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National Institutes of Health

Nanomedicine Roadmap Initiative

Aquaporin Water Channels

Structures and Functions

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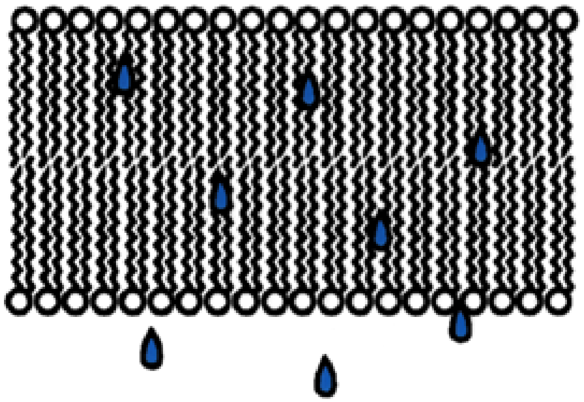
Transmembrane water permeability—Current view

Bilayer Diffusion



All biological membranes

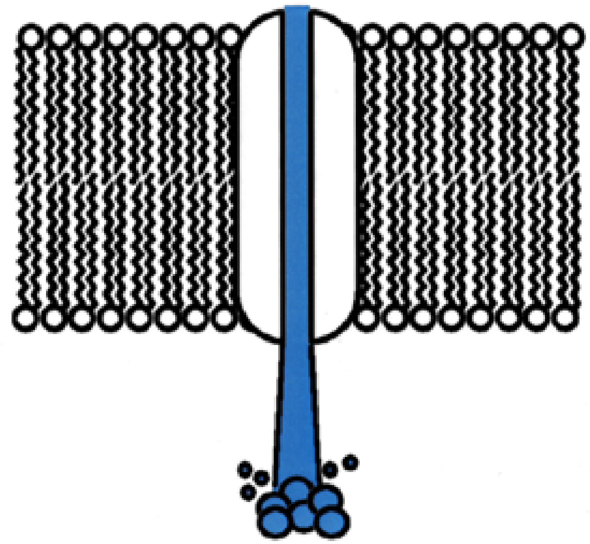
Low capacity

Bi-directional

No known inhibitors

E_a ~10 kcal/mol

Aquaporin Water Channels



Renal tubules, secretory glands, red cells

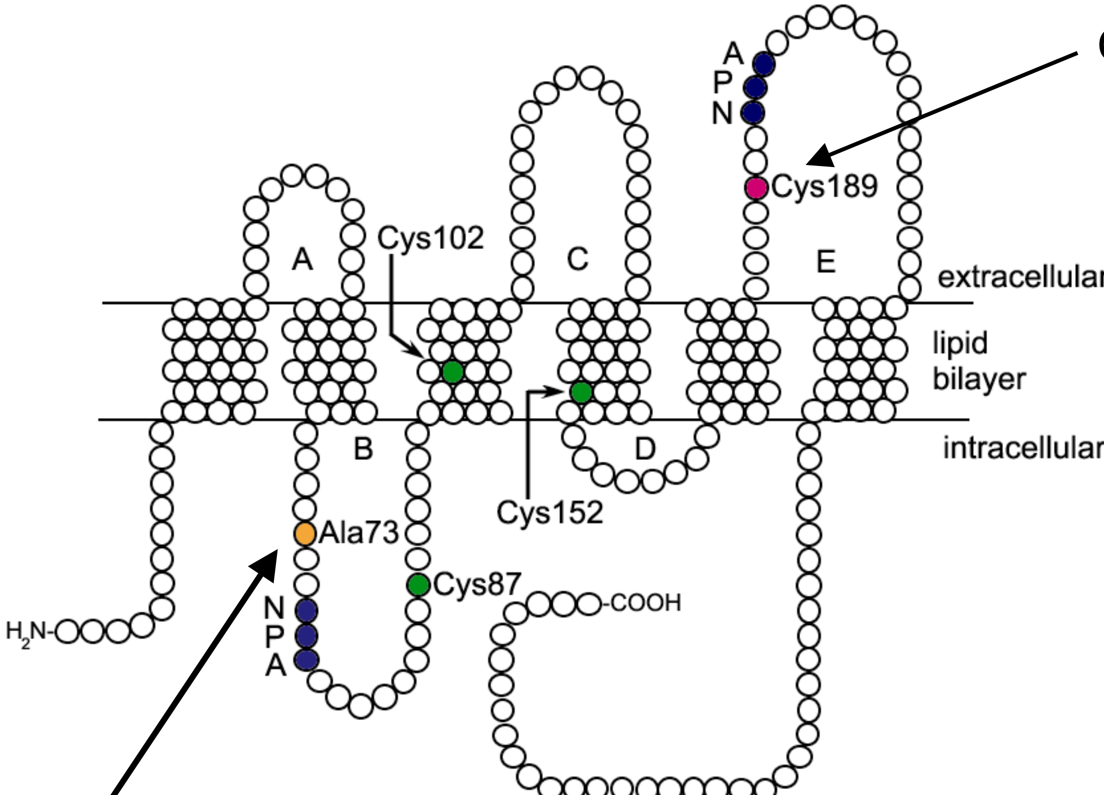
High capacity for H_2O, not H_3O^+

Directed by osmotic gradients

Reversibly inhibited by Hg^{++}

E_a <5 kcal/mol

Structure of AQP1
Hg^{++} inhibitory site



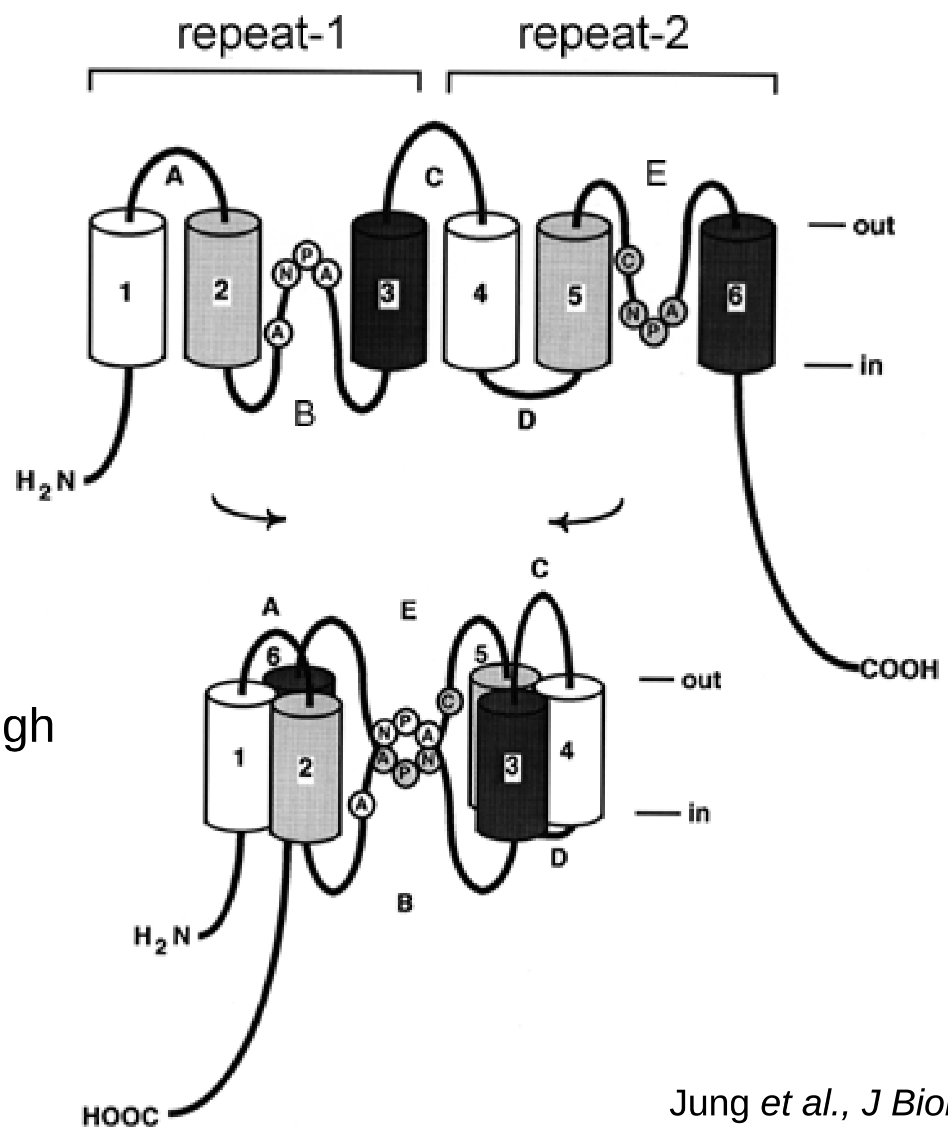
Cys189 is Hg^{++} inhibitory site

A73C becomes Hg^{++} inhibited

Do loops B and E form an aqueous pore?

Preston *et al., J Biol Chem,* 1993
Jung *et al., J Biol Chem,* 1994

Structure of AQP1
The Hourglass Model



Tandem repeats oriented at 180°

Aqueous pore through each subunit

Jung *et al., J Biol Chem,* 1994

Structure of AQP1

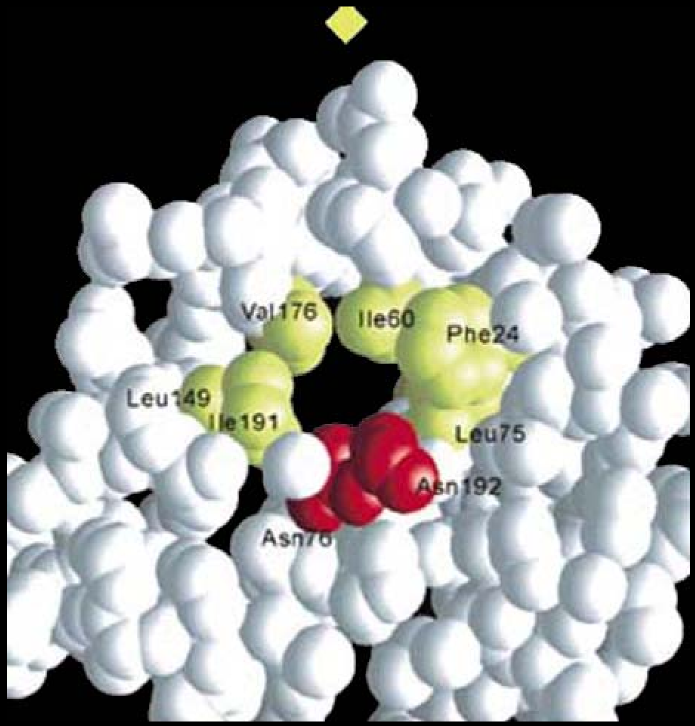
Membrane crystallography (with Y. Fujiyoshi, Kyoto and A. Engel, Basel)

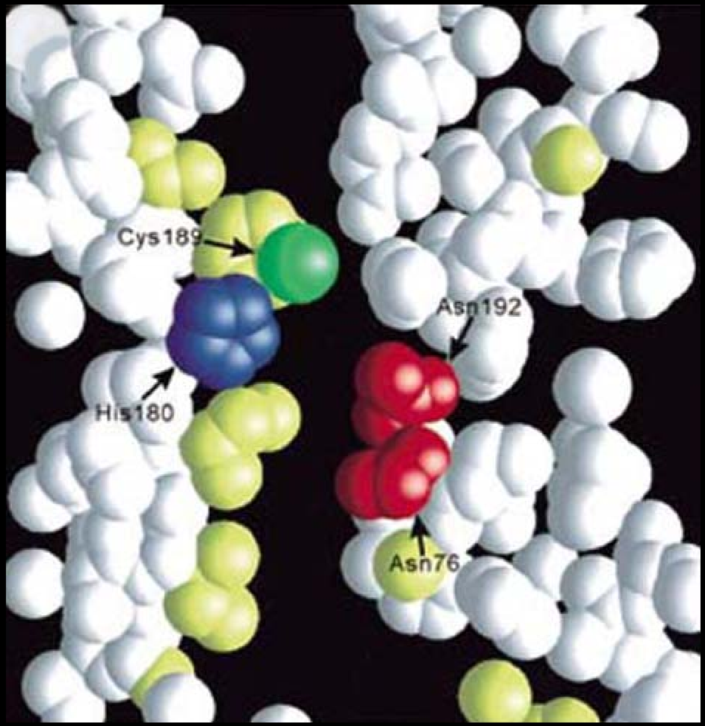
Reconstituted into membranes

Water permeability 100% retained

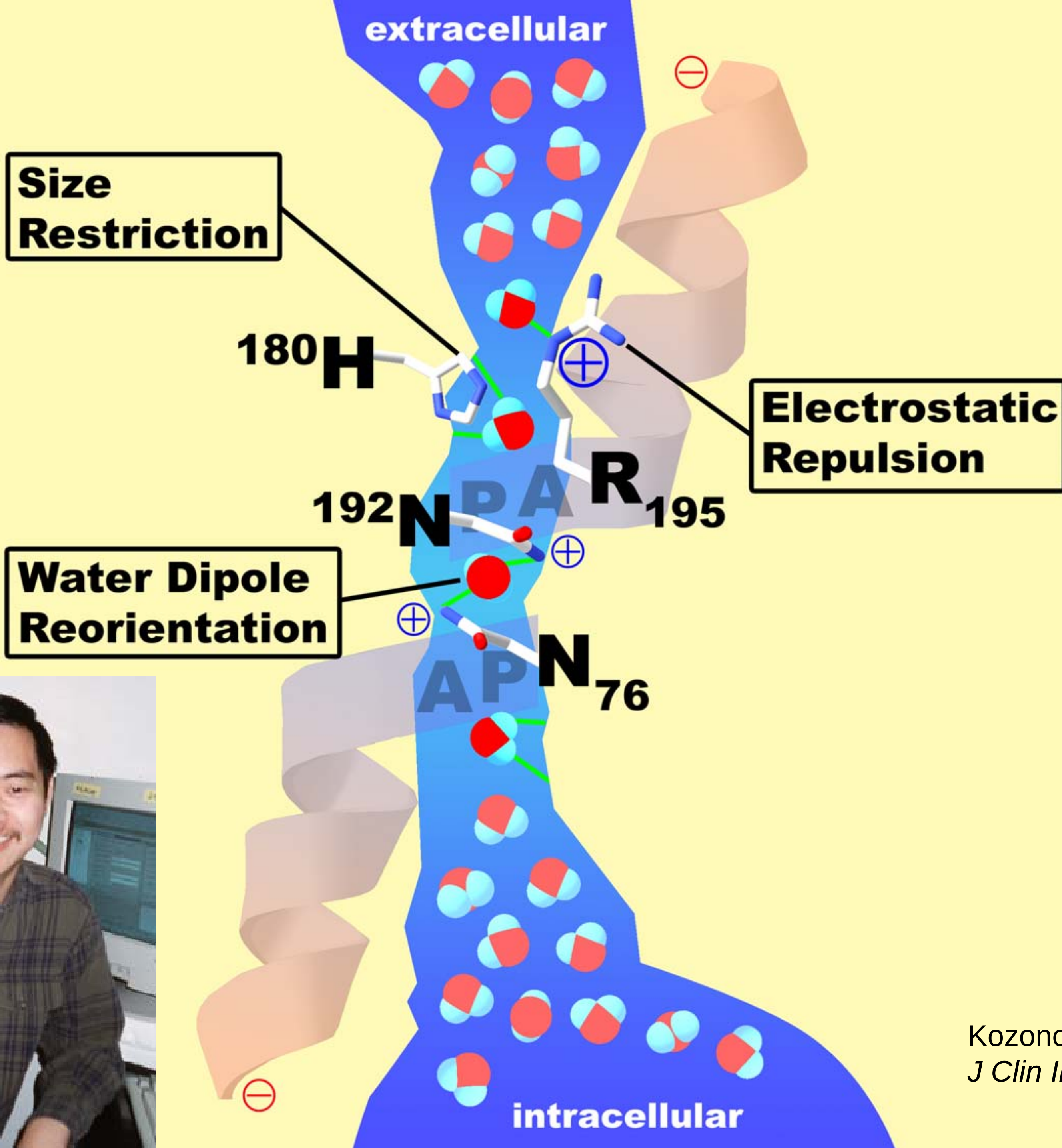
Cryo-EM and atomic force microscopy

3-D electron density map at 3.8Å



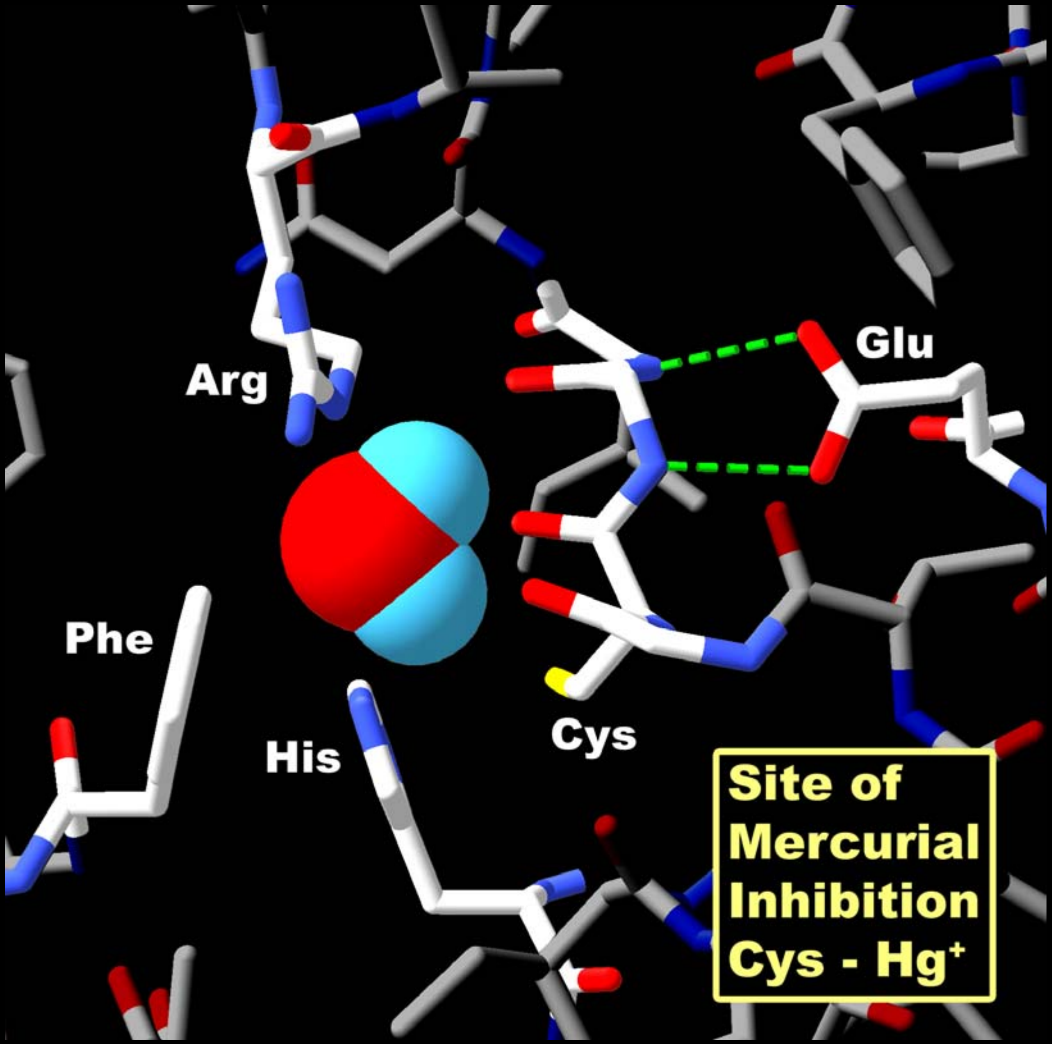


Walz *et al., J Biol Chem,* 1994; *EMBO J,* 1994; *Nature Struct Biol,* 1995; *J Mol Biol,* 1996; *Nature* 1997; Mitsuoka *et al., J Struct Biol,* 1999; Murata *et al., Nature,* 2000

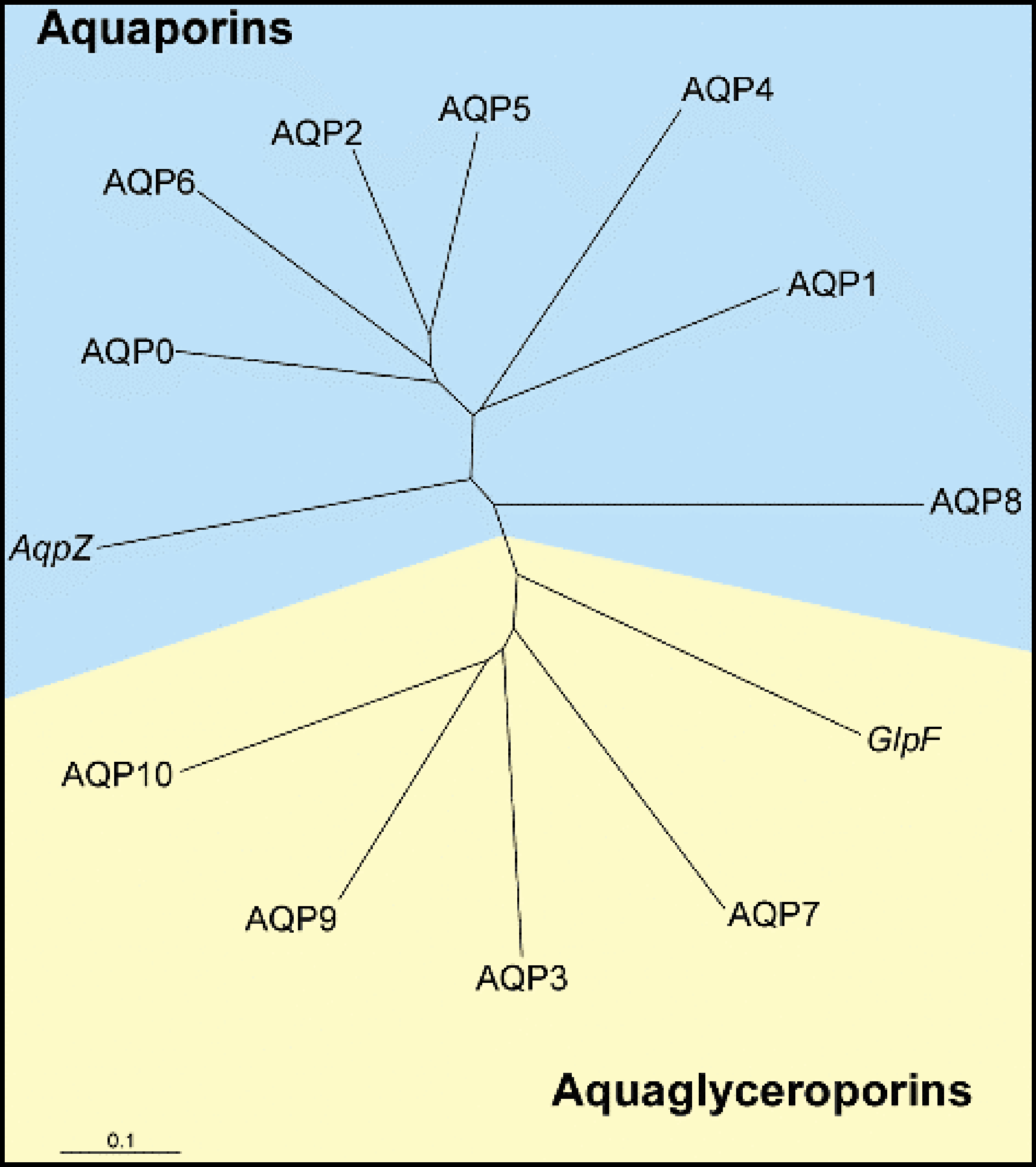


Kozono *et al.*,
J Clin Invest, 2002

Structure of AQP1
Hg^{++} inhibitory site



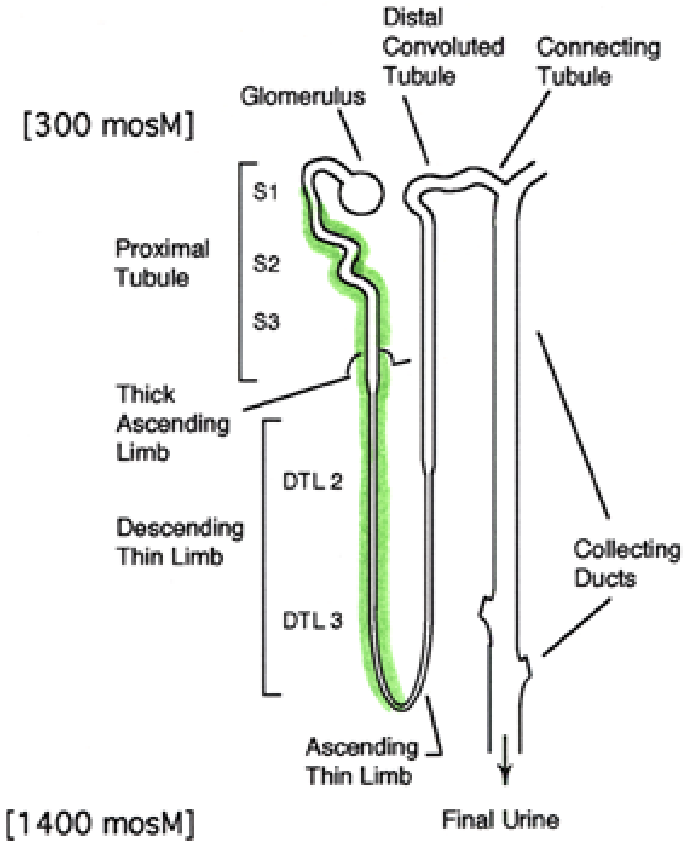
Human Aquaporin Repertoire

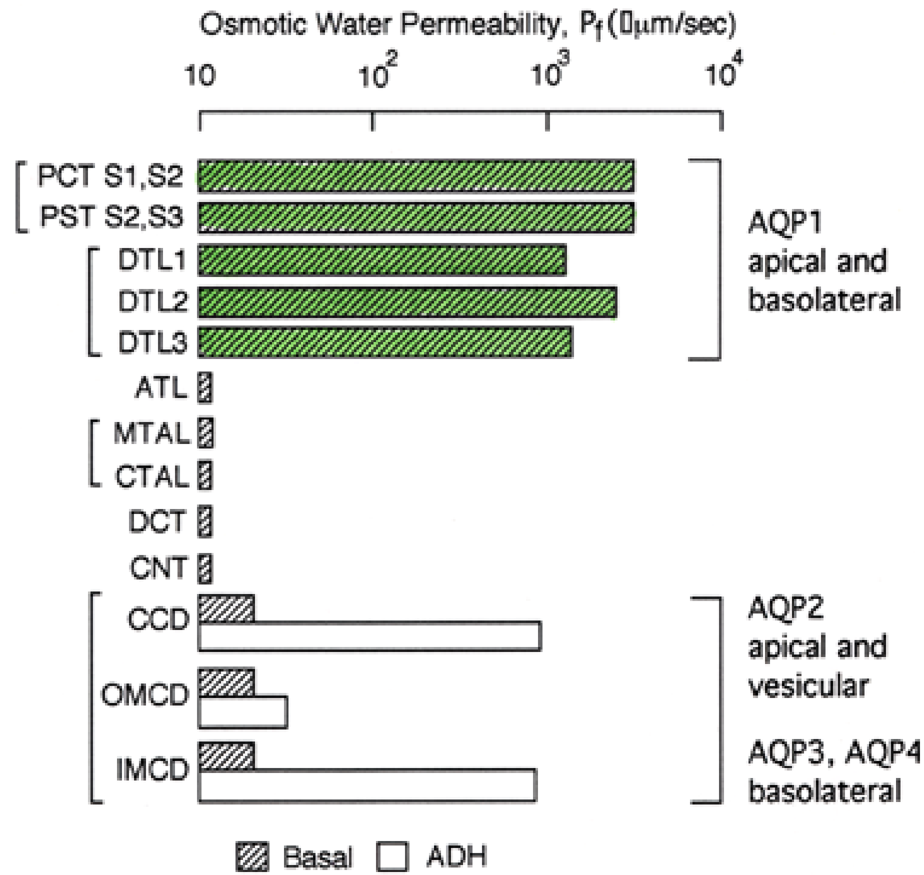


Localization of AQP1 in kidney

(with Søren Nielsen, Aarhus)

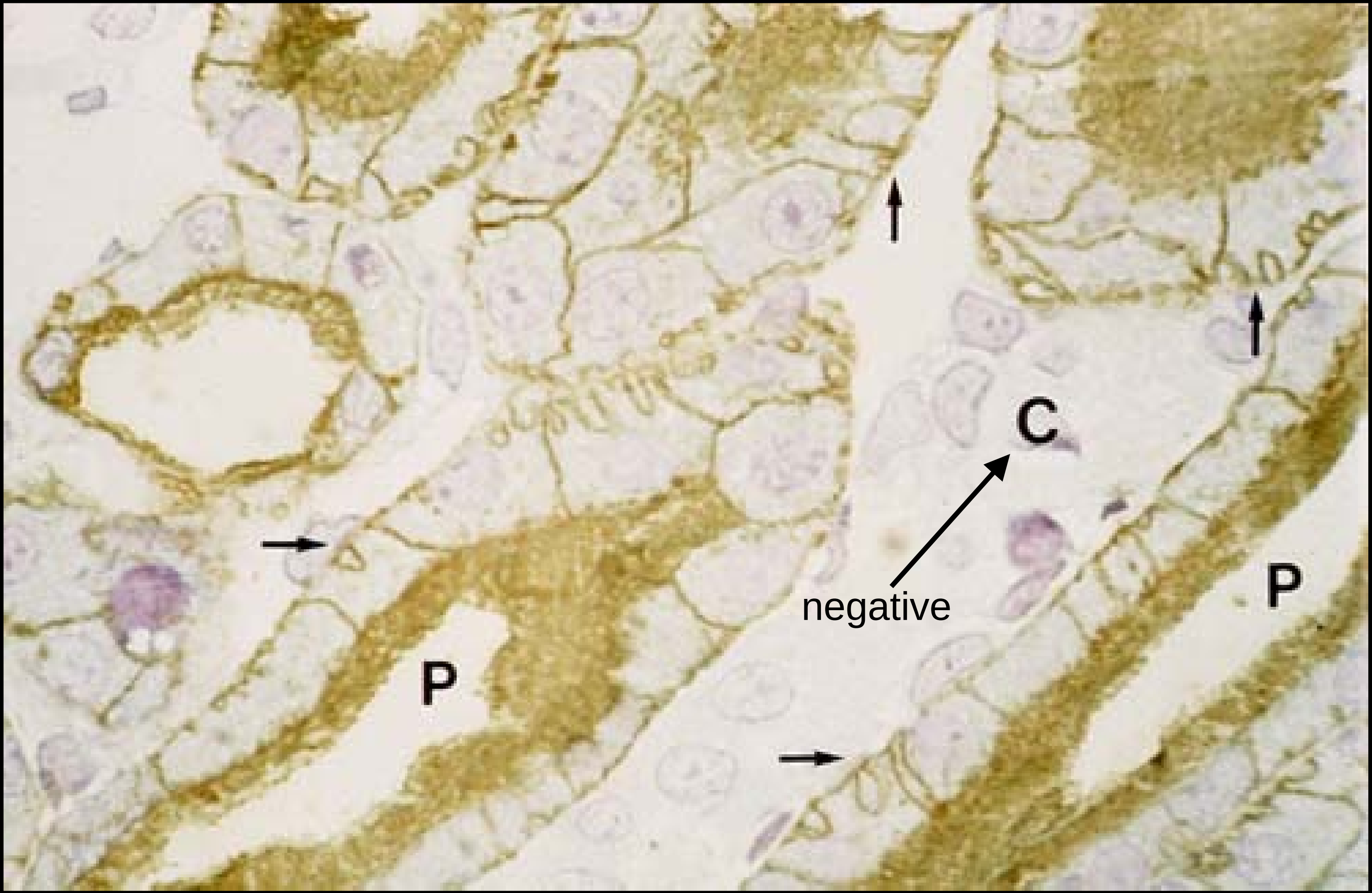
Aquaporin distribution—Renal water permeability





Nielsen *et al., J Cell Biol,*1993

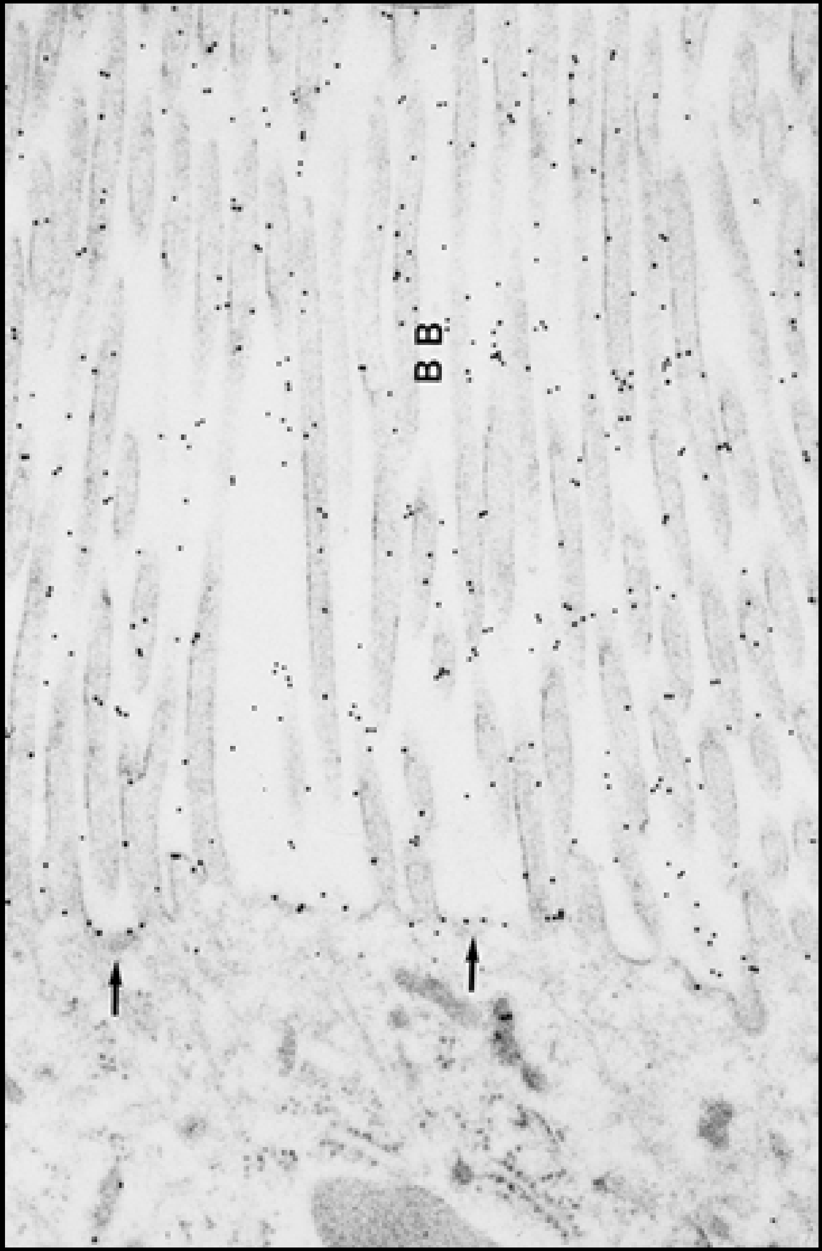
AQP1 in proximal nephron



P, proximal tubule lumen   C, collecting duct

Nielsen *et al.*, *J Cell Biol*,1993

AQP1 in proximal nephron

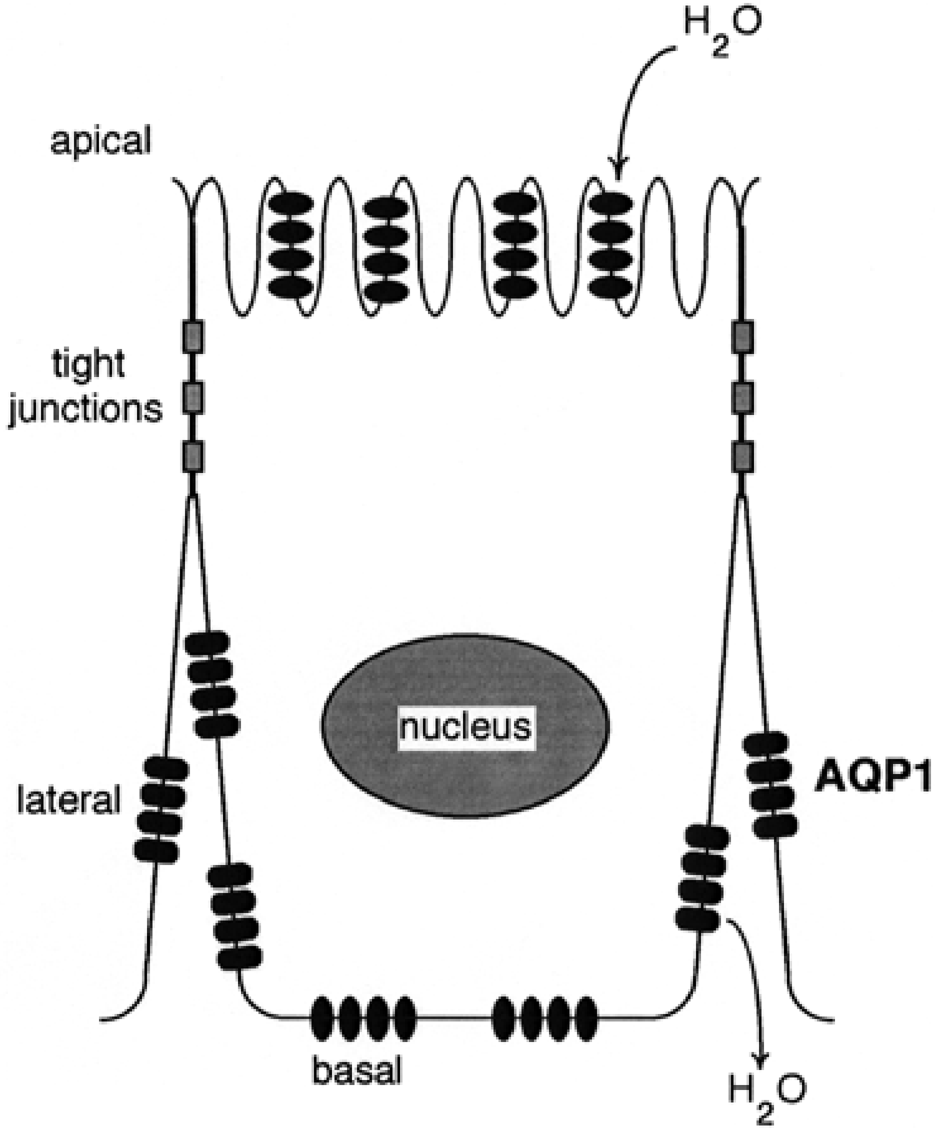


BB, apical brush border

arrows, endocytic invaginations

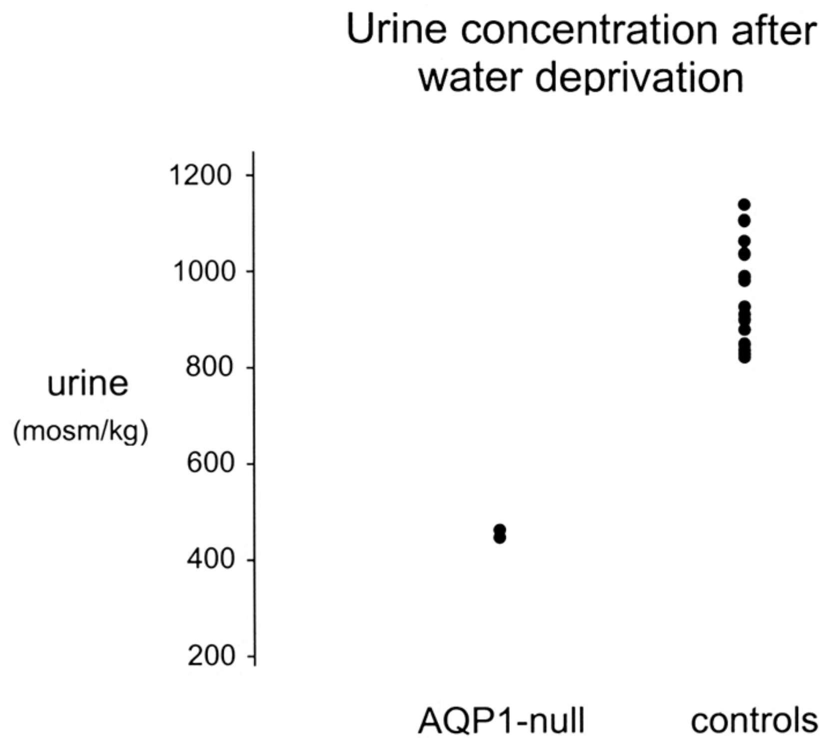
Nielsen *et al.*, *J Cell Biol*, 1993

AQP1-mediated constitutive transcellular water movements



AQP1 null humans—Renal concentration defect

(Landon King and Mike Choi, JHMI)



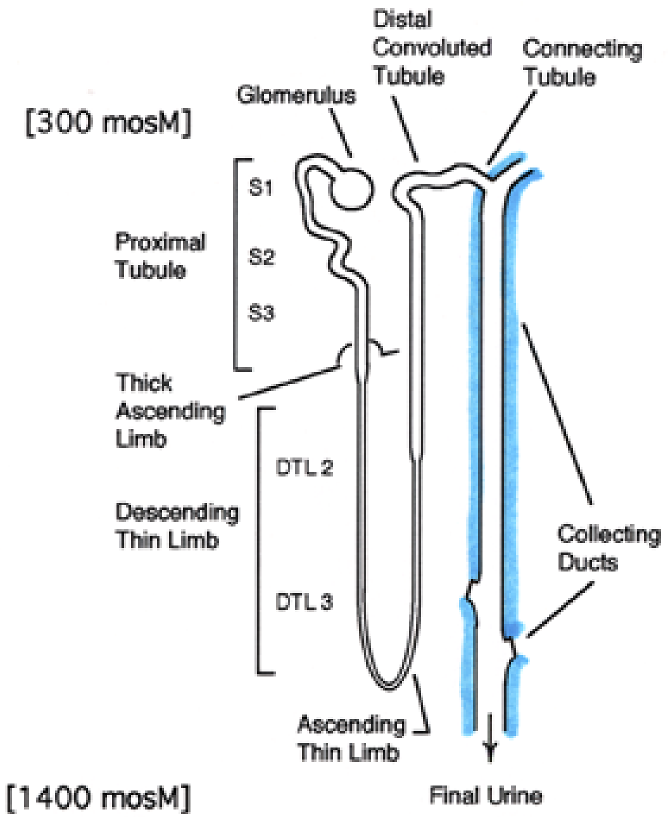
Dx—Mild Nephrogenic Diabetes Insipidus

King *et al., New Engl J Med, 2001*

AQP2—A regulated water channel

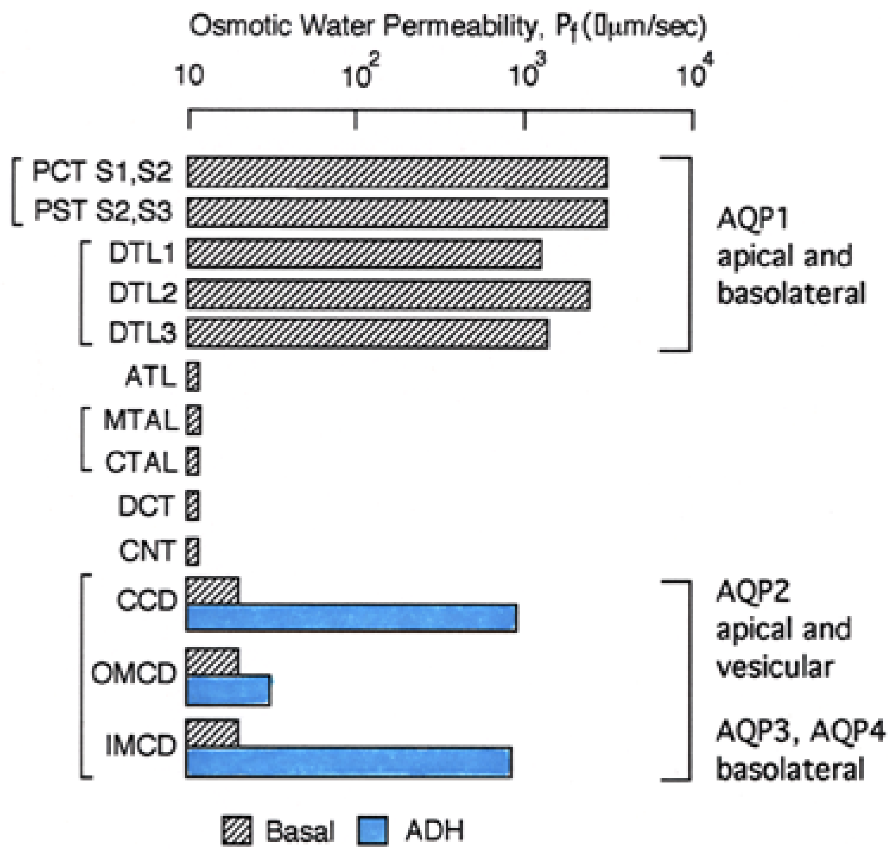
cDNA cloned by homology

(Fushimi *et al., Nature,* 1993)



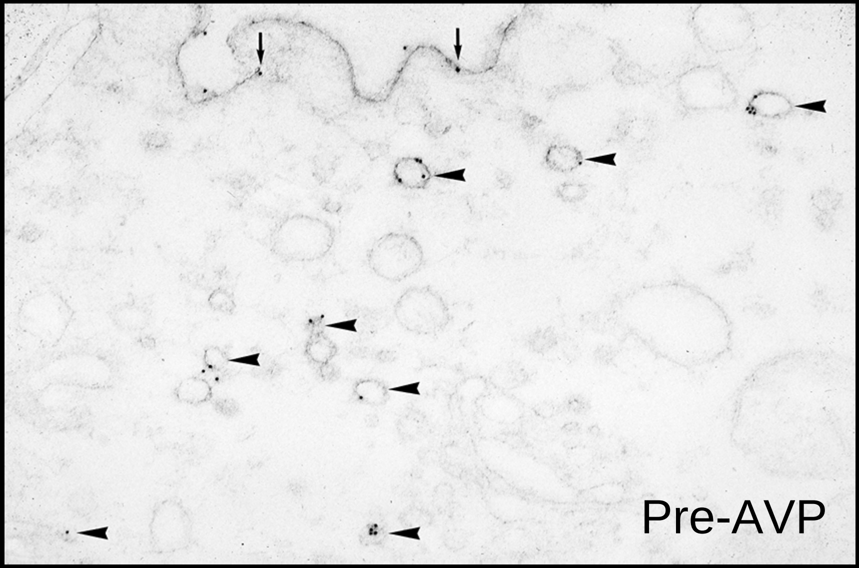
AQP2 localization in kidney

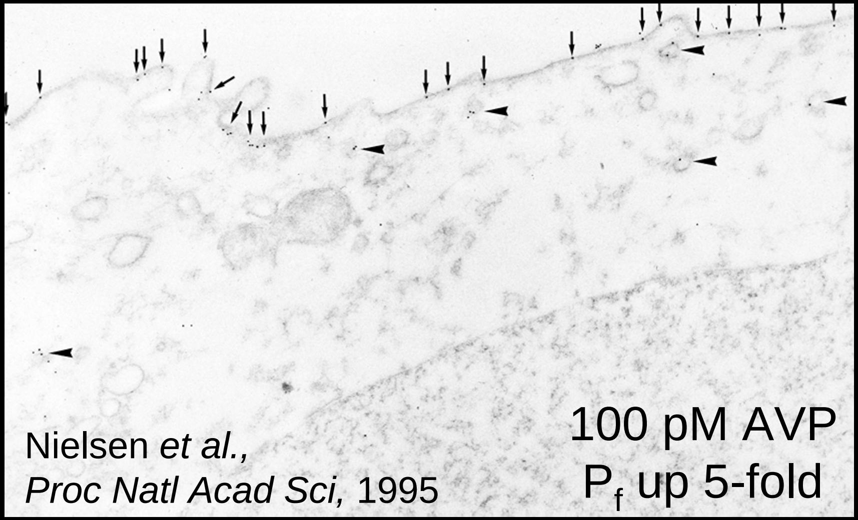
(Nielsen *et al., Proc Natl Acad Sci,* 1993)

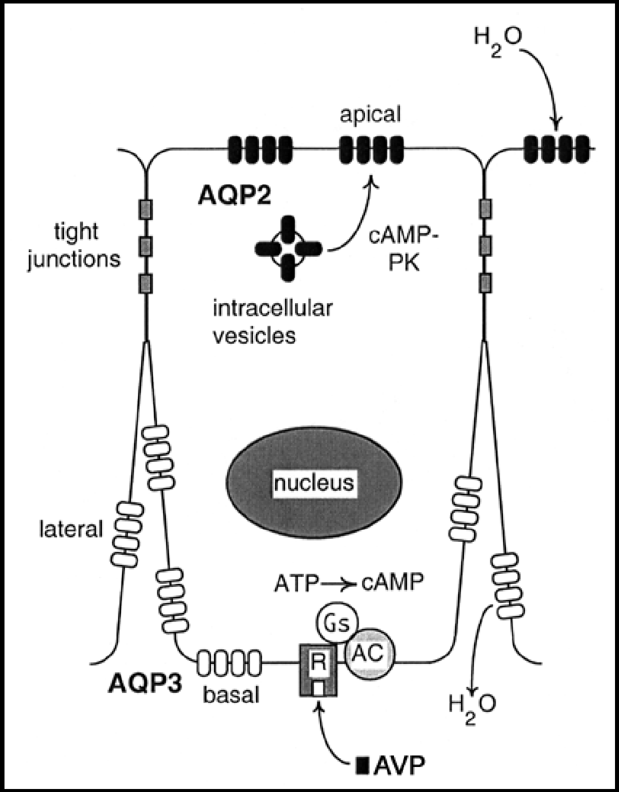


AQP2—Acute regulation by AVP

Isolated renal collecting ducts







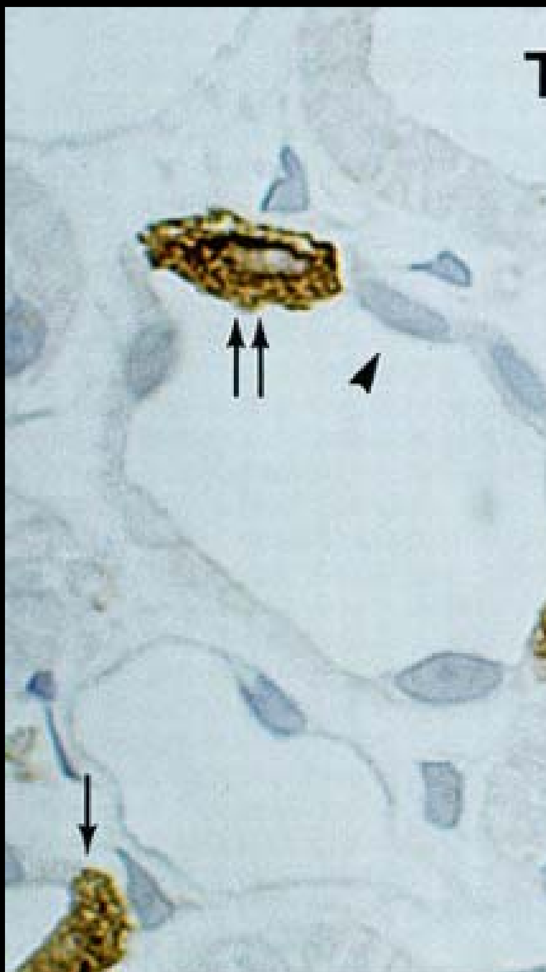
Inherited defects (rare)
- Nephrogenic DI (severe)

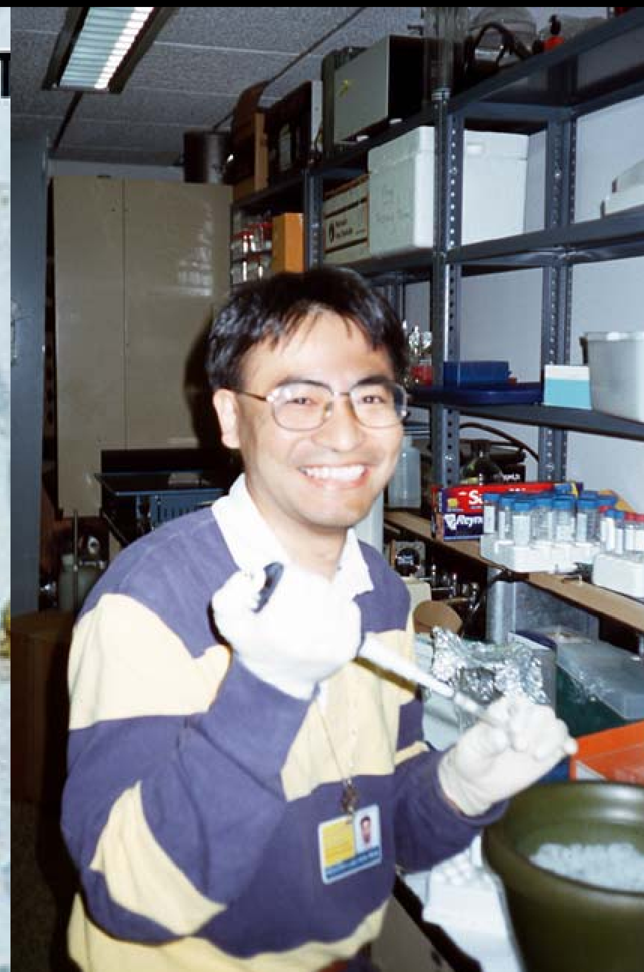
Acquired defects (very common)
- Overexpression—Fluid retention
- Underexpression—Enuresis

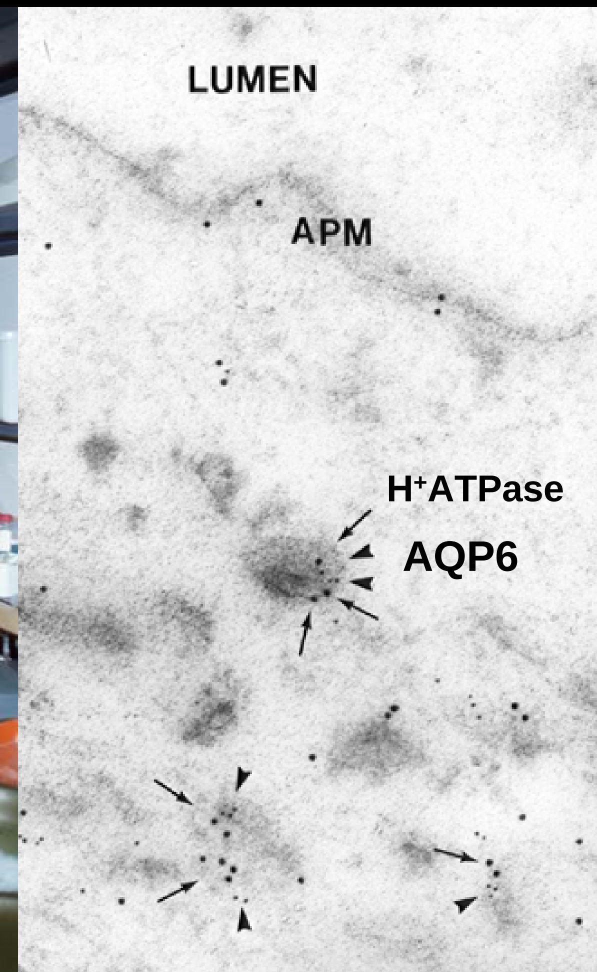
AQP6—Exclusively intracellular

Renal collecting duct a-intercalated cells (acid secretory)

Colocalizes in intracellular vesicles with H^+ ATPase



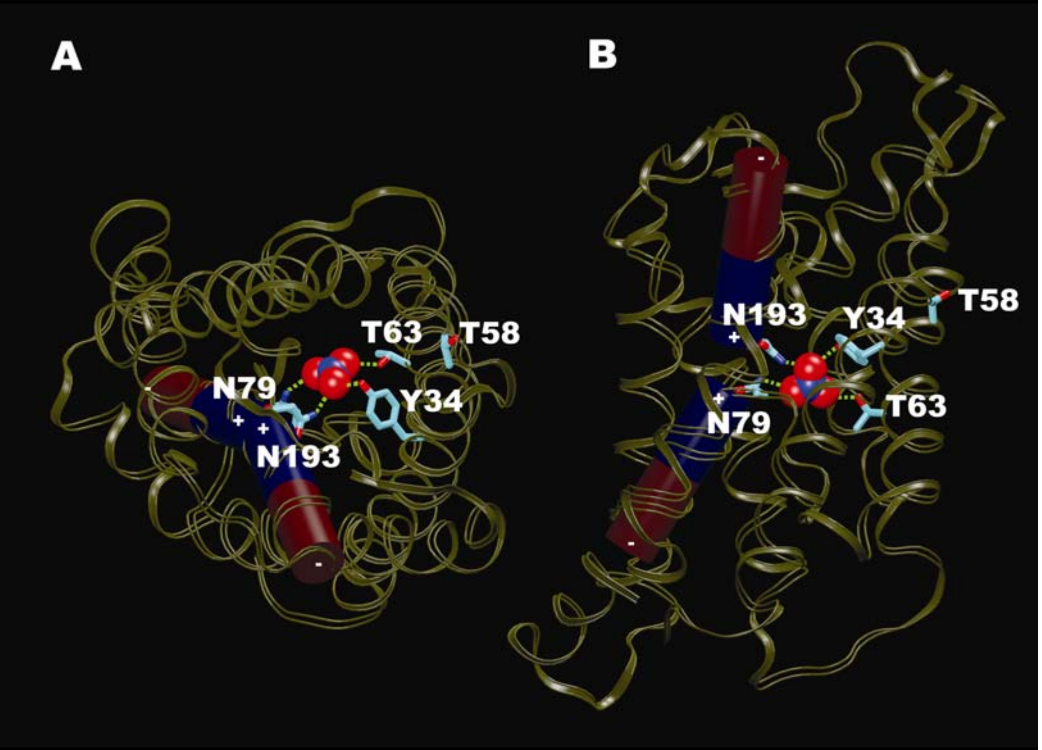


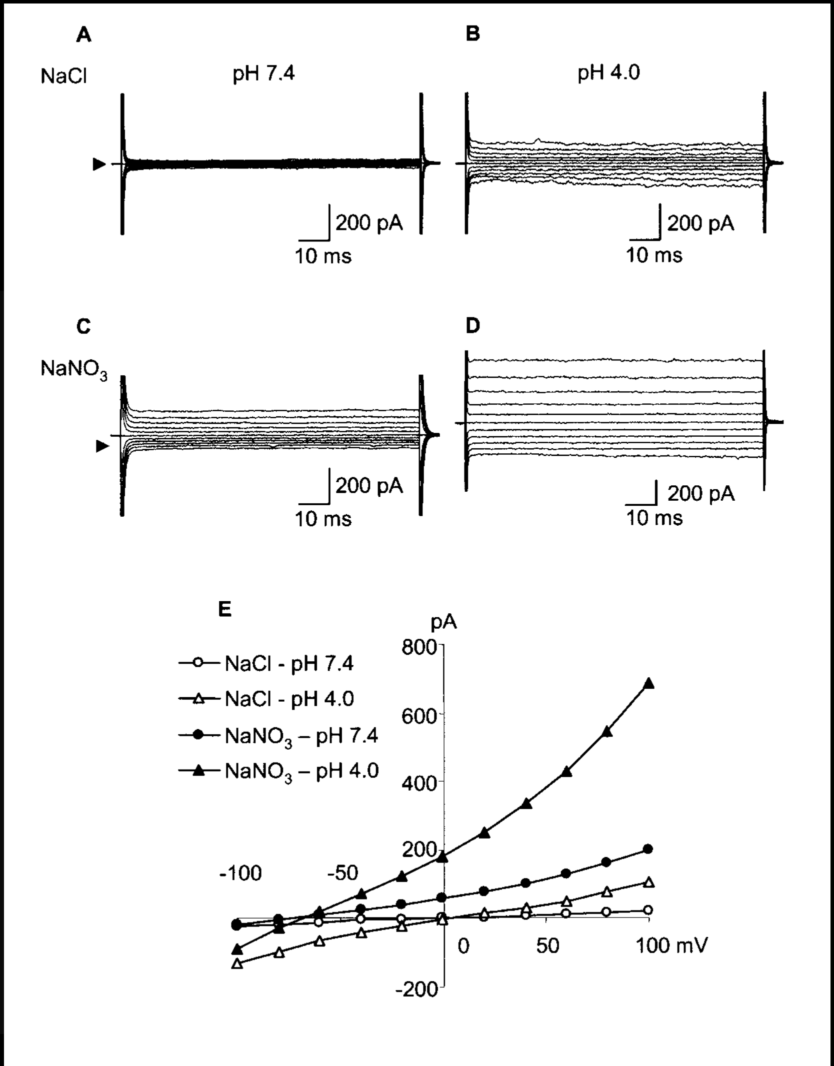


Yasui *et al., Proc Natl Acad Sci,* 1999
Yasui *et al., Nature, 1999*

AQP6—Nitrate induced-fit gating

Anion permeation
- Expressed in cultured mammalian cells
- $NO_3^- >> I^- >> Cl^- > Br^-$
- Requirement for Tyr-34 and Thr-63



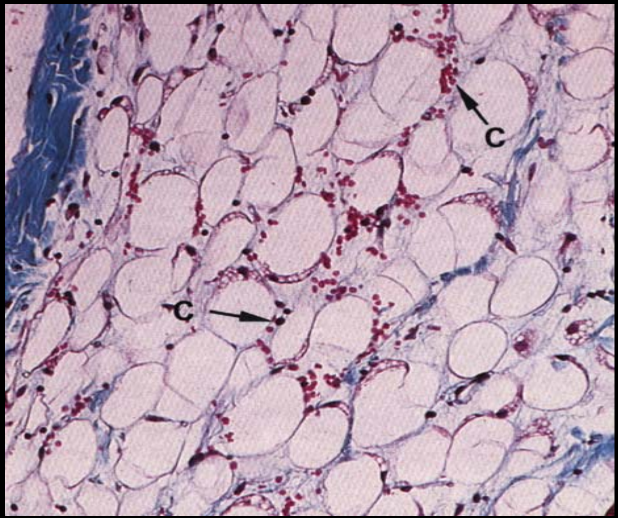


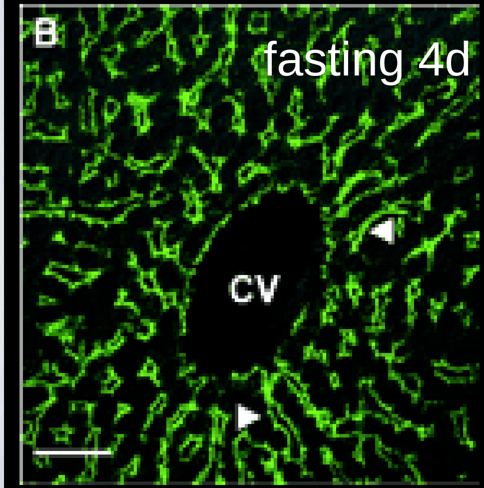
Ikeda *et al., J Biol Chem, 2002*

AQP7 and 9—Glycerol metabolism

AQP7 in adipose tissue
- Glycerol + water permeation
- Suppressed by insulin

AQP9 in liver
- Glycerol, water, urea permeation
- Increased by fasting or diabetes



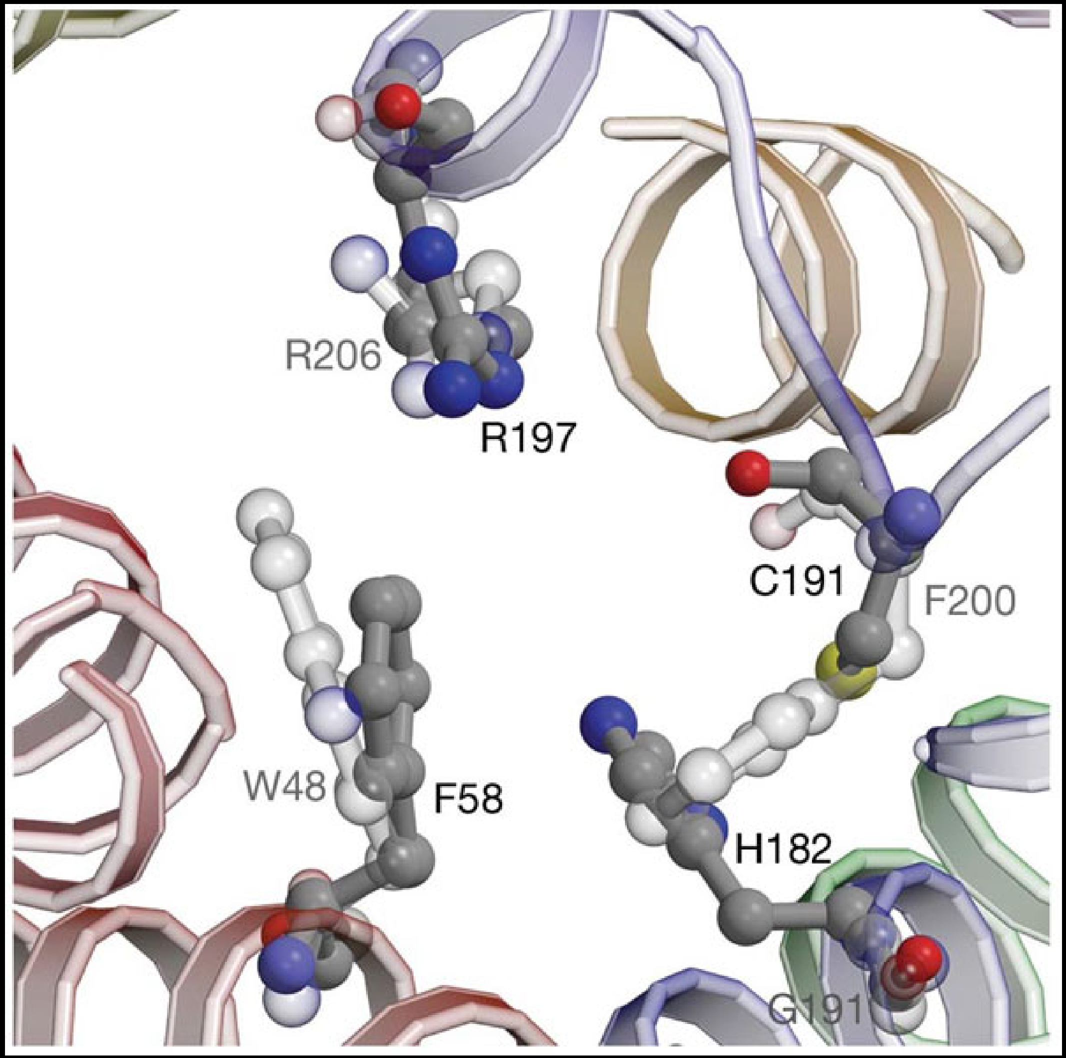


Kishida *et al., J Biol Chem,* 2000
Kuriyama *et al., Diabetes,* 2002

Tsukaguchi *et al., J Clin Invest,* 1998
Carbrey *et al., Proc Natl Acad Sci,* 2003

Starvation—AQP7 releases glycerol derived from fat catabolism.
AQP9 facilitates hepatic glycerol uptake for gluconeogensis.

Structures of AQP1 and GlpF



Fu *et al., Science,* 2000
Sui *et al., Nature,* 2001

Aquaporin water channels

Freely permeated by H_2O, not H_3O^+

Certain homologs permeated by
glycerol, nitrate, or arsenite

Structural models explain functions

Implicated in multiple clinical disorders
- Renal-vascular diseases
- Brain injury and edema
- Loss of vision
- Starvation
- Thermal stress

Expressed throughout nature