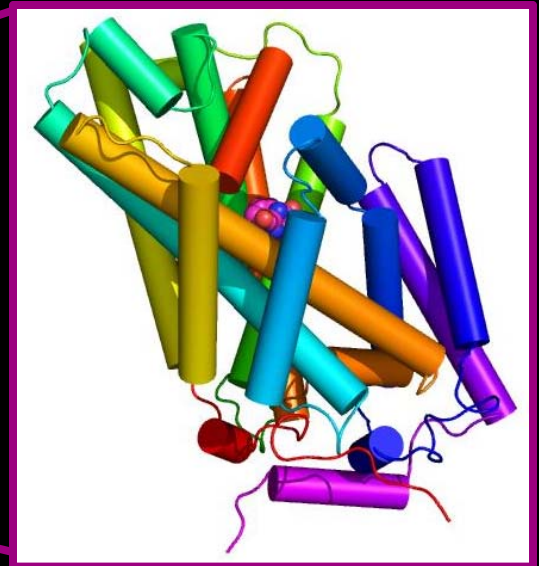
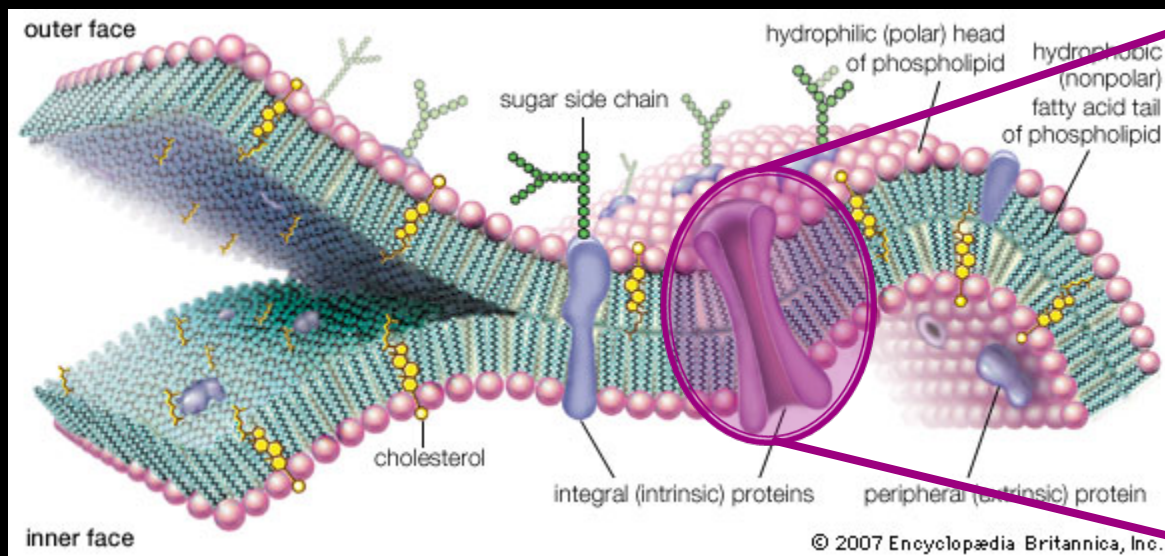


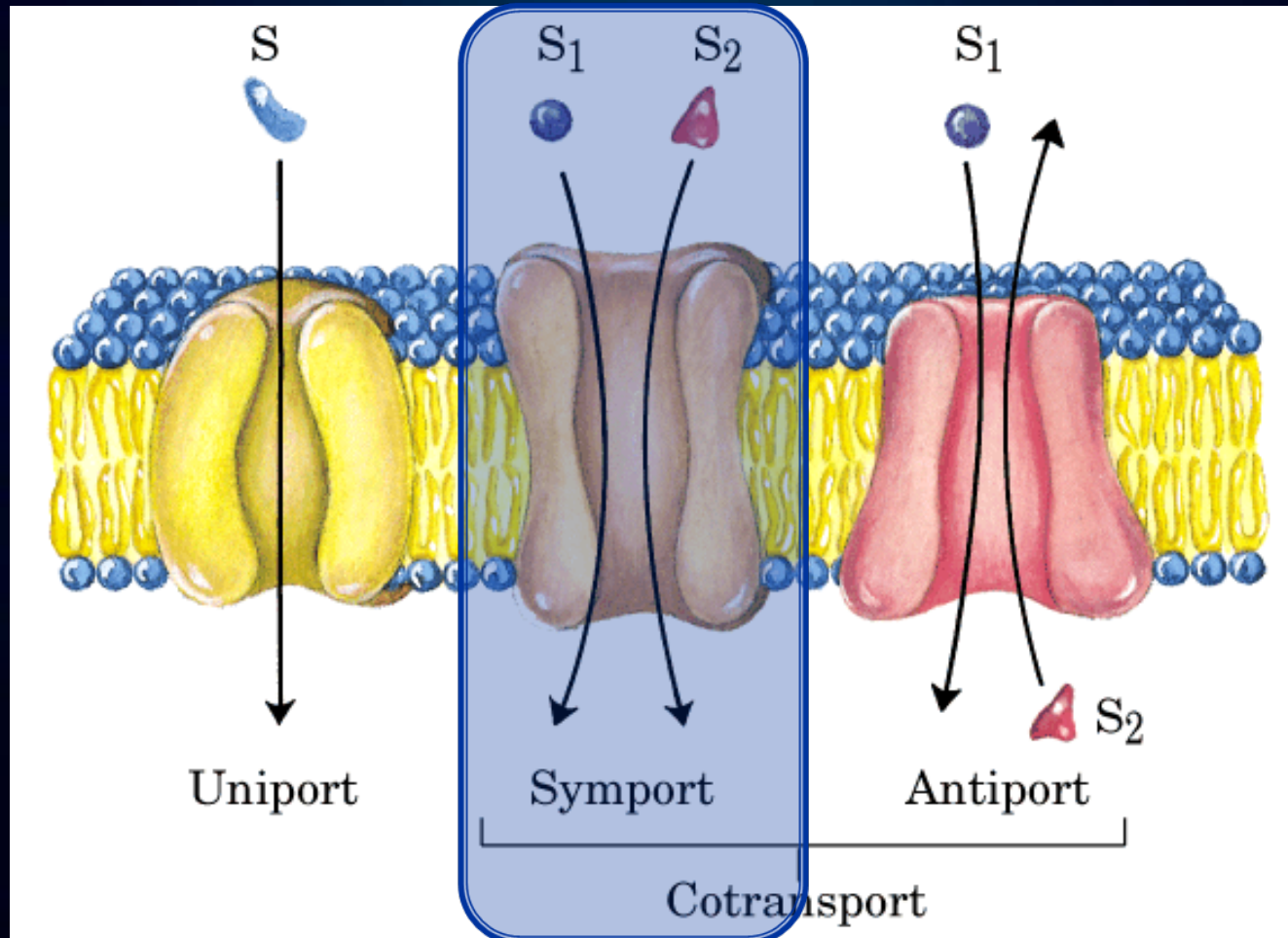
The Crystal Structure of a Sodium Galactose Transporter Reveals Mechanistic Insights into Na⁺/Sugar Symport



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Salem Faham

Background: Membrane Transport



Alternating Access

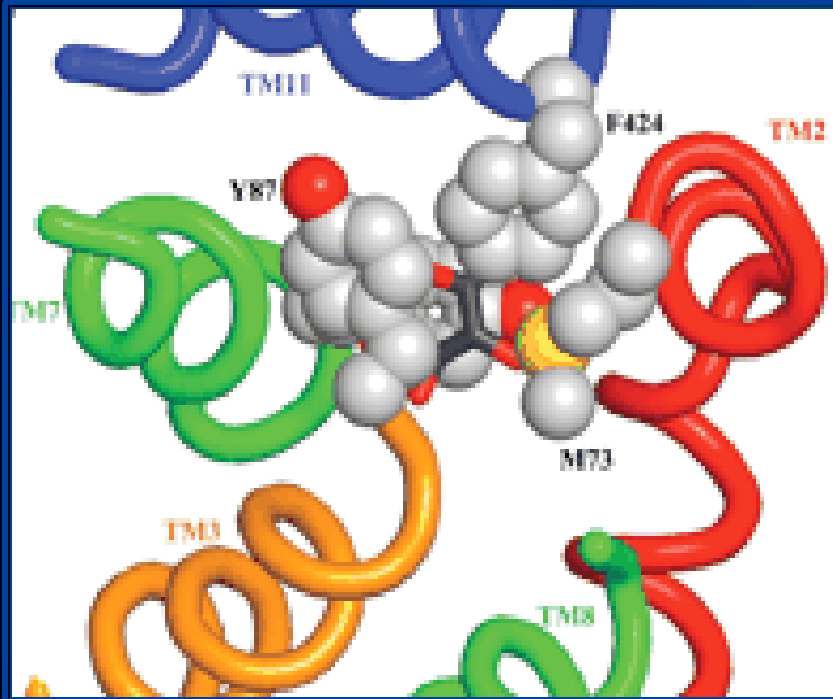
The means by which a membrane protein exposes an active site on either side of the membrane, allowing the passage of ions and solutes into or out of the cell

In spite of functional studies supporting the alternating access pathway, there is a complete absence of supporting structural data

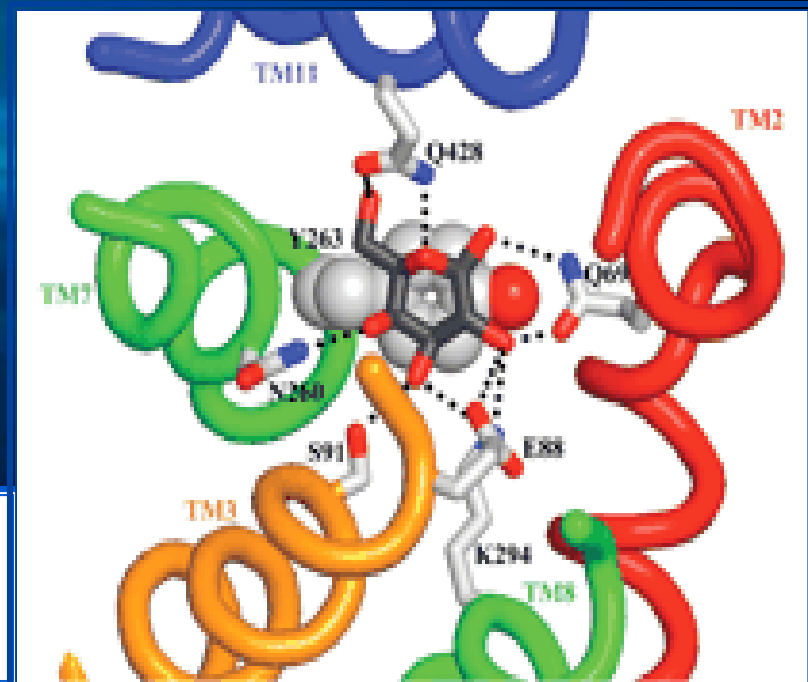
Solute Sodium Symporters (SSS)

- Protein family
- Cotransports Na^+ with sugars, amino acids, inorganic ions or vitamins
- Members are important in human physiology and disease
 - Mutations in glucose and iodide symporters (SGLT₁ and NIS) result in congenital metabolic disorders glucose-galactose malabsorption (GGM) and iodide transport defect (ITD)
 - SGLTs are currently being targeted in drug trials for type II diabetes

Active Site

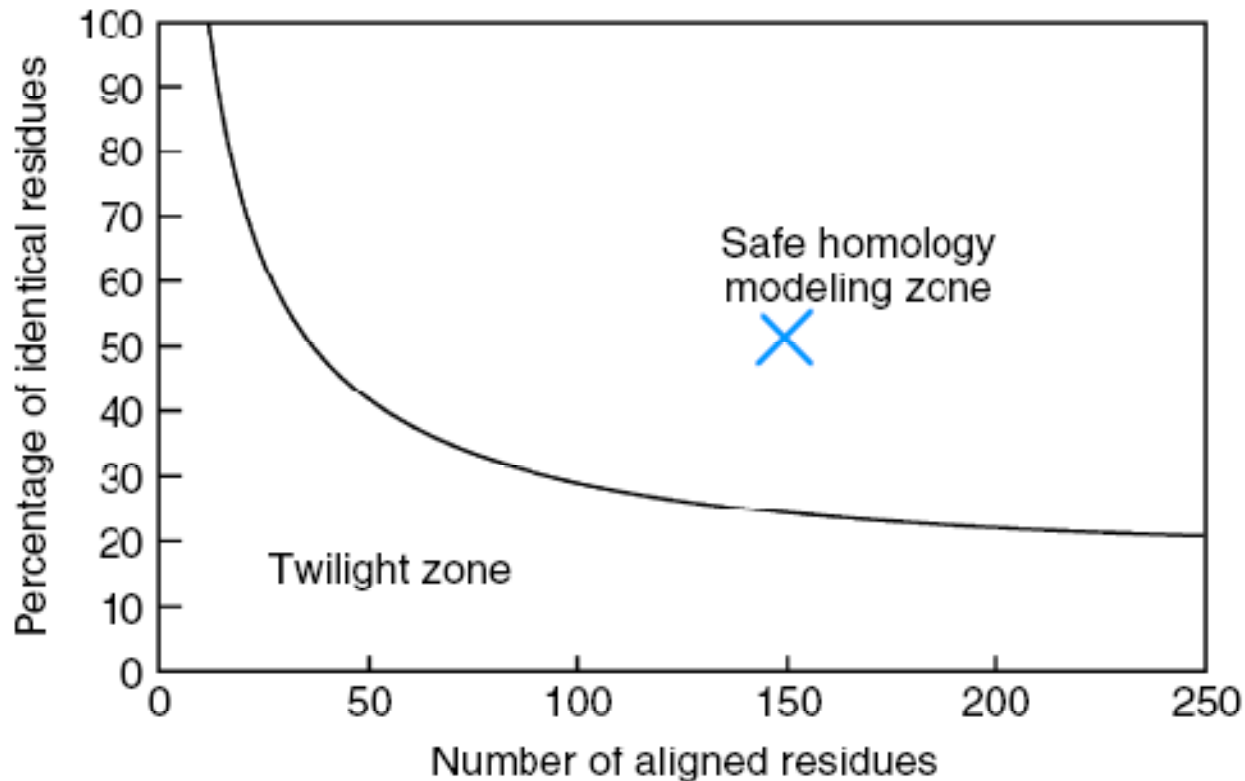


Galactose binding site:
hydrophobic gate residues
(viewed from the extracellular side)



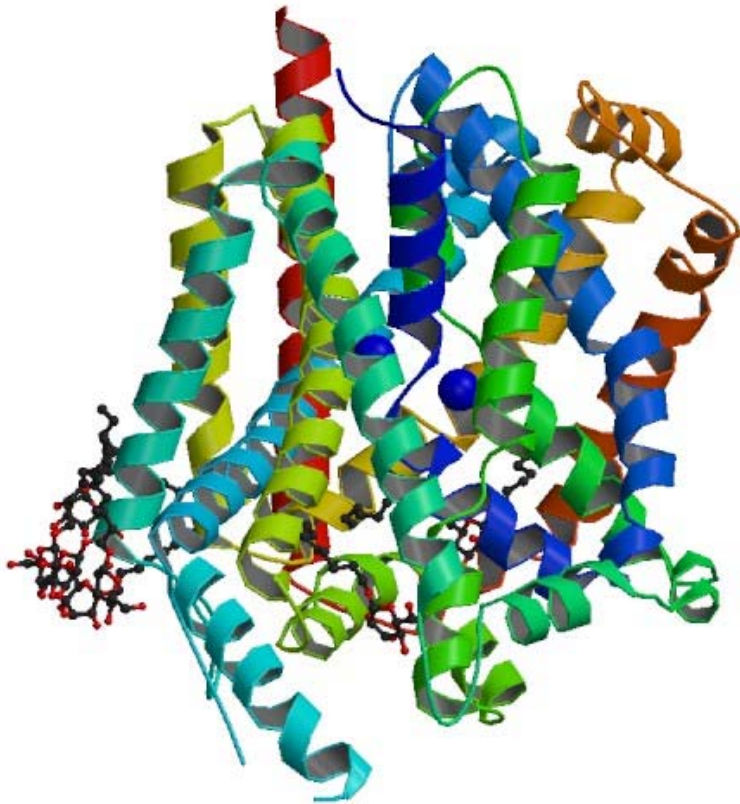
Galactose binding site with extracellular
hydrophobic gate residues removed to
view the site. From Faham et al.

To propose a mechanism for alternating access...

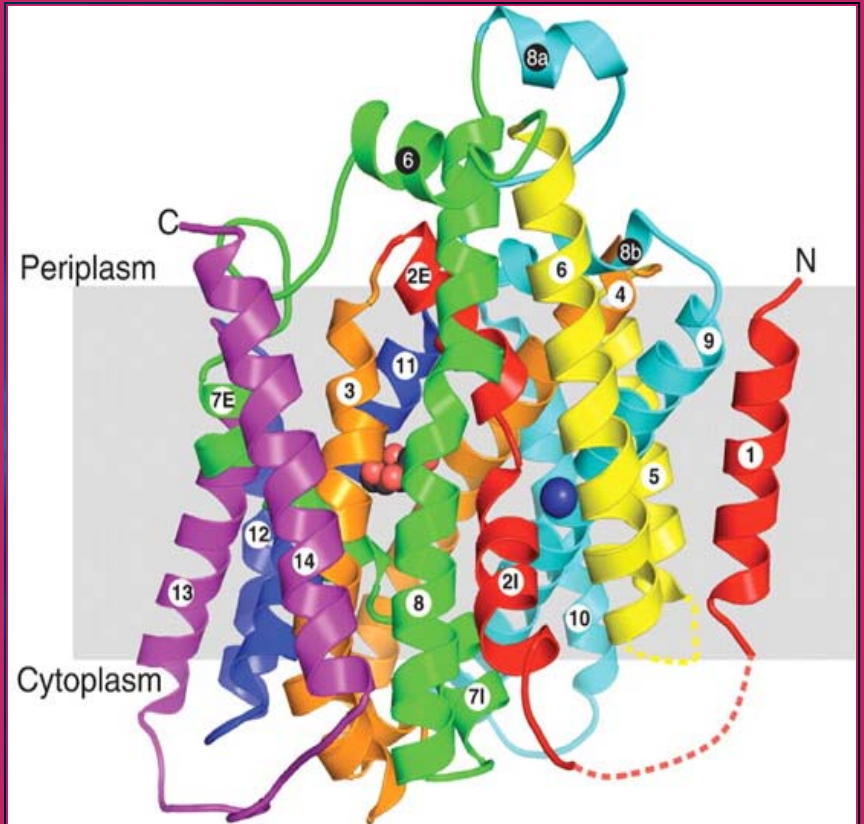


Two zones of sequence alignments. Blue X indicates an example of two proteins with 150 aligned residues that share a 50% sequence identity (figure from Kreiger et al).

LeuT: 16% sequence identity

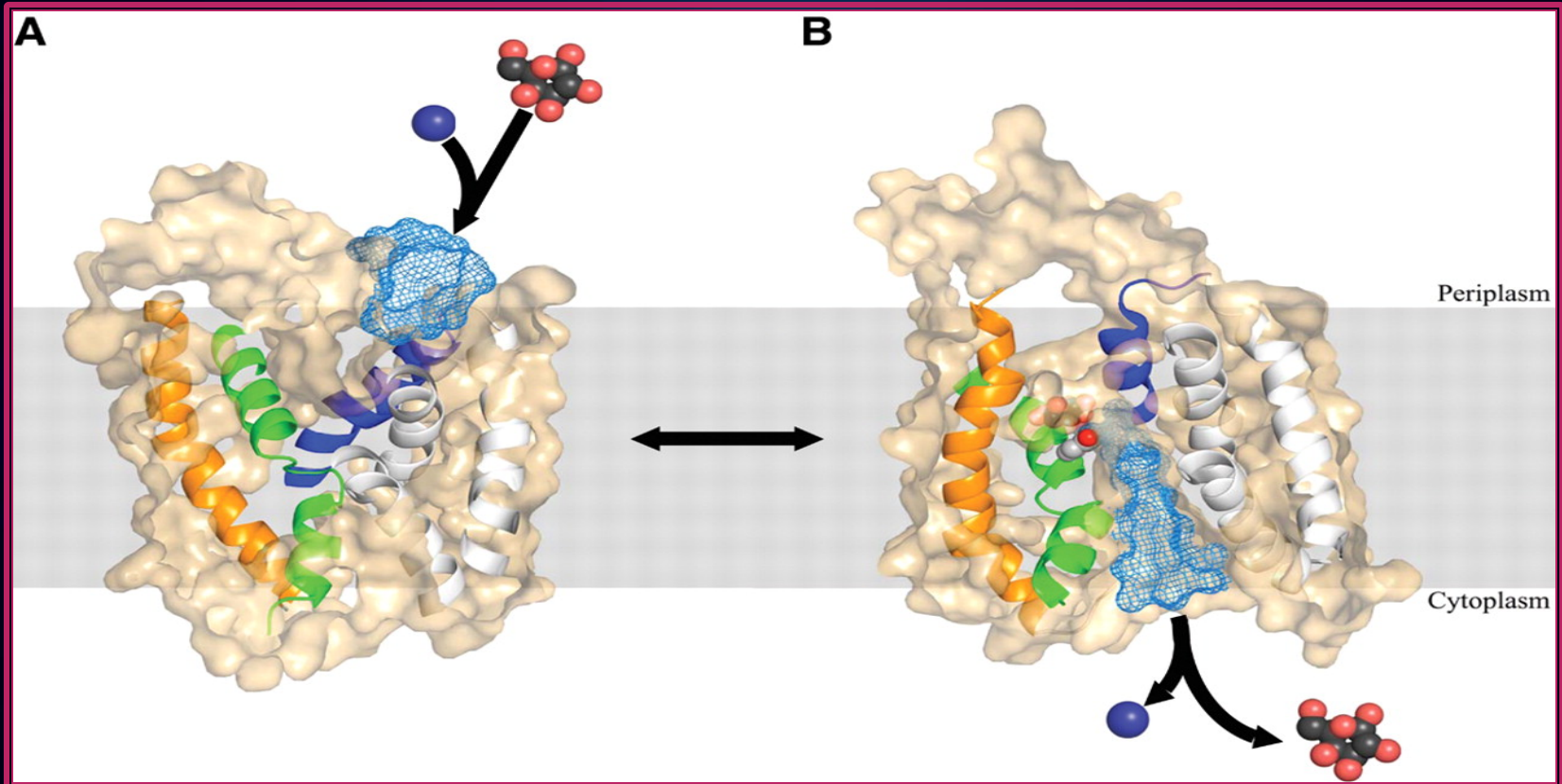


LeuT



vSGLT

Modeling Alternating Access



Structure of vSGLT. A) Outward facing model based on LeuT, B) inward-facing model based on X-ray crystallography. Helices shown are those that likely play an important role in alternating access. From *Faham et al.*

My Research: The Weighted Ensemble Approach

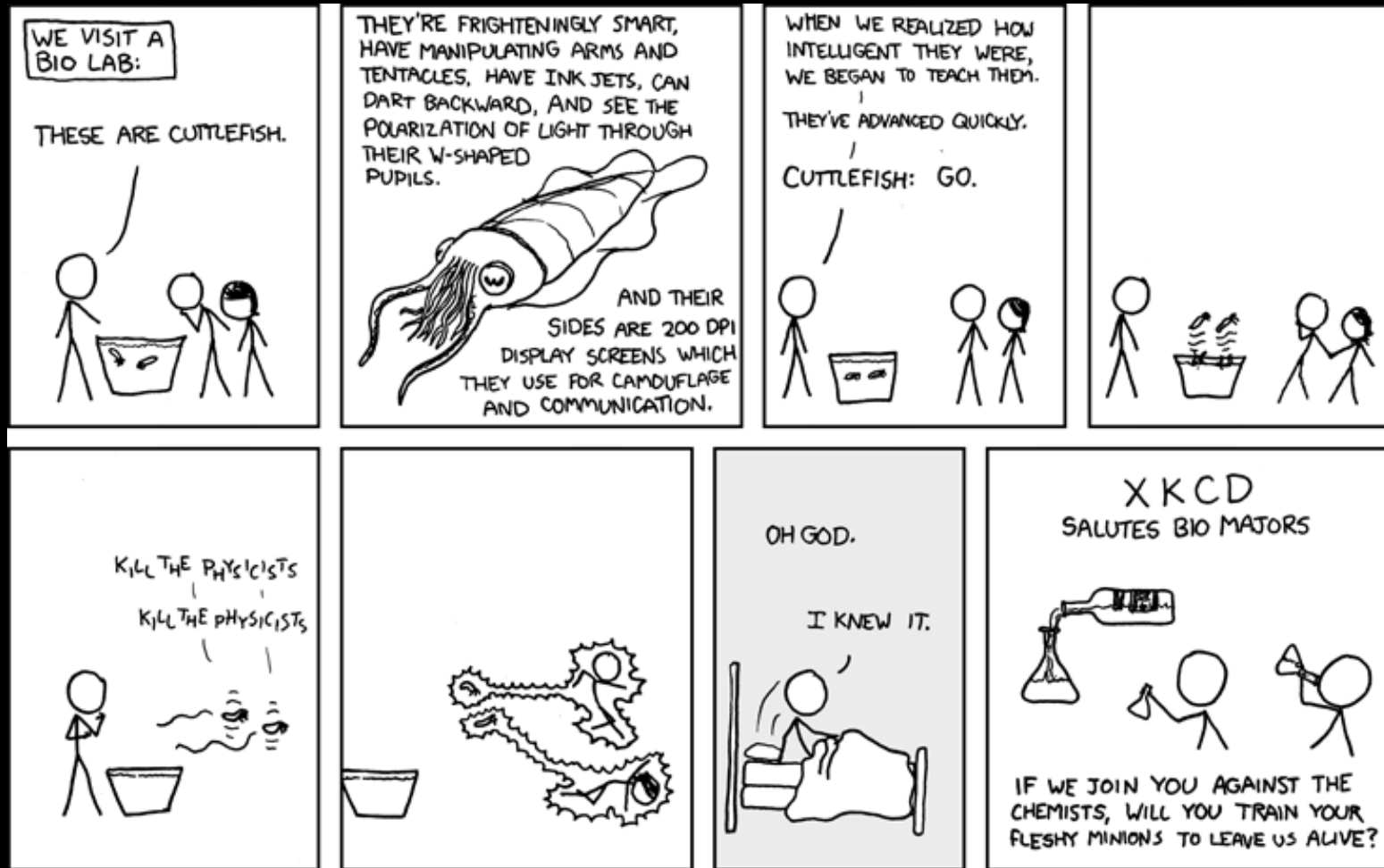
Objective 1: Analyze weighted ensemble trajectories generated from an outward-facing model of vSGLT based on the structure of LeuT

Objective 2: Use homology modeling based on Mhp1 to propose a more accurate outward-facing structure for vSGLT

Objective 3: Create more accurate alternating access trajectories for vSGLT, again using the WE approach

Our overall objective is to provide an accurate description of the alternating access pathway for the galactose transporter vSGLT

And finally: a word from xkcd on interdepartmental collaboration...



References

Faham, S., A. Watanabe, G.M. Besserer, D. Cascio, A. Specht, B.A. Hirayama, E.M. Wright, J. Abramson. 2008. "The Crystal Structure of a Sodium Galactose Transporter Reveals Mechanistic Insights into Na⁺/Sugar Symport." *Science*. Vol 321: 810-814.

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