3d molecular designs
Transforming Science Learning

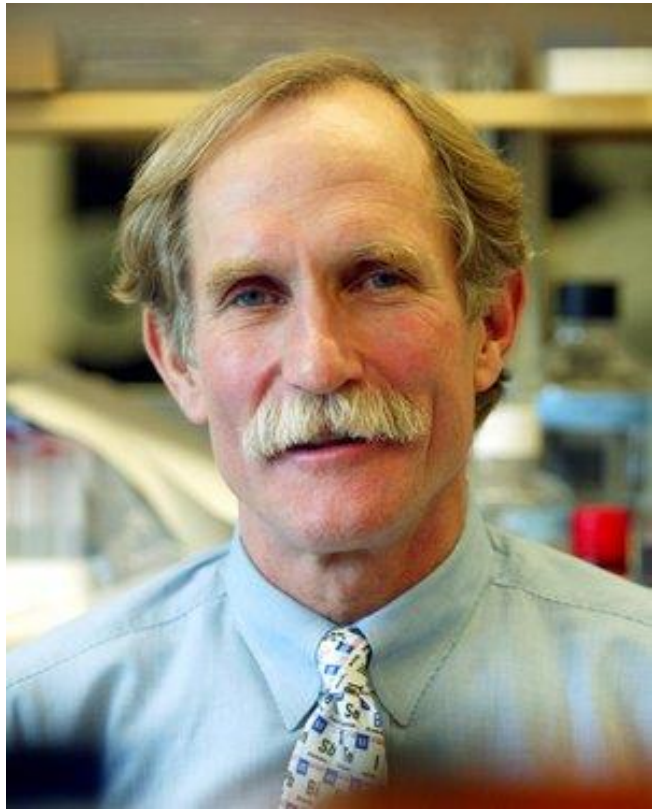
Exploding Frog eggs…

Teaching how is science done?

Tim Herman

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

Teaching the process of science…..

Imagine that….

…you were a graduate student in Peter Agre's lab in the late 1980s"

What was known about aquaporin in 1992?

- Abundant protein in rbc membranes
- Cloned cDNA → mRNA transcript
- 269 amino acid protein

Isolation of the cDNA for erythrocyte integral membrane protein of 28 kilodaltons: Member of an ancient channel family GREGORY M. PRESTON AND PETER AGRE

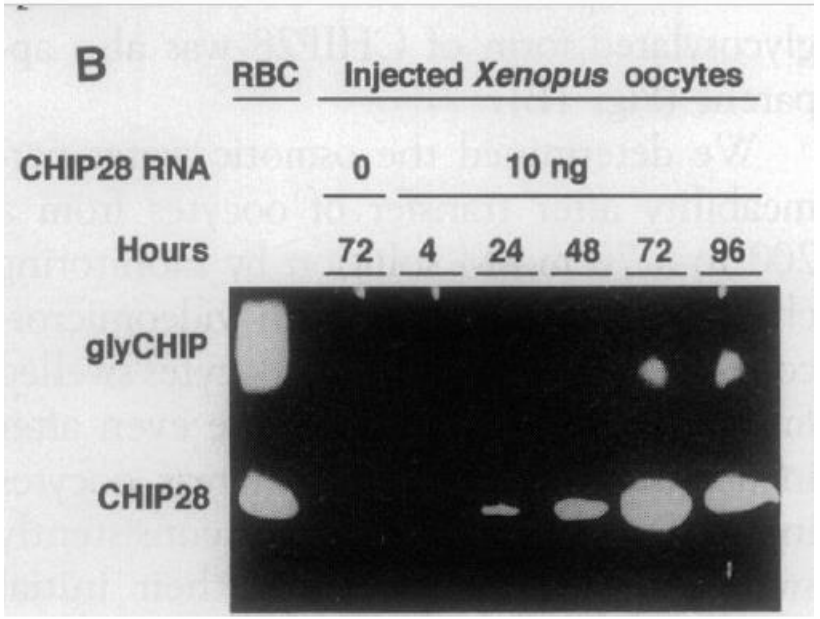
Proc. Nati. Acad. Sci. USA
Vol. 88, pp. 11110-11114, December 1991

```
-38                                  GCACCCGGCAGCGGTCTCAGGCCAAGCCCCCTGCCAGC  -1

  1  ATGGCCAGCGAGTTCAAGAAGAAGCTCTTCTGGAGGGCAGTGGTGGCCGAGTTCCTGGCC  60
  1   M  A  S  E  F  K  K  K  L  F  W  R  A  V  V  A  E  F  L  A   20

 61  ACGACCCTCTTTGTCTTCATCAGCATCGGTTCTGCCCTGGGCTTCAAATACCCGGTGGGG  120
 21   T  T  L  F  V  F  I  S  I  G (S) A  L  G  F  K  Y  P  V  G   40

121  AACAACCAGACGGCGGTCCAGGACAACGTGAAGGTGTCGCTGGCCTTCGGGCTGAGCATC  180
 41   N  N  Q  T  A  V  Q  D  N  V  K  V  S  L  A  F  G  L  S  I   60

181  GCCACGCTGGCGCAGAGTGTGGGCCACATCAGCGGCGCCCACCTCAACCCGGCTGTCACA  240
 61   A  T  L  A  Q  S  V  G  H  I  S  G  A  H  L  N  P  A  V  T   80

241  CTGGGGCTGCTGCTCAGCTGCCAGATCAGCATCTTCCGTGCCCTCATGTACATCATCGCC  300
 81   L  G  L  L  L  S  C  Q  I  S  I  F  R  A  L  M  Y  I  I  A  100

301  CAGTGCGTGGGGGCCATCGTCGCCACCGCCATCCTCTCAGGCATCACCTCCTCCCTGACT  360
101   Q  C  V  G  A  I  V  A  T  A  I  L  S  G  I  T  S  S  L  T  120

361  GGGAACTCGCTTGGCCGCAATGACCTGGCTGATGGTGTGAACTCGGGCCAGGGCCTGGGC  420
121   G  N  S  L  G  R  N  D  L  A  D  G  V  N  S  G  Q  G  L  G  140

421  ATCGAGATCATCGGGACCCTCCAGCTGGTGCTATGCGTGCTGGCTACTACCGACCGGAGG  480
141   I  E  I  I  G  T  L  Q  L  V  L  C  V  L  A  T  T  D  R  R  160

481  CGCCGTGACCTTGGTGGCTCAGCCCCCCTTGCCATCGGCCTCTCTGTAGCCCTTGGACAC  540
161   R  R  D  L  G  G  S  A  P  L  A  I  G  L  S  V  A  L  G  H  180

541  CTCCTGGCTATTGACTACACTGGCTGTGGGATTAACCCTGCTCGGTCCTTTGGCTCCGCG  600
181   L  L  A  I  D  Y  T  G  C  G  I  N  P  A  R  S  F  G  S  A  200

601  GTGATCACACACAACTTCAGCAACCACTGGATTTTCTGGGTGGGGCCATTCATCGGGGGA  660
201   V  I  T  H  N  F  S  N  H  W  I  F  W  V  G  P  F  I  G  G  220

661  GCCCTGGCTGTACTCATCTACGACTTCATCCTGGCCCCACGCAGCAGTGACCTCACAGAC  720
221   A  L  A  V  L  I  Y  D  F  I  L  A  P  R  S  S  D  L  T  D  240

721  CGCGTGAAGGTGTGGACCAGCGGCCAGGTGGAGGAGTATGACCTGGATGCCGACGACATC  780
241   R  V  K  V  W  T  S  G  Q  V  E  E  Y  D  L  D  A  D  D  I  260

781  AACTCCAGGGTGGAGATGAAGCCCAAATAGAAGGGGTCTGGCCCGGGCATCCACGTAGGG  840
261   N  S  R  V  E  M  K  P  K ...                                269
```

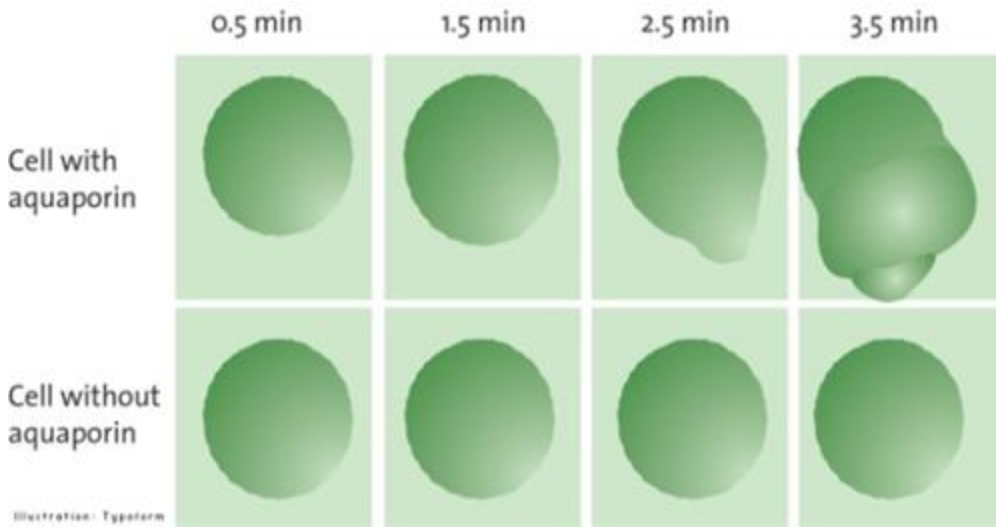
Appearance of Water Channels in Xenopus Oocytes Expressing Red Cell CHIP28 Protein

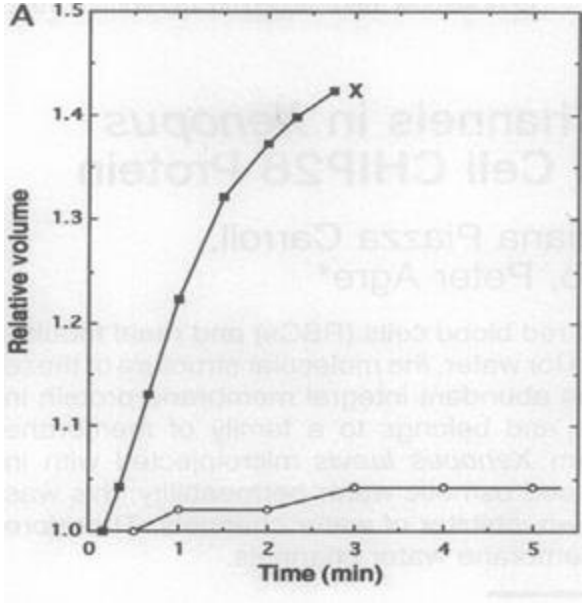
Gregory M. Preston, Tiziana Piazza Carroll, William B. Guggino, Peter Agre*

SCIENCE * VOL. 256 * 17 APRIL 1992



Micro-injection of aquaporin (CHIP28) mRNA into frog oocytes





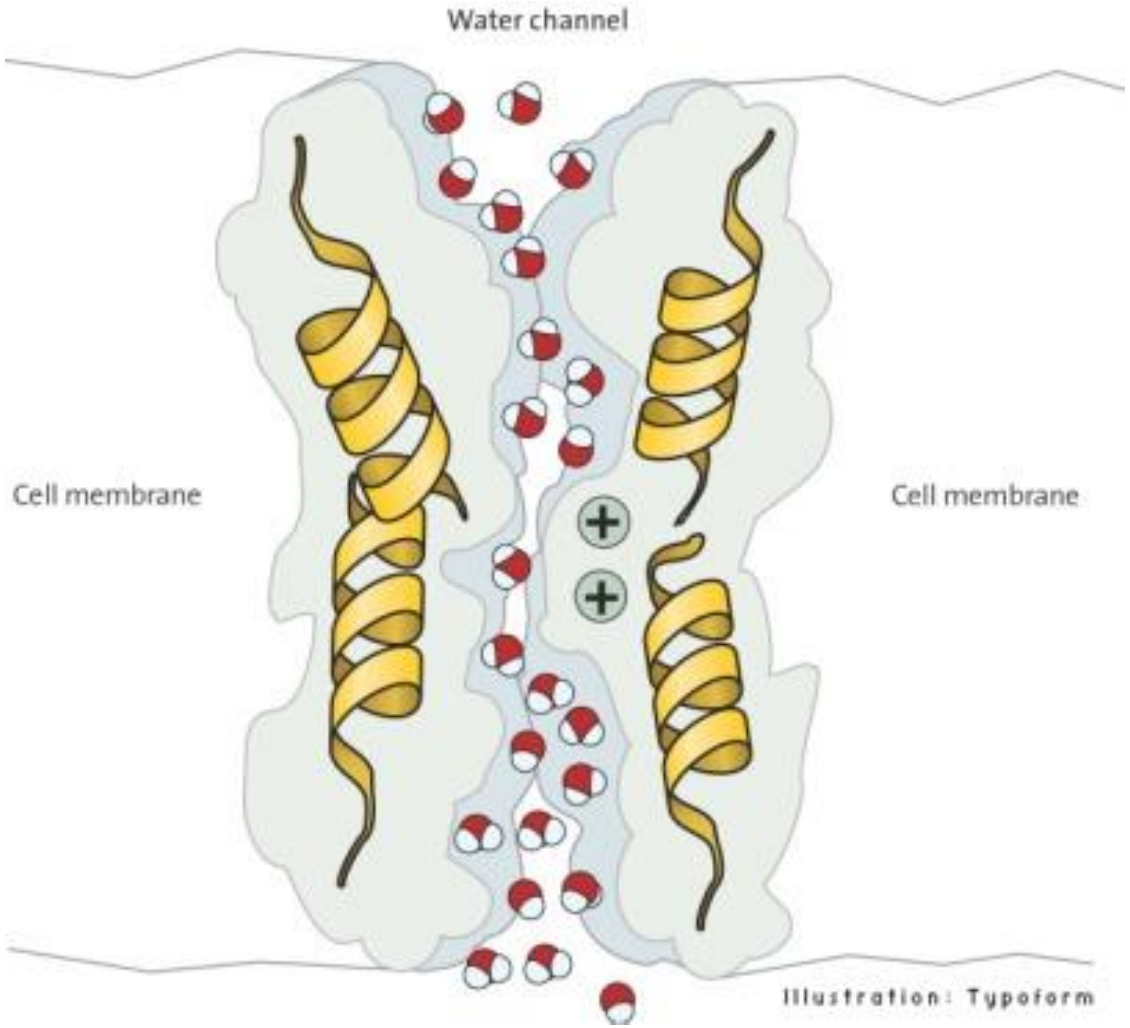
Gregory Preston

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

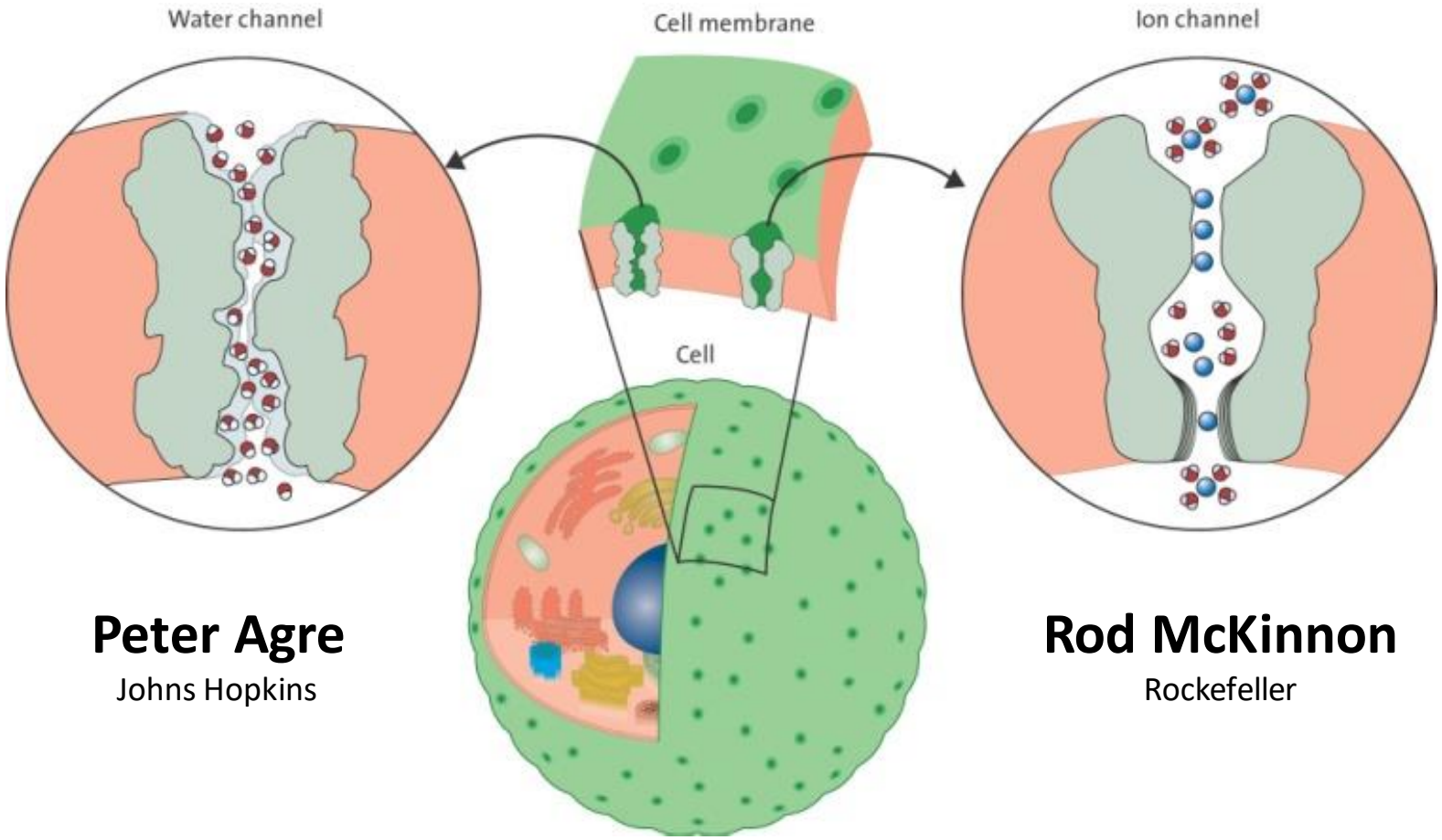
Gregory M. Preston, Tiziana Piazza Carroll,
William B. Guggino, Peter Agre*

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.

And now,….the molecular story

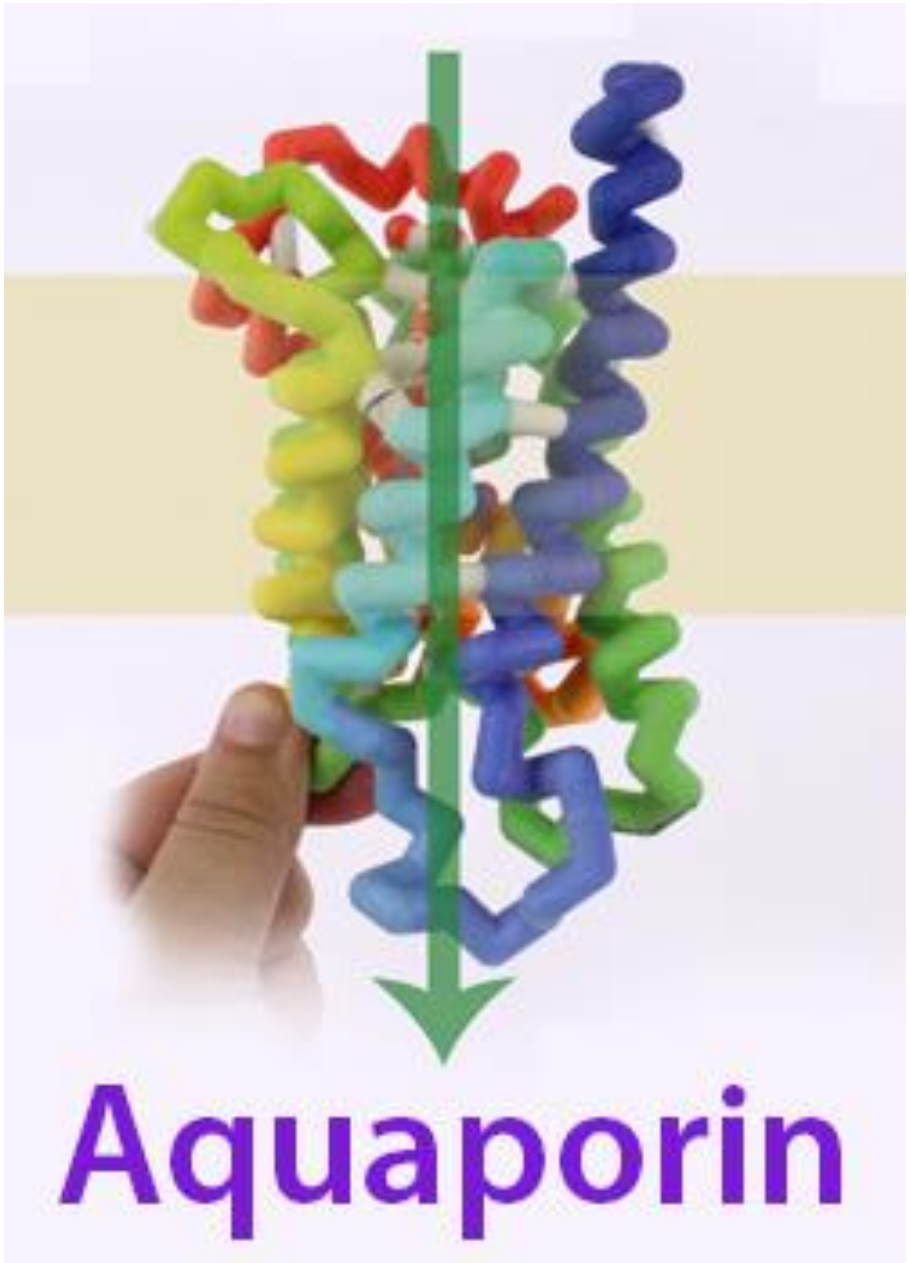


The 2003 Nobel Prize in Chemistry



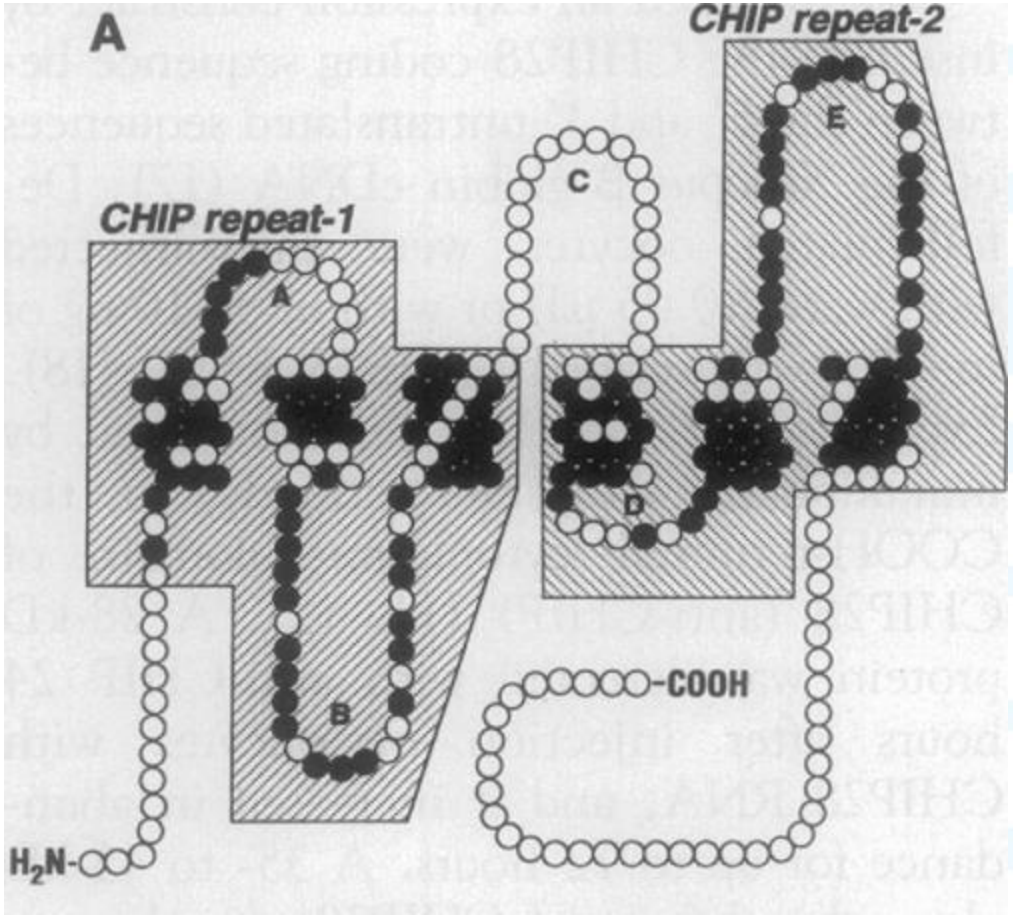
Peter Agre
Johns Hopkins

Rod McKinnon
Rockefeller


Aquaporin

1992 “Model” of Aquaporin

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

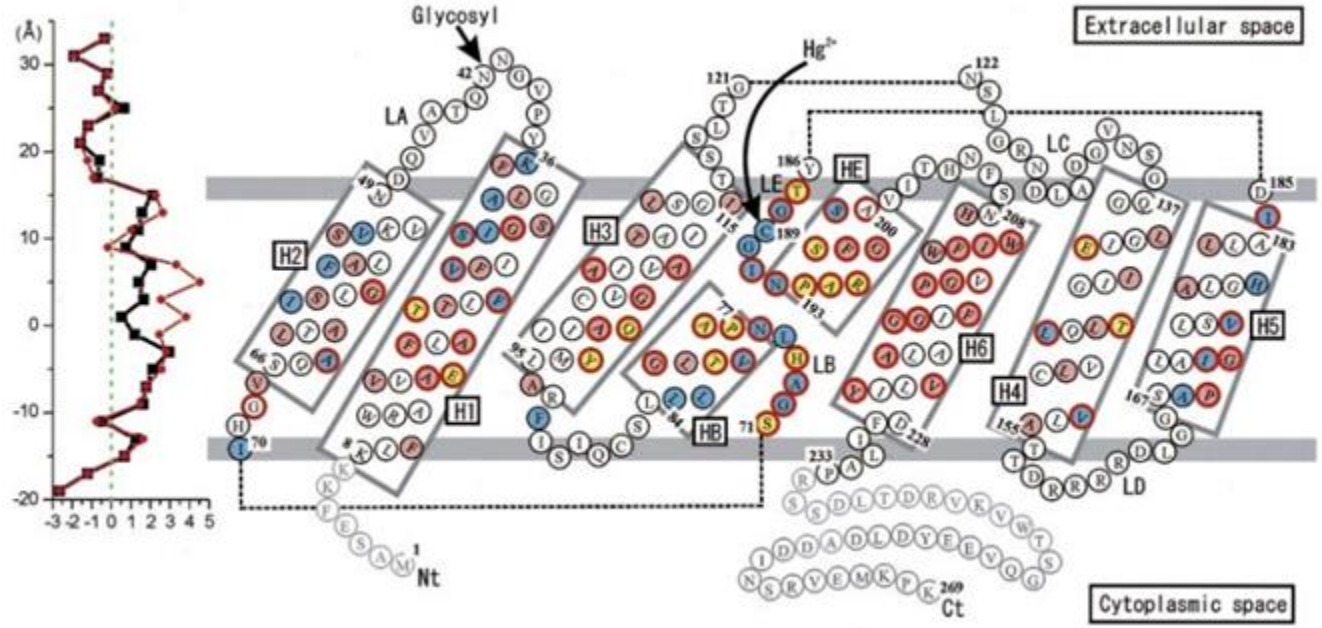


Structural determinants of water permeation through aquaporin-1

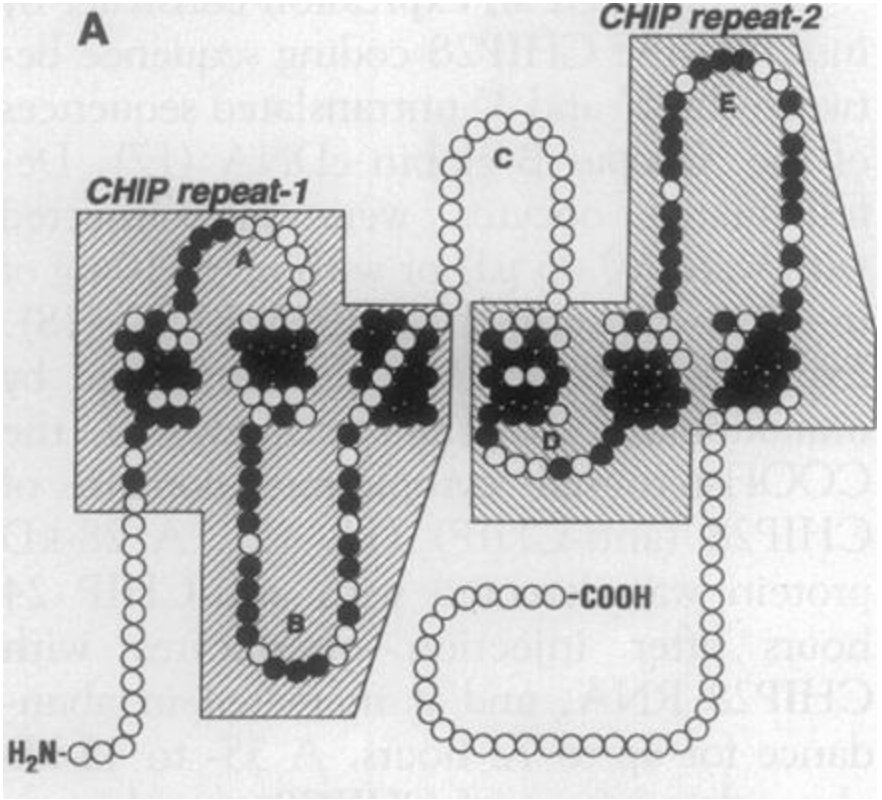
Kazuyoshi Murata*†, Kaoru Mitsuoka†‡, Teruhisa Hirai†‡, Thomas Walz§, Peter Agre‖, J. Bernard Heymann¶, Andreas Engel¶ & Yoshinori Fujiyoshi‡

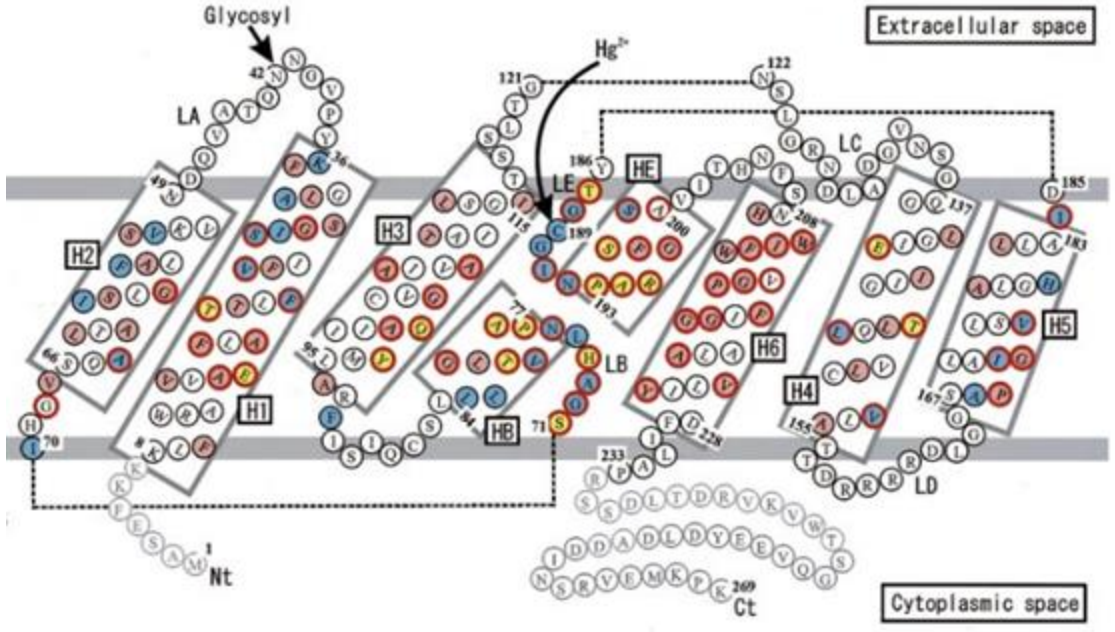
* *National Institute for Physiological Sciences, Okazaki 444-8585, Japan*
‡ *Department of Biophysics, Faculty of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto, 606-8502, Japan*
§ *Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, Massachusetts, 02115-5730, 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.*

NATURE | VOL 407
5 OCTOBER 2000. pp599



Agre “model”, 1992





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

Let's look at some models…..

Alpha Helix

what's so special about 7-helix bundles?

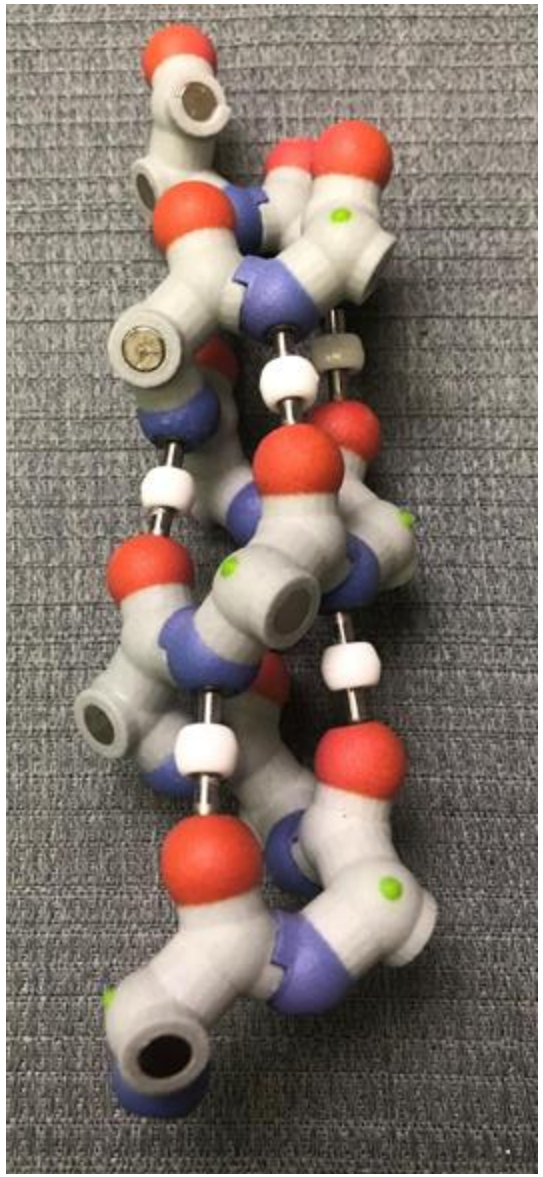
Aquaporin

at 3.8 Angstrom resolution

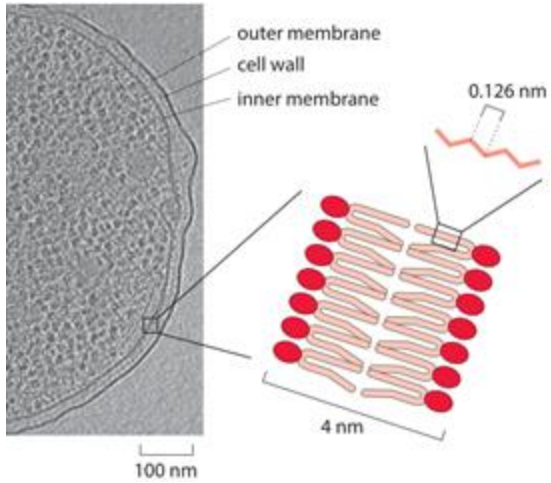
… and now at 0.9 Angstrom resolution

Molecular Dynamics… a computational model

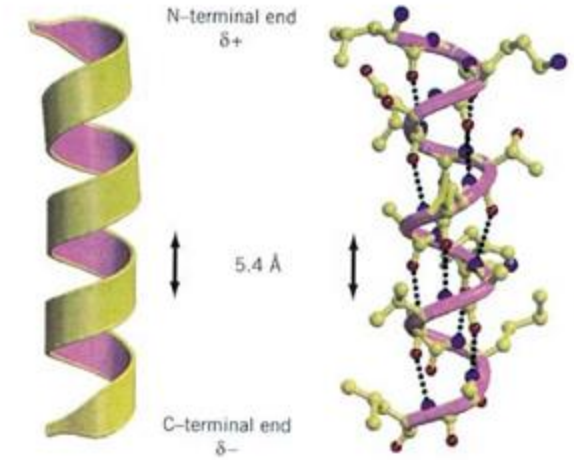
Why are transmembrane proteins often composed of bundles of alpha helices?



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



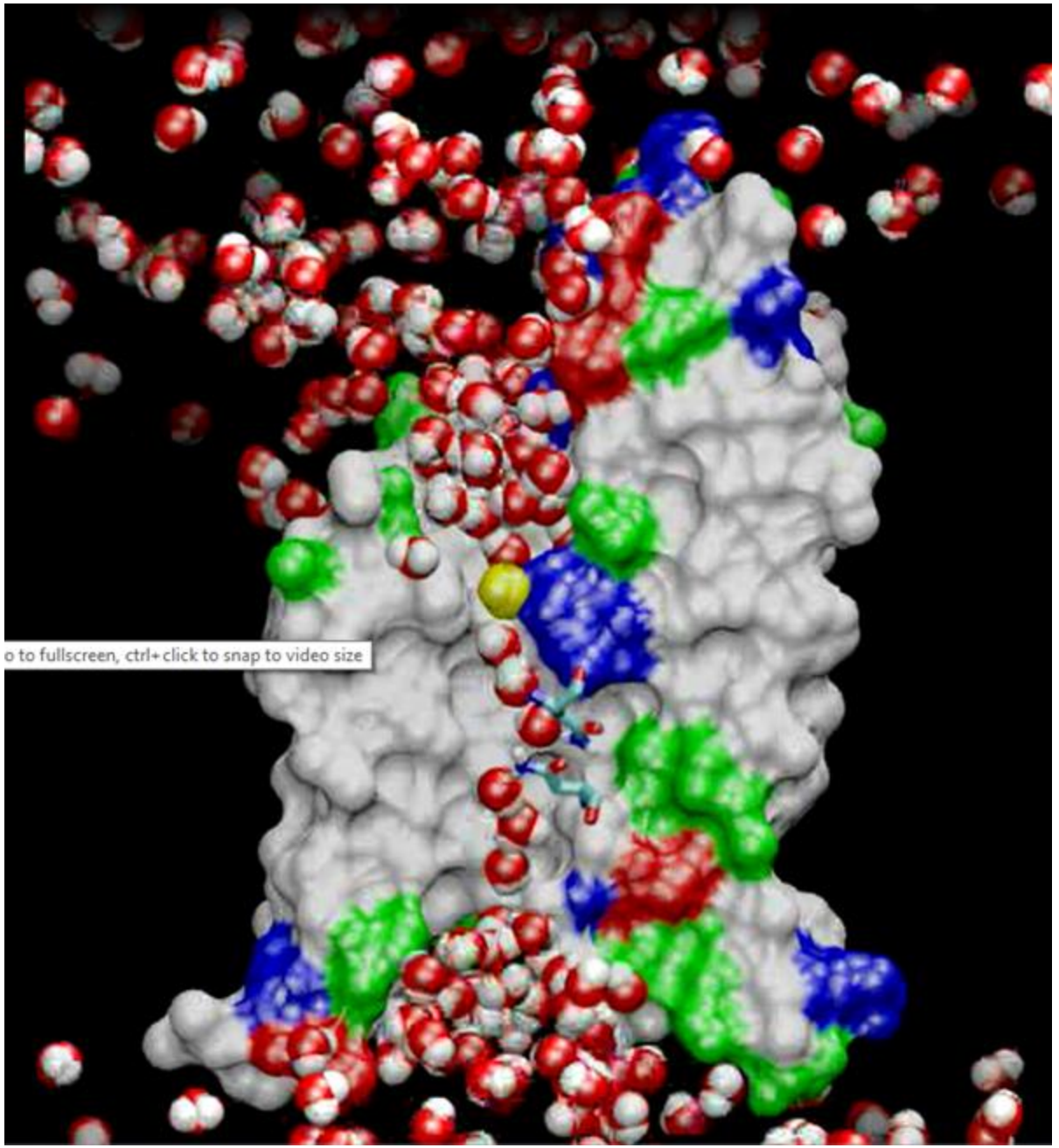
A lipid bilayer
is ~ 3nm thick



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

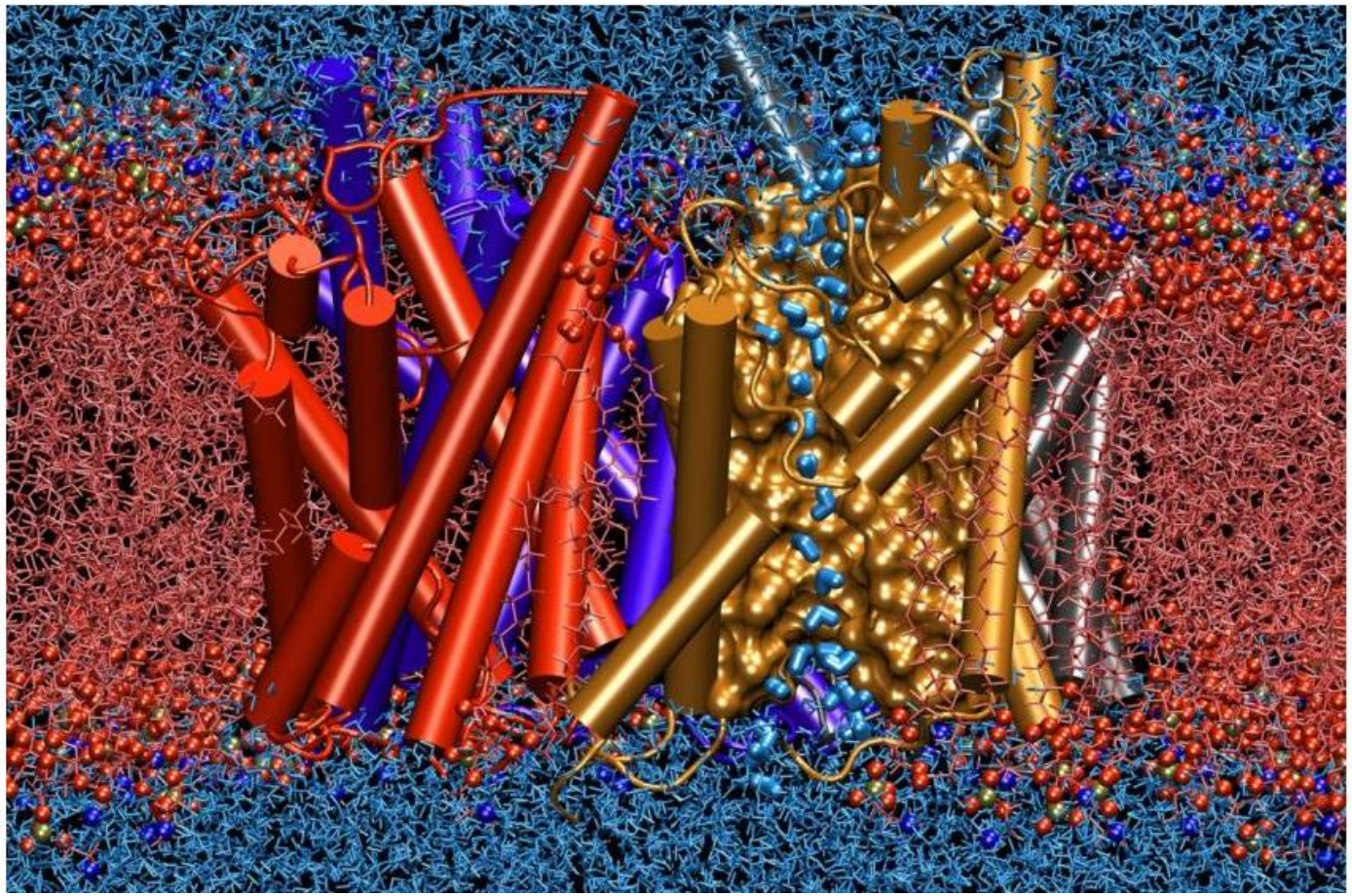


THEORETICAL and COMPUTATIONAL BIOPHYSICS GROUP

Home | Research | Publications | Software | Instruction | News | Galleries | Facilities | About Us

- Home
- Overview
- Publications
- Research
  - Membrane Biology
  - Mechanobiology
  - Nanoengineering
  - Bioenergetics
  - SMD/IMD
  - Quantum Biology
  - Neurobiology
  - X-ray/Cryo-EM Modeling with MDFF
  - Driving Biomedical Projects
  - Collaborations
  - Other Topics
- Software
- Outreach

Structure, Dynamics, and Function of Aquaporins



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

Peter Agre…

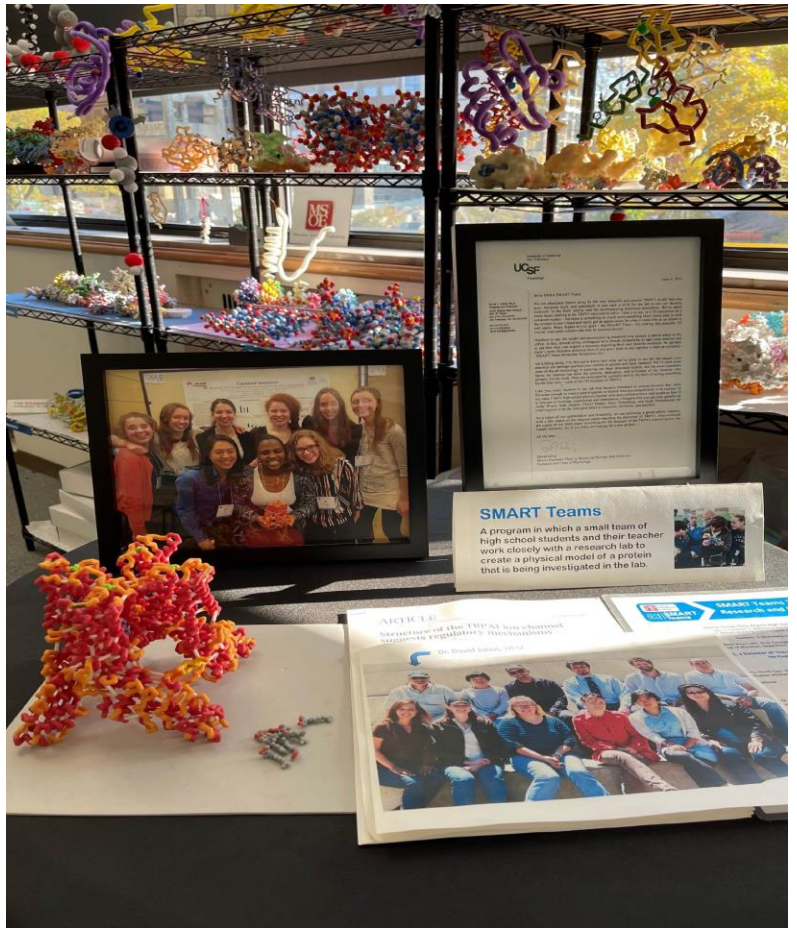
with his favorite model

…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