Cryo-EM for Paediatric Disease Research at Leeds Instruct Centre

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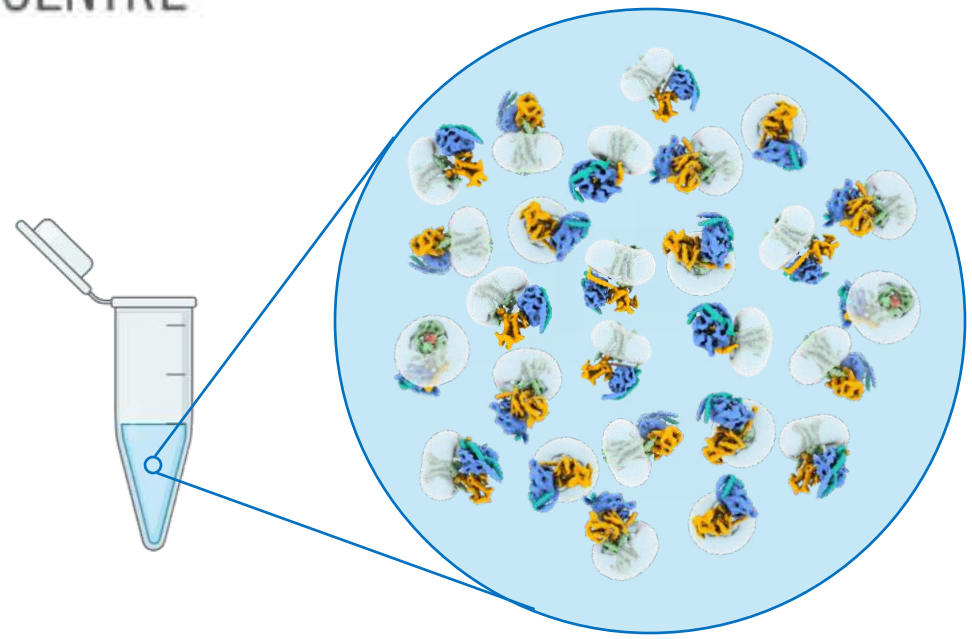
‘The real voyage of discovery consists not in seeking new landscapes, but in having new eyes.’

- Marcel Proust

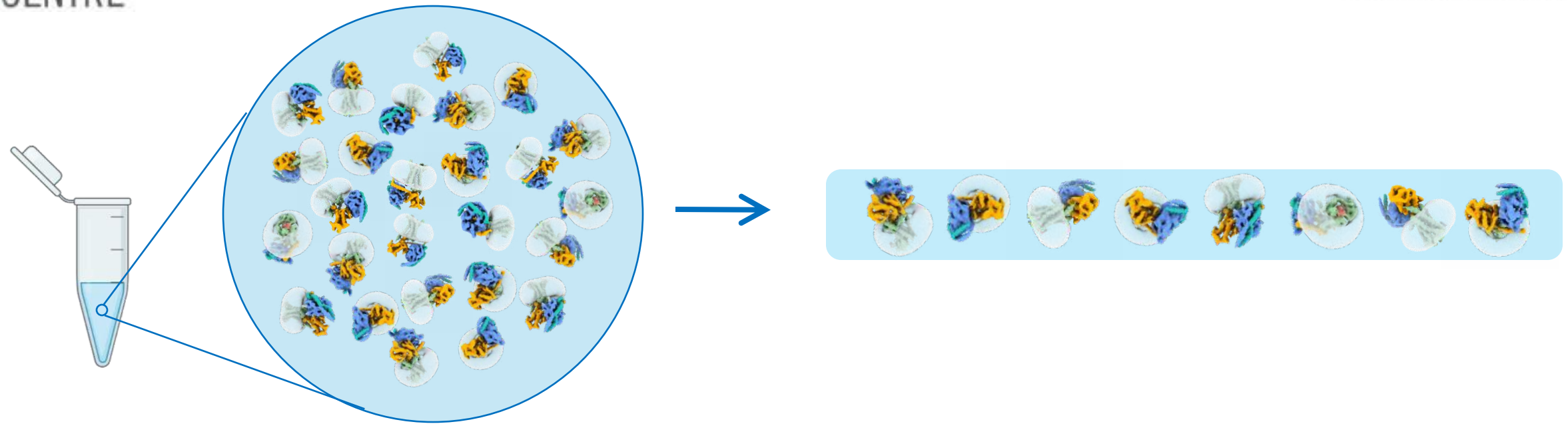
Outline

1. How does single-particle cryo-EM work?
2. Single-particle cryo-EM in paediatric disease research: examples
3. Cryo-EM at the Leeds Instruct Centre

Single Particle **Cryo-EM**



Single Particle **Cryo-EM**



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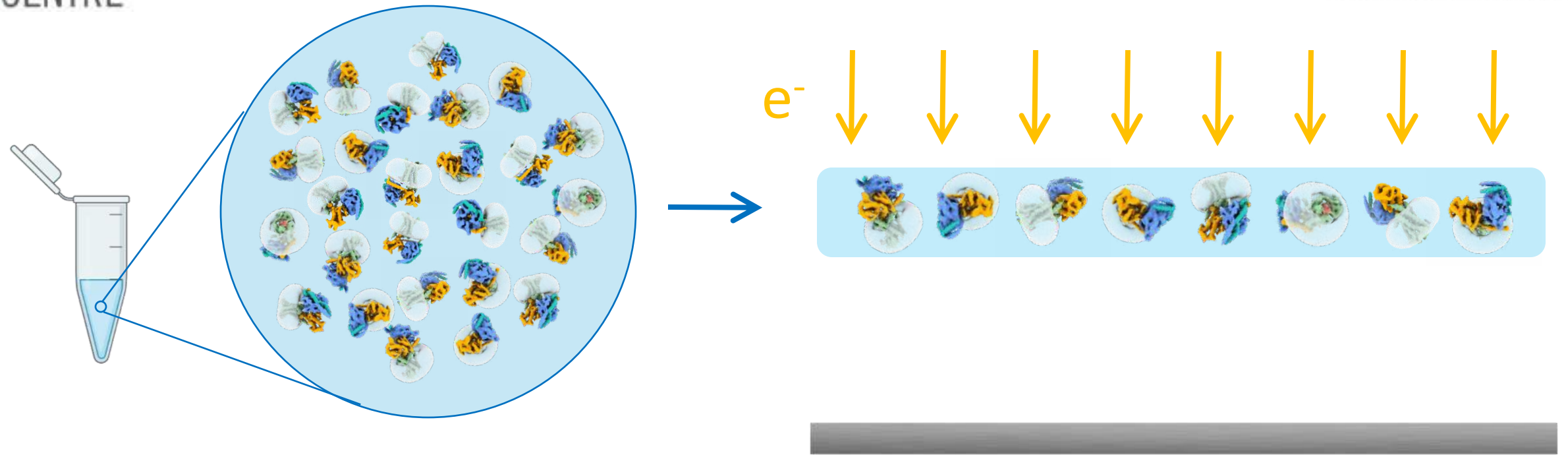

ASTBURY CENTRE

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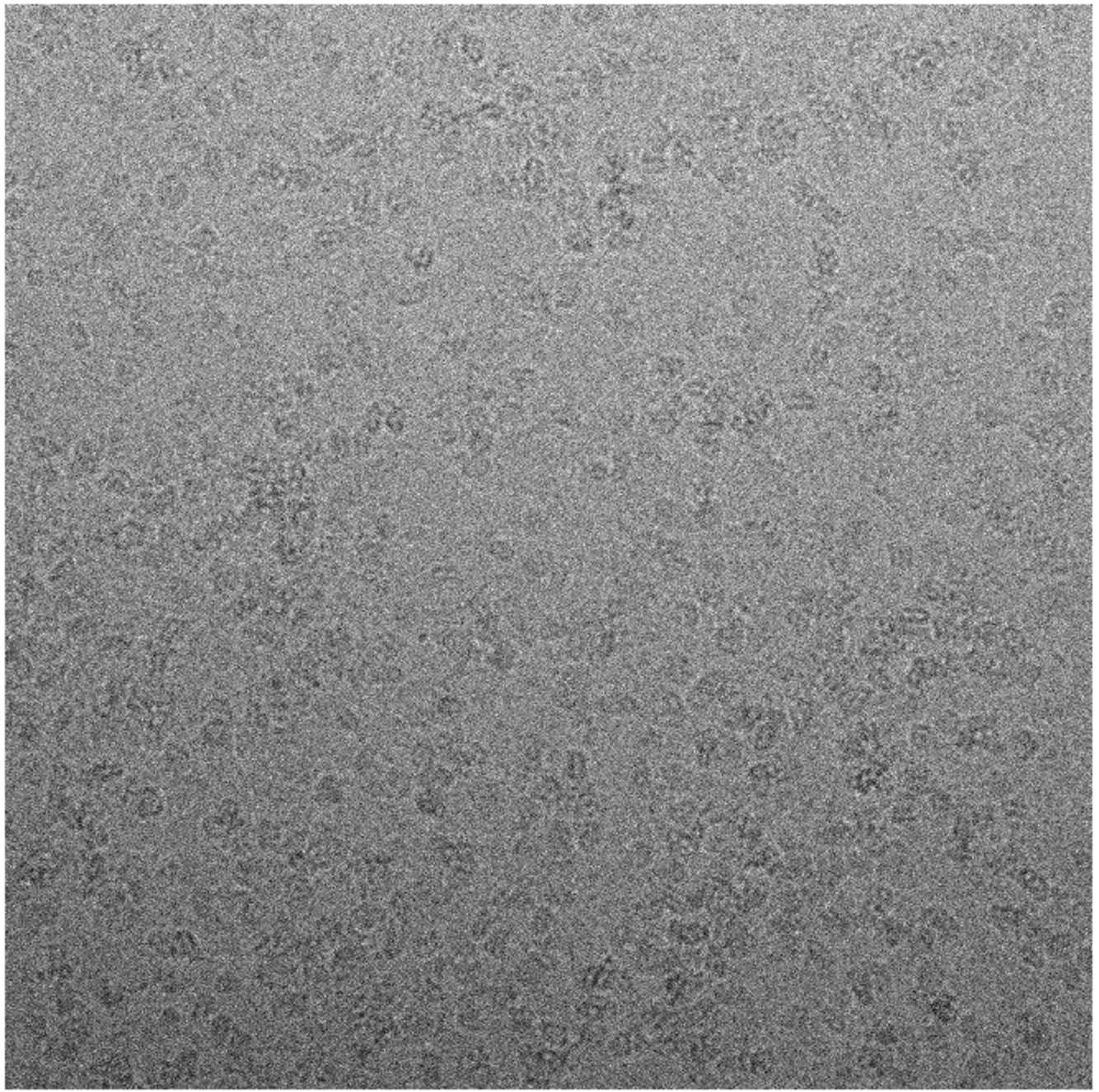

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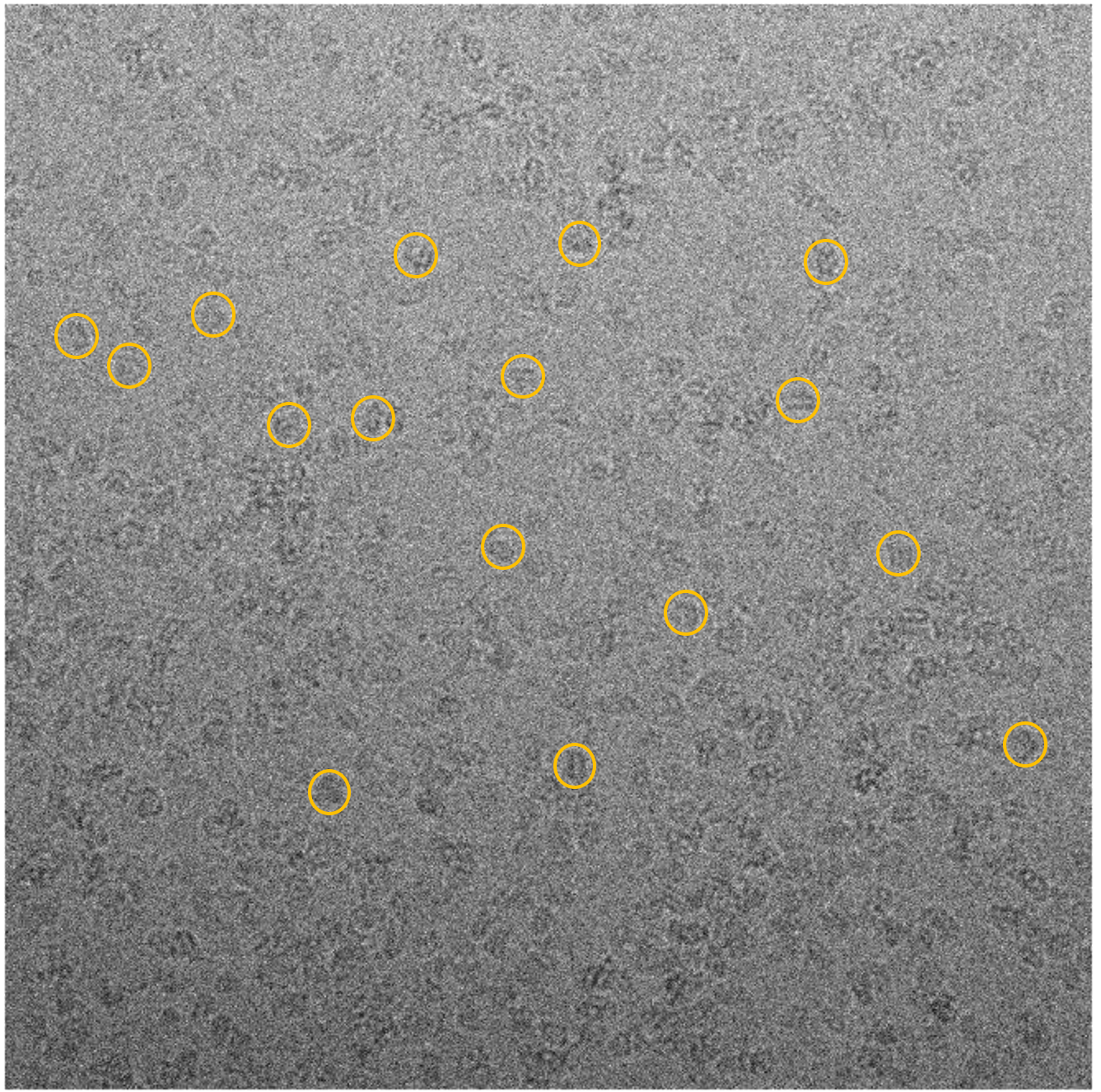

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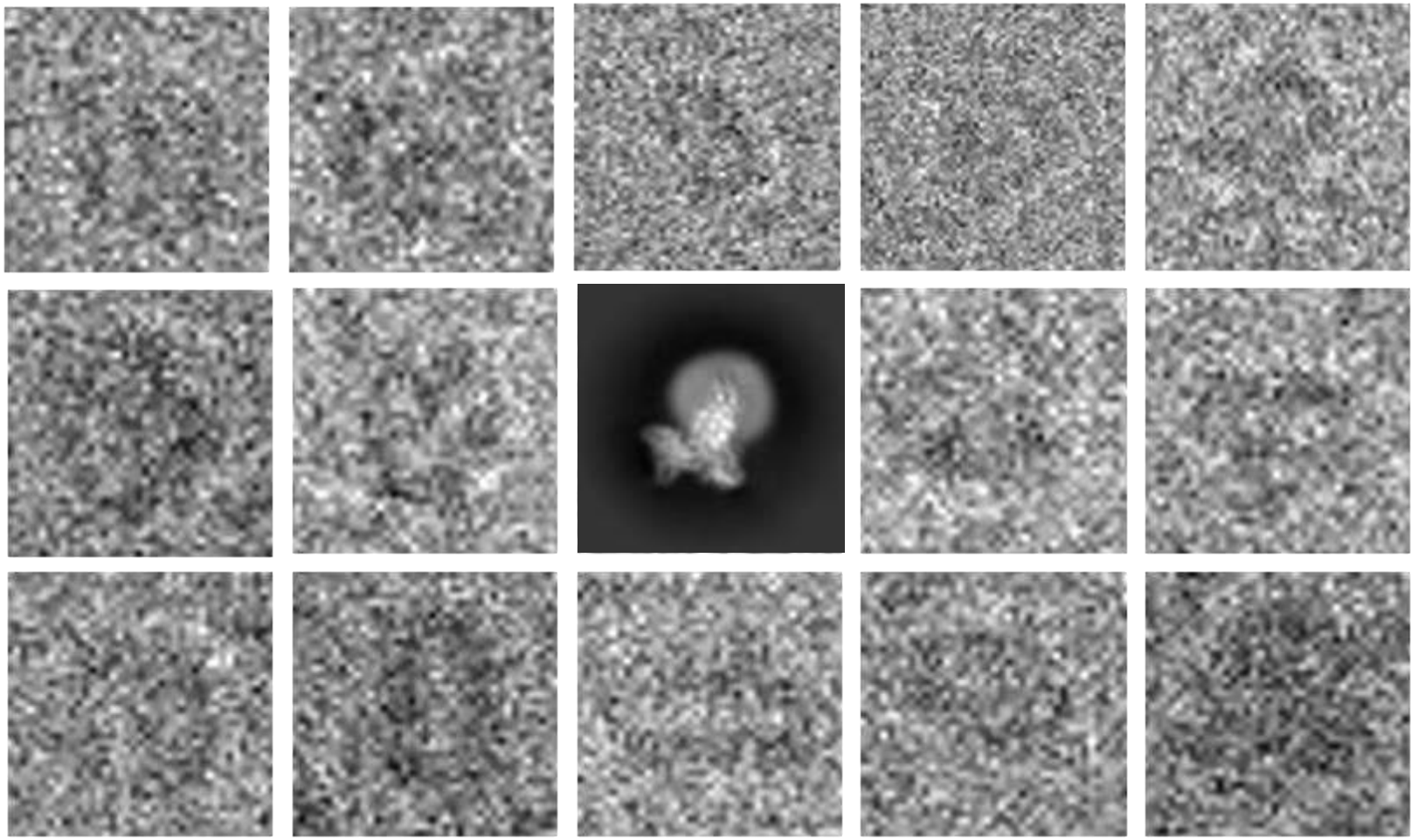

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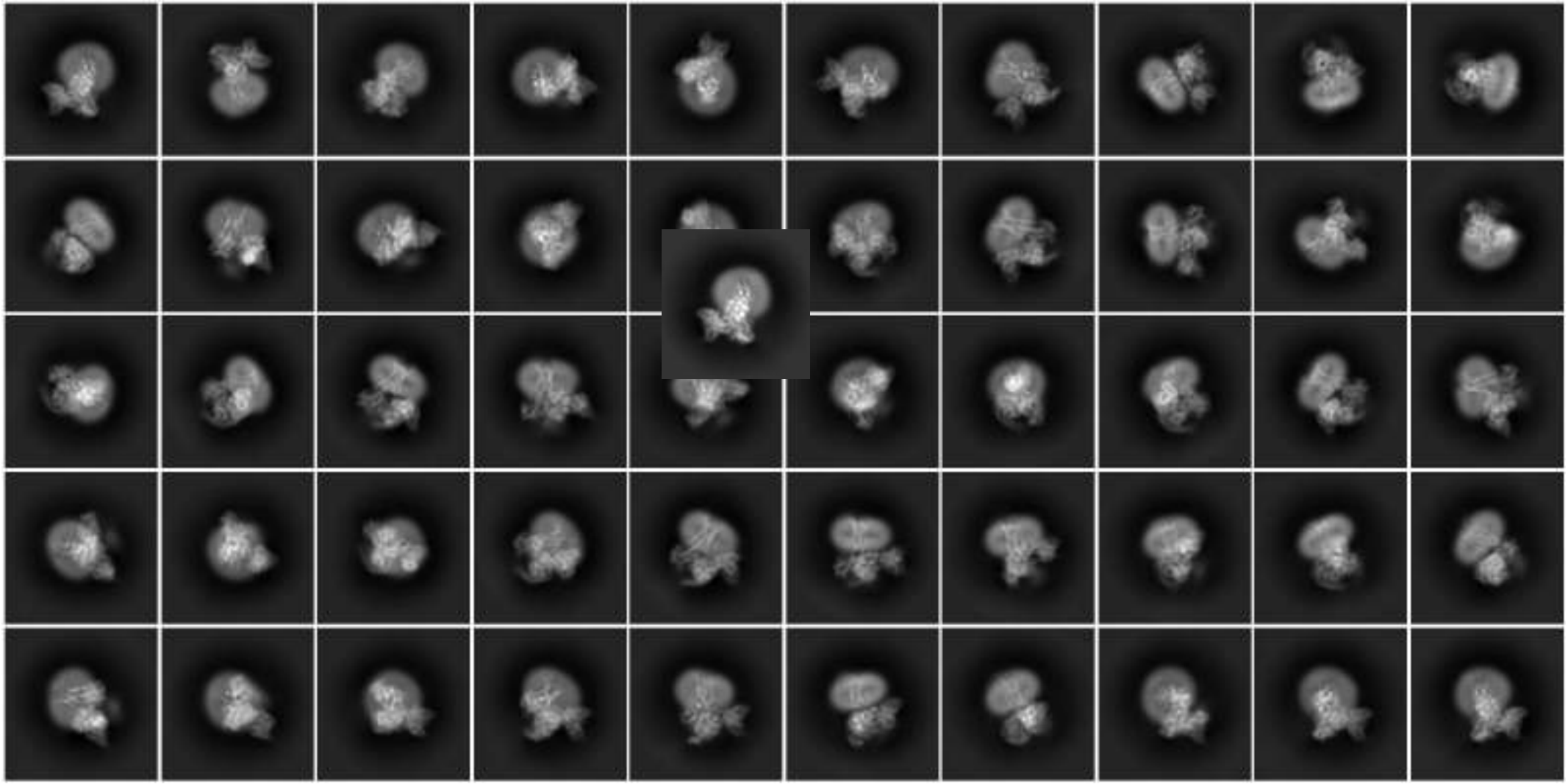

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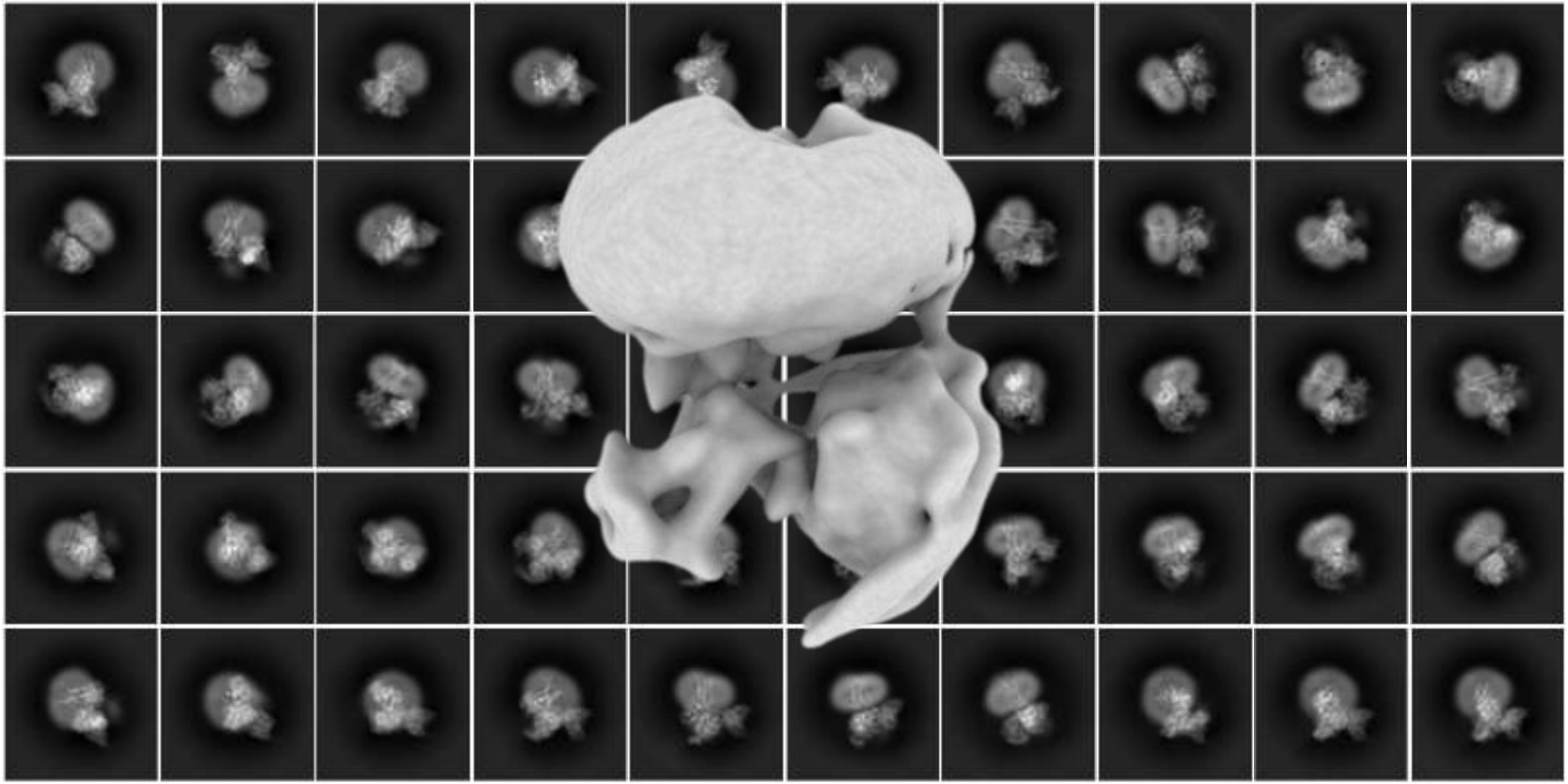

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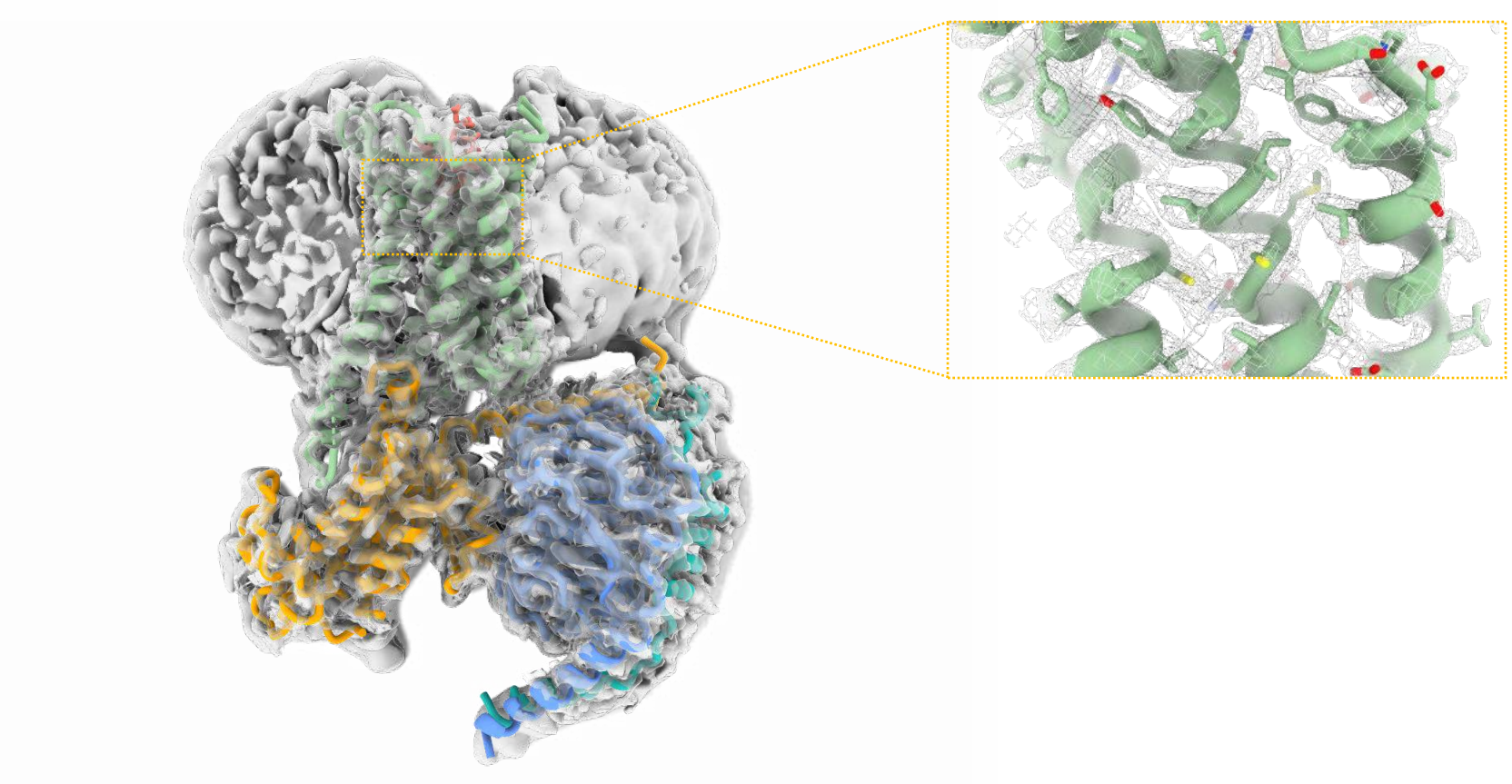
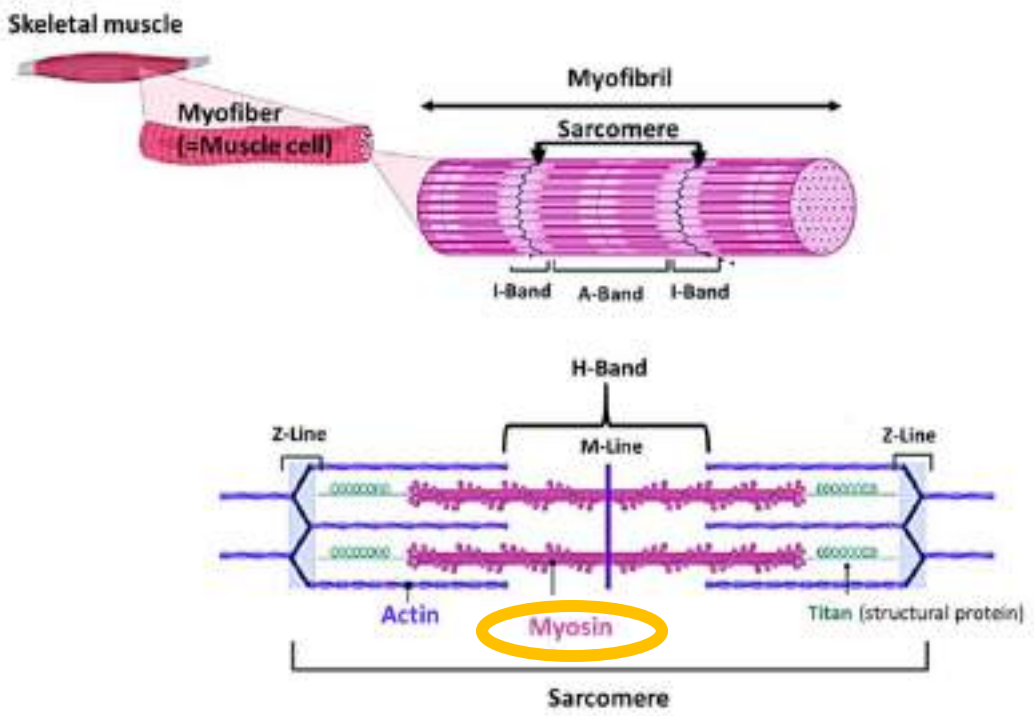
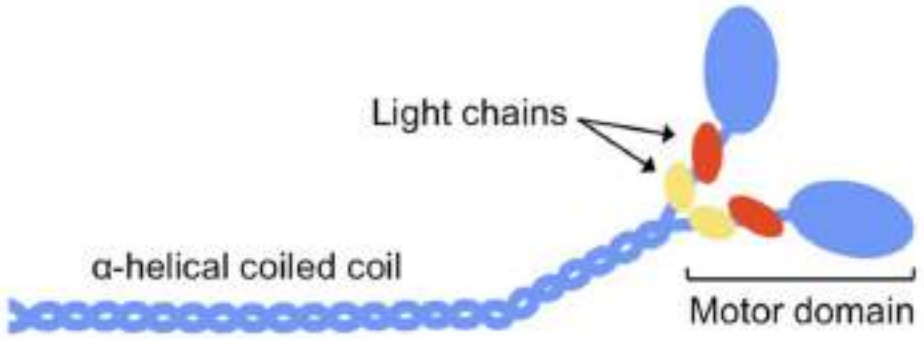


Example 1

Structural Insights into Cardiac Myosin Drug Discovery

- **Myosin** is the motor protein that drives contraction within your muscle through its interaction with filamentous actin
- Cardiac myosin **(MYH7)** is one of the most frequently mutated genes in inherited cardiomyopathy
- ~20–35% of genetically confirmed **hypertrophic cardiomyopathy (HCM)** cases carry **MYH7** mutations
- Although less common in children than adults, paediatric HCM is often more severe

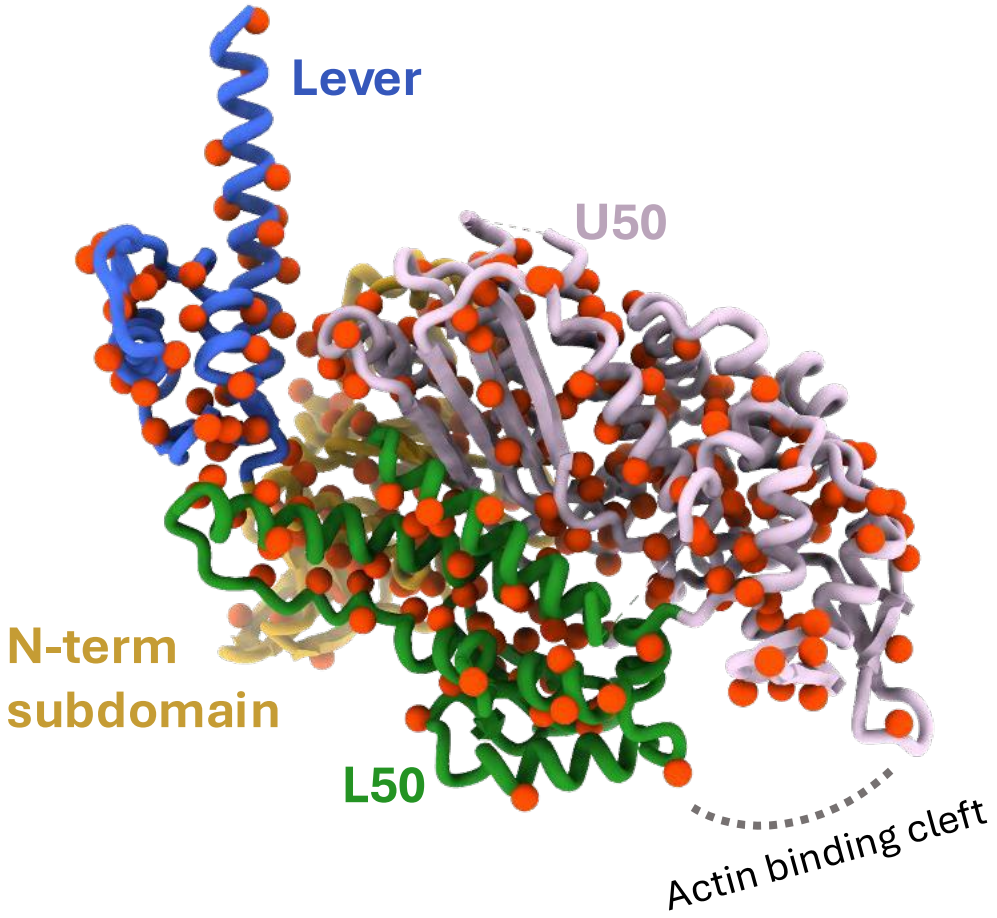




Example 1

Structural Insights into Cardiac Myosin Drug Discovery

Motor domain MYH7 mutations associated with hypertrophic cardiomyopathy

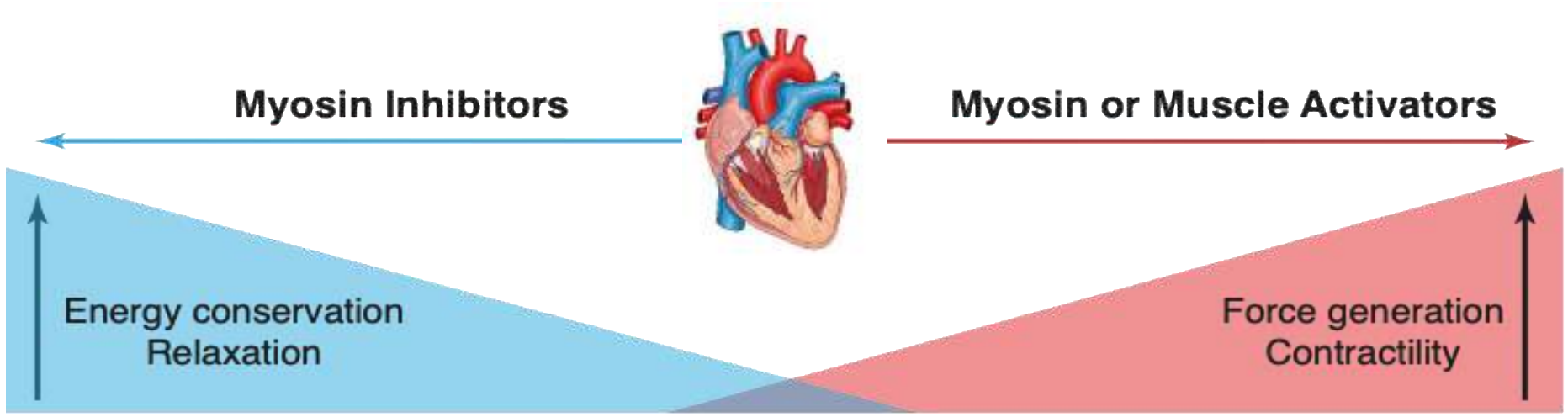


HCM-associated mutations alter the activity of the myosin causing **hypercontractility** – hyperactive myosin generates excessive force and slows relaxation of the heart muscle

Example 1

Structural Insights into Cardiac Myosin Drug Discovery

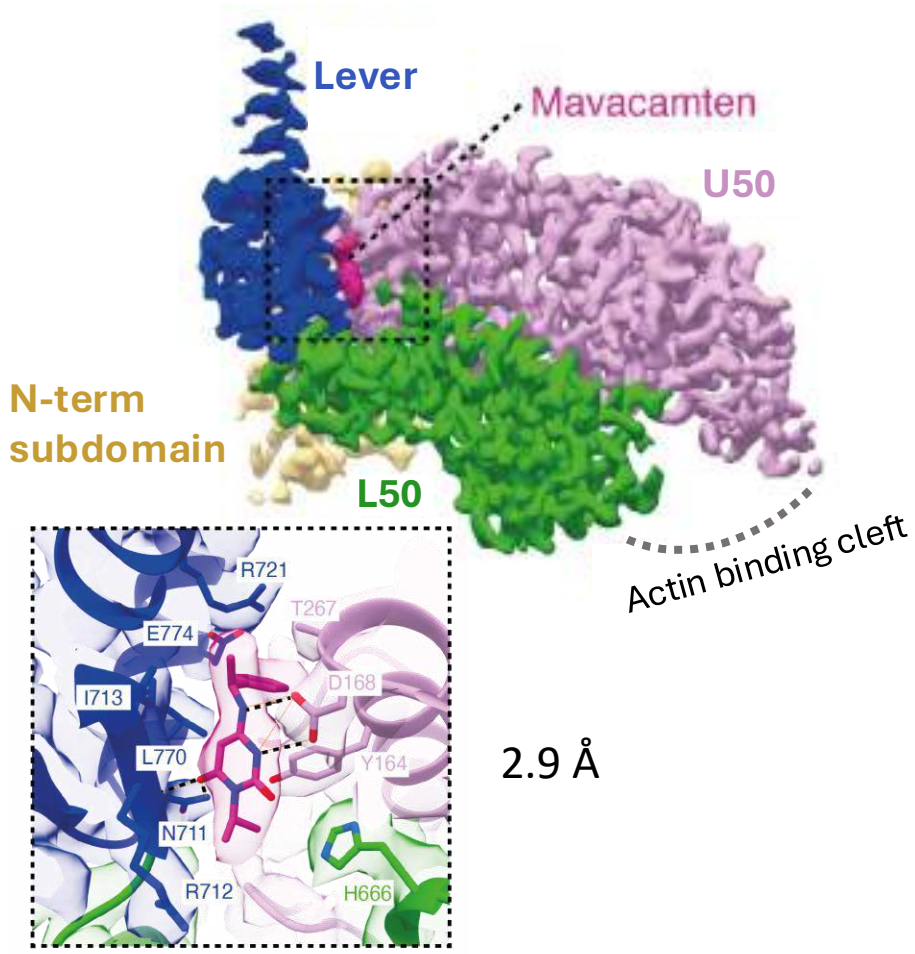
- Myosin modulators are promising treatments for cardiomyopathy
- Aficampten and Mavacampten are in Phase III clinical trials for adolescence and paediatric patients (CEDAR-HCM and SCOUT-HCM)
- The detailed molecular mechanism is not known



Example 1

Structural Insights into Cardiac Myosin Drug Discovery

Cryo-EM structures of myosin motors with inhibitors bound



2.9 Å

Charlie Scarff

Sean McMillan

Hannah Makhlouf

McMillan et al. Sci. Advances 2026

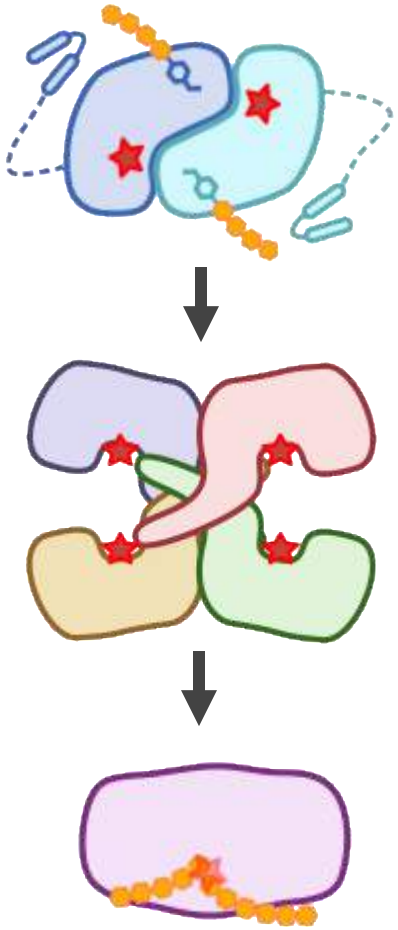
Example 2

Understanding Glycogen Synthesis Disorders by Cryo-EM

Glycogen

- Energy store in muscles
- Blood-sugar homeostasis in liver
- ~ 50,000 glucose units

Glycogen Synthesis



Glycogenin

- Autoglycosylates at Y195
- Chains up to 12 glucose units
- α-1,4 linkages
- Muscle and liver isoforms

Glycogen Synthase

- Extends glucose chains
- α-1,4 linkages
- Muscle and Liver isoforms

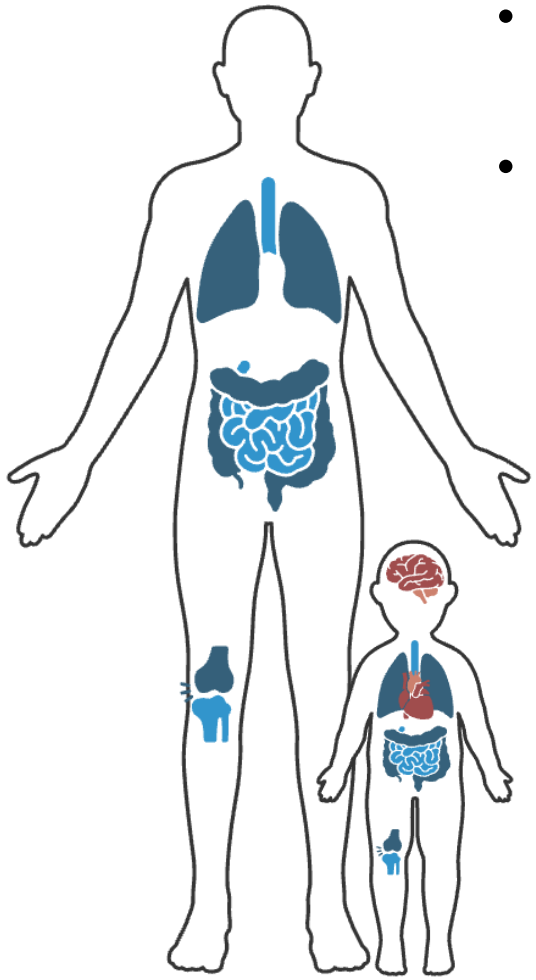
Glycogen Branching Enzyme

- Rearranges glucose chains
- Adds α-1,6 linkages
- A single isoform

Dysregulated Glycogen Metabolism Leads to Disease

- **Pompe Disease**
- **McArdle Disease**
- **Lafora Disease**
- **Type 2 Diabetes**

Pompe Disease



- Caused by loss-of-function mutations in the gene encoding lysosomal acid α-glucosidase
- Symptoms caused by glycogen accumulation in skeletal and cardiac muscle

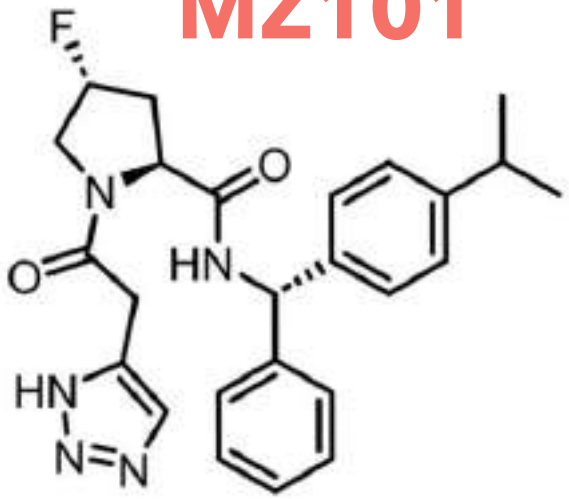
Symptoms:

- ***Developmental delay***
- ***Enlarged heart***
- Progressive muscle weakness
- Difficulty swallowing + loss of bladder/bowel control
- Enlarged liver
- Difficulty breathing + respiratory infections

Example 2

Understanding Glycogen Synthesis Disorders by Cryo-EM

MZ101



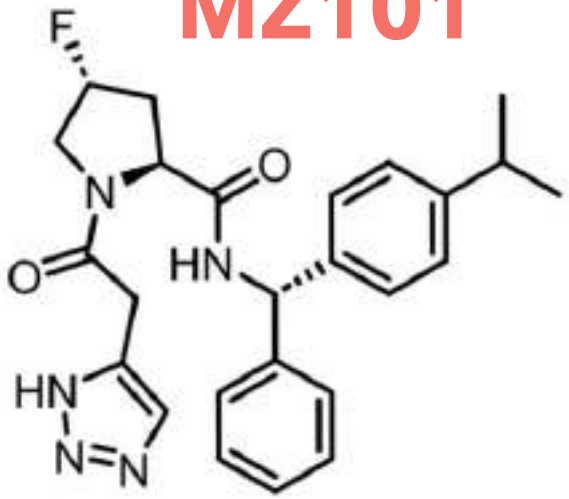
- *GS1-Specific* Inhibitor
- MAZE Therapeutics 2024
- Pompe Disease clinical trials

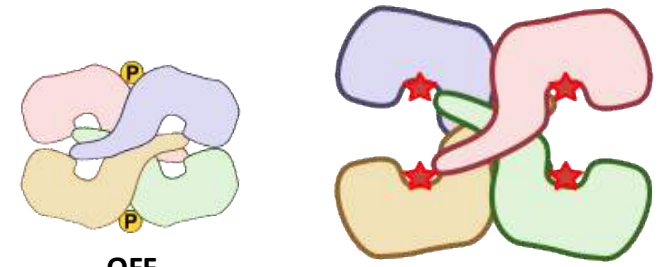
→ Where does it bind?
→ How does it inhibit?
→ How is it isoform specific?

Example 2

Understanding Glycogen Synthesis Disorders by Cryo-EM

MZ101





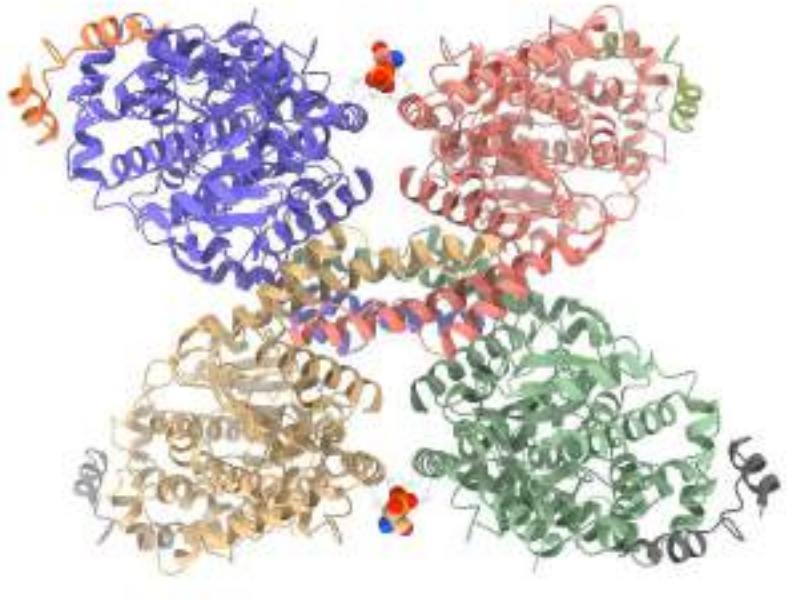
Less glycogen synthesis

More glycogen synthesis

Emma Cowan

Elton Zeqiraj

- *GS1-Specific* Inhibitor
- MAZE Therapeutics 2024
- Pompe Disease clinical trials

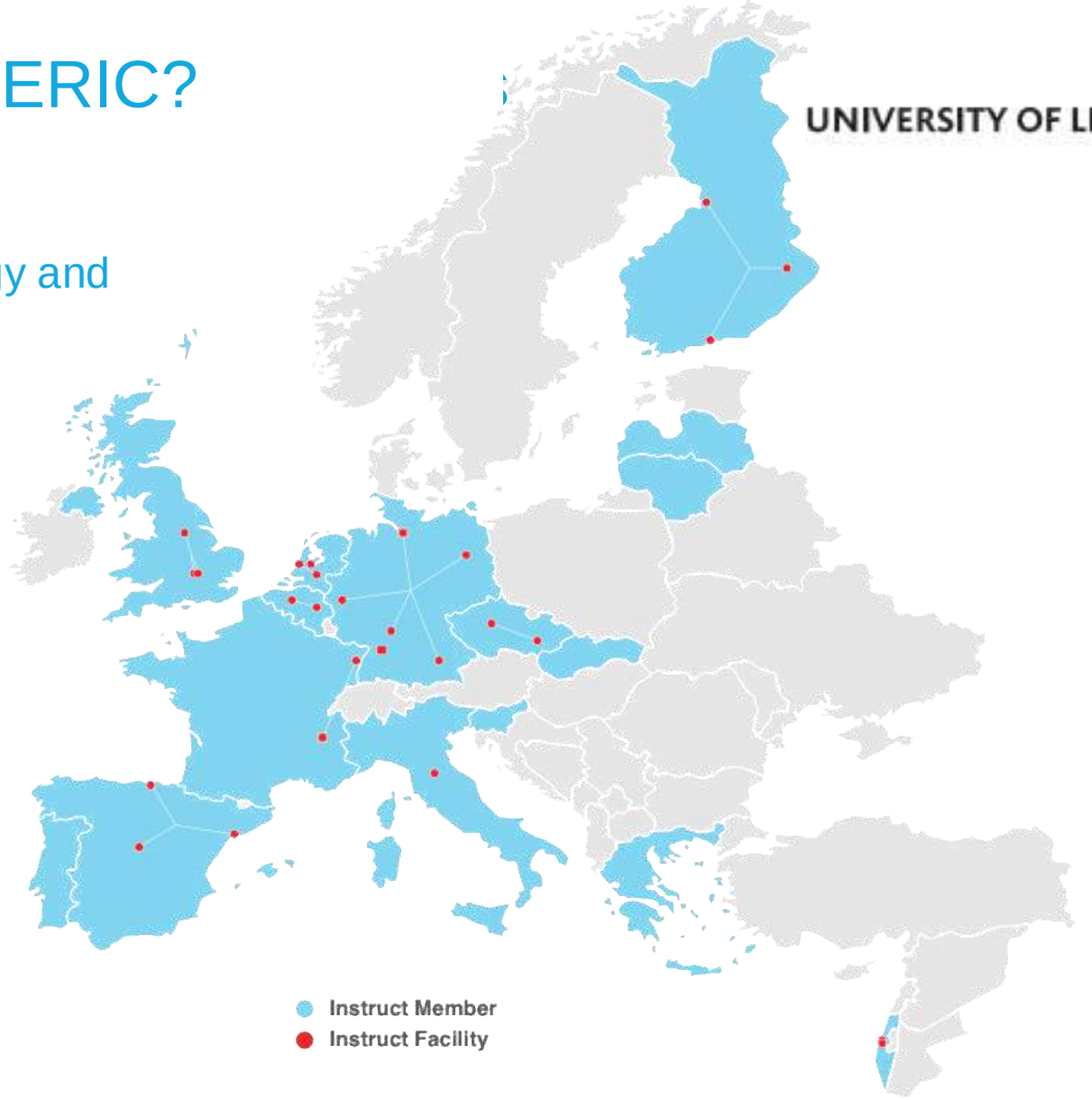


→ Where does it bind?
→ How does it inhibit?
→ How is it isoform specific?

What is Instruct-ERIC?

Instruct-ERIC is the single point of access to technology and expertise for structural biology research.

The Instruct consortium comprises **11 Instruct Centres** that offer access to **29 facilities** across Europe.



- Access to Instruct services
- Free Access
- Travel or sample shipping
- Accommodation

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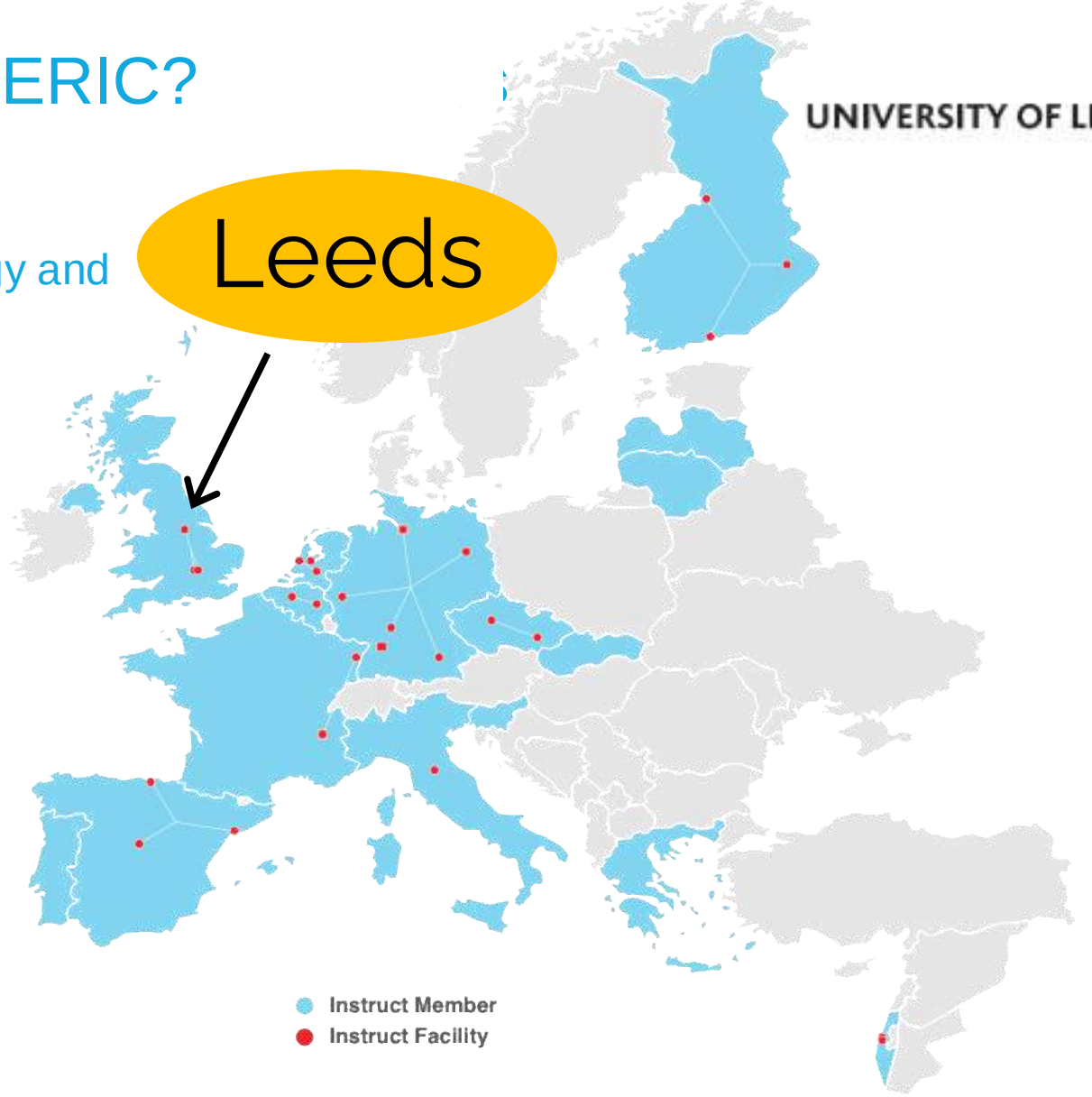

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Leeds Instruct Centre for cryo-EM

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Our Capabilities:

- 2x Titan Krios G2 Microscopes + Falcon 4 + Selectris Energy filter
- Vitrobot IV and Leica EM GP plunge freezers
- Hydra FIB-SEM and High Pressure Freezer, cryo-confocal to support *in situ* cryo-electron tomography pipelines

Our Services:

- Sample preparation, screening, and data collection for both **single-particle cryo-EM** and **cryo-electron tomography**
- Sample to structure
- Options for in-person or remote access available

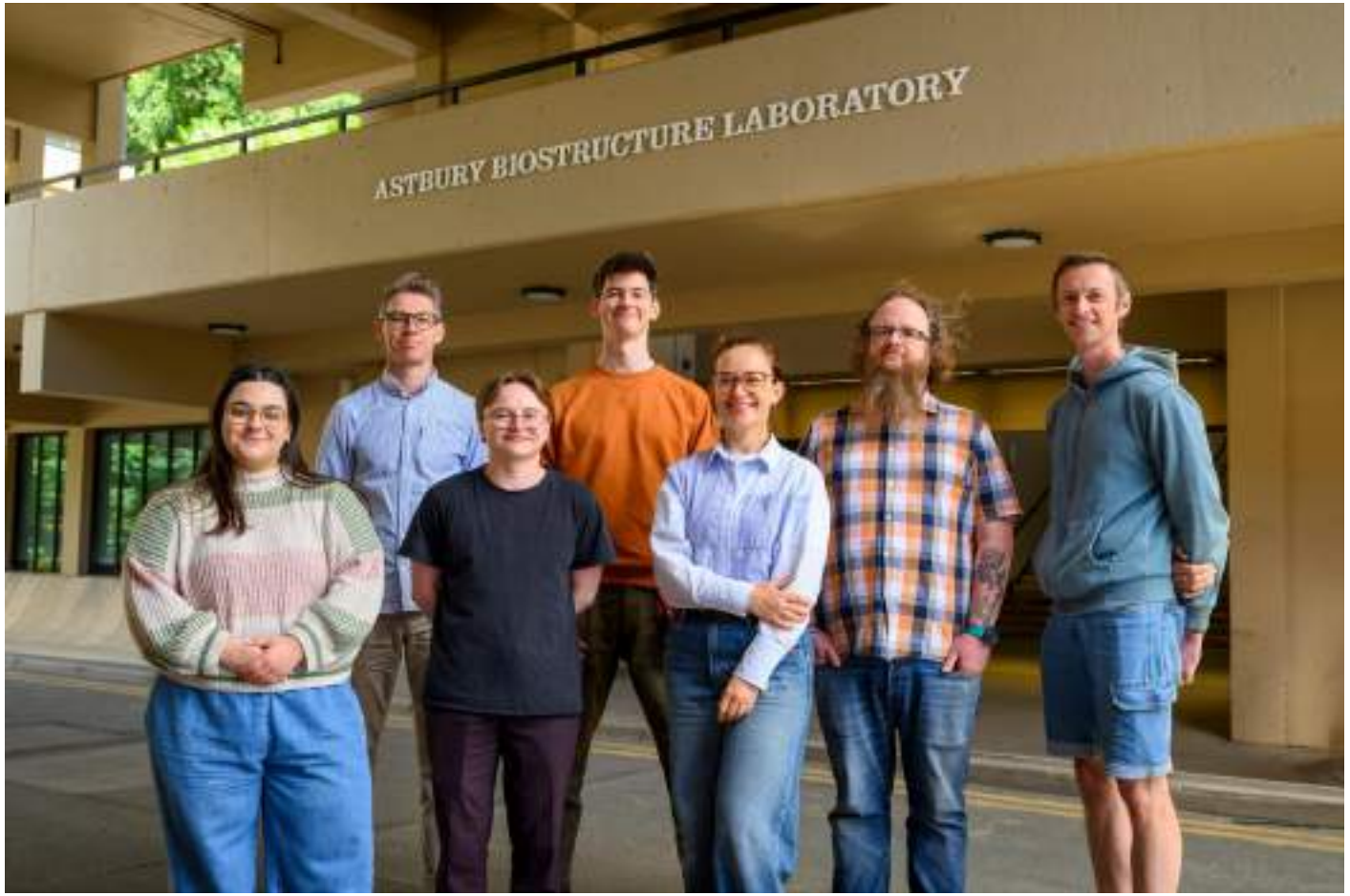
Leeds Instruct Centre for cryo-EM

Cryo-EM Team

Foteini Bifsa

Csaba Zoltan Kibedi Szabo

Charlie Lovatt



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Emma Cowan

Charlie Scarff
Sean McMillan
Hannah Makhlouf

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