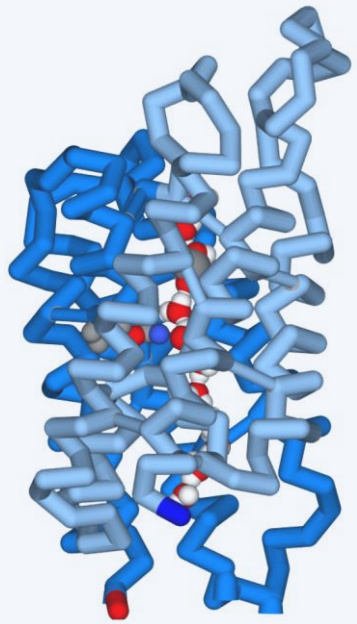
3d molecular designs
Transforming Science Learning

Introducing Mighty Models…

…from the water channel to action potentials

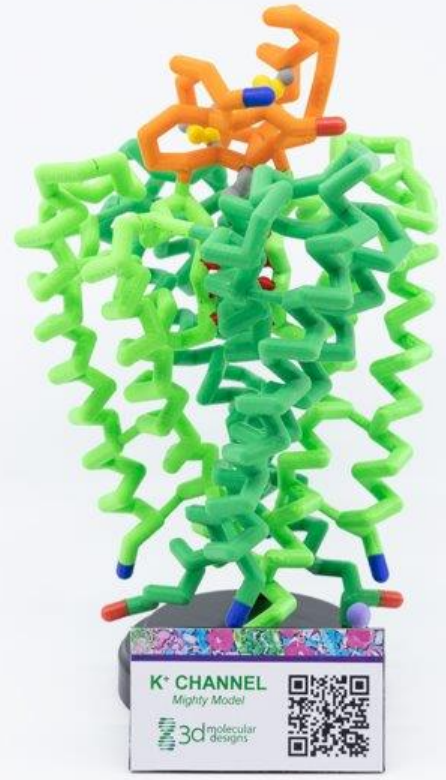
Tim Herman
3D Molecular Designs

Aquaporin
Mighty Model



Hg atom

Potassium Channel
Mighty Model



Scorpion toxin

Sodium Channel
Mighty Model

Small molecule inhibitor

The Discovery of AQP1

(…in the early 1990's…)

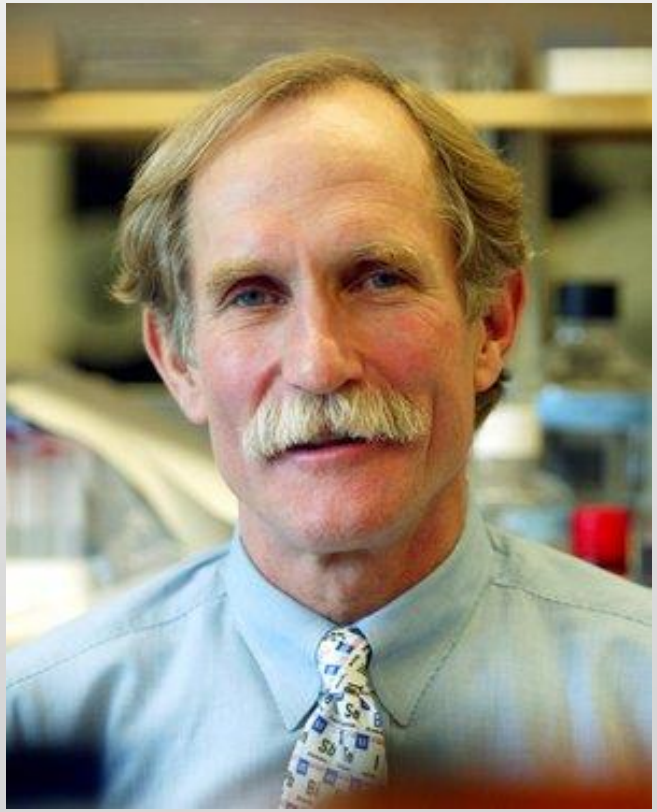
"The field was essentially stuck, but following the well-known scientific approach known as *sheer blind luck*, we stumbled upon the protein that is the answer to the question …

Do water channels exist?"

From Peter Agre's Nobel Lecture

2003 Nobel Prize in Chemistry

The Nobel Prize in Chemistry 2003 was awarded "for discoveries concerning channels in cell membranes" jointly with one half to Peter Agre "for the discovery of water channels" and with one half to Roderick MacKinnon "for structural and mechanistic studies of ion channels."



Peter Agre

Roderick MacKinnon

Appearance of Water Channels in *Xenopus* Oocytes Expressing Red Cell CHIP28 Protein

Gregory M. Preston, Tiziana Piazza Carroll,
William B. Guggino, Peter Agre*

Water rapidly crosses the plasma membrane of red blood cells (RBCs) and renal tubules through specialized channels. Although selective for water, the molecular structure of these channels is unknown. The CHIP28 protein is an abundant integral membrane protein in mammalian RBCs and renal proximal tubules and belongs to a family of membrane proteins with unknown functions. Oocytes from *Xenopus laevis* microinjected with in vitro–transcribed CHIP28 RNA exhibited increased osmotic water permeability; this was reversibly inhibited by mercuric chloride, a known inhibitor of water channels. Therefore it is likely that CHIP28 is a functional unit of membrane water channels.

Science **256**, 365-387 (1992)

Appearance of Water Channels in Xenopus Oocytes Expressing Red Cell CHIP28 Protein

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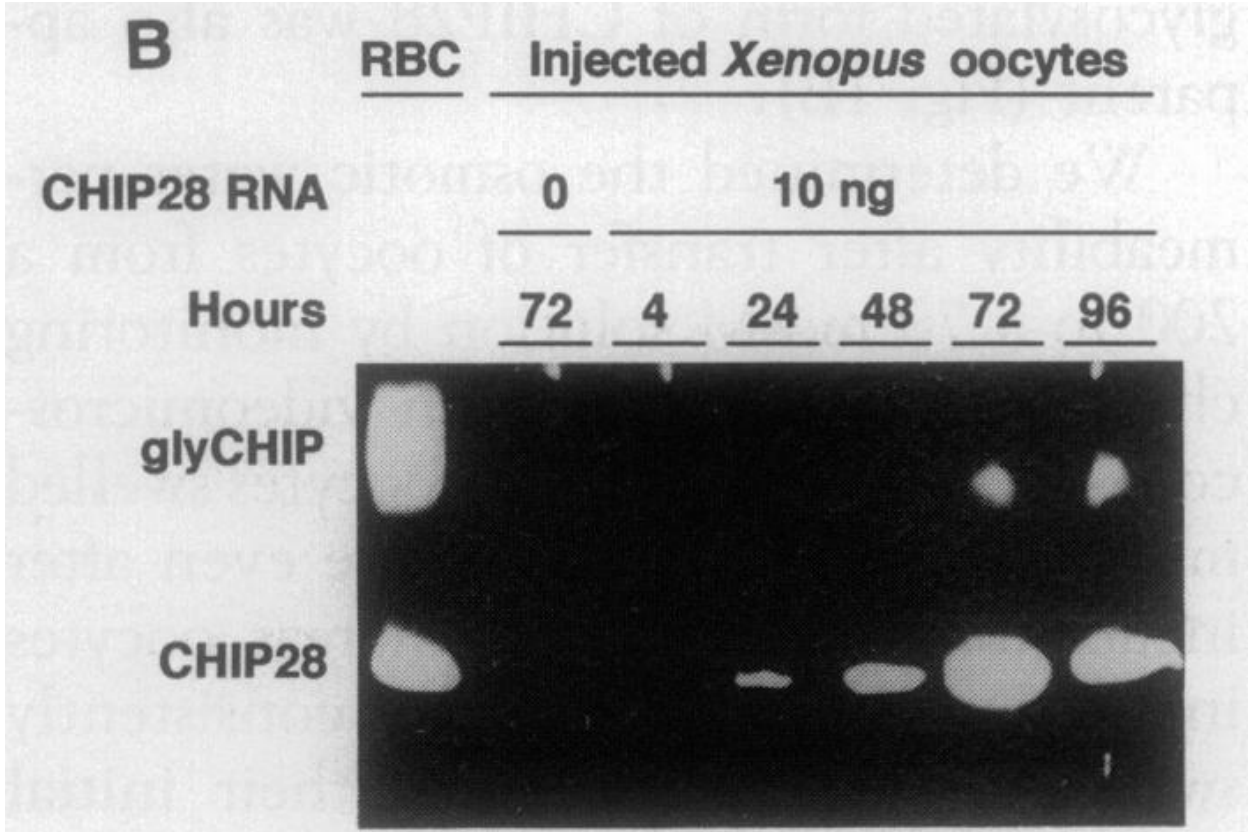
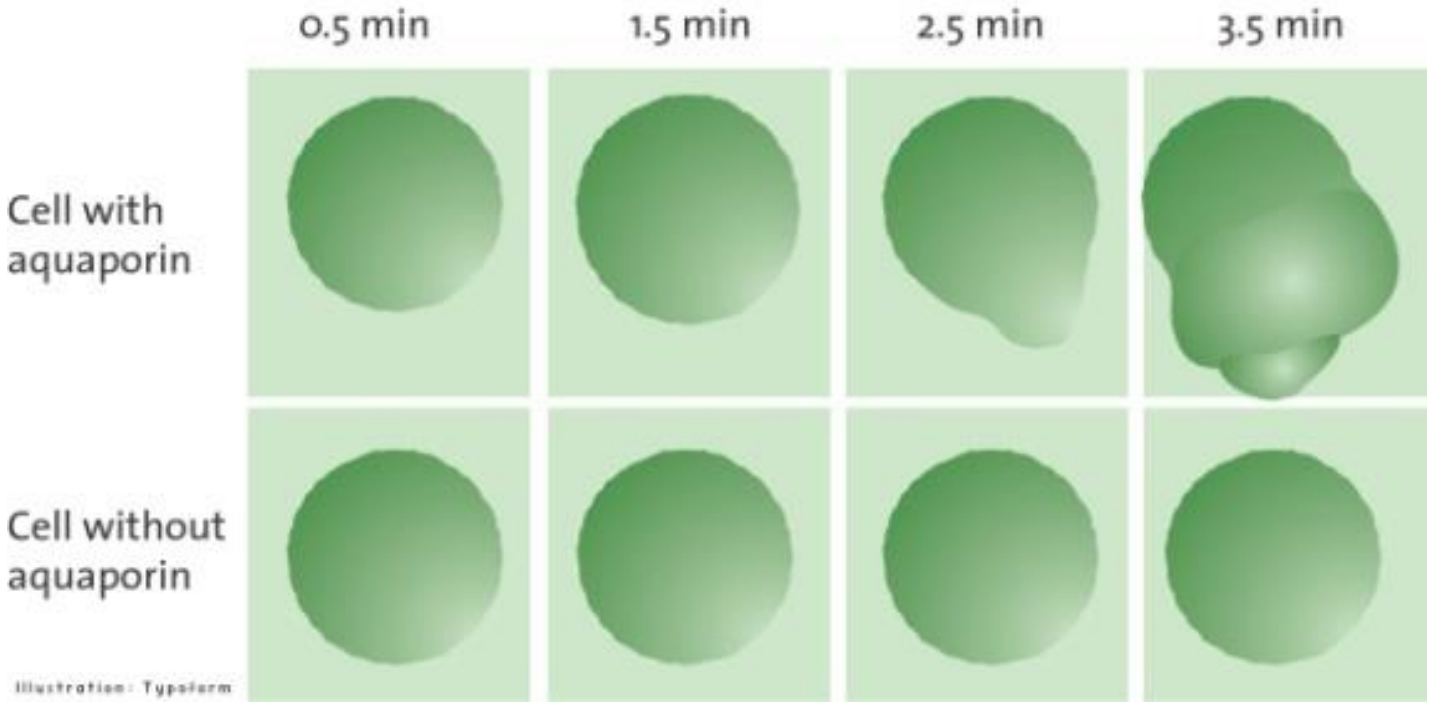
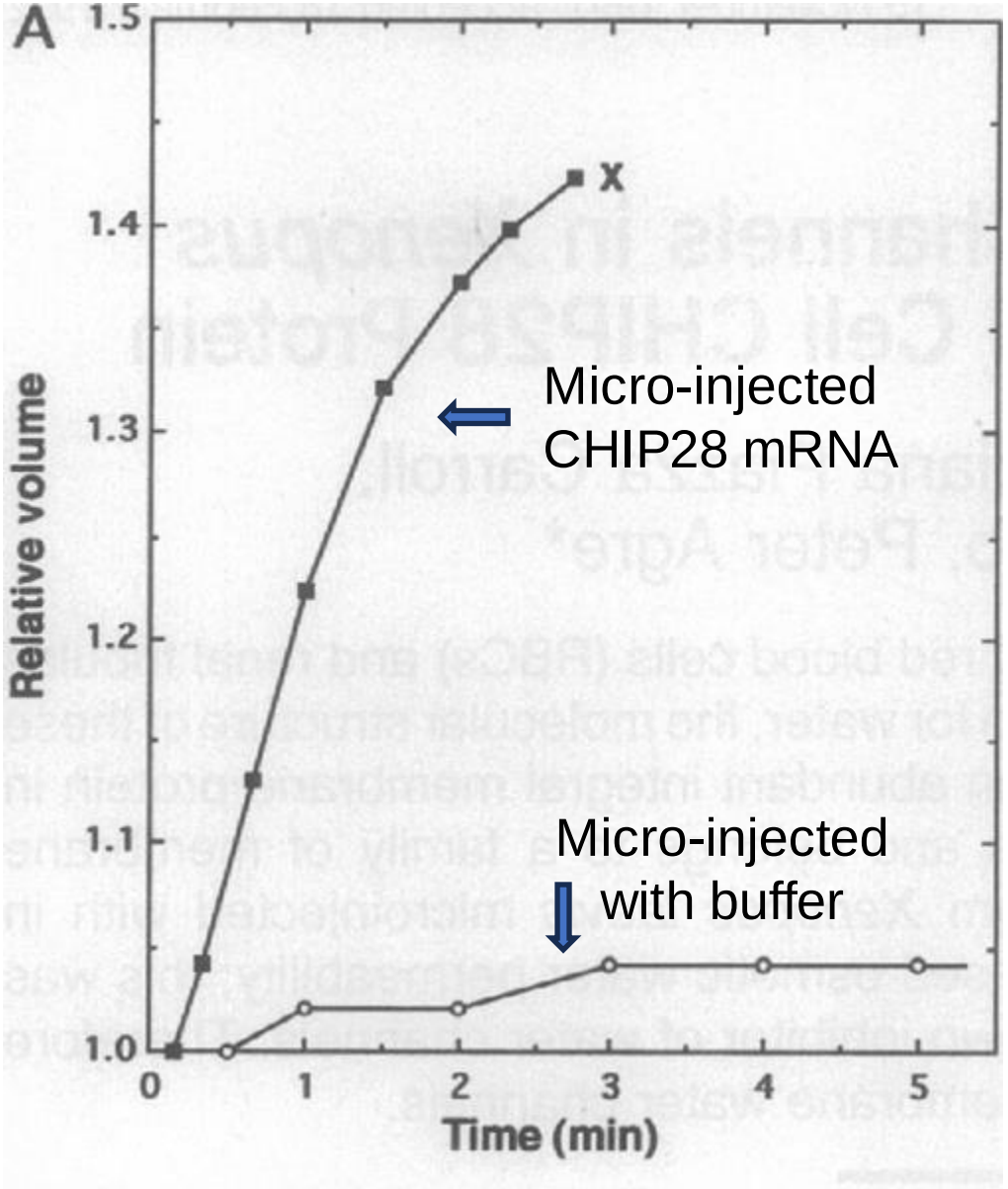
SCIENCE * VOL. 256 * 17 APRIL 1992

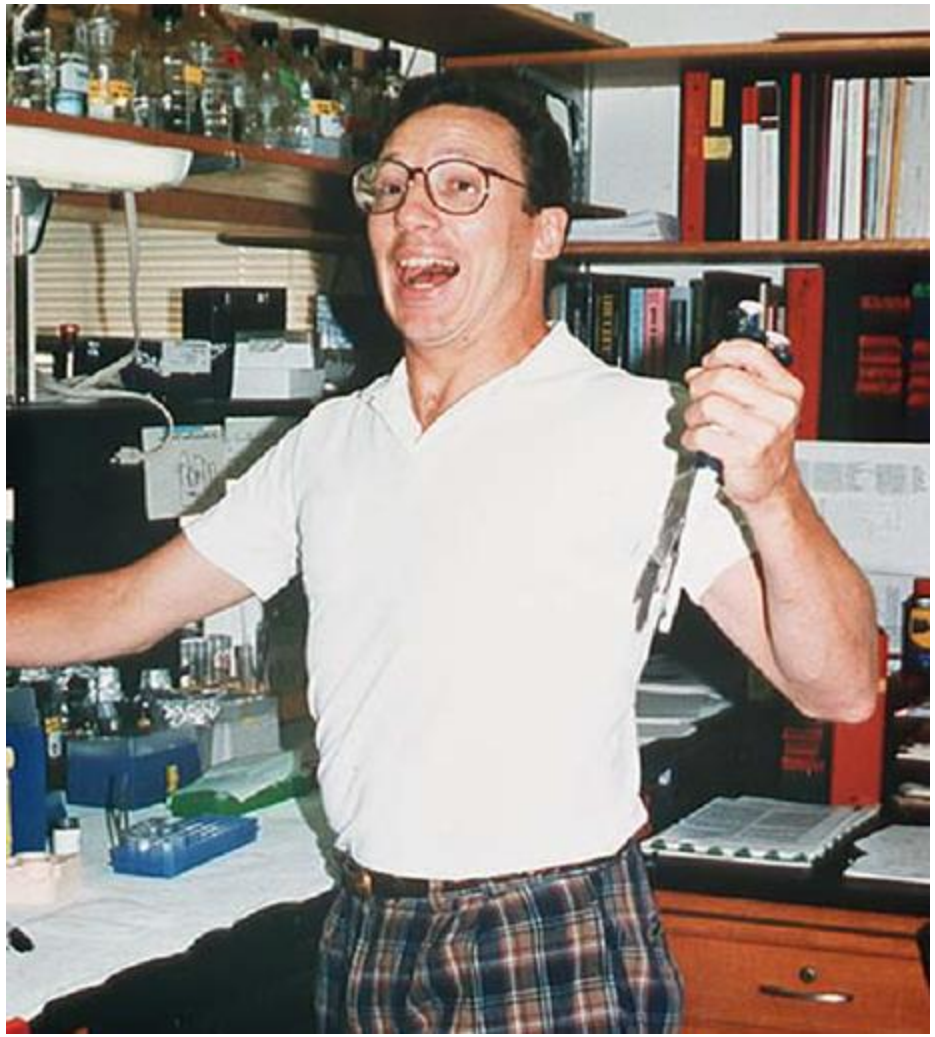


The Famous *Exploding Frog Egg Experiment*

Aquaporin mRNA micro-injected into Xenopus eggs

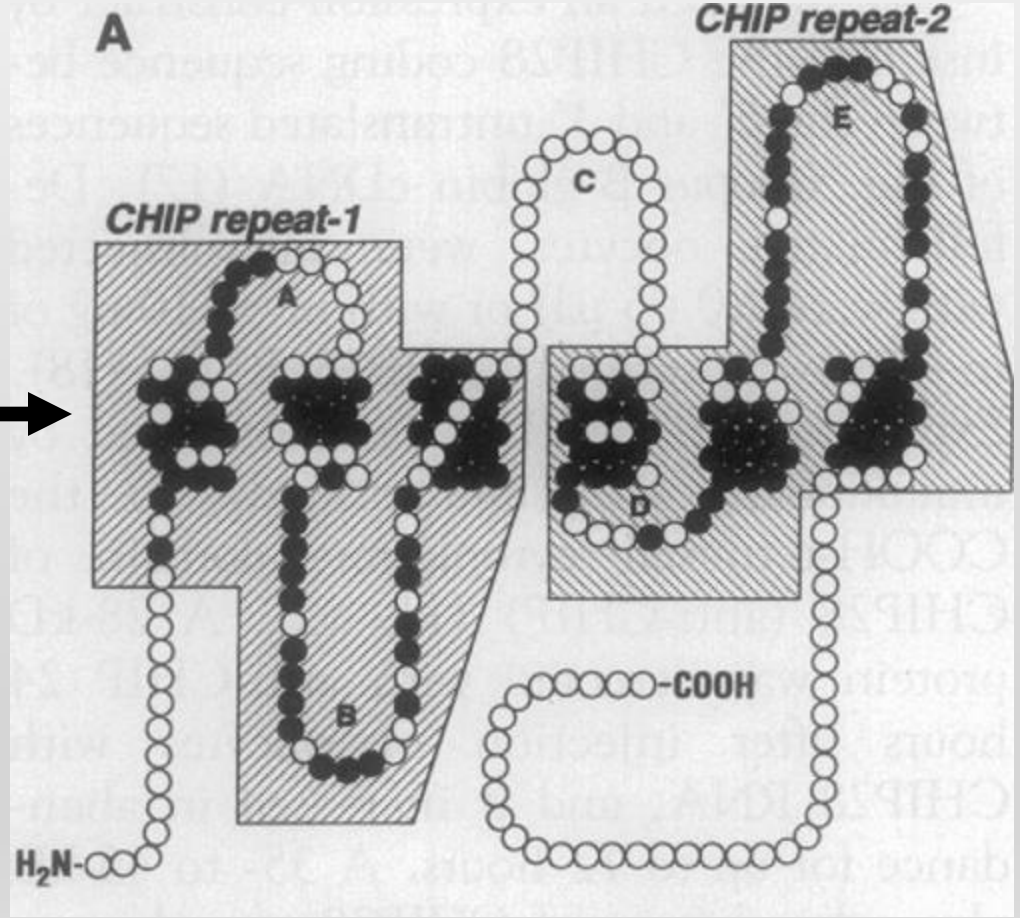



A
1.5
1.4
1.3
1.2
1.1
1.0
Relative volume
X
Micro-injected
CHIP28 mRNA
Micro-injected
with buffer
0
1
2
3
4
5
Time (min)



1992 “Model” of Aquaporin

- Based on its Amino Acid Sequence
- 6 Transmembrane Helices
- 2-Fold Symmetry



Structural determinants of water permeation through aquaporin-1

Kazuyoshi Murata*†, Kaoru Mitsuoka†‡, Teruhisa Hirai†‡, Thomas Walz§, Peter Agre‖, J. Bernard Heymann¶, Andreas Engel¶ & Yoshinori Fujiyoshi‡

* *National Institute for Physiological Sciences, Okazaki 444-8585, Japan*
‡ *Department of Biophysics, Faculty of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto, 606-8502, Japan*
§ *Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, Massachusetts, 02115-5730, USA*
‖ *Departments of Biological Chemistry and Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205-2185, USA*
¶ *M. E. Müller-Institute for Microscopy at the Biozentrum, University of Basel, Basel CH-4056, Switzerland*
† *These authors contributed equally to this work.*

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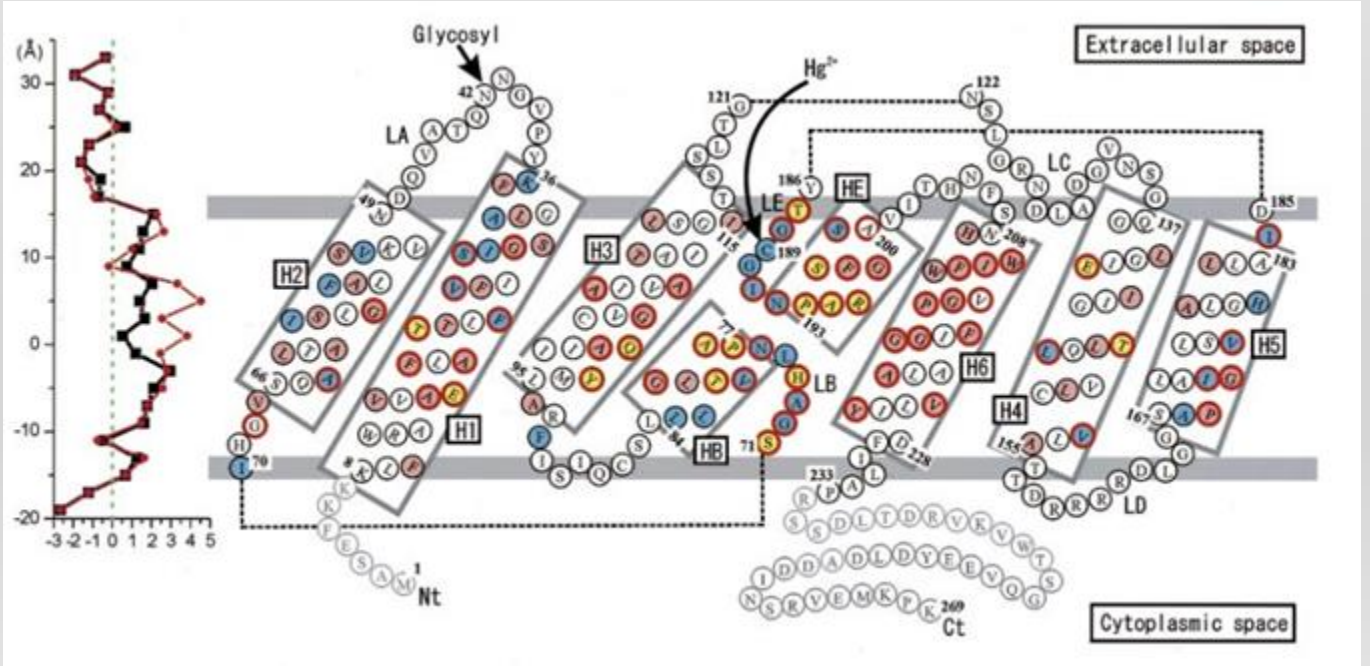
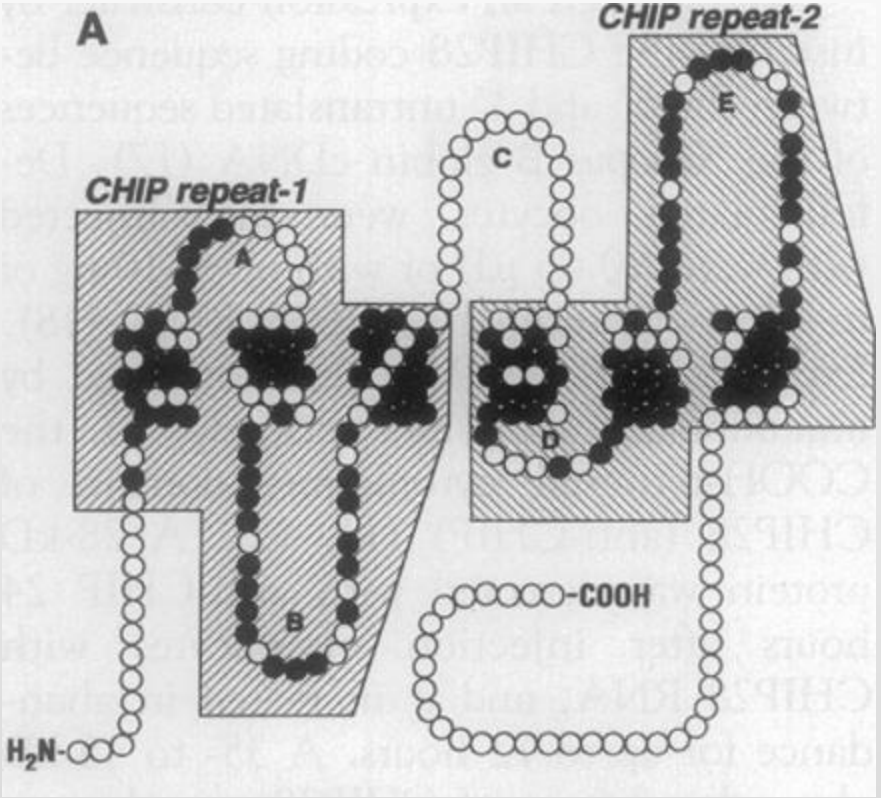
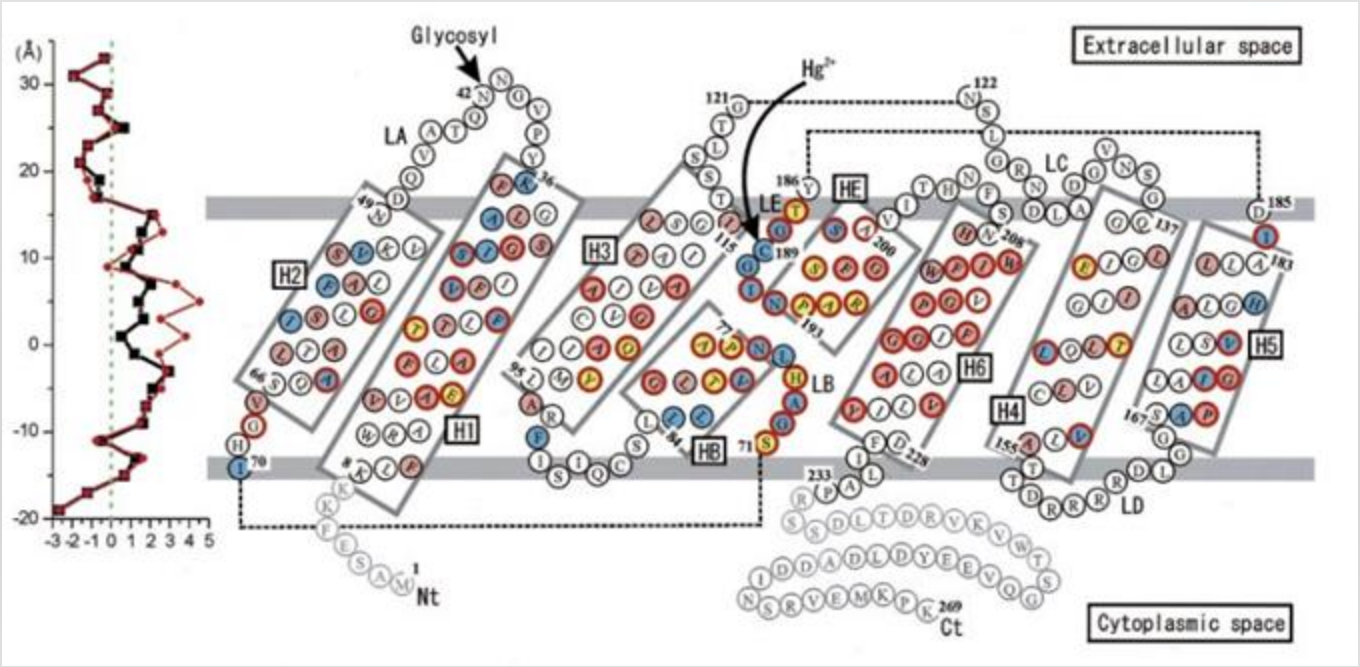


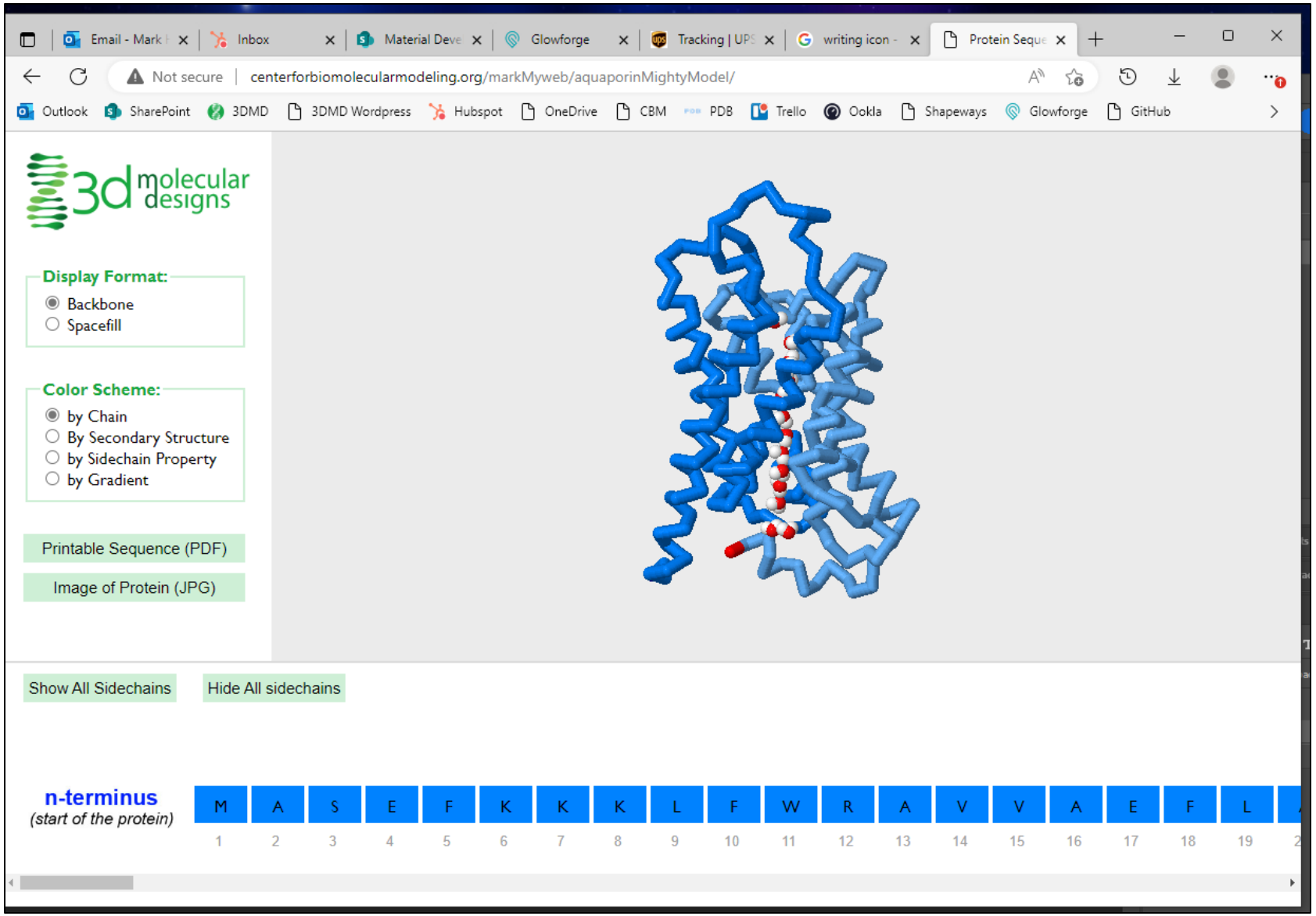
Agre “model”, 1992

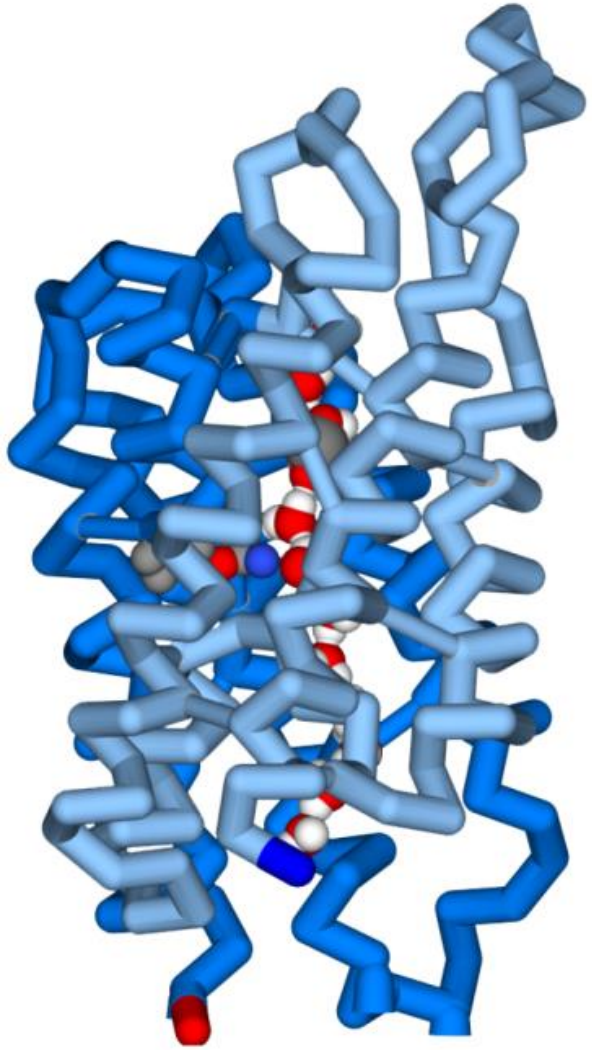




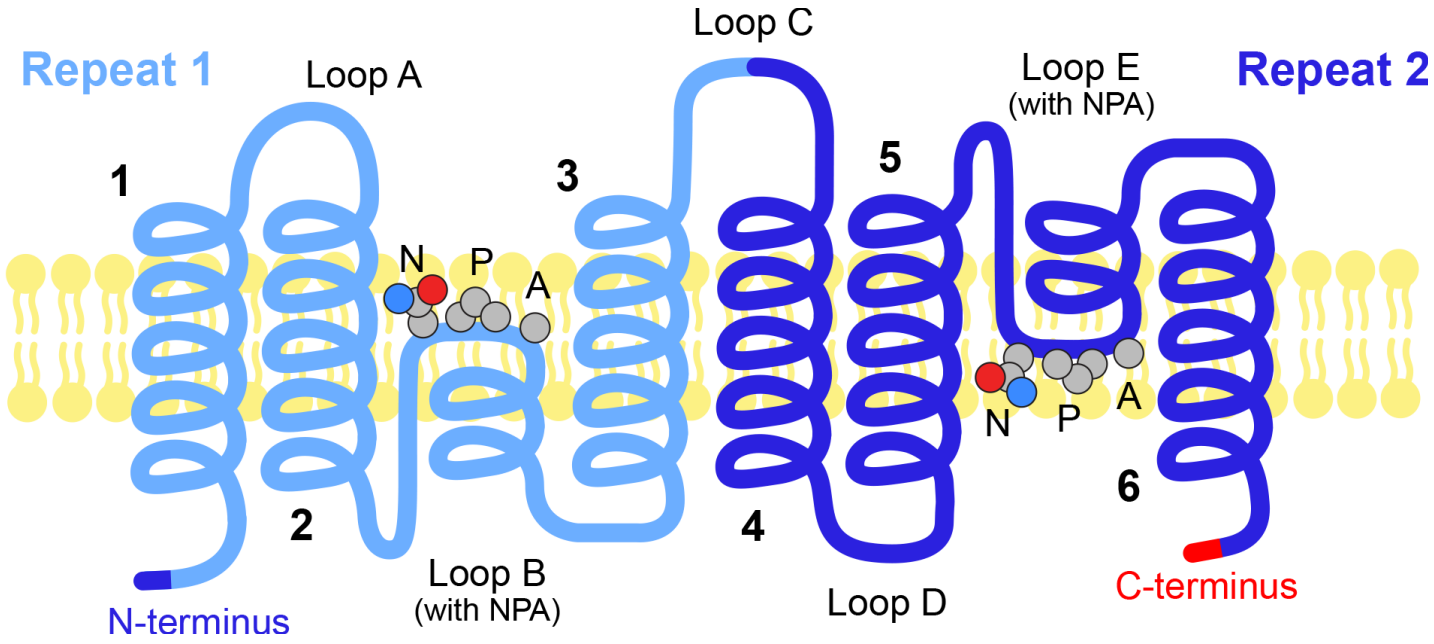
Murata model,… based on x-ray diffraction, 2000

Protein Exploratorium

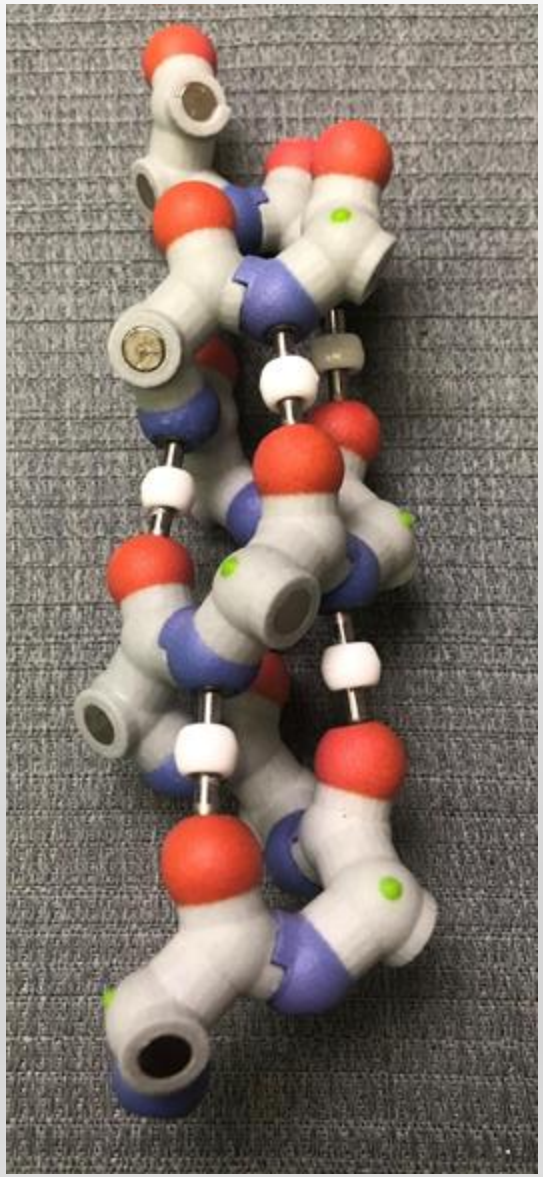




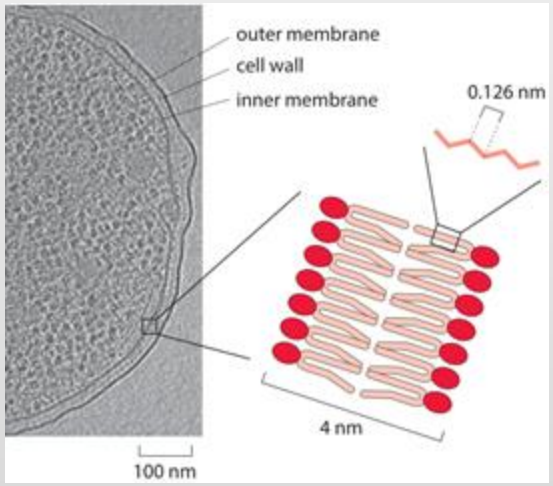
What is Aquaporin?



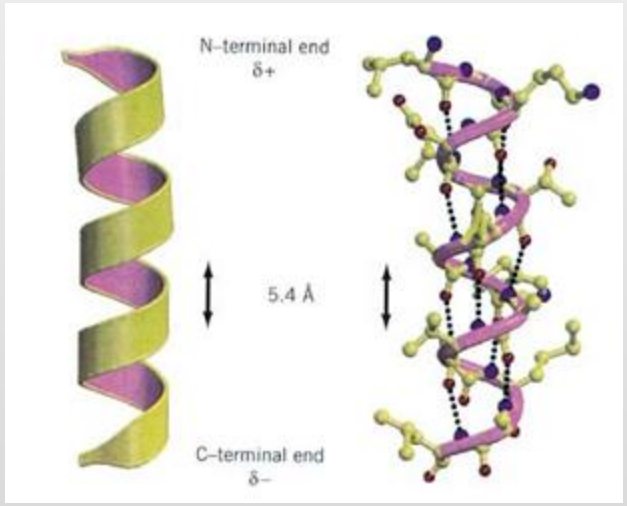
Why are transmembrane proteins often composed of bundles of alpha helices?



How many turns of the helix are required to span a membrane?



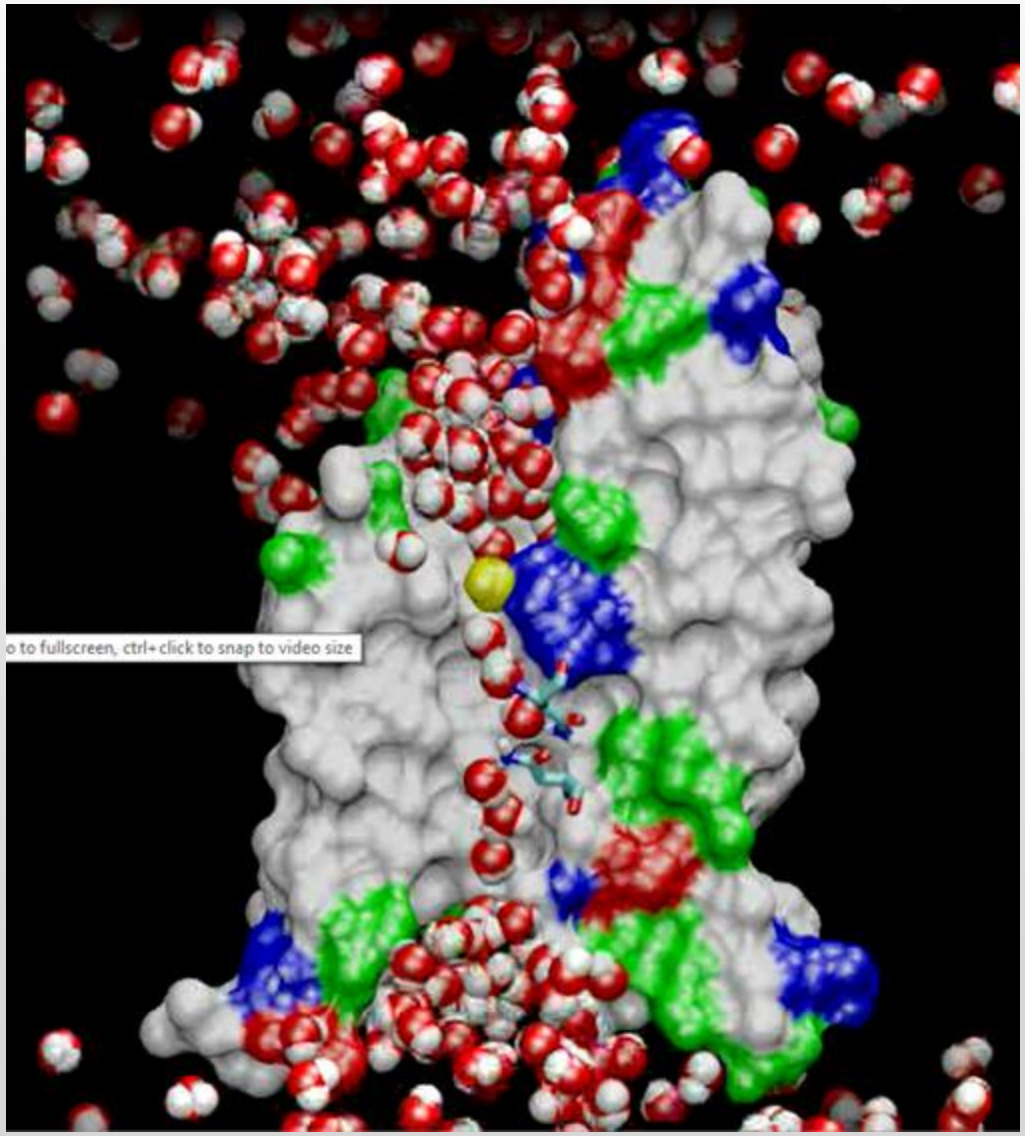
A lipid bilayer
is ~ 3nm thick



An alpha helix makes on complete turn in 0.54 nm

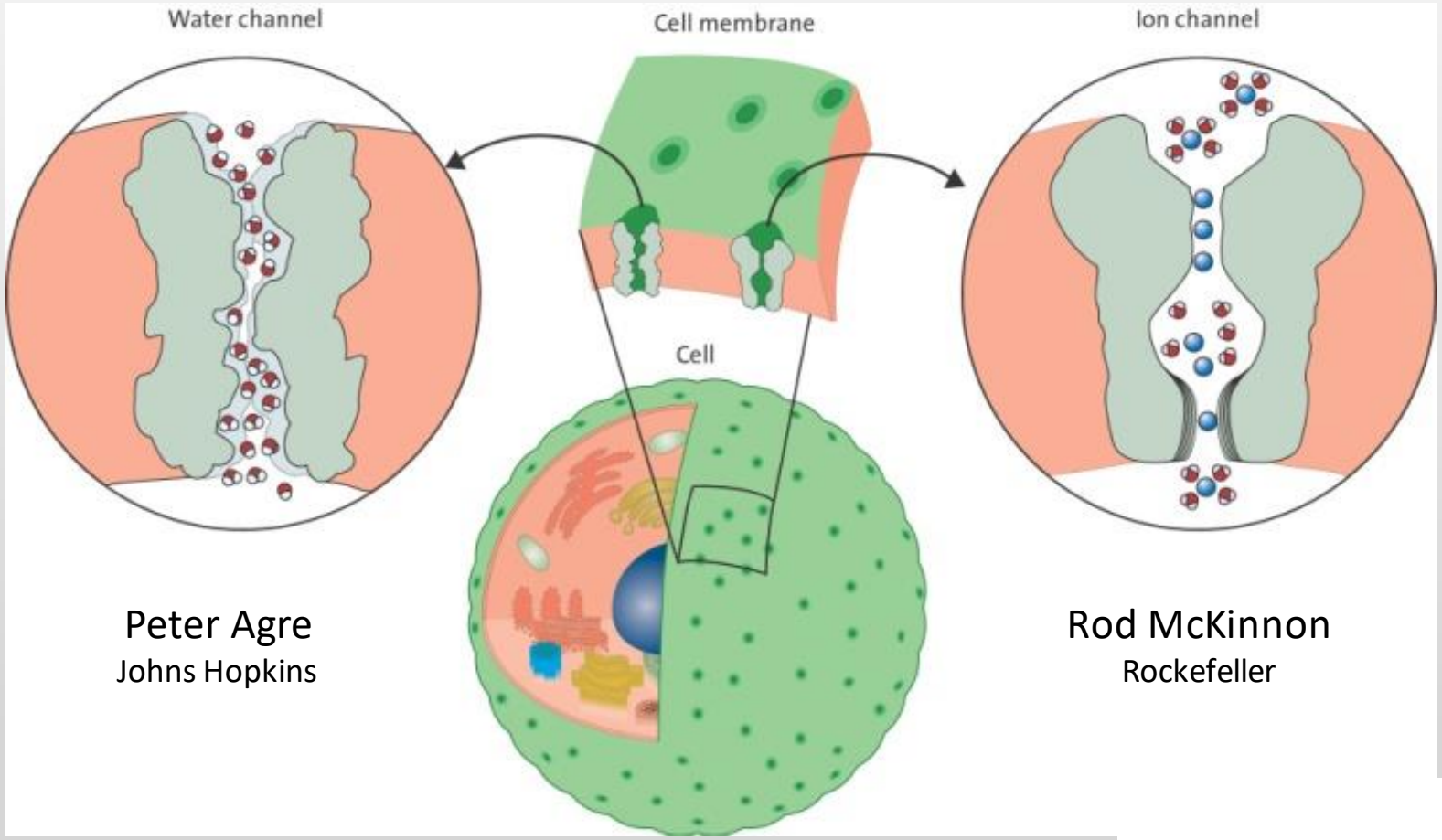
3nm / .54 nm/turn = ~ 6 turns of an alpha helix to span a membrane.
(22 amino acids)

A molecular dynamics simulation from the Klaus Shulten group at UIUC



https://www.ks.uiuc.edu/Research/aquaporins/

The 2003 Nobel Prize in Chemistry



The ion channels…. for K^+ and Na^+

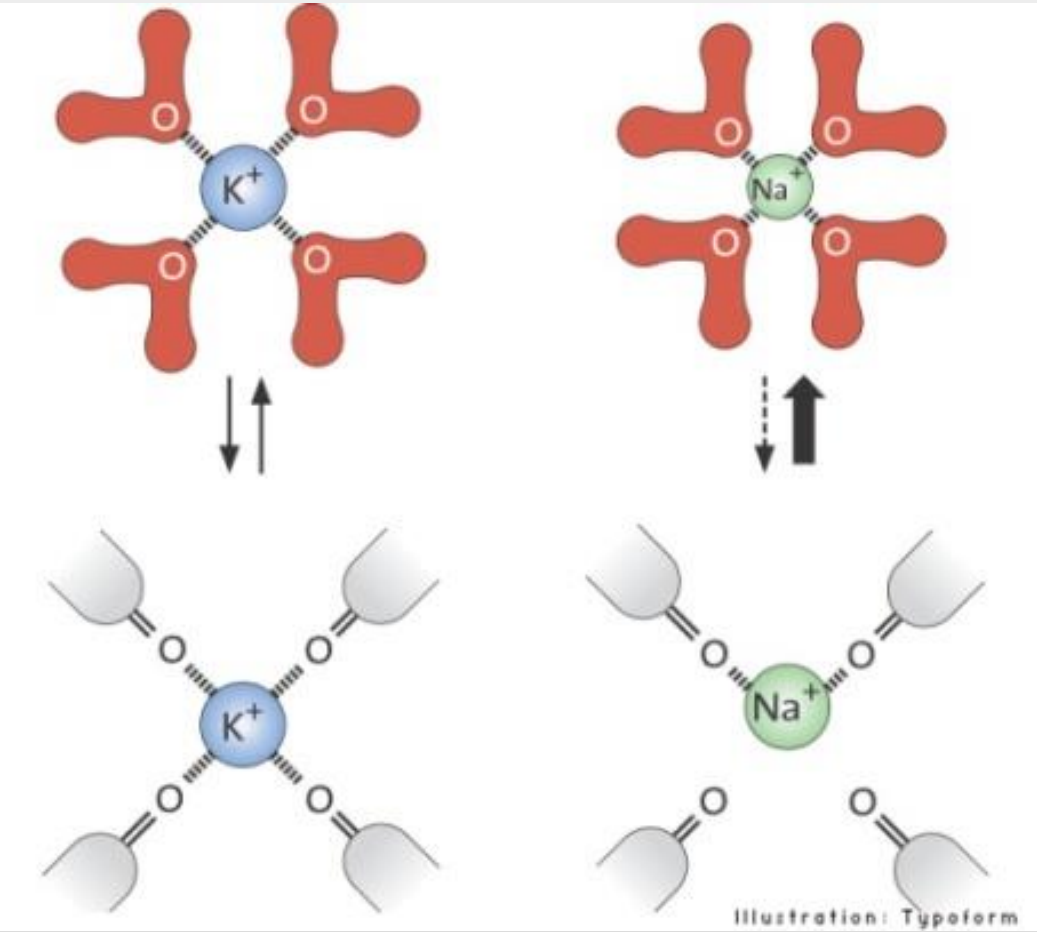
These two ion channels are responsible for the action potentials that drive our neurons…

- *They are very fast…*
- *They are very specific…*
- *They are regulated by voltage sensor domains…*


K+ CHANNEL
Mighty Model
3d molecular designs


Na+ CHANNEL
Mighty Model
1 angstrom = 3.5mm
Based on 6a95 pdb
3d molecular designs

Why K^+,… but not Na^+

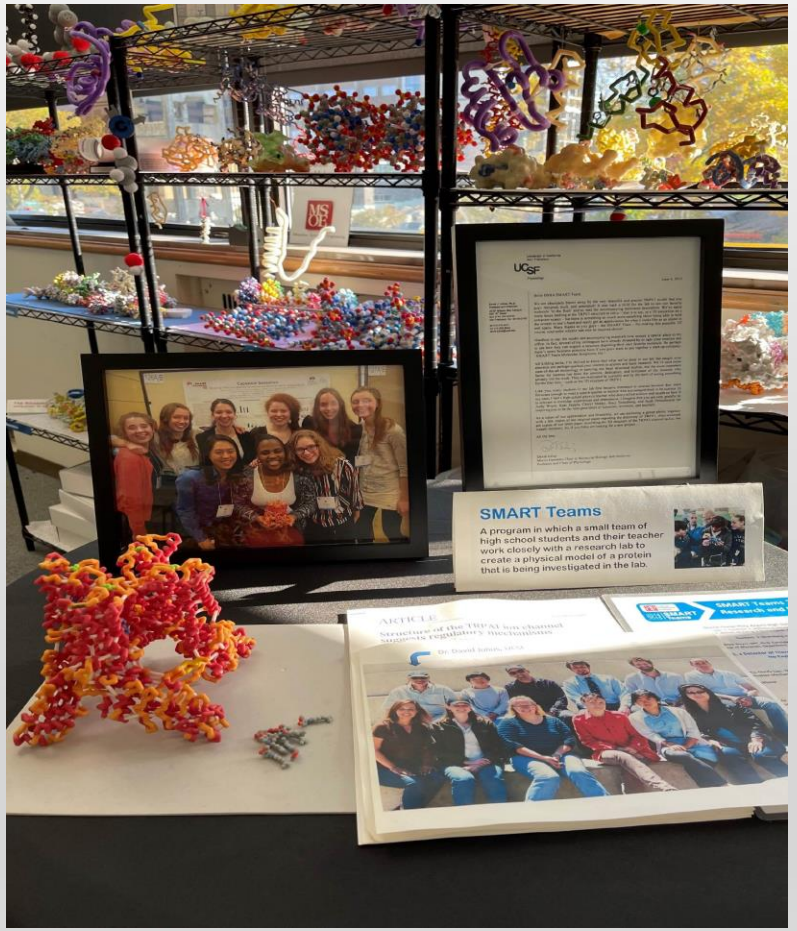


…and now,… yet another Nobel Prize-winning Channel Protein

2021 Nobel Prize in Physiology or Medicine …. to **David Julius**

The Pain Receptor

TRPV1



A 2015 SMART Team Project

Peter Agre with Aquaporin Model