

22 March 2017

Padjadjaran University

Bandung, Indonesia

International Peace Foundation

Bridges Dialogue

Opening Doors Worldwide through Medical Science

Peter Agre, M.D.

Bloomberg Distinguished Professor

Director, Johns Hopkins Malaria Res Inst

Bloomberg School of Public Health

Baltimore, Maryland



World Views of United States Science

Country	U.S. in general		U.S. science & technol	
	Favorable	Unfavorable	Favorable	Unfavorable
Morocco	11%	88	90	08
Saudi Arabia	04	94	48	51
Jordan	15	78	83	13
Lebanon	20	69	52	46
UAE	14	73	84	12

From: Arab Views toward America, Zogby 2004

Science Diplomacy in the 21st Century

1. Scientific upbringing
2. Science as an international career
3. Science and human rights
4. Science diplomacy visits



Ancestral home in Gaaserud, Norway



Court Agre in his lab, 1950



Linus Pauling, Ph.D.
Physical Chemist
California Inst
Technology



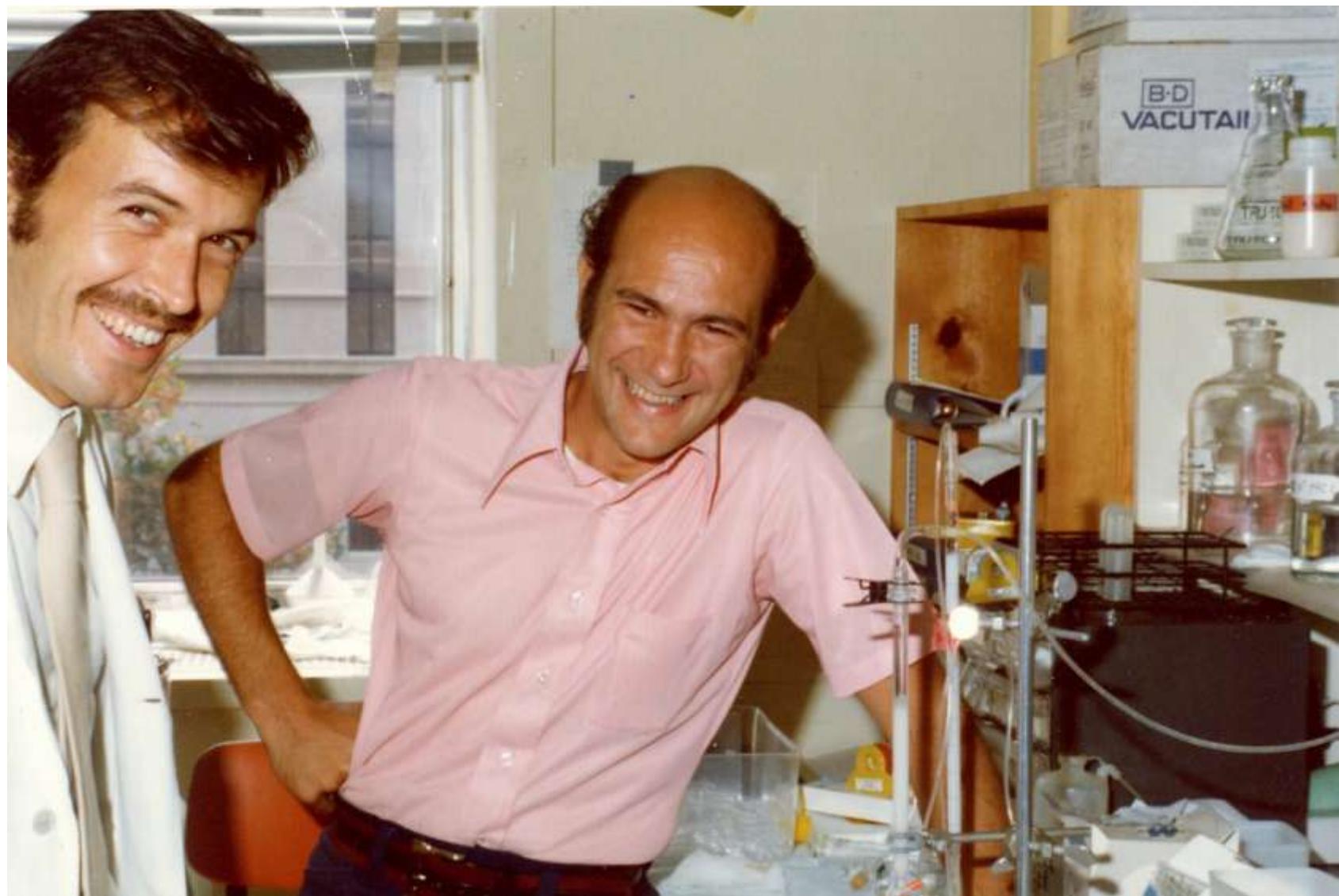
Linus Pauling

White House, 1962
Leading nuclear testing protest

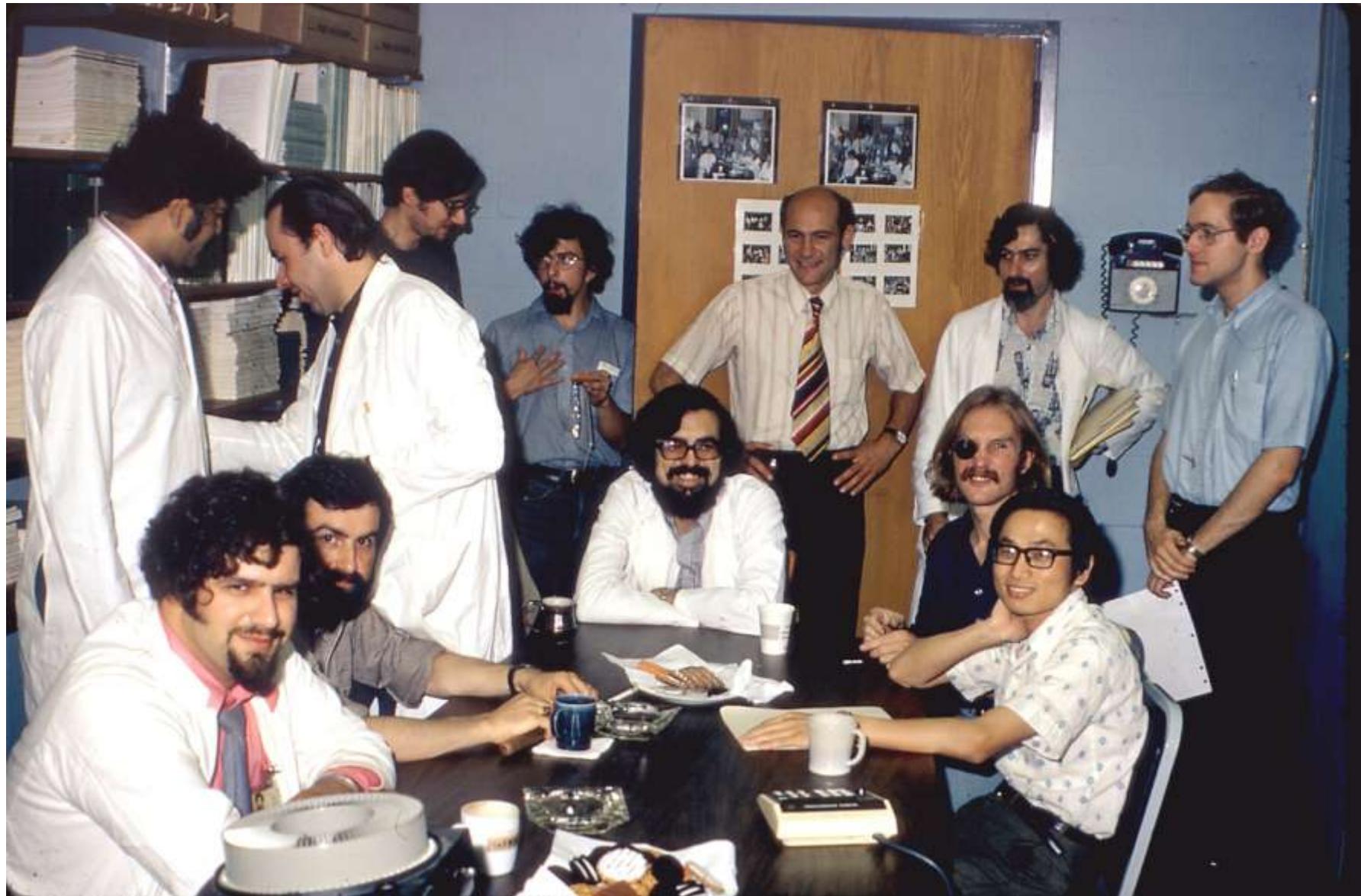
1954 Nobel Prize in Chemistry
1962 Nobel Peace Prize



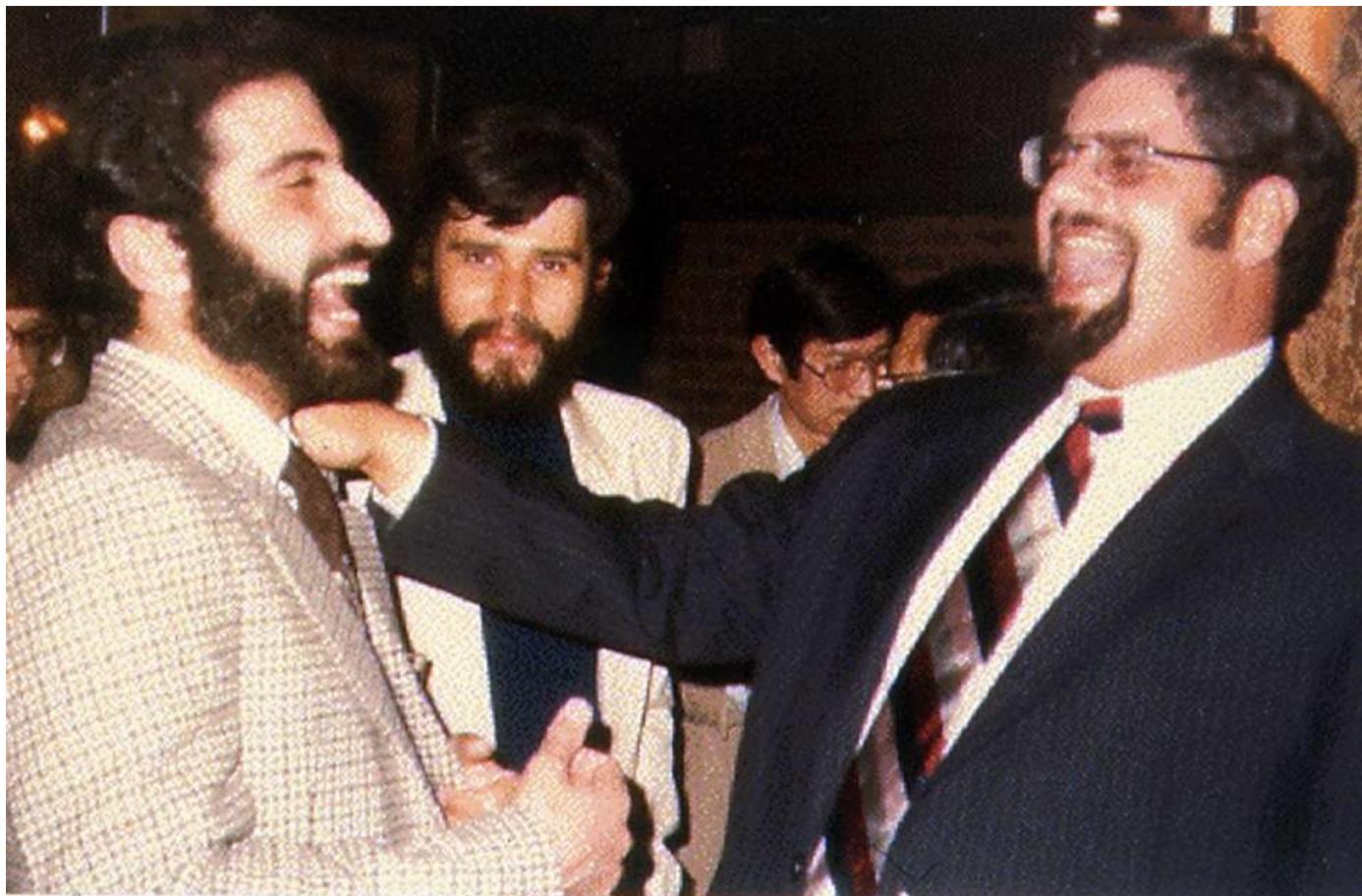
en route to Johns Hopkins, 1970



Gianfredo and Pedro



Cuatrecasas Lab, 1974



Naji and Marvin

Science Diplomacy in the 21st Century

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2. Science as an international career
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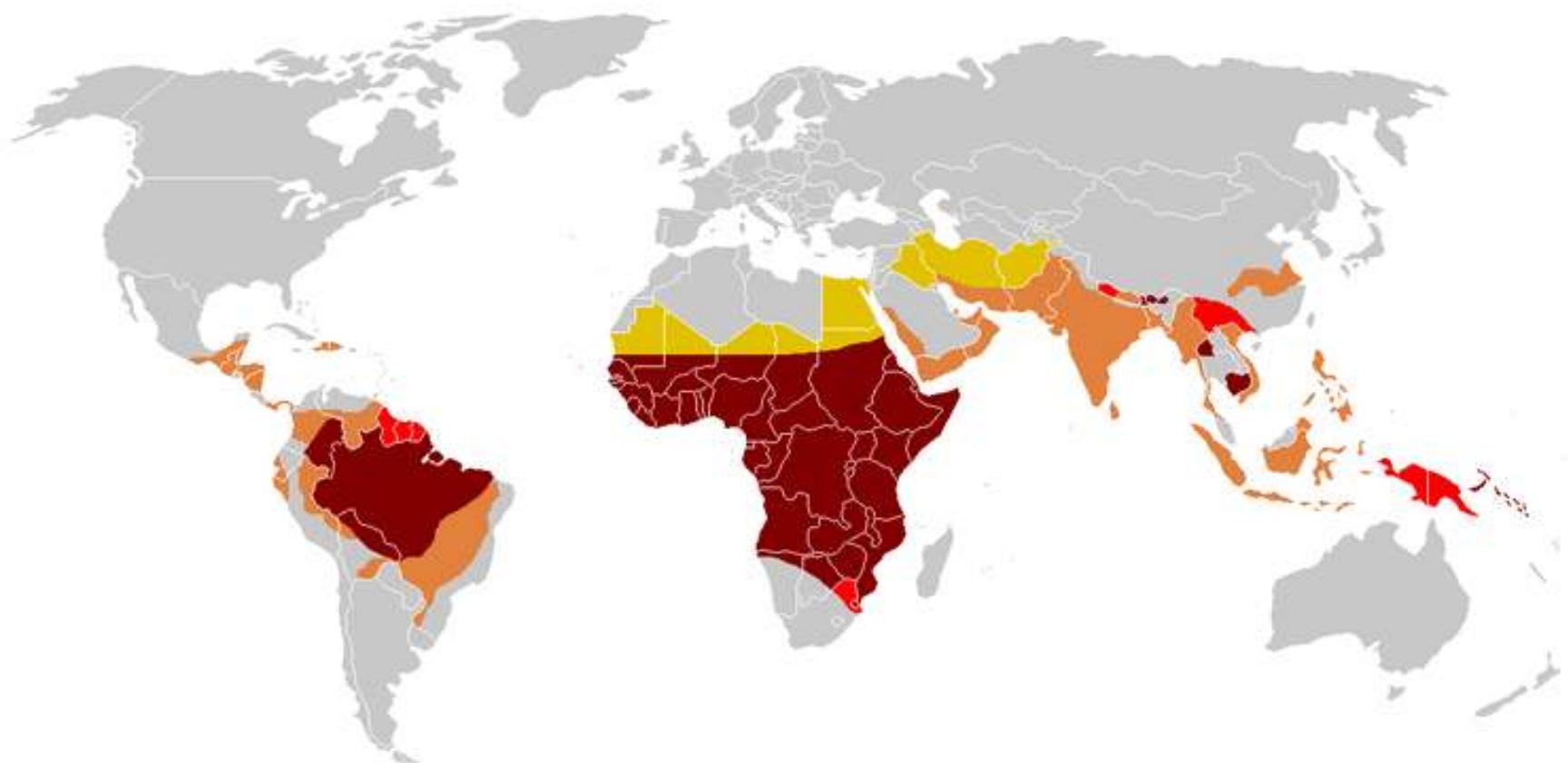


10 December 2003

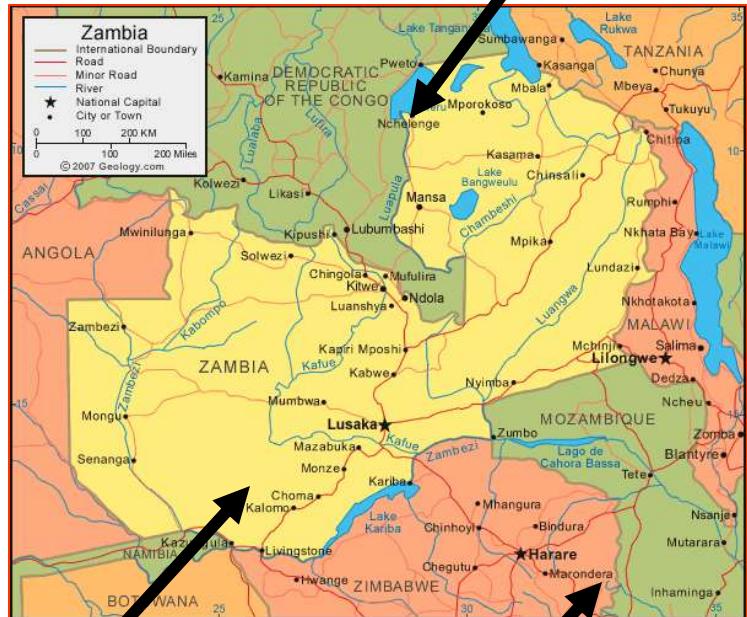
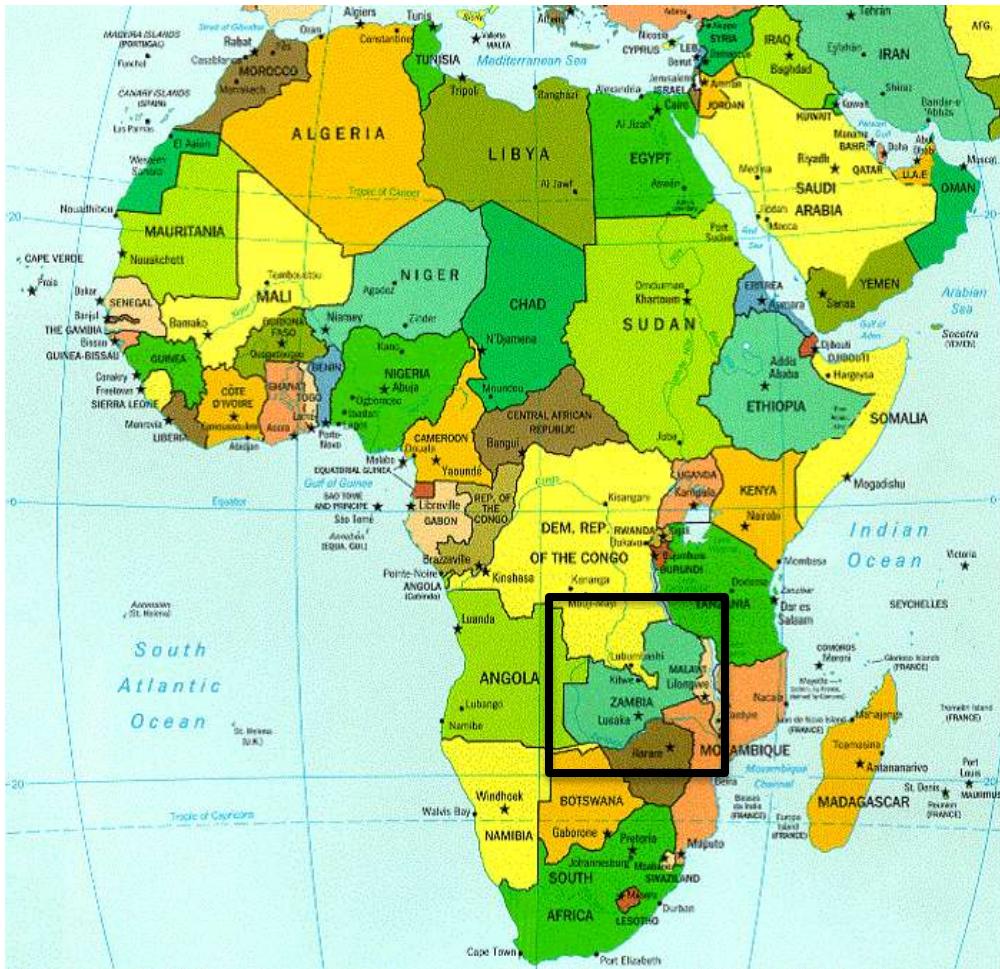


World Malaria Map

NIH International Centers of Excellence
for Malaria Research



International Center of Excellence for Malaria in Southern Africa



Nchelenge, ZM
Kilwa, DRC
Uncontrolled

Macha, ZM
Controlled

Mutasa, ZW
Resurgent



Zambia



SINMBE ENT

AUTO PARTS MOTOR BIKE S-ARES
SUPPLIES TRANSPORTERS



TOYOTA

50



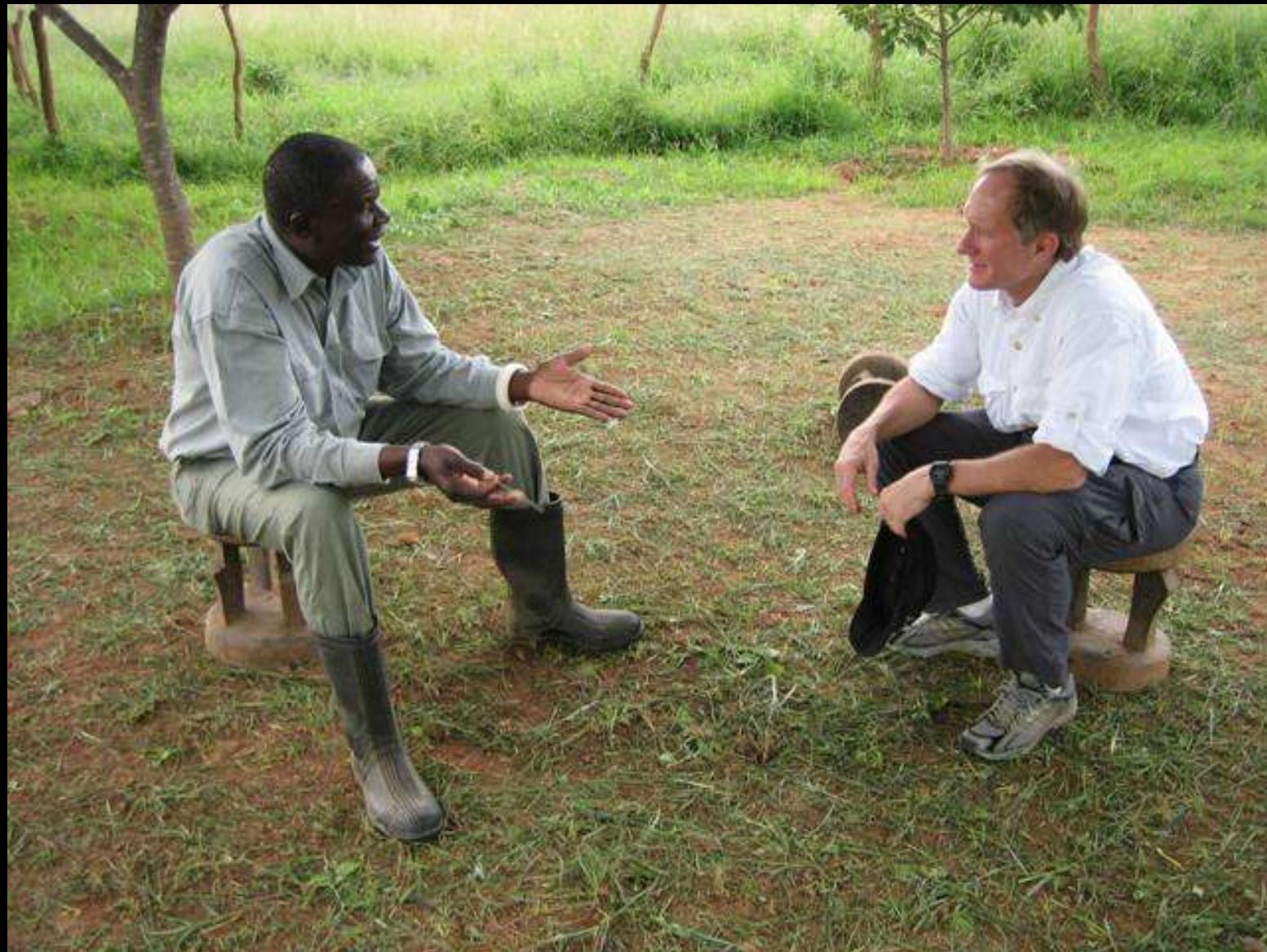
**J & J COFFINS
& CASKETS**
UNITURTLE AGENTS



Children of rural Africa



Consequences of cerebral malaria



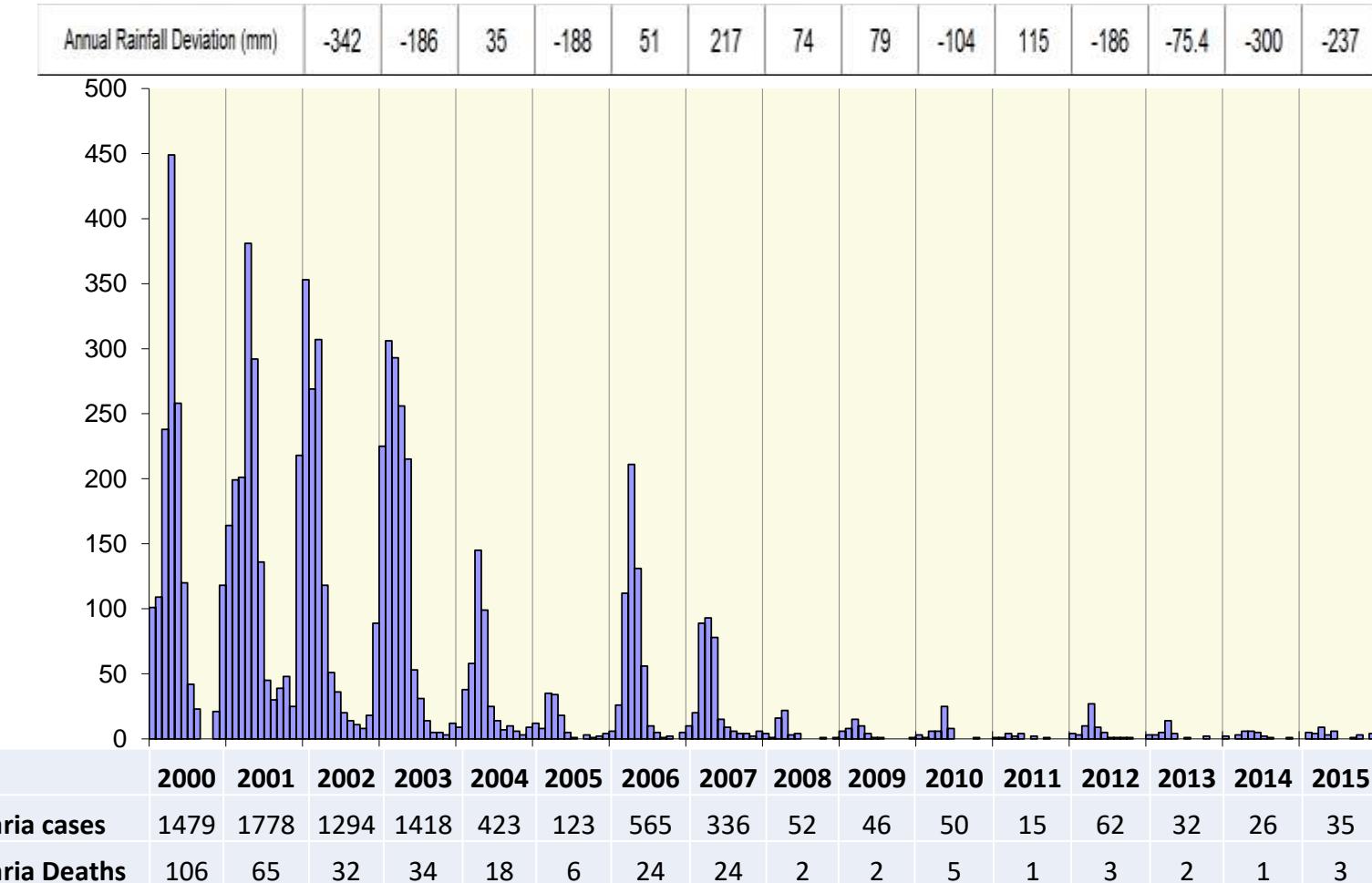








Child Malaria - Macha Hospital, Zambia



















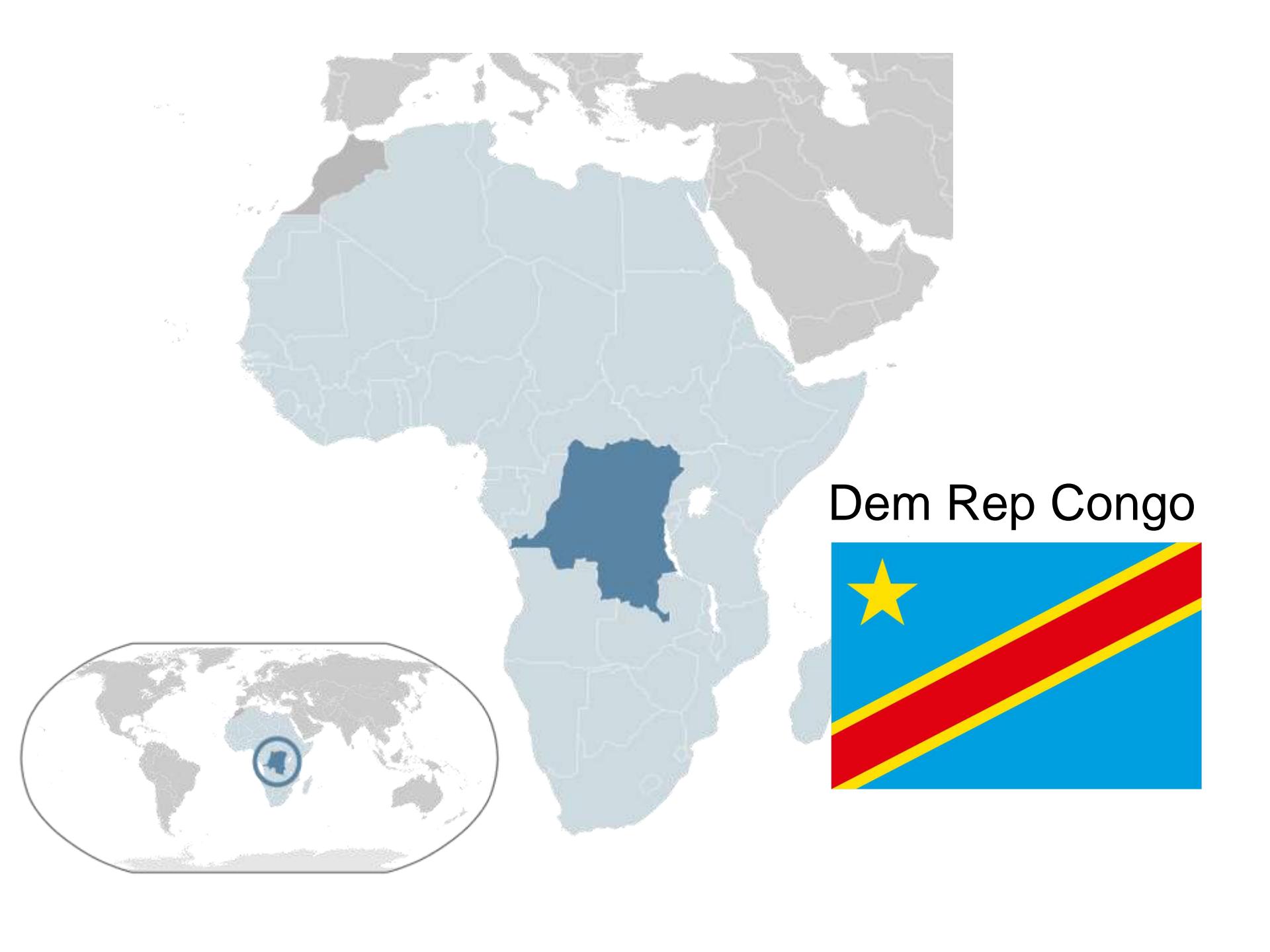












Dem Rep Congo





La Commande des
Syllabus de PEDIATRIE primaire
fin ce Samedi 14/02/2015

MU 6500FC (bundest TP)
éle de Kaelb) - 5#

Cologie Wagen
Ped. 2017

- 10









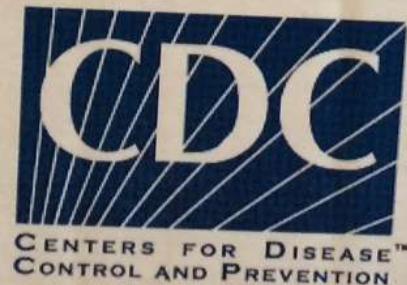
THE
MANFIELD
FAMILY
MEMORIAL

SITE
OF
HAMMARSKJÖLD
PLANE CRASH
18TH SEPTEMBER 1961



USAID
FROM THE AMERICAN PEOPLE

PRESIDENT'S MALARIA INITIATIVE















Zimbabwe







His Excellency, the President of the Republic of Zimbabwe, Cde. Robert Gabriel Mugabe







MUTERERE
HIGH SCHOOL

MUTERERE
HIGH SCHOOL

2572

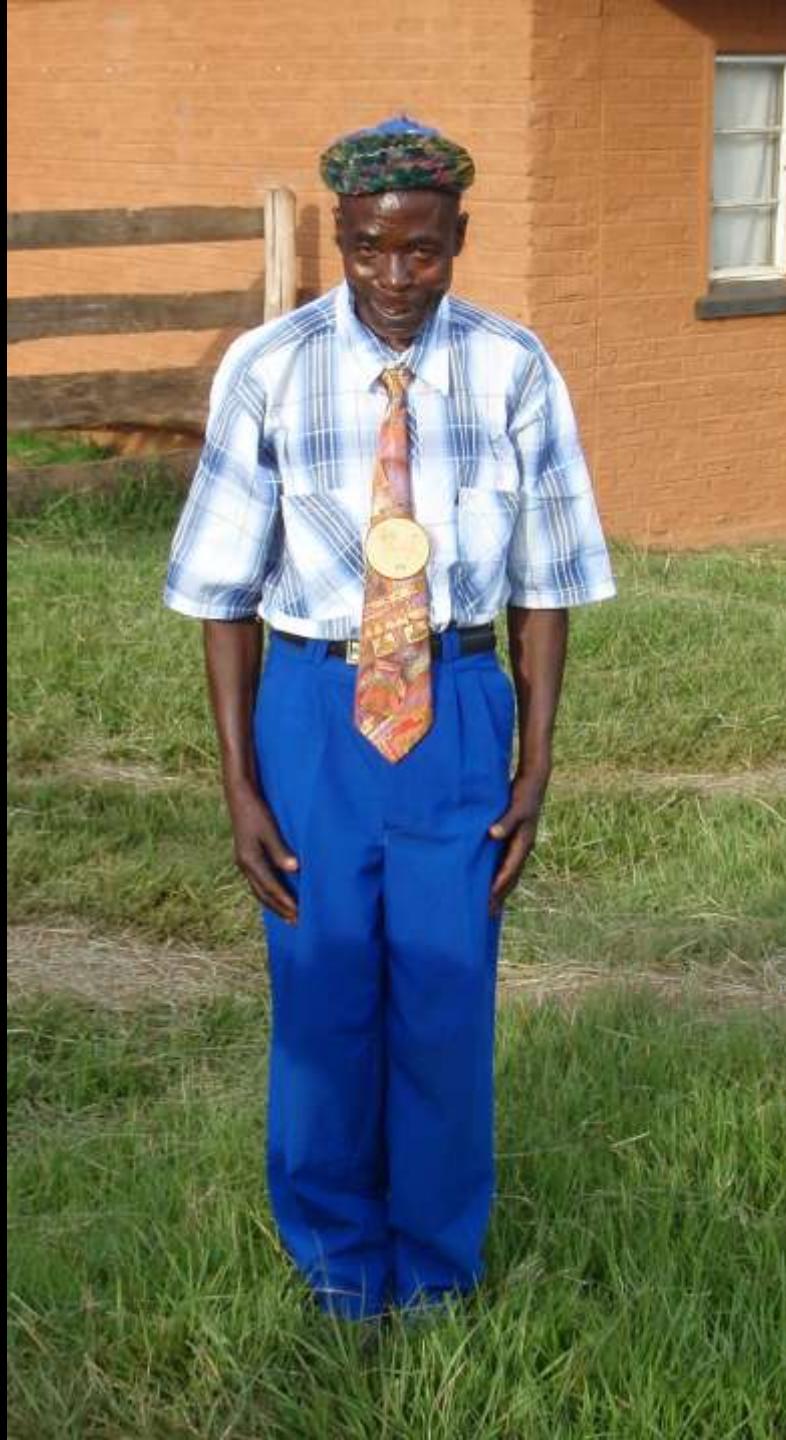












ST. PETER'S CLINIC







Science Diplomacy in the 21st Century

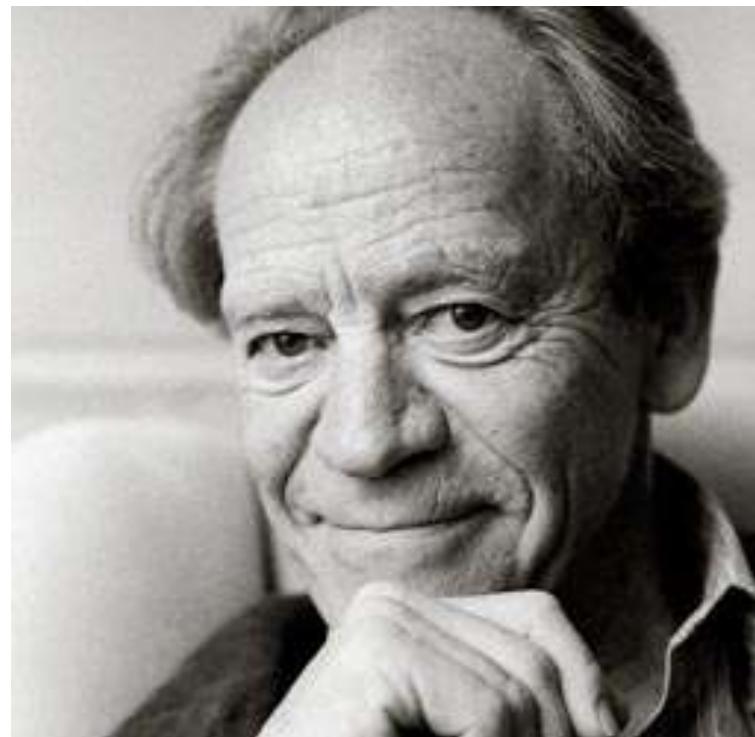
1. Scientific upbringing
2. Science as an international career
3. Science and human rights
4. Science diplomacy visits

U.S. National Academy of Sciences Committee on Human Rights

Scientists, engineers,
and health professionals

Appeals and moral support

More than 600 cases resolved



Torsten Wiesel, MD
Chair 1996-2005

Egyptian sociologist, Saad Ibrahim, PhD
Released from prison, 2003



Bulgarian Nurses and Palestinian Physician On trial in Libya, 2005



Arrival in Bulgaria after release from Libyan prison, 2007



Indian Pediatrician, Dr. Binayak Sen
Released on bail 25 May 2009
Convicted with life sentence 24 Dec 2010

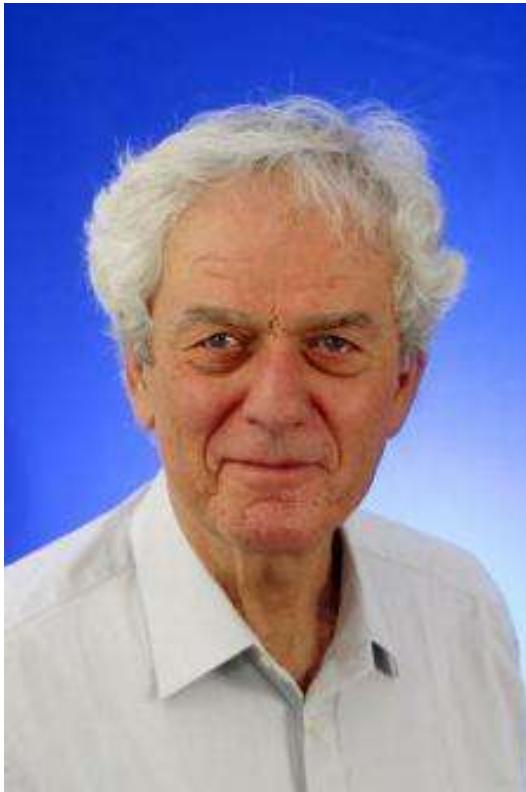


IPSO—Israeli Palestinian Science Organization

Founded 2006 to foster and sustain cooperation between scientists

Funds joint scientific research proposals

UNESCO Affiliate



Menahem Yaari, PhD (Stanford)
President Israeli Academy of
Science and Humanities



Sari Nusseibeh, PhD (Harvard)
President Al Quds University

Science Diplomacy in the 21st Century

1. Scientific upbringing
2. Science as an international career
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AAAS Center for Science Diplomacy

Vaughan Turekian PhD, Director

Cuba

Myanmar (Burma)

Iran

DPRK (North Korea)



Cuba



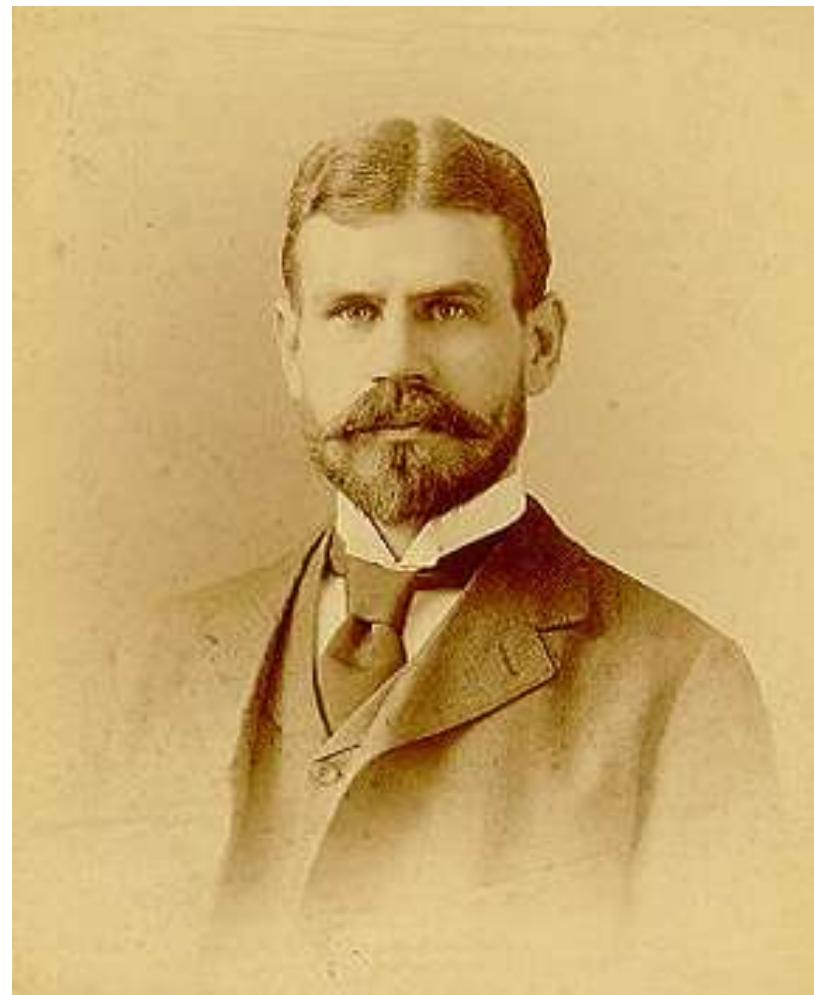




1900 Yellow Fever Commission in Havana



Carlos Finlay 1833-1915



Jesse Lazear 1866-1900

IN MEMORY OF
JESSE WILLIAM LAZEAR
BORN 2 MAY 1866 AT BALTIMORE
GRADUATED IN ARTS AT
THE JOHNS HOPKINS UNIVERSITY IN 1889
AND IN MEDICINE AT COLUMBIA UNIVERSITY IN 1892
IN 1895-96 ASSISTANT RESIDENT PHYSICIAN
IN THE JOHNS HOPKINS HOSPITAL
MEMBER OF THE YELLOW FEVER COMMISSION IN 1900
WITH THE RANK OF ACTING ASSISTANT SURGEON
HE DIED OF YELLOW FEVER AT QUEMADOS CUBA
25 SEPTEMBER 1900.

WITH MORE THAN THE COURAGE AND DEVOTION OF THE
SOLDIER HE RISKED AND LOST HIS LIFE TO SHOW HOW A
FEARFUL PESTILENCE IS COMMUNICATED AND HOW ITS
RAVAGES MAY BE PREVENTED.

EN MEMORIA DE LA COLABORACION CIENTIFICA ENTRE EL MEDICO
CUBANO CARLOS J. FINLAY Y JESSE W. LAZEAR, DE LA UNIVERSIDAD
JOHNS HOPKINS, EN LOS EXPERIMENTOS PARA COMPROBAR LAS
TEORIAS ORIGINALES DE FINLAY SOBRE EL AGENTE TRANSMISOR
DE LA FIEBRE AMARILLA. SUS RESULTADOS ABRIERON EL CAMINO
PARA ELIMINAR ESE AZOTE DE LOS TROPICOS. EN ARAS DE ESE
PROPOSITO, LAZEAR OFRENDO SU VIDA.

LA HABANA, FEBRERO DE 2015. AÑO DEL CENTENARIO DEL DECESO DE
CARLOS J. FINLAY.

THE HEALTH ADVISORY BOARD FROM THE JOHNS HOPKINS BLOOMBERG
SCHOOL OF PUBLIC HEALTH, BALTIMORE, MARYLAND, USA.
LA ACADEMIA DE CIENCIAS DE CUBA.



Havana Cuba















Faces of Cuban Science







Universidad de la Habana



Universidad de la Habana



Myanmar (Burma)

























Islamic Republic of Iran

















THE SONS OF HERM
ARE THE LINES OF
THE ANCESTORS

Rassem
The Arabesque
Inventor of
Penina Kays









قلاش پرای گشودن گروههای «فنی» مذاکرات
ایران و امریکا راه پیشرفت مذاکرات را بررسی می کنند

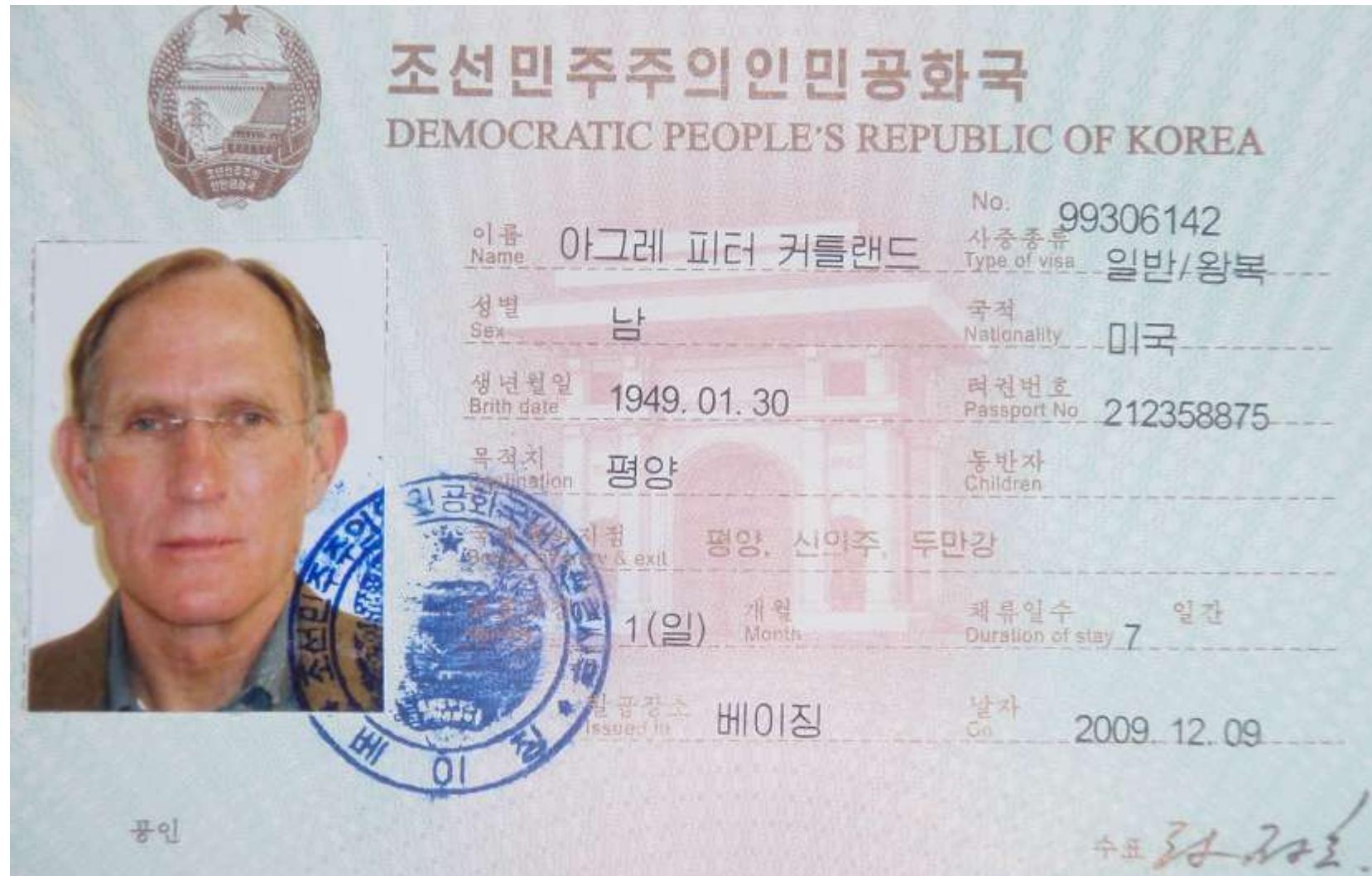




DPR Korea







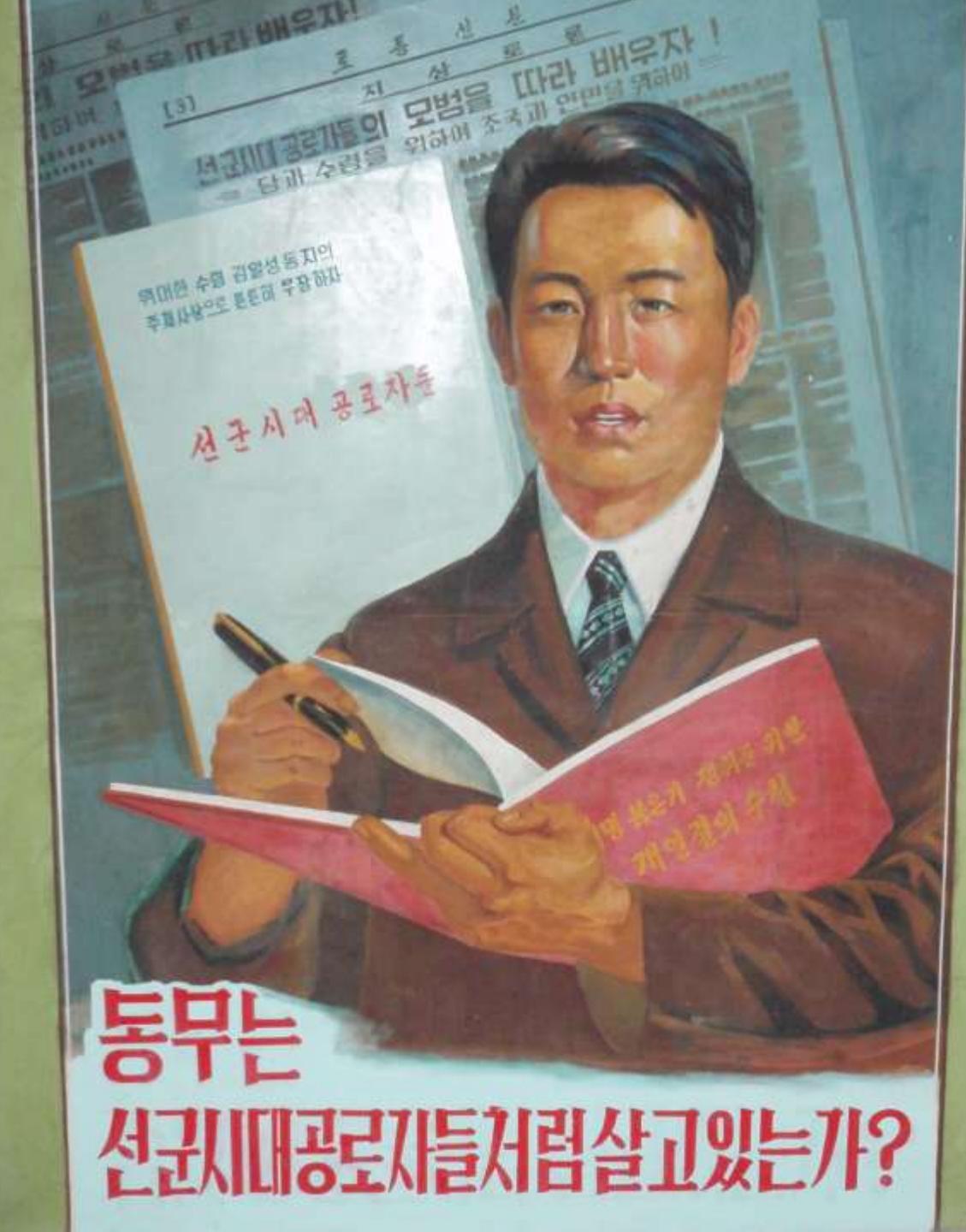
Pyongyang DPRK







“Juche” – Korean self reliance



동무는
선군시대공로자들처럼 살고 있는가?



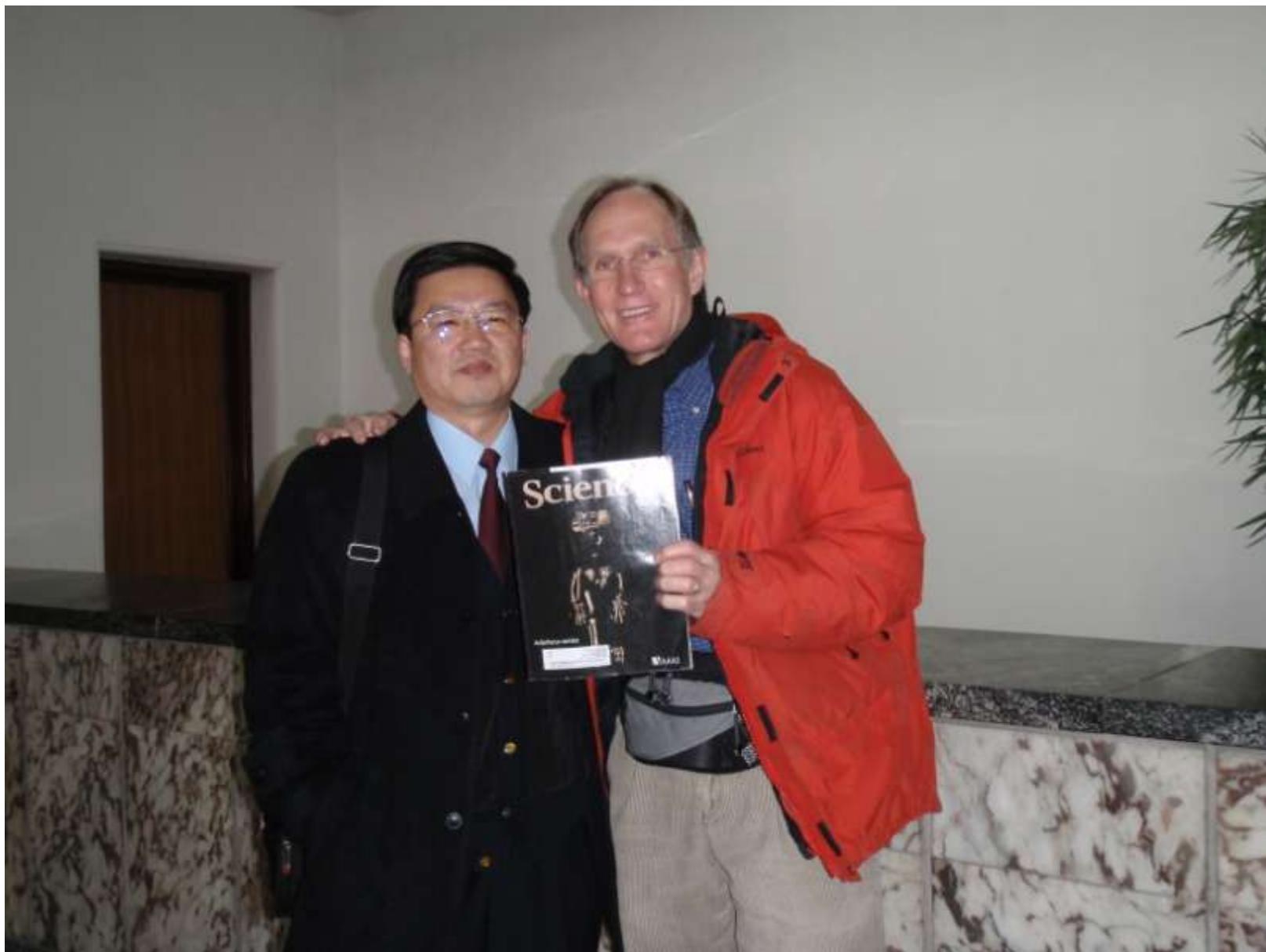
Kim Jong Il and Kim Il Song



US-DPRK Science Engagement Consortium









Faces of North Korean Science



Faces of North Korean Science



Faces of North Korean Science



Faces of North Korean Science

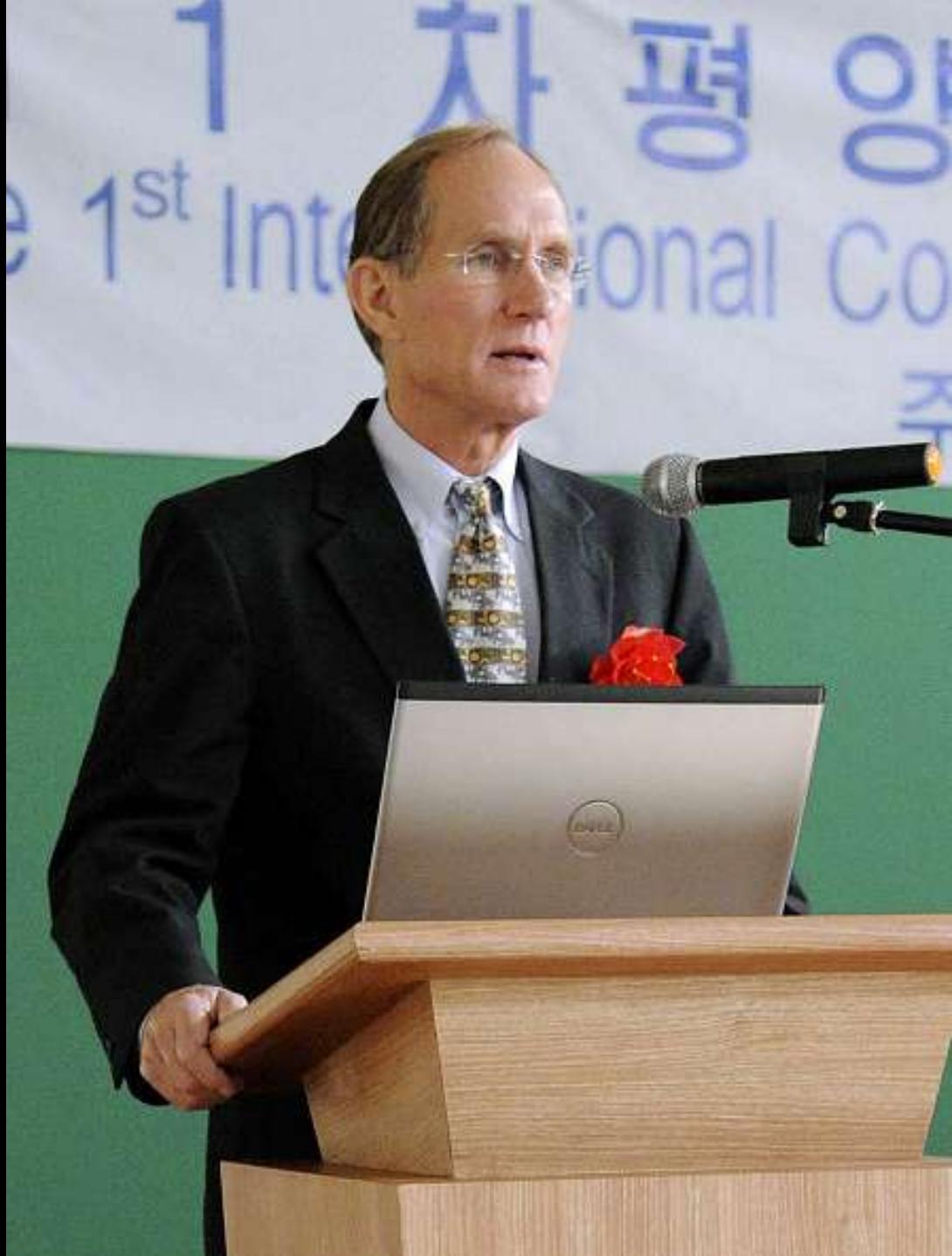


Pyongyang University of Science and Technology











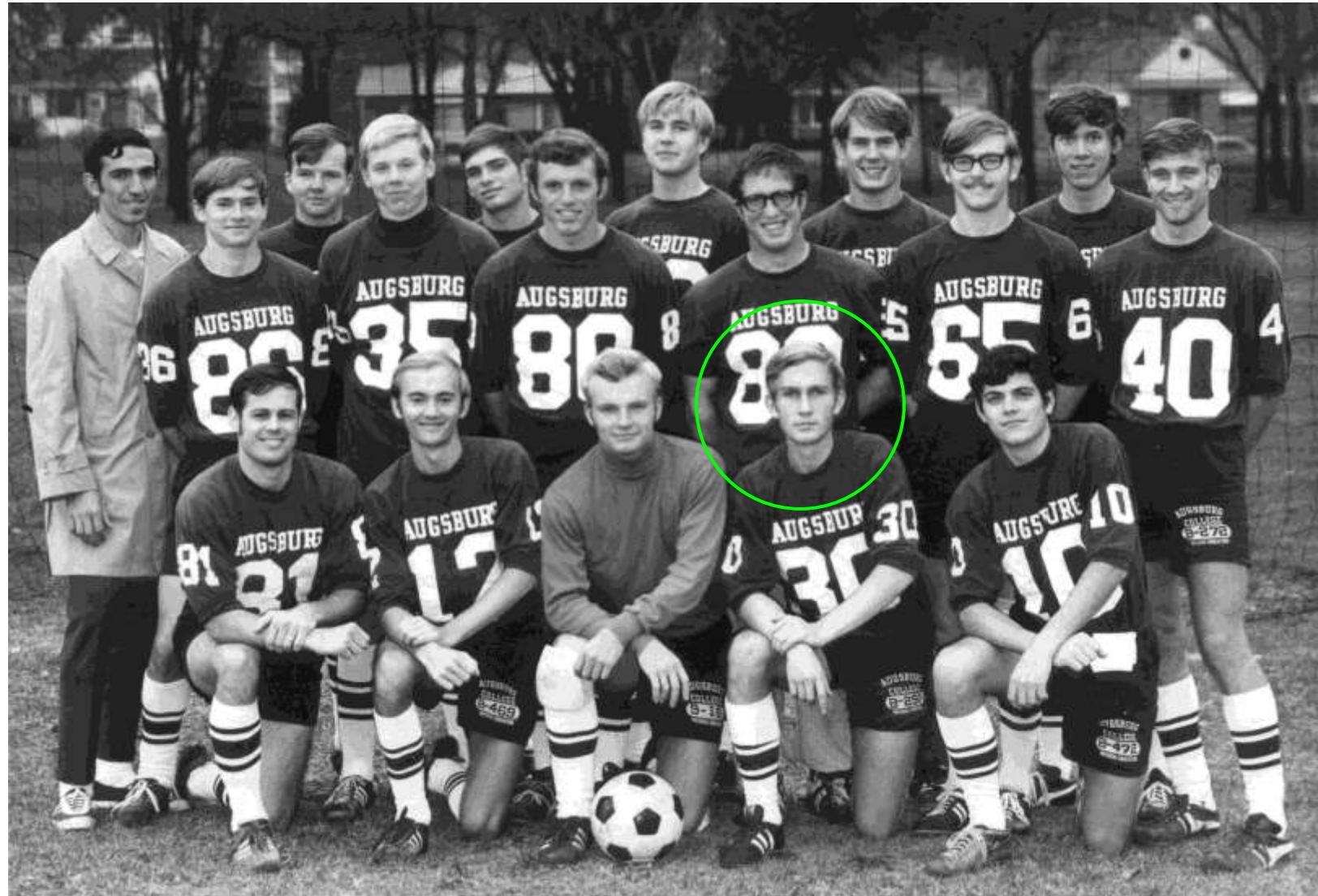




Wei Ji
Mandarin for “crisis”

危 机

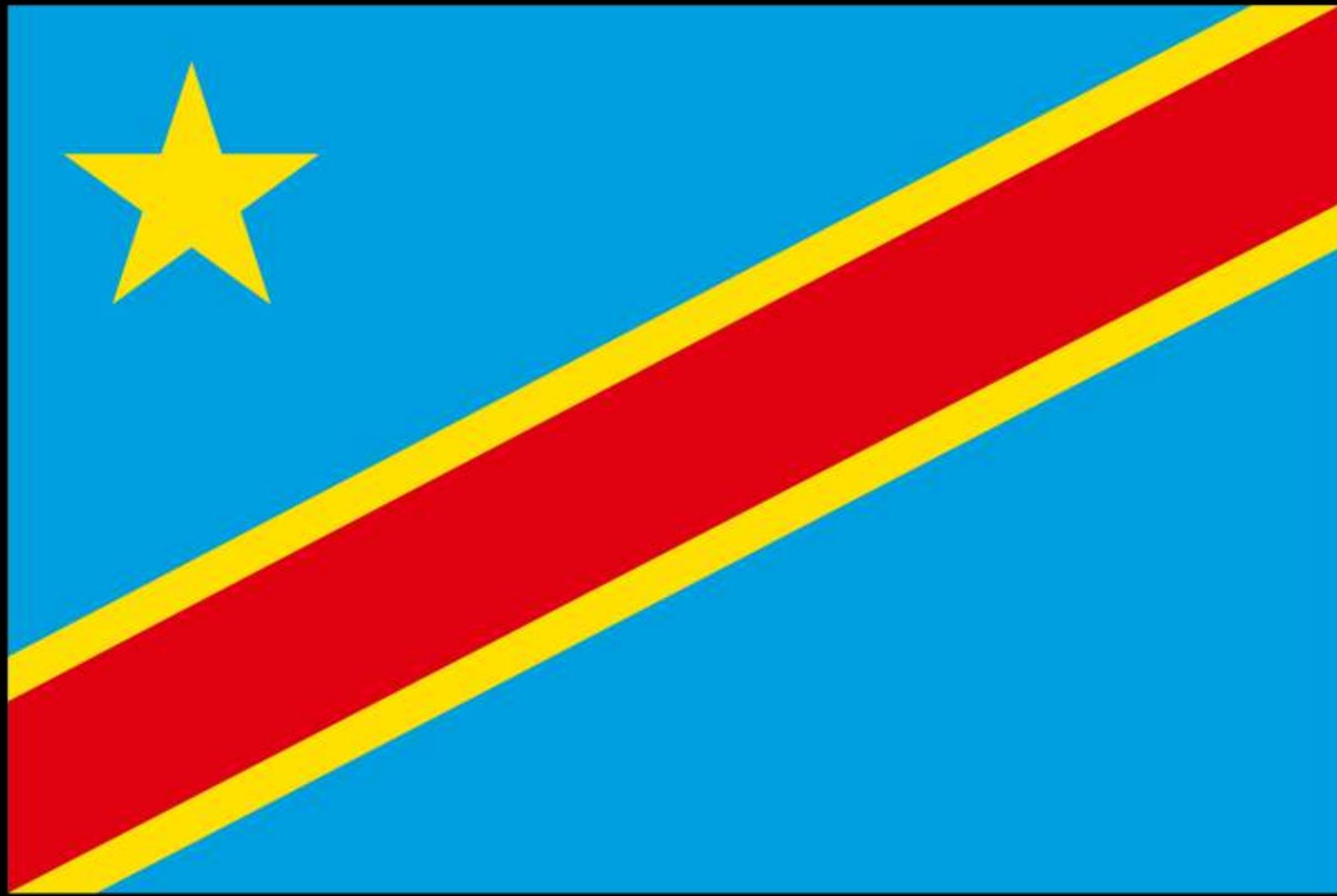
danger opportunity



Augsburg Men's Soccer Team, 1969



Minnesotan Origins, 1965



بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِيْمِ



بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِيْمِ







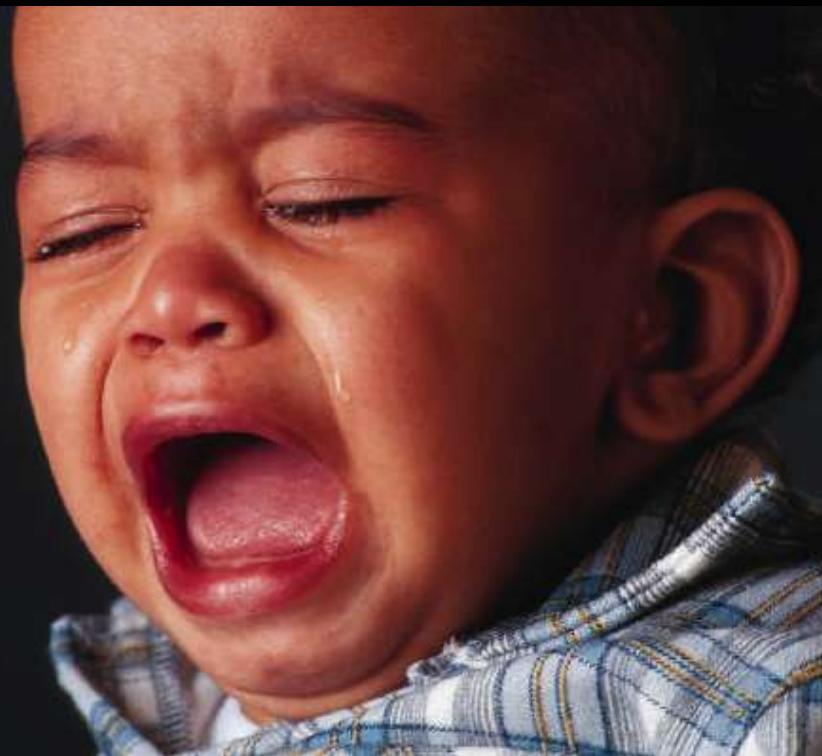






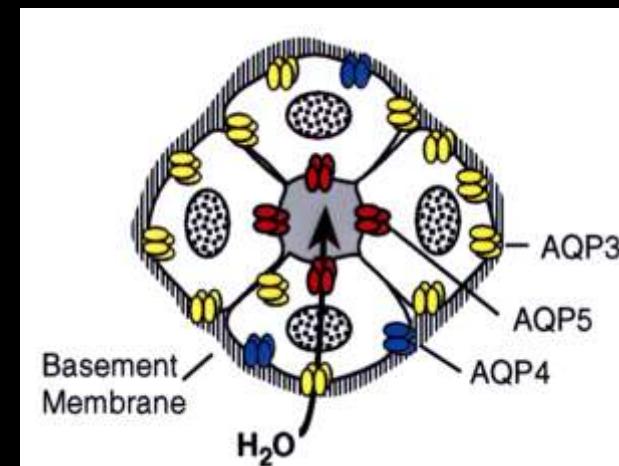
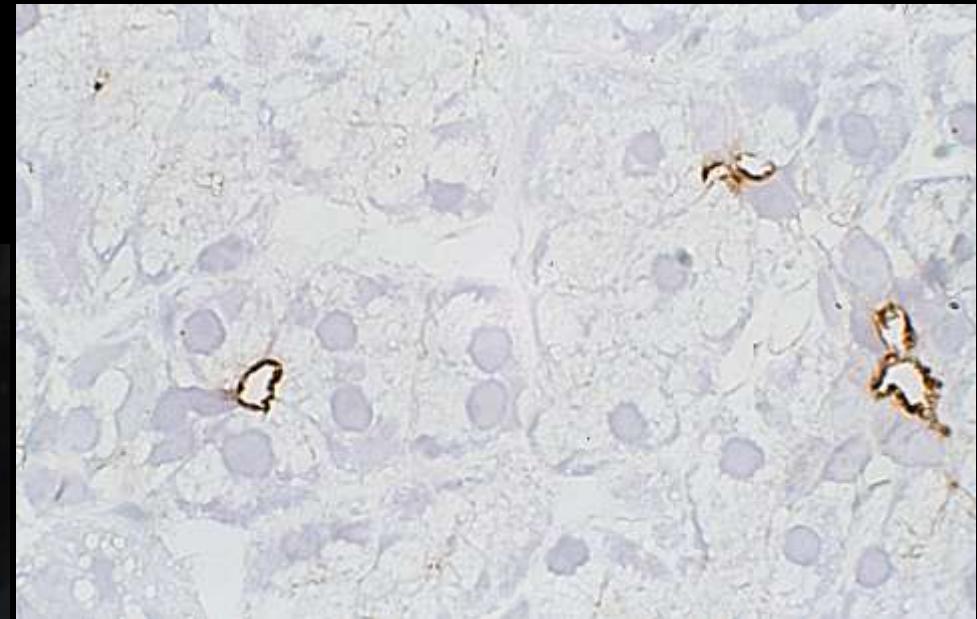
AQP5—Secretory glands

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



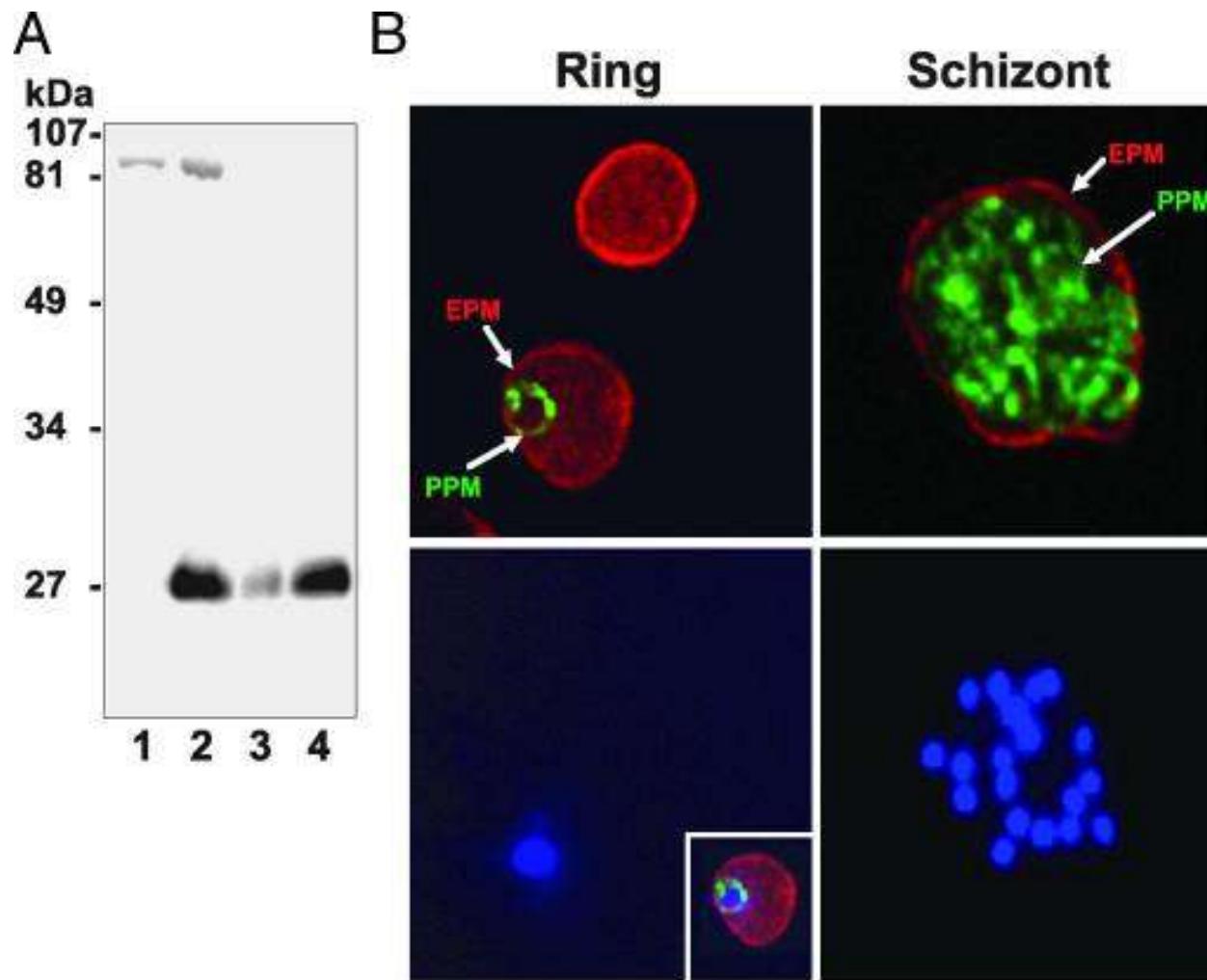
Type 1 pneumocytes

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



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

Aquaglyceroporin PbAQP increases malaria virulence



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

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

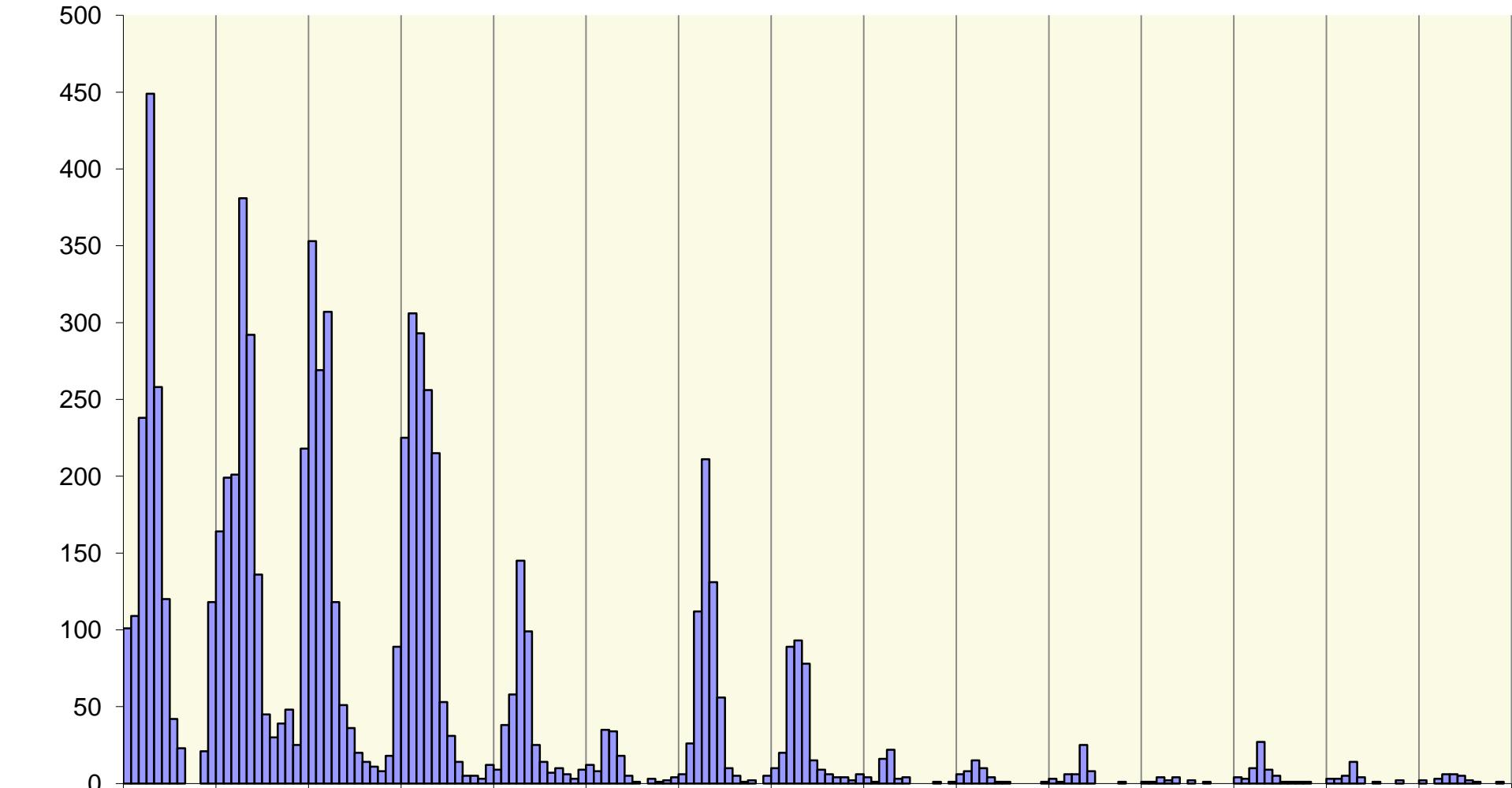
Arsenic toxicity

Expressed throughout nature



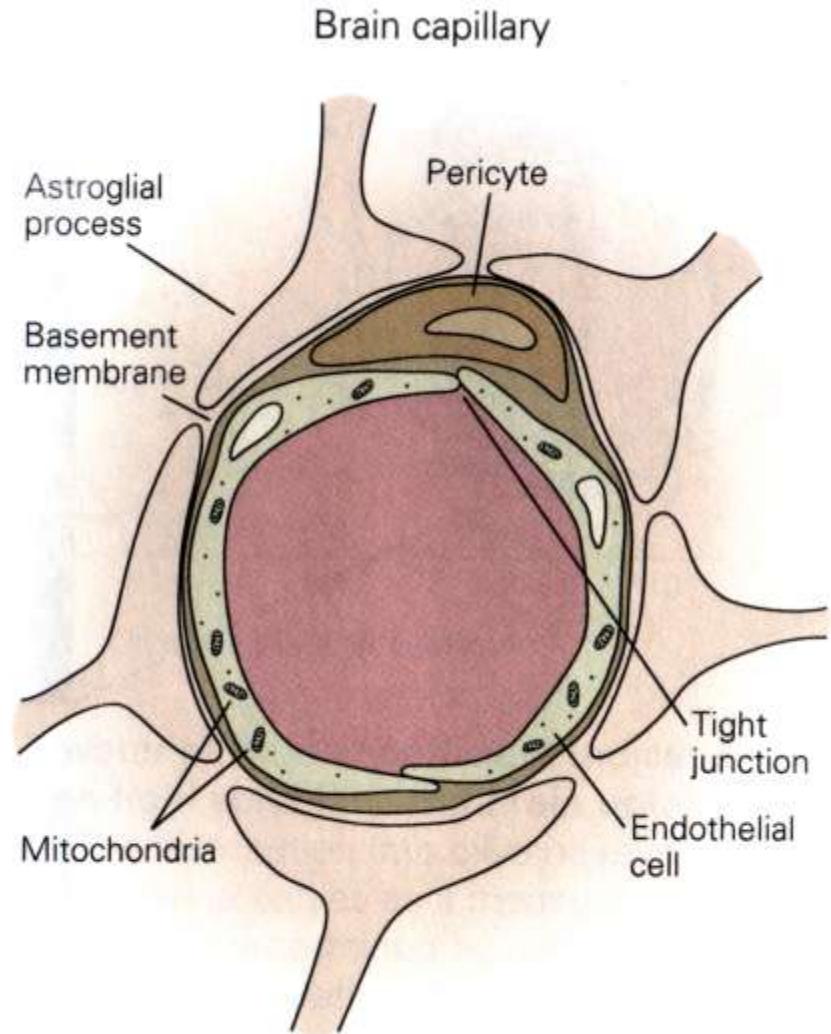
Child Malaria - Macha Hospital, Zambia

Annual Rainfall Deviation (mm)	-342	-186	35	-188	51	217	74	79	-104	115	-186	-75.4	-300
--------------------------------	------	------	----	------	----	-----	----	----	------	-----	------	-------	------



Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Malaria Cases	1479	1778	1294	1418	423	123	565	336	52	46	50	15	62	32	26
Malaria Deaths	106	65	32	34	18	6	24	24	2	2	5	1	3	2	1

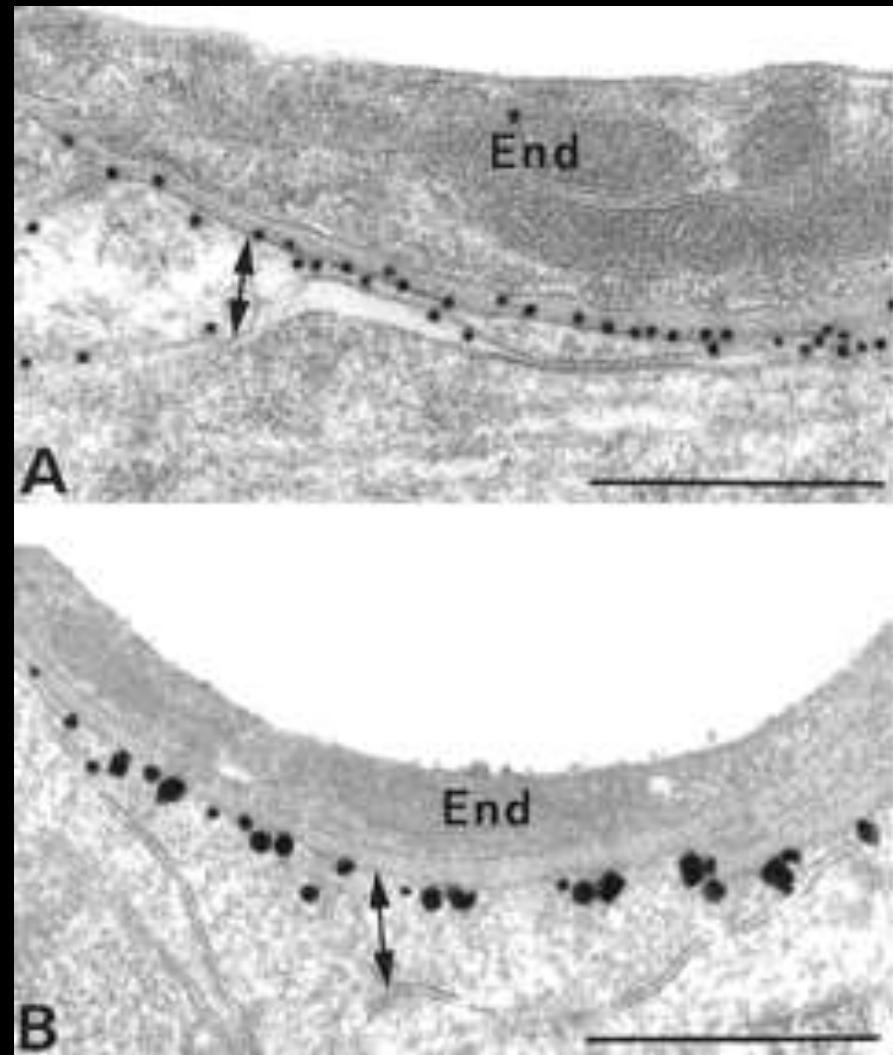
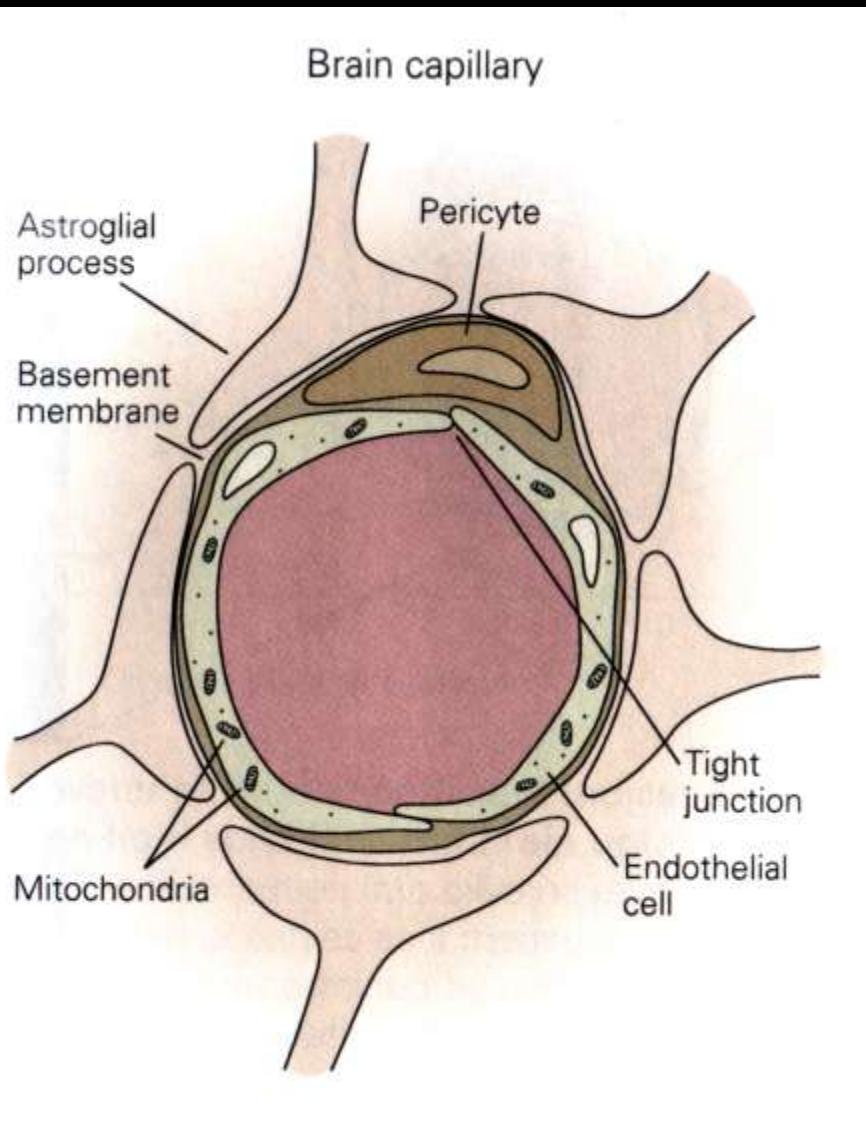
AQP4 water channel in brain



Nielsen et al., *J Neurosci* 1997

AQP4—Blood brain barrier

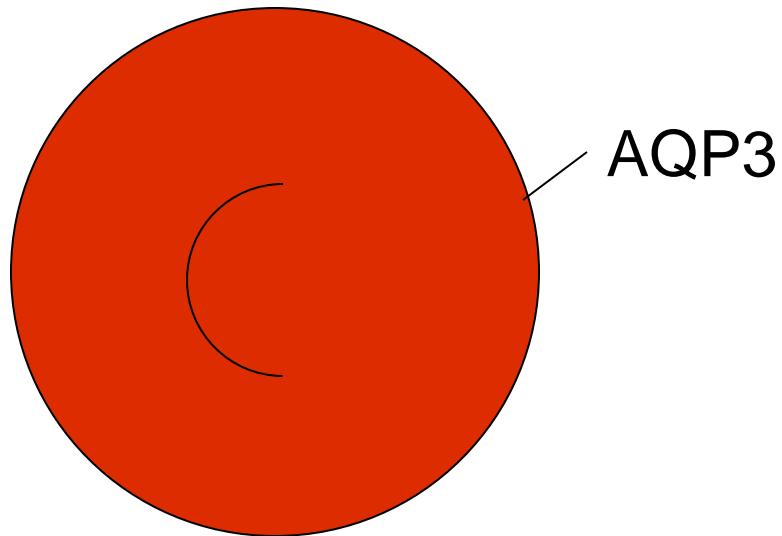
(with Ole Petter Ottersen, Oslo)



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

Aquaglyceroporin—AQP3 in red cells

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

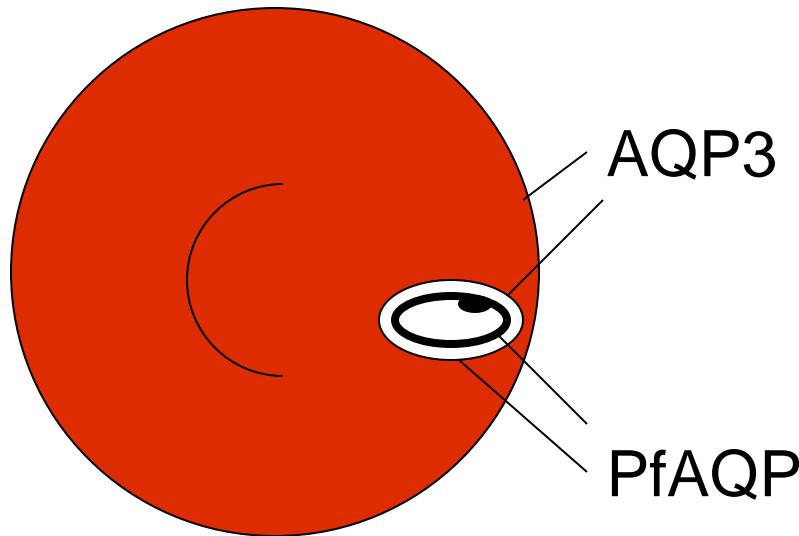


Roudier et al., *J Biol Chem*, 2002a,b

Aquaglyceroporins in malaria

Pathway for glycerol transport

PM, PVM, PPM

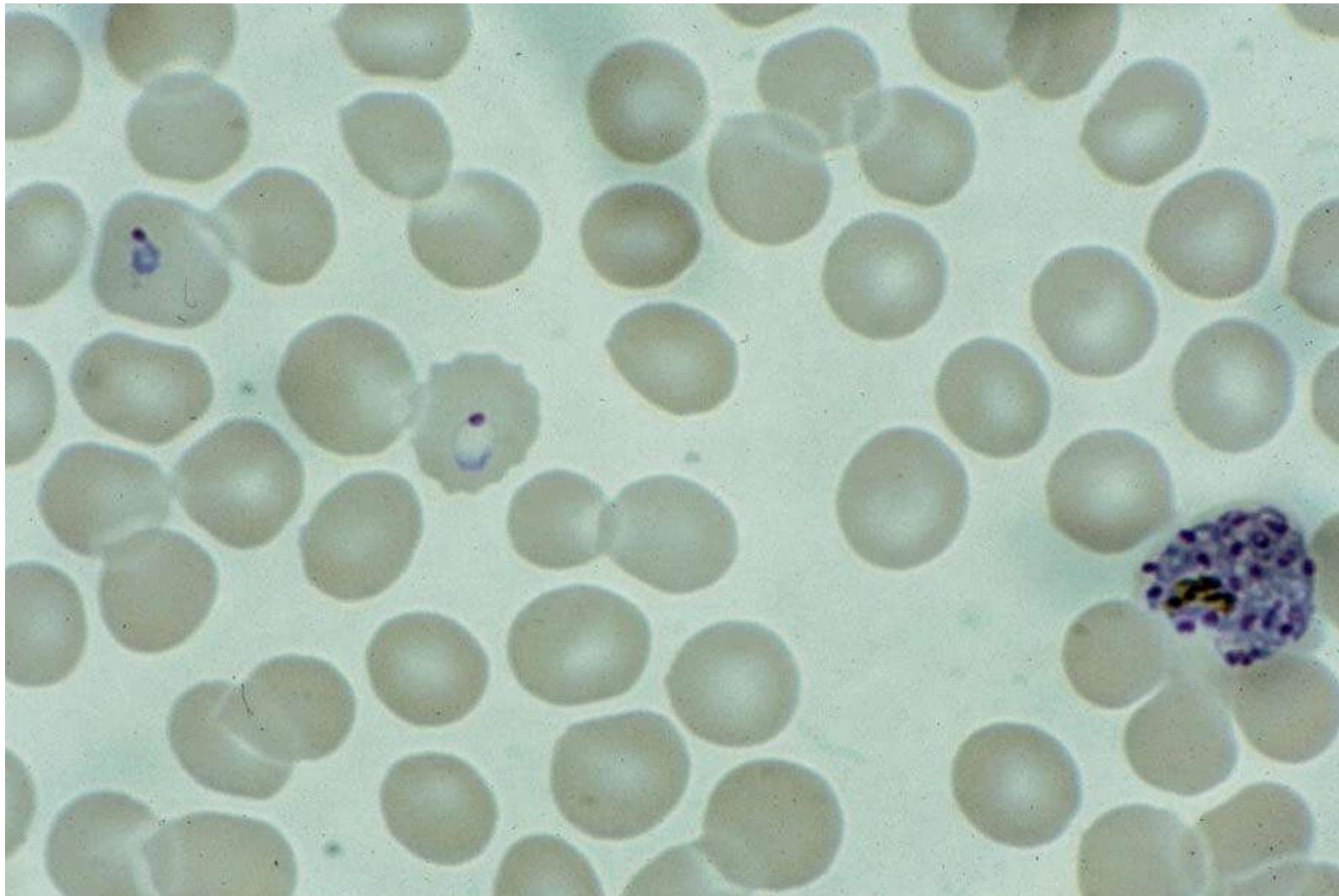


Hansen *et al.*, *J Biol Chem*, 2002

Beitz, Pavlovic-Djuranovic *et al.*, *Proc Natl Acad Sci*, 2004

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

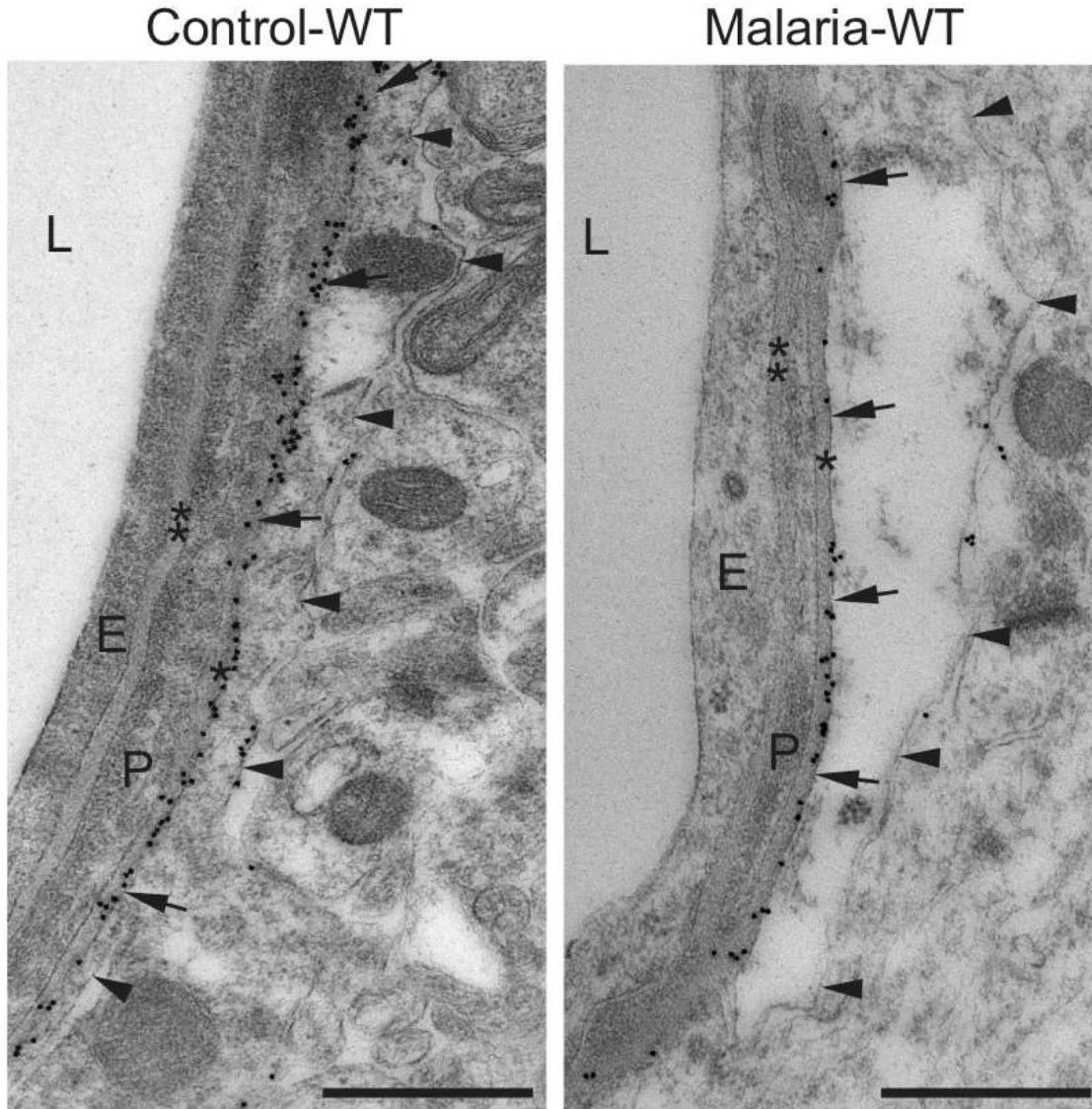
Plasmodium infected red blood cells



Anopheles gambiae



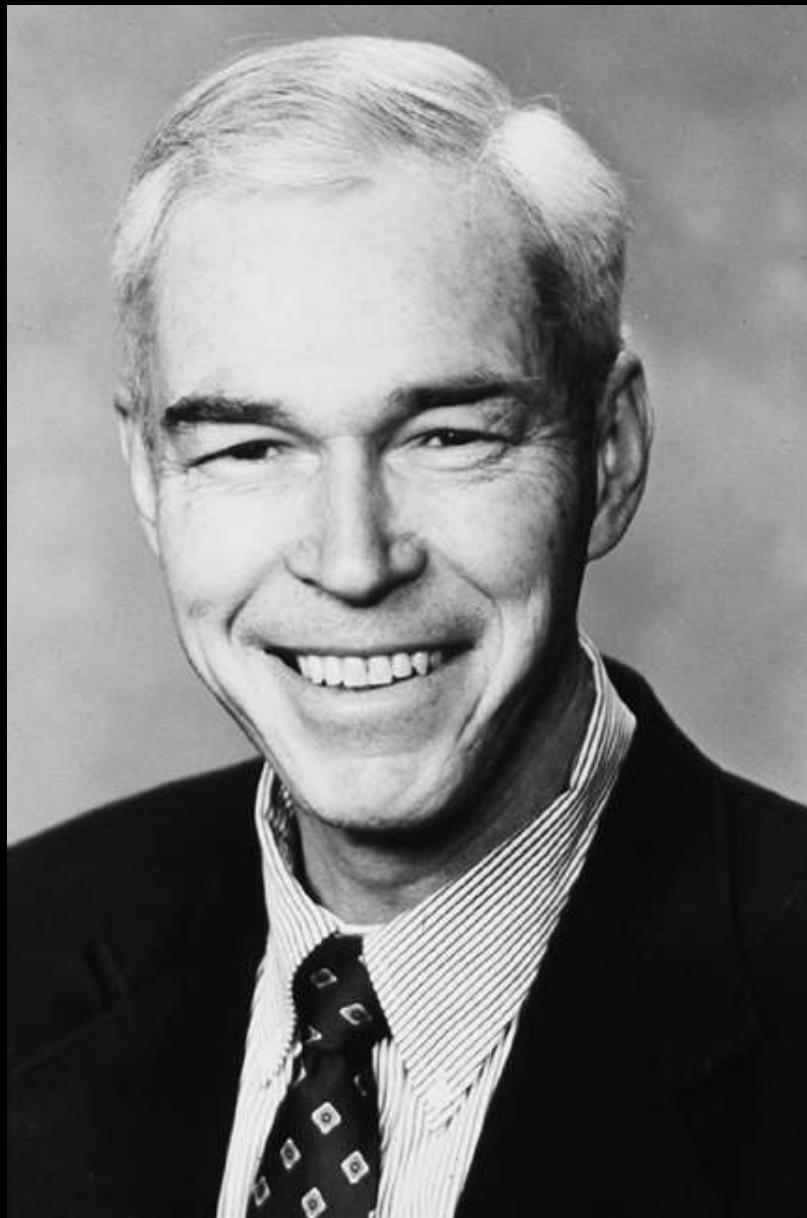
Aquaporin-4 in murine cerebral malaria









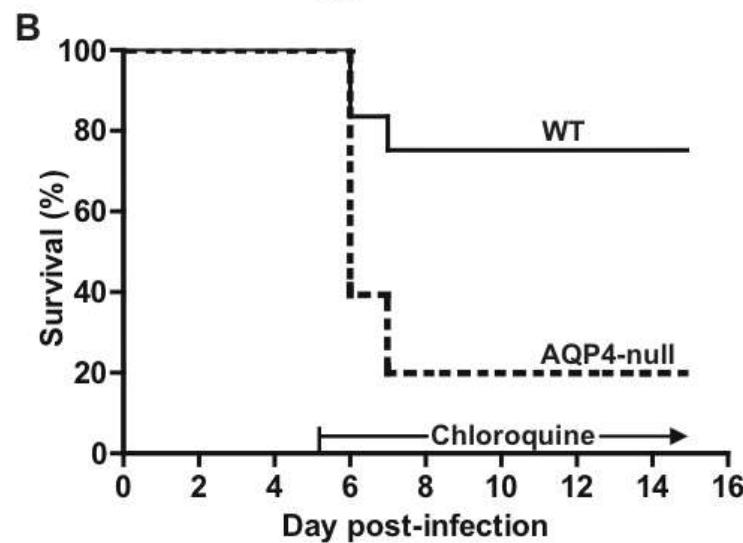
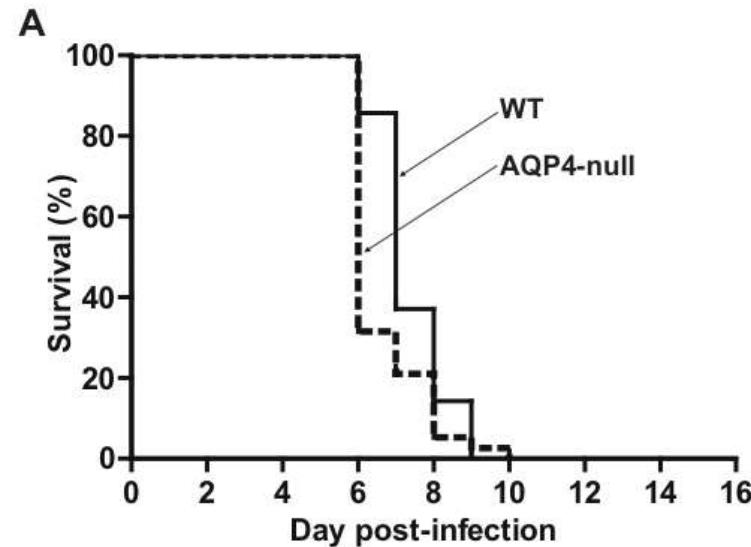


John C. Parker, M.D. 1935-1993

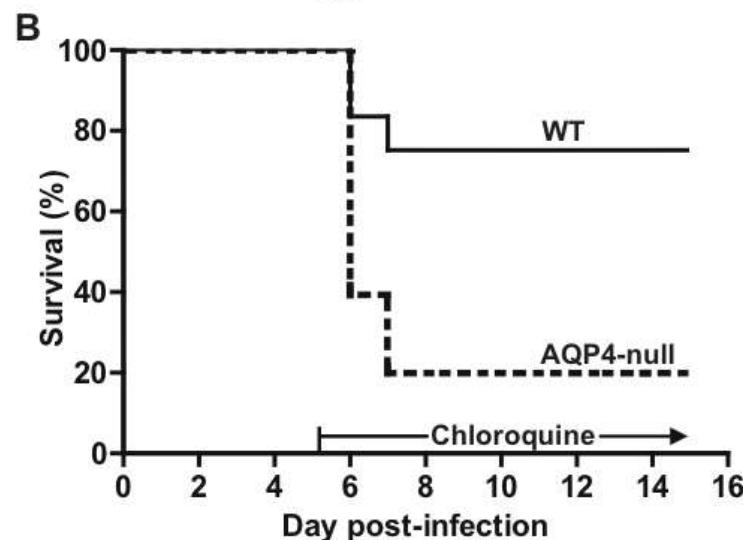
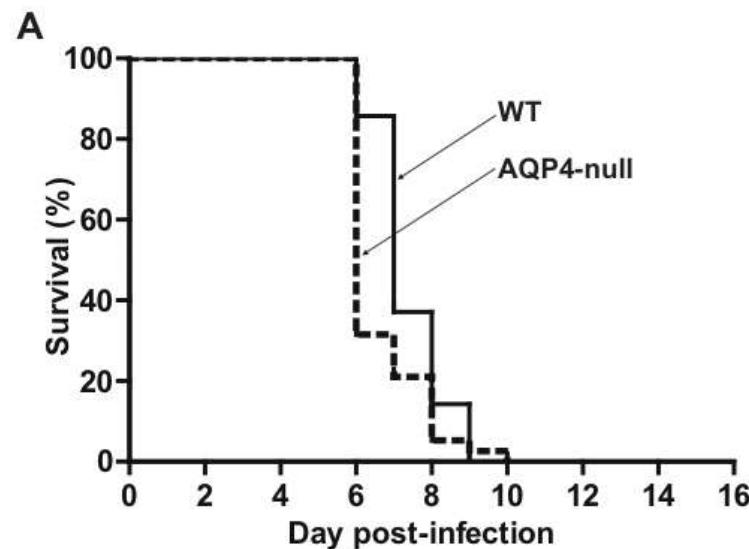




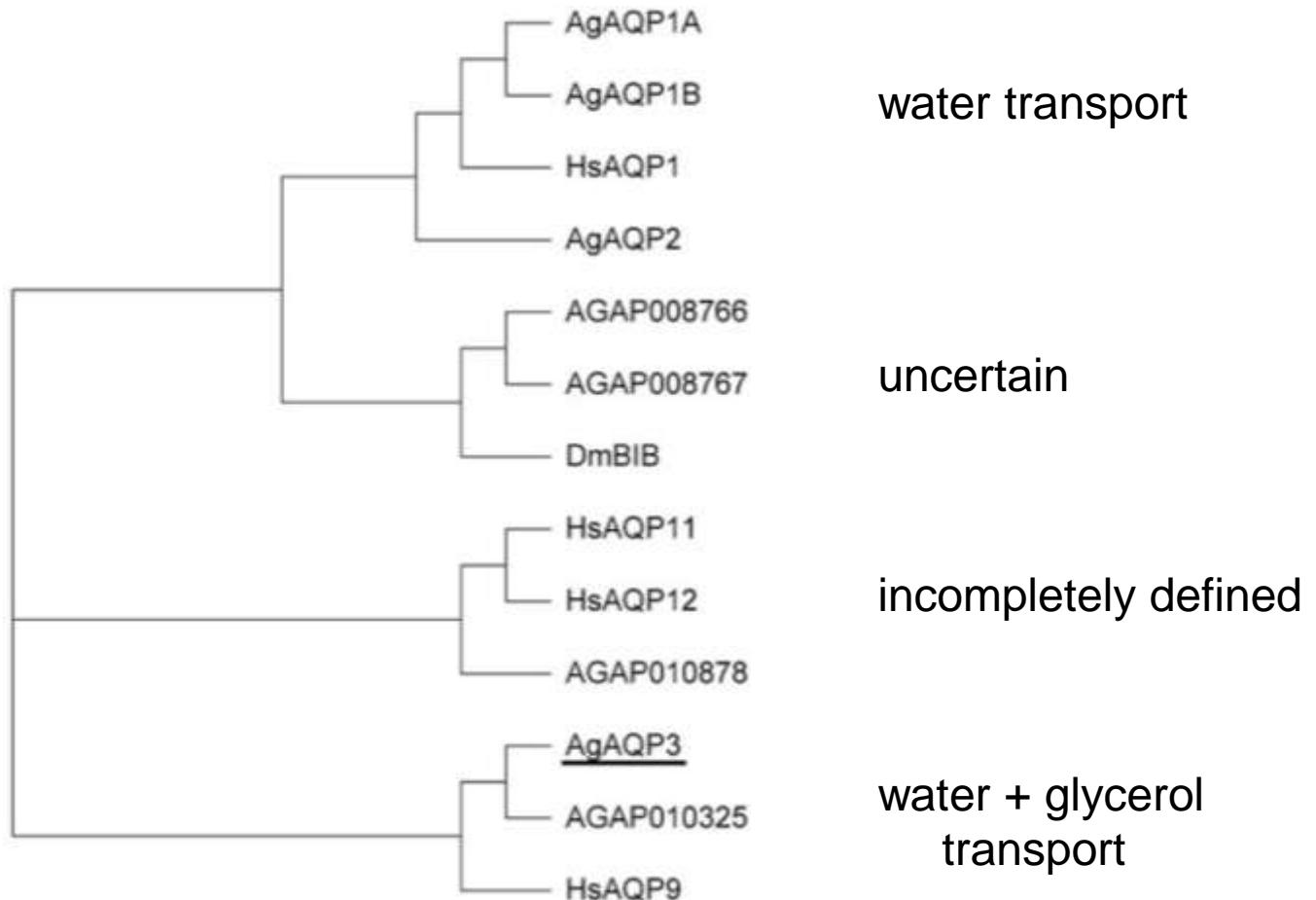
Aquaporin-4 in murine cerebral malaria



Aquaporin-4 in murine cerebral malaria



Aquaporins in *Anopheles gambiae*

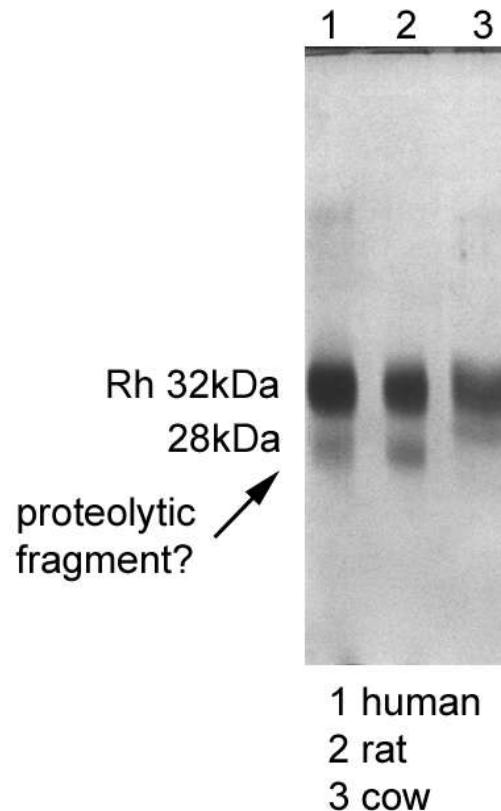


Liu et al., Proc Natl Acad Sci, 2011
Tsujimoto et al., PLoS One, 2013
Liu et al., Biol Cell, 2016

Discovery of Aquaporin-1

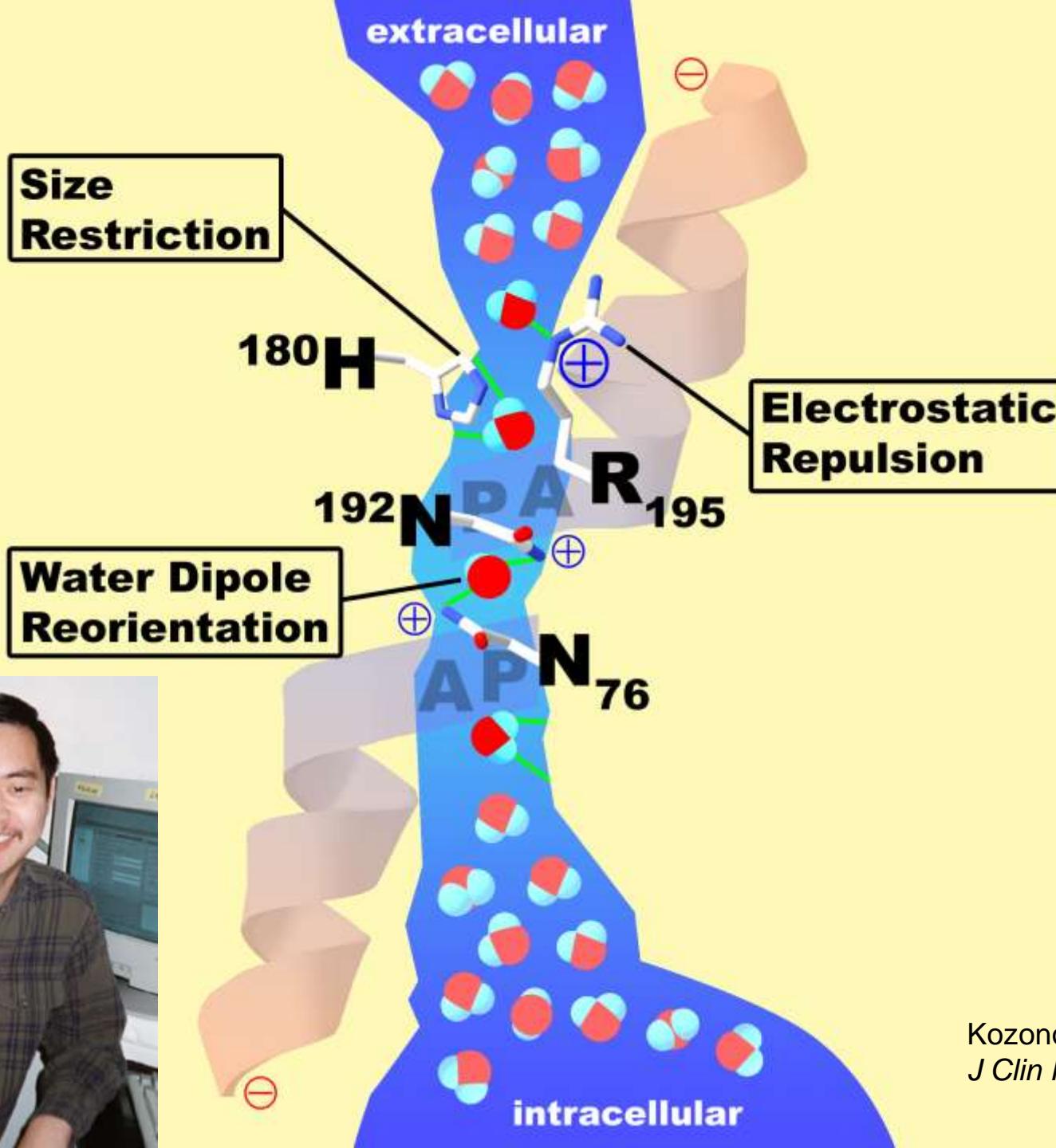
A serendipitous observation

Contaminant in 32 kDa
Rh preparations



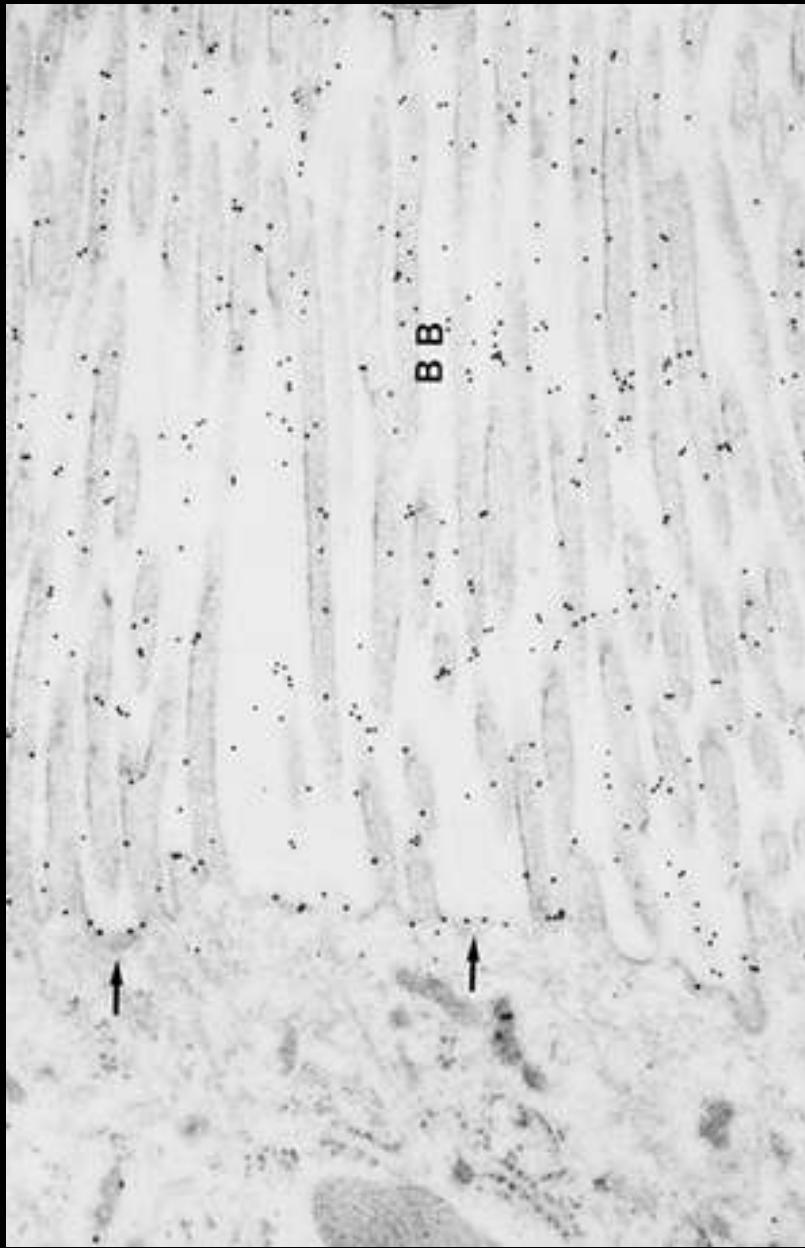
Denker *et al.*, *J Biol Chem*, 1988





Kozono et al.,
J Clin Invest, 2002

AQP1 in proximal nephron

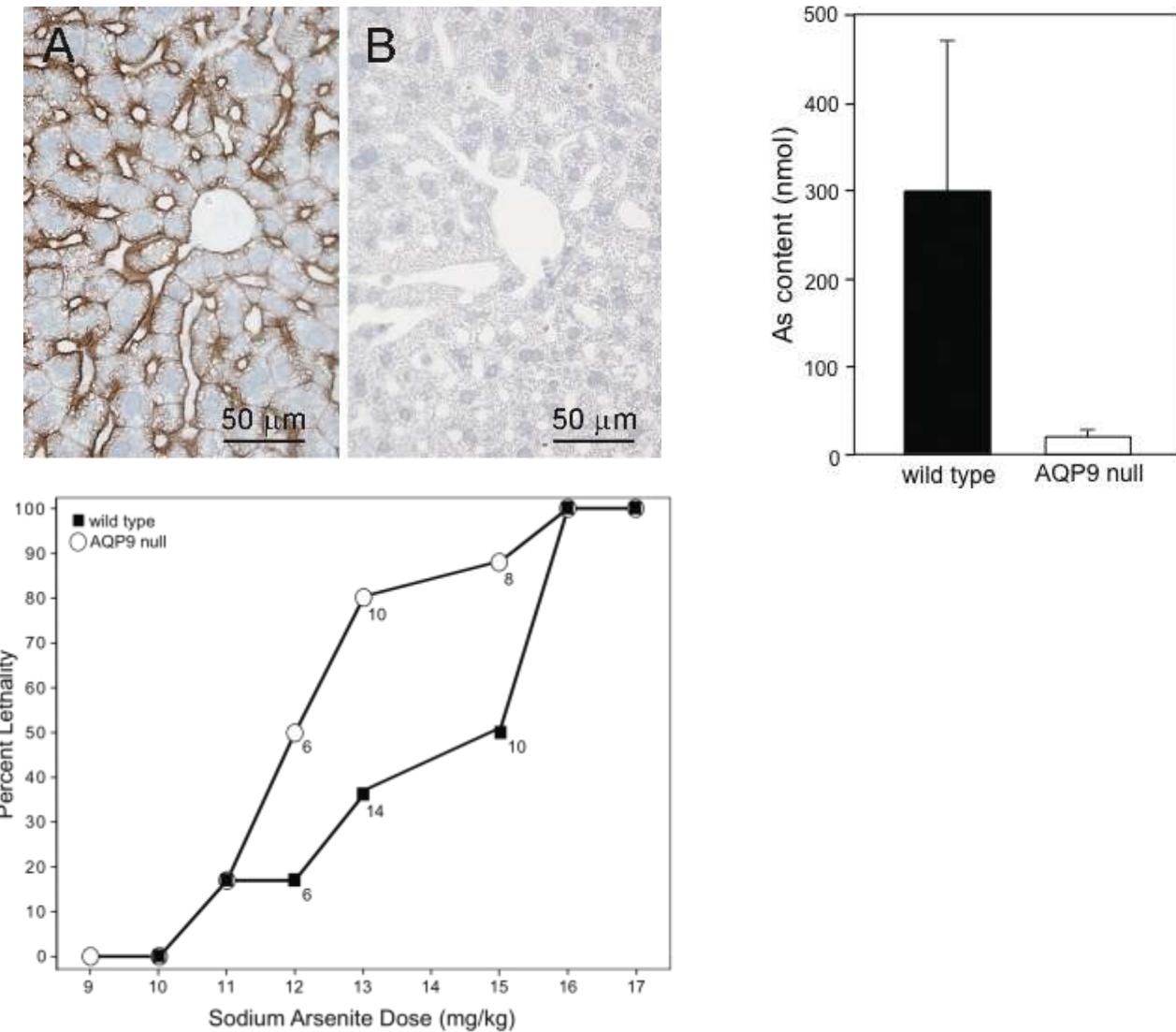


BB, apical
brush border

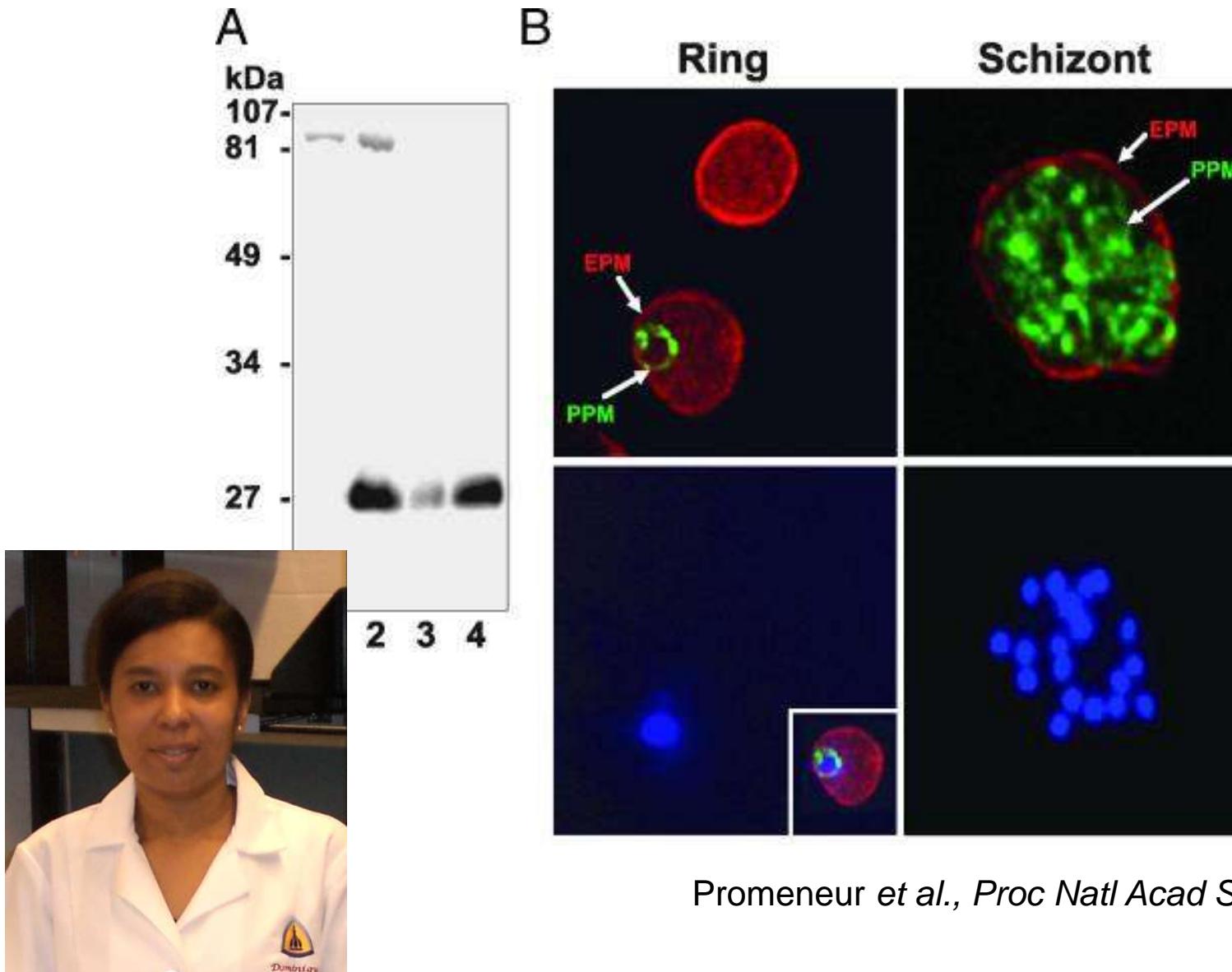
arrows, endocytic
invaginations

Nielsen et al.,
J Cell Biol, 1993

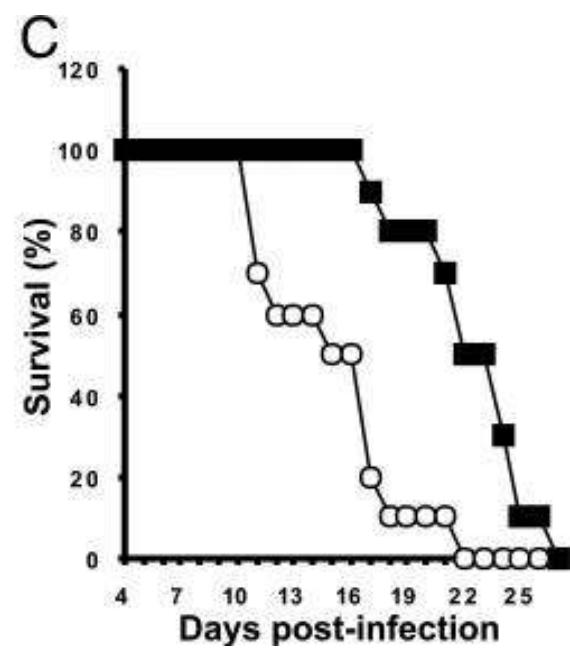
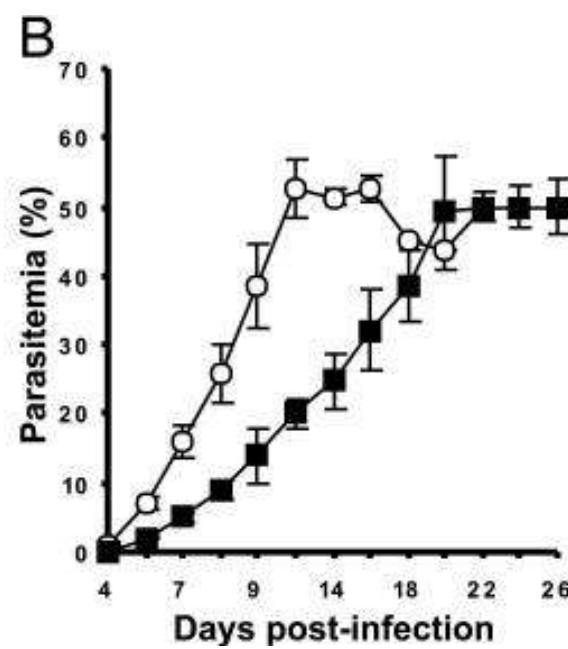
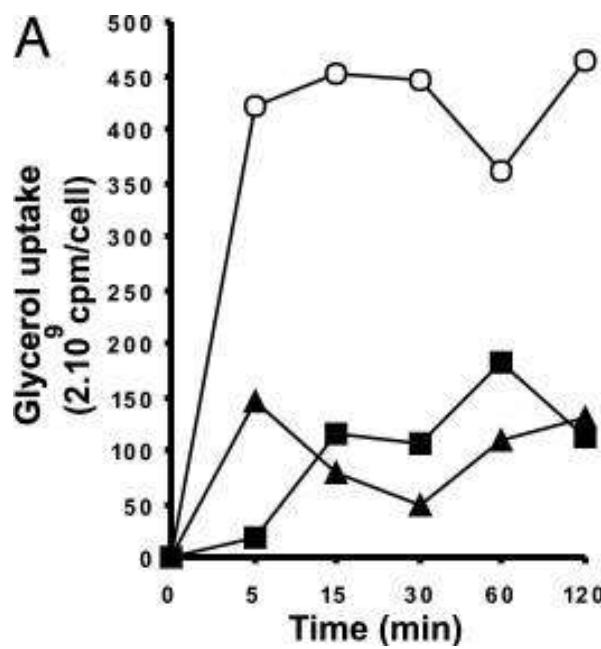
Arsenic toxicity in aquaglyceroporin-9 null mice



Aquaglyceroporin PbAQP increases malaria virulence



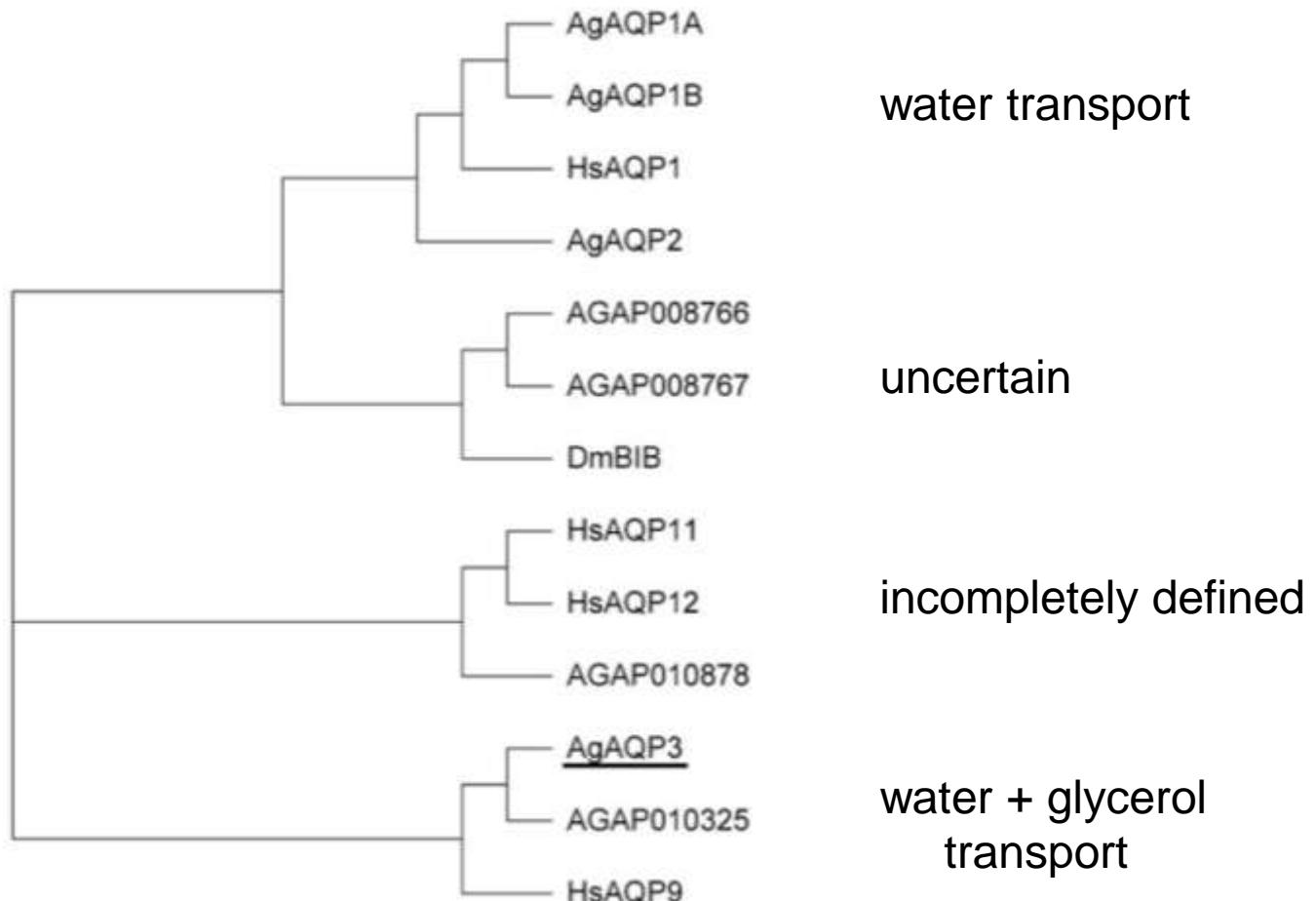
Aquaglyceroporin PbAQP increases malaria virulence



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

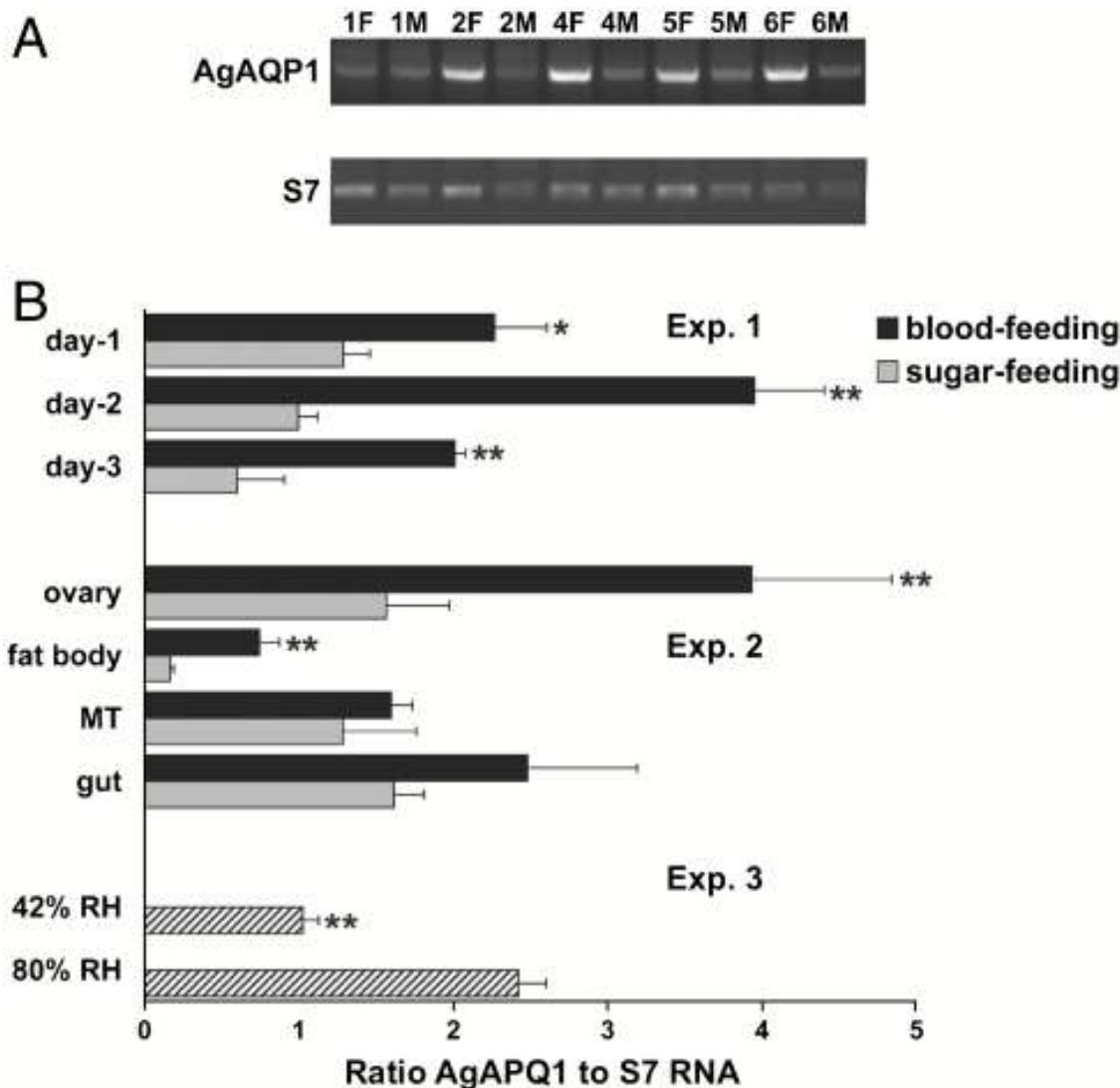
Liu, Promeneur *et al.*, *Proc Natl Acad Sci*, 2007

Aquaporins in *Anopheles gambiae*

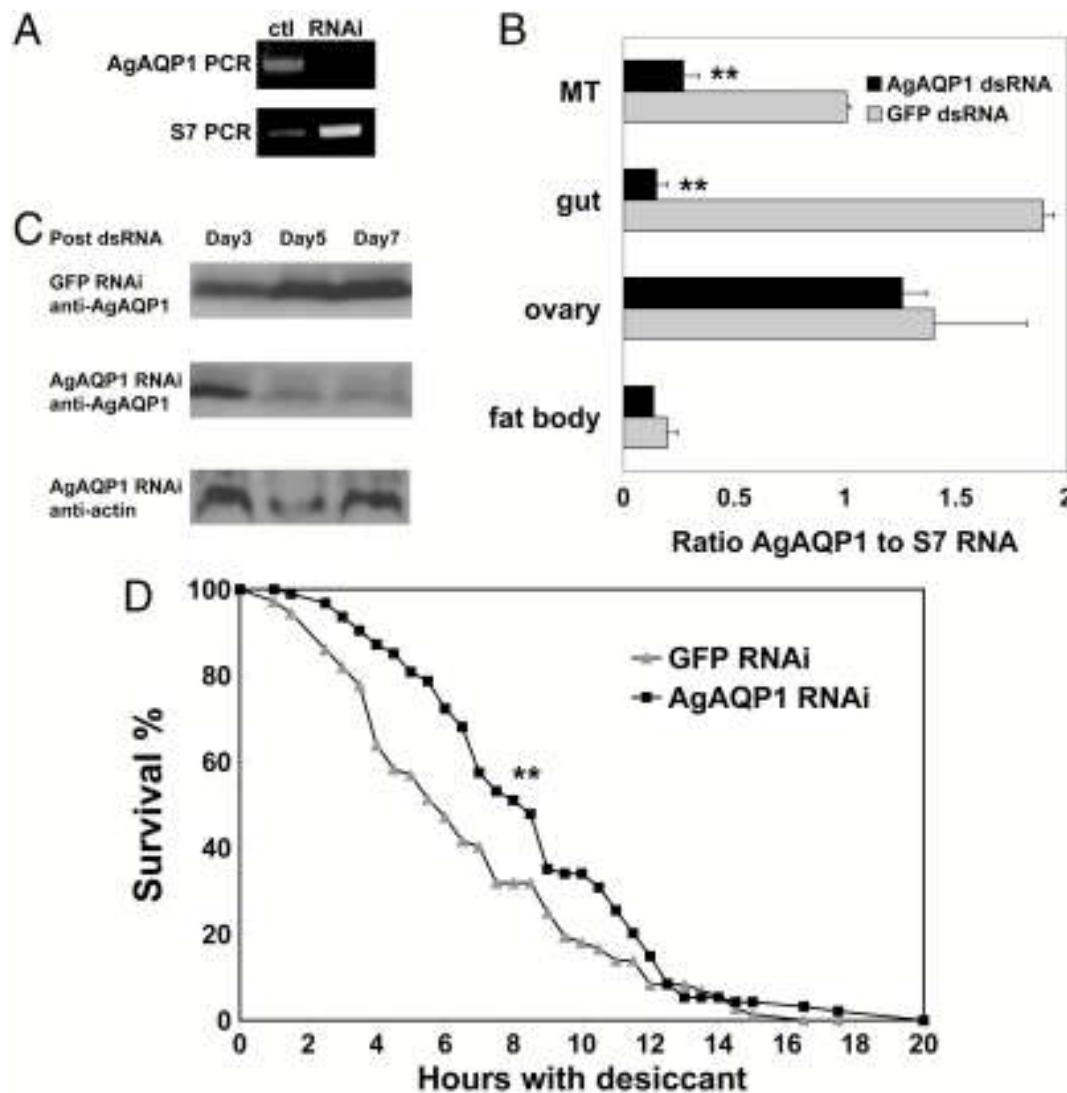


Liu et al., Proc Natl Acad Sci, 2011
Tsujimoto et al., PLoS One, 2013
Liu et al., Biol Cell, 2016

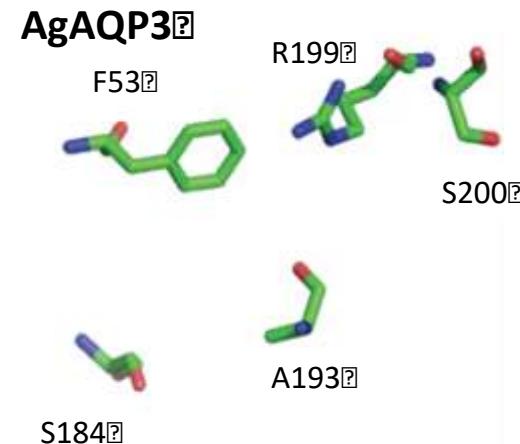
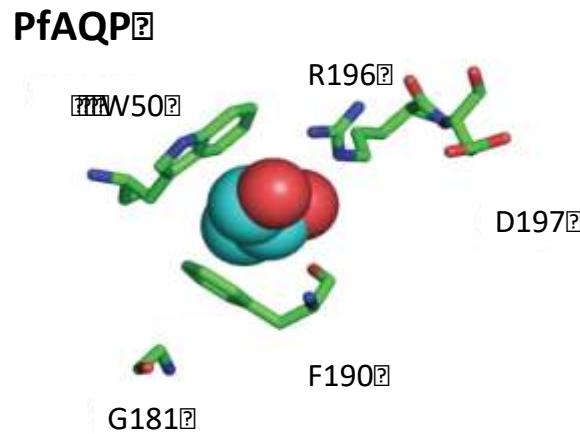
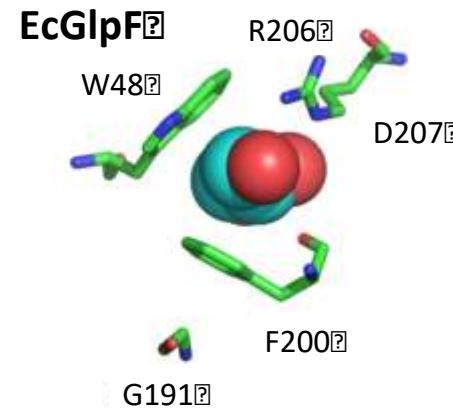
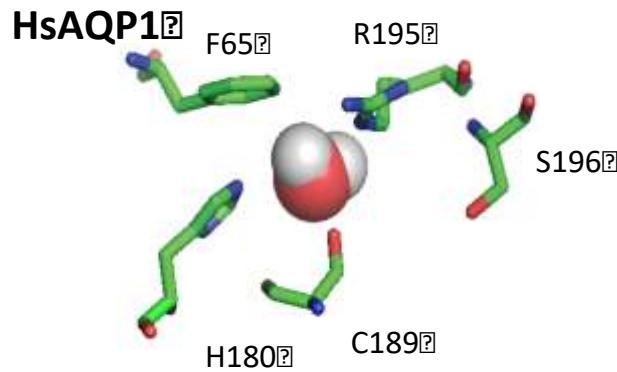
AgAQP1 – blood feeding and humidity



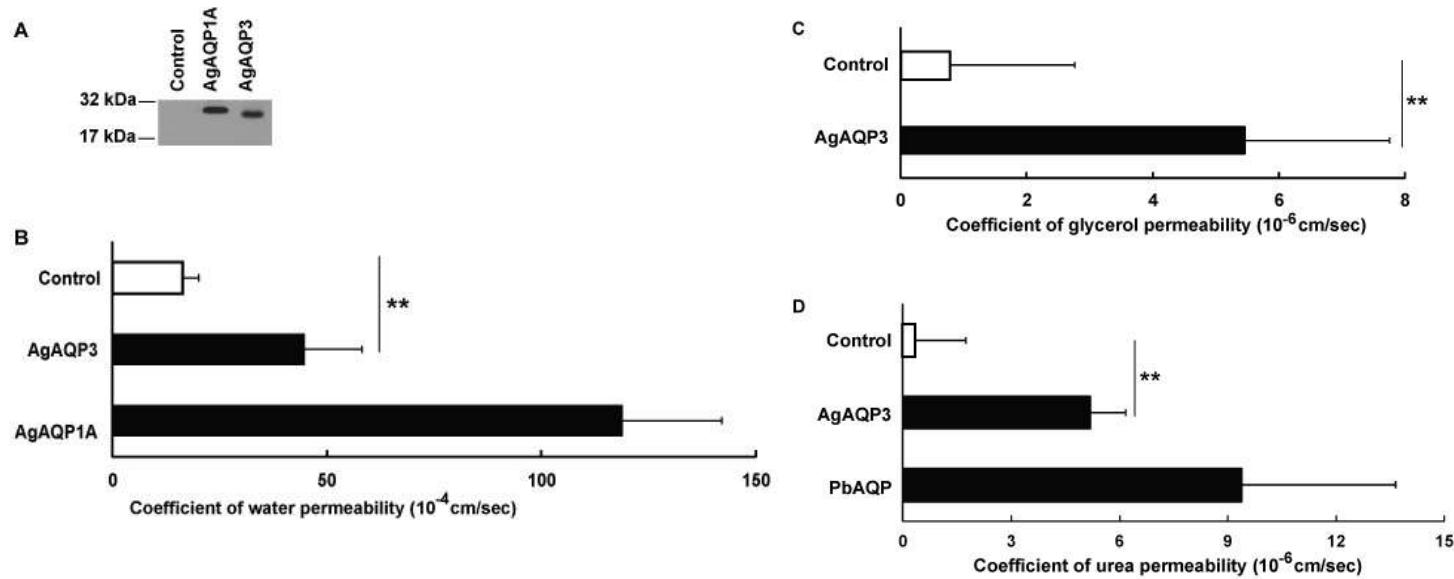
AgAQP1 – dessication sensitivity



AgAQP3 – atypical pore lining residues

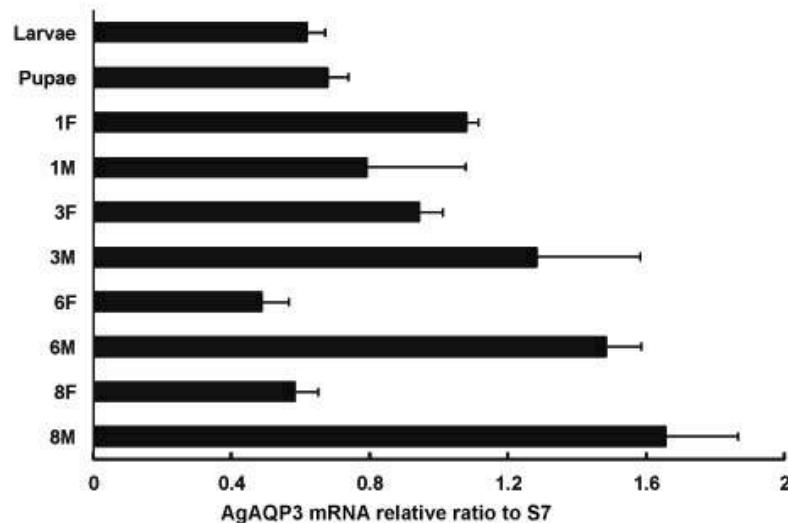


AgAQP3 – water + glycerol transport

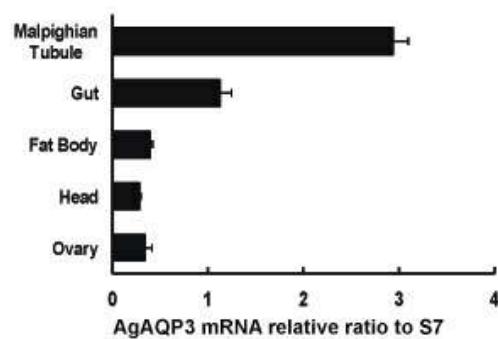


AgAQP3 – expression patterns

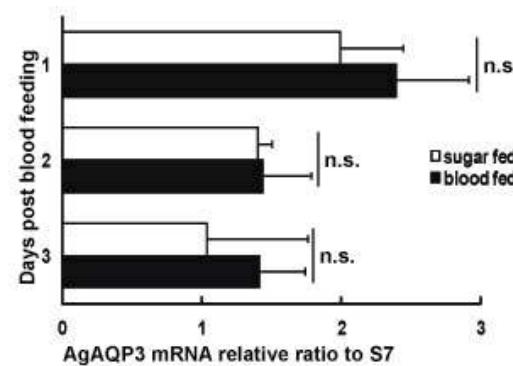
A?



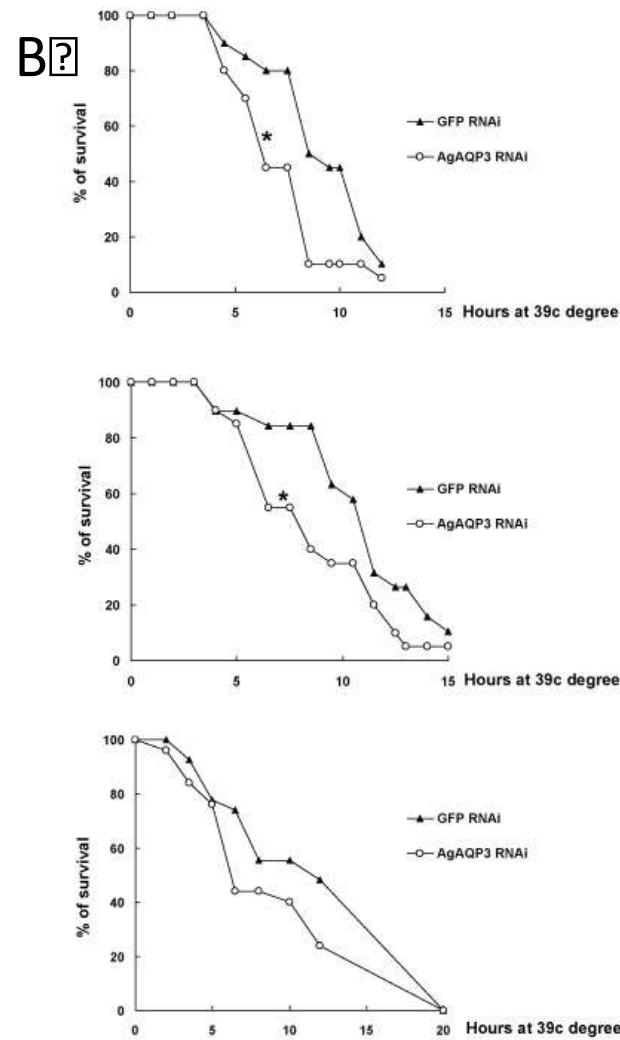
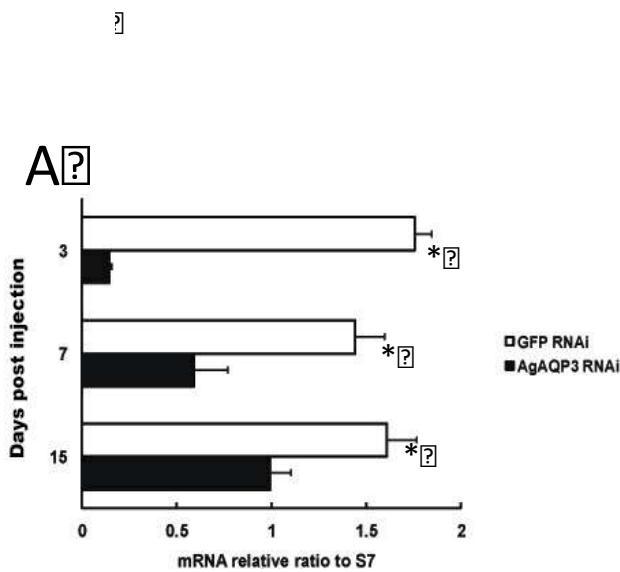
B?



C?

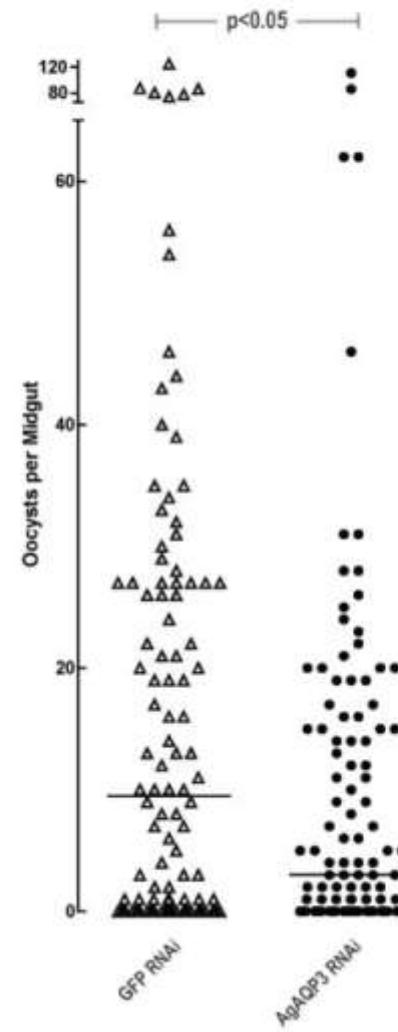
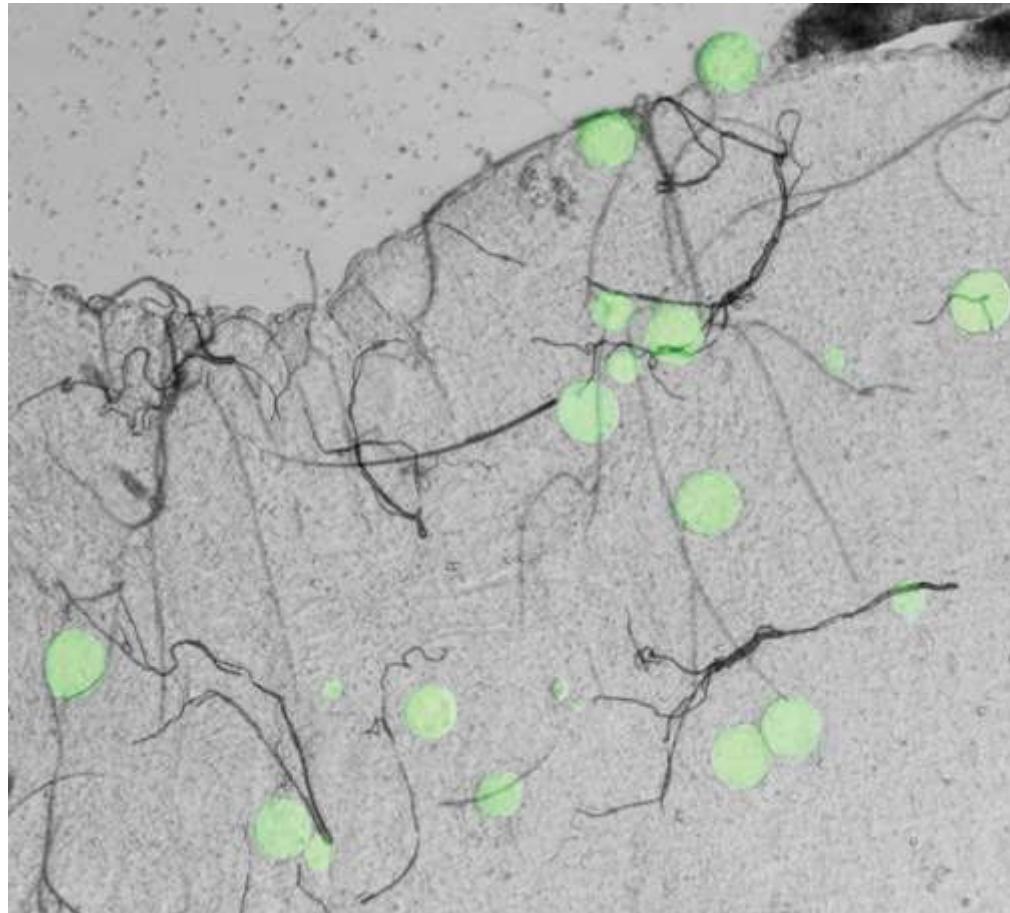


AgAQP3 – dessication resistance

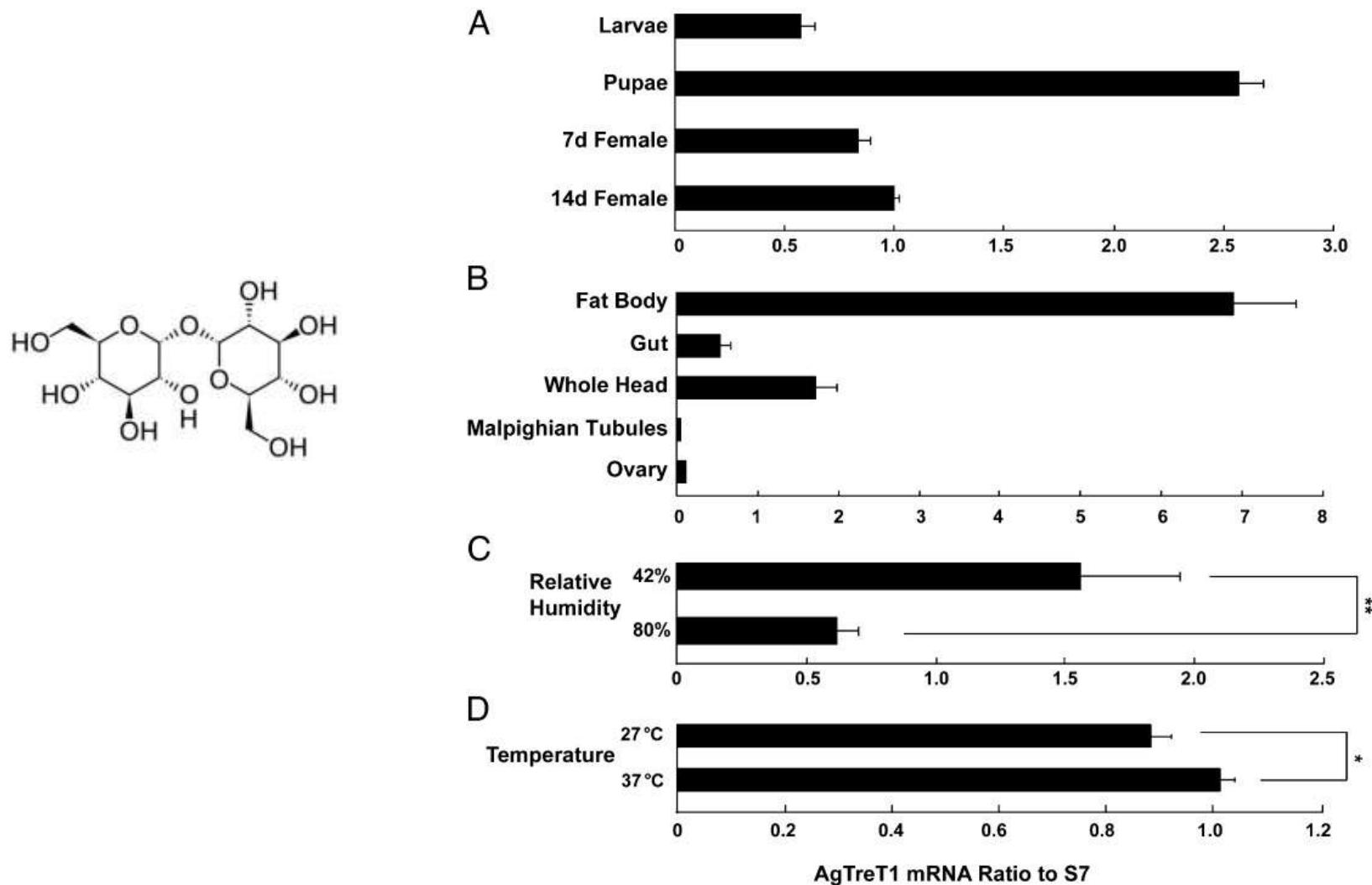


AgAQP3 – midgut malaria invasion

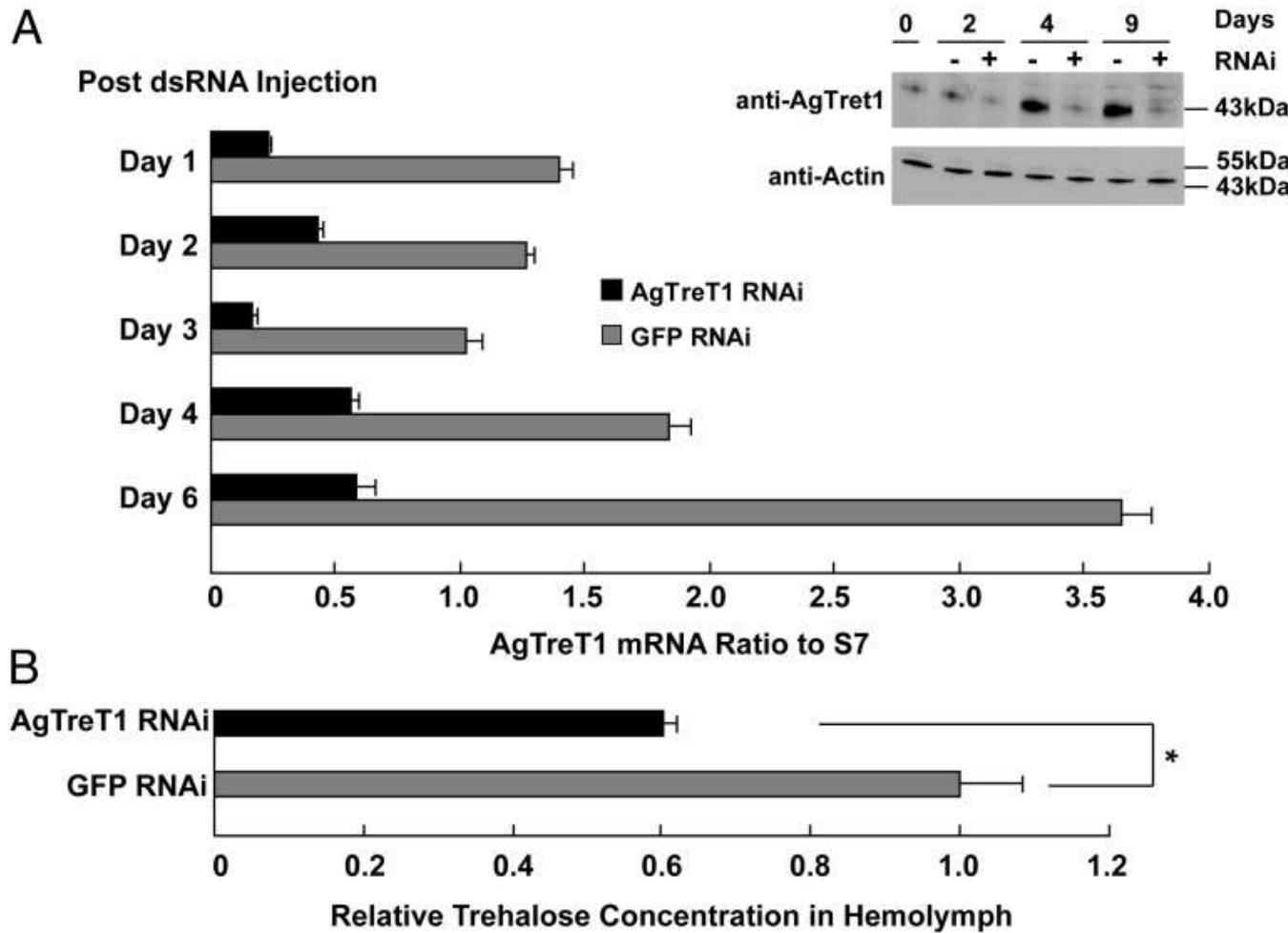
Fig 6



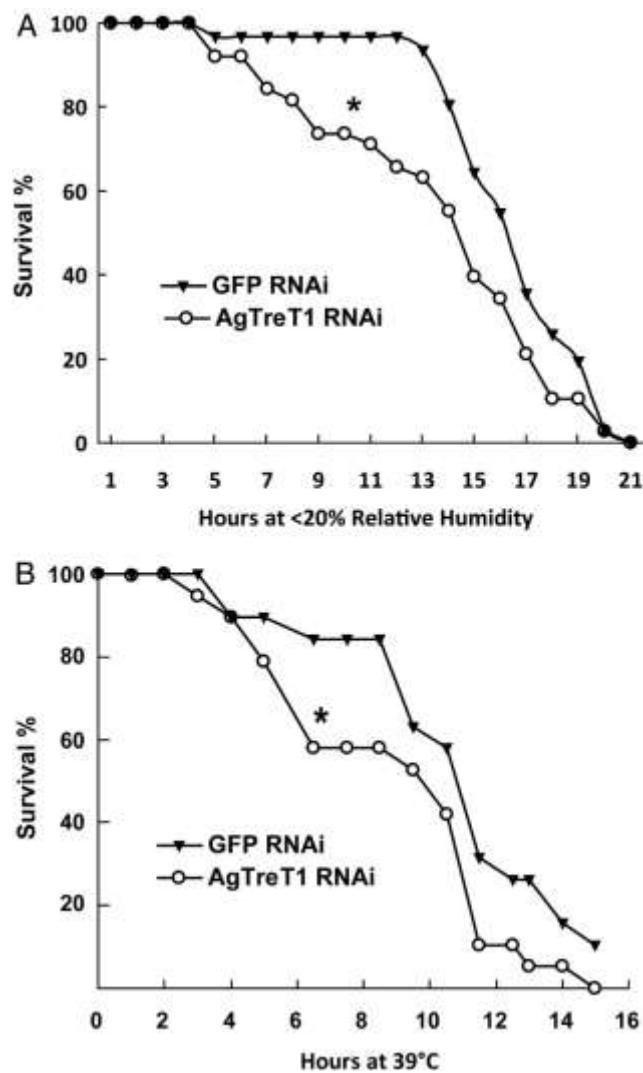
AgTreT1 – trehalose transporter



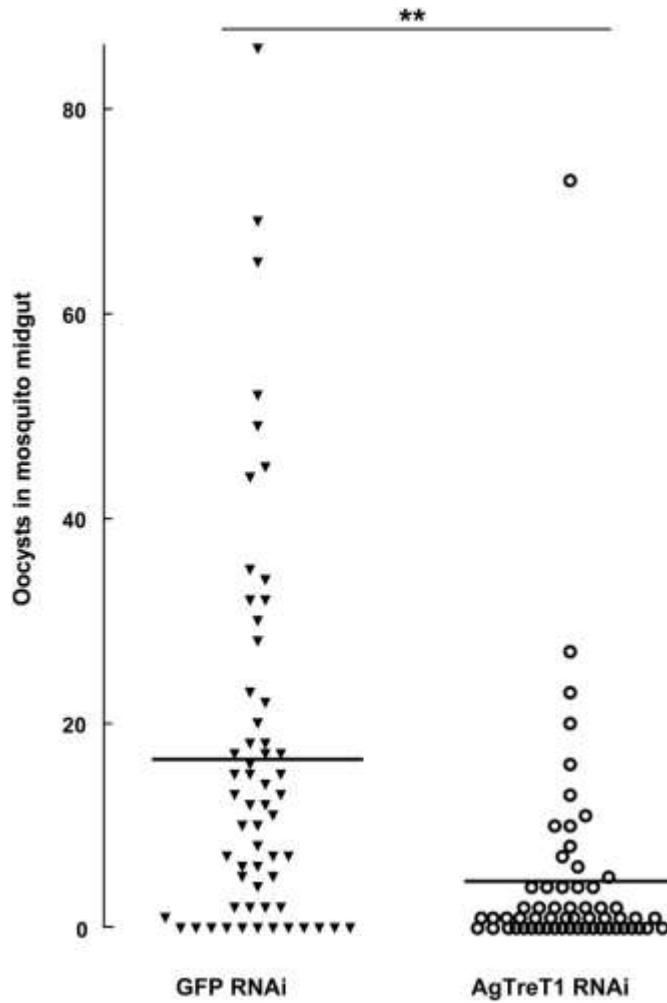
AgTreT1 – trehalose transporter



AgTreT1 – dessication and heat resistance

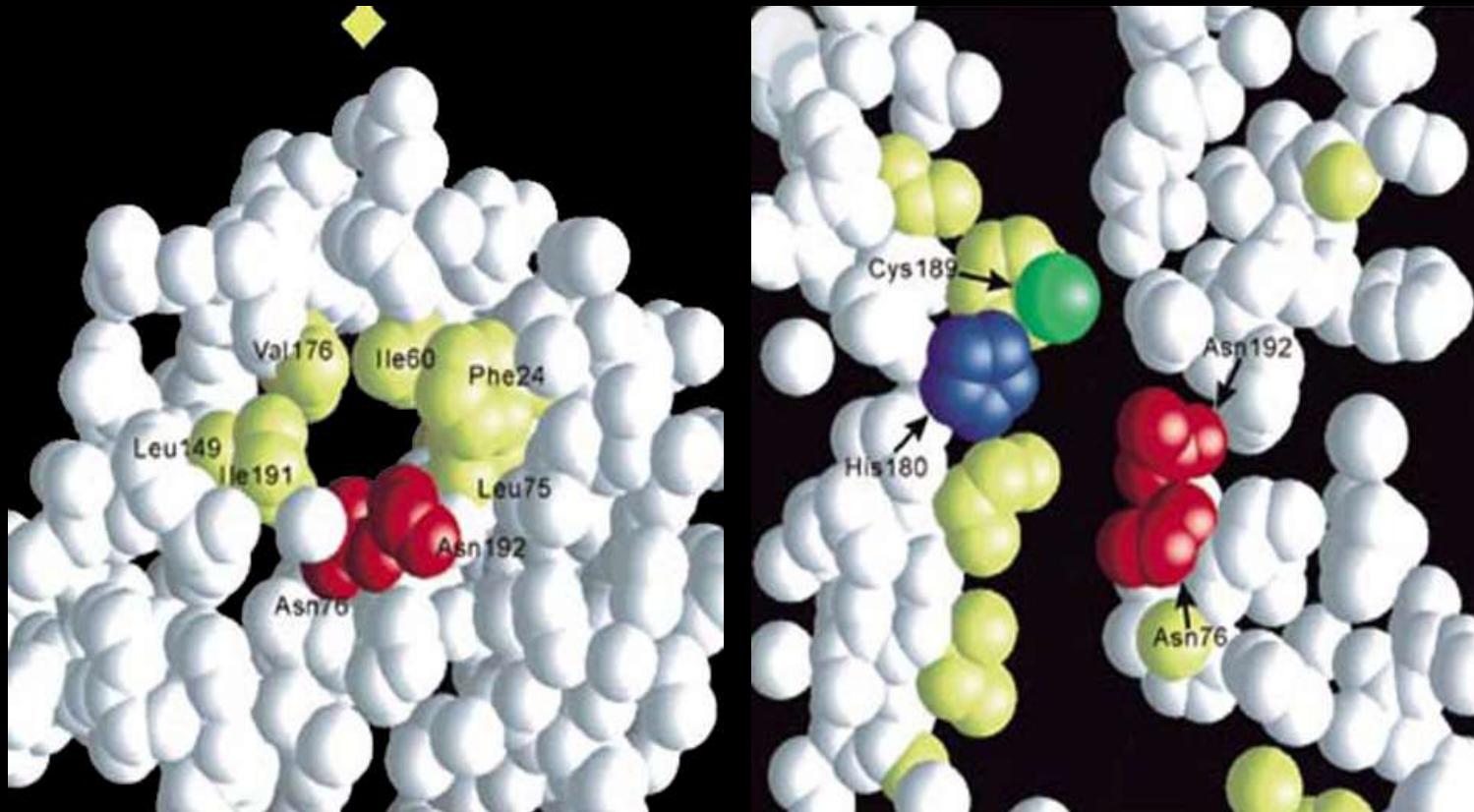


AgTreT1 – midgut malaria invasion



Structure of AQP1

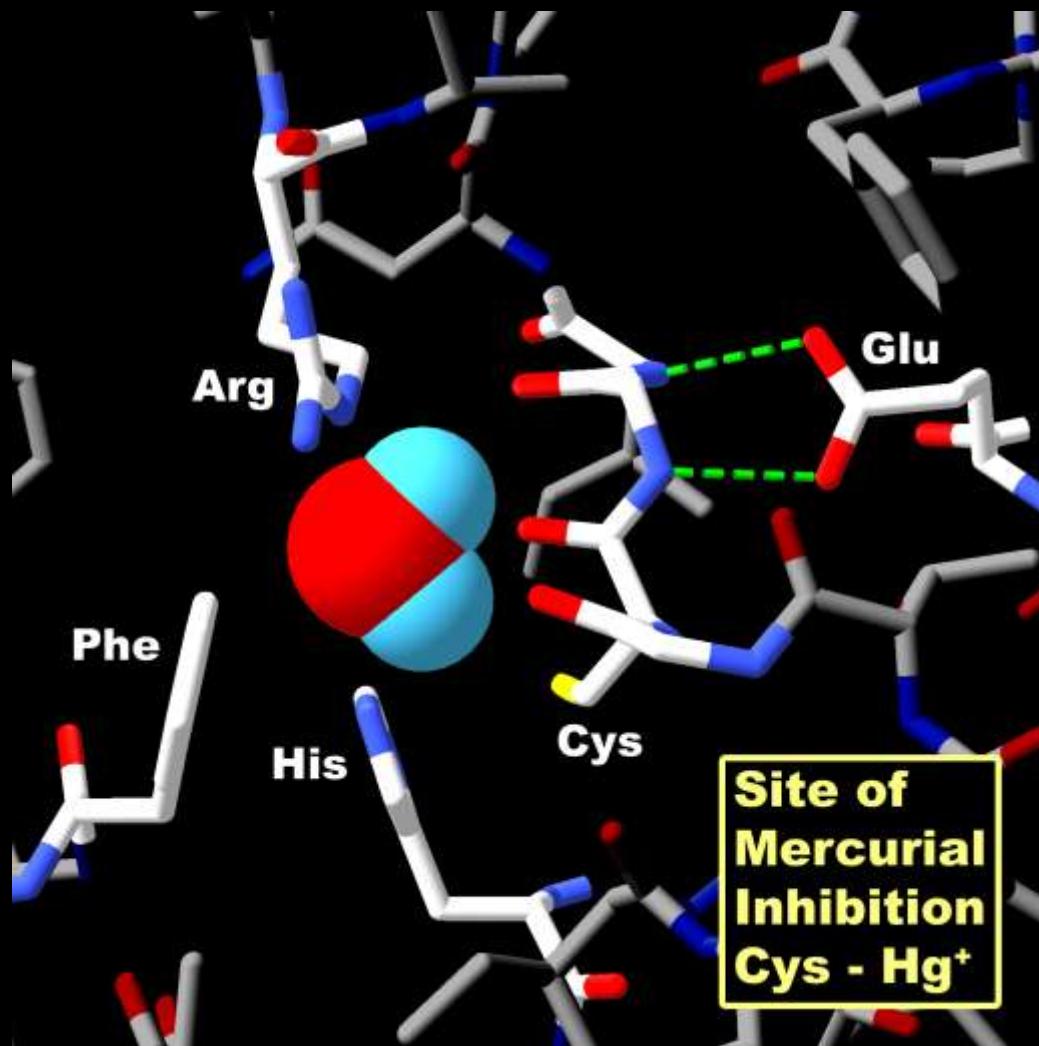
Membrane crystallography (with Y. Fujiyoshi, Kyoto and A. Engel, Basel)



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

Structure of AQP1

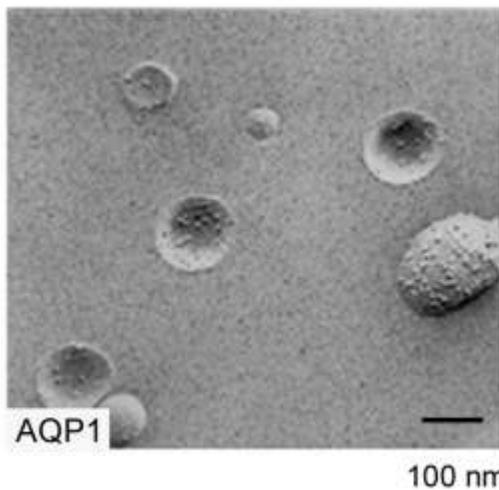
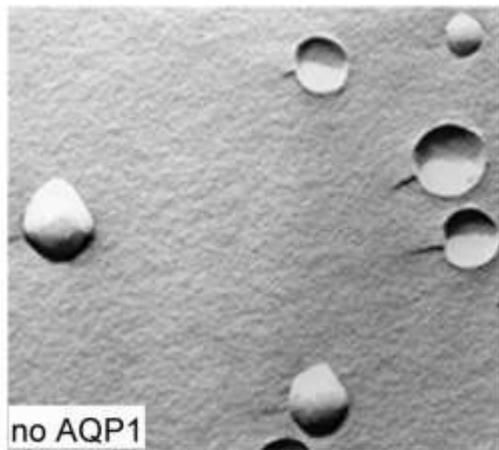
Hg⁺⁺ inhibitory site



Verification of AQP1 function

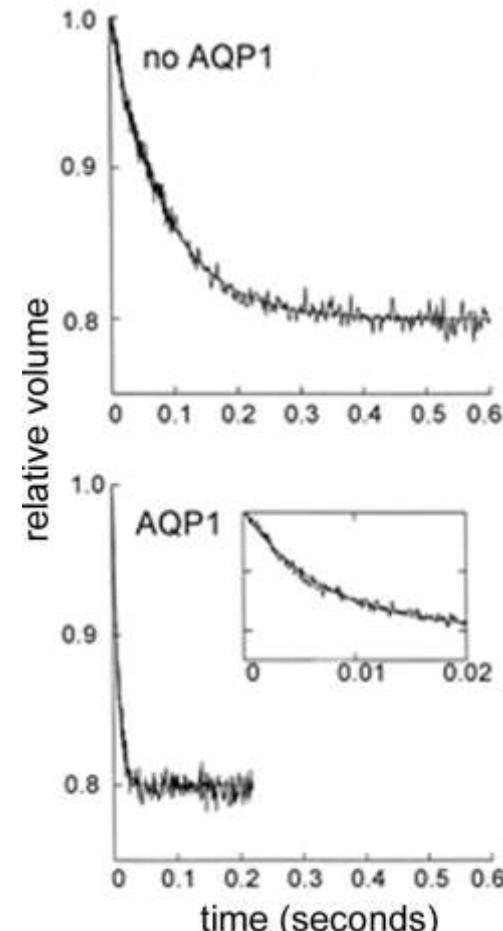
Functional reconstitution

Reconstituted membranes



Zeidel et al., *Biochemistry* 1992, 1994

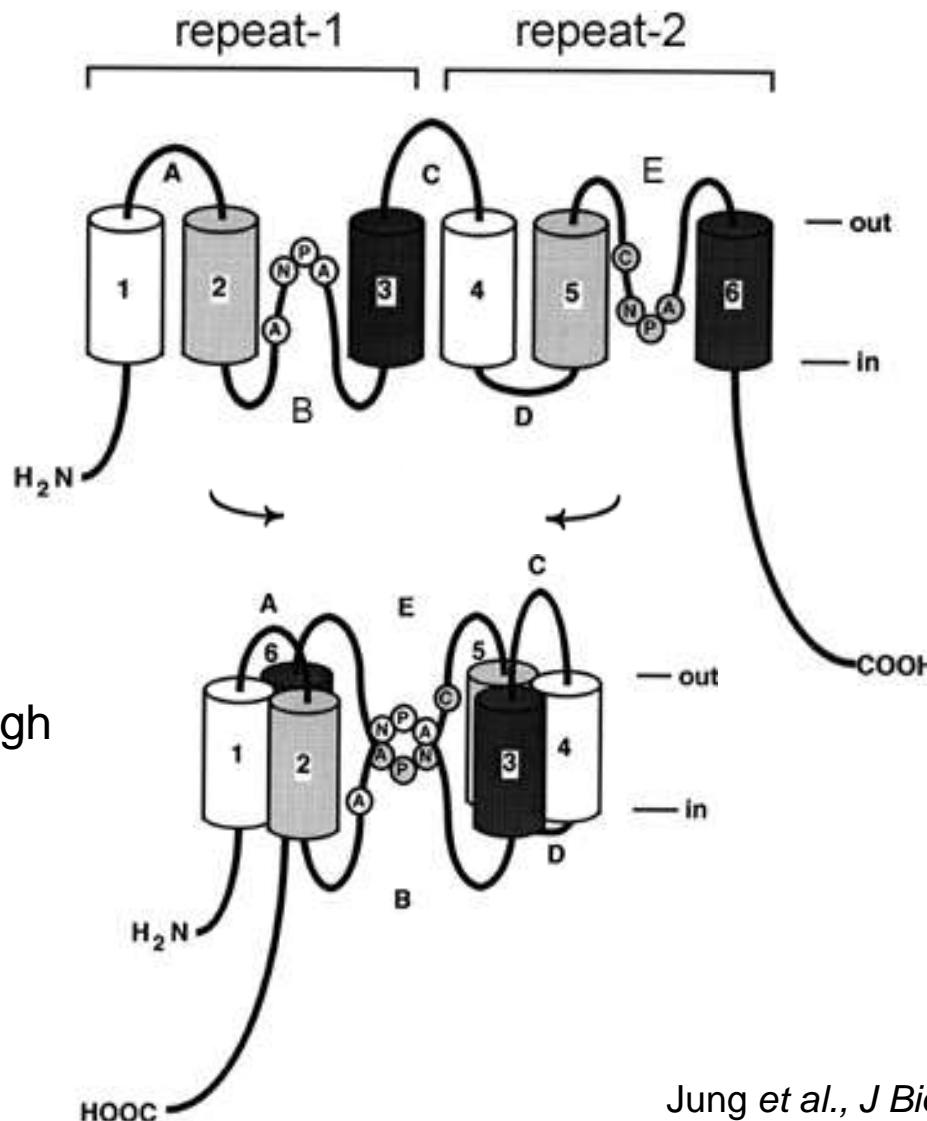
Stopped-flow
water permeability



Structure of AQP1

The Hourglass Model

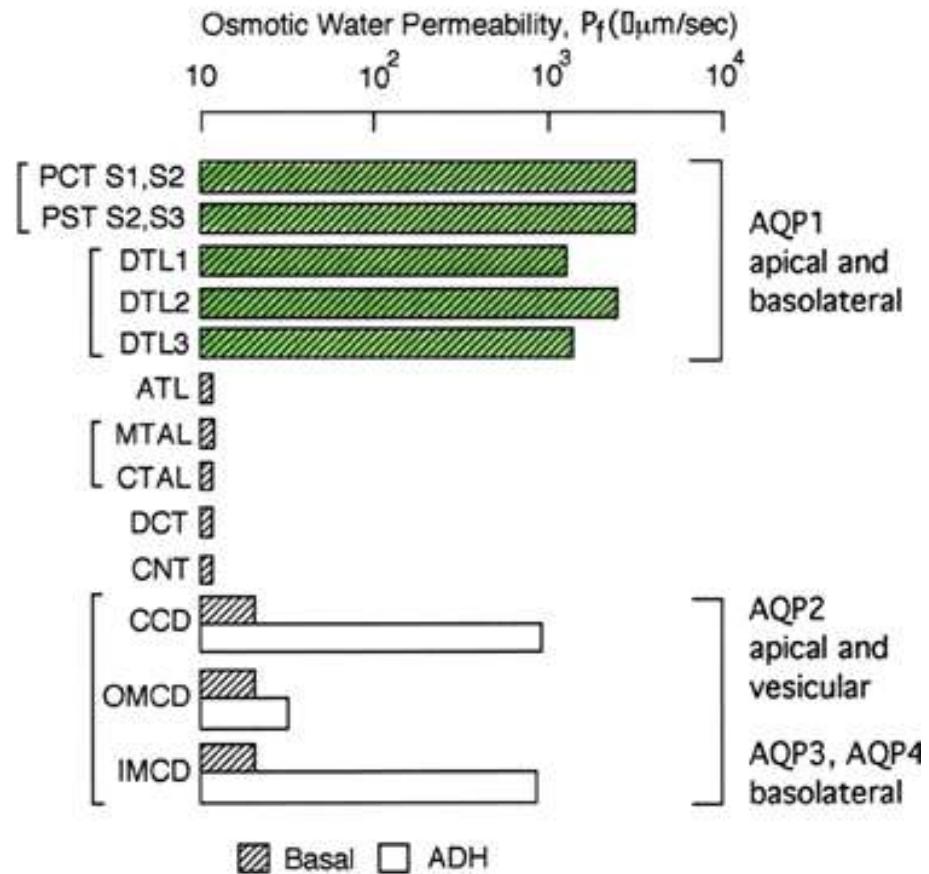
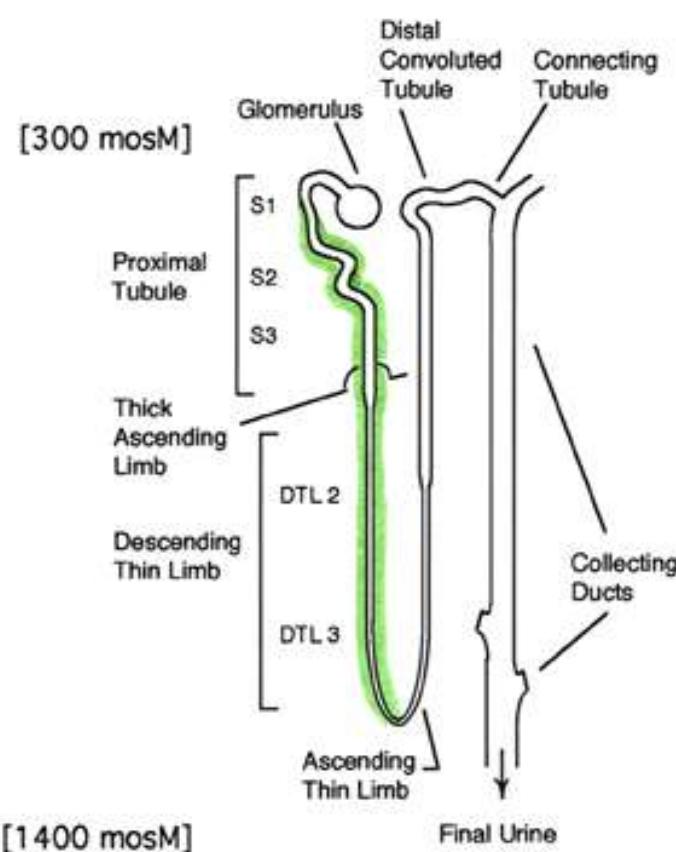
Tandem repeats
oriented at
 180°



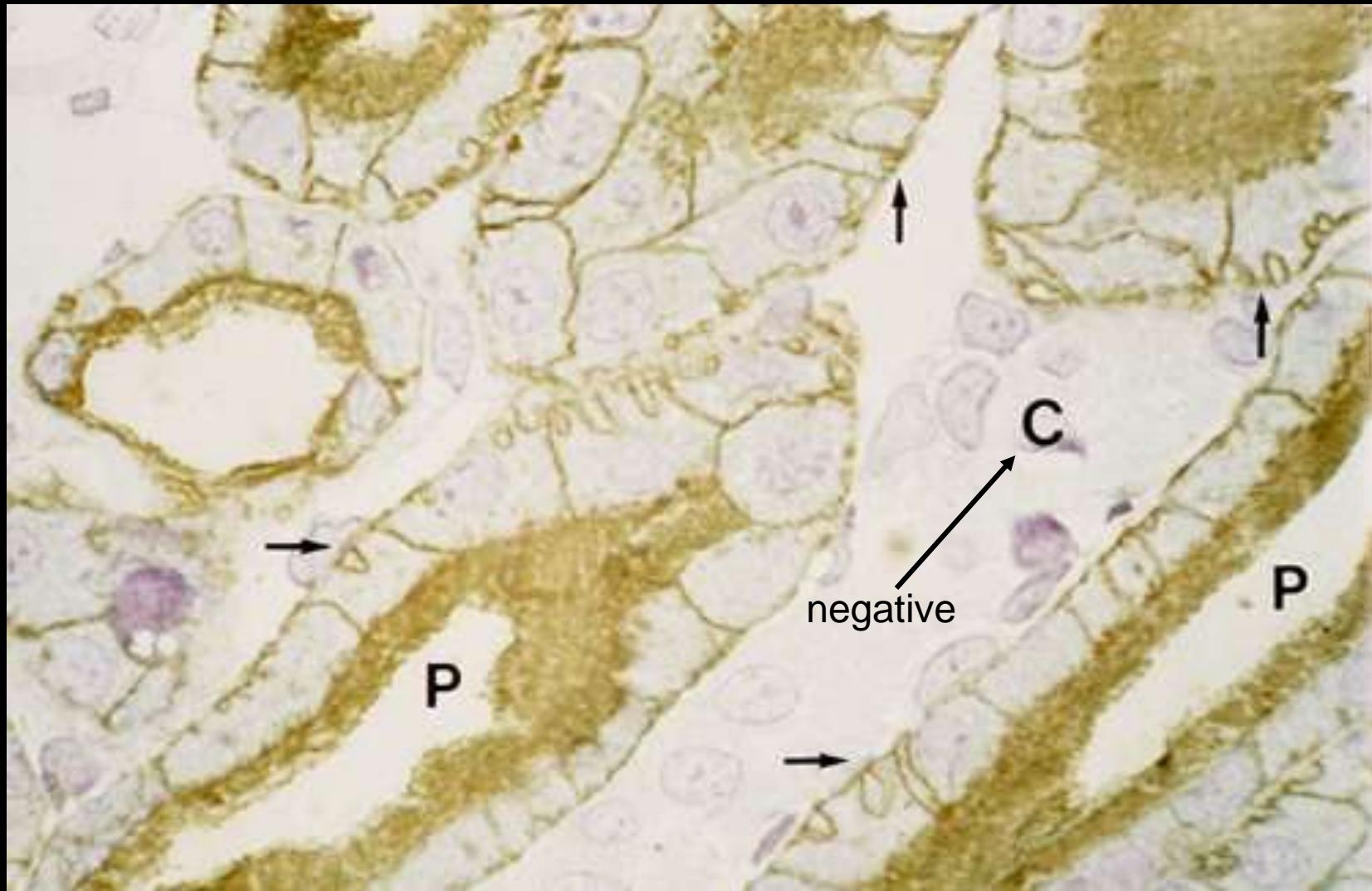
Localization of AQP1 in kidney

(with Søren Nielsen, Aarhus)

Aquaporin distribution—Renal water permeability



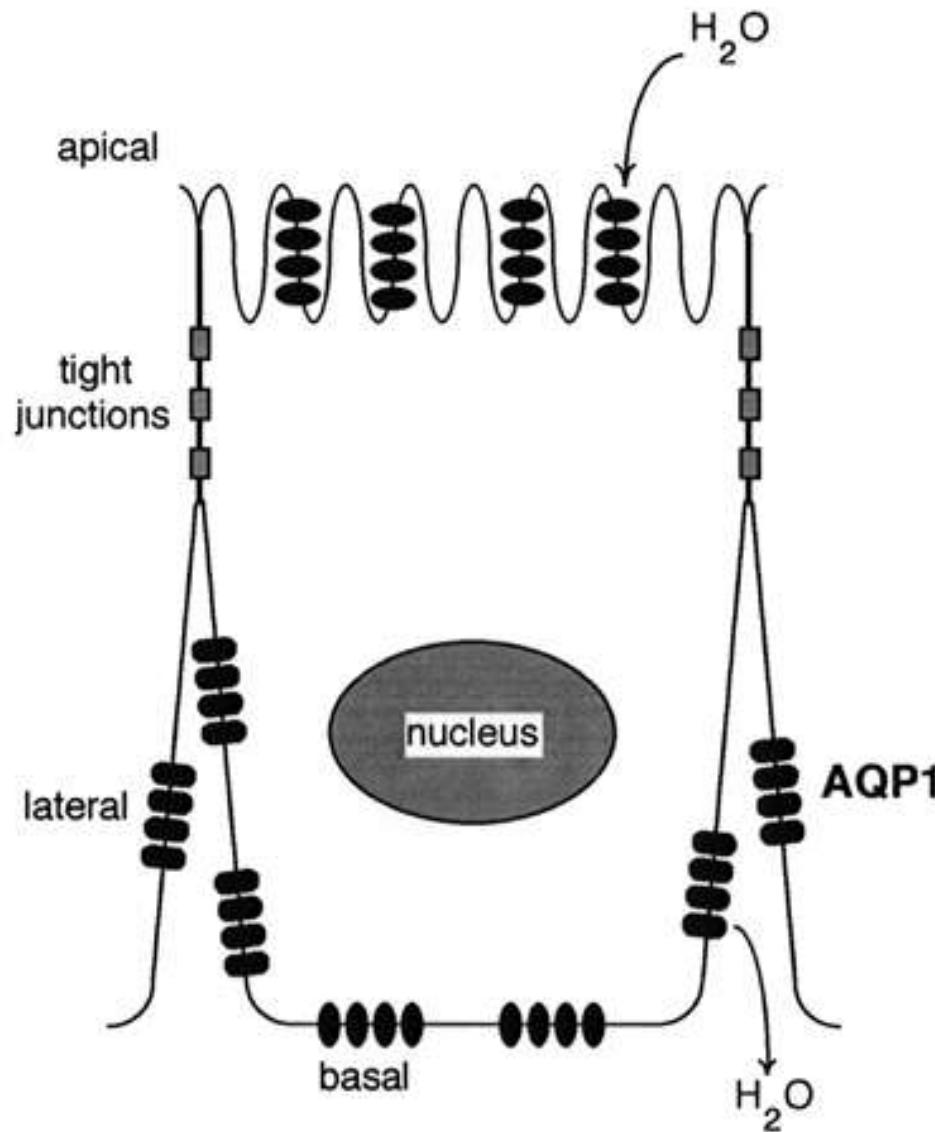
AQP1 in proximal nephron



P, proximal tubule lumen C, collecting duct

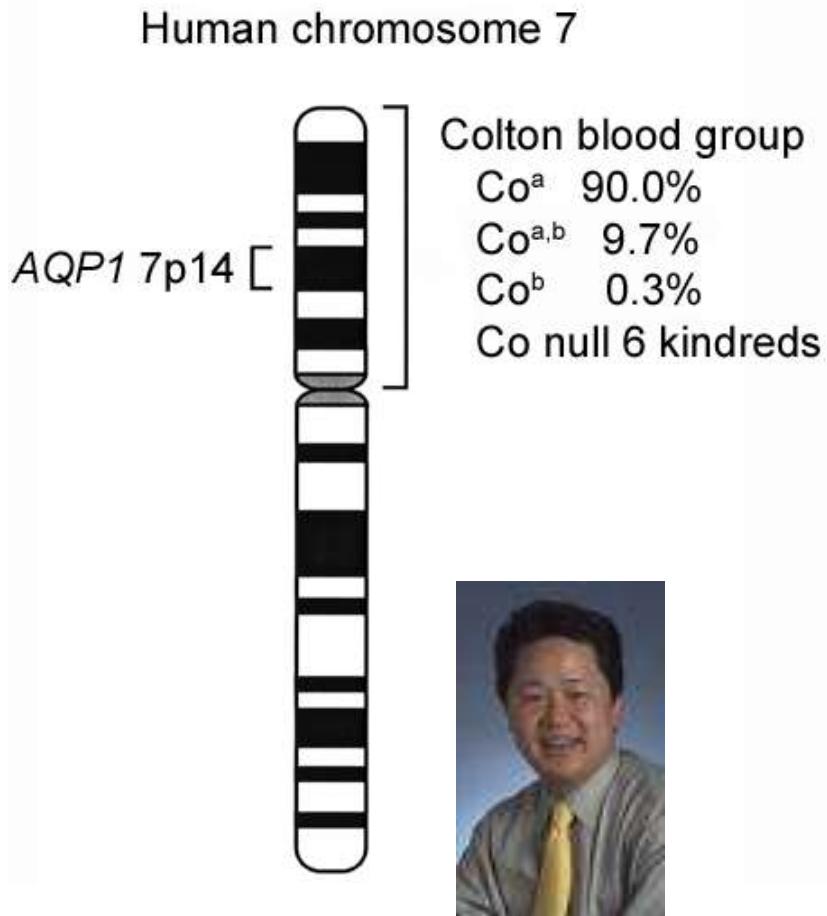
Nielsen et al., *J Cell Biol*, 1993

AQP1-mediated constitutive transcellular water movements

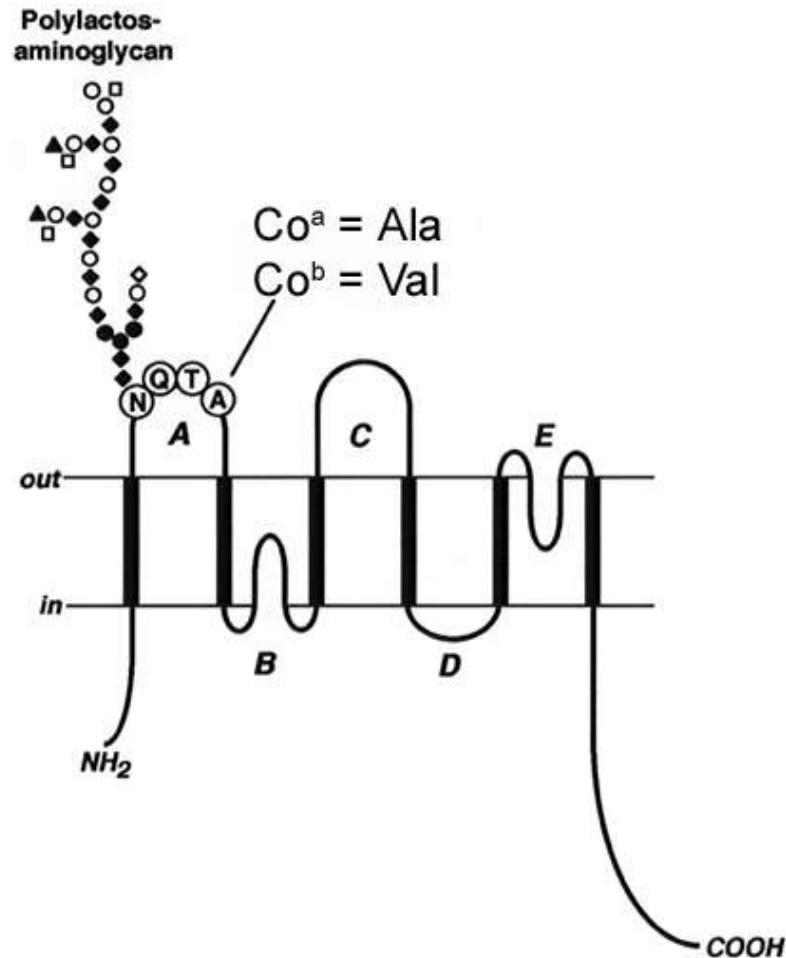


AQP1 and the Colton antigen

Coincidental chromosomal locus



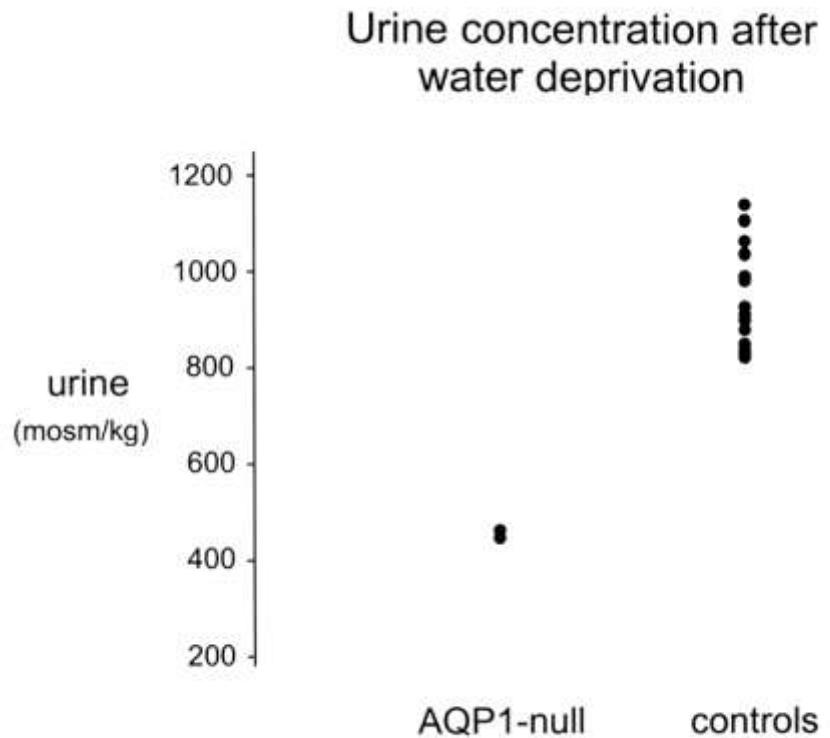
Surface polymorphism



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

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

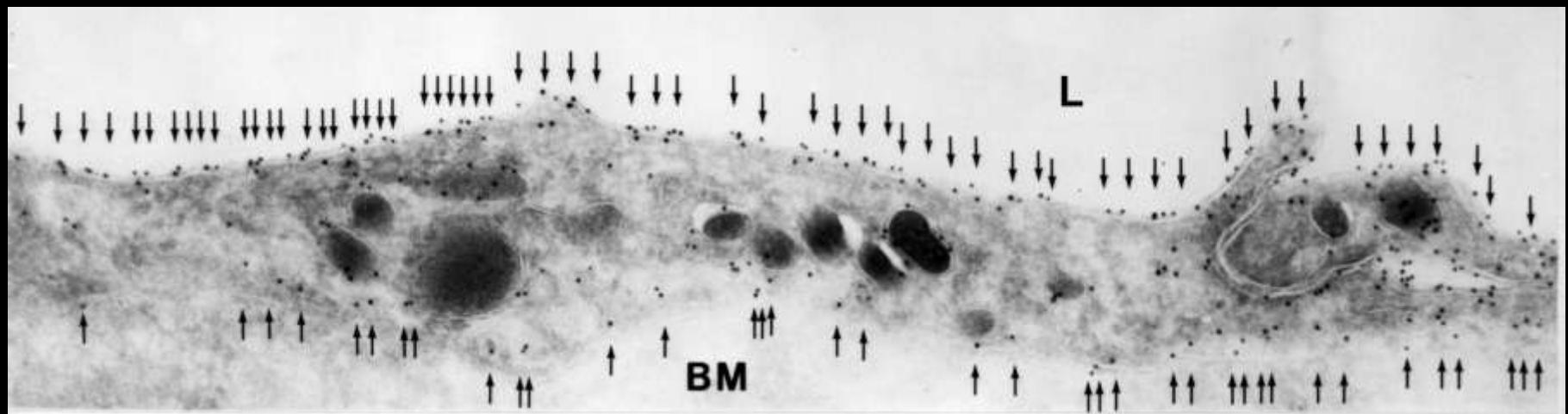
AQP1 null humans—Renal concentration defect (Landon King and Mike Choi, JHMI)



Dx—Mild Nephrogenic Diabetes Insipidus

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

AQP1 in human capillary endothelium



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

AQP1 null humans

Pulmonary capillary defect

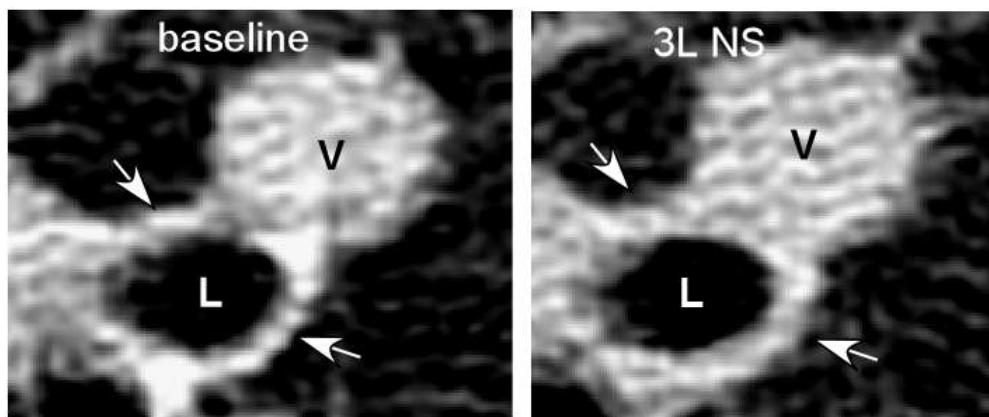
Johns Hopkins Hospital inpatient study

Baseline—High resolution CT scan of lung

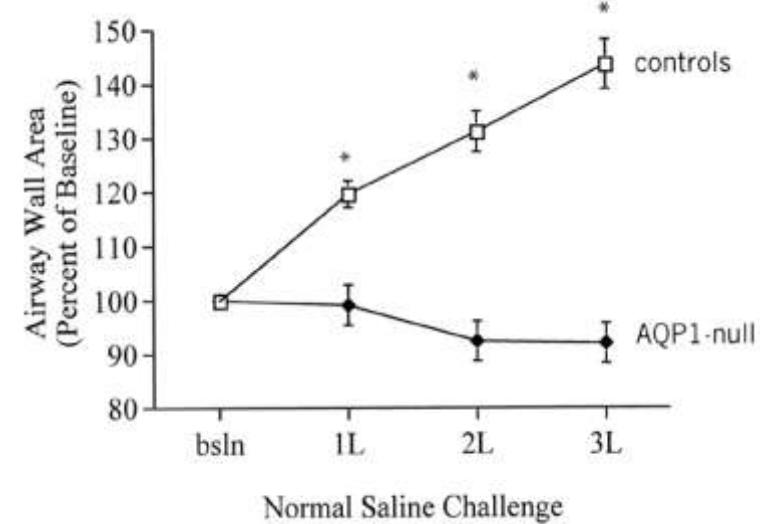
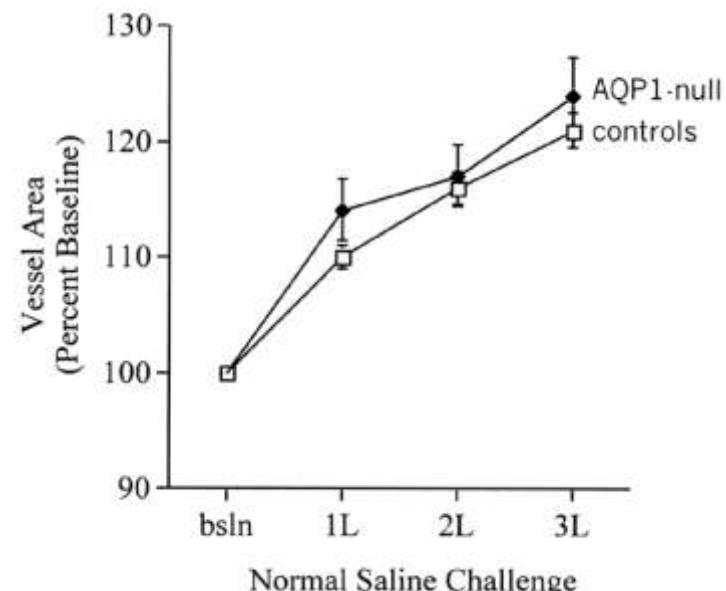
Rapid—Saline infusion, 3 x 1 liter

Repeat—HRCT scans after each liter

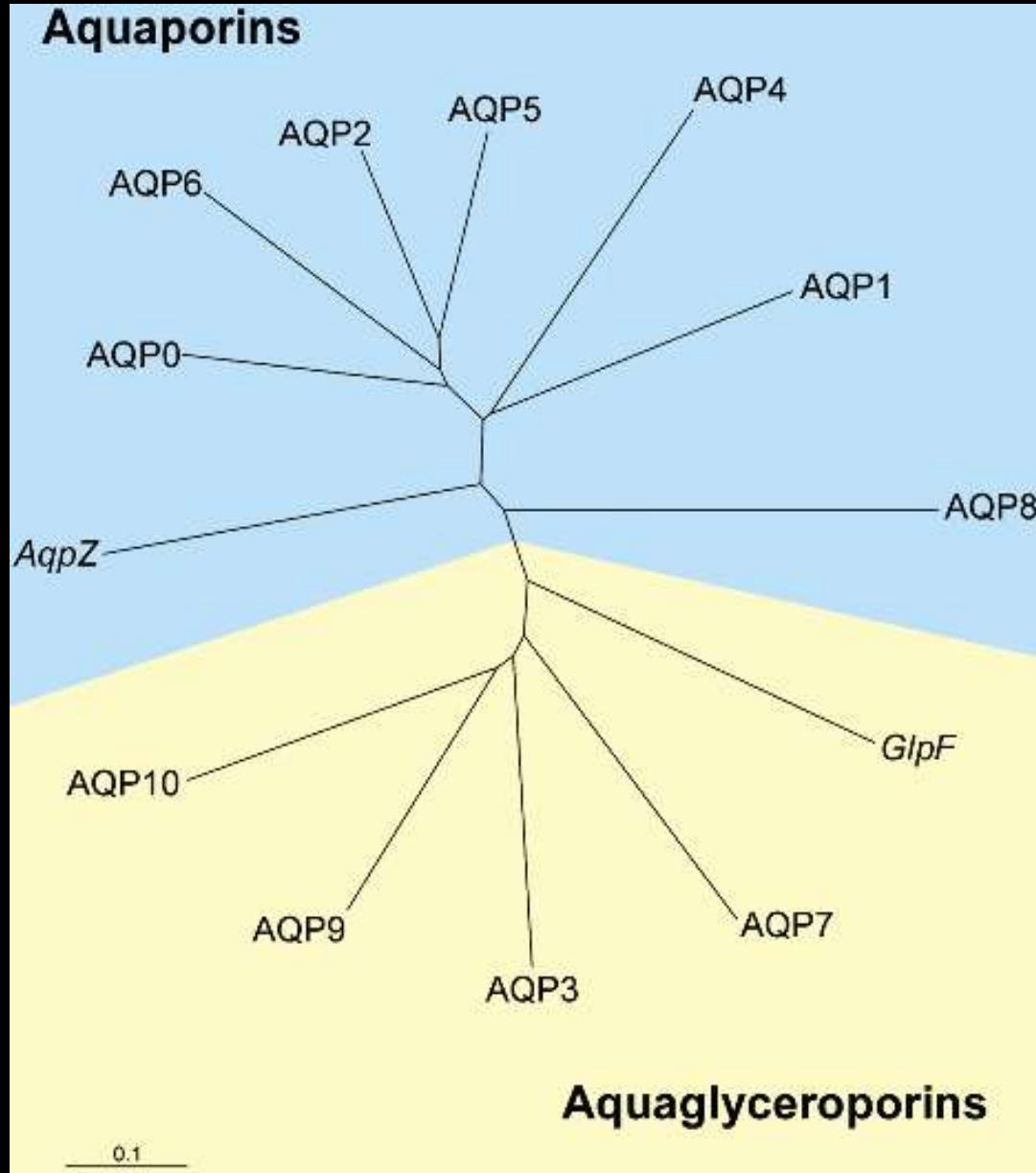
Measure—Bronchiolar (1-5 mm) wall thickness



Dx—Decreased vascular
water permeability



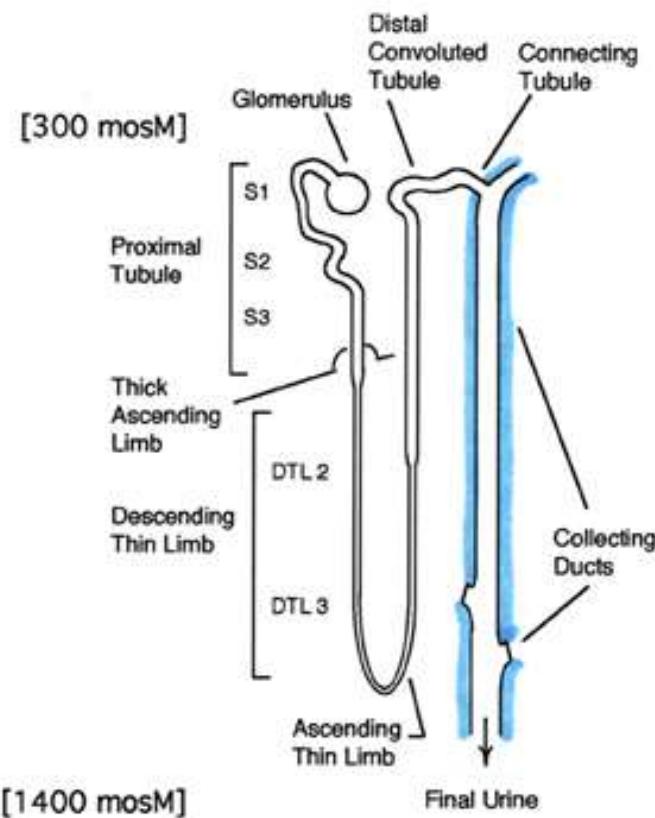
Human Aquaporin Repertoire



AQP2—A regulated water channel

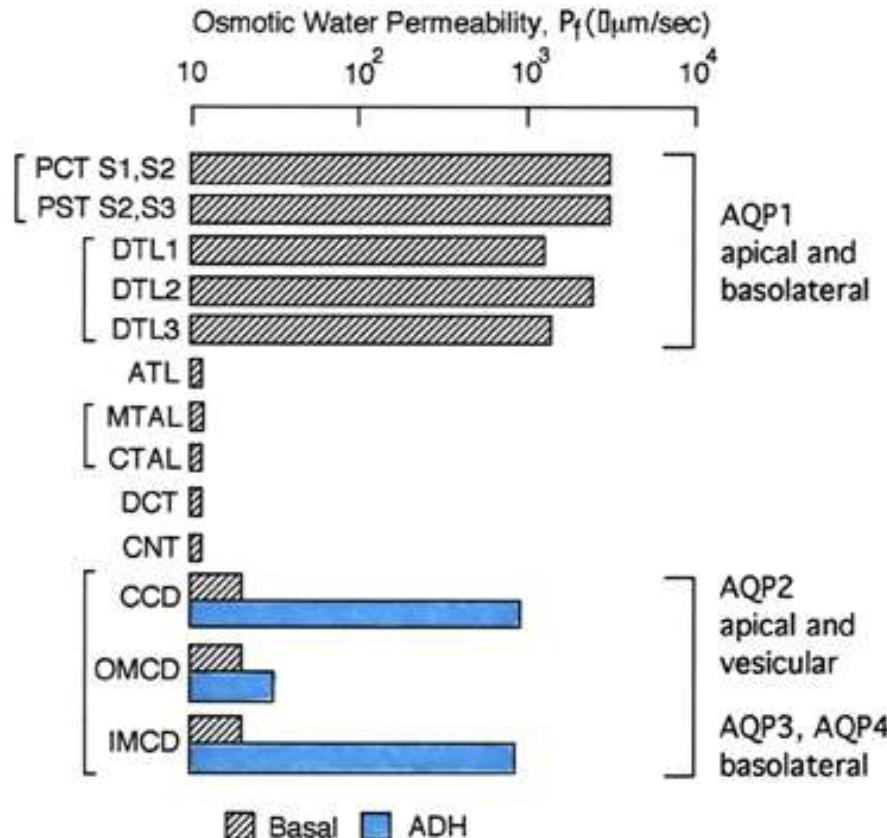
cDNA cloned by homology

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



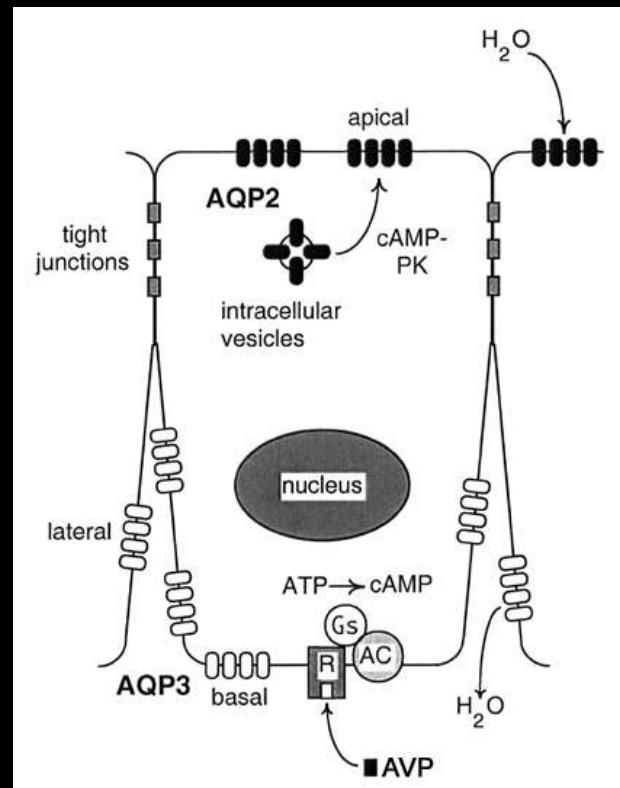
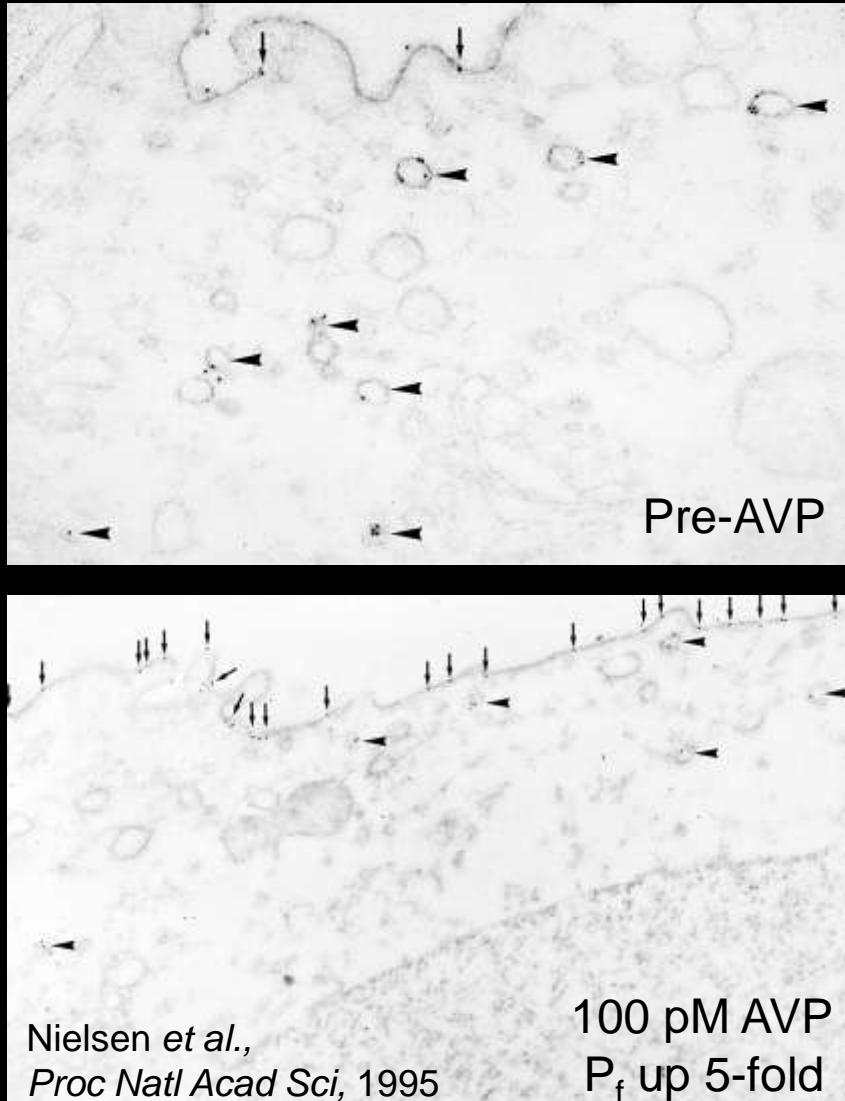
AQP2 localization in kidney

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



AQP2—Acute regulation by AVP

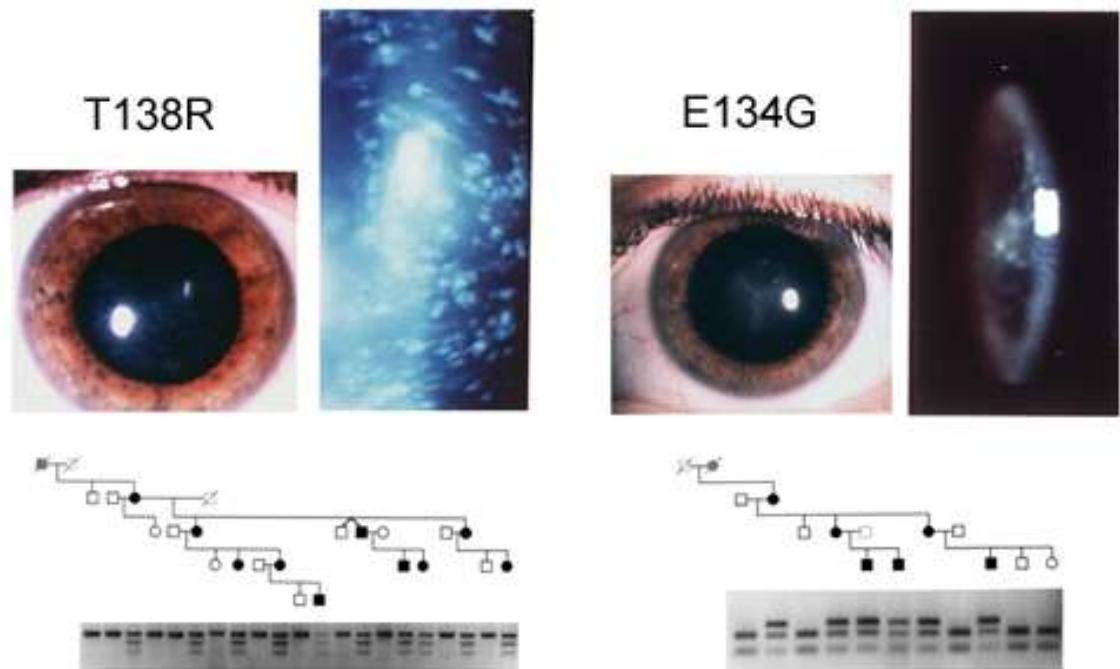
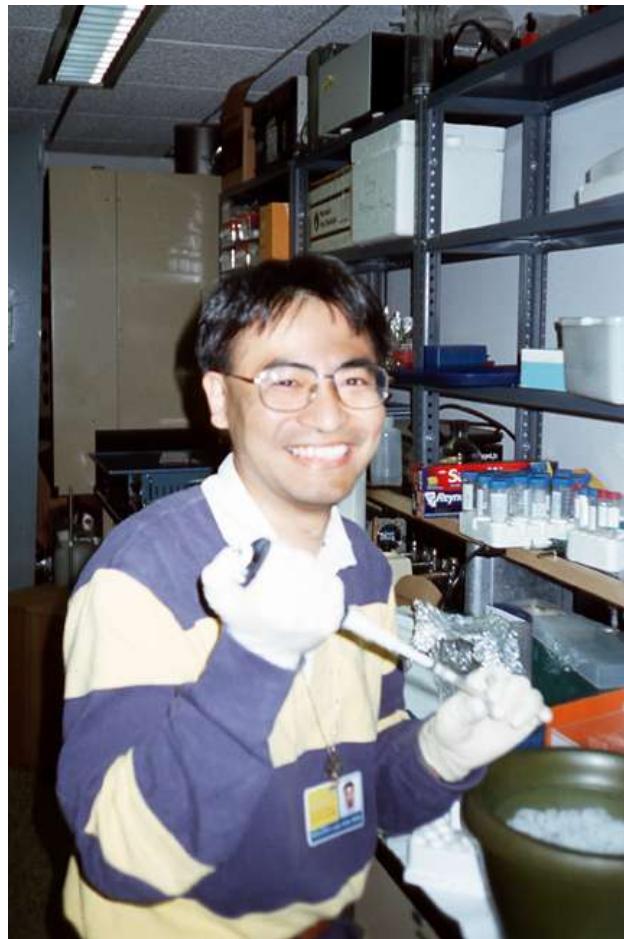
Isolated renal collecting ducts



Inherited defects (rare)
Nephrogenic DI (severe)

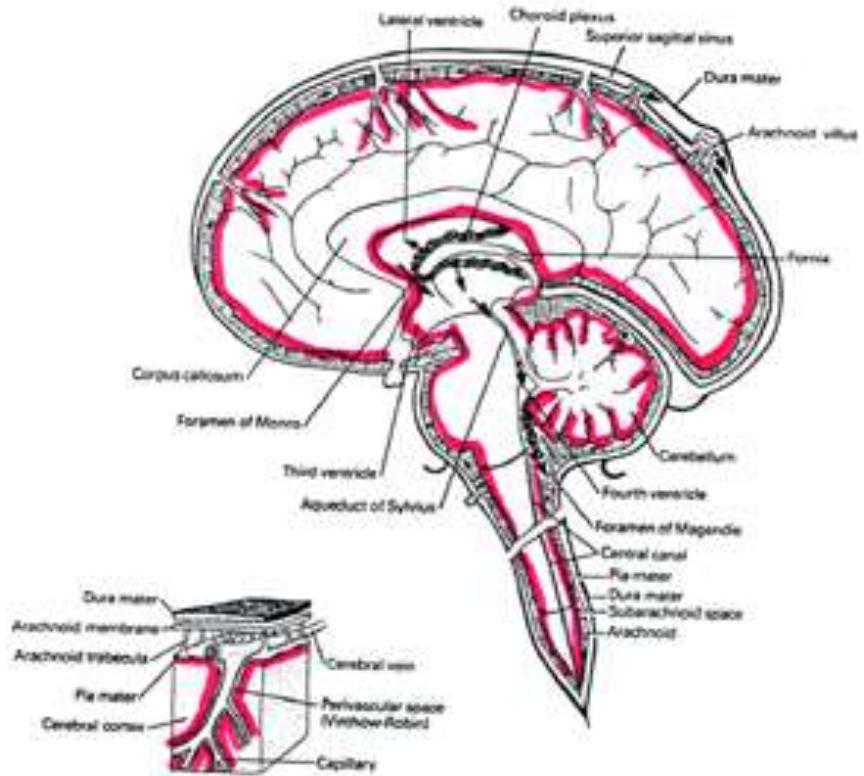
Acquired defects (very common)
Overexpression—Fluid retention
Underexpression—Enuresis

AQP0 and congenital cataracts



Francis et al., *Human Mol Genetics* 2000

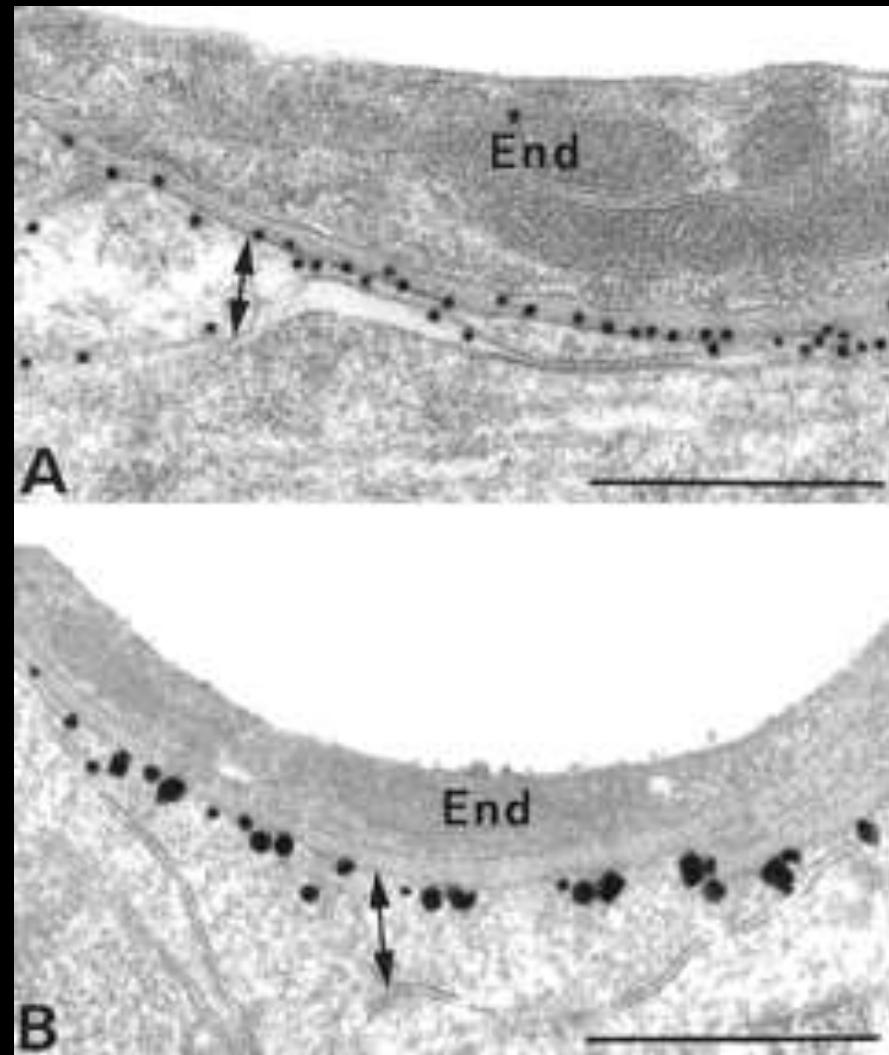
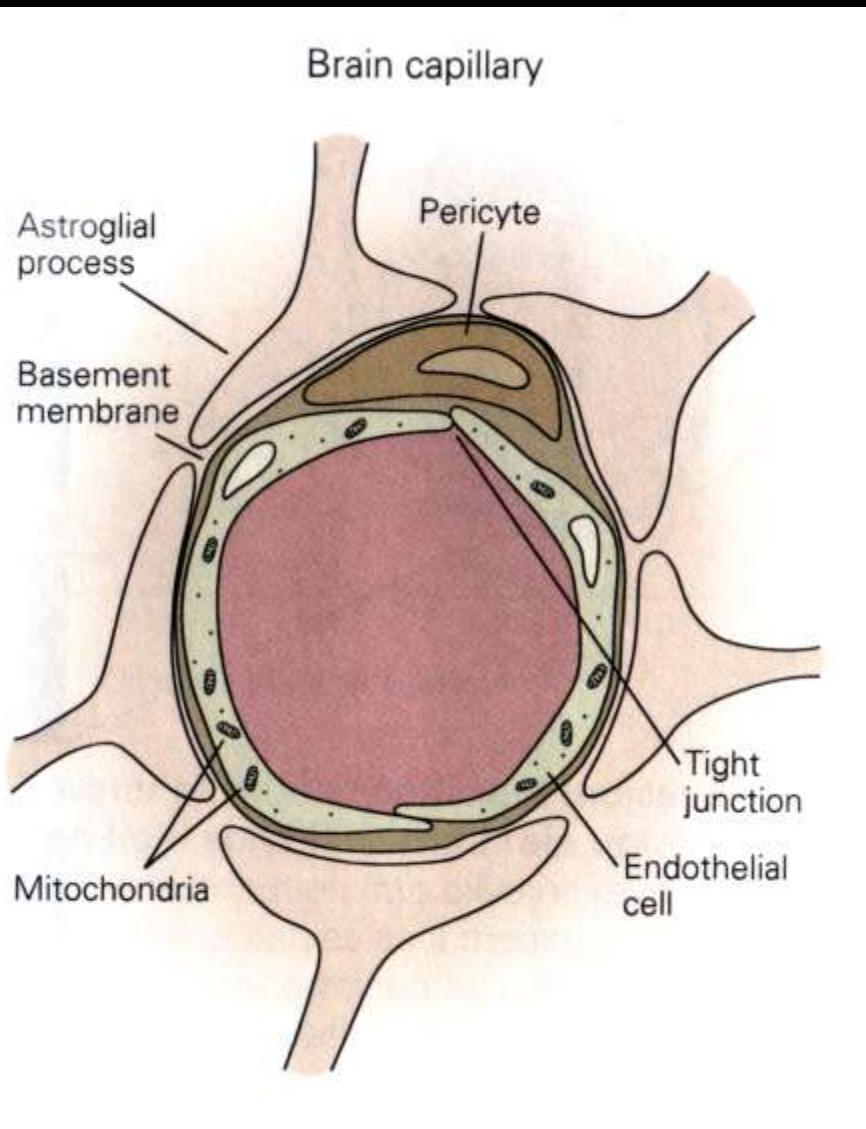
AQP4 water channel in brain



Nielsen *et al.*, J Neurosci 1997

AQP4—Blood brain barrier

(with Ole Petter Ottersen, Oslo)

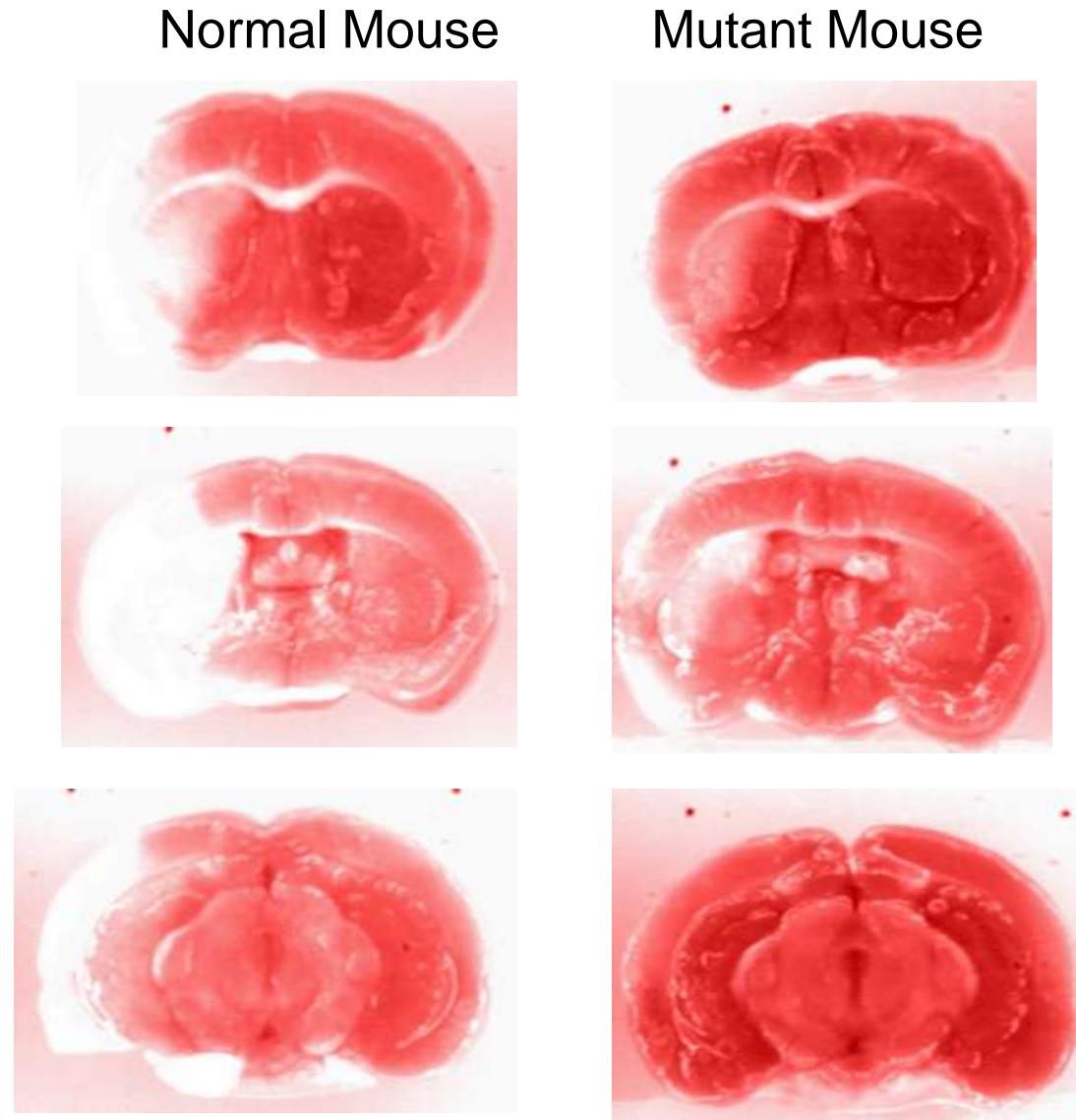


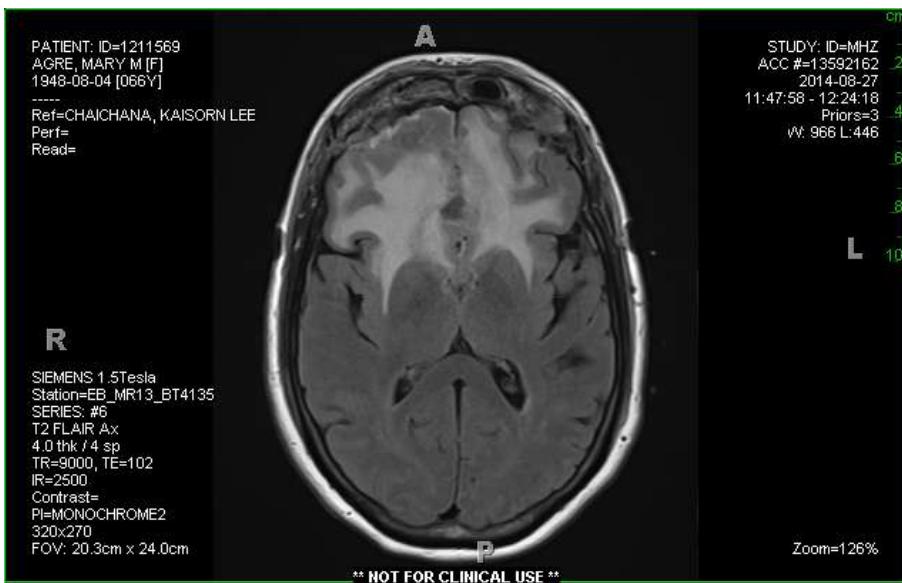
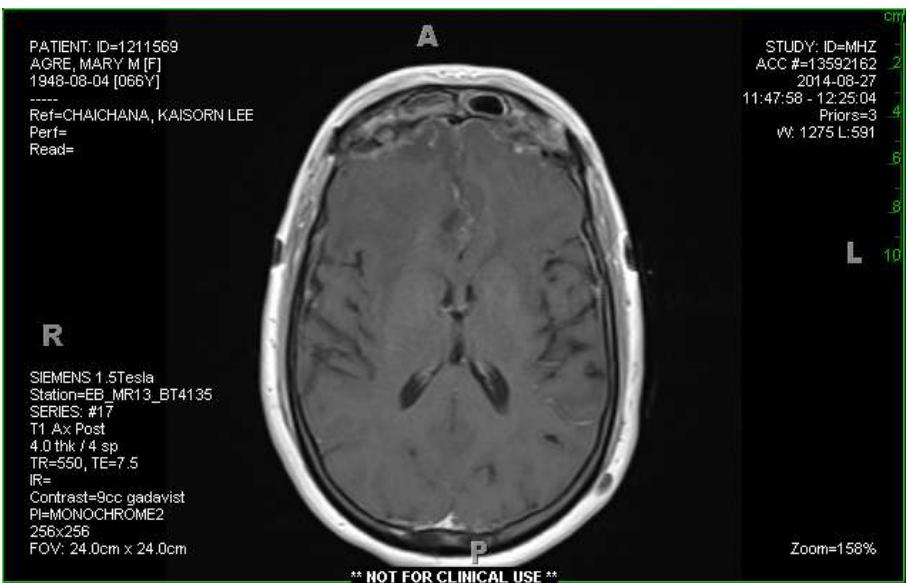
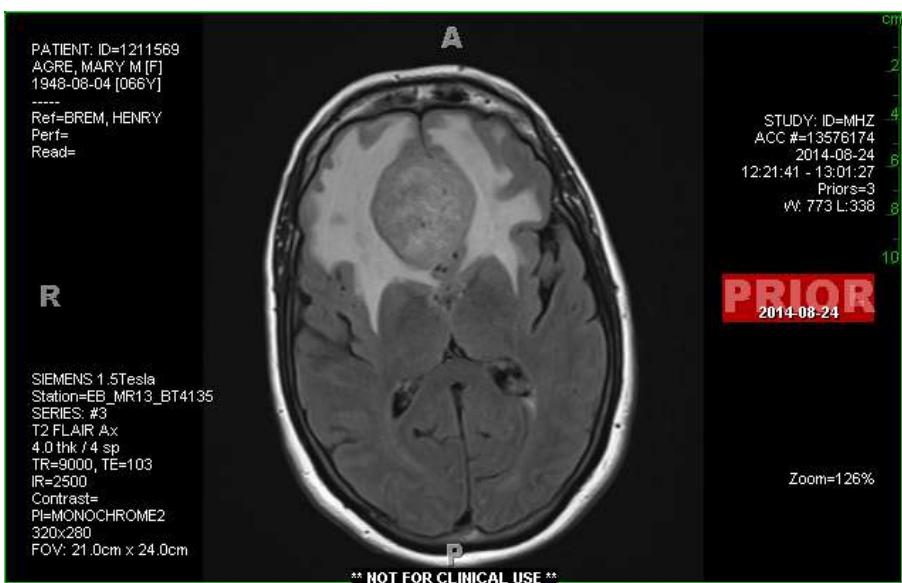
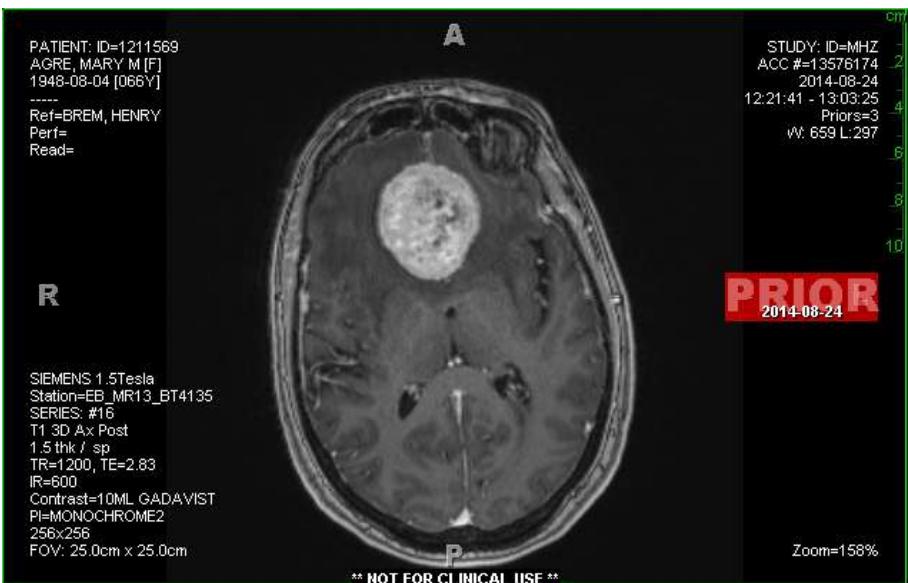
Nielsen et al., *J Neurosci*, 1997
Nagelhus et al., *J Neurosci*, 1998

AQP4—accelerated brain damage



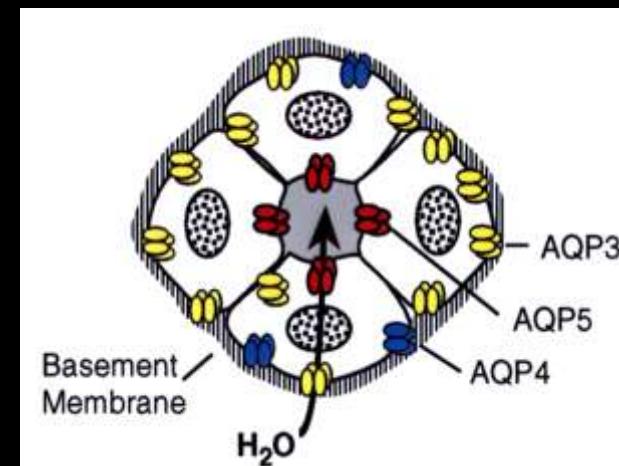
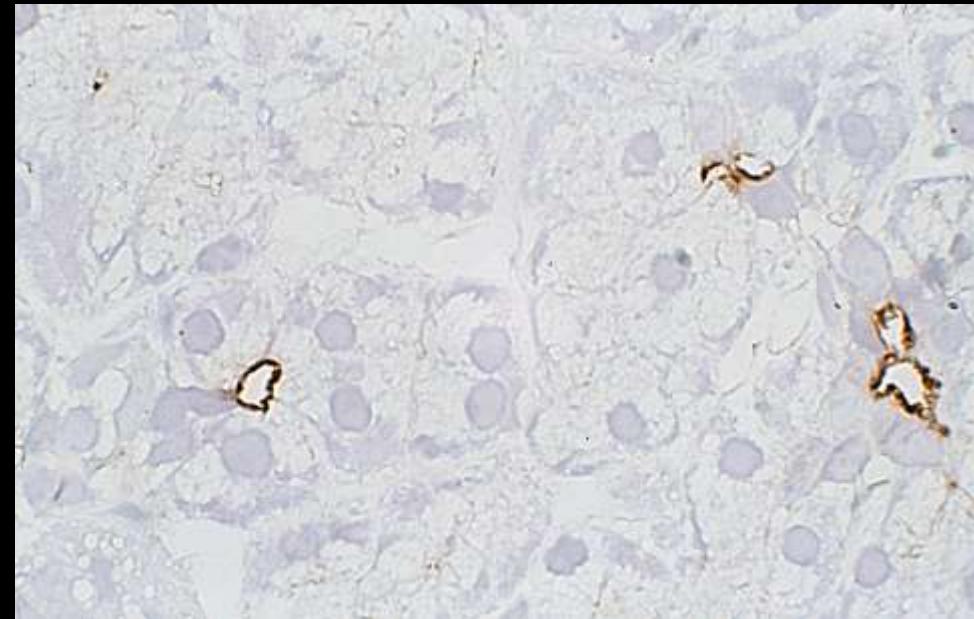
Amiry-Moghaddam *et al.*,
Proc Natl Acad Sci 2003





AQP5—Secretory glands

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

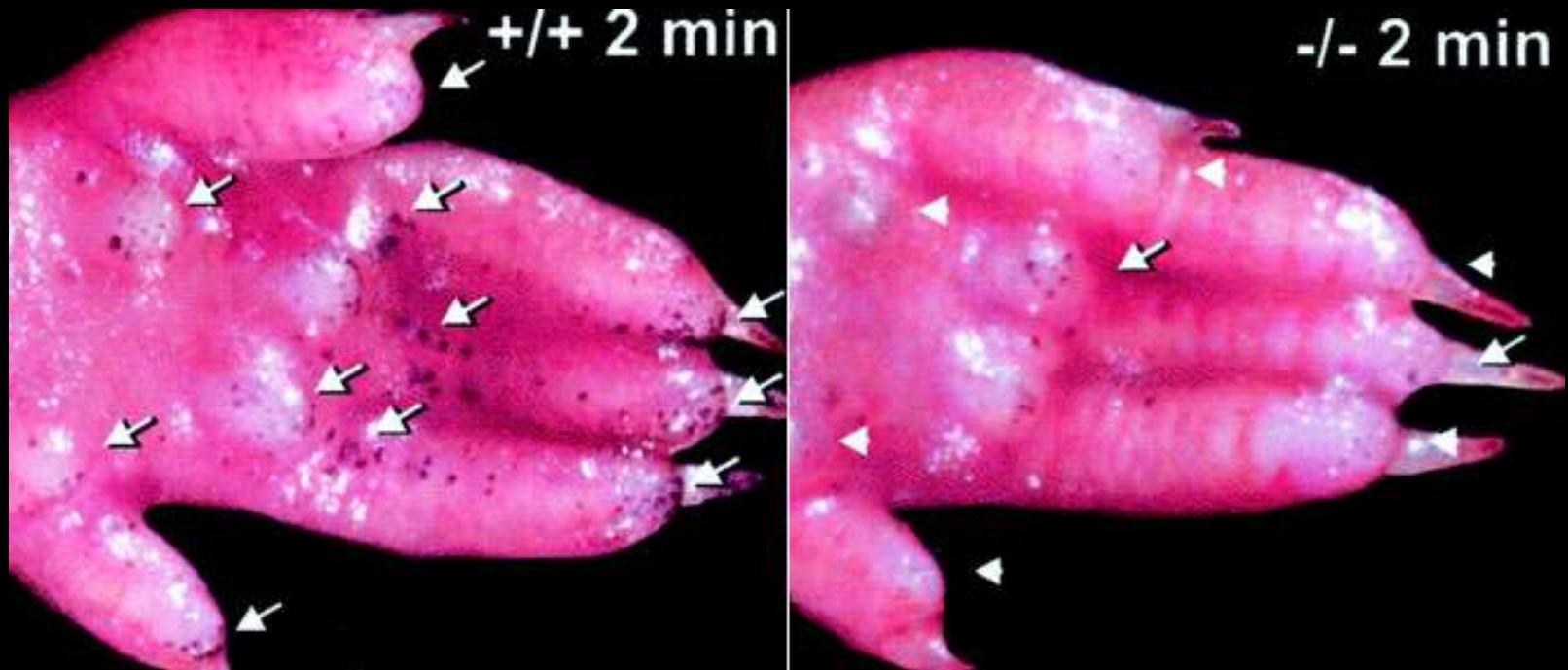


Raina *et al.*, *J Biol Chem*, 1995

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

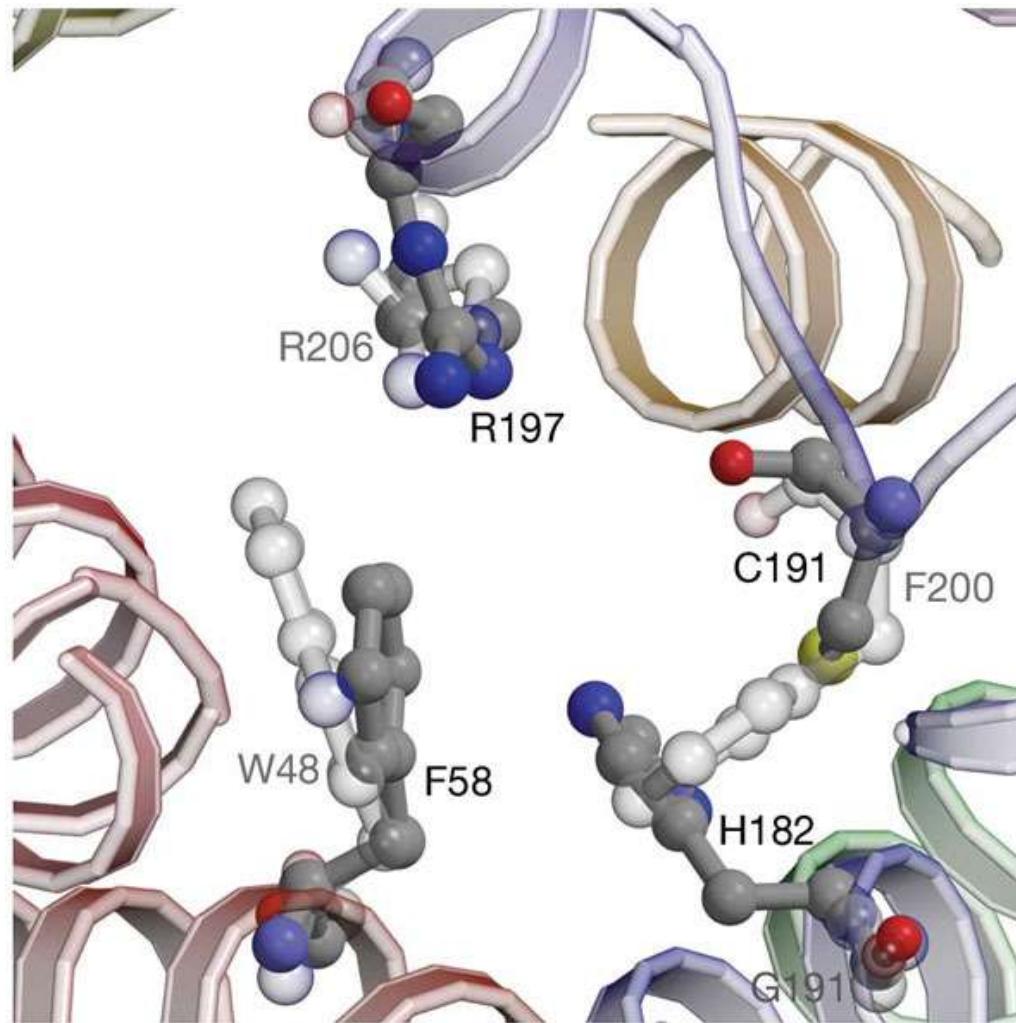
AQP5—Secretory glands

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



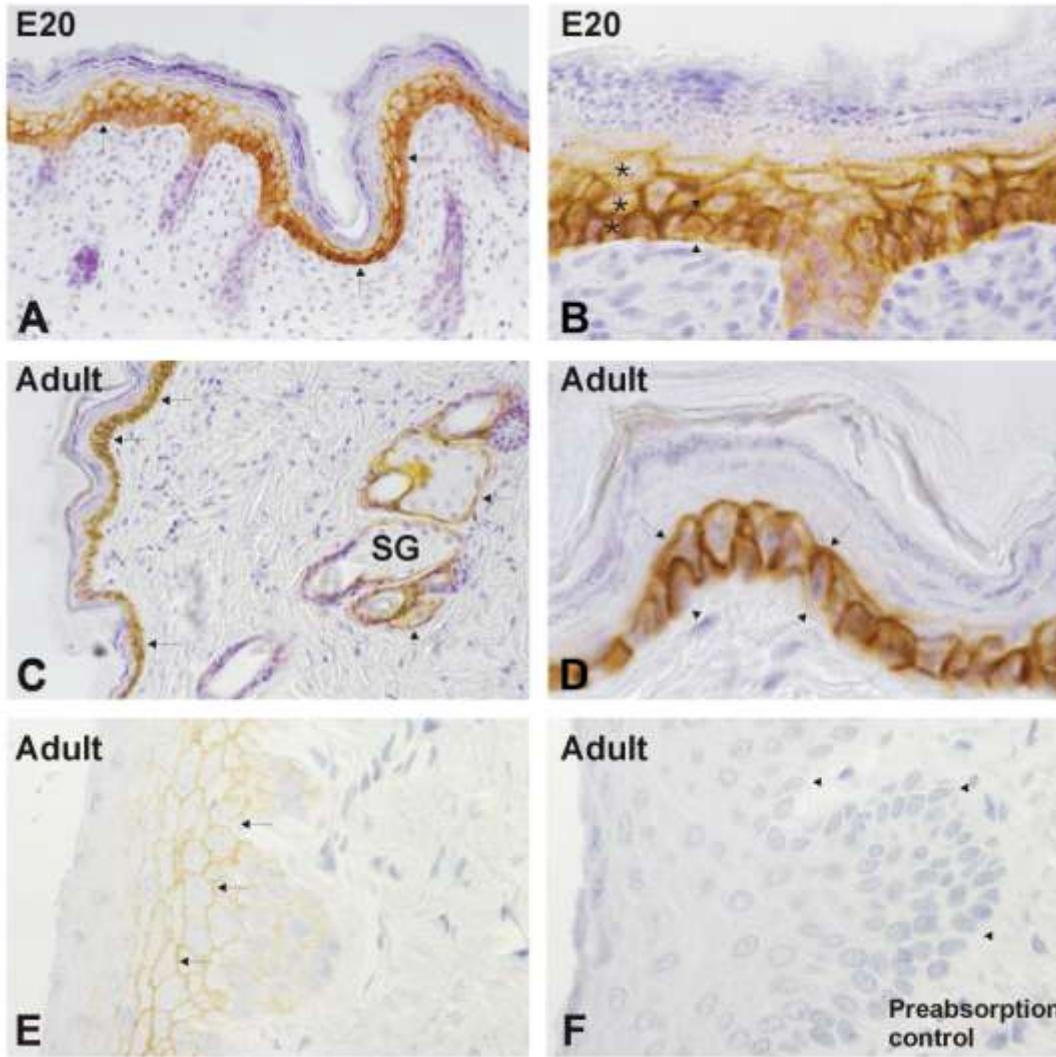
Nejsum et al., Proc
Natl Acad Sci, 2002

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***

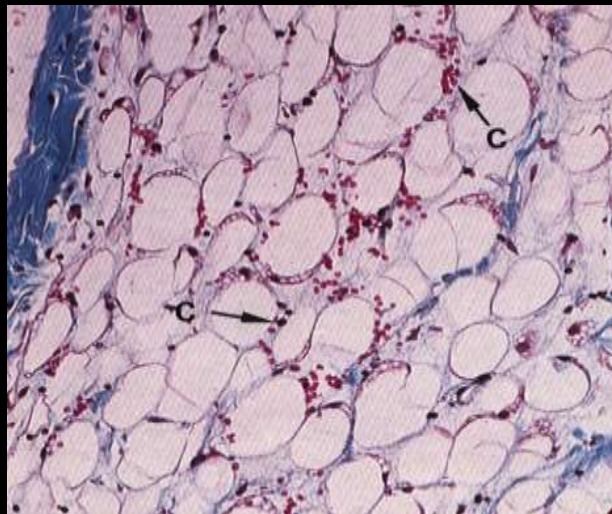
Les travaux liés à l'exceptionnelle découverte du rôle des aquaporines en général ont été récompensés par le Prix Nobel de Chimie en 2003.



AQP7 and 9—Glycerol metabolism

AQP7 in adipose tissue

Glycerol + water permeation
Suppressed by insulin



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

Starvation—AQP7 release
AQP9 facilitates

AQP9 in liver

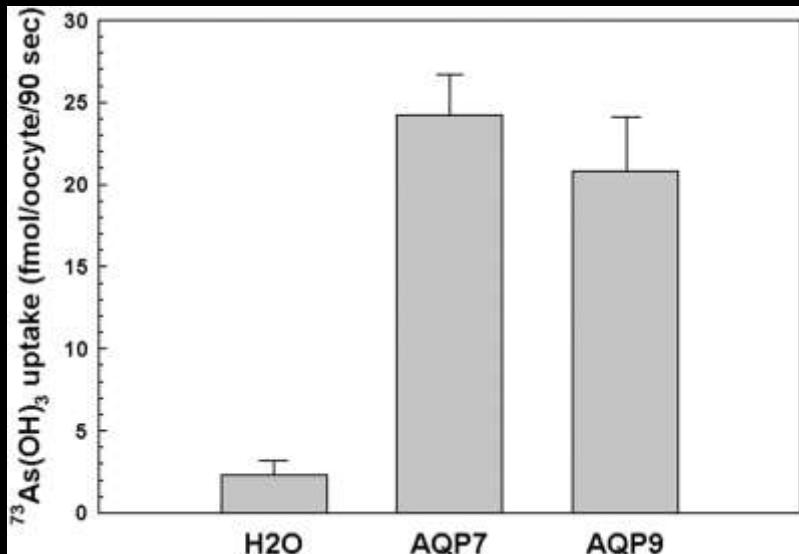
Glycerol, water, urea permeation
Increased by fasting or diabetes



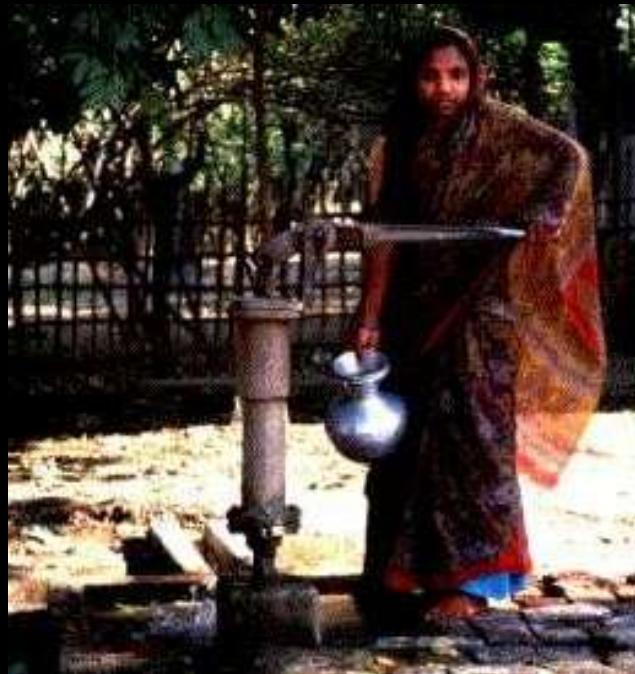
AQP7 and 9—Heavy metal transport

(with Barry Rosen, Wayne State)

Arsenite—transported by AQP7 and by AQP9.



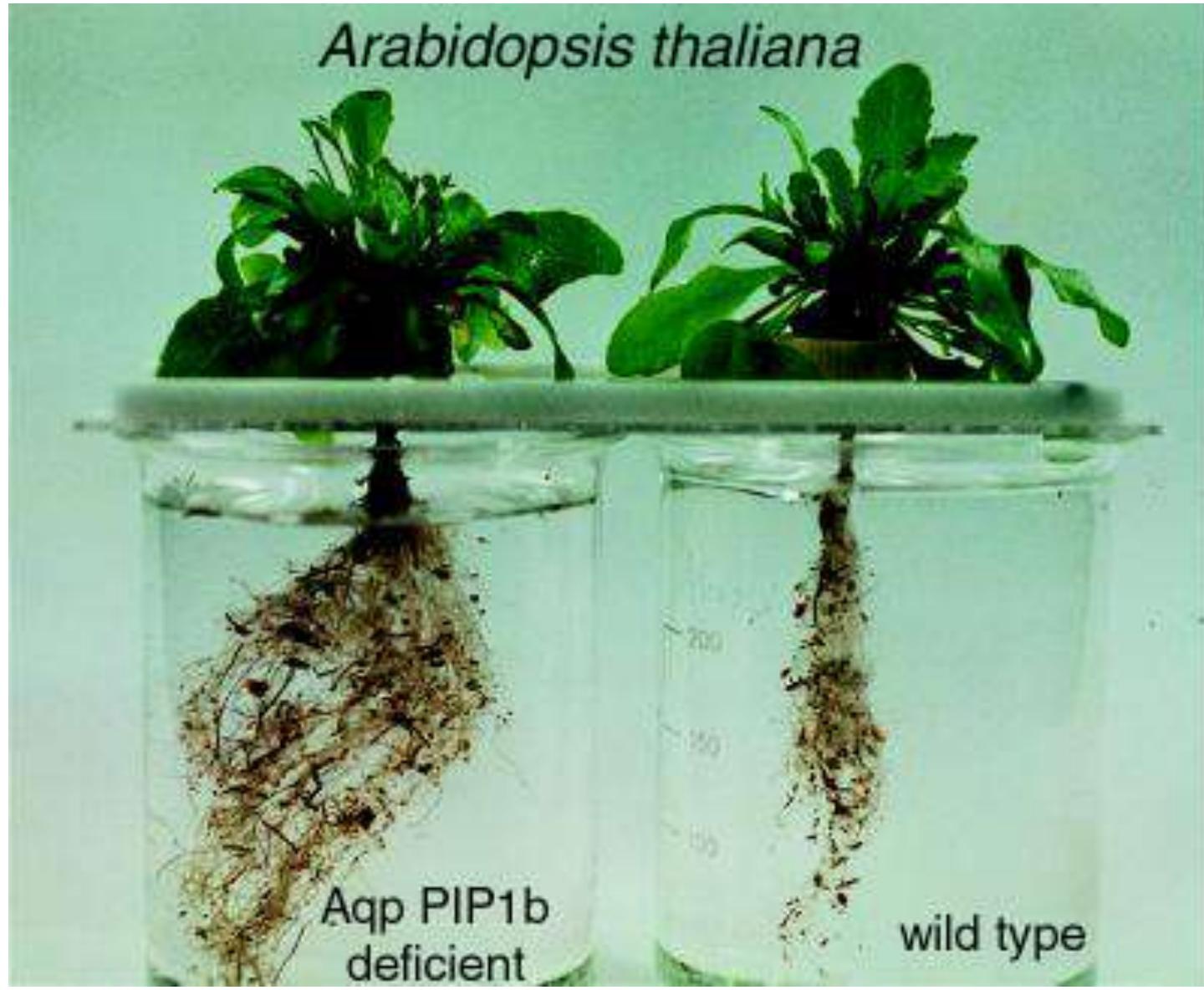
Liu *et al.*, *Proc Natl Acad Sci*, 2002



As(OH)₃ uncharged at pH 7.

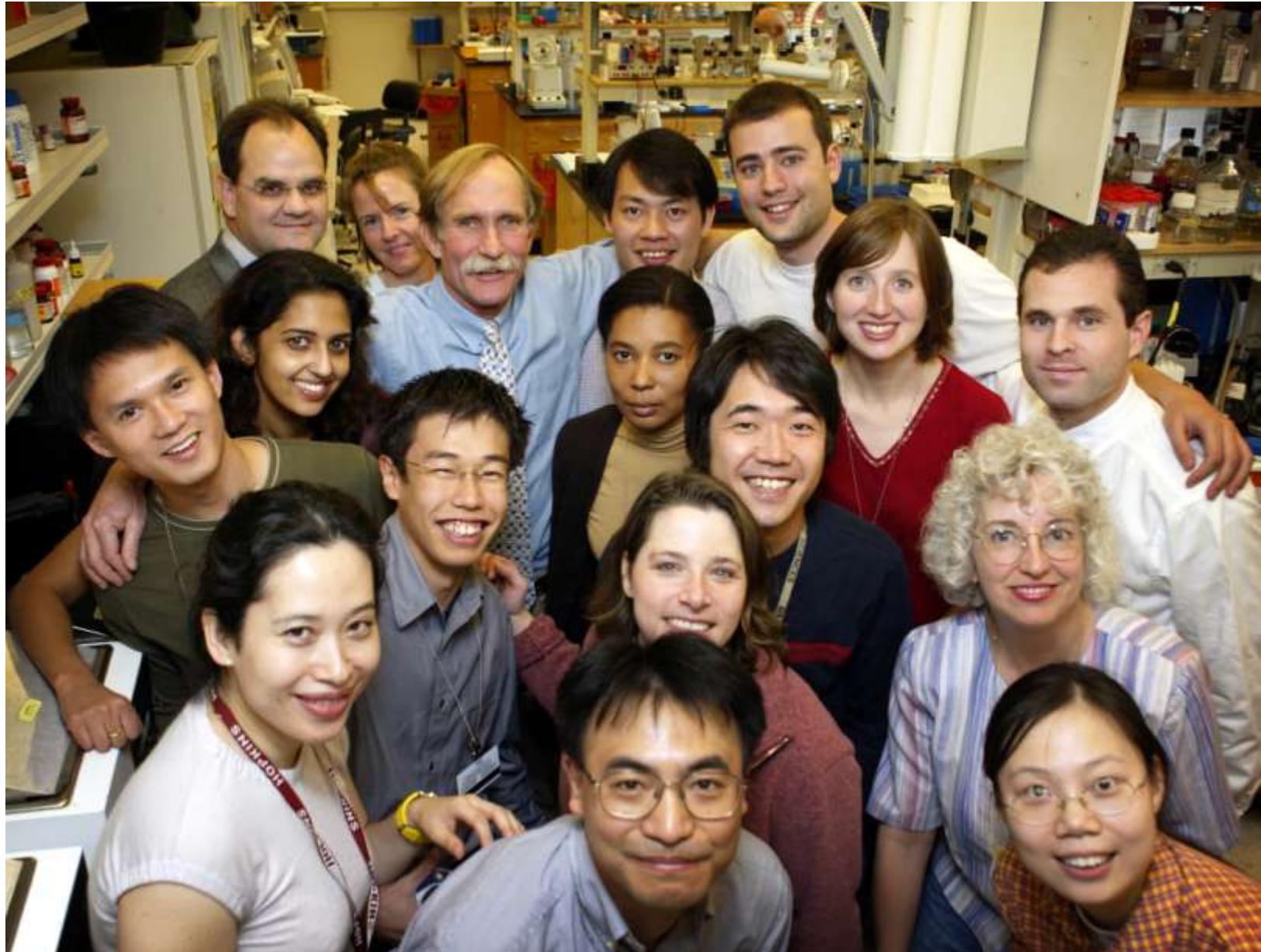
Predictor of epidemic arsenic poisoning hepatotoxicity?

Arabidopsis thaliana



Kaldenhof et al., *Plant J* 1998

8 October 2003



WELLS
Discount
LIQUORS

PARKING 

CONGRATS
DR AGRE

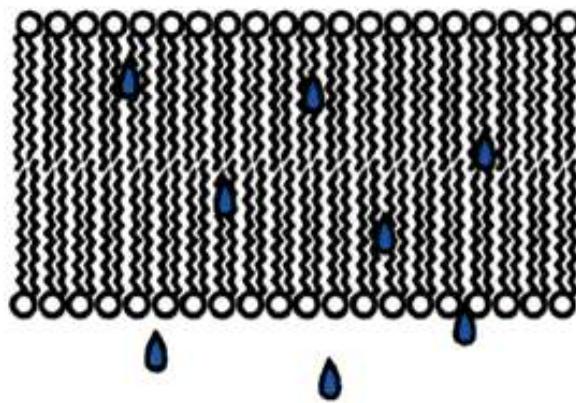




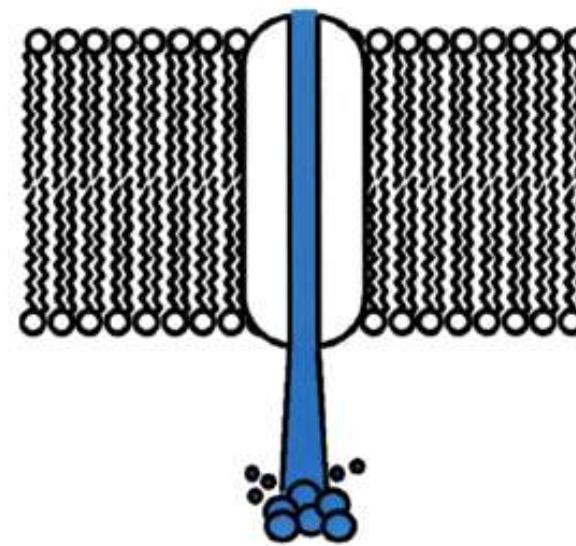


Transmembrane water permeability—Current view

Bilayer Diffusion



Aquaporin Water Channels



All biological membranes

Low capacity

Bi-directional

No known inhibitors

$E_a \sim 10$ kcal/mol

Renal tubules, secretory glands, red cells

High capacity for H_2O , not H_3O^+

Directed by osmotic gradients

Reversibly inhibited by Hg^{++}

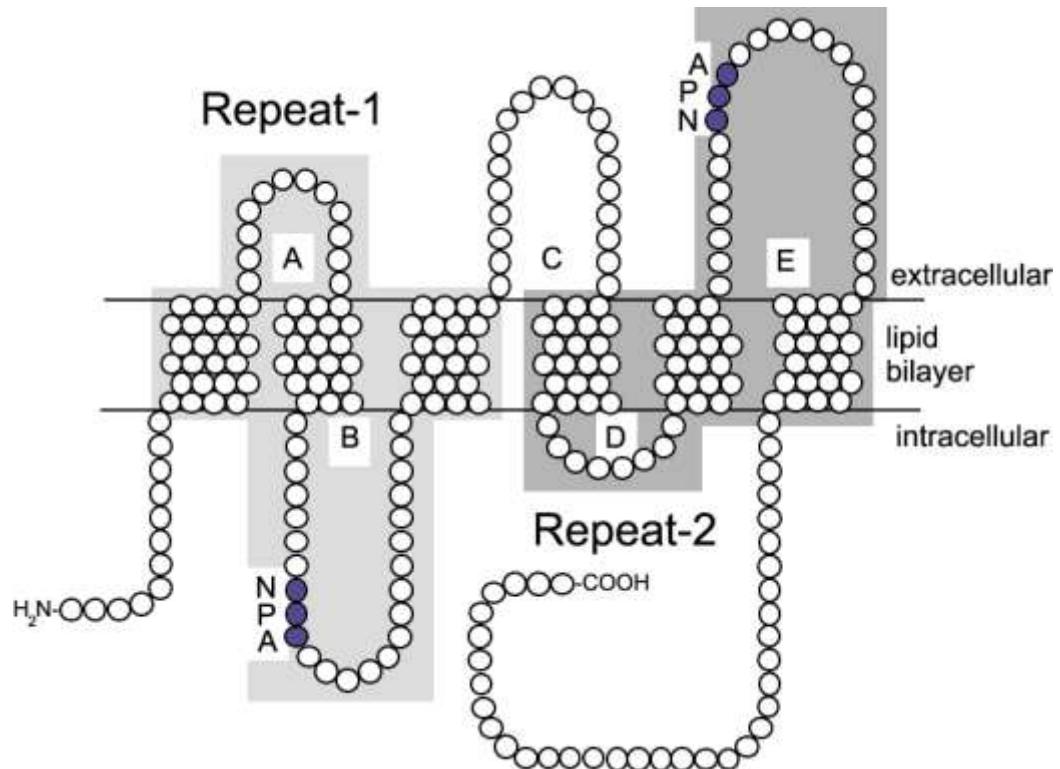
$E_a < 5$ kcal/mol

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

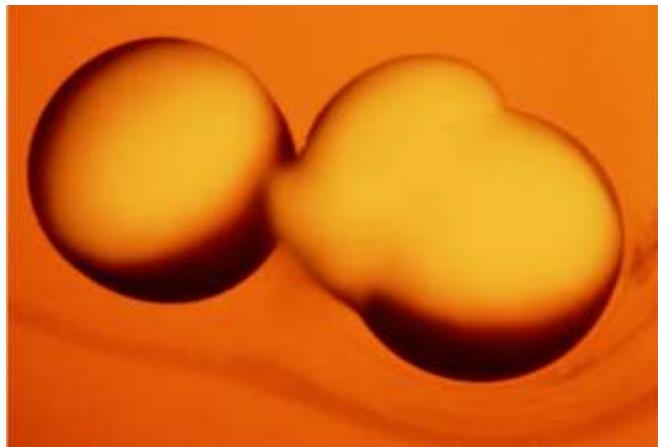
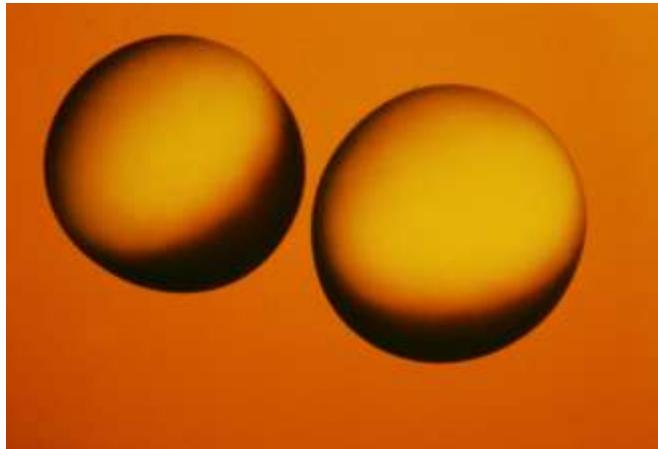
Plants—Nod, TIP, TUR, TobRB47

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



EN MEMORIA DE LA COLABORACION CIENTIFICA ENTRE EL MEDICO
CUBANO CARLOS J. FINLAY Y JESSE W. LAZEAR, DE LA UNIVERSIDAD
JOHNS HOPKINS, EN LOS EXPERIMENTOS PARA COMPROBAR LAS
TEORIAS ORIGINALES DE FINLAY SOBRE EL AGENTE TRANSMISOR
DE LA FIEBRE AMARILLA. SUS RESULTADOS ABRIERON EL CAMINO
PARA ELIMINAR ESE AZOTE DE LOS TROPICOS. EN ARAS DE ESE
PROPOSITO, LAZEAR OFRENDO SU VIDA.

LA HABANA, FEBRERO DE 2015. AÑO DEL CENTENARIO DEL DECESO DE
CARLOS J. FINLAY.

THE HEALTH ADVISORY BOARD FROM THE JOHNS HOPKINS BLOOMBERG
SCHOOL OF PUBLIC HEALTH, BALTIMORE, MARYLAND, USA.
LA ACADEMIA DE CIENCIAS DE CUBA.





