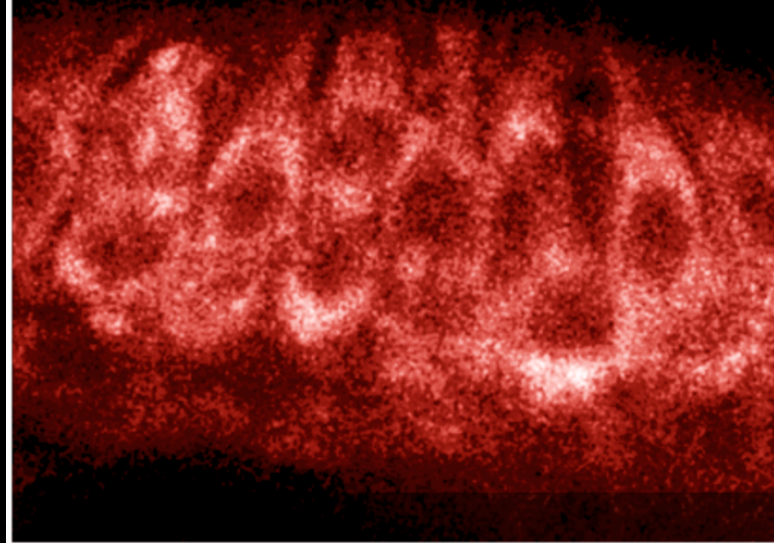
Detection of protein complexes *in vivo*



Rolling circle amplifies
fluorescent oligonucleotide

Usher proteins form complexes *in vivo*

Cdh23 - Ush1c

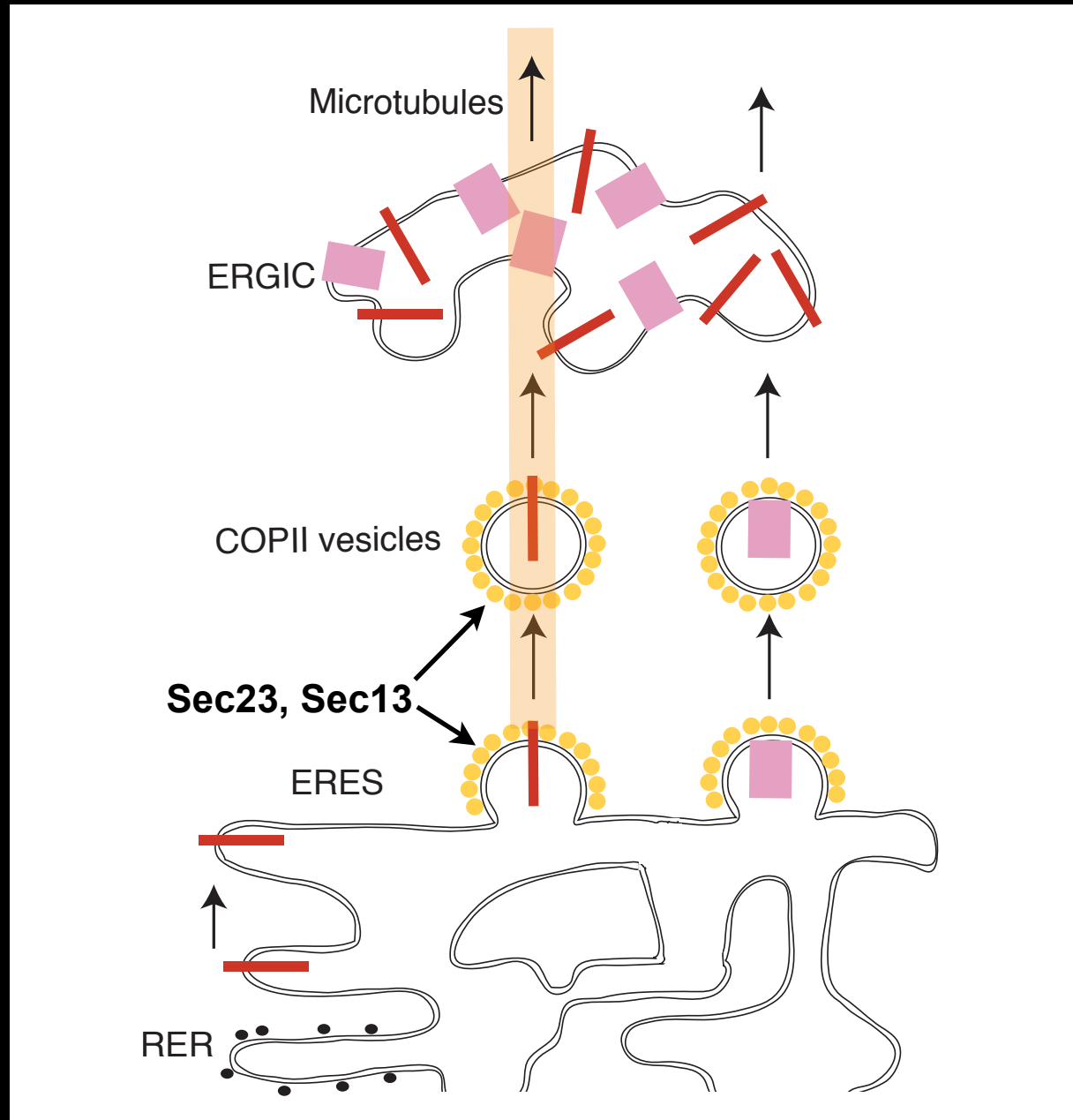


Cdh23 - Ush1c in *ush1c*^{-/-}



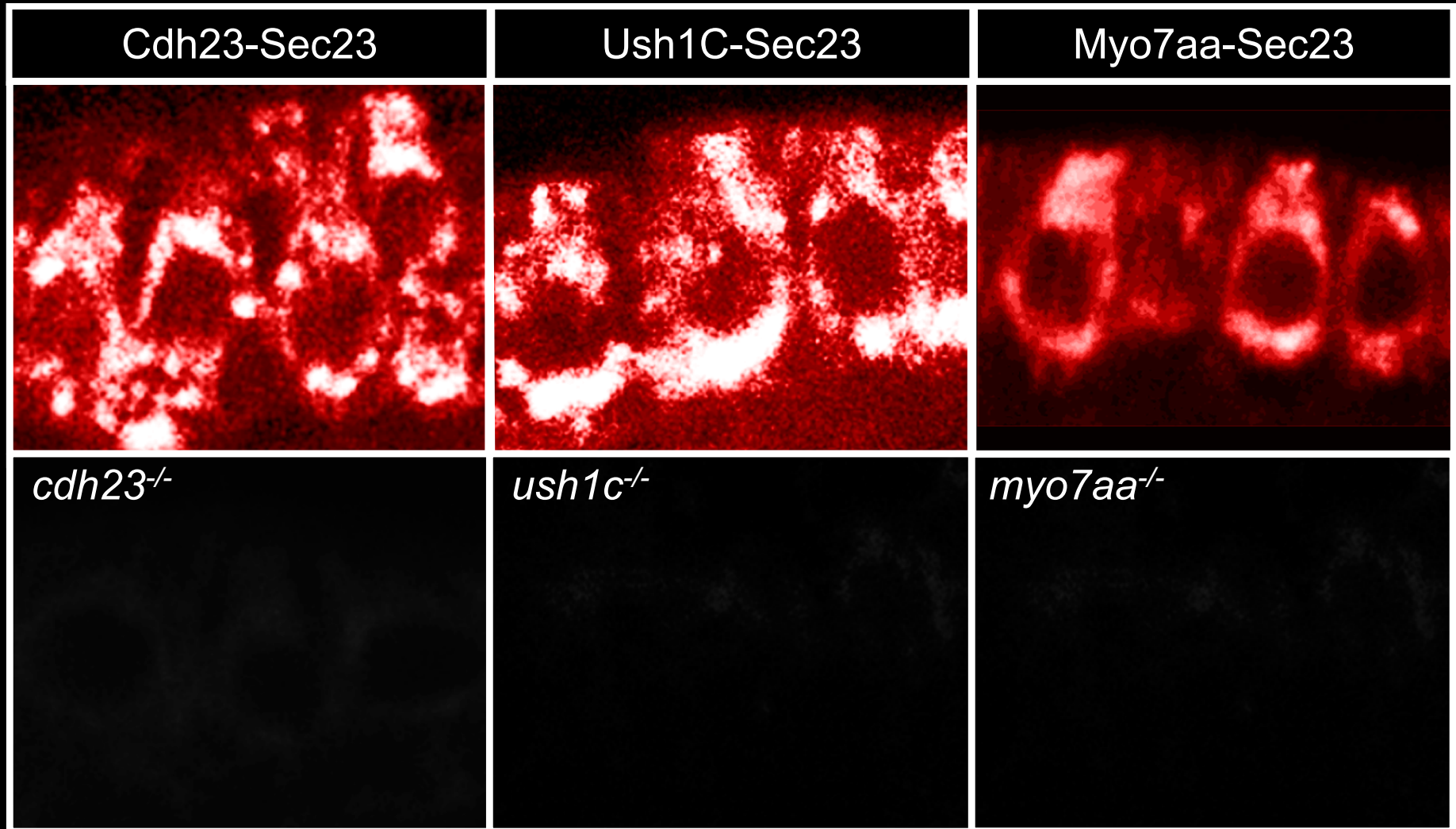
(Bernardo Blanco)

Membrane proteins are trafficked from the ER in COPII vesicles

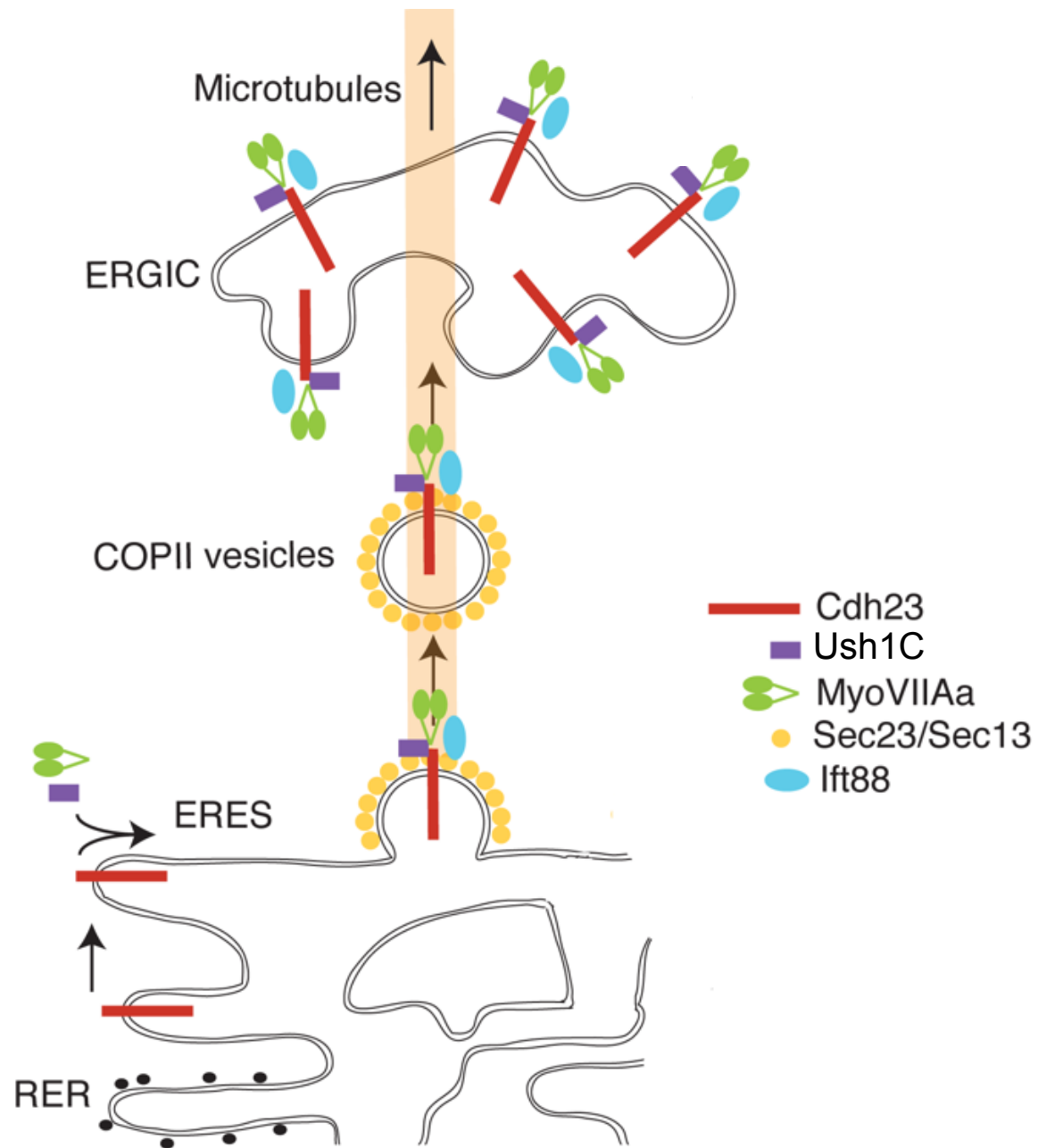


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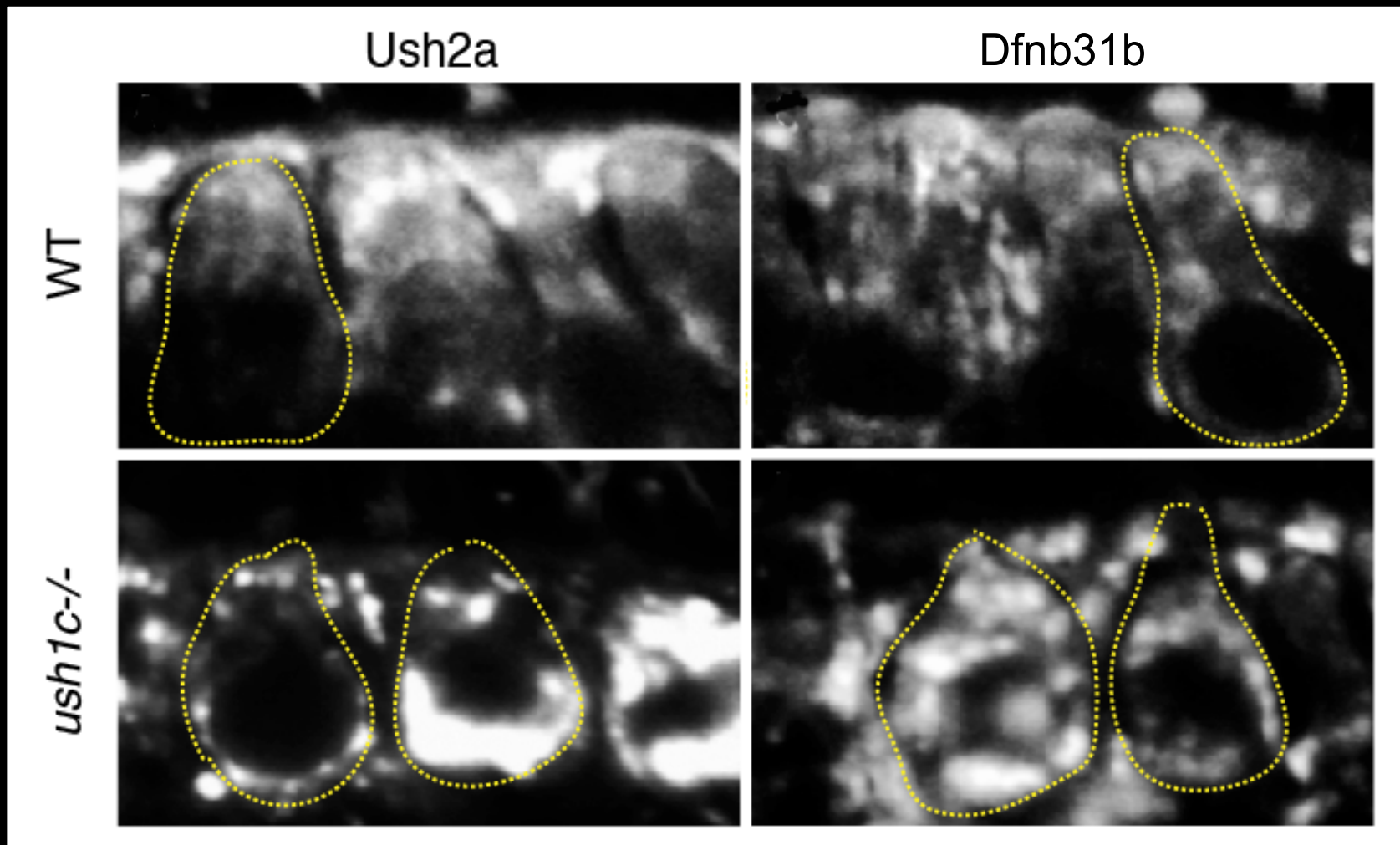
Usher protein complex preassembles in the ER



Usher protein complex is trafficked via microtubules

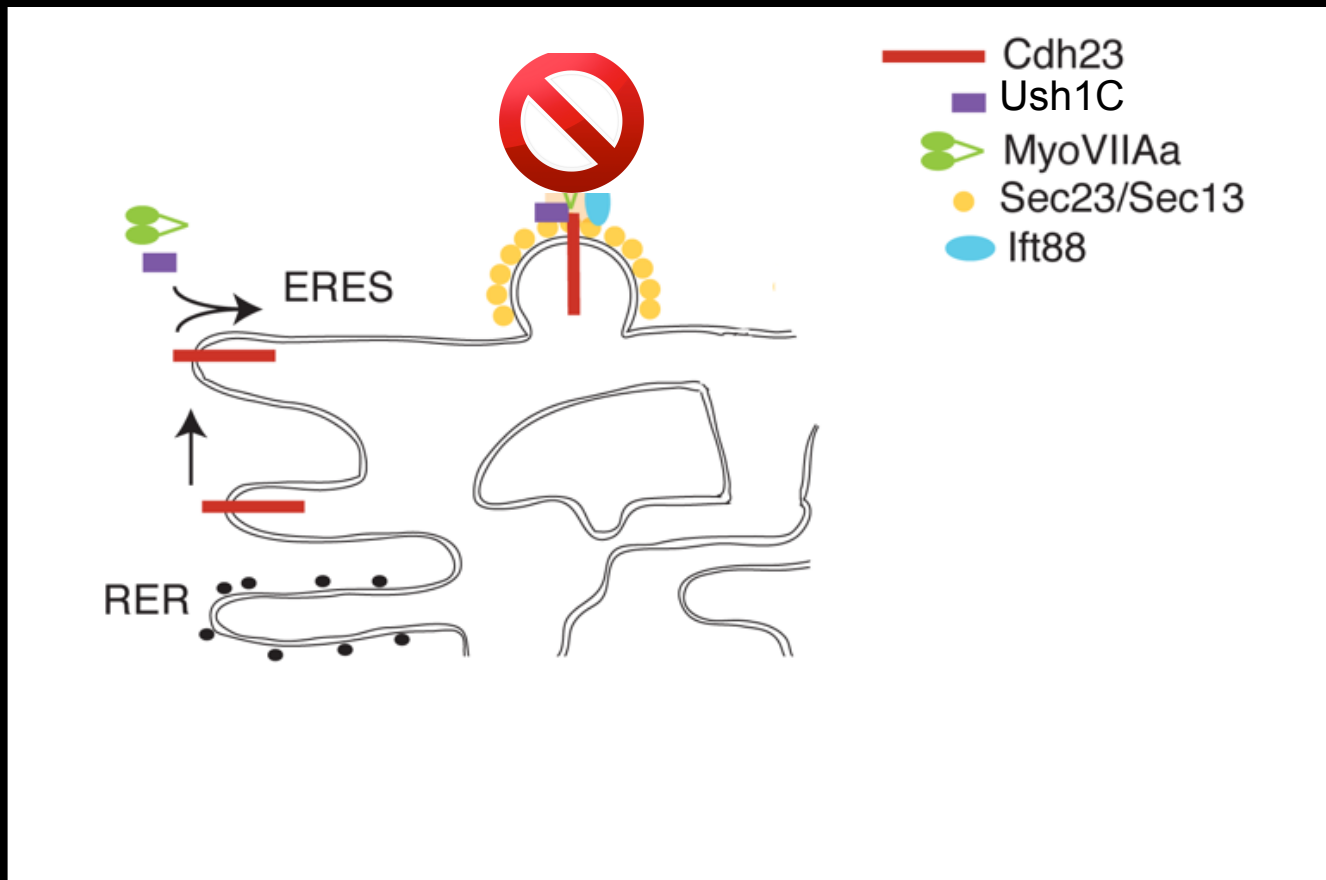


Usher proteins are retained in the ER in mutants

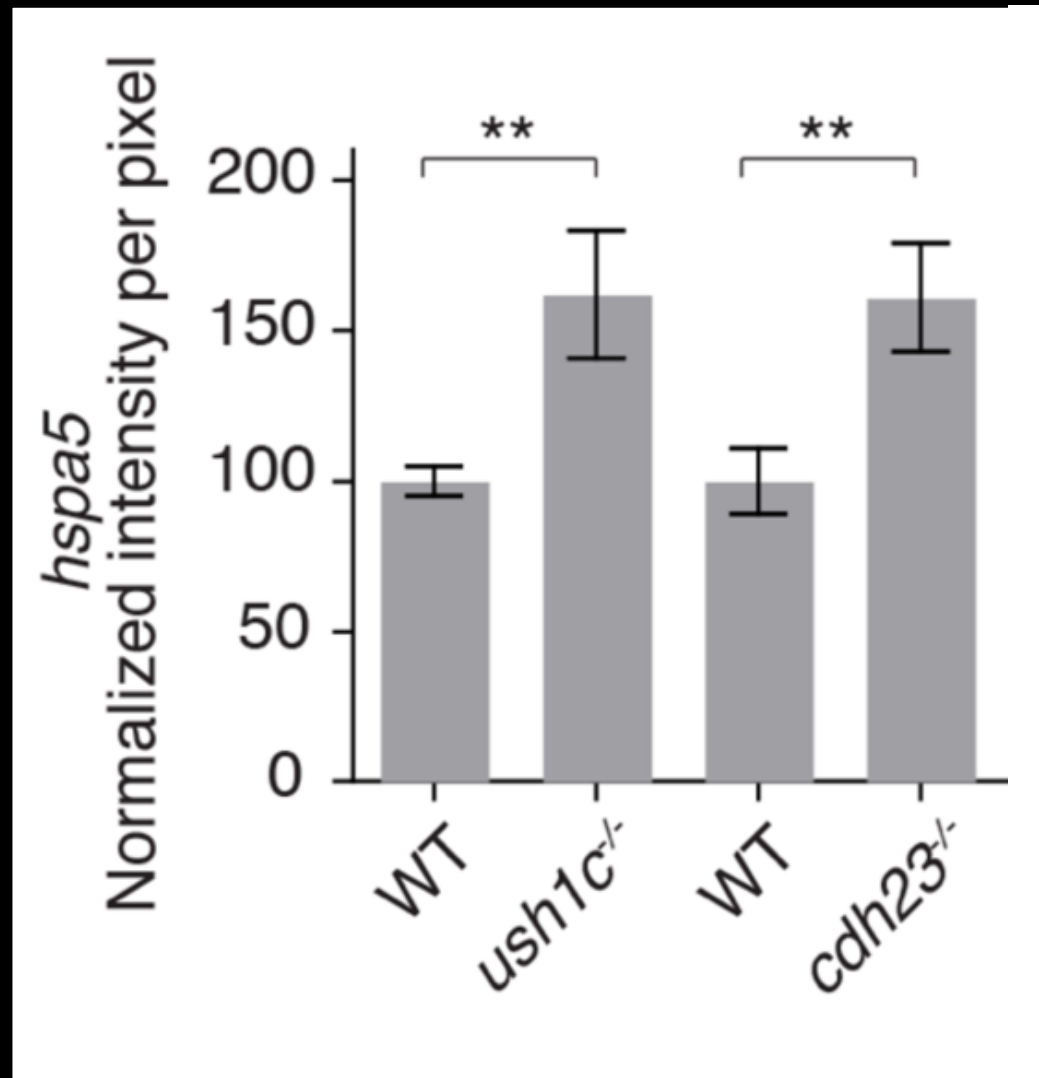


(Bernardo Blanco-Sánchez)

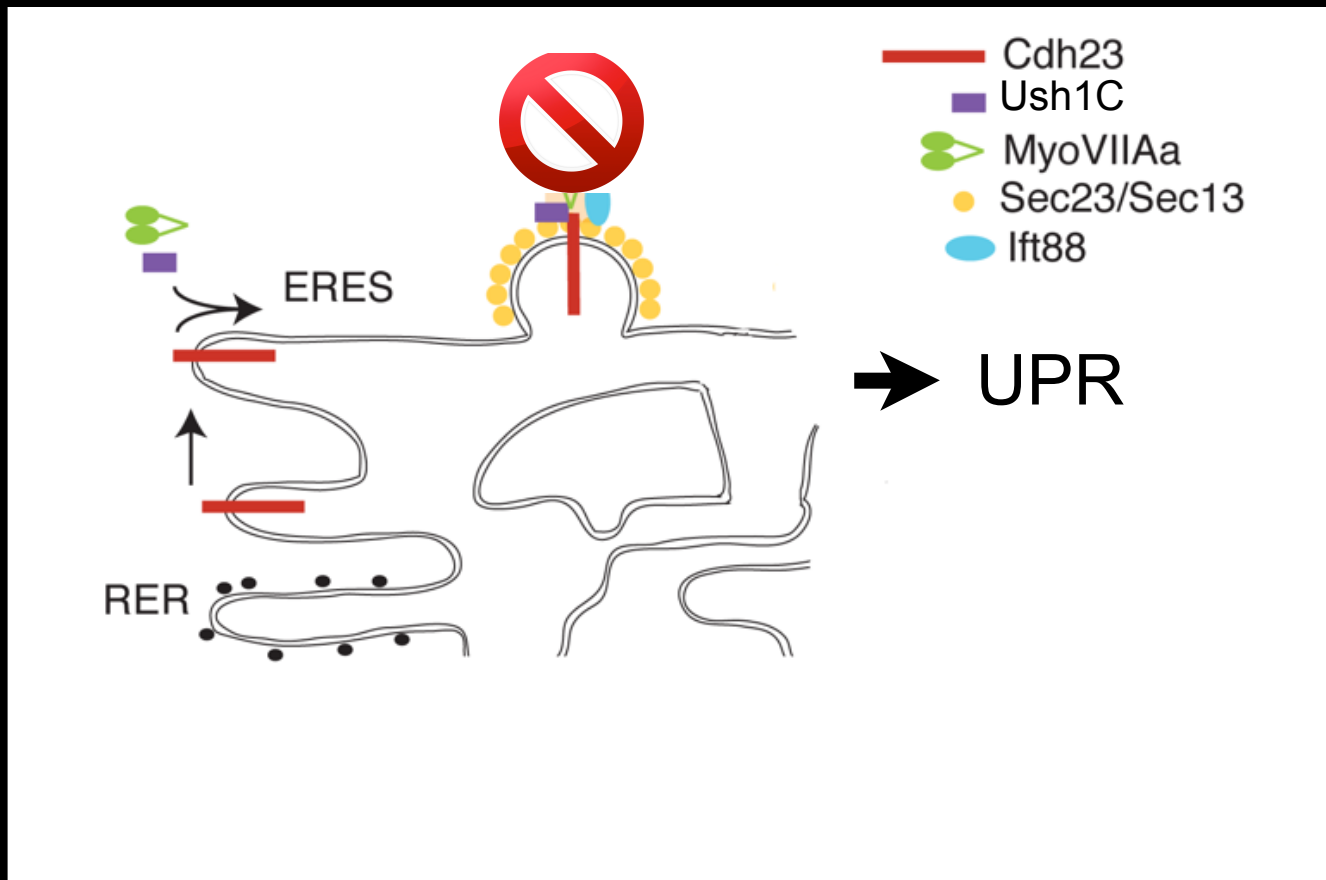
Usher mutations block complex formation and Usher proteins accumulate in the ER



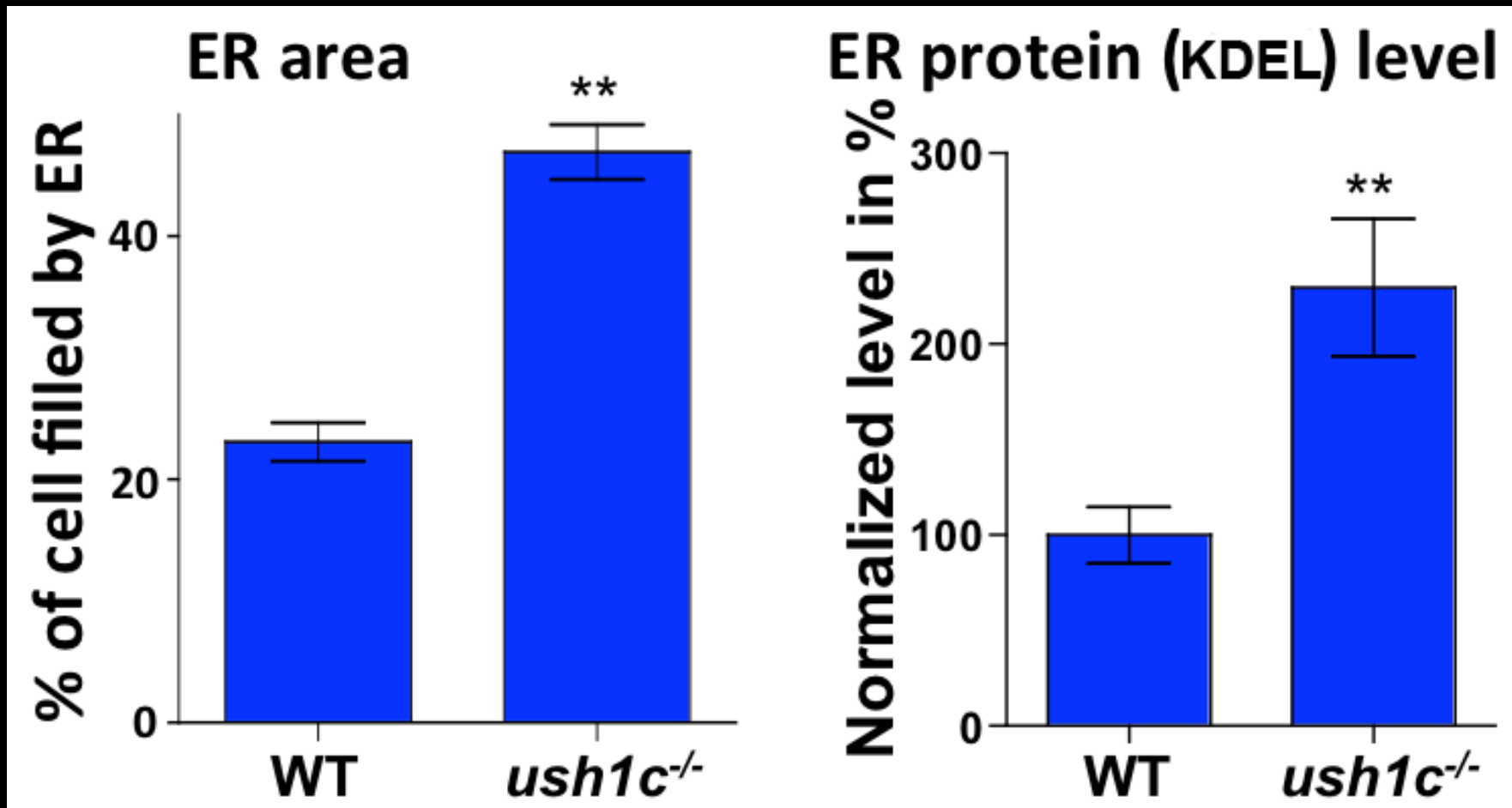
Usher mutations trigger the unfolded protein response



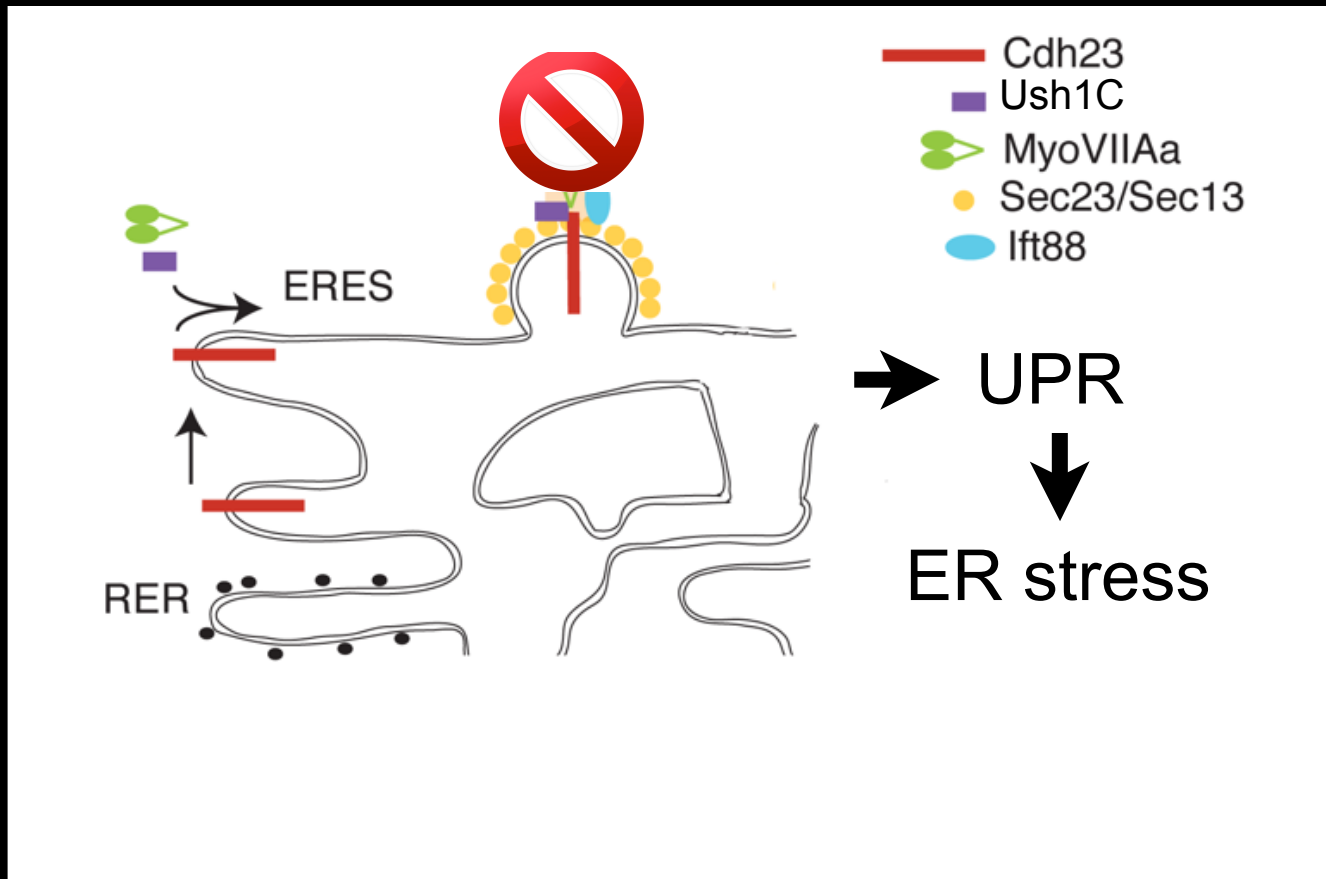
Usher mutations block complex formation, proteins accumulate in the ER and trigger the unfolded protein response



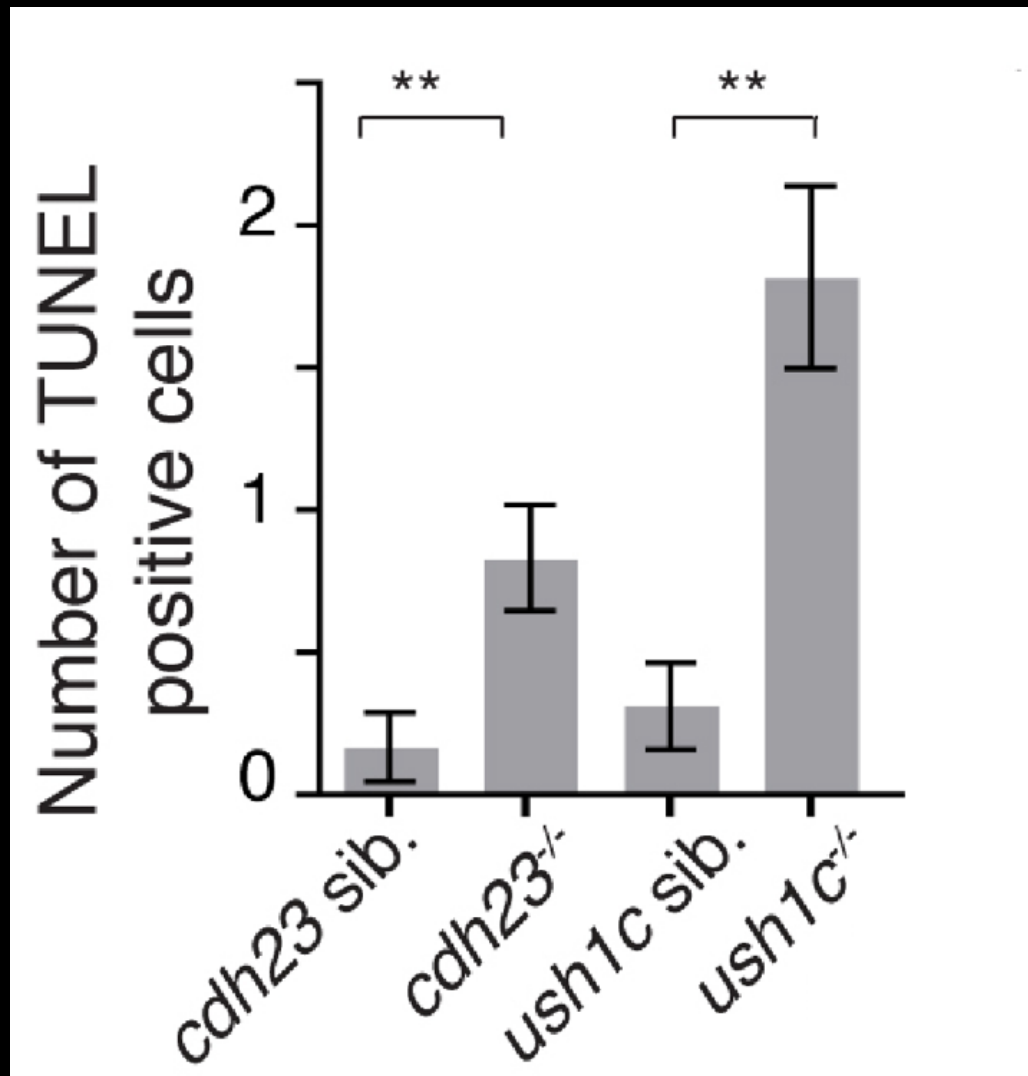
Usher mutations induce ER stress



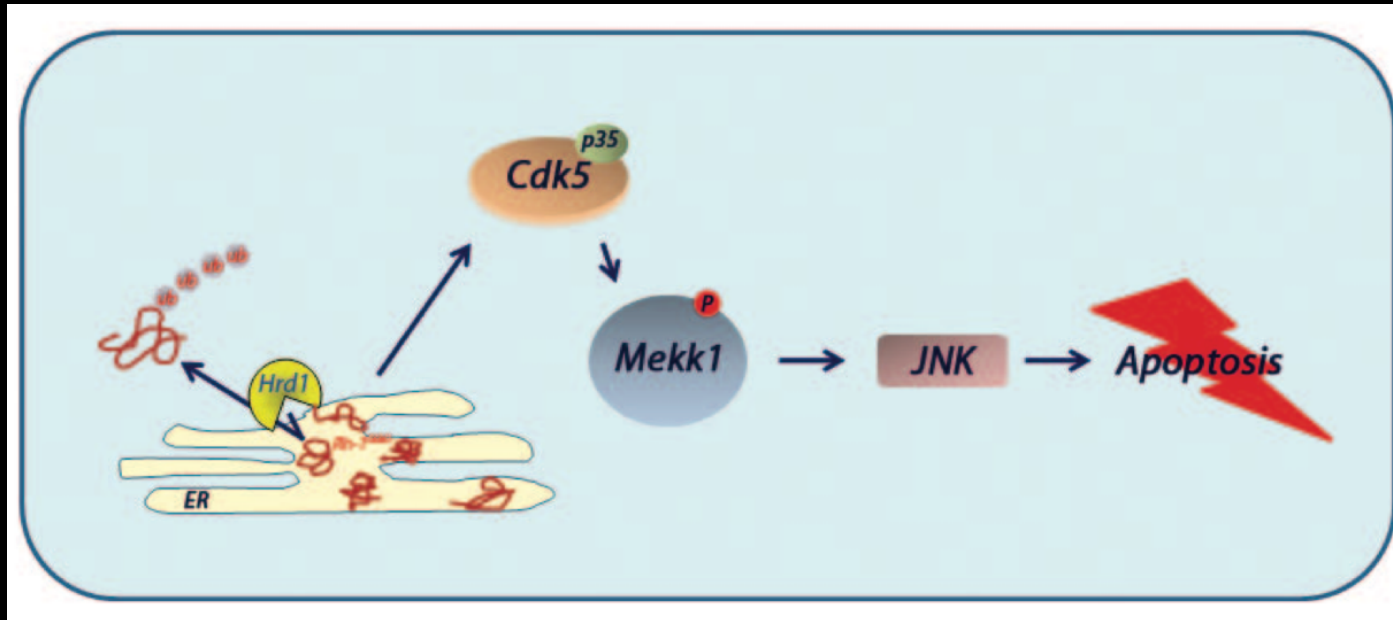
Usher mutations block complex formation, trigger the unfolded protein response, and lead to ER stress



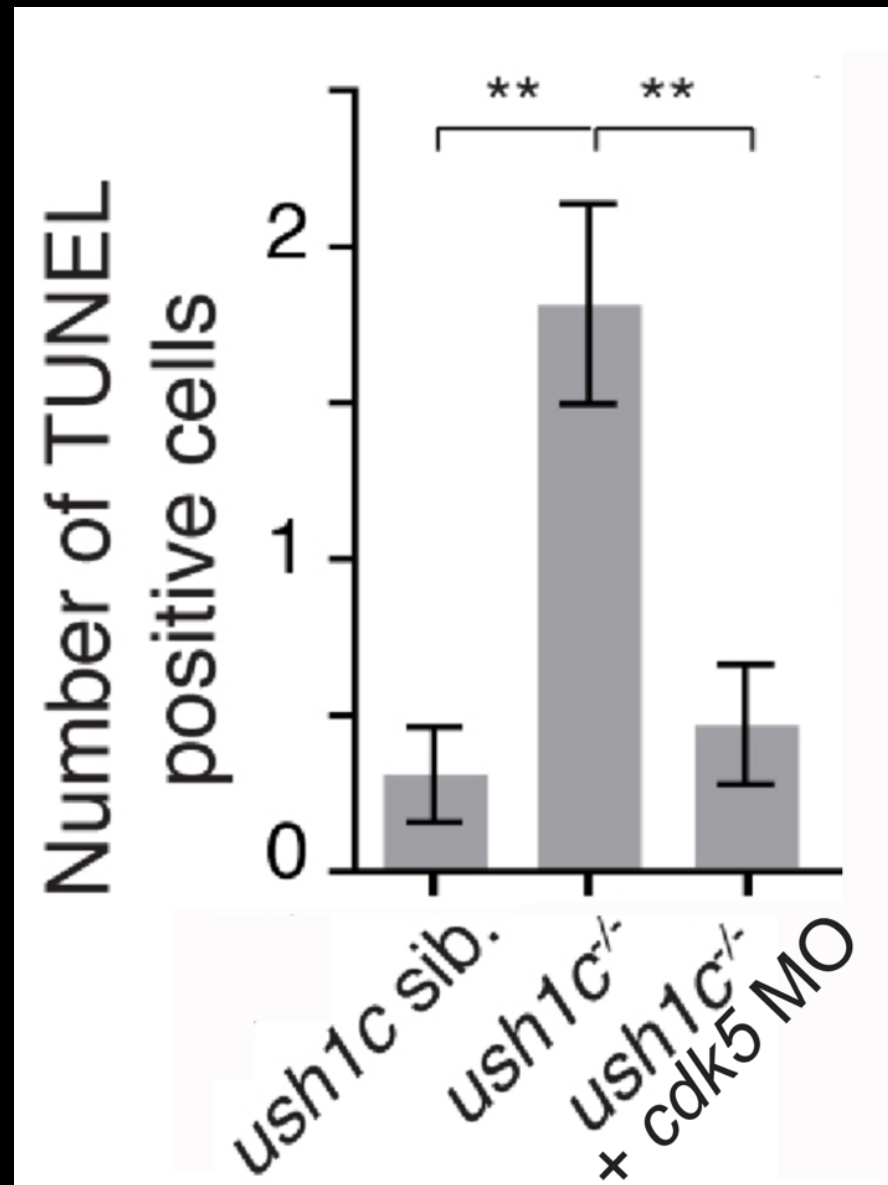
Usher mutations cause cell death



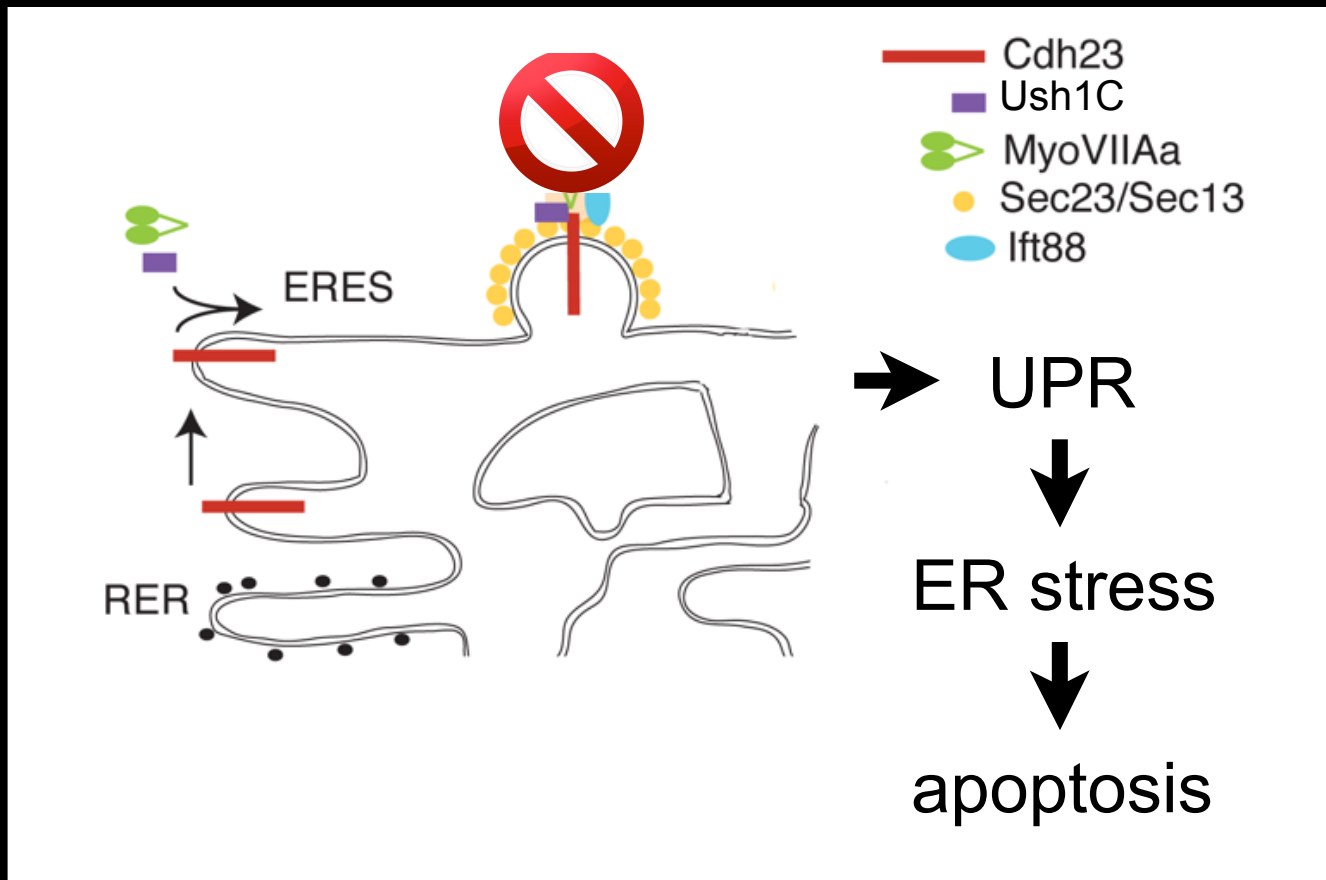
Cdk5 mediates cell death due to ER stress



ER stress causes cell death



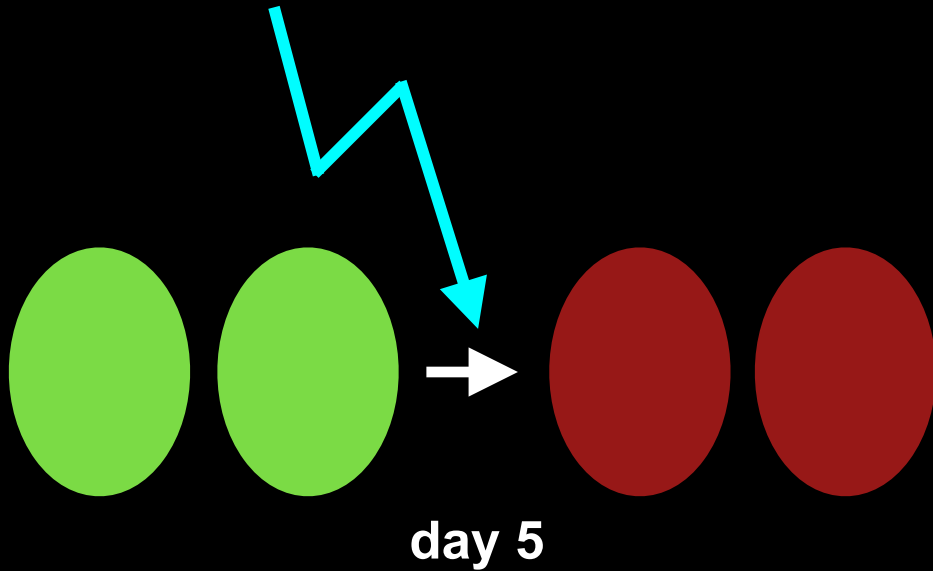
Usher mutations block complex formation, trigger the unfolded protein response, and lead to ER stress and cell death



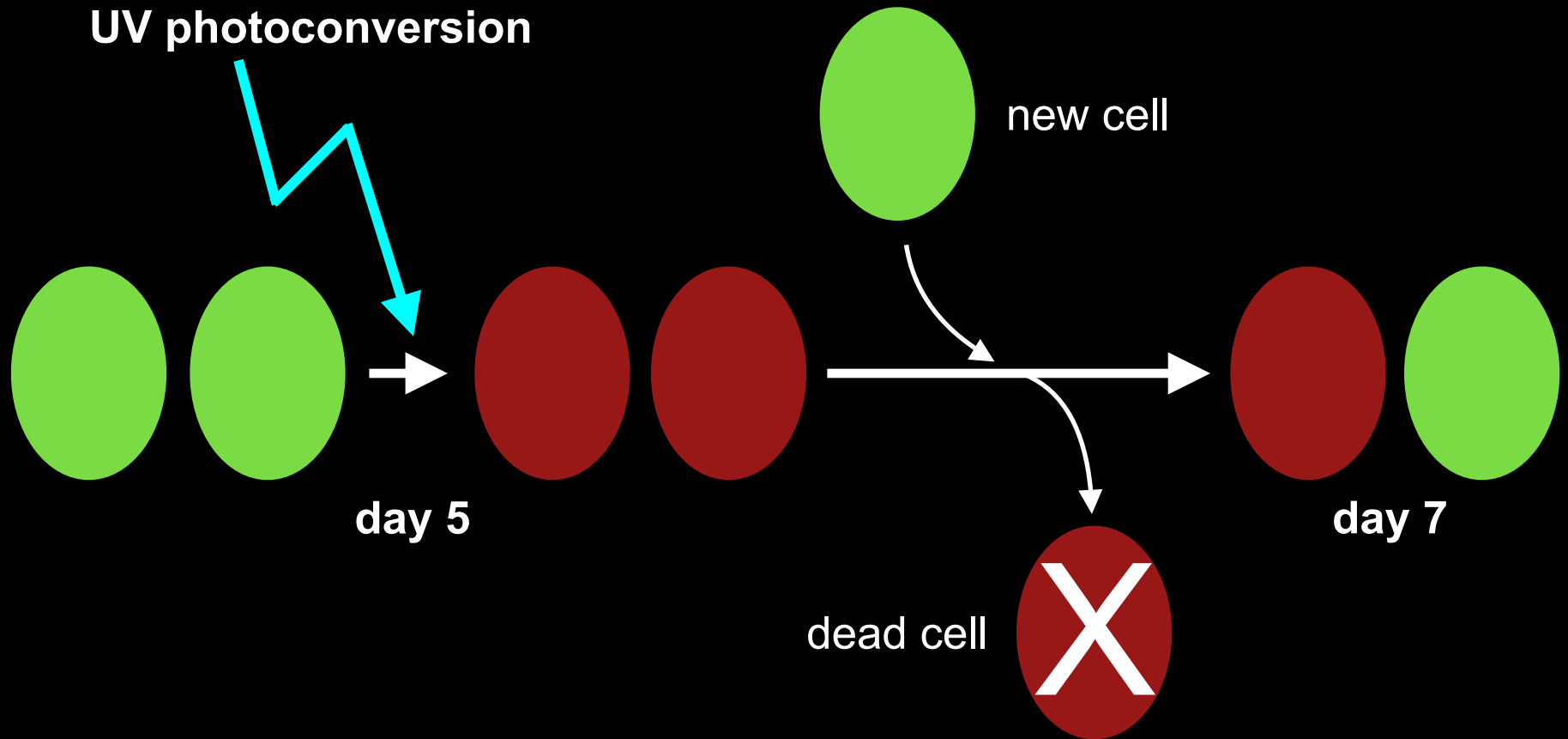
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Kaede photoconversion to track cell death

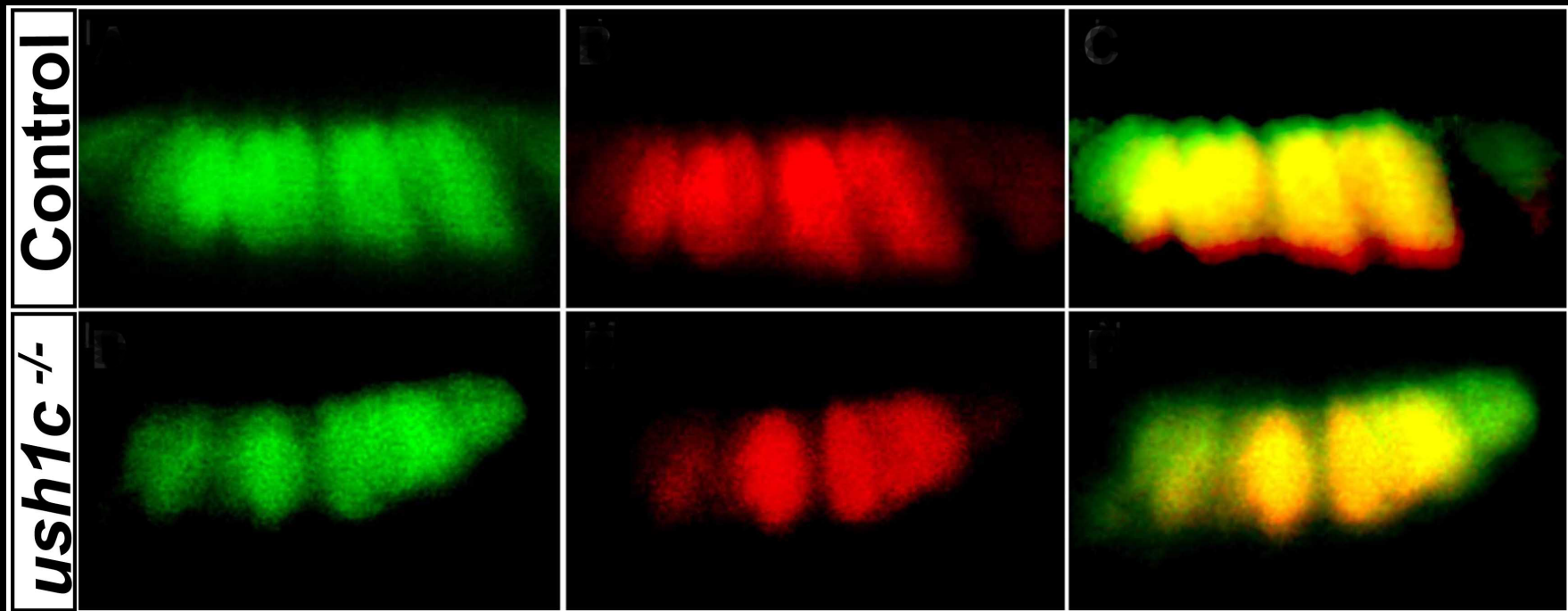
UV photoconversion



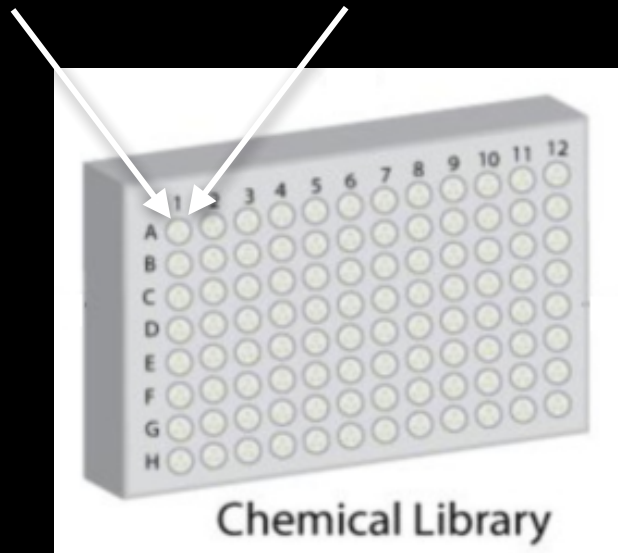
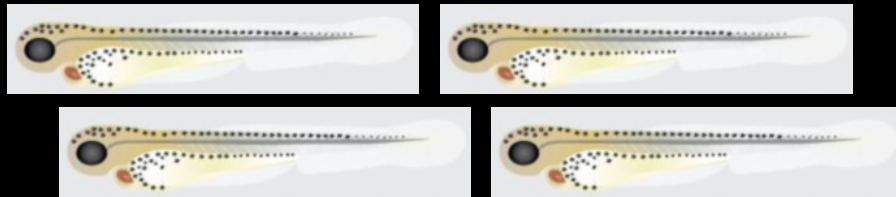
Kaede photoconversion to track cell death



A screen for compounds that reduce cell death

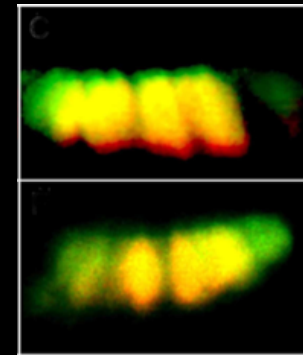


A screen for compounds that reduce cell death



1,000's of compounds

UV photoconversion



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