Nobel Prize Inspiration Initiative

In partnership with AstraZeneca

Presents

Professor Peter Agre

2003 Nobel Laureate in Chemistry

Aquaporin Water Channels: From Atomic Structure to Clinical Medicine

Wednesday 26 June 2013,
10:00am – 11:20am

St Petersburg State Medical University

26 June 2013

Nobel Prize Inspiration Initiative

St Petersburg State Medical University

Russia

Aquaporin Water Channels:
From Atomic Structure to Clinical Medicine

Peter Agre, M.D.

University Professor and Director

Johns Hopkins Malaria Research Institute

Bloomberg School of Public Health

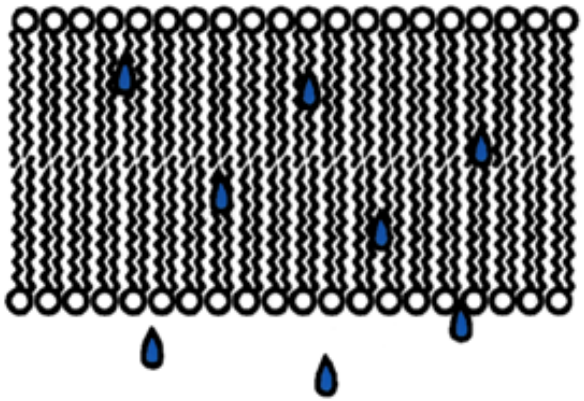
Baltimore, Maryland


ПЕТРУ ПЕРВОМУ
ЕКАТЕРИНА ВТОРАЯ
ЛЕТА 1782


College

Transmembrane water permeability—Current view

Bilayer Diffusion



All biological membranes

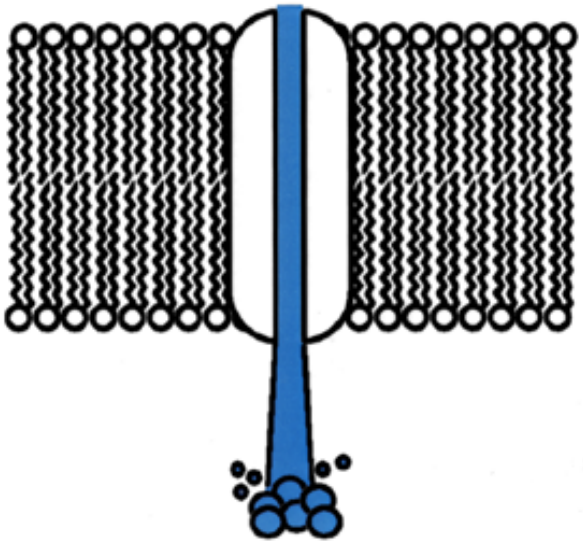
Low capacity

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

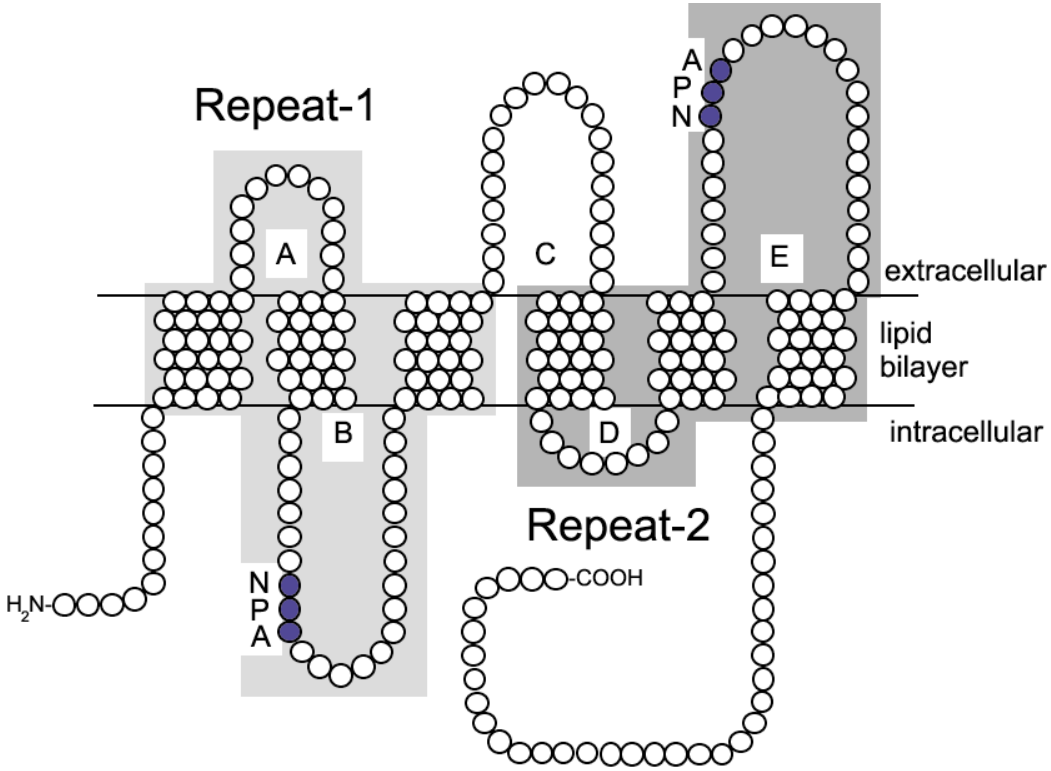
Reversibly inhibited by Hg^{++}

E_a <5 kcal/mol

Discovery of Aquaporin-1
Molecular cloning

28 kDa polypeptide (269 aa)

Internal tandem repeat



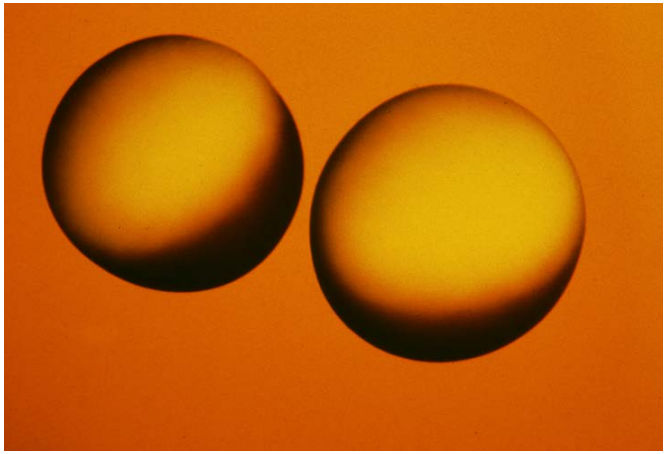
Recognition of homologs

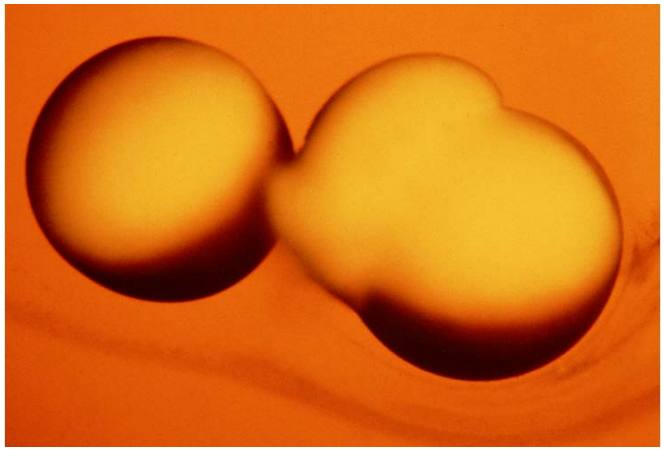
- Bovine lens—MIP
- Drosophila brain—Bib
- E. coli—GlpF
- Plants—Nod, TIP, TUR, TobRB47

Preston & Agre, *Proc Natl Acad Sci,* 1991

Discovery of Aquaporin-1

Functional expression (with Wm. Guggino, JHMI)



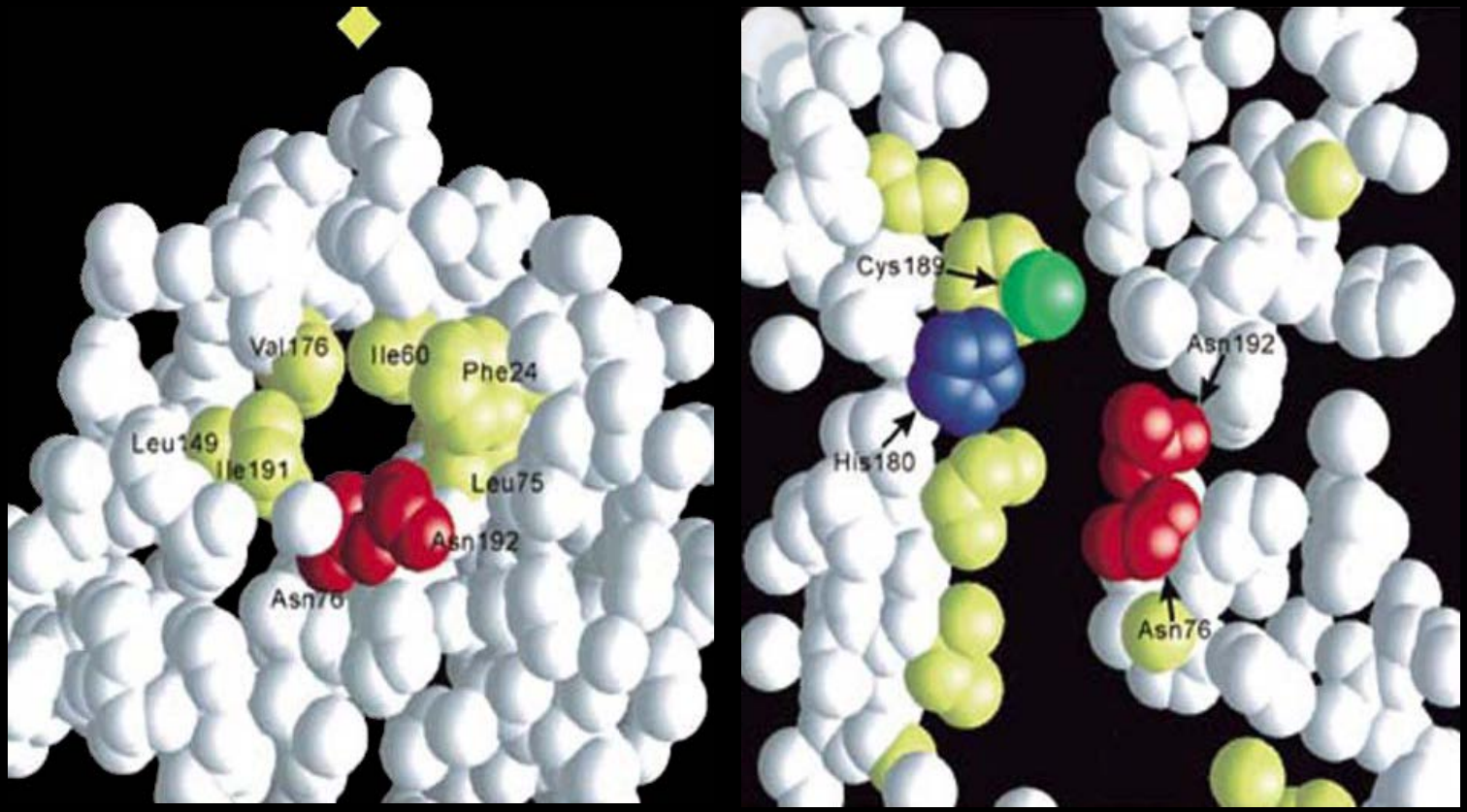


Hypo-osmolar swelling
Hg^{++} inhibited, no currents

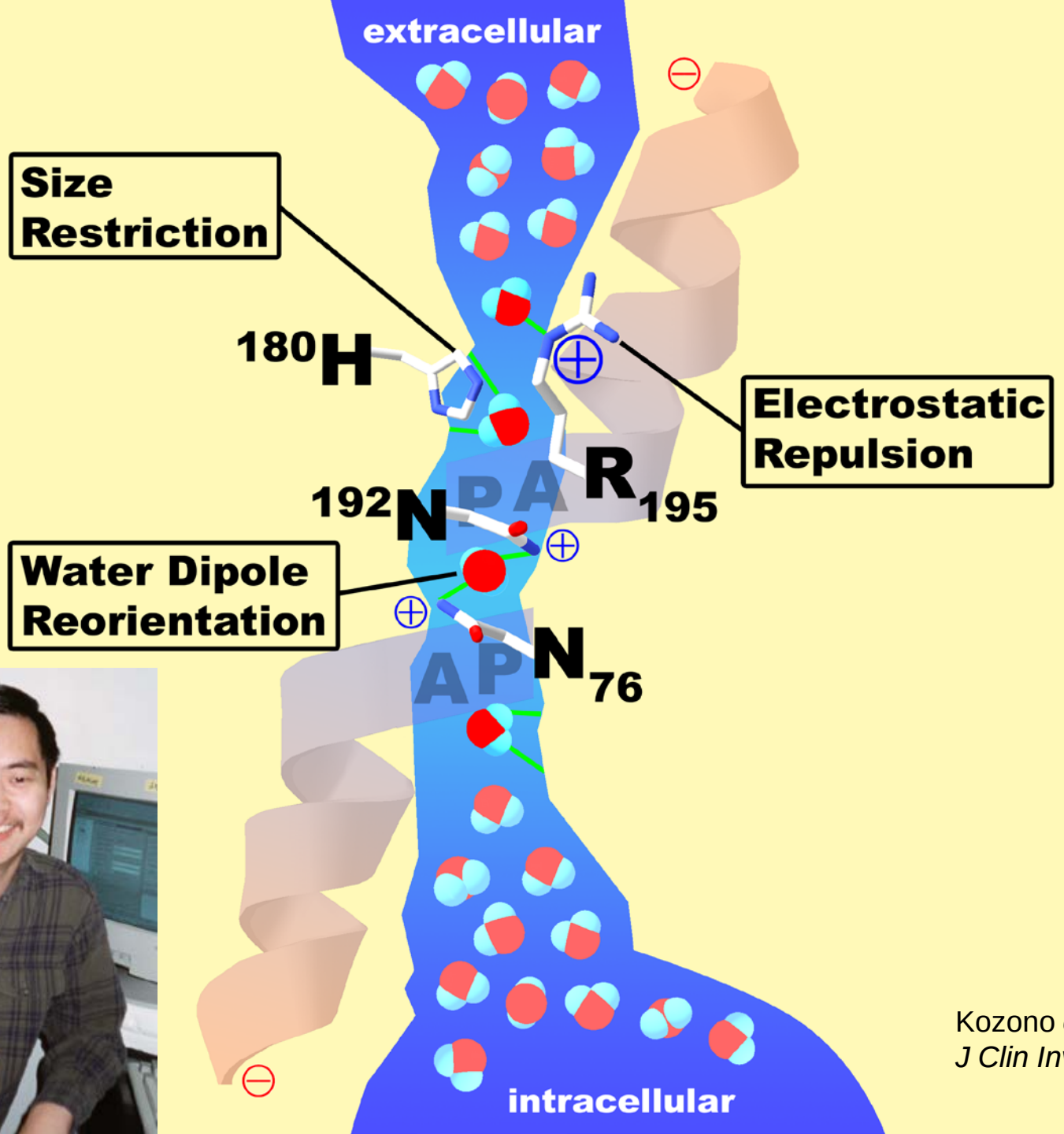
Preston *et al., Science* 1992

Structure of AQP1

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



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

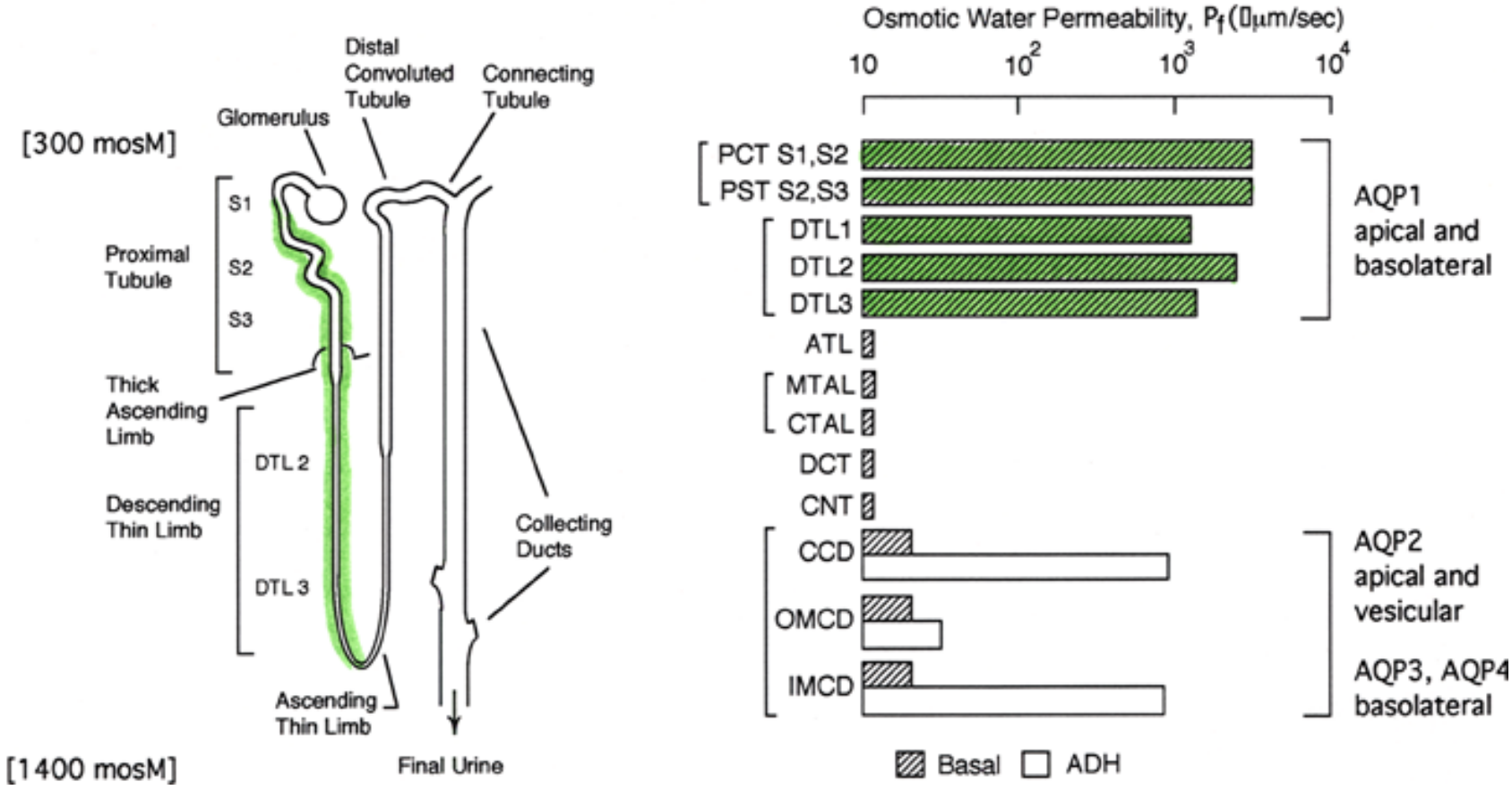


Kozono *et al.*,
J Clin Invest, 2002

Localization of AQP1 in kidney

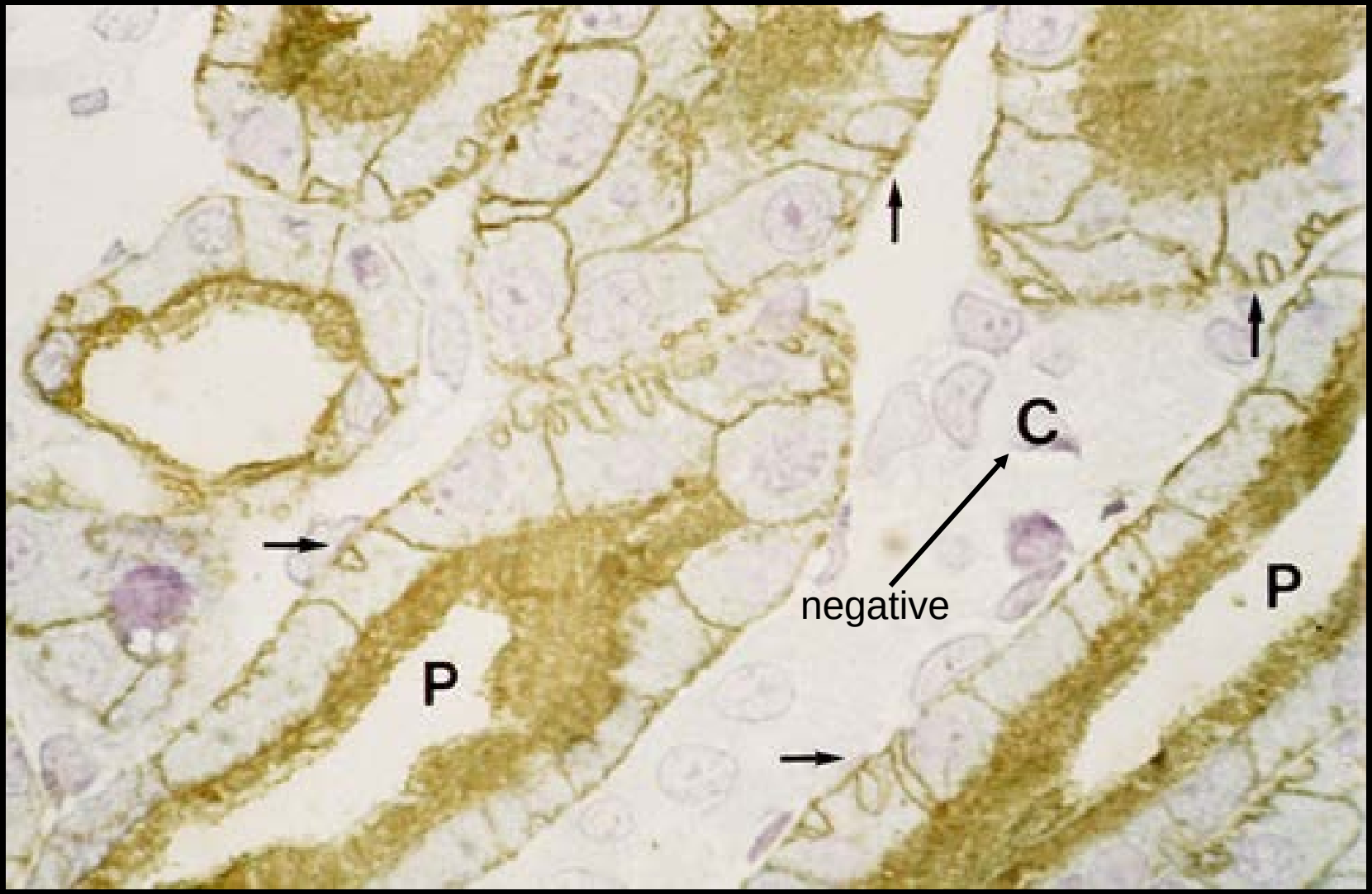
(with Søren Nielsen, Aarhus)

Aquaporin distribution—Renal water permeability



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

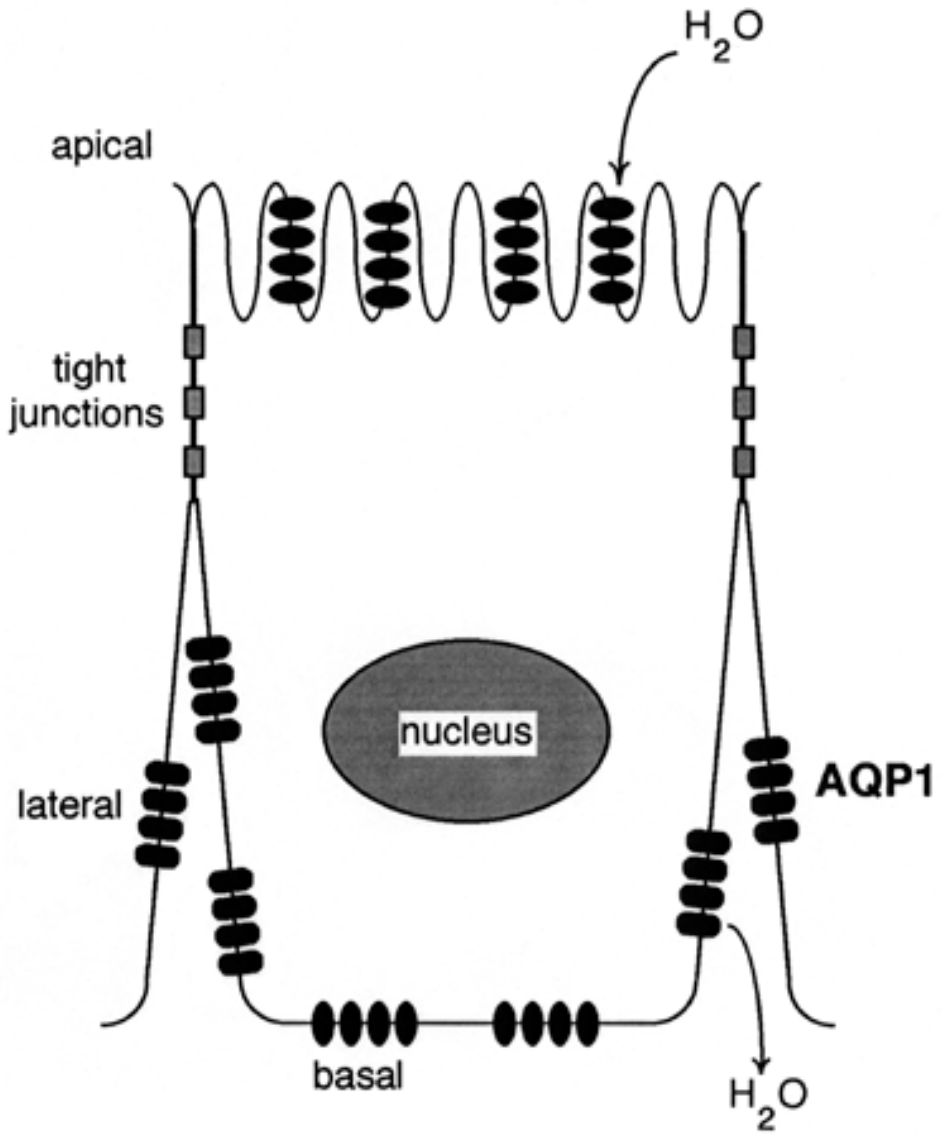
AQP1 in proximal nephron



P, proximal tubule lumen C, collecting duct

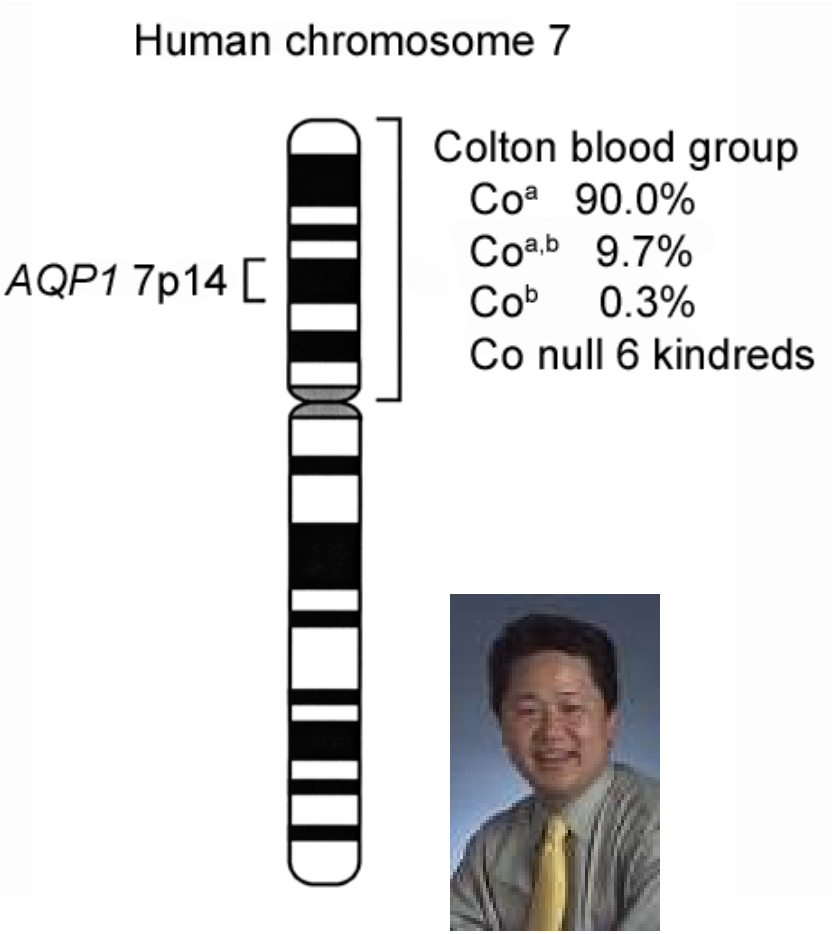
Nielsen *et al., J Cell Biol,*1993

AQP1-mediated constitutive transcellular water movements



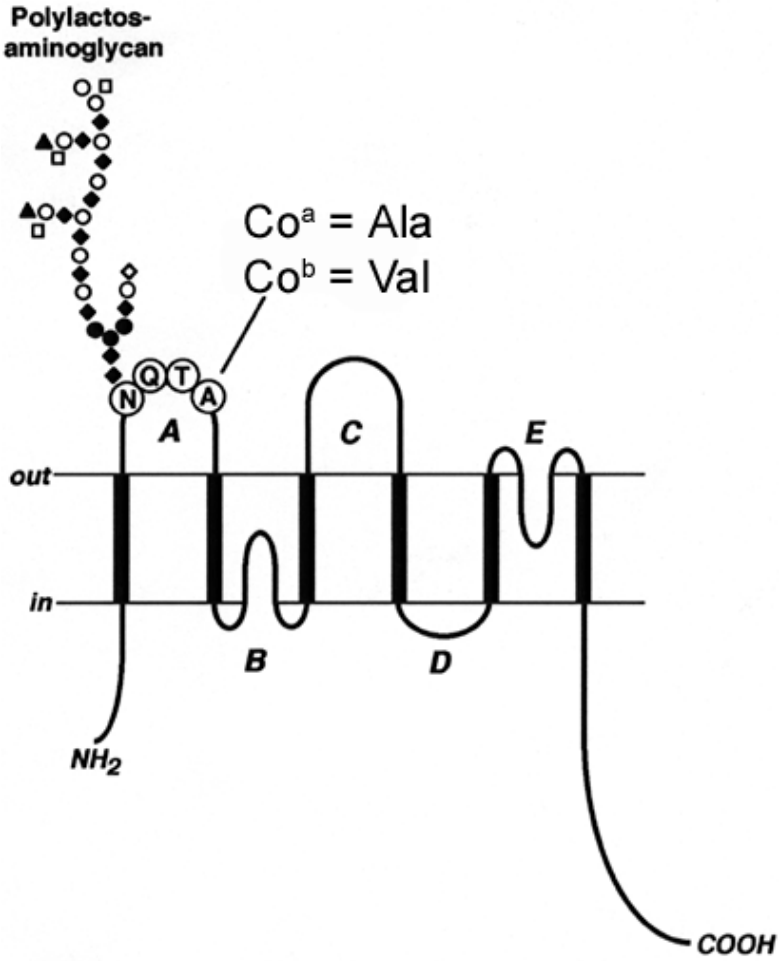
AQP1 and the Colton antigen

Coincidental chromosomal locus



Moon *et al., J Biol Chem,*1993

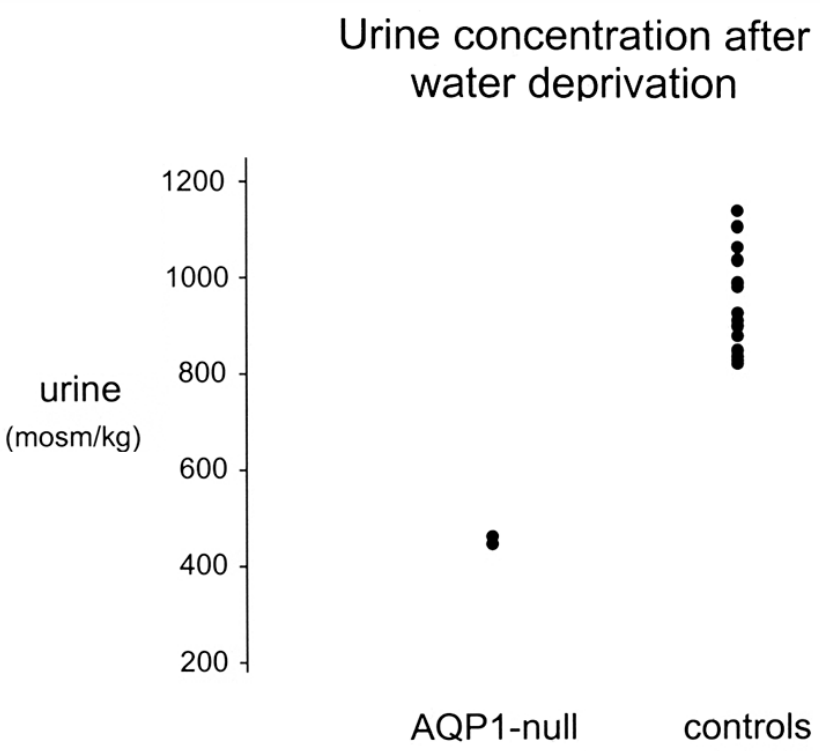
Surface polymorphism



Smith *et al., J Clin Invest,*1994

AQP1 null humans—Renal concentration defect

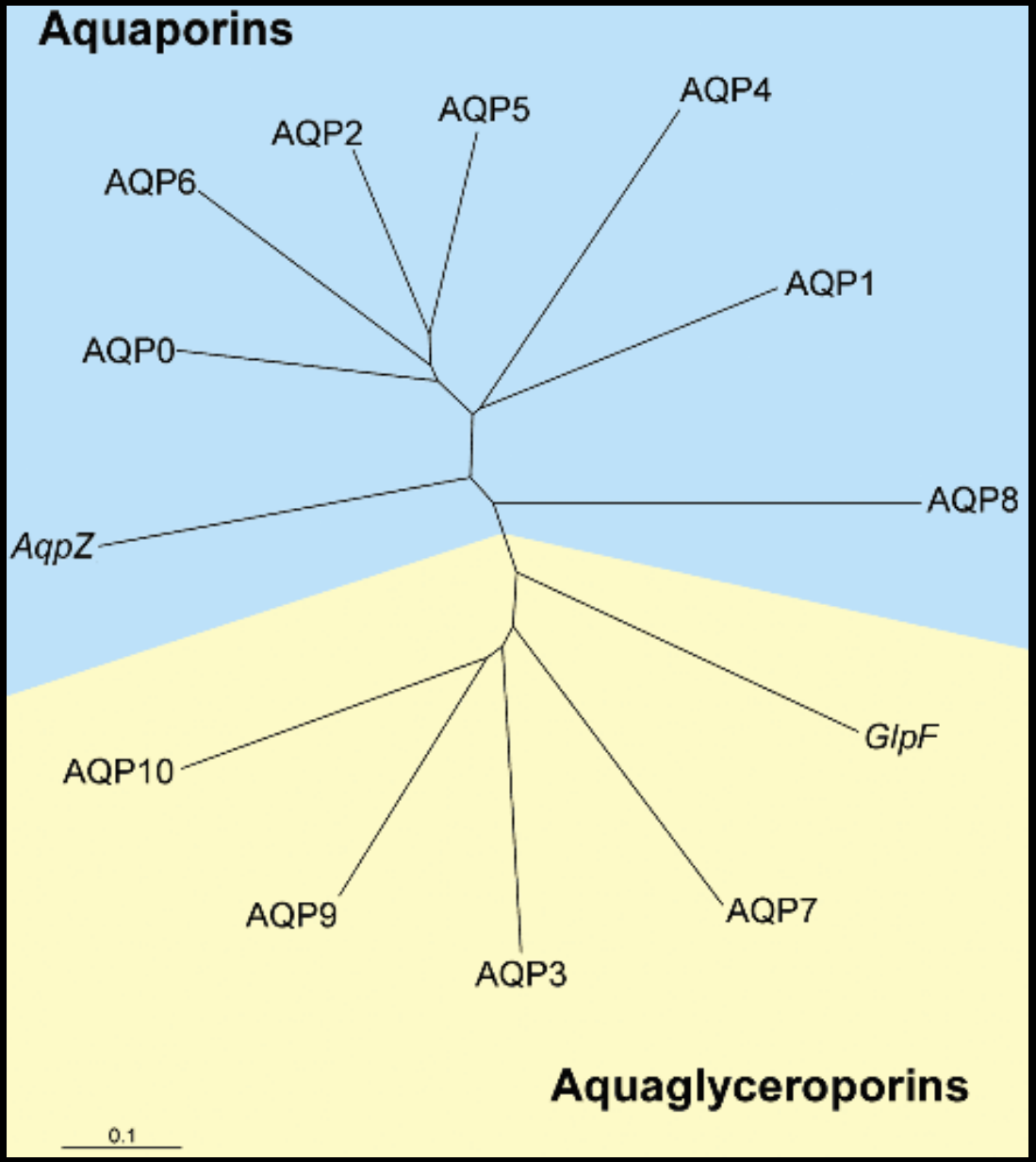
(Landon King and Mike Choi, JHMI)



Dx—Mild Nephrogenic Diabetes Insipidus

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

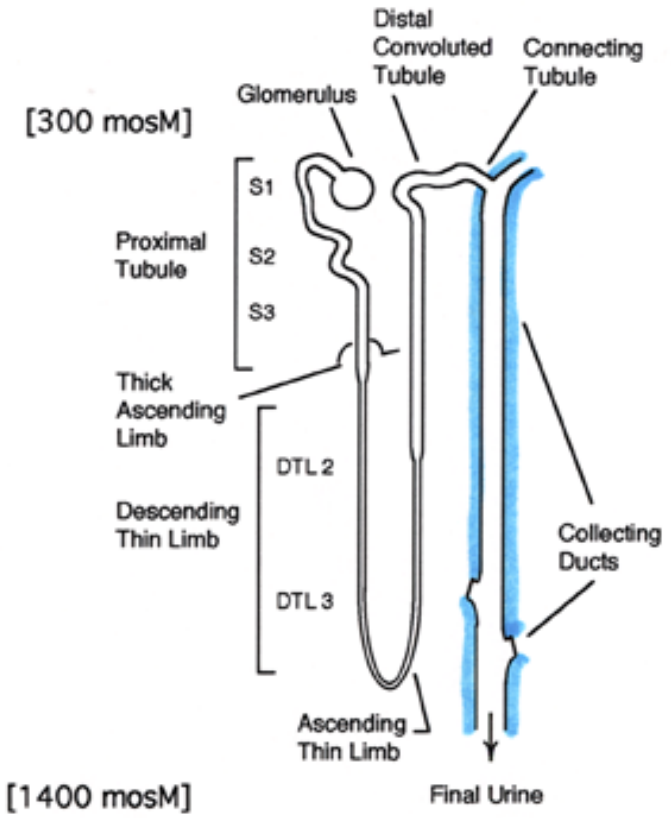
Human Aquaporin Repertoire



AQP2—A regulated water channel

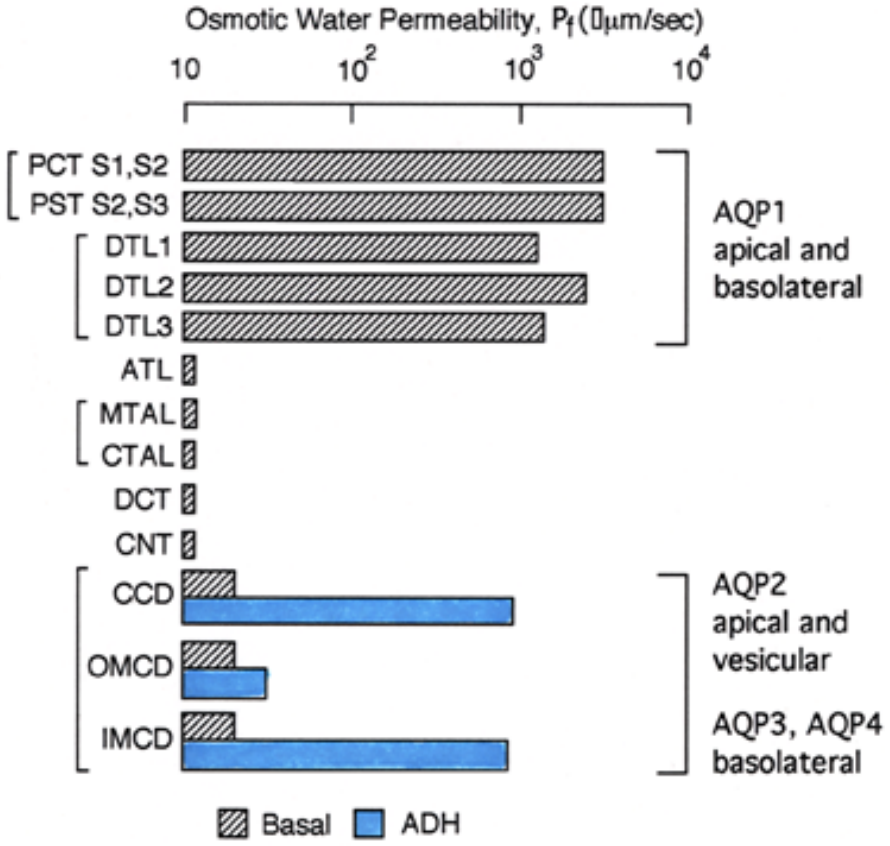
cDNA cloned by homology

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



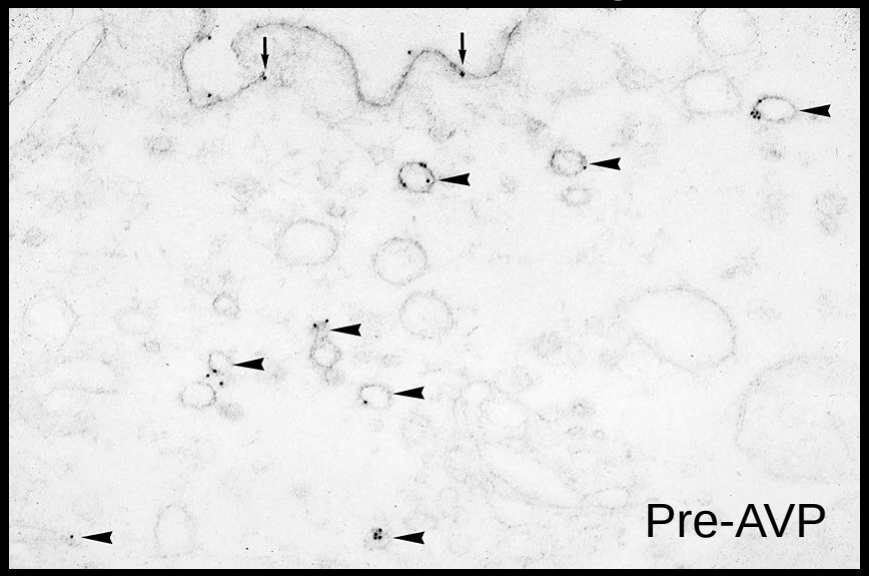
AQP2 localization in kidney

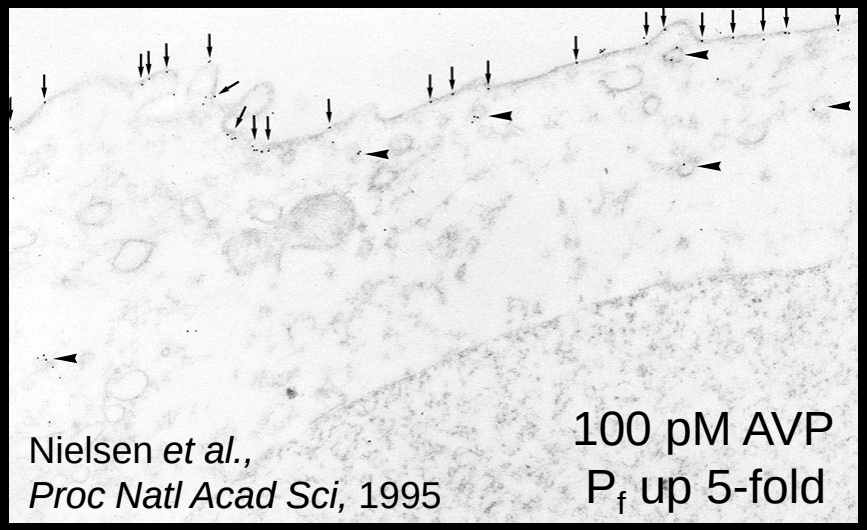
(Nielsen *et al., Proc Natl Acad Sci,* 1993)



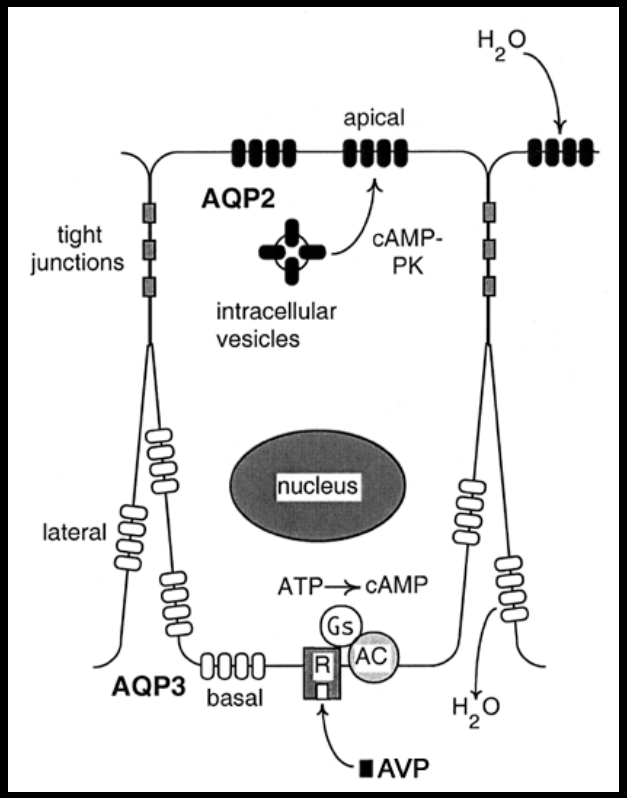
AQP2—Acute regulation by AVP

Isolated renal collecting ducts





Nielsen *et al.*,
Proc Natl Acad Sci, 1995



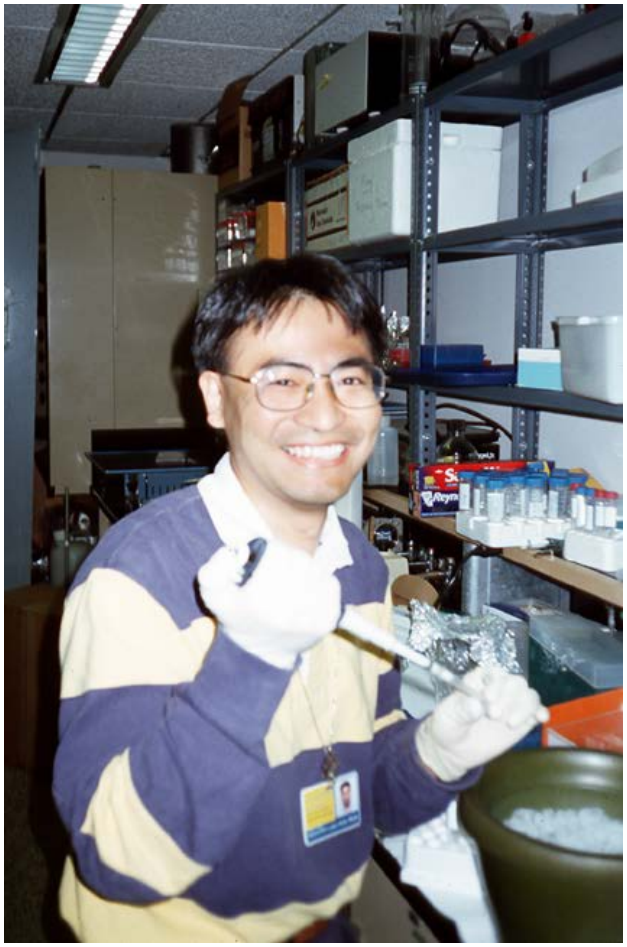
Inherited defects (rare)

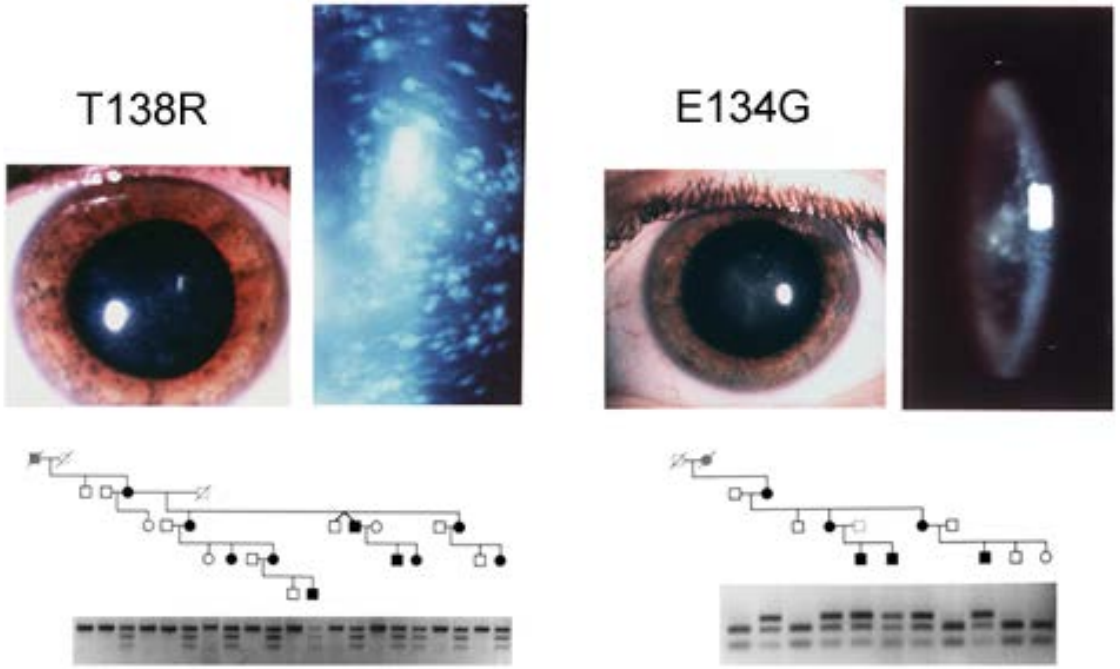
- Nephrogenic DI (severe)

Acquired defects (very common)

- Overexpression—Fluid retention
- Underexpression—Enuresis

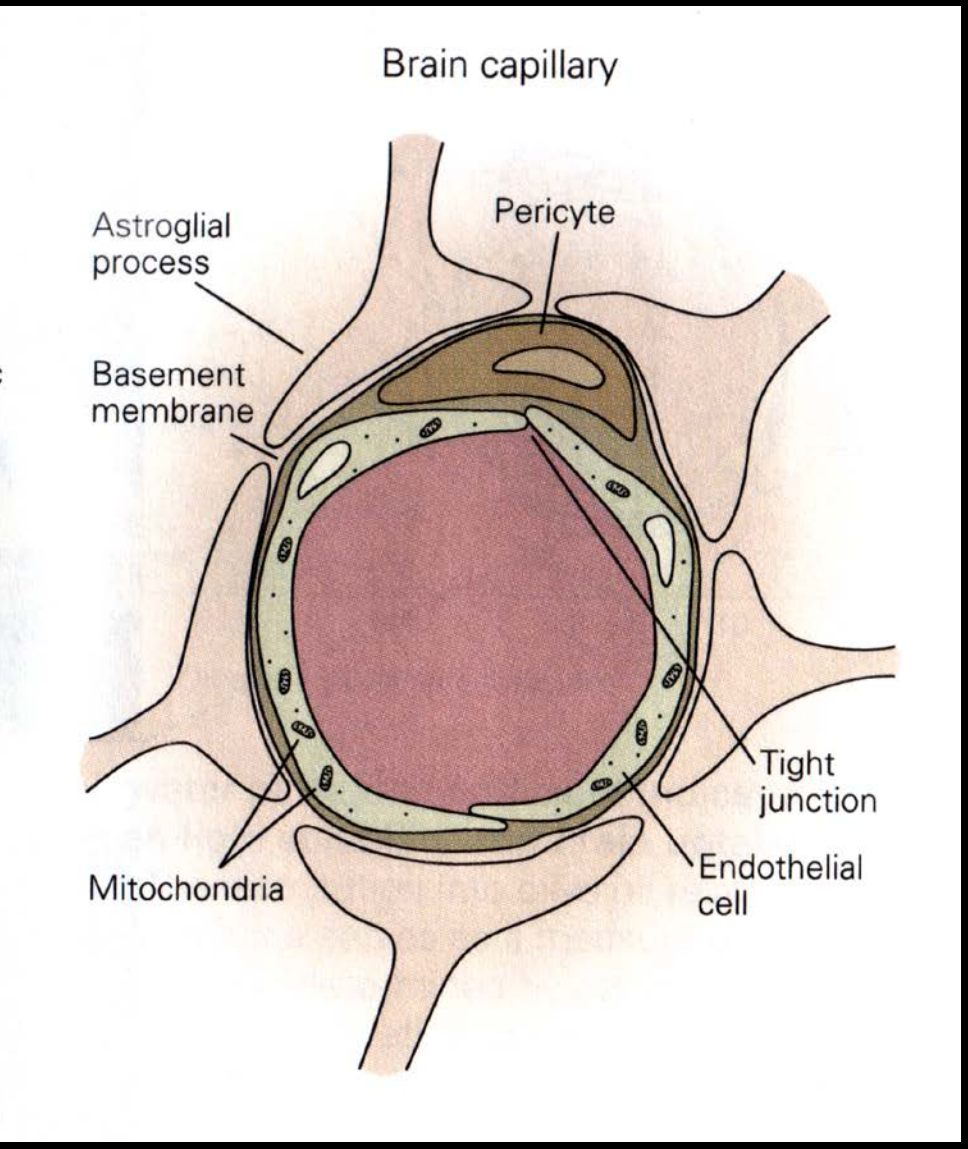
AQP0 and congenital cataracts

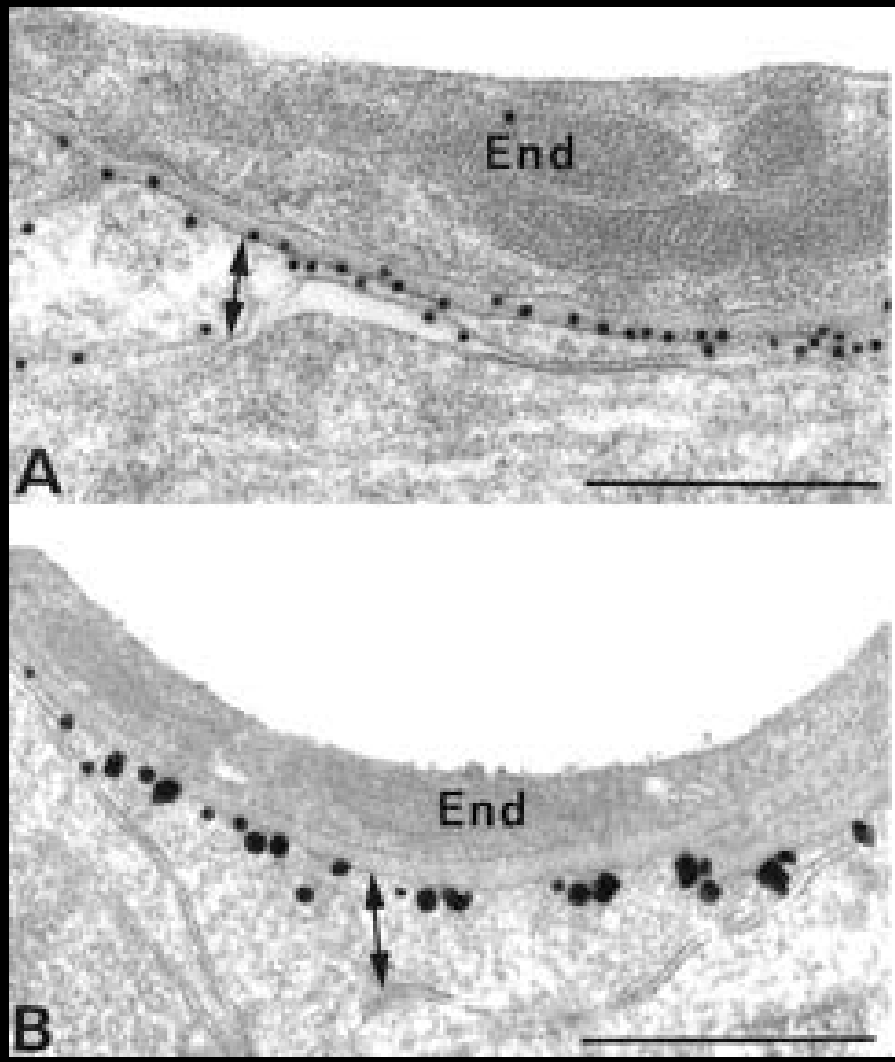




Francis *et al., Human Mol Genetics* 2000

AQP4—Blood brain barrier
(with Ole Petter Ottersen, Oslo)





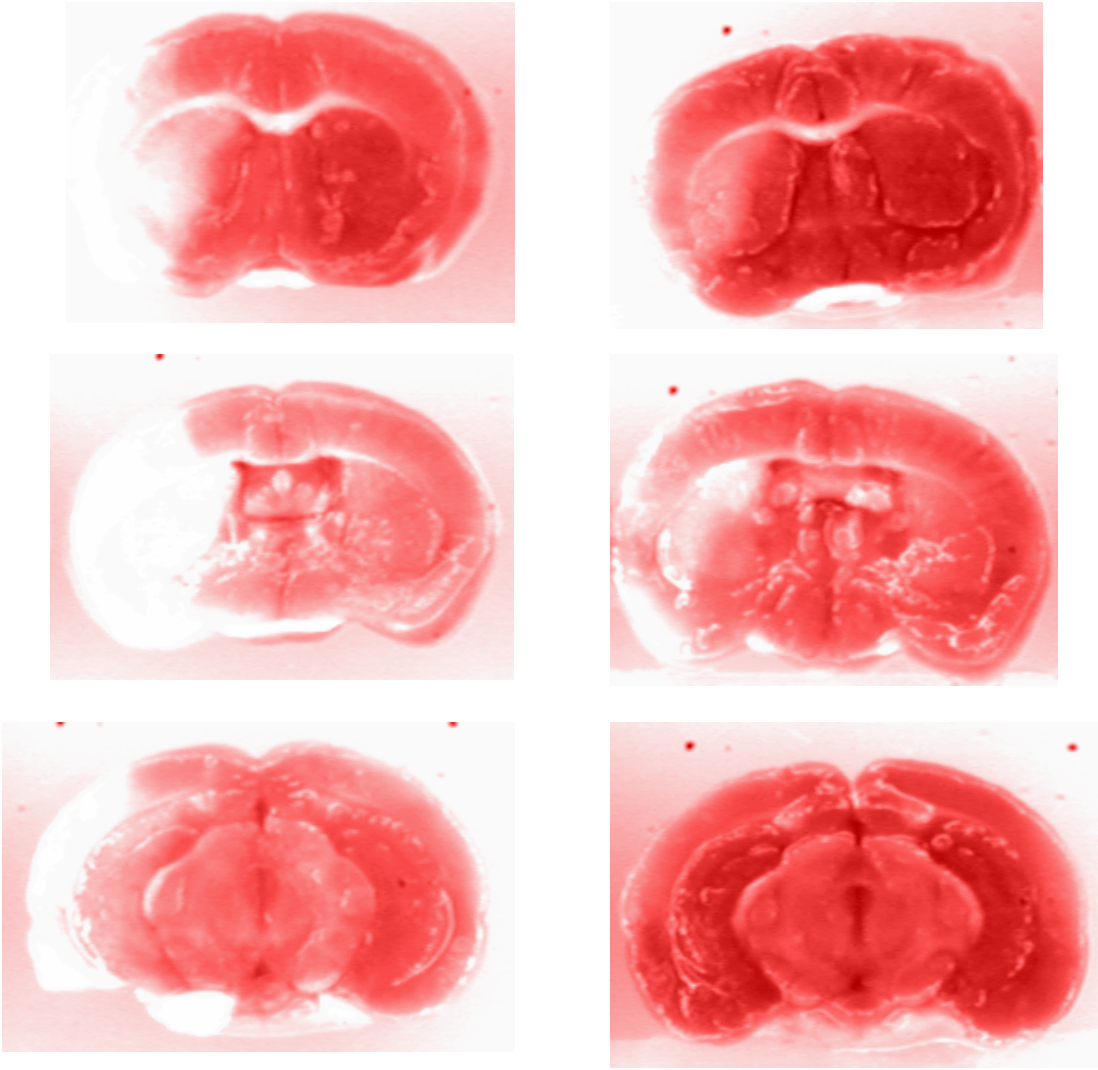
Nielsen *et al.*, *J Neurosci*, 1997
Nagelhus *et al.*, *J Neurosci*, 1998

AQP4—accelerated brain damage

Amiry-Moghaddam *et al.*,
Proc Natl Acad Sci 2003

Normal Mouse

Mutant Mouse

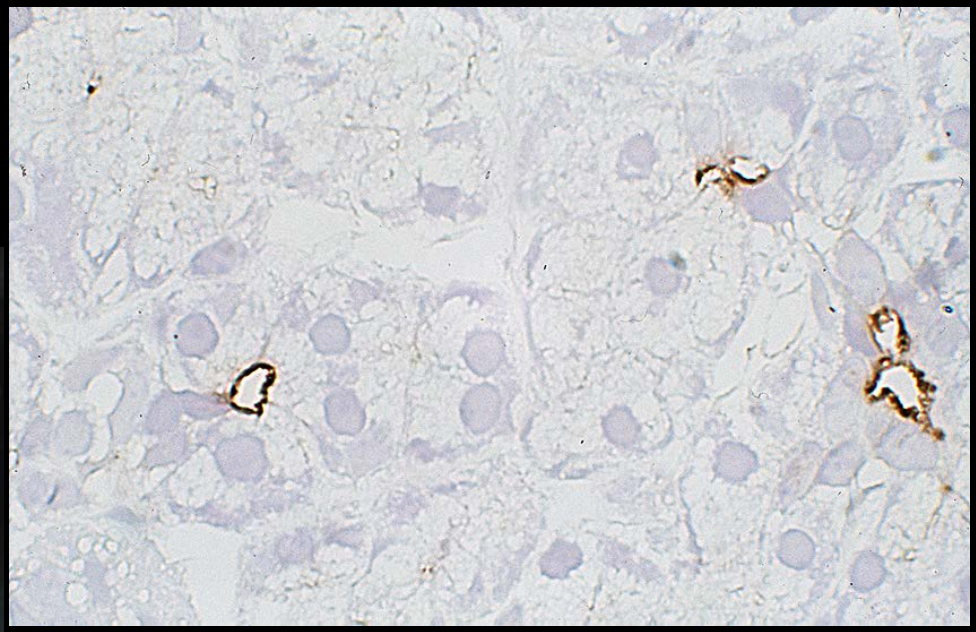


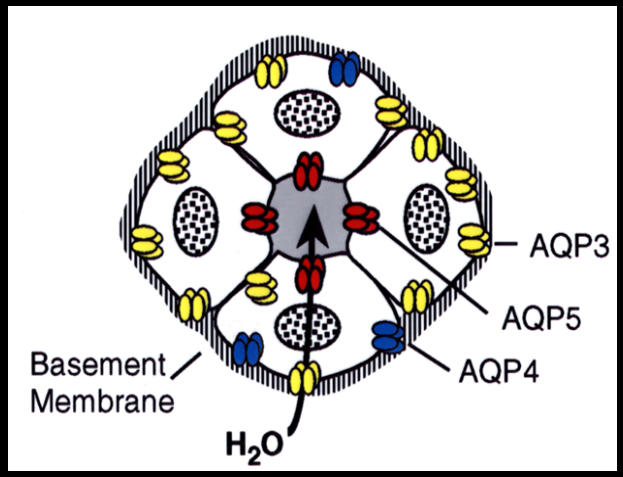
AQP5—Secretory glands

cDNA cloned from salivary gland
Lacrimal, submucosal, and
sweat glands

Type 1 pneumocytes

Raina *et al., J Biol Chem,* 1995

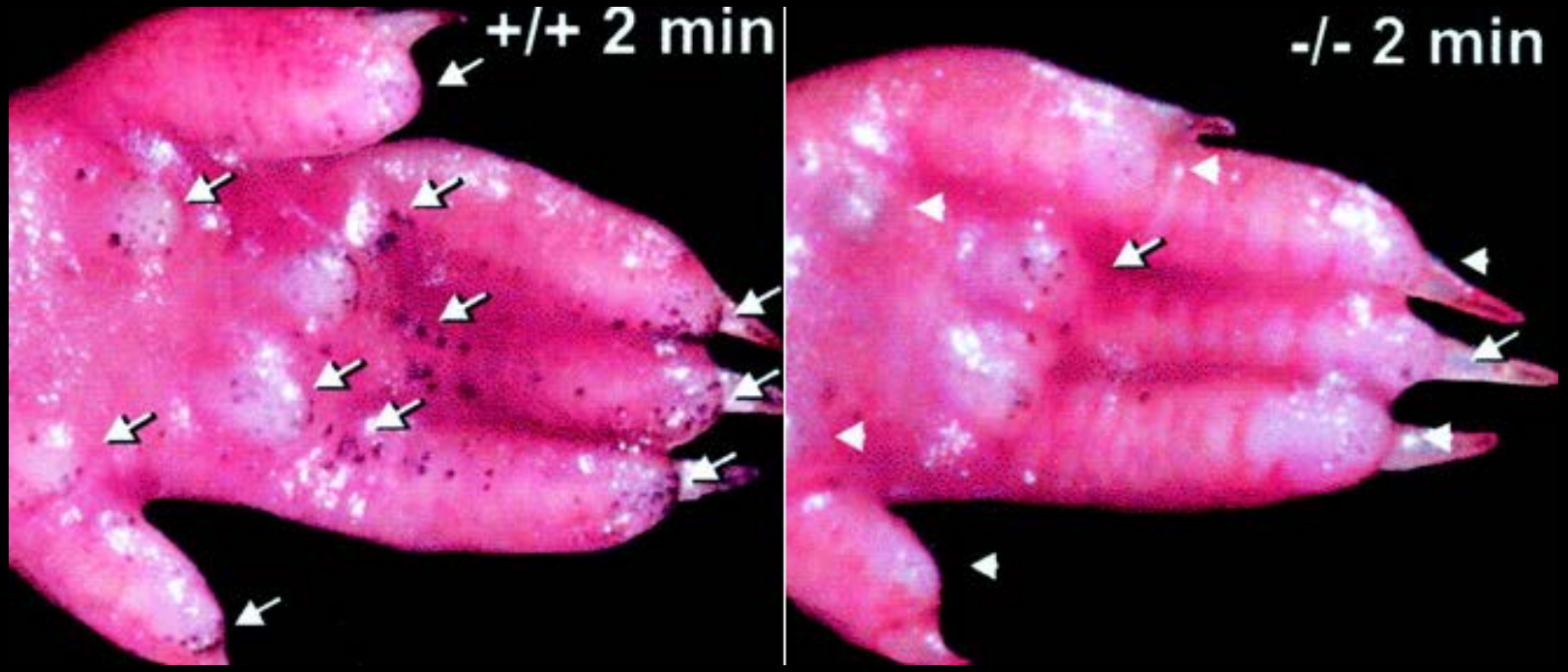




Nielsen *et al., Am J Physiol,* 1997

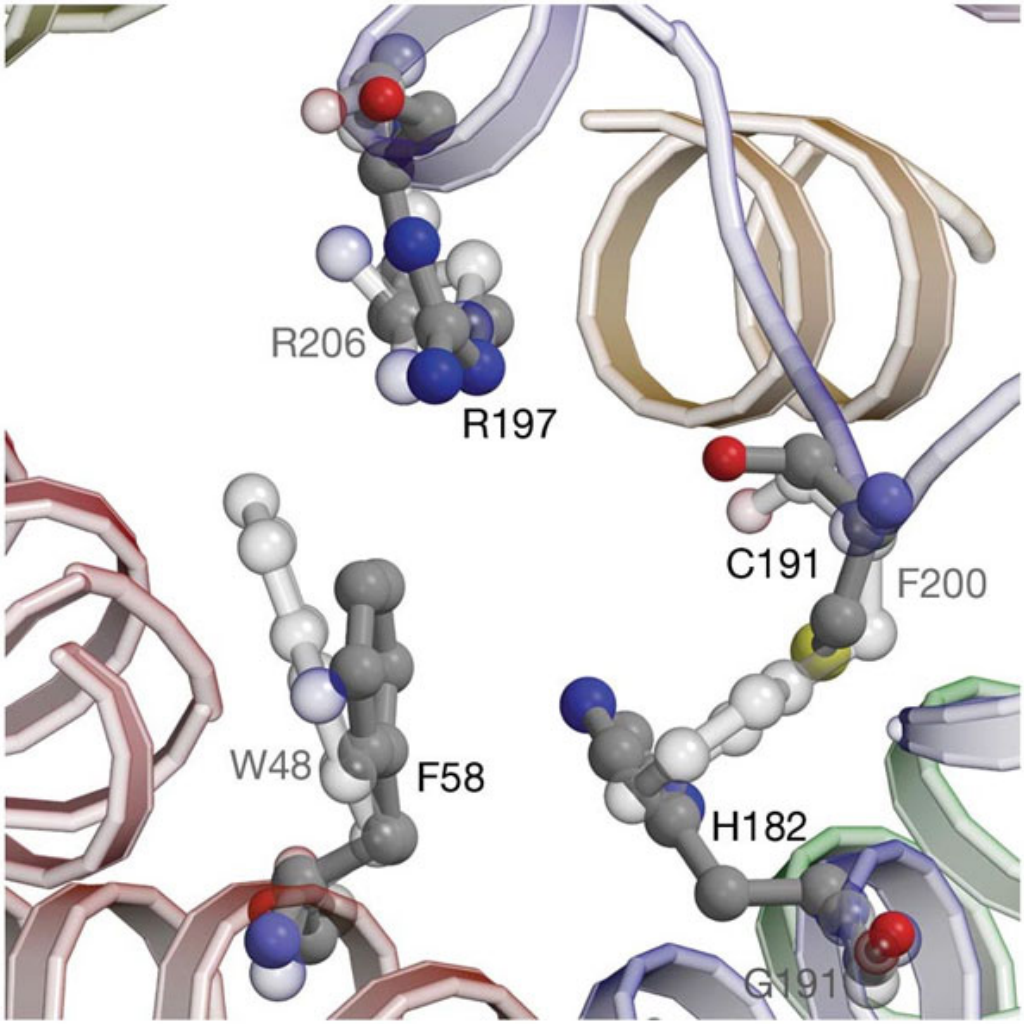
AQP5—Secretory glands

Pilocarpine induced sweat gland function—Wild type vs. AQP5 null mice



Nejsum *et al., Proc Natl Acad Sci,* 2002

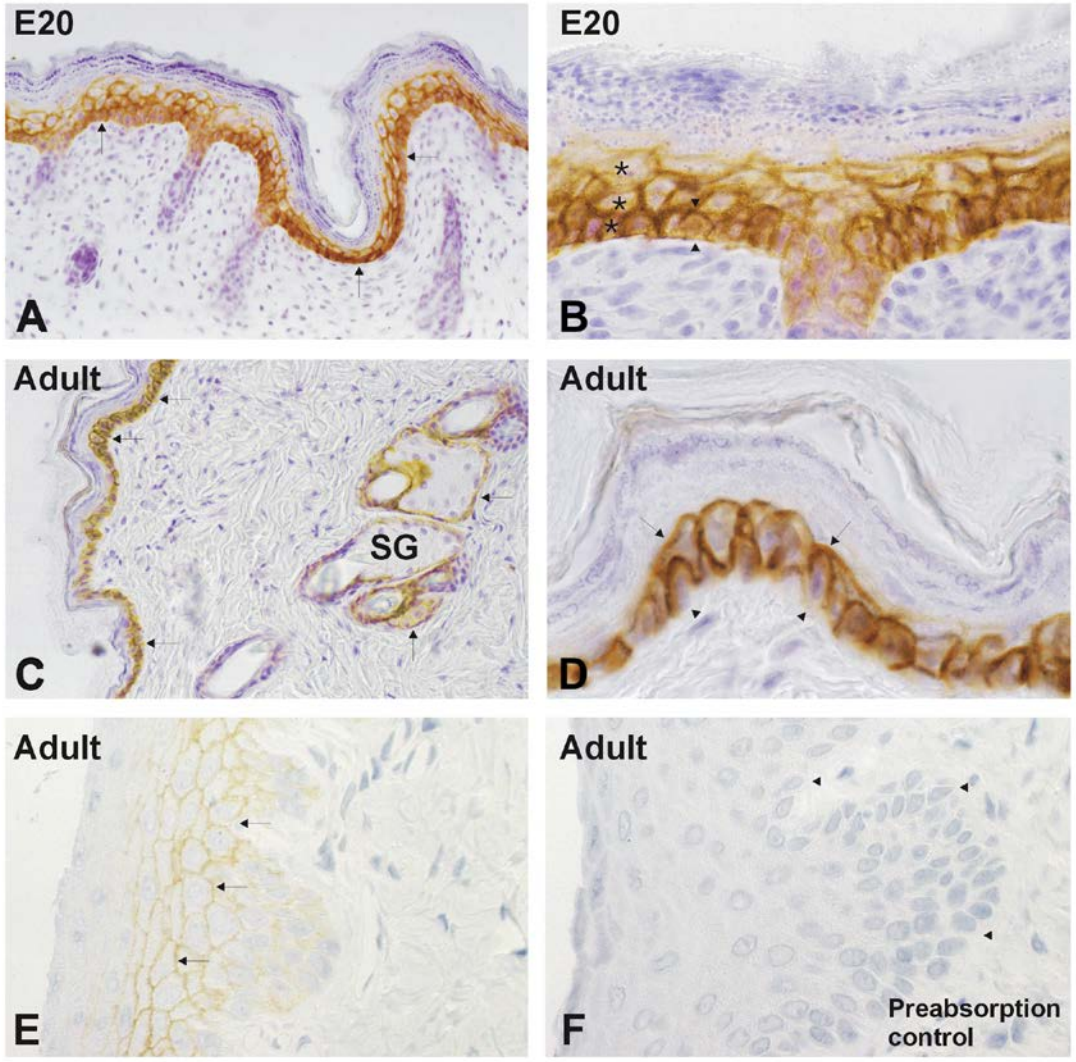
Pore diameters AQP1 vs GlpF



Sui *et al., Nature,* 2001

Aquaglyceroporin—AQP3 in skin

Expression in wound healing and aging



Johan Ågren,
unpublished

Jamais votre peau n'a été aussi belle.

HYDRACTION

La déshydratation se ressent mais surtout elle se voit : teint terne, ridules de déshydratation,...
Pour en finir, Dior crée HYDRACTION, un soin hydratant* innovant aux résultats spectaculaires !

Hydratation Profonde : irriguée** grâce à la technologie Aquaporine exclusive, votre peau retrouve un confort extrême et longue durée.

Hydratation Visible : désaltérée grâce au complexe Aquacapt™, votre peau renaît, belle et pulpeuse.

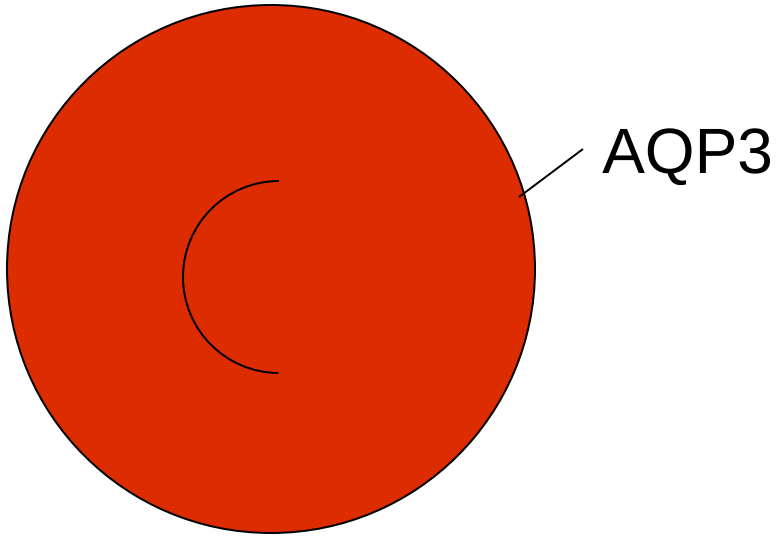
Des résultats spectaculaires :

71% des femmes se trouvent plus belles après application d'HYDRACTION***

Les travaux liés à l'exceptionnelle découverte du rôle des aquaporines en général ont été récompensés par le Prix Nobel de Chimie en 2003.

Aquaglyceroporin—AQP3 in red cells

Pathway for glycerol transport
Site of high frequency GIL antigen
AQP3-null humans

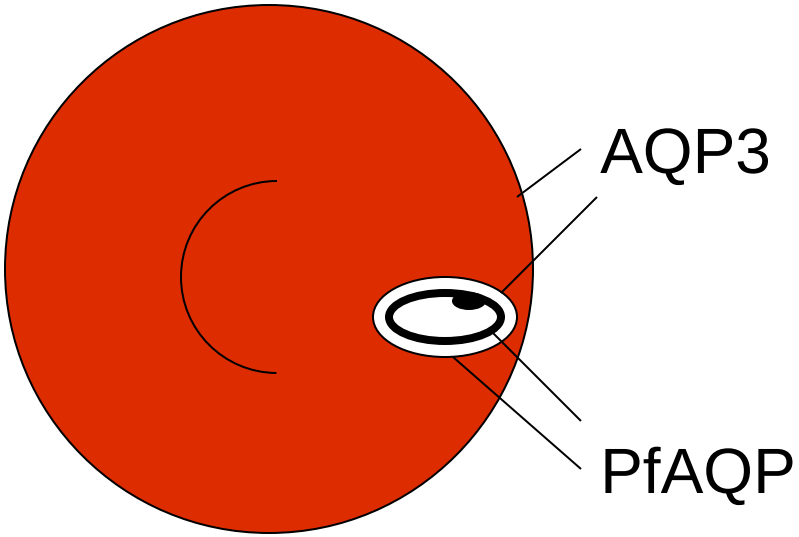


Roudier *et al., J Biol Chem,* 2002a,b

Aquaglyceroporin in *Plasmodium falciparum*

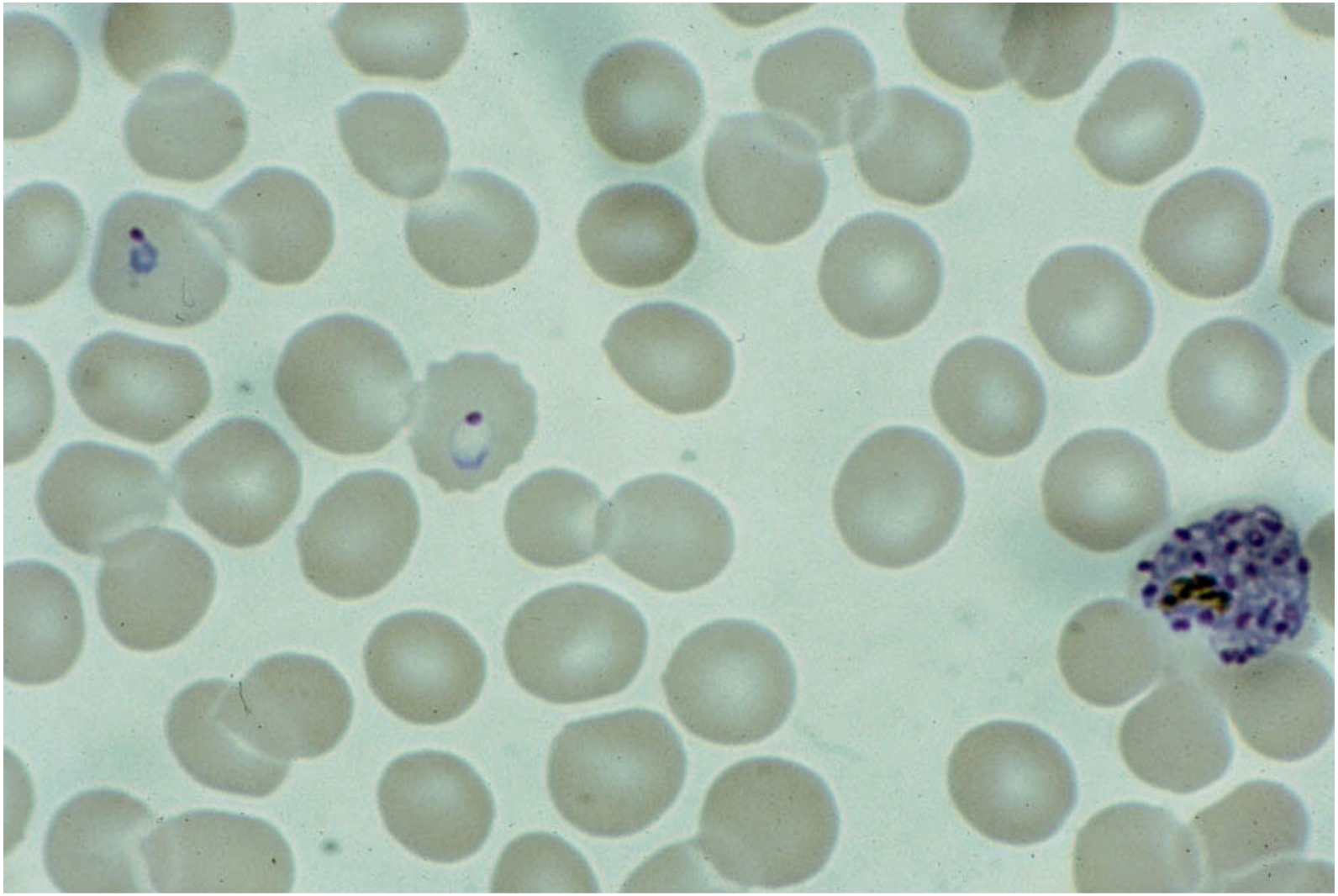
Pathway for glycerol transport

PM, PVM, PPM

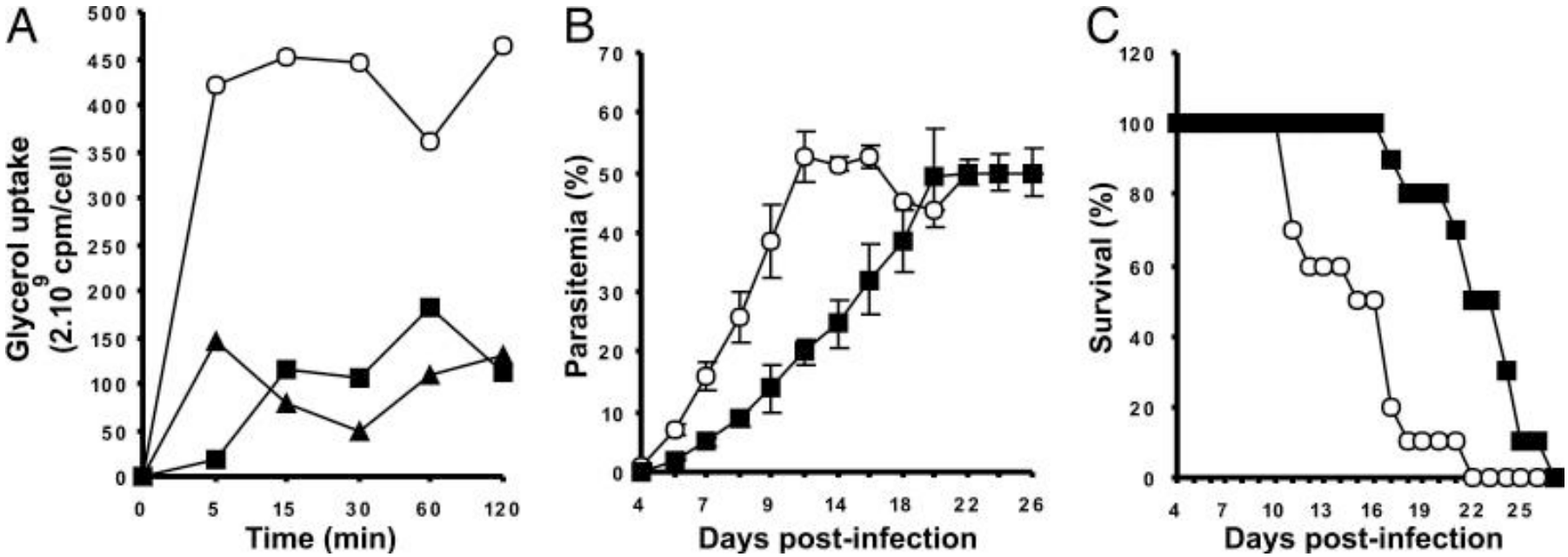


Hansen *et al., J Biol Chem,* 2002
Promeneur *et al., Proc Natl Acad Sci,* 2007

Plasmodium falciparum



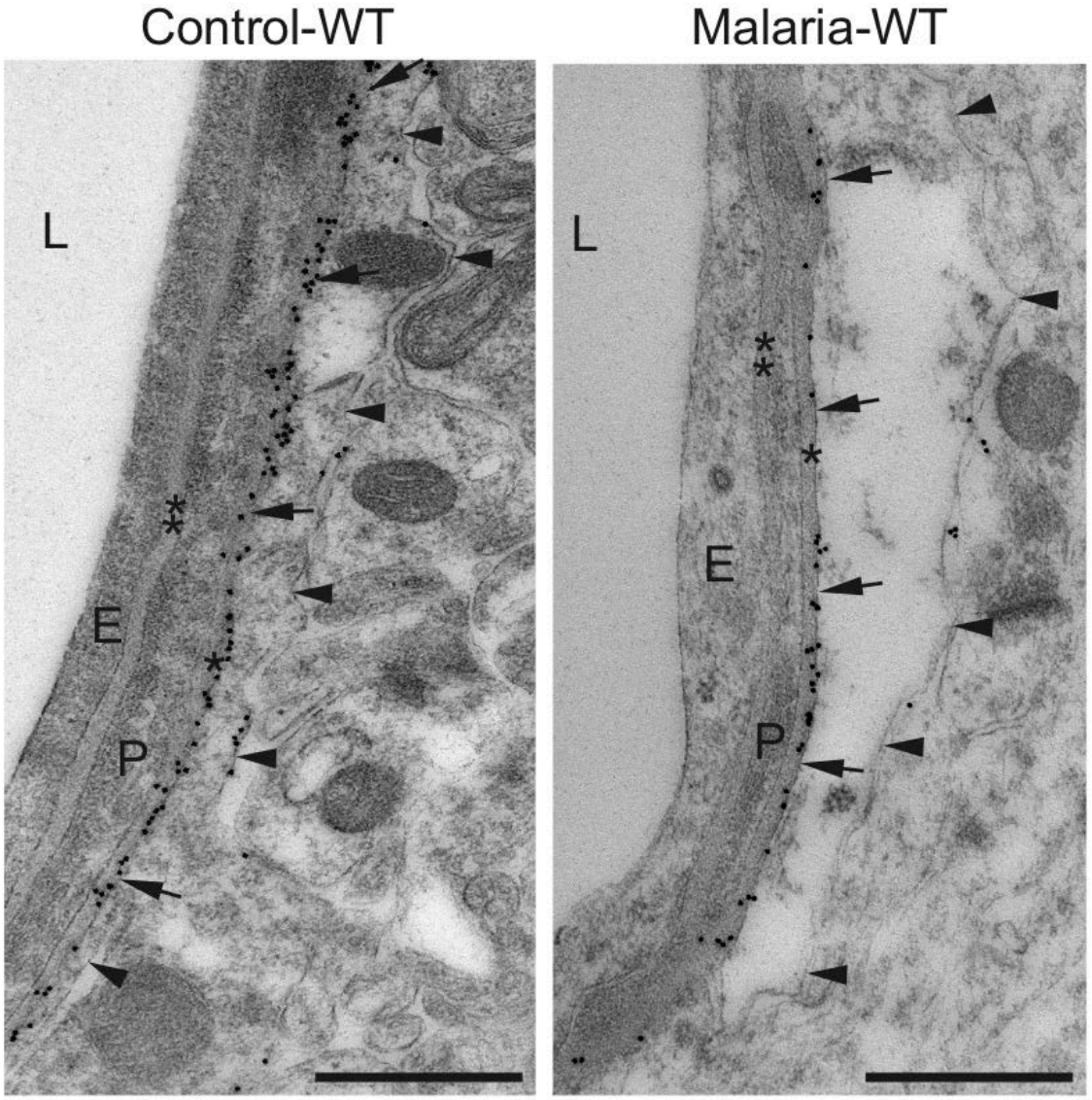
Aquaglyceroporin PbAQP increases malaria virulence



Promeneur *et al., Proc Natl Acad Sci,* 2007


SOCCER
12
ROLL MODE

Aquaporin-4 in murine cerebral malaria



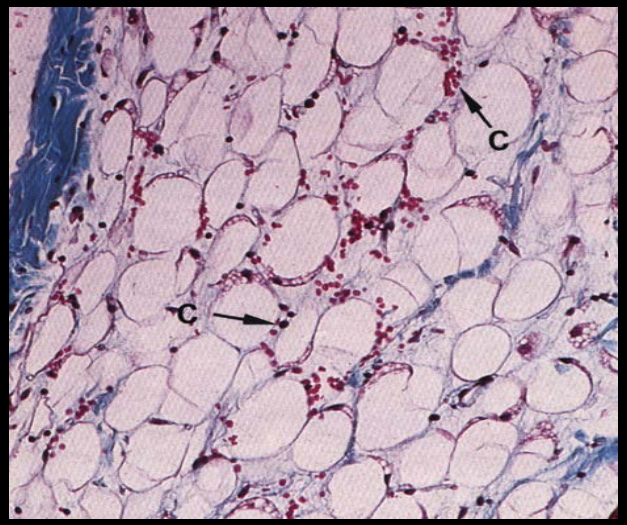
Promeneur *et al., Proc Natl Acad Sci,* 2013

Anopheles gambiae

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



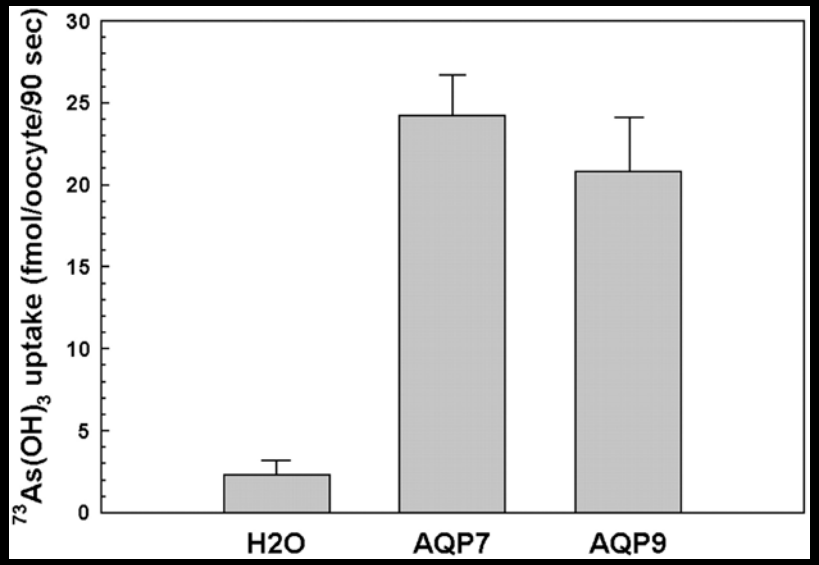
Kishida *et al., J Biol Chem,* 2000
Kuriyama *et al., Diabetes,* 2002

Starvation—AQP7 release
AQP9 facilitate

AQP7 and 9—Heavy metal transport

(with Barry Rosen, Wayne State)

Arsenite—transported by AQP7 and by AQP9.

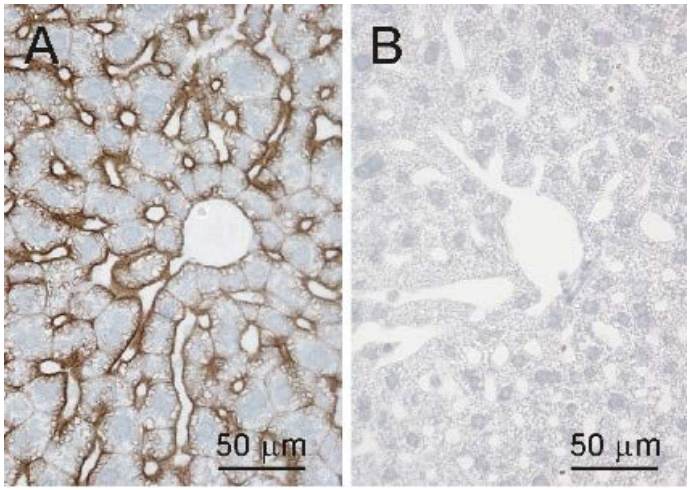


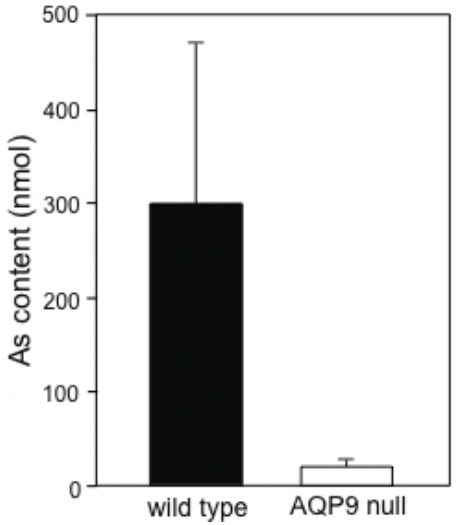
Liu *et al., Proc Natl Acad Sci,* 2002

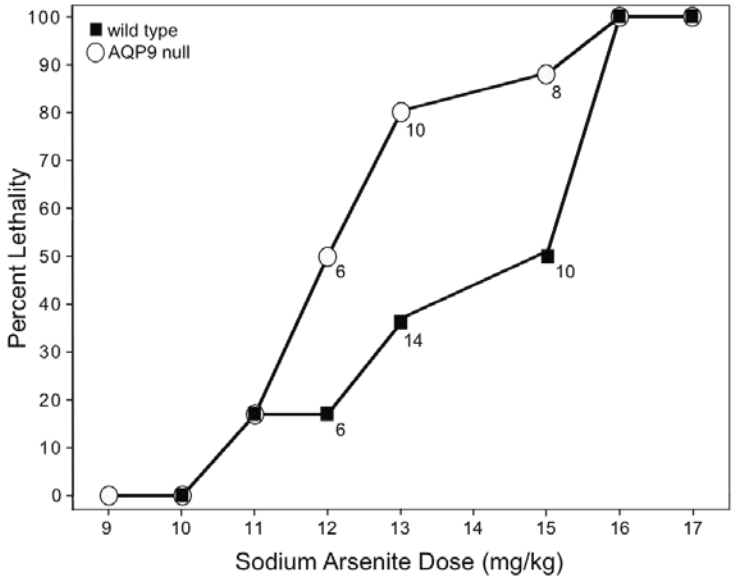
$As(OH)_3$ uncharged at pH 7.

Predictor of epidemic arsenic poisoning hepatotoxicity?

Arsenic toxicity in aquaglyceroporin-9 null mice







Carbrey *et al., Proc Natl Acad Sci,* 2009

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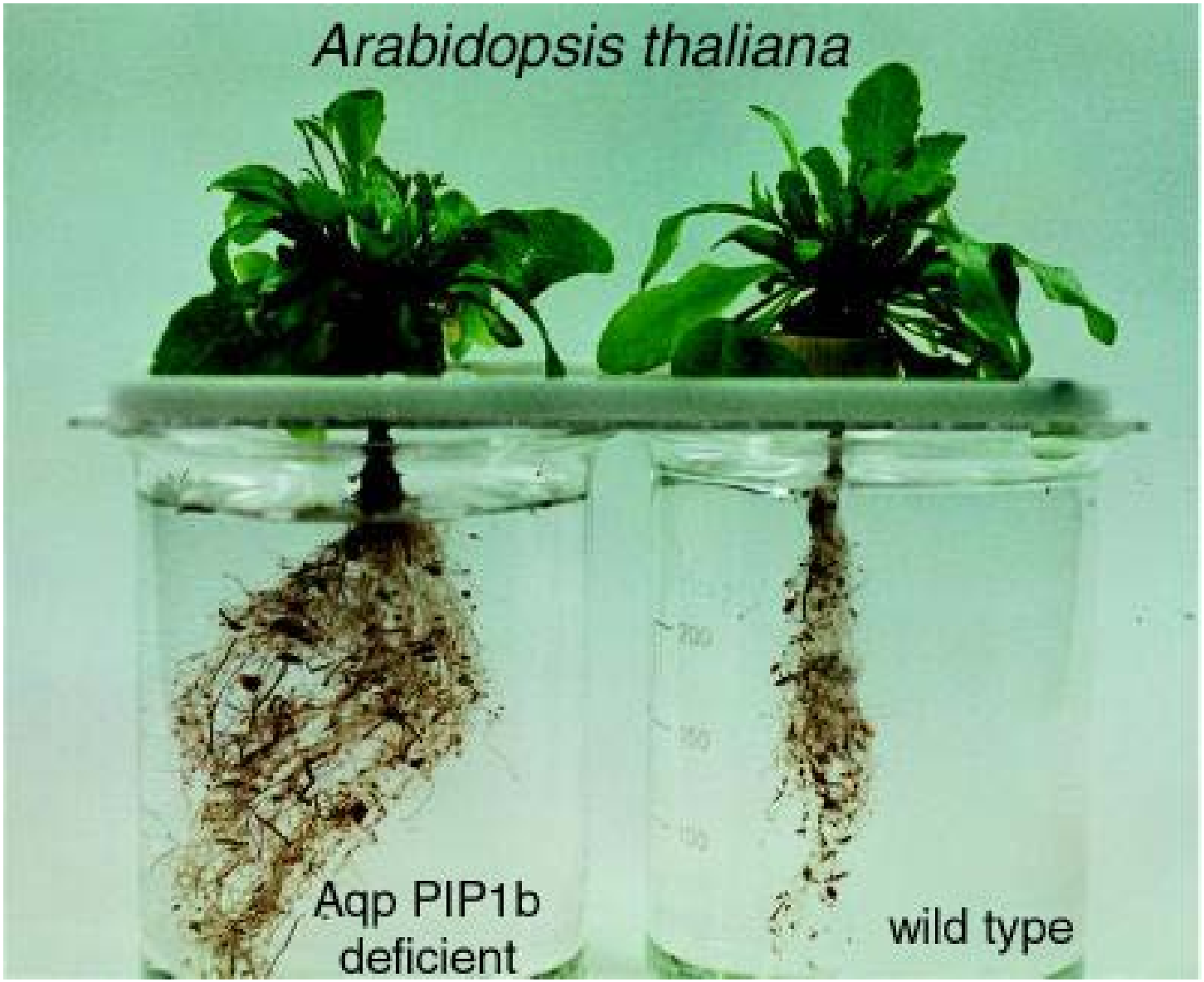


Kaldenhof *et al., Plant J* 1998

Aquaporin water channels

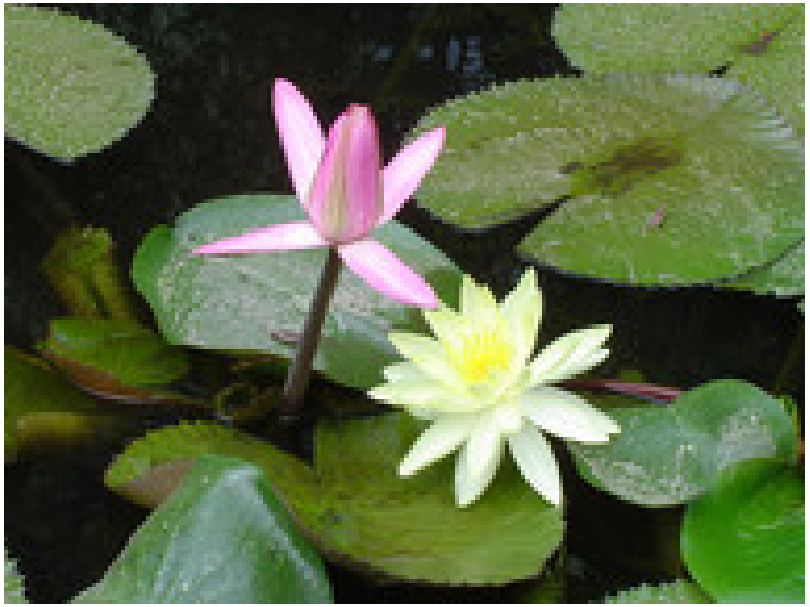
Freely permeated by H_2O, not H_3O^+

Certain homologs permeated by
glycerol, nitrate, or arsenite

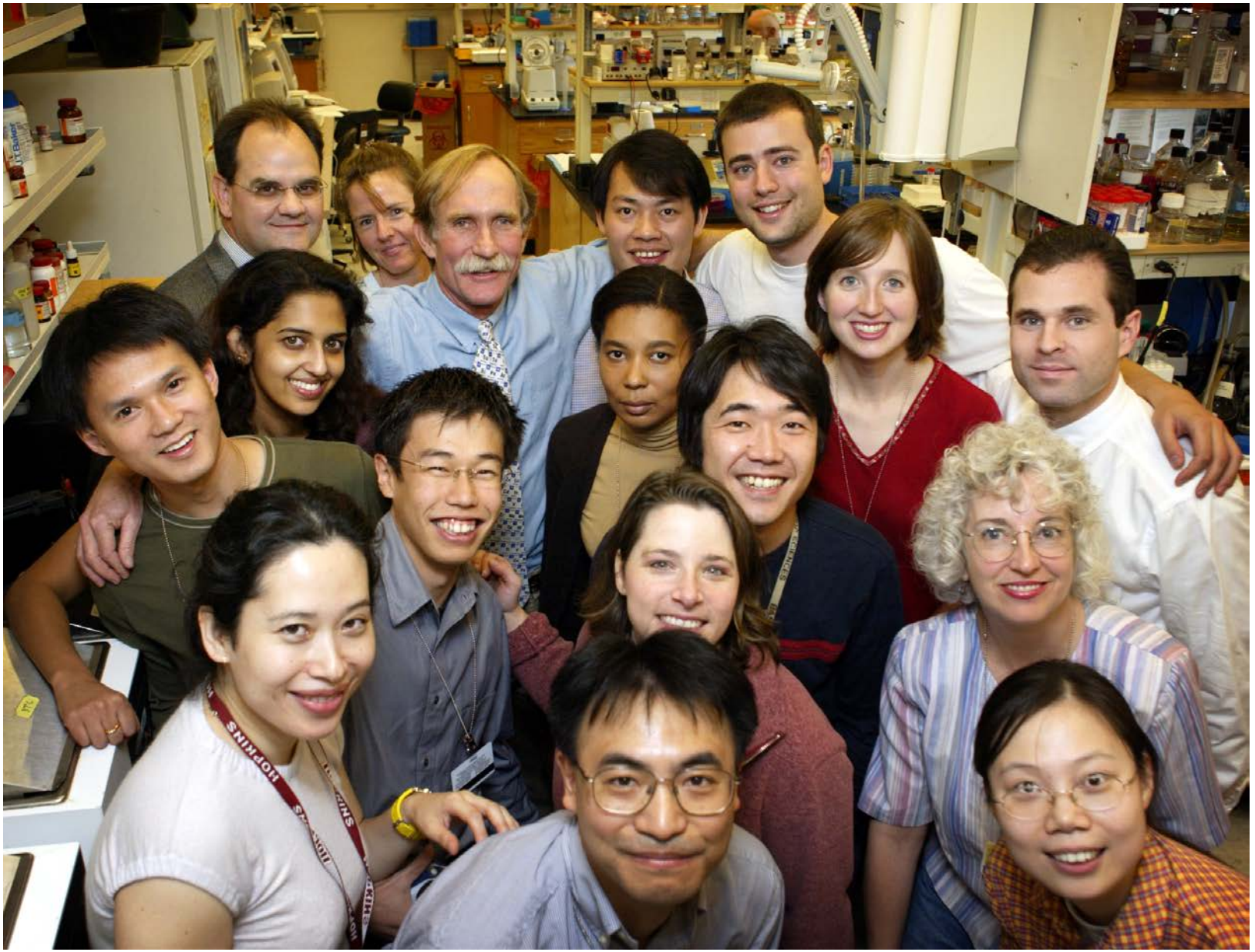
Structural models explain functions

Implicated in multiple clinical disorders
- Renal-vascular diseases
- Loss of vision
- Brain injury and edema
- Hyperthermia
- Starvation and obesity
- Malaria and infectious diseases
- Arsenic toxicity

Expressed throughout nature



8 October 2003




WELLS
Discount
LIQUORS
PARKING
CONGRATS
DR AGRE

10 December 2003

Nobel Prize Inspiration Initiative

In partnership with AstraZeneca

Presents

Professor Peter Agre

2003 Nobel Laureate in Chemistry

Aquaporin Water Channels: From Atomic Structure to Clinical Medicine

Wednesday 26 June 2013,
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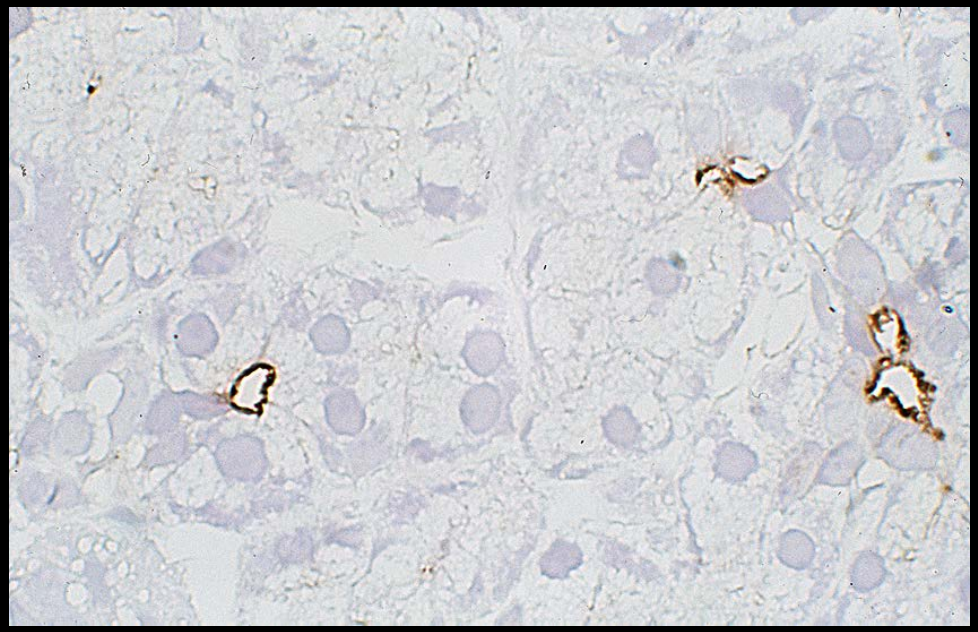
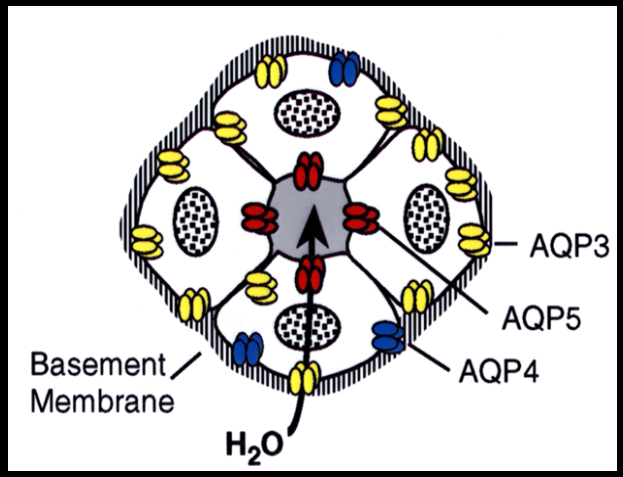
St Petersburg State Medical University

AQP5—Secretory glands

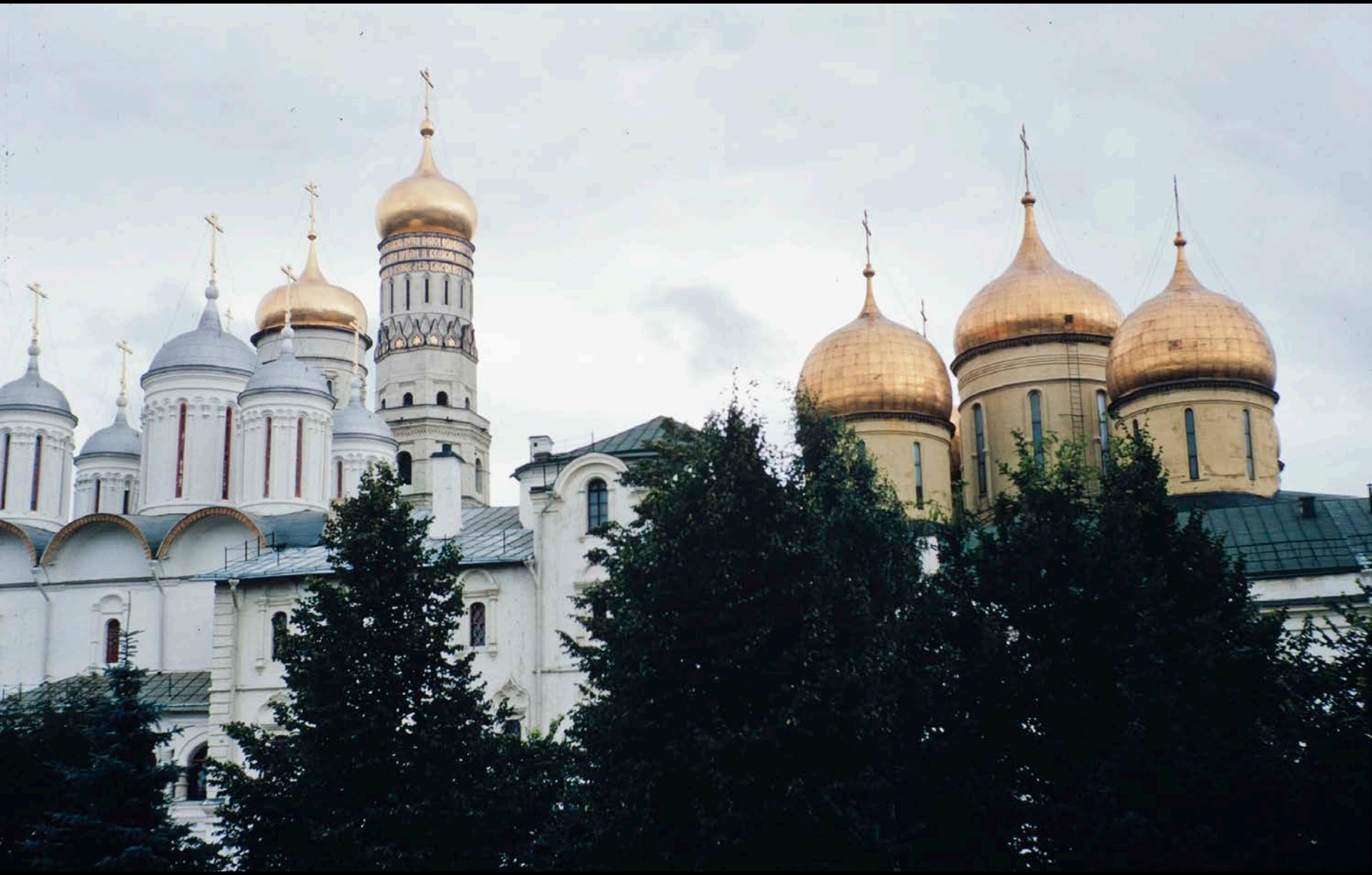
cDNA cloned from salivary gland
Lacrimal, submucosal, and
sweat glands

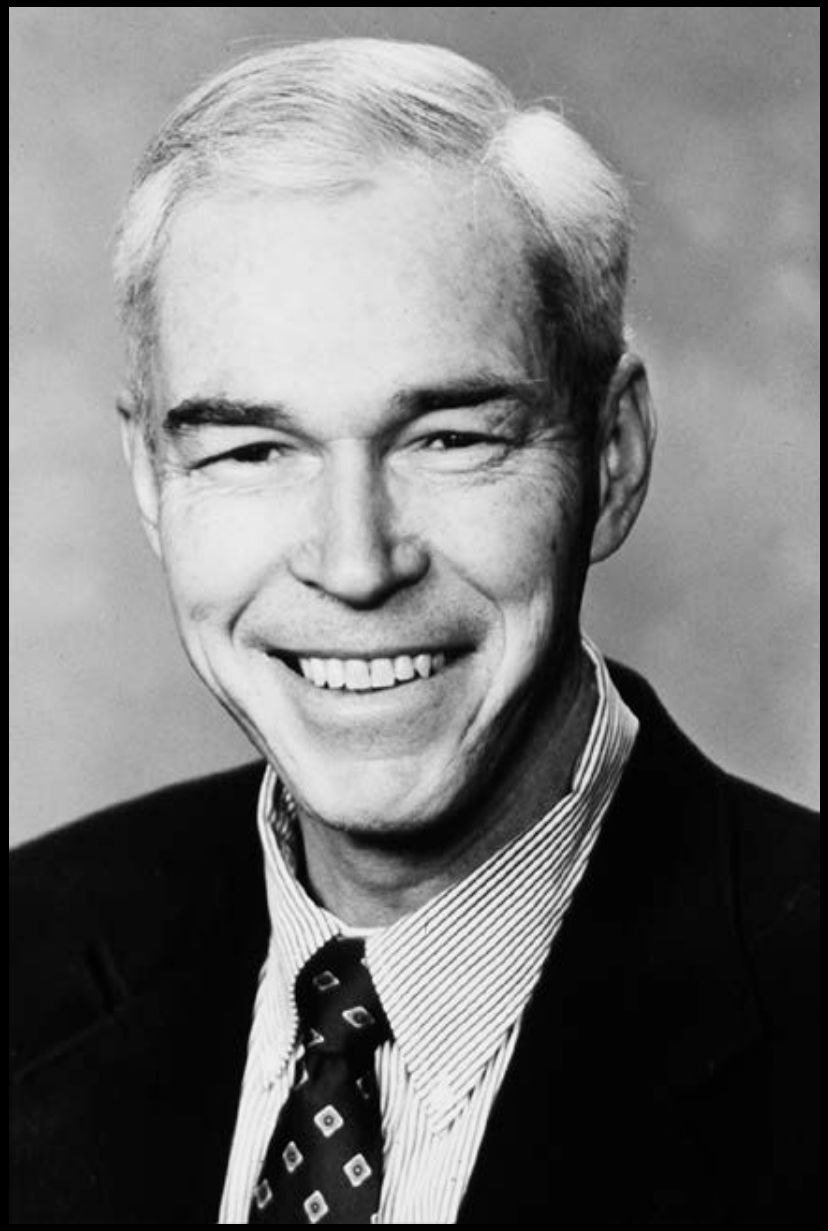




Raina *et al., J Biol Chem,* 1995

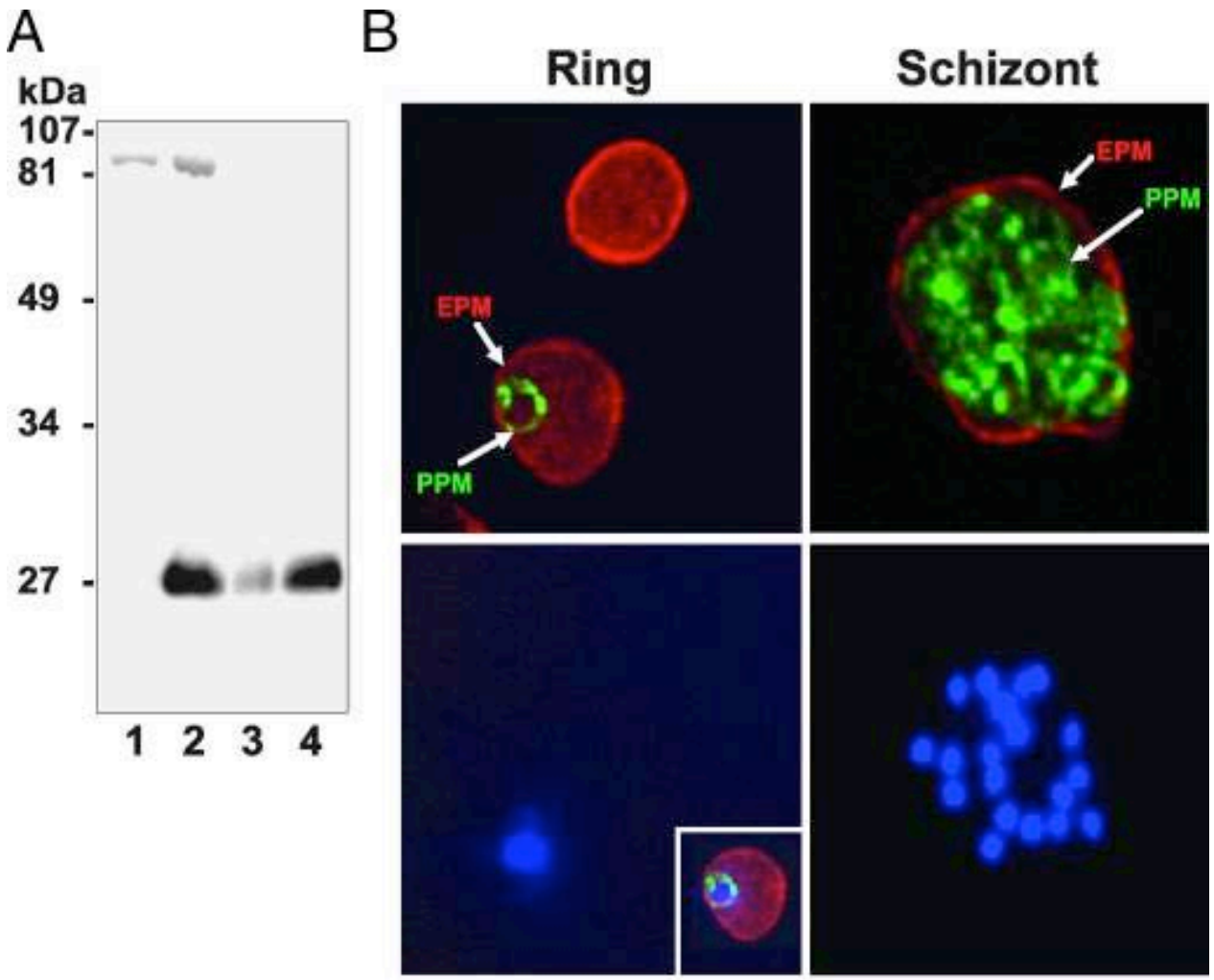
Nielsen *et al., Am J Physiol,* 1997





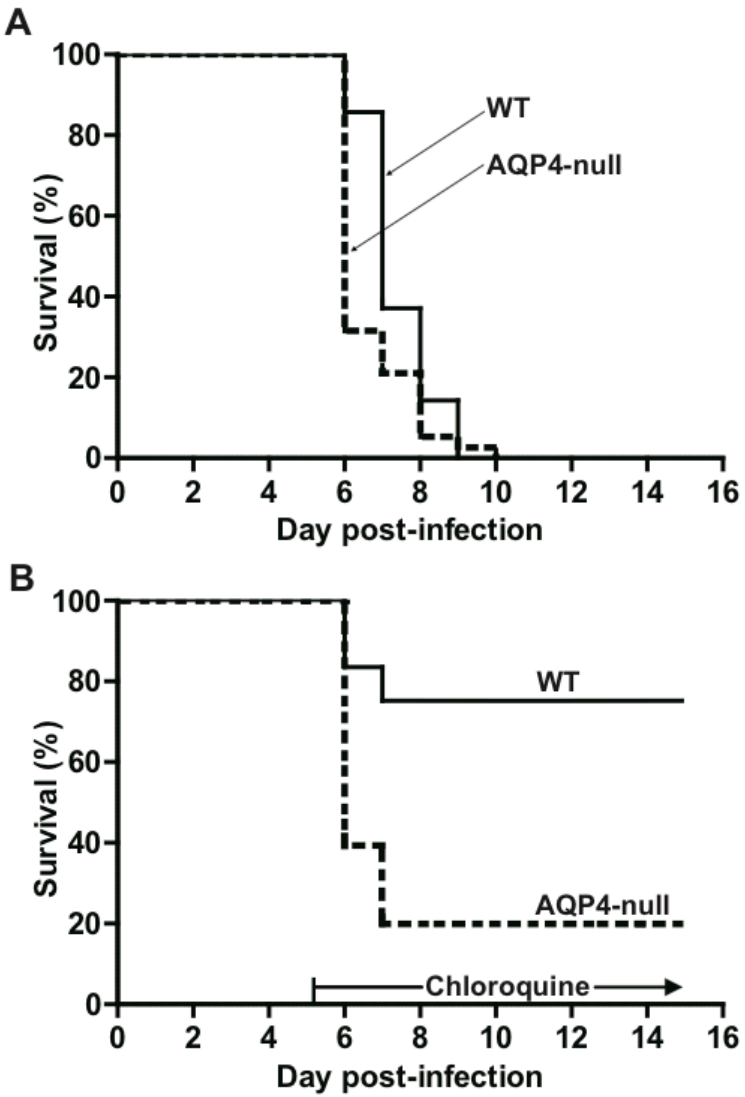
John C. Parker, M.D. 1935-1993

Aquaglyceroporin PbAQP increases malaria virulence



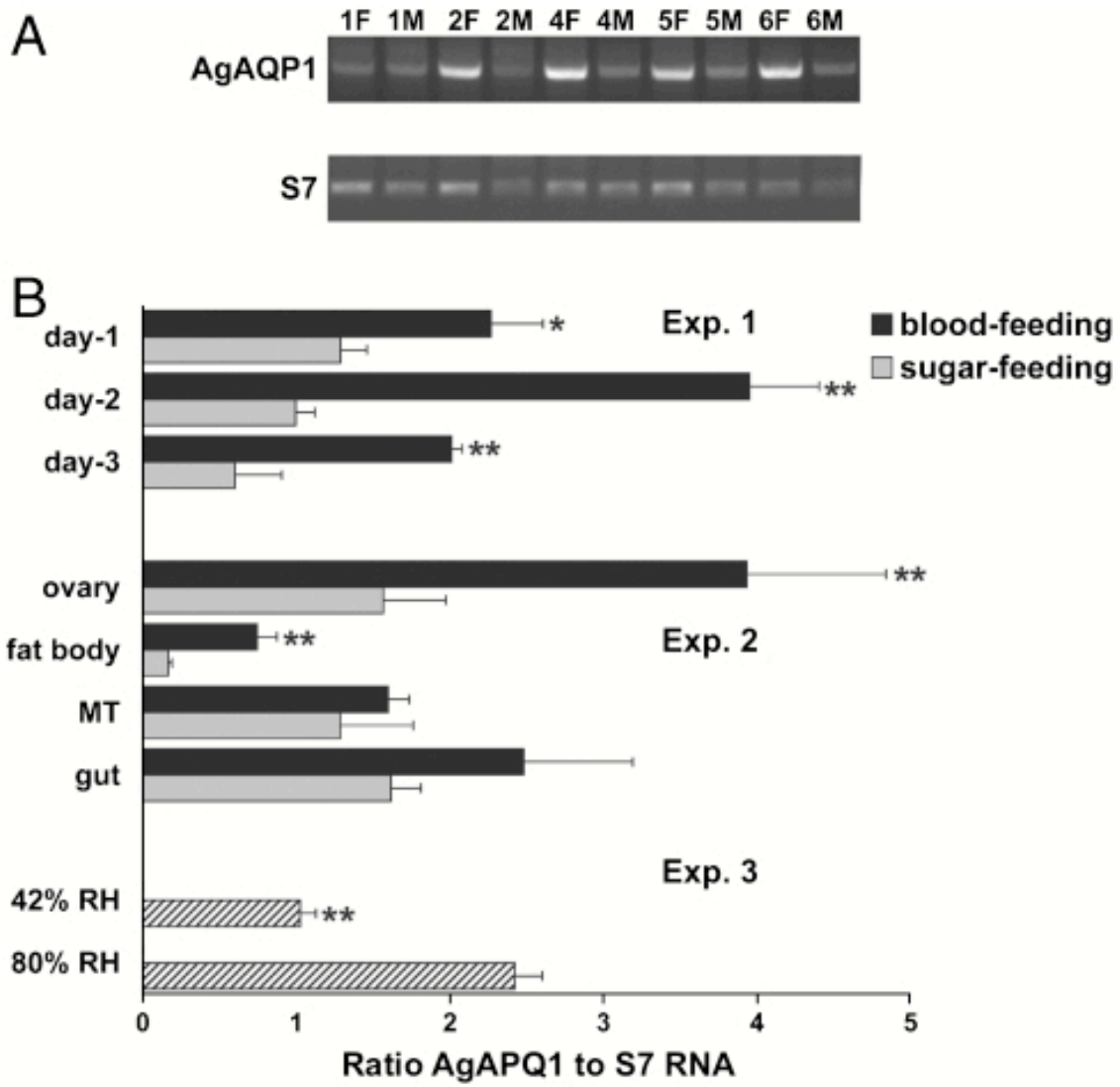
Promeneur *et al., Proc Natl Acad Sci,* 2007

Aquaporin-4 in murine cerebral malaria



Promeneur *et al., Proc Natl Acad Sci,* 2013

AgAQP1 – blood feeding and humidity

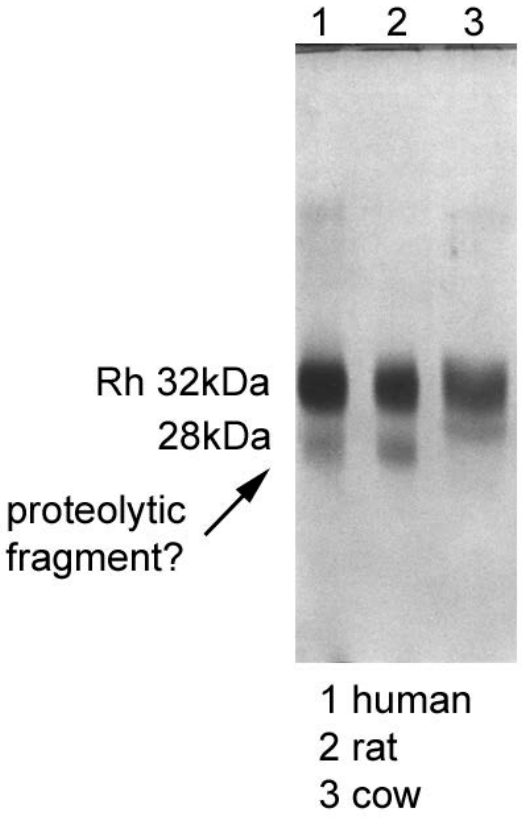


Liu *et al., Proc Natl Acad Sci,* 2011

Discovery of Aquaporin-1

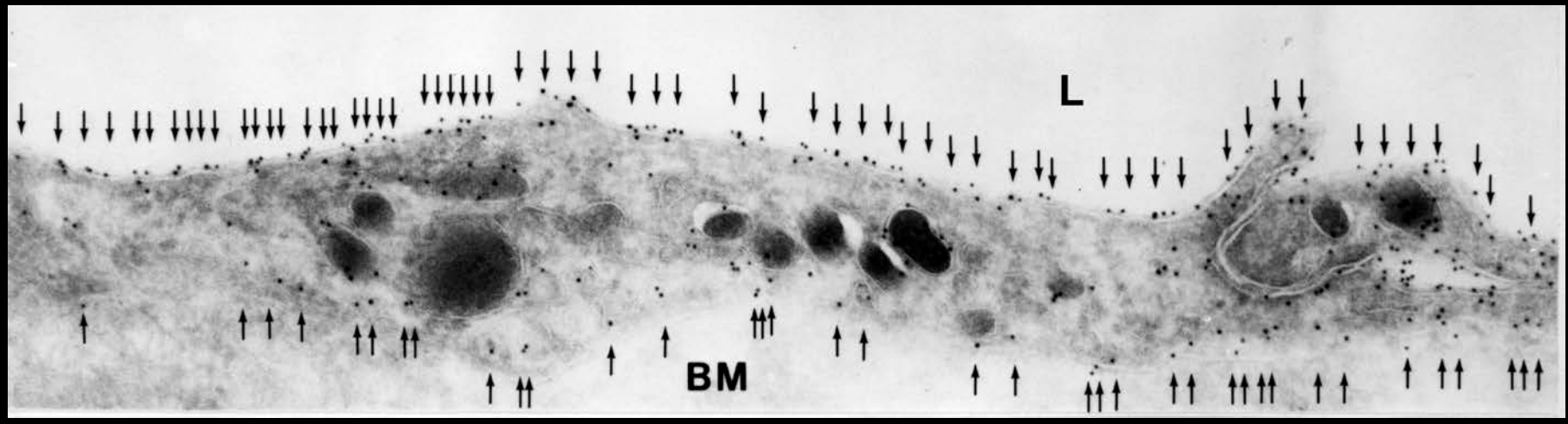
A serendipitous observation

Contaminant in 32 kDa
Rh preparations



Denker *et al., J Biol Chem,* 1988

AQP1 in human capillary endothelium

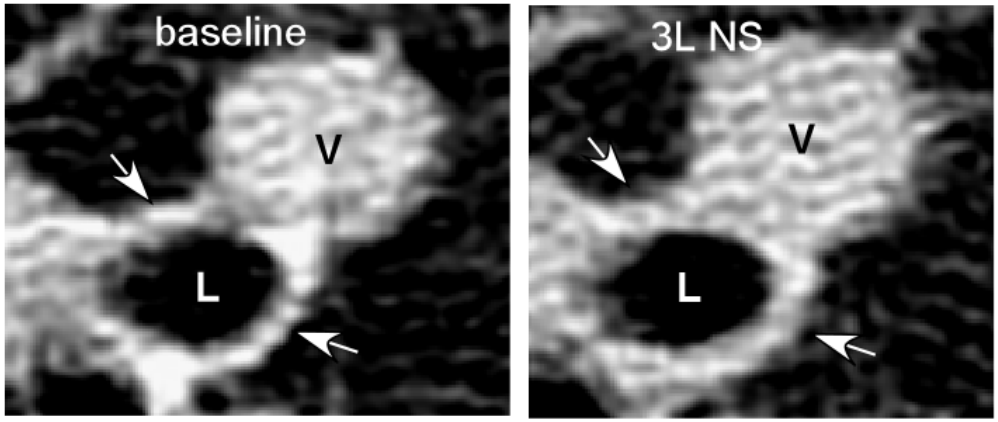


King *et al., Proc Natl Acad Sci,* 2002

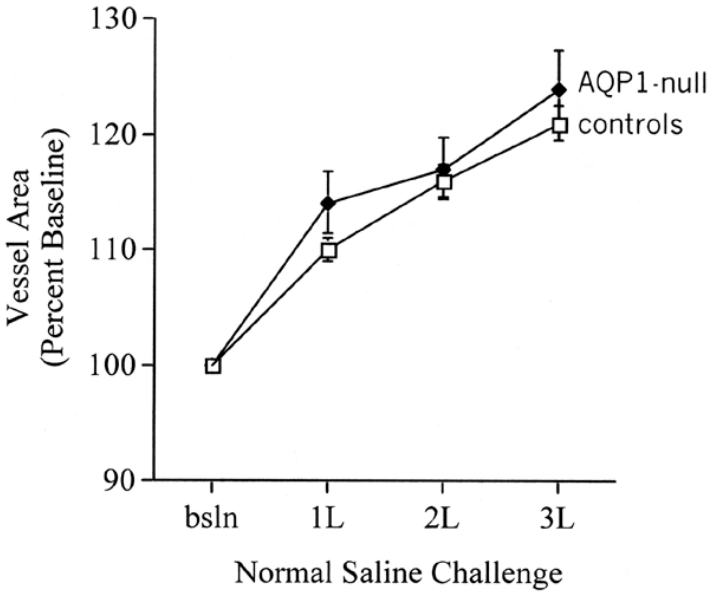
AQP1 null humans

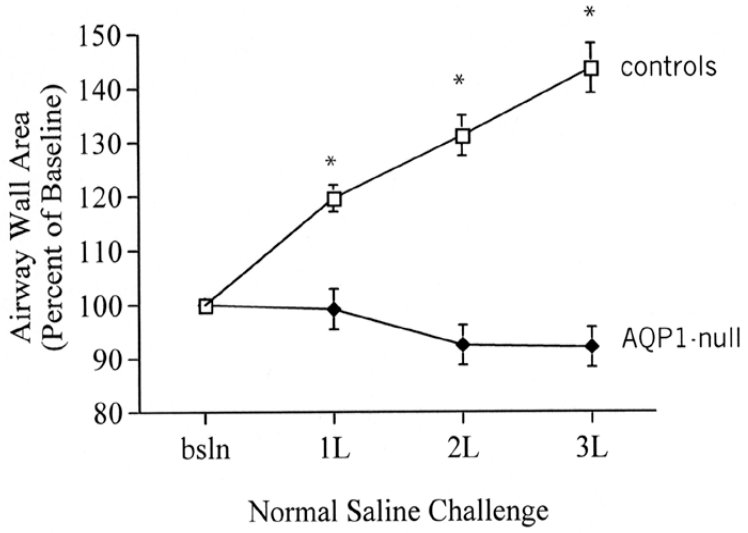
Pulmonary capillary defect

Johns Hopkins Hospital inpatient study
Baseline—High resolution CT scan of lung
Rapid—Saline infusion, 3 x 1 liter
Repeat—HRCT scans after each liter
Measure—Bronchiolar (1-5 mm) wall thickness



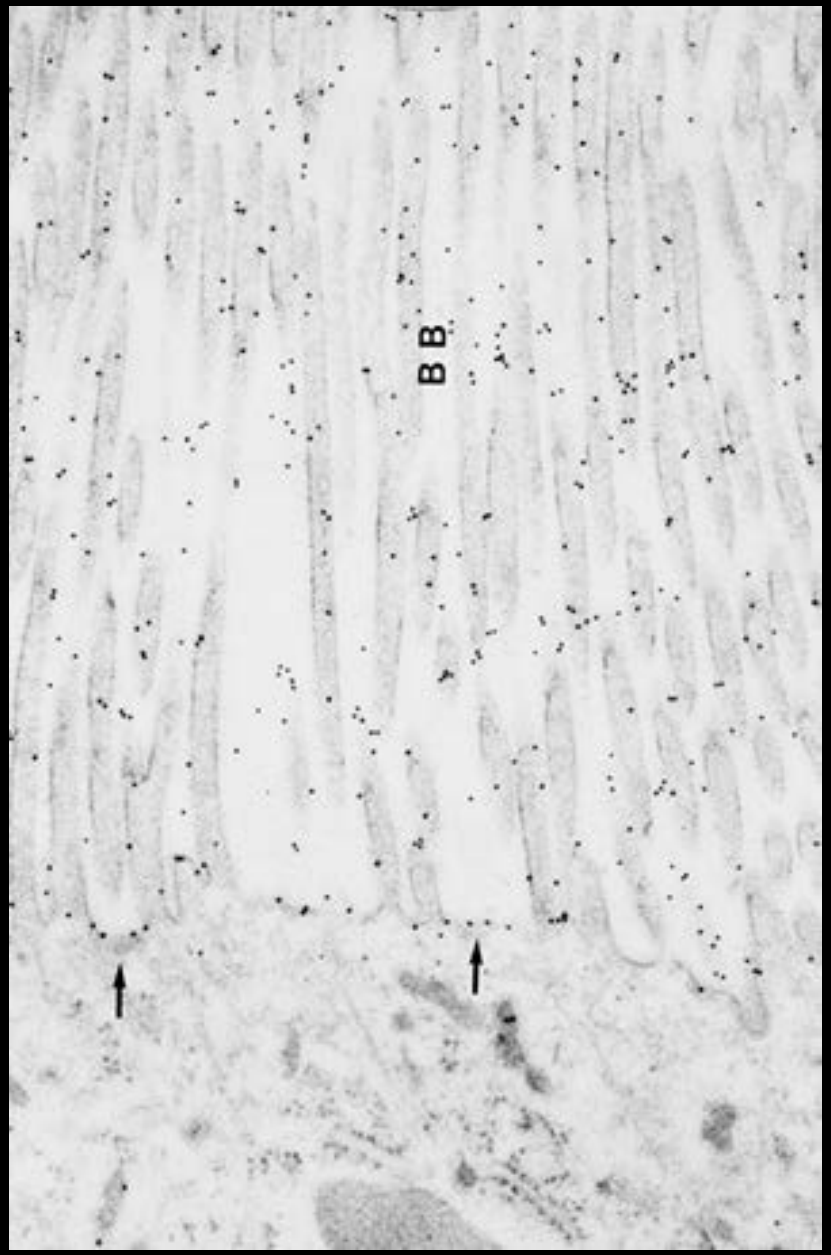
Dx—Decreased vascular water permeability





King *et al., Proc Natl Acad Sci,* 2002

AQP1 in proximal nephron



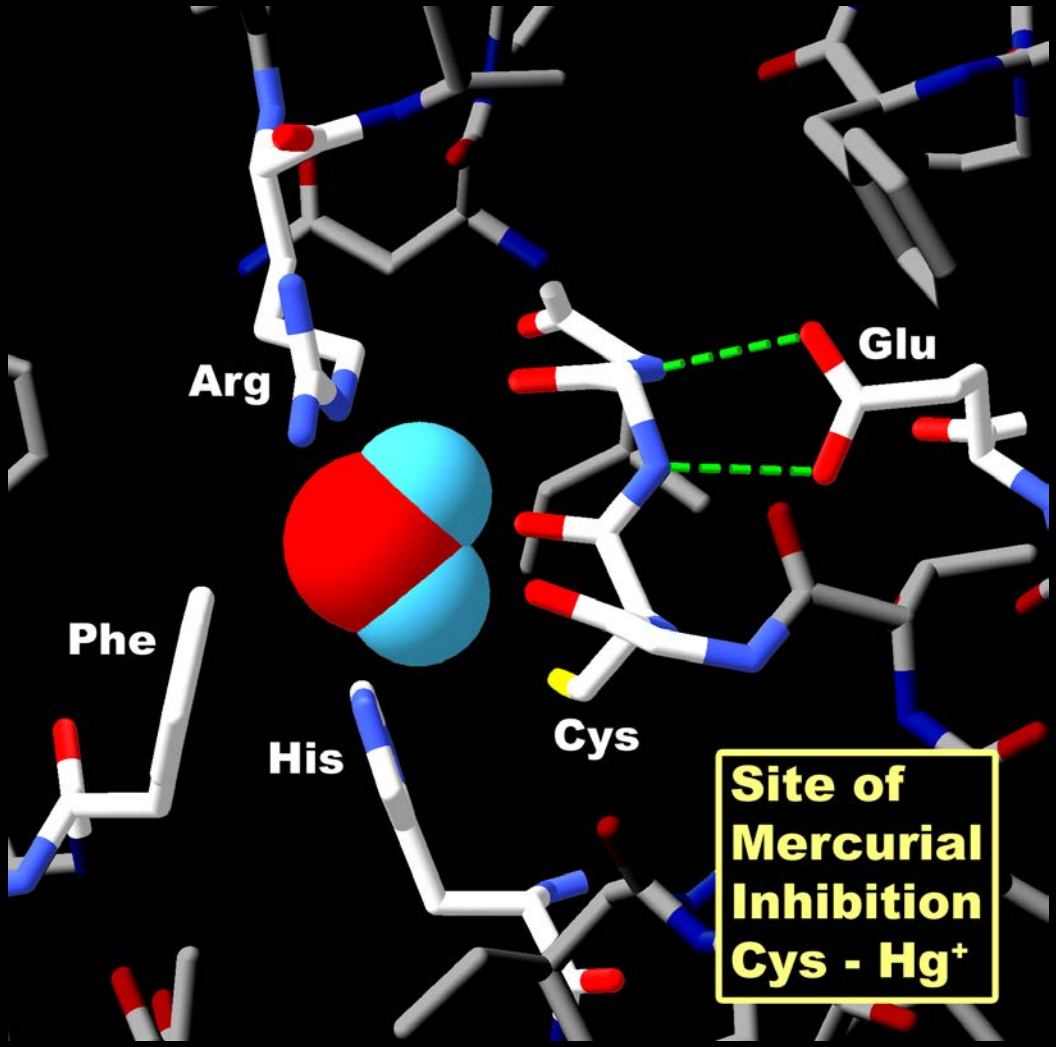
BB, apical brush border

arrows, endocytic invaginations

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

Structure of AQP1

Hg^{++} inhibitory site



Nobel Prize Inspiration Initiative

In partnership with AstraZeneca

Presents

Professor Peter Agre

2003 Nobel Laureate in Chemistry

Aquaporin Water Channels: From Atomic Structure to Clinical Medicine

Wednesday 26 June 2013,
10:00am – 11:20am

St Petersburg State Medical University