MRC Laboratory of Molecular Biology

LMB: blue skies thinking

Hugh Pelham

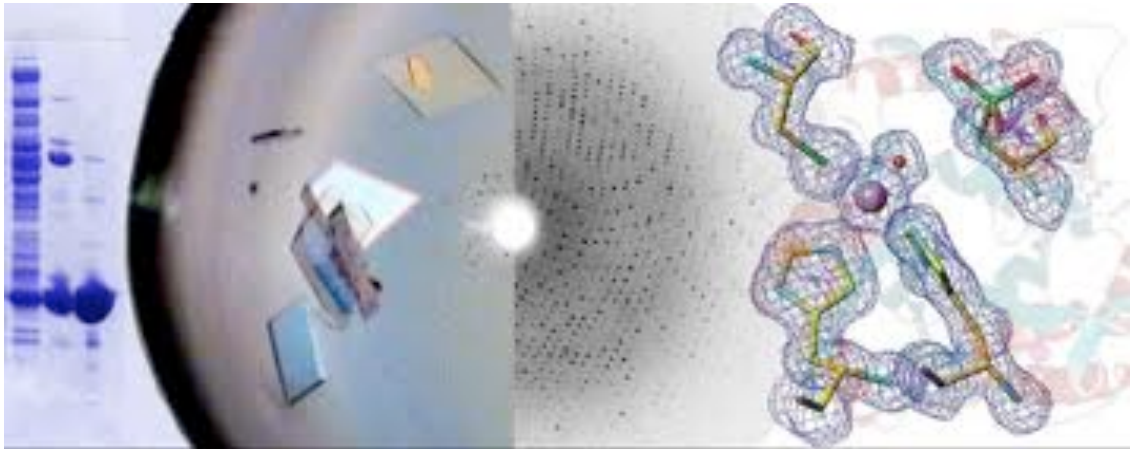
How does LMB fit into the CBC?

- The MRC Laboratory of Molecular Biology was founded in 1962 in the belief that molecular biology would one day impact on medicine.
- DNA sequencing, monoclonal antibodies and protein structure determination have amply justified that belief.
- Since the 1980s LMB has been well engaged with industry.
- The major impact has come from new methods, and the application of these has almost always been done by, or in collaboration with, industry.
- Our role is to try to do the (currently) impossible, not duplicate development work.
- We look for (sometimes unexpected) medical applications of our work.

Structural biology – a major strength

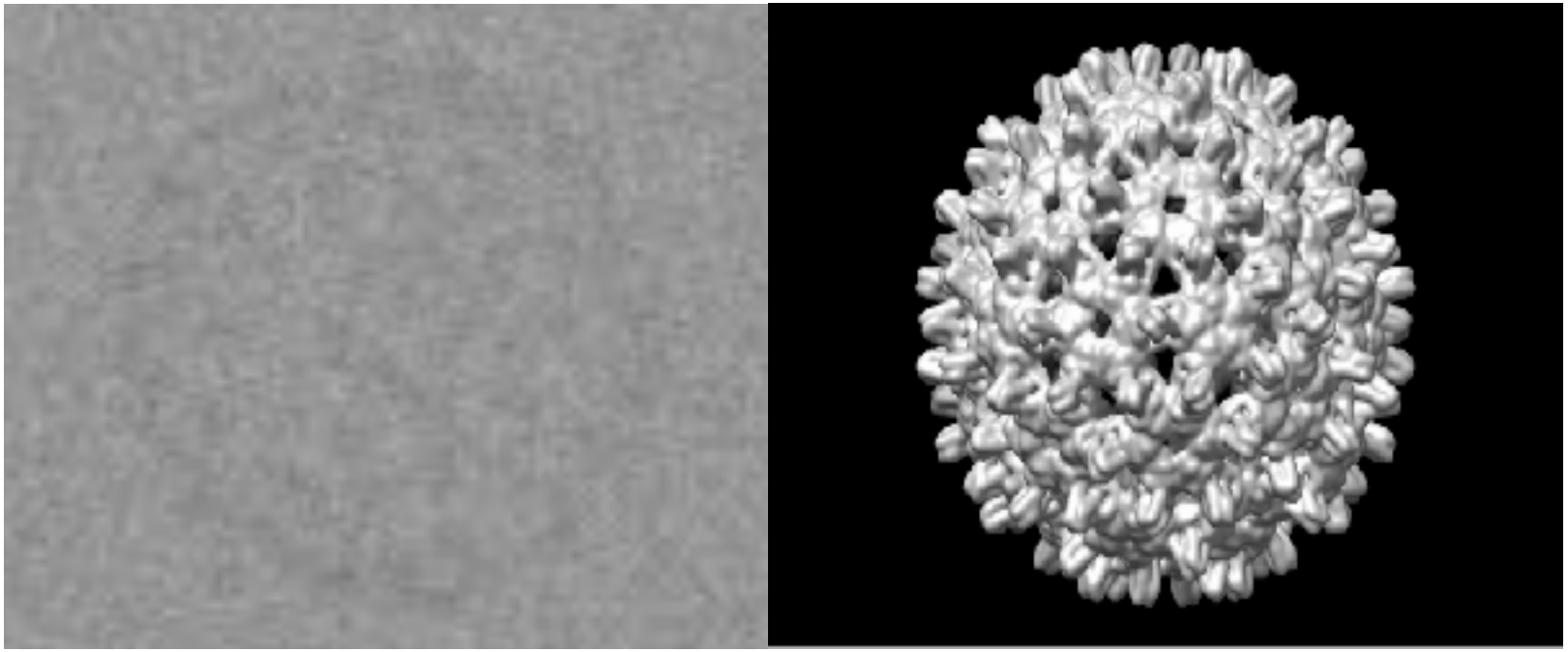
X-ray crystallography

For over 50 years, determining the atomic structures of proteins has been the domain of X-ray crystallography



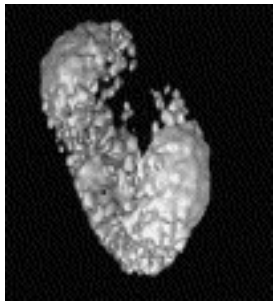
But getting protein crystals is difficult

The single particle EM approach

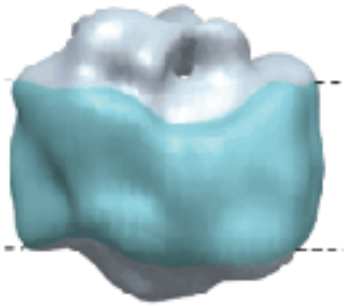


Hepatitis B virus core

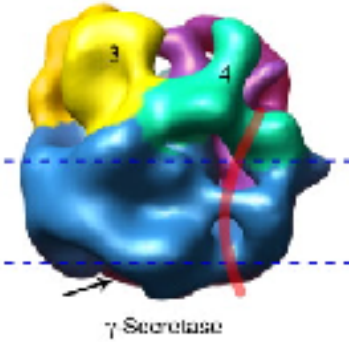
Gamma secretase



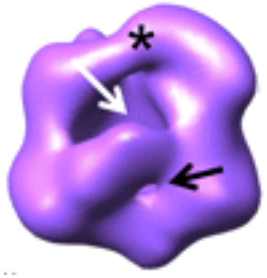
Ogura et al. *BBRC* *2006*



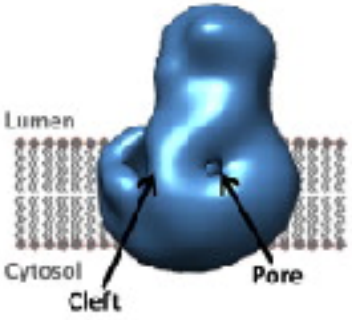
Lazarov et al. *PNAS* *2006*



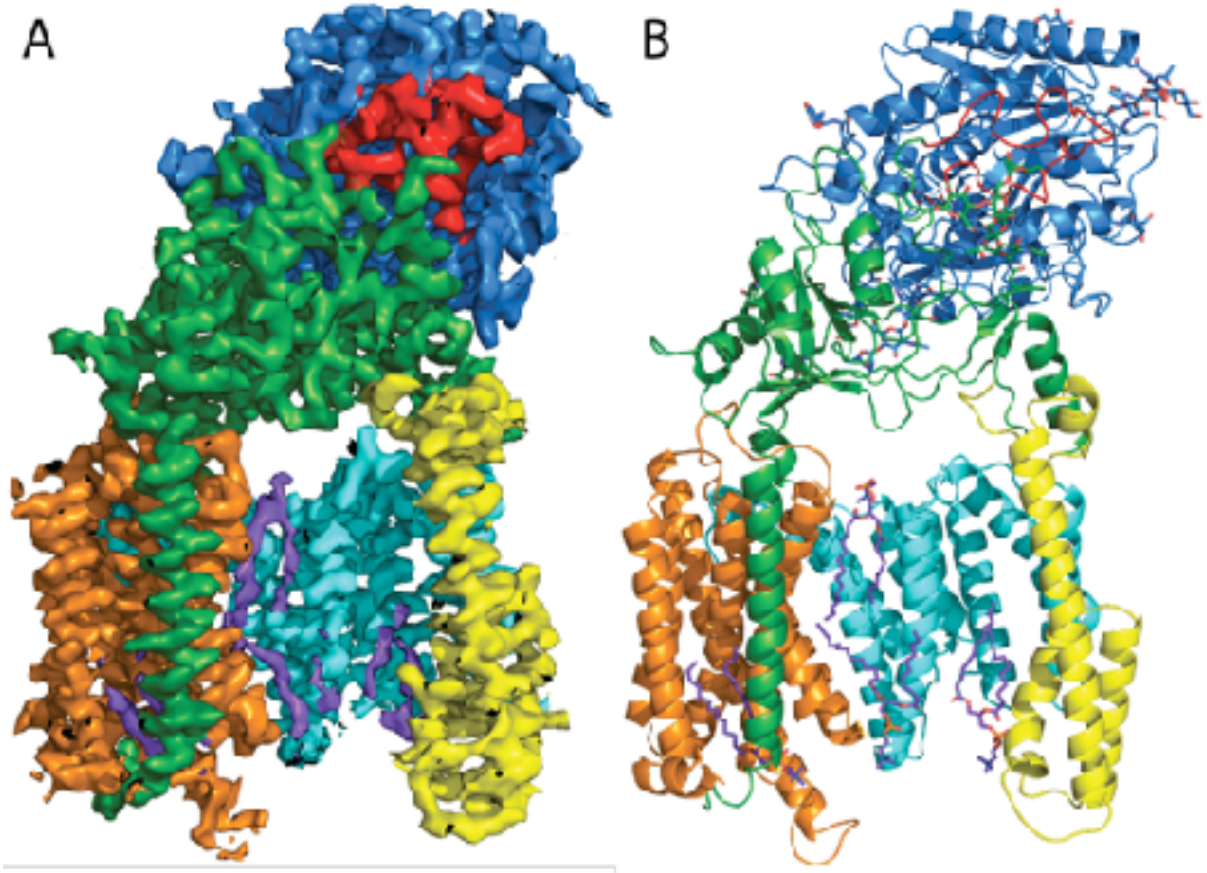
Osenkowski et al. *JMB* *2009*



Renzi et al. *JBC* *2011*

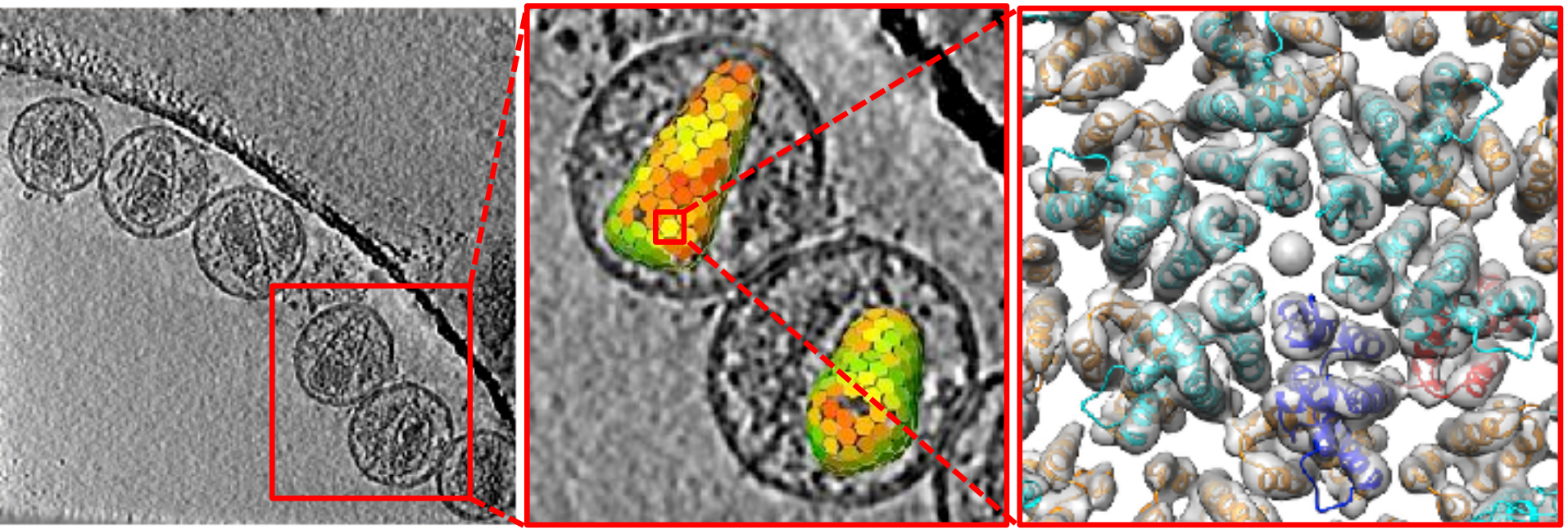


Li et al. *STRUCTURE* *2014*



LMB 2015

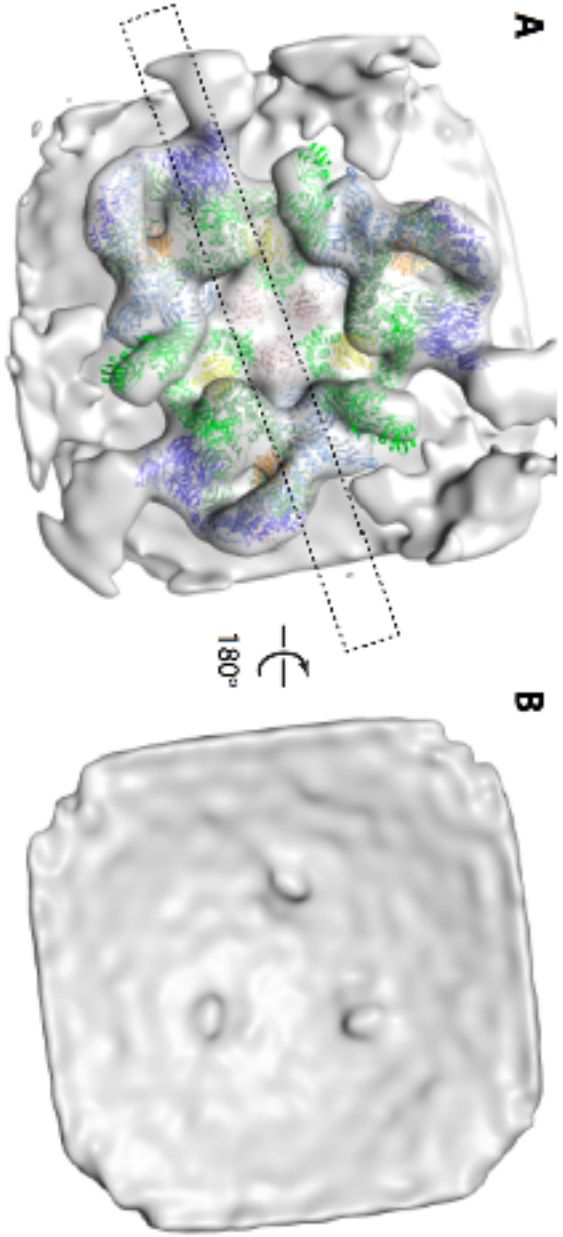
Mature HIV-1 core by cryo-ET



The structure of the CA hexamer can be resolved “in situ” within the virus

Mattei *et al* 2017

COPI vesicle coat in the cell



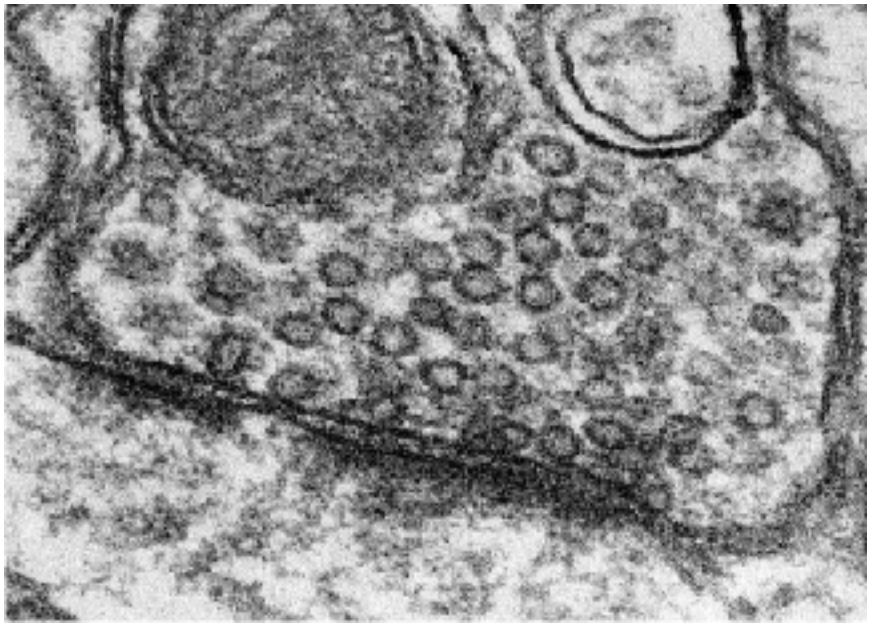
The same approaches can be used within cells and tissues

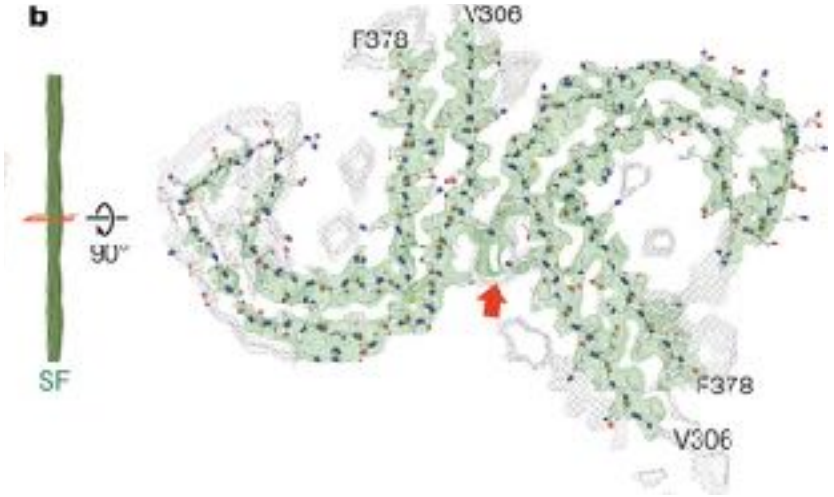
Bykov *et al* 2017

Areas of interest

- Structural Biology – cryo-EM, major biological complexes, GPCRs
- Synapses, neural circuits, neurodegeneration, circadian rhythms
- Protein quality control, membrane traffic, brain organoids
- DNA replication and repair, innate immunity, synthetic biology, cancer

Structural neuroscience





Tau filament from Alzheimer's brain

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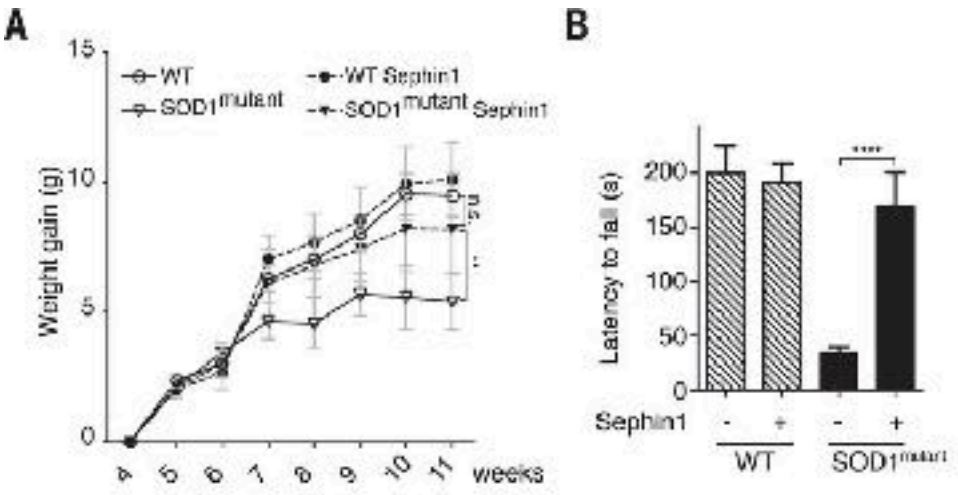
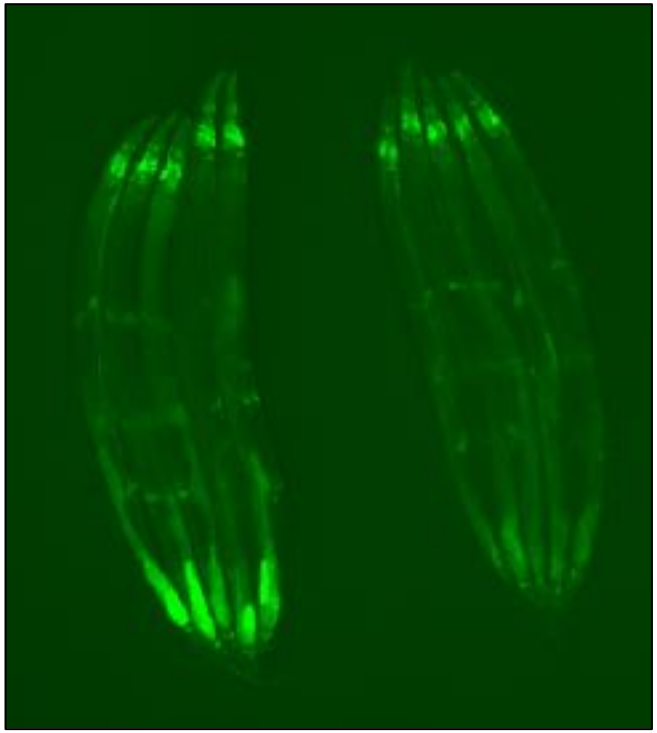
Stress responses and protein quality control



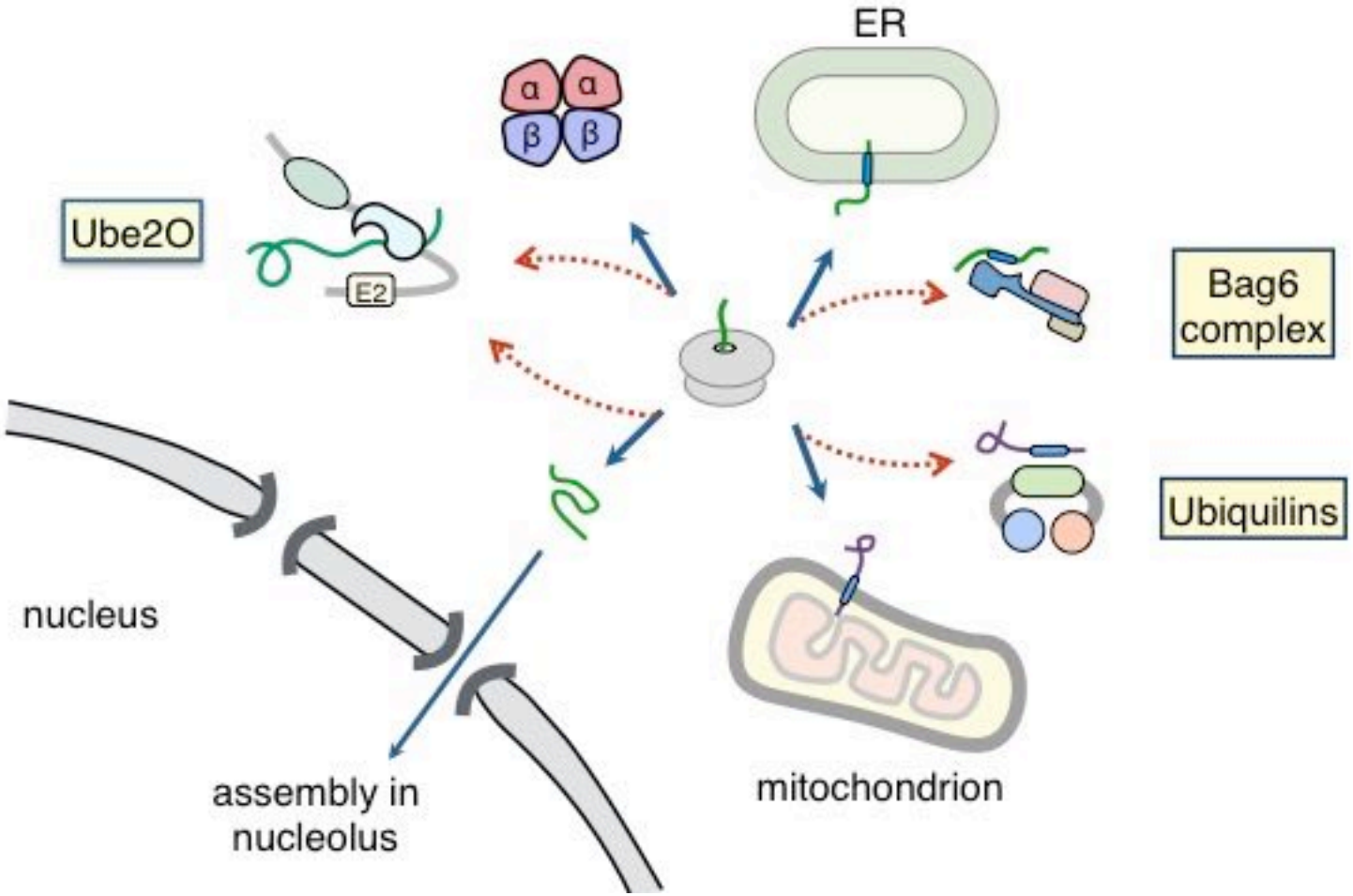
Sephin 1 is a compound that enhances the unfolded protein response and protects animal models of motor neuron disease (SOD1 ALS)

Stress responses and protein quality control

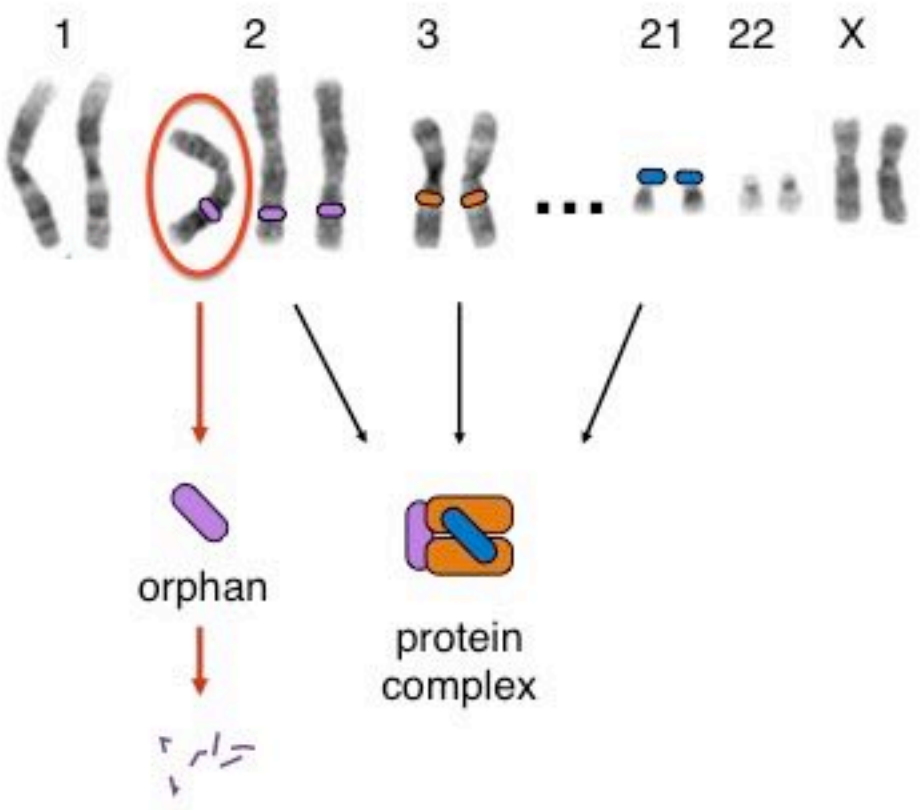
- octopamine



Stress responses and protein quality control



Protein quality control and cancer



elevated QC dependence due to:

- increased orphan load
- increased mutation load
- higher protein synthesis

Could quality control be a target for tumour treatment?

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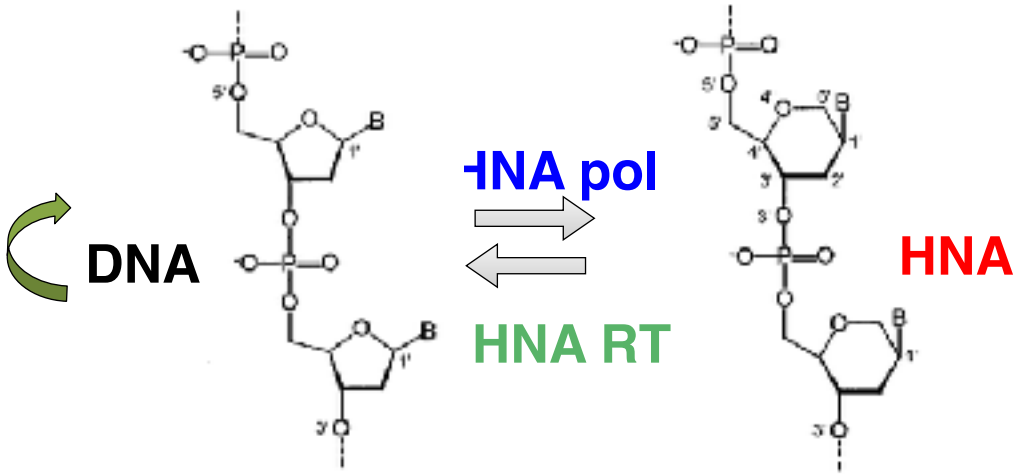
Novel nucleic acids



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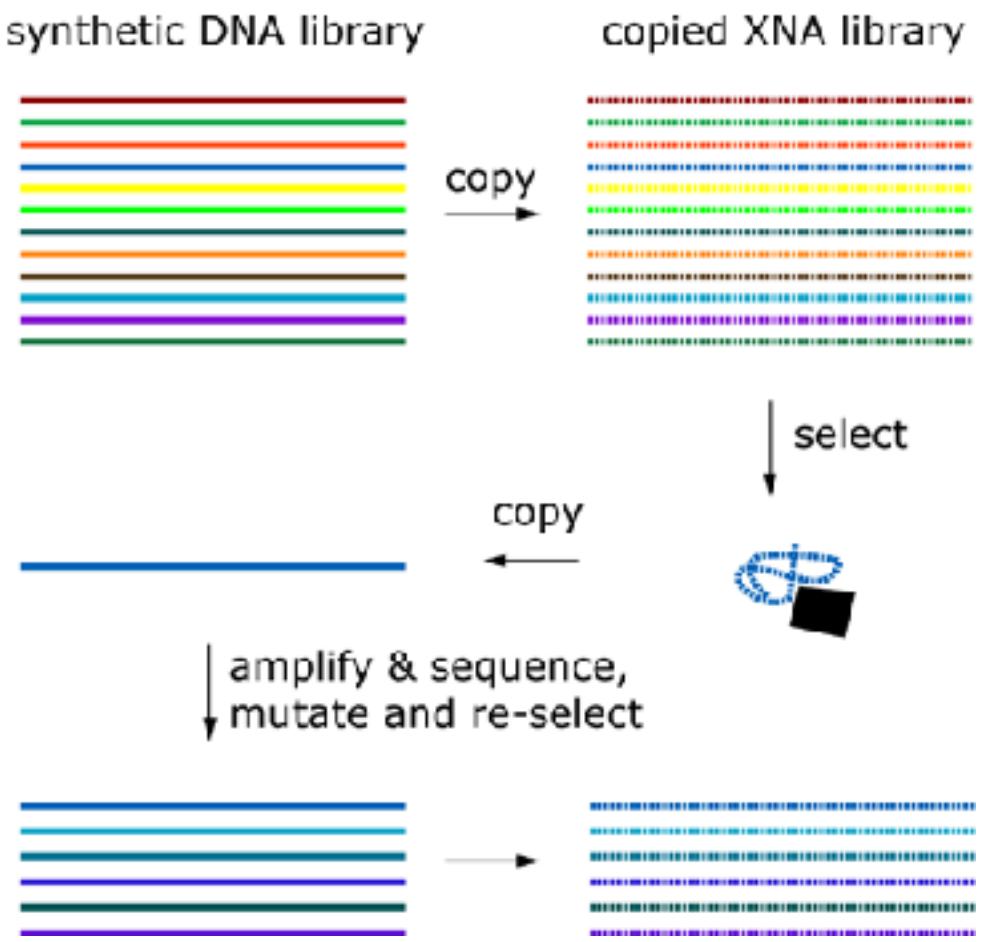
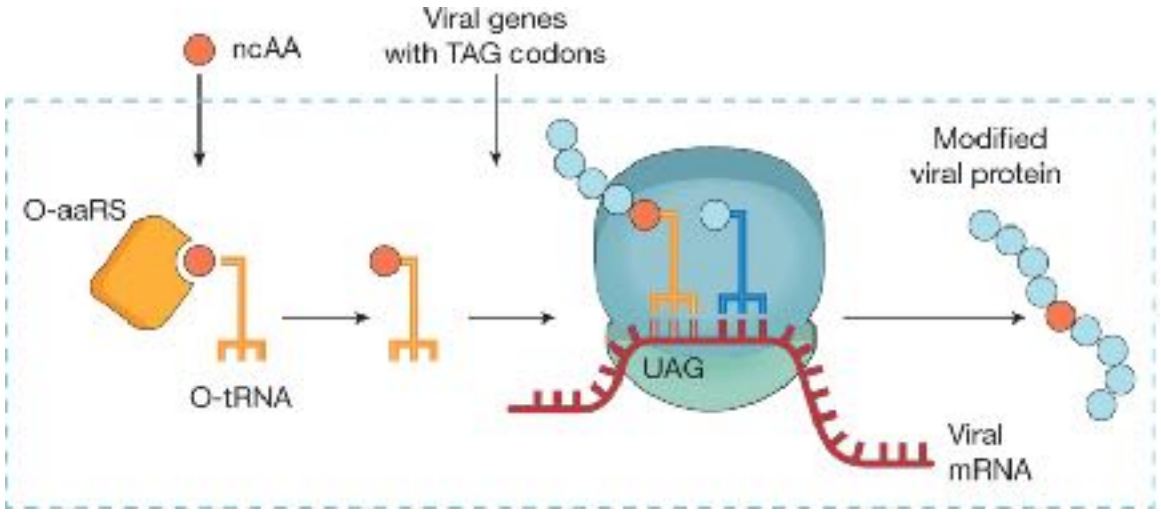
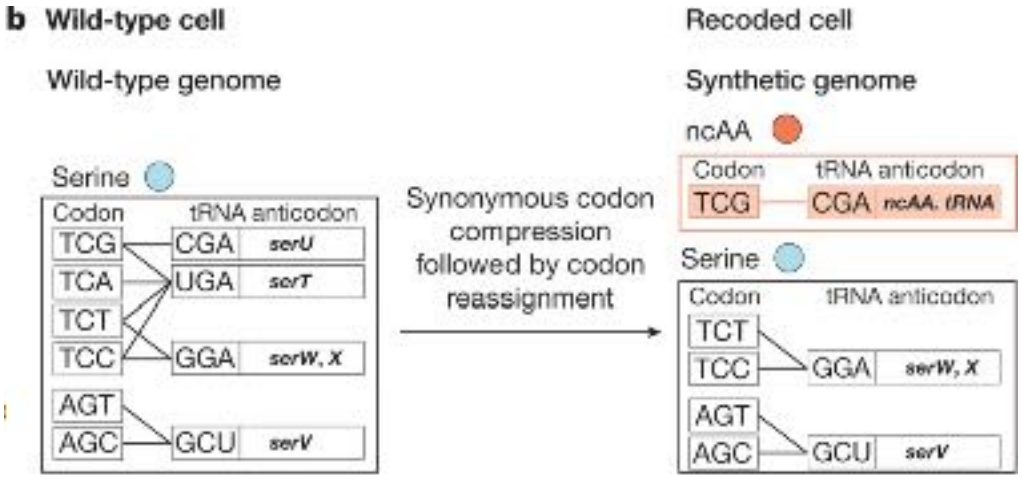


Novel proteins





How does LMB fit into the CBC?

- We do basic science, with an eye on methods and applications.
- Applications come through start-up companies, collaborations, IP licensing.
- Our students and postdocs join the workforce, creating many links.
- We aim to stay at the cutting edge of our fields of interest, and look to the long term future.
- Good things take time, and much of what we do now has roots deep in the past.

Mapping the (fly) brain