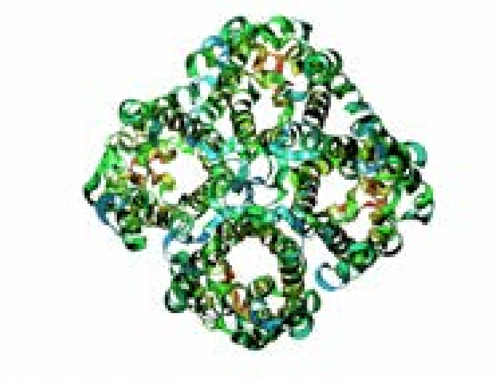
Water Transport:
From Terrestrial Adaptation to Clinical Medicine



Prof. Dr. Med O. Devuyst

Brussels, May 23, 2014

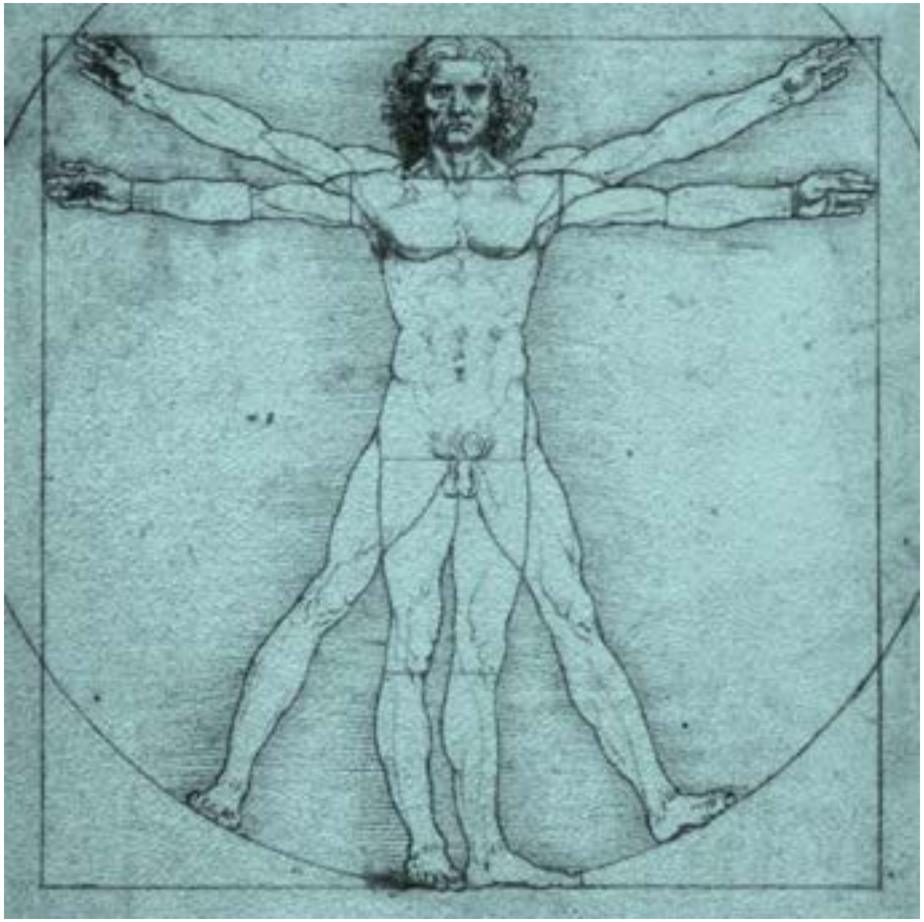
University of Zurich[UZH]

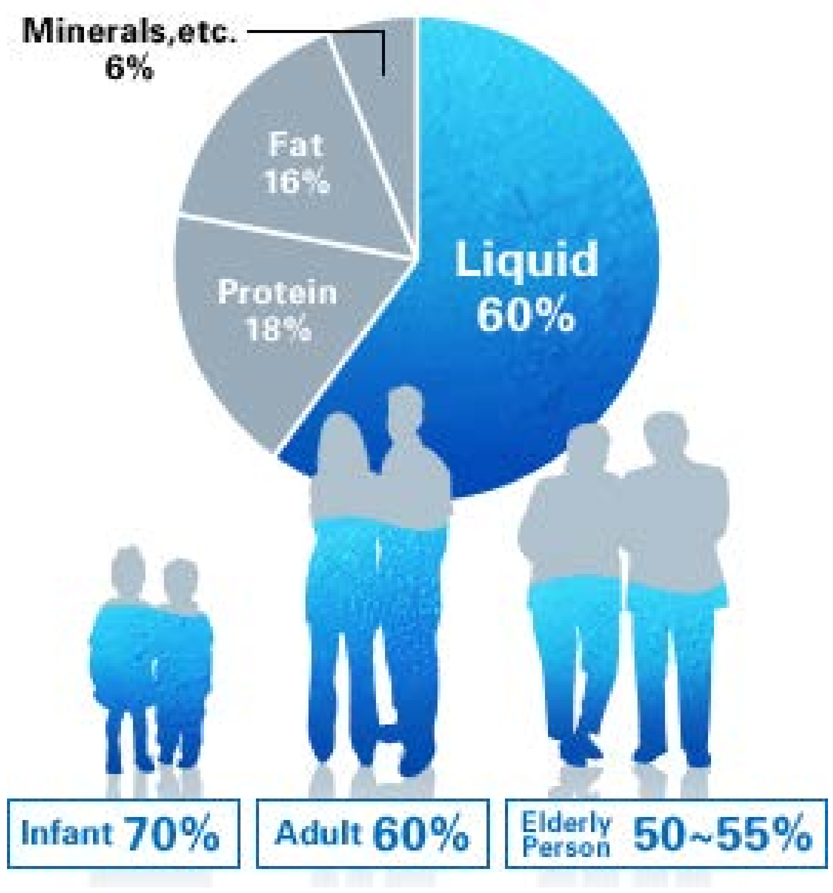
KIDNEY
CONTROL OF HOMEOSTASIS
SWISS NATIONAL CENTRE
OF COMPETENCE IN RESEARCH

UCL
Université
catholique
de Louvain

From the waves of the North Sea

To the impetuous mountain rivers

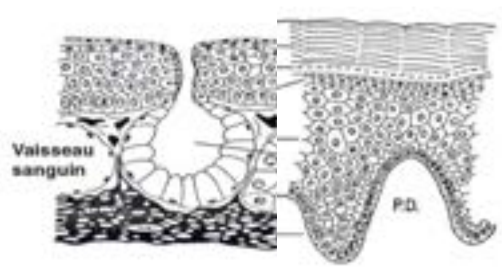


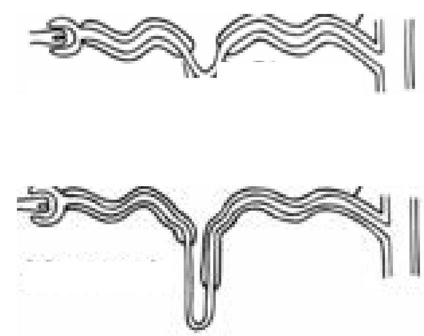


Minerals,etc.
6%
Fat
16%
Protein
18%
Liquid
60%
Infant 70%
Adult 60%
Elderly Person 50~55%

Devonian times, ~ 375 million years ago

Need to decrease water losses:





Lung

Skin

Kidney

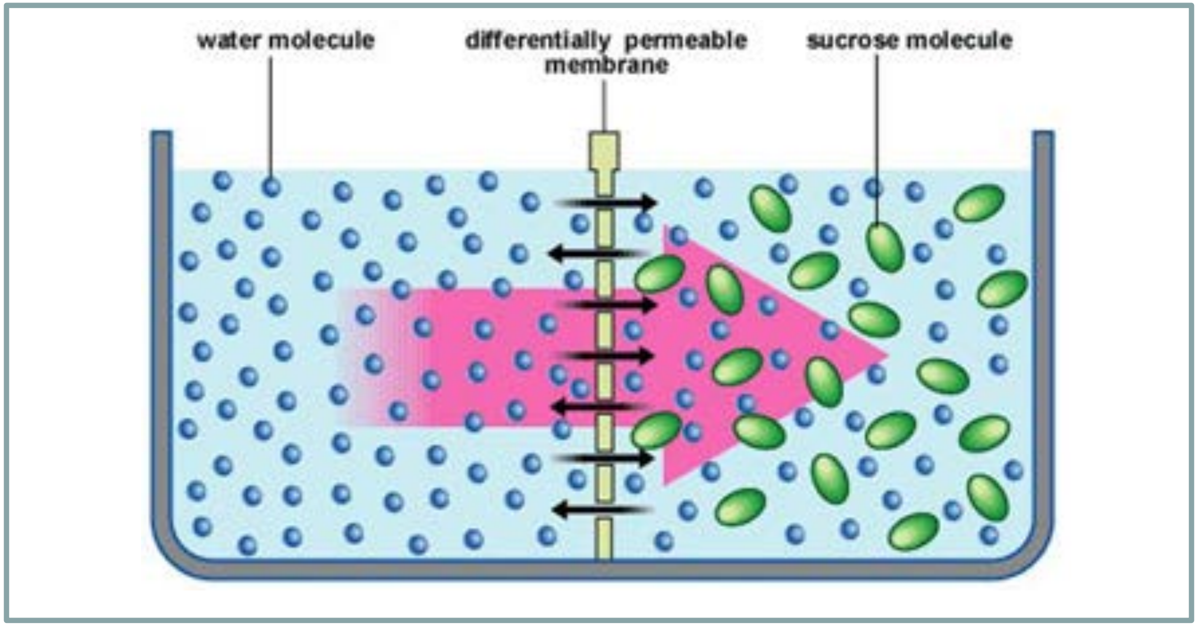
The evolution of man, from fish to college graduate.

Zurich, Switzerland, around 1850

Karl Wilhelm von Nägeli (1817 – 1891)

- 1840 doctorate from the University of Zurich
- 1855 professor of botany at UZH

Naegeli, Carl Wilhelm von. 1856.
Die Individualität in der Natur mit vorzüglicher Berücksichtigung des Pflanzenreiches. Zürich

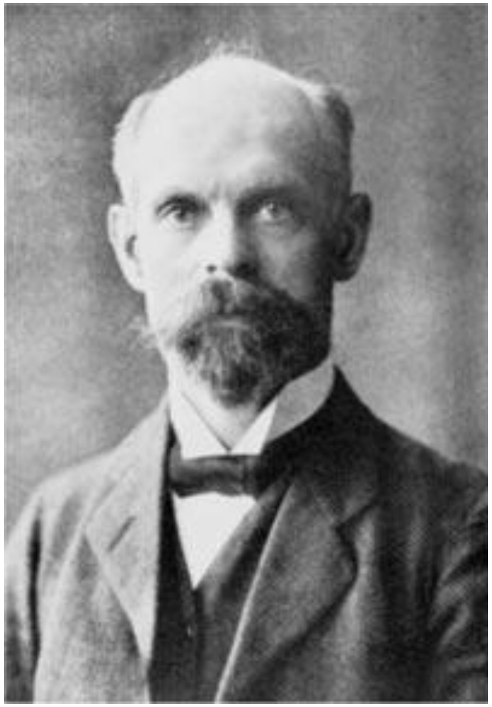


Osmosis

Overton CE (1899)

On the general **osmotic properties of the cell**, their probable origin, and their significance for physiology.

Vierteljahrsschr Naturforsch Ges Zurich 44: 88–135

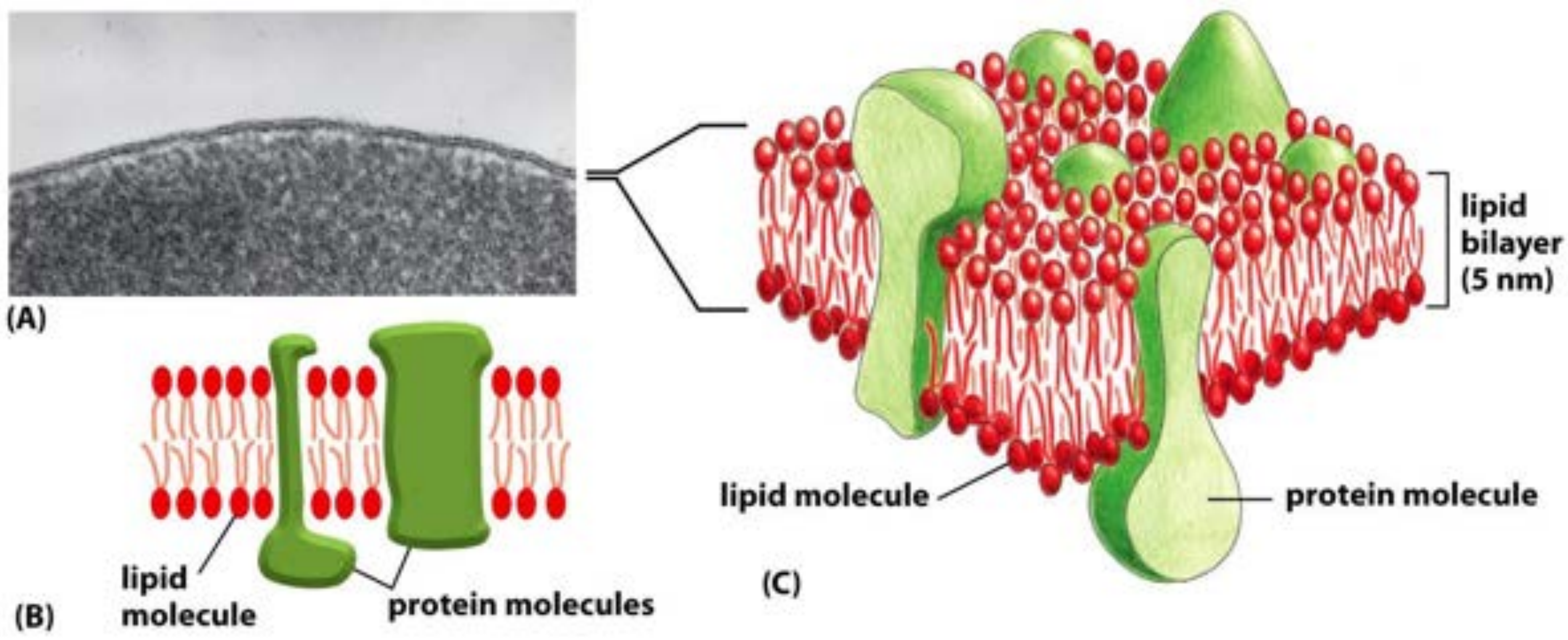


Charles Ernest Overton (1865–1933)

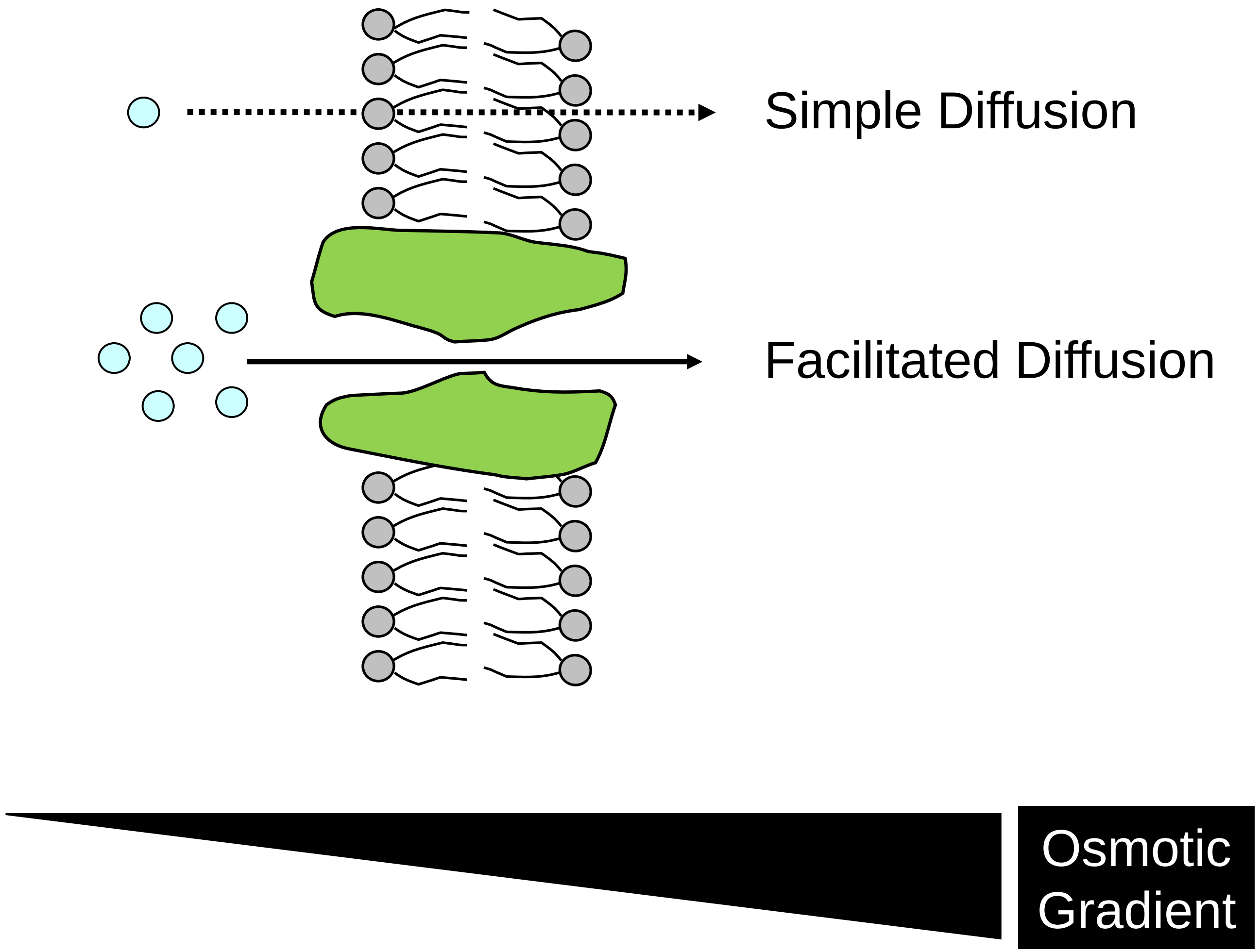
In 1890, Overton wurde er «Privatdocent der Biologie» an der Universität Zürich.

The Overton Rule

- *The boundary of cells is mostly constituted of a lipidic material*
- *Non-lipophilic substances (incl. **water**) must use specific pathways*

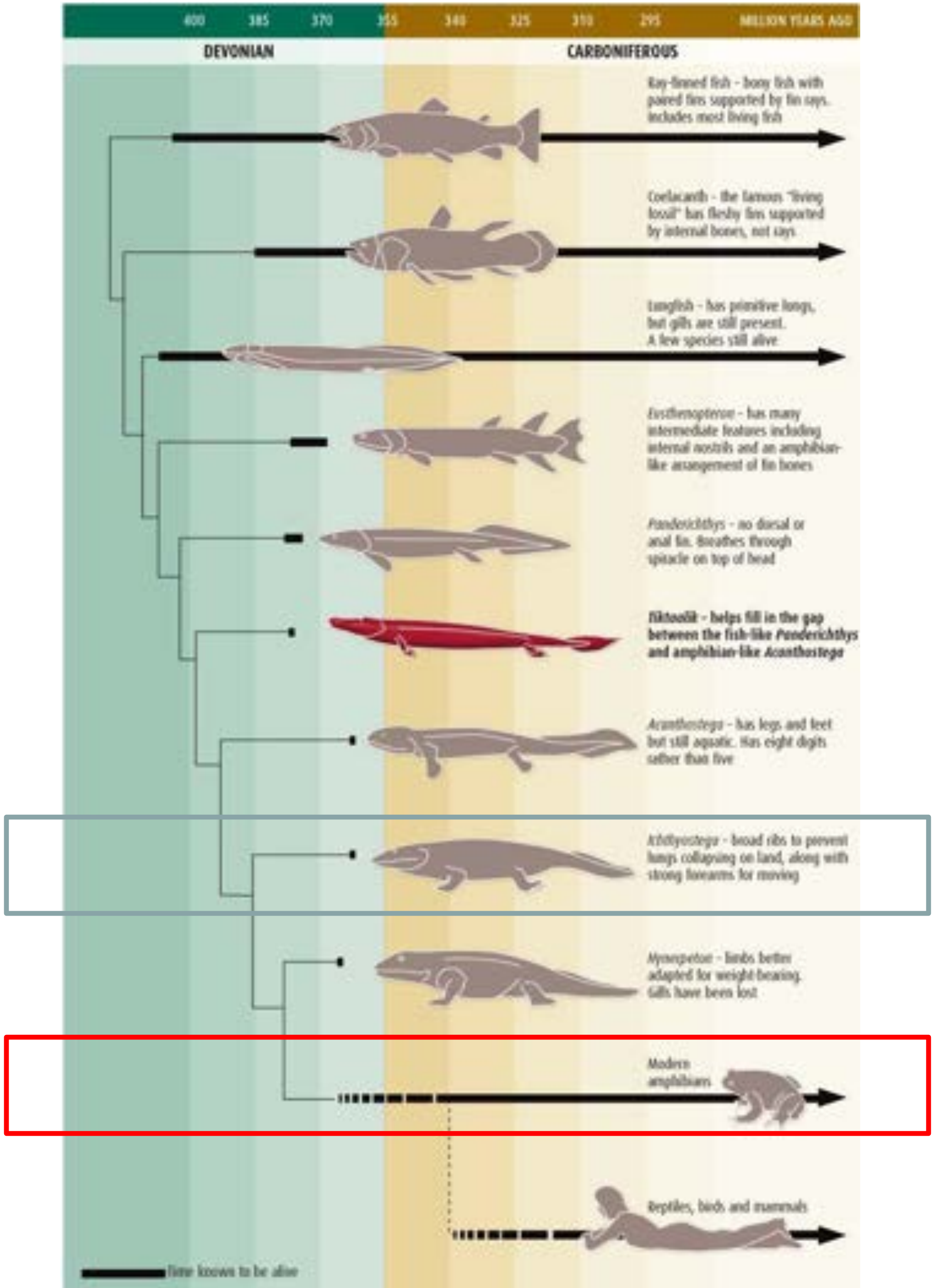


Debate: Water Permeability of Cell Membranes ?

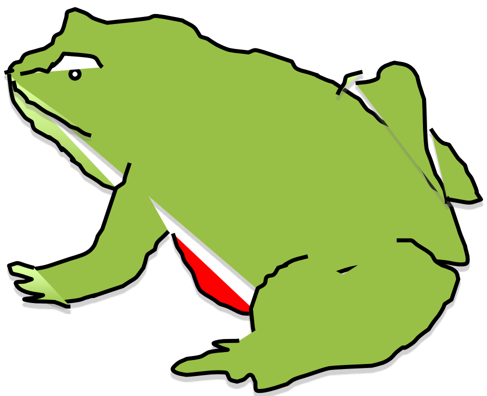


Prescott DM et al. *Acta Physiol Scand* 1953

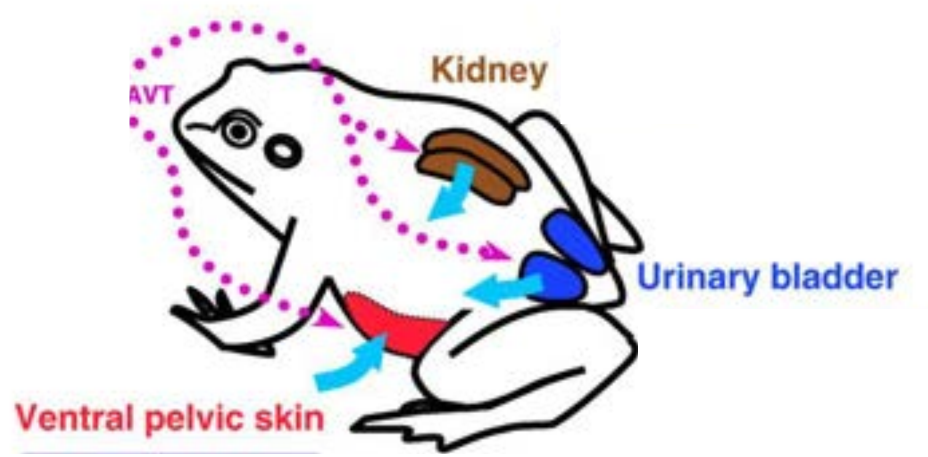
Amphibians evolved
from fishes in just
a few millions years



Adaptation to Terrestrian Life : Amphibians



AVT = Arginine VasoTocin



Water losses +++
- Glandular skin
- Diluted urine

Transport systems
- Abdominal skin
- Urinay bladder

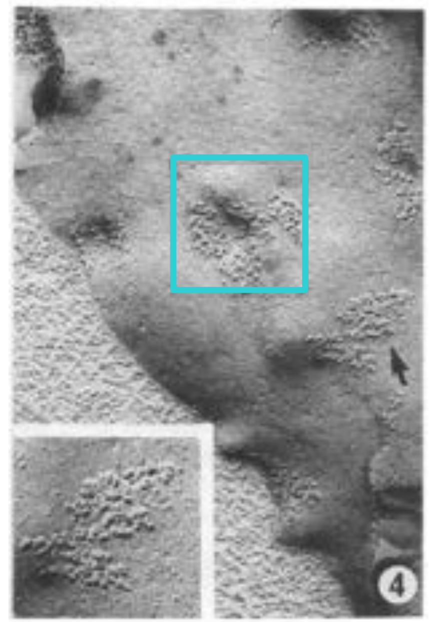
Susuki & Tanaka Comp Biochem Physiol, 2009

First Visualisation of Water Transport: Frog Bladder

Rana esculenta

x70 000

+ AVT →



x110 000 x70 000

→ *Facilitated water diffusion across membranes*

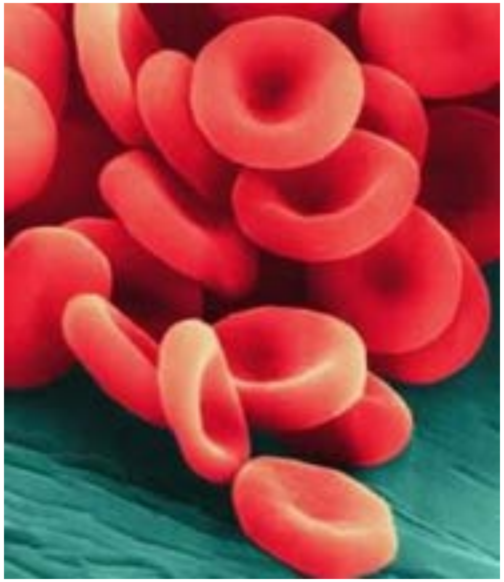
Bourguet et al, Biophys J, 1976

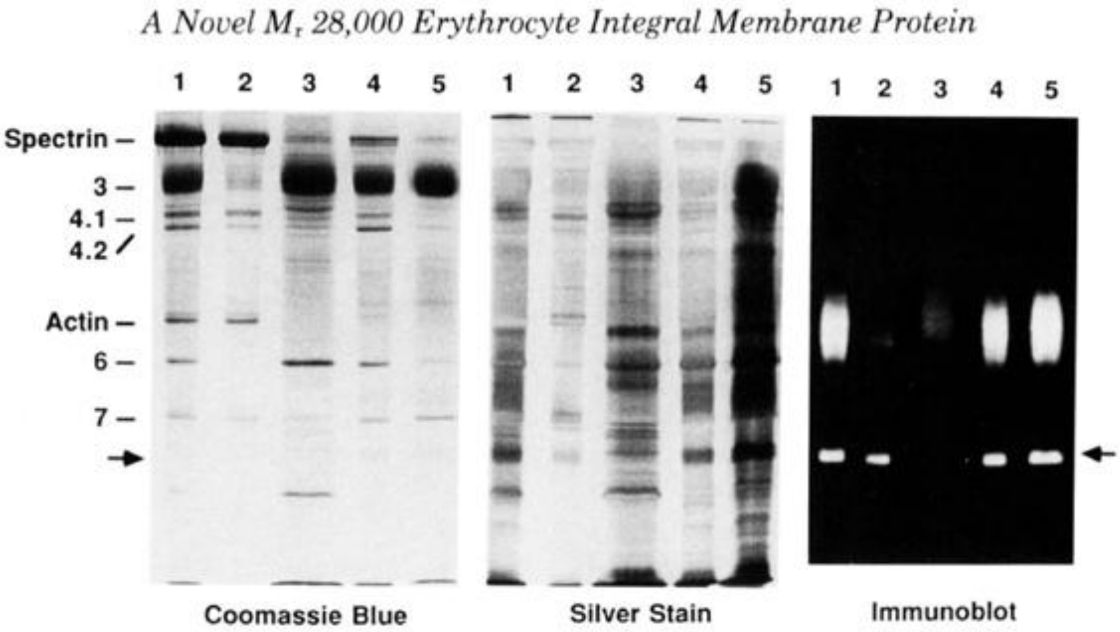
The race to discover the Water channel gene

The Journal of Biological Chemistry 263 : 15634-42, 1988

Identification, Purification, and Partial Characterization of a Novel Mr 28,00 Integral Membrane Protein from Erythrocytes and renal Tubules

Denker BM, Smith BL, Kuhajda FP, Agre P.





CHIP28 is not the Rhesus antigen – then what ?

CHIP 28 : Channel-like Integral Membrane Protein

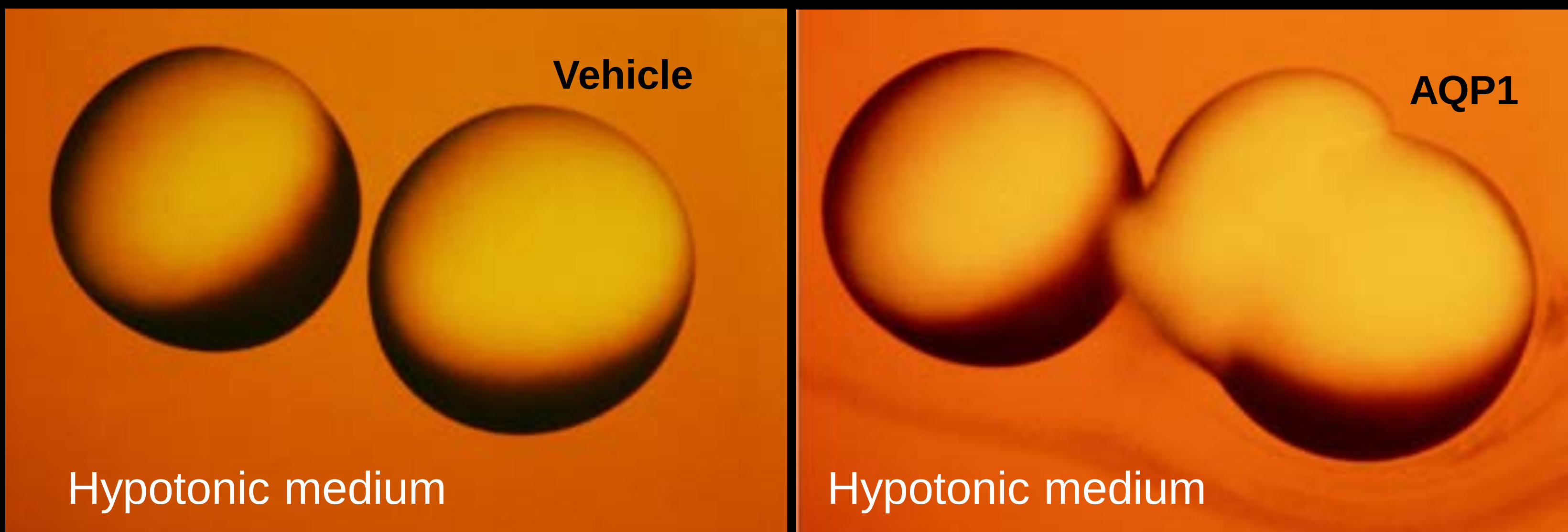
Is CHIP28 the long sought-after water channel ?

- cD… …brane protein
- …gy with channels (MIP cornea)
- …Mw 28 kDa
- 150,000 copies/RBC

→ Xenopus swelling assay: W.B. Guggino

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

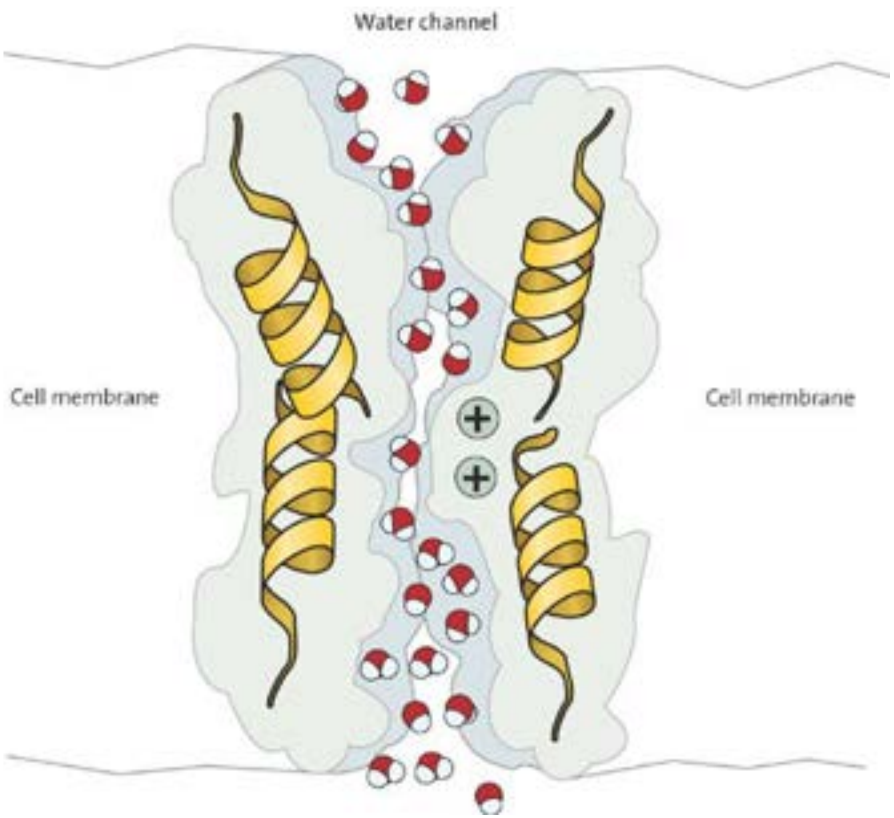
Gregory M. Preston, Tiziana Piazza Carroll,
William B. Guggino, Peter Agre*

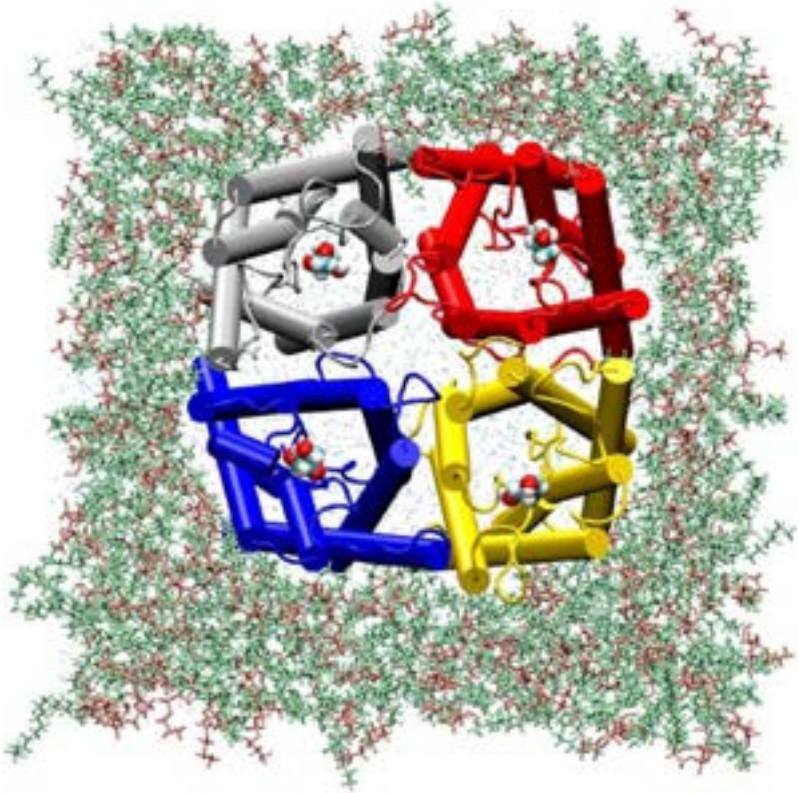


Cell swelling → facilitated water transport

SCIENCE • VOL. 256 • 17 APRIL 1992

Structure of Aquaporins

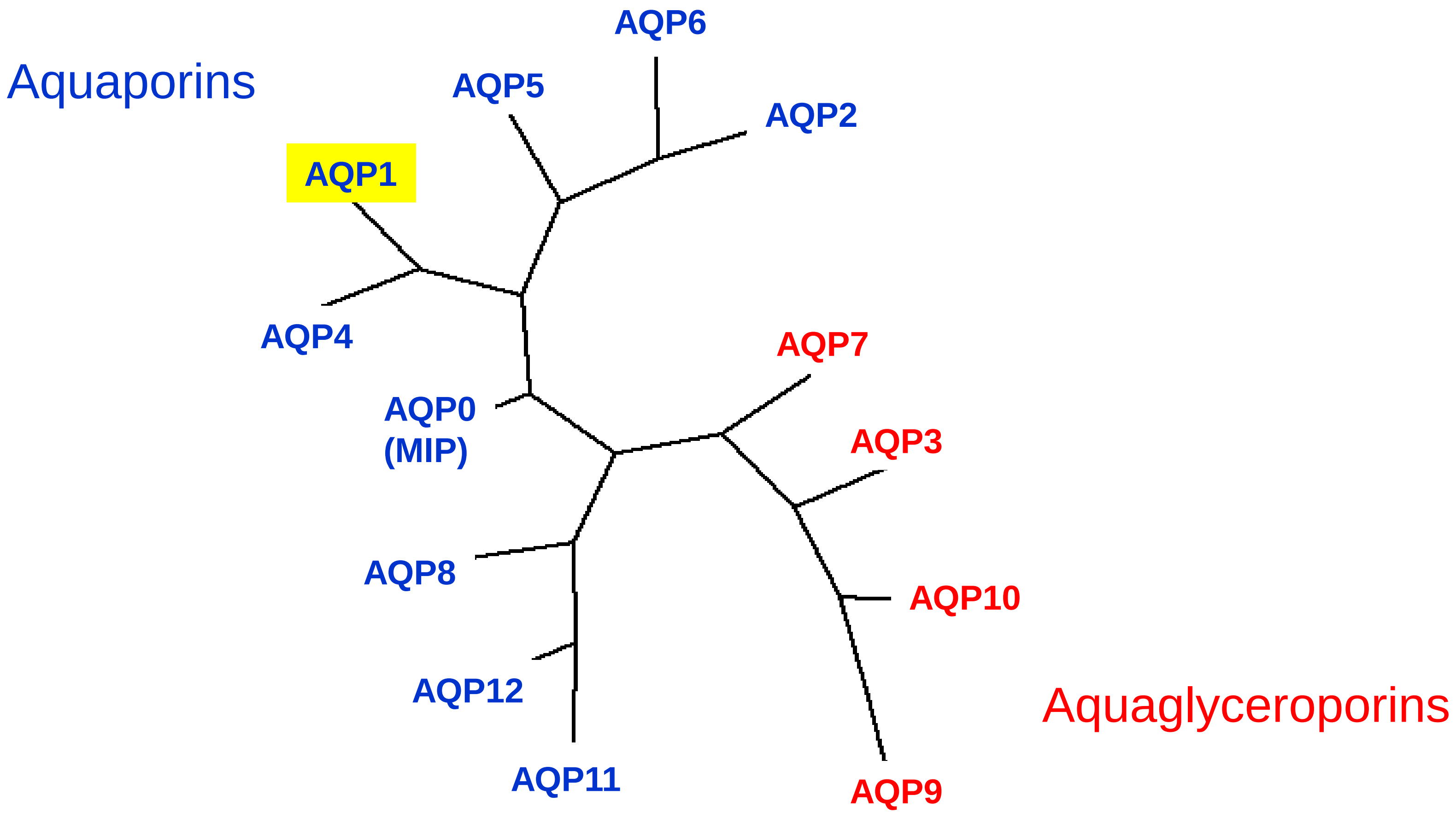




AQP1 tetramers: 3 billions of water molecules per second

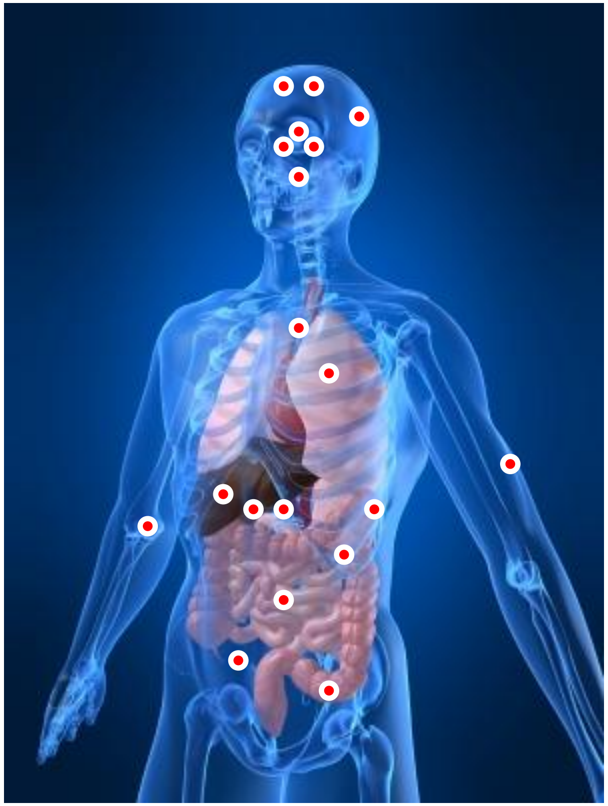
Walz T et al. Nature 387, 1997 Wang et al. Structure 13, 2005

The Family of Human Aquaporins



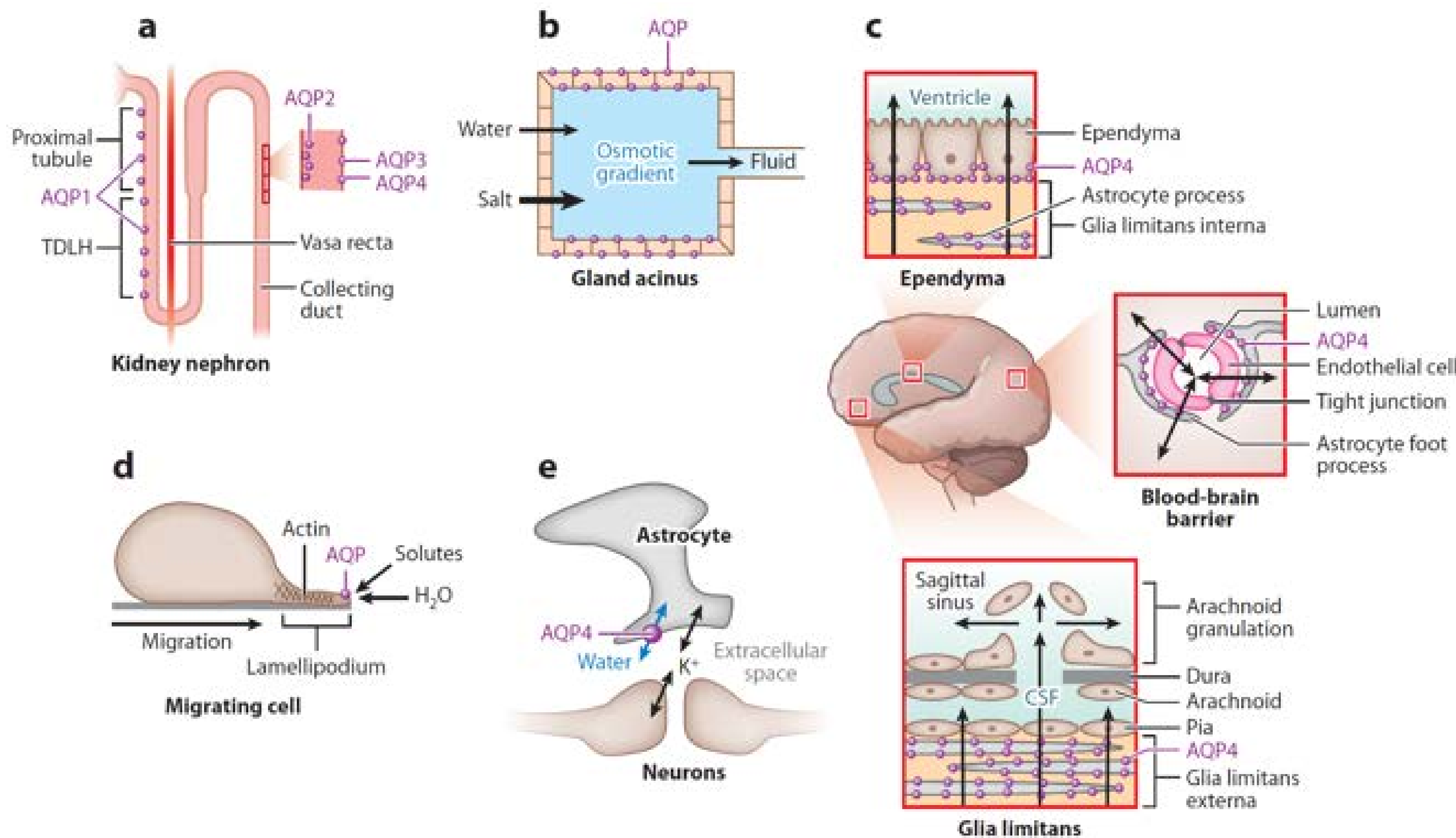
Distribution of Human Aquaporins

Aquaporin (AQP)	Tissue or Cell Type
AQP0	Eye (Lens)
AQP1	Choroid Plexus, Erythrocytes, Eye (Cornea), Gallbladder, Kidney, Lung, Liver, Pancreas
AQP2	Kidney
AQP3	Erythrocytes, Eye (Conjunctiva), Kidney, Skin, Upper Respiratory Tract
AQP4	Brain (Glial Cells), Eye (Retina), Kidney, Muscle
AQP5	Lacrimal Gland, Lung, Salivary Gland, Skin (Sweat Glands)
AQP6	Kidney
AQP7	Adipocytes, Kidney, Testis
AQP8	Colon, Kidney, Liver, Pancreas
AQP9	Brain, Leukocytes, Liver, Spleen
AQP10	Small Intestine

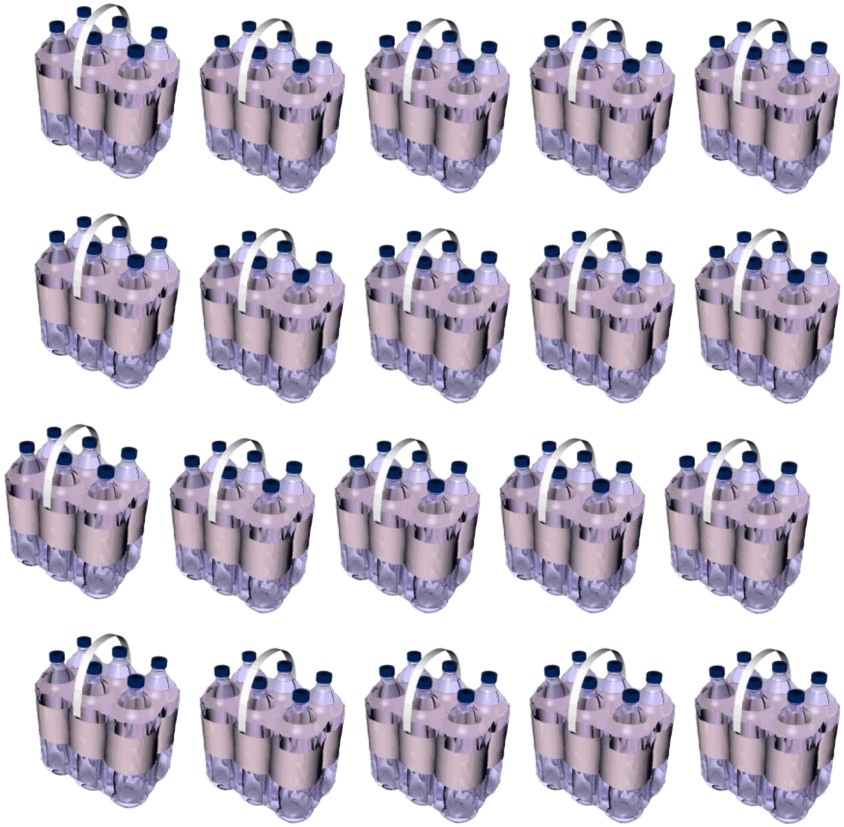


Nat Rev Mol Cell Biol 2004

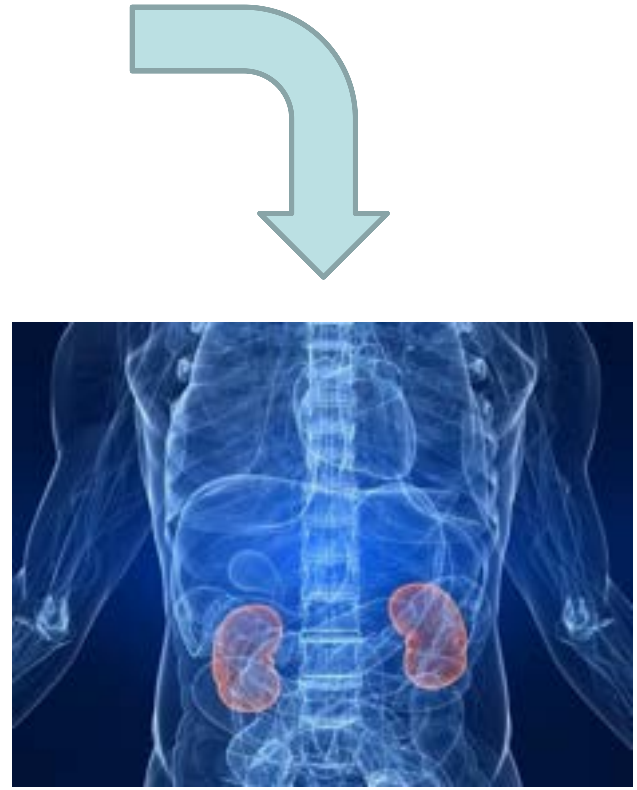
Aquaporins in Clinical Medicine

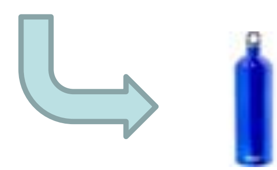


Verkman, *Ann Rev Med* 2012



Filtration ~ 180L/day



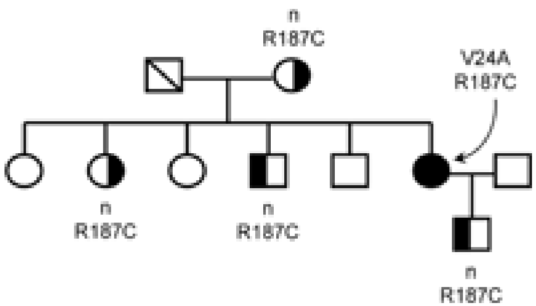


The kidneys reabsorb water massively

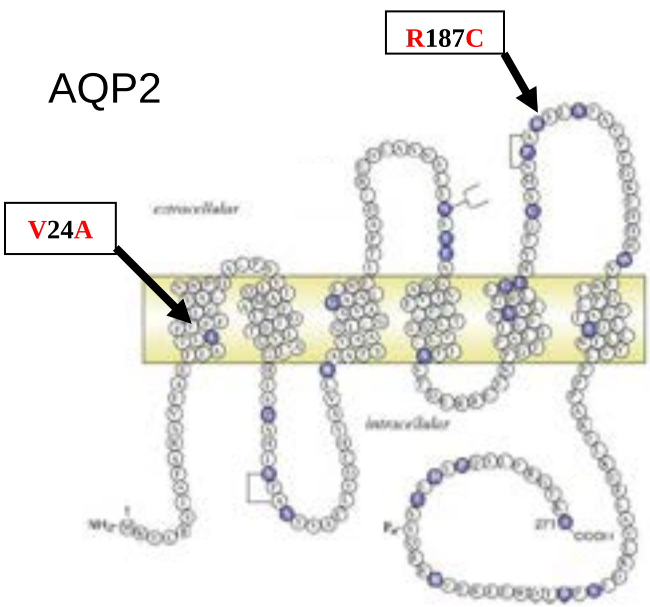
Urine ~ 1L/day

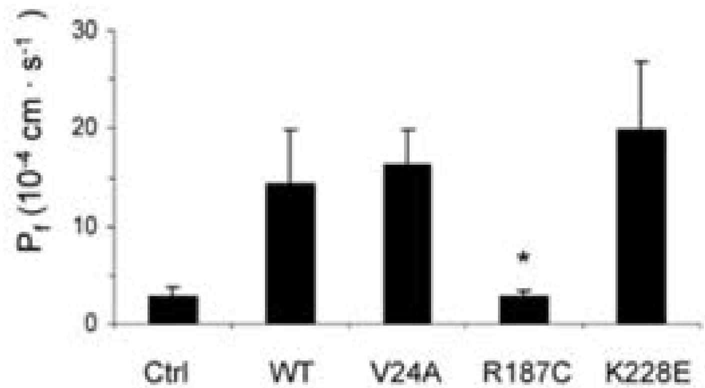
Sylvie, 39 year-old : Needs to drink 15-20 liters a day

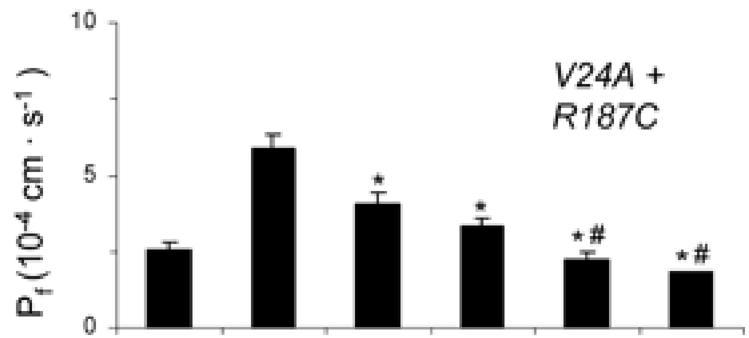
- Urinates: 15 L/day
- Difficult scolarity, multiple hospitalizations (dehydration)



AQP2







mutant	0	5	5	5	5	5
R187C	0	0	2.5	5	7.5	10

J Physiol 588: 2205-18, 2010

The Nobel Prize in Chemistry 2003

« for discoveries concerning channels in cell membranes »

Peter Agre & Roderick MacKinnon

"The Eucerin Aquaporin-Active provides a maximum hydration to the skin thanks to the discovery of biologist Peter Agre…"

Aquaporins:

Plumbing system for peritoneal dialysis

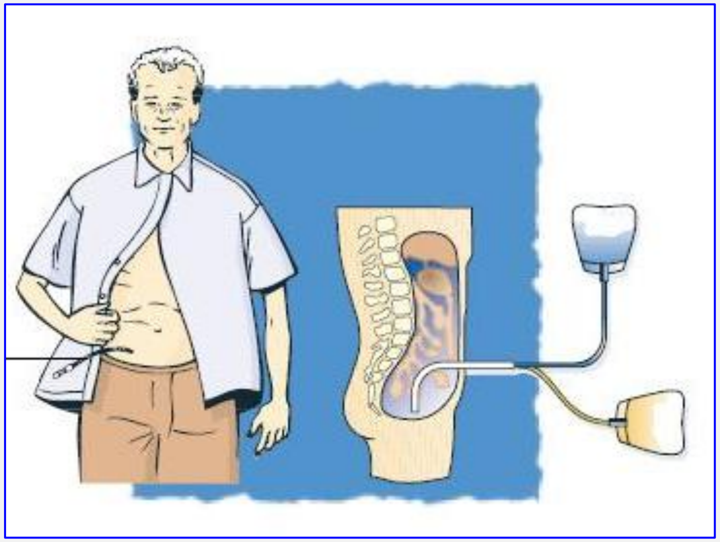
Peritoneal Dialysis as Renal Replacement Therapy

- Peritoneal dialysis: a growing mode of RRT

- >200.000 patients treated worldwide
  11% of all dialysis patients

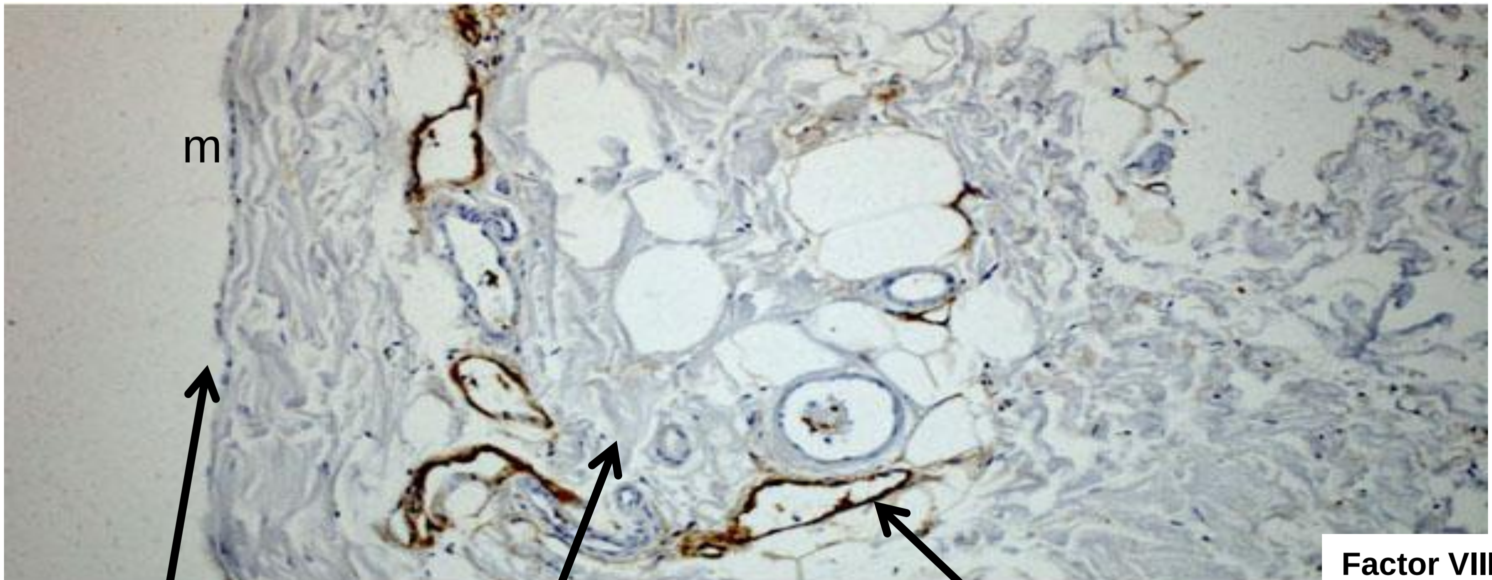
- Advantages of PD:
  - *Relatively easy*
  - *Home-based therapy*
  - *Cheaper than in-center hemodialysis*

- Continuous dialysis
  across natural membrane



Jain et al, *J Am Soc Nephrol* 2012

The Peritoneal Membrane



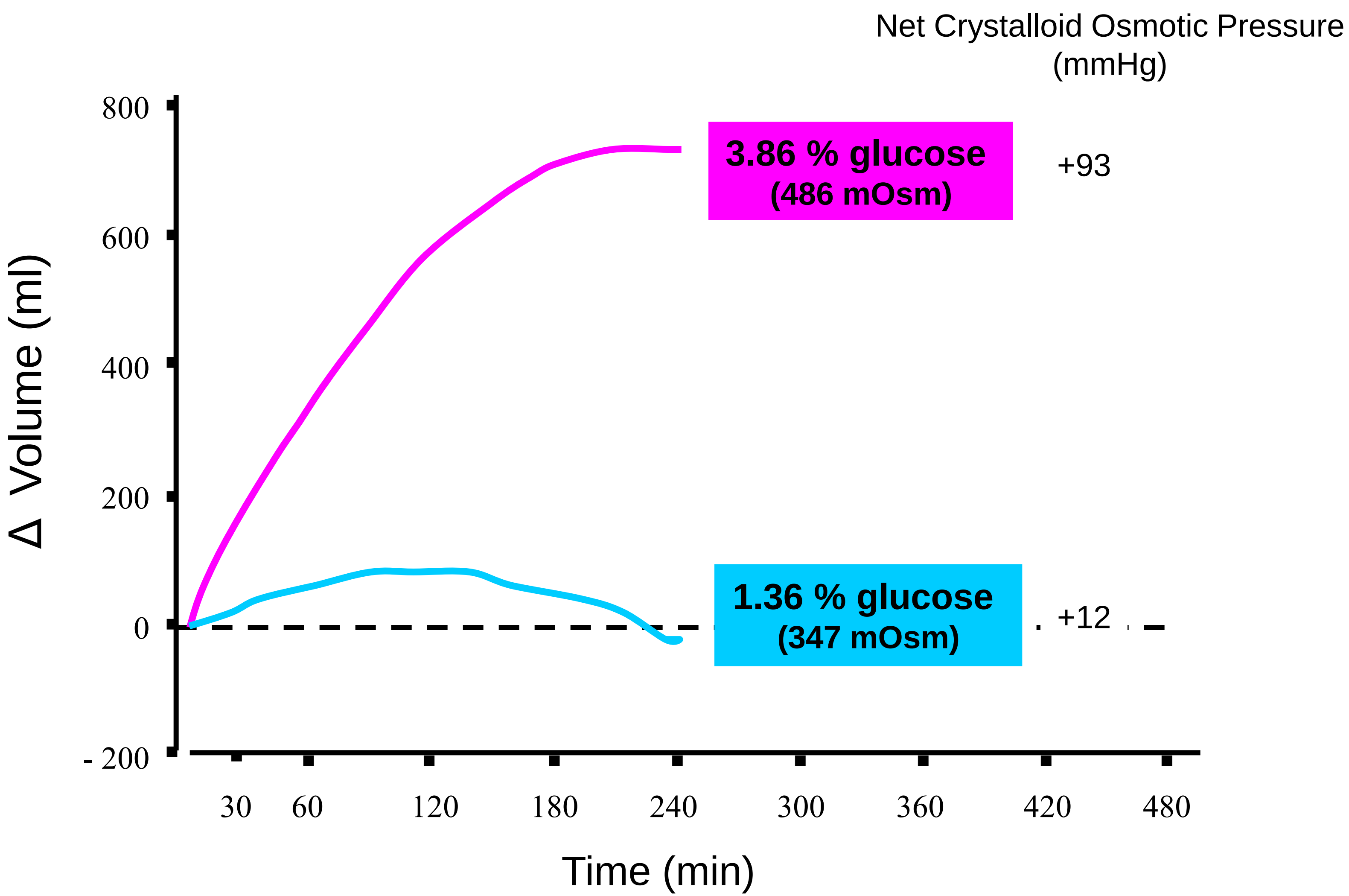
Mesothelium

Interstitium

Capillary endothelium

Main functional barrier to solute & fluid transport

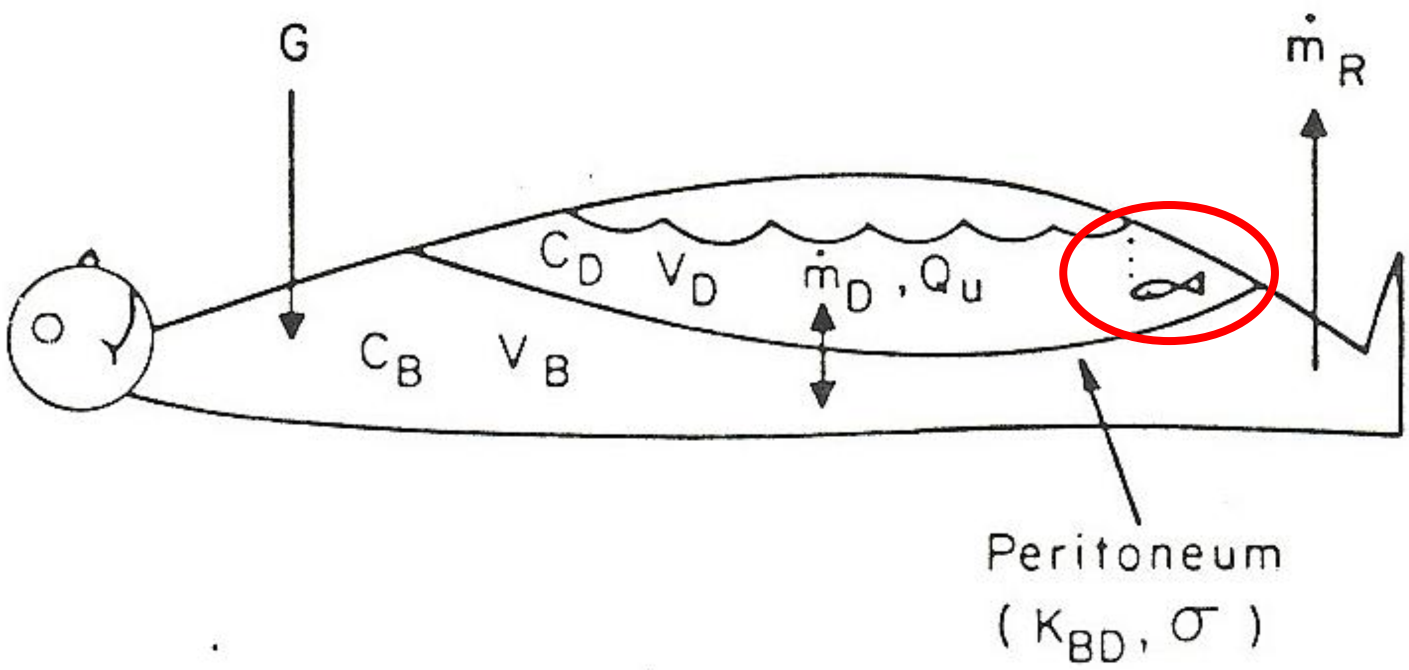
Water Removal : Glucose as an Osmotic Agent



from Krediet Kluwer 2000

Peritoneal Transport: Models from the 1980's

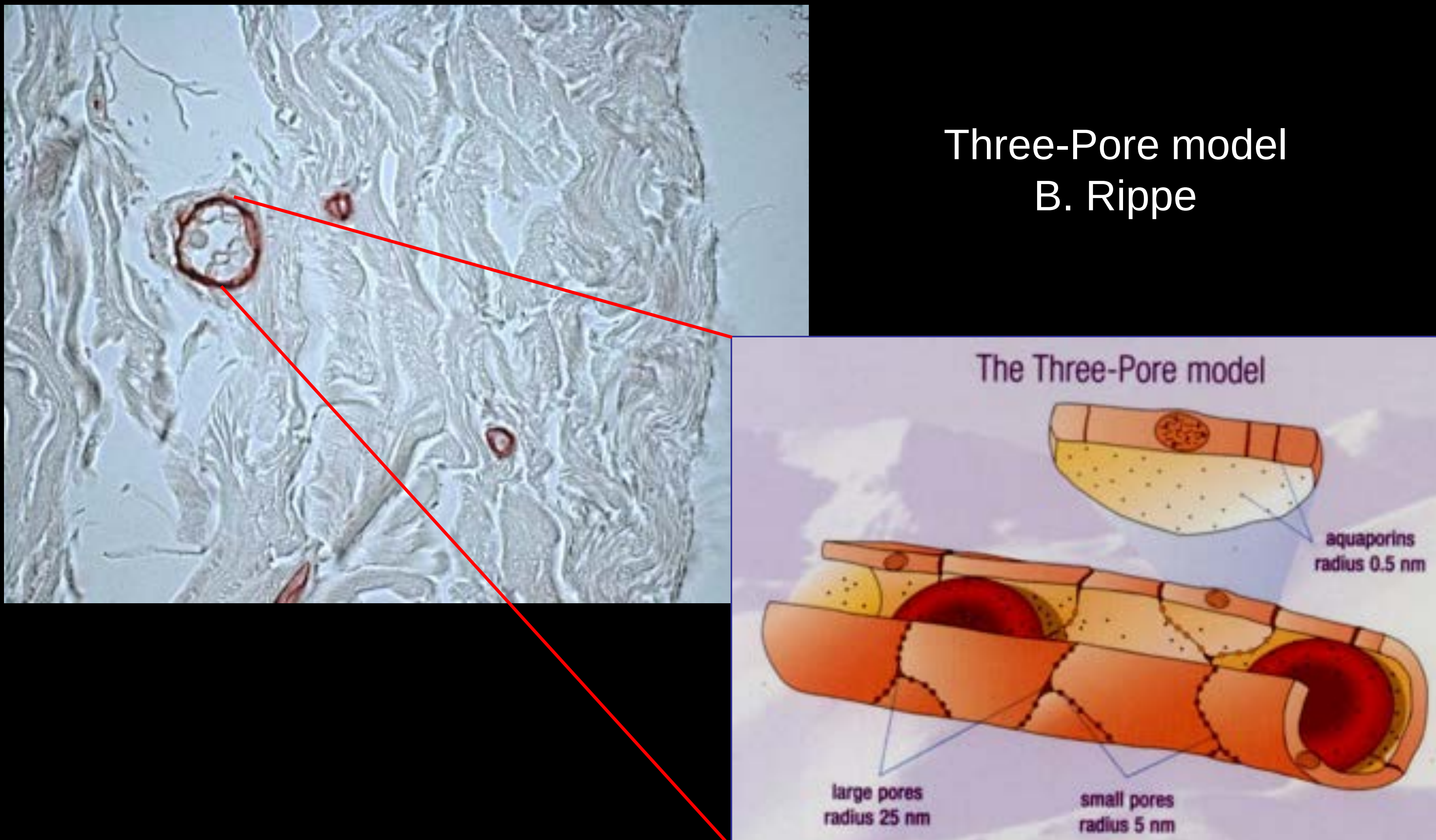
Advanced mathematical modeling using **black-box-model**



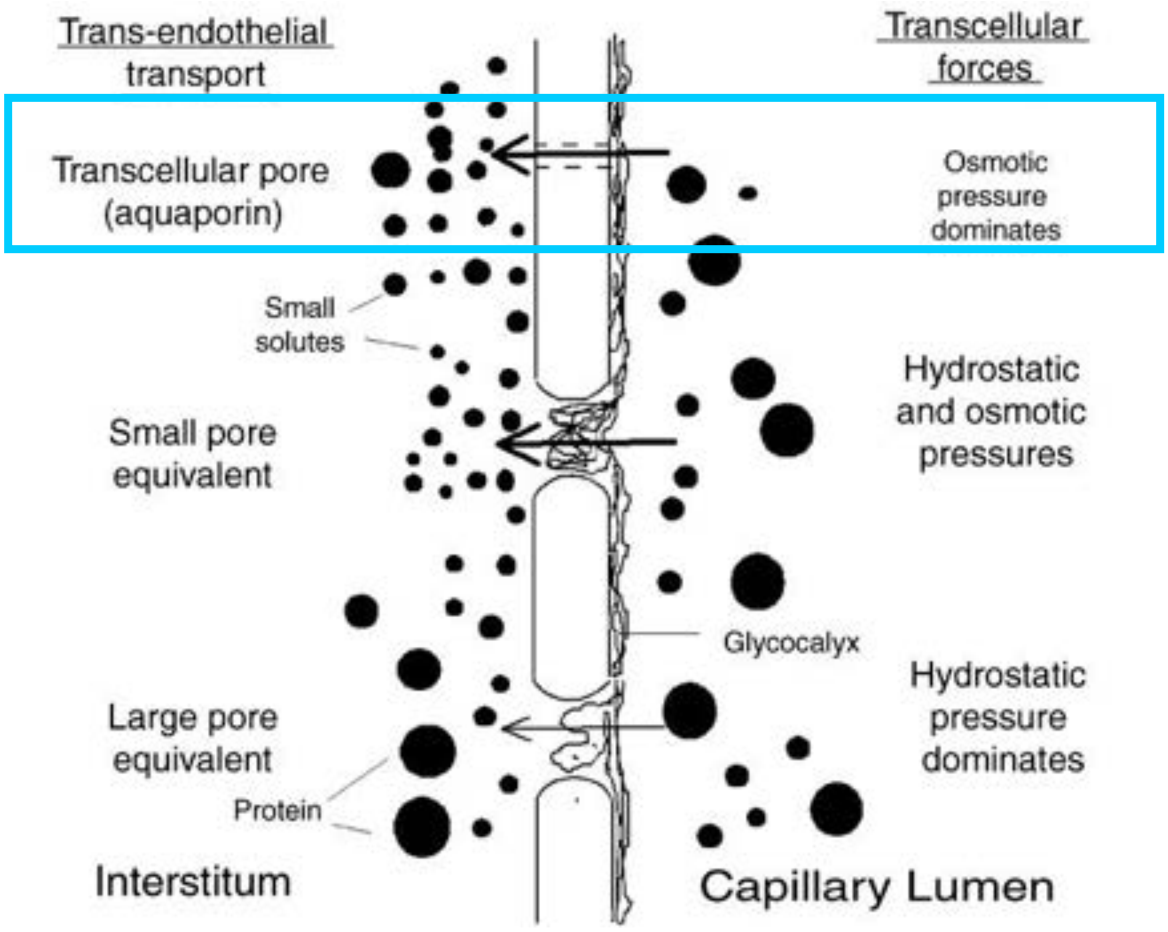
Transport Kinetics, In: Peritoneal Dialysis, 3rd Edition, Kluwer Academic Publ, Eds. Popovich, Moncrief and Pyle, Chap. 6, pp. 96-116, 1989

The Endothelium as a Functional Barrier in PD

Three-Pore model
B. Rippe

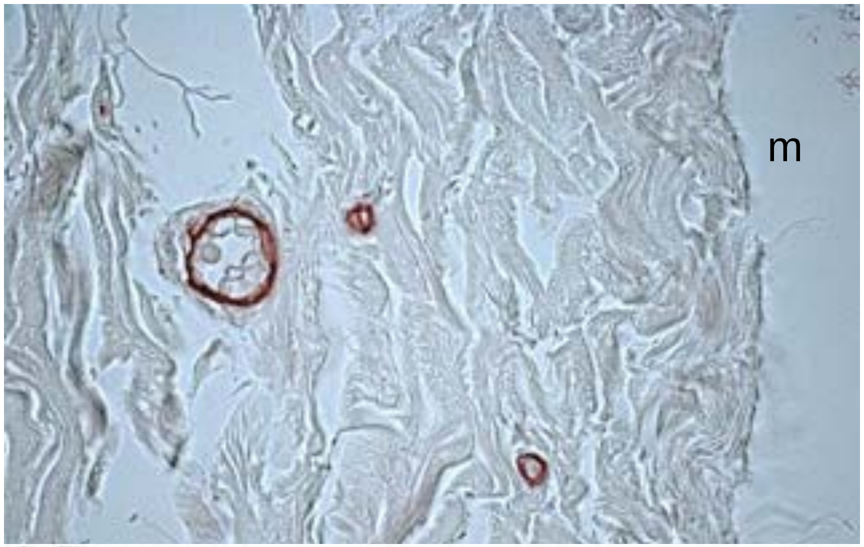


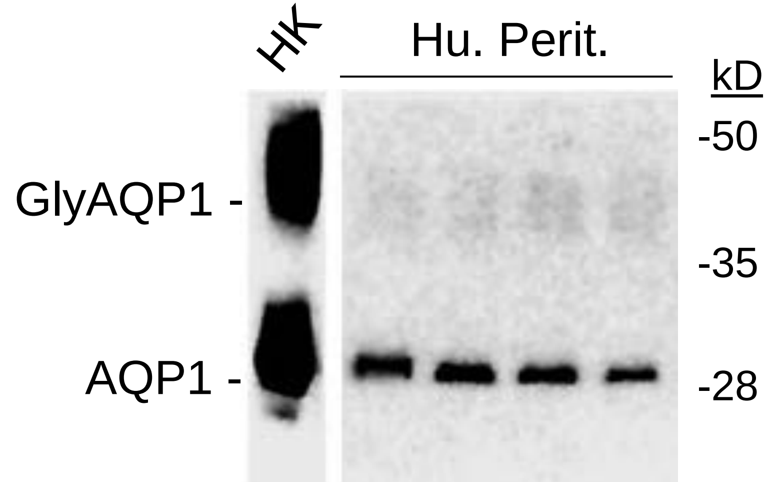
Ultrasmall Pores across the Endothelium

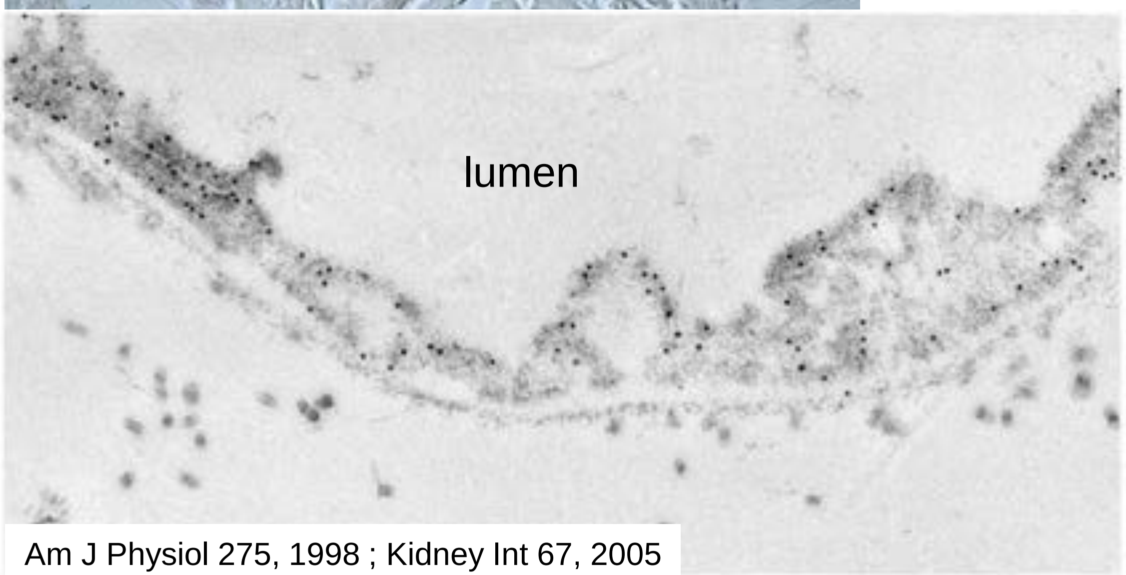


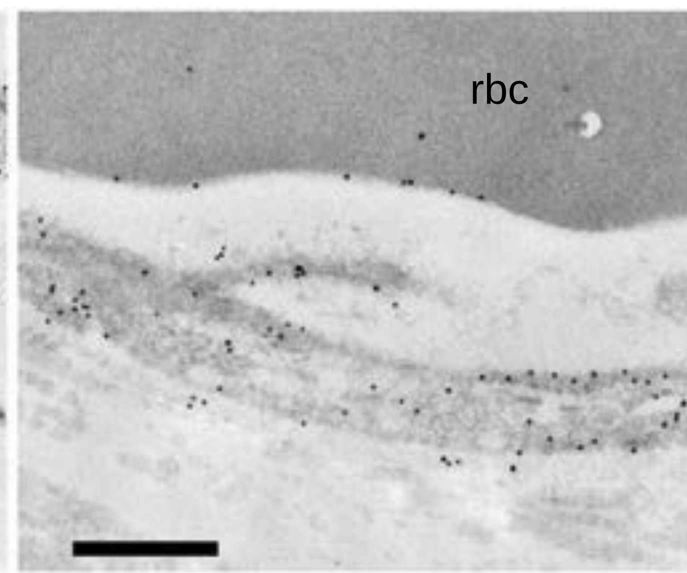
Ultrasmall pores : predict to account for 50% of water removal (UF)

Distribution of Aquaporin-1 in the Endothelium Lining Peritoneal Capillaries



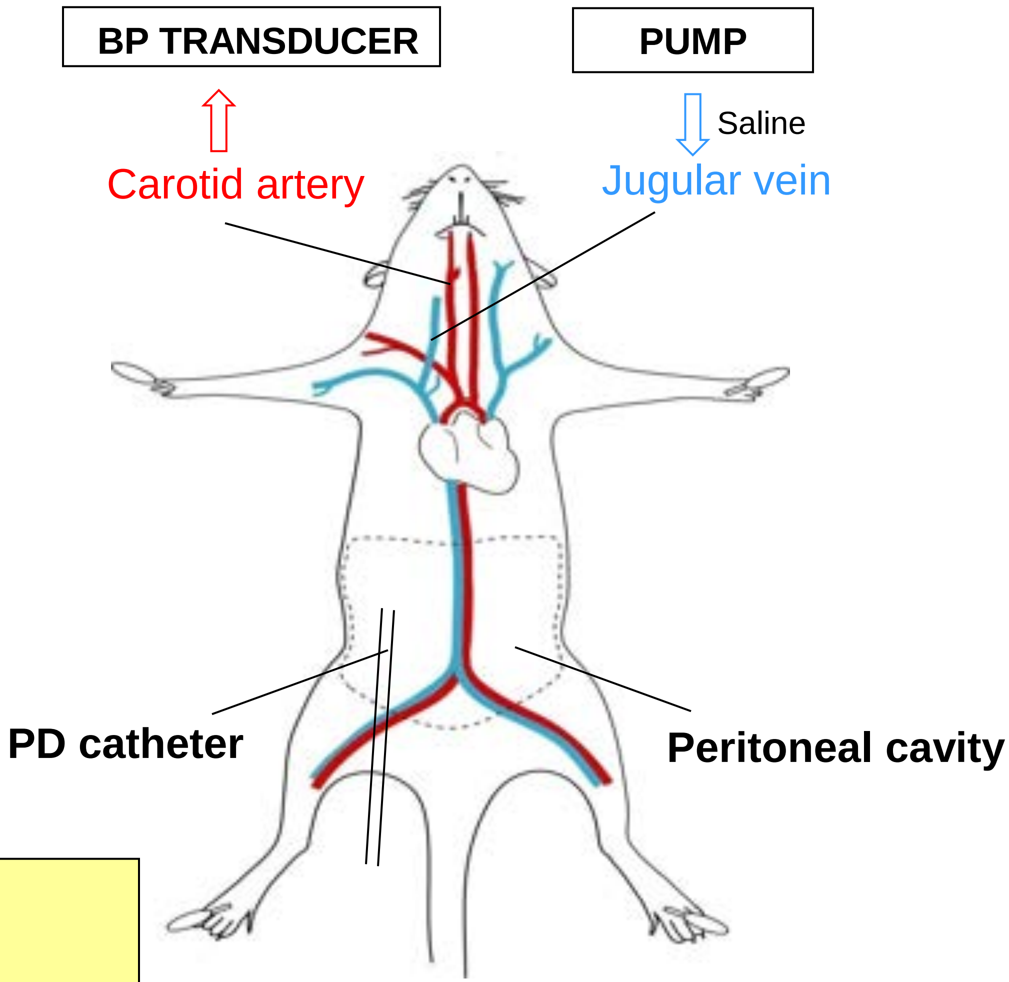






Am J Physiol 275, 1998 ; Kidney Int 67, 2005

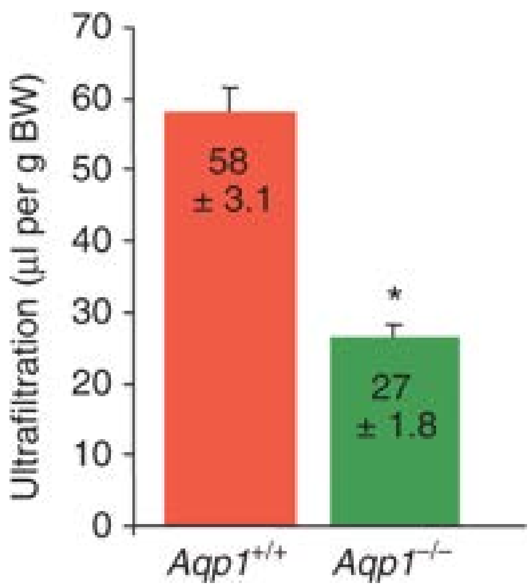
Peritoneal Dialysis in Mouse

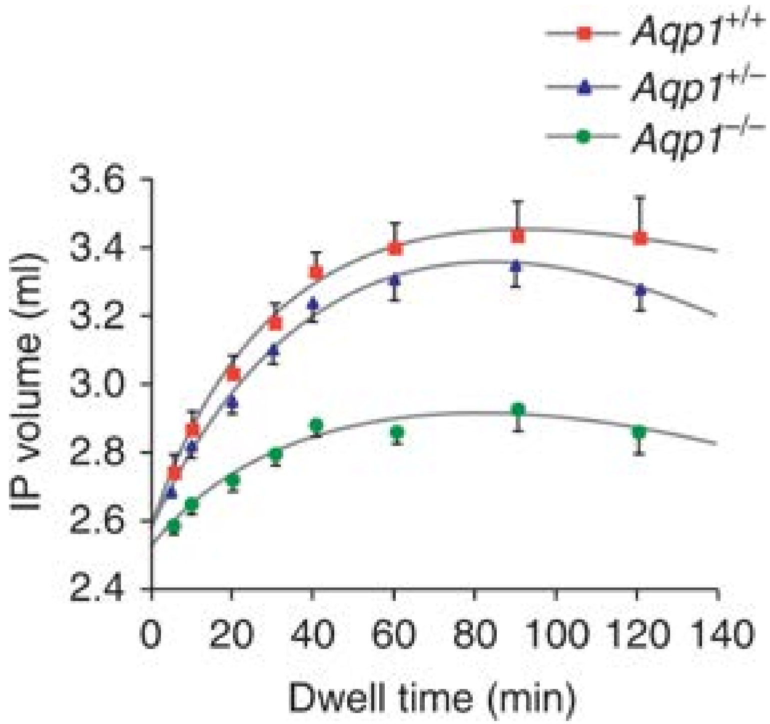


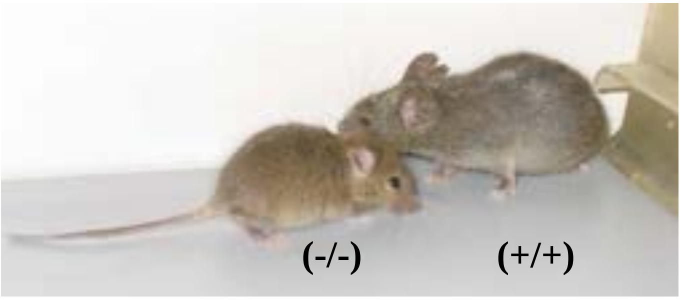
2-hour PET
2.5 ml dialysate
Sampling T0, T30, T60, T120
Synchron CX5 Beckman

Ni et al. Kidney Int 67; 2005

Peritoneal Dilaysis in *Aqp1* Mice

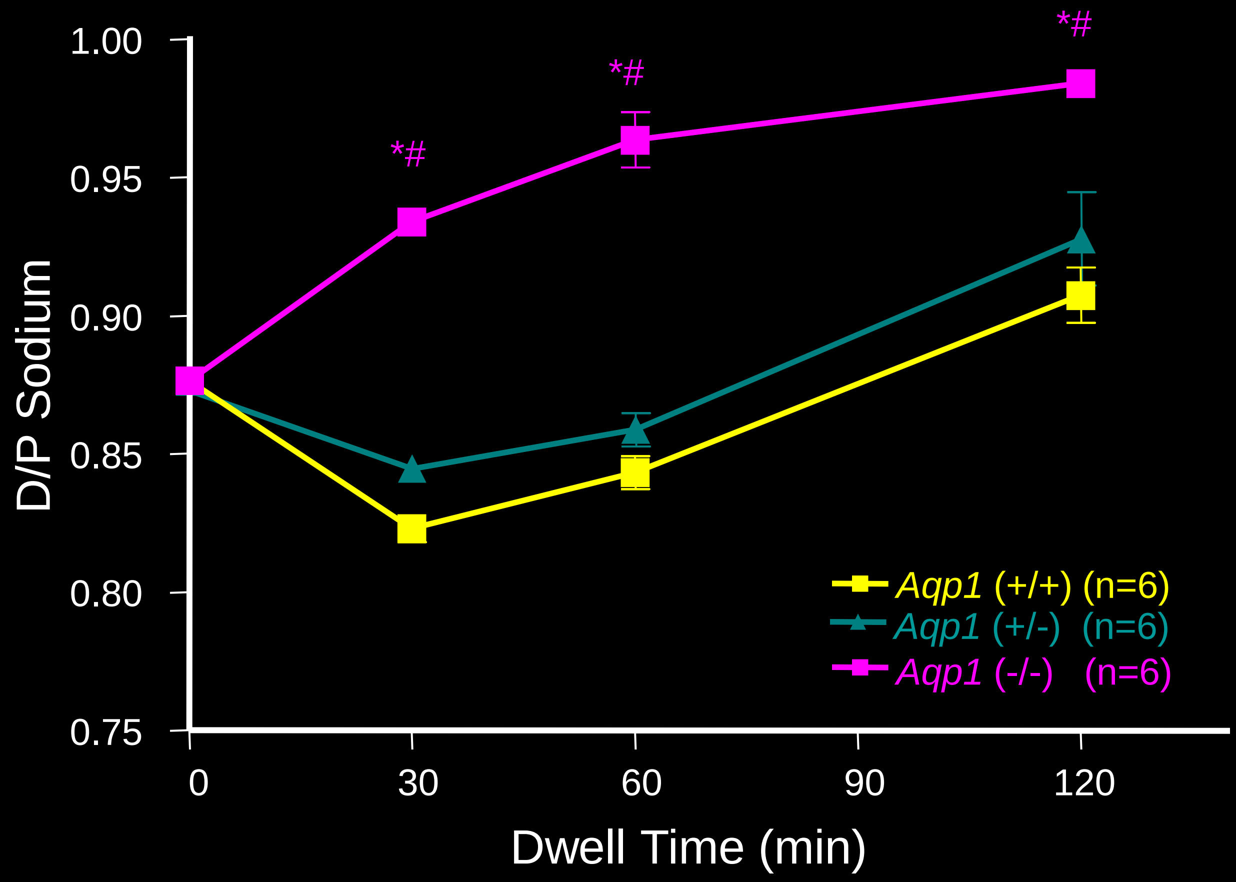






Ni J et al. *Kidney Int* 2006; 69: 1518-25

Sodium Sieving in *Aqp1* KO Mice



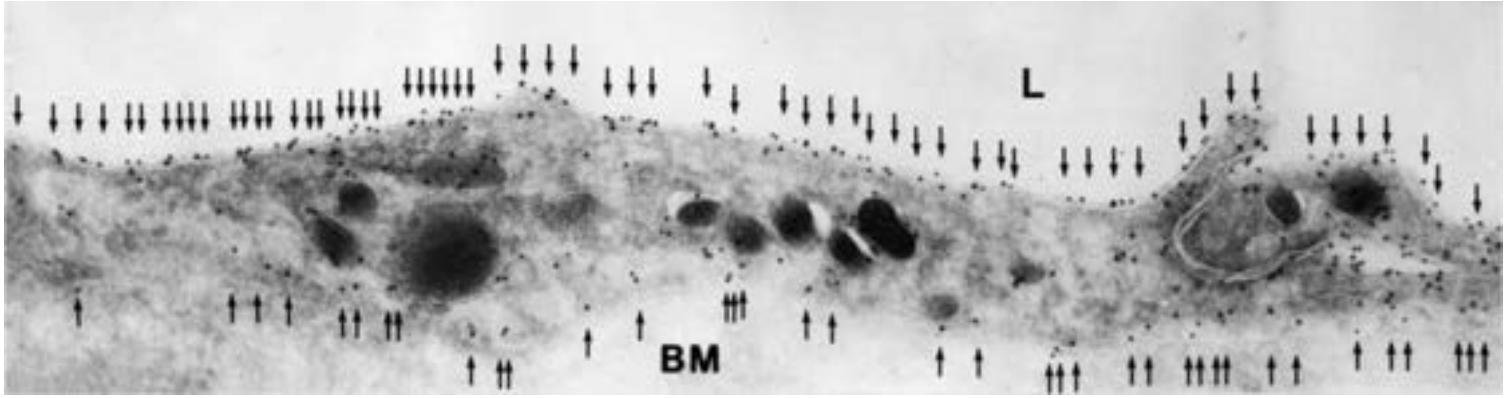
PET: 2ml, 7% glucose dialysate, 2 hours

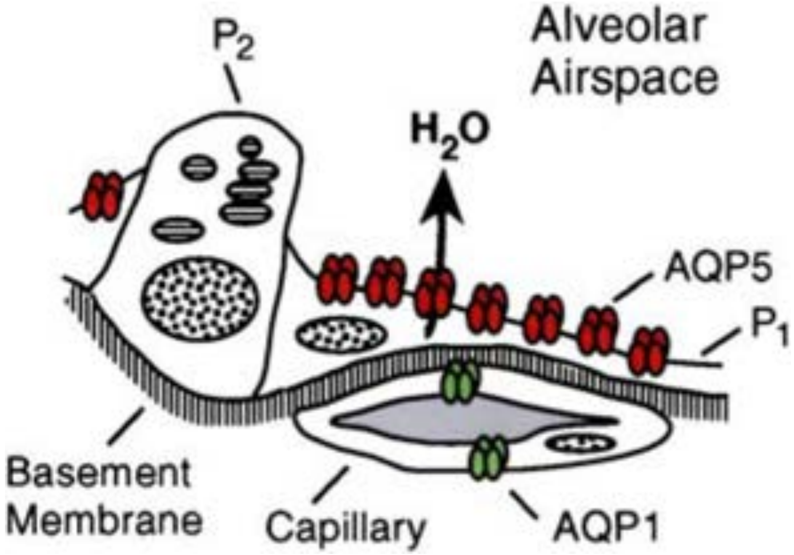
Ni et al. Kidney Int 69, 2006

Inducing aquaporins to improve dialysis ?

Dexamethasone accelerates fetal lung maturation

AQP1 in Capillary Endothelium : Lung



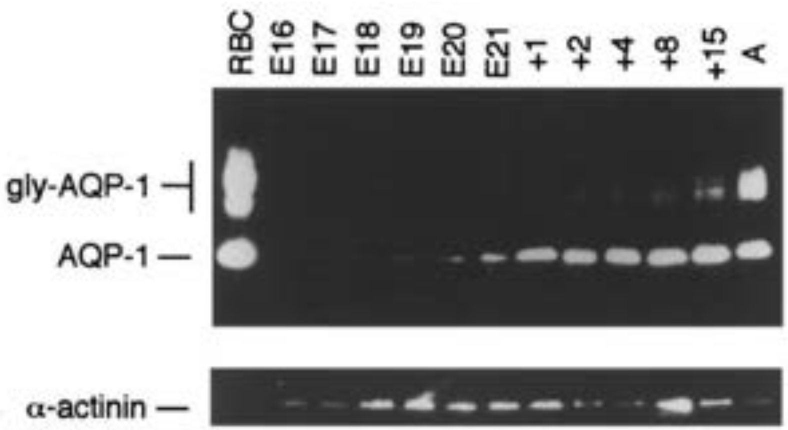


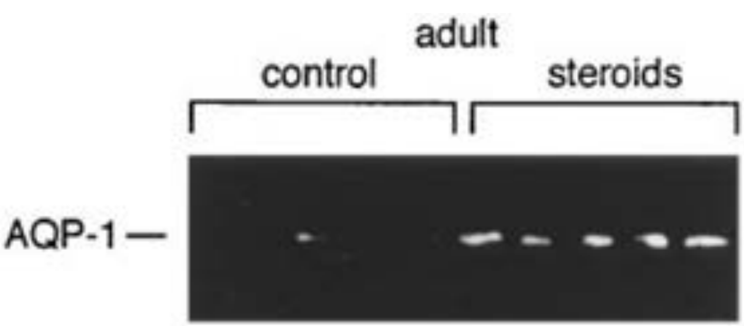
Aquaporin-1 Water Channel Protein in Lung

Ontogeny, Steroid-Induced Expression, and Distribution in Rat

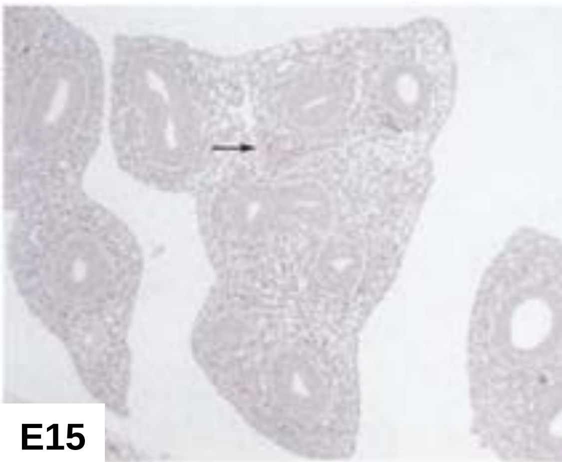
Landon S. King,*‡ Søren Nielsen,§ and Peter Agre*‖

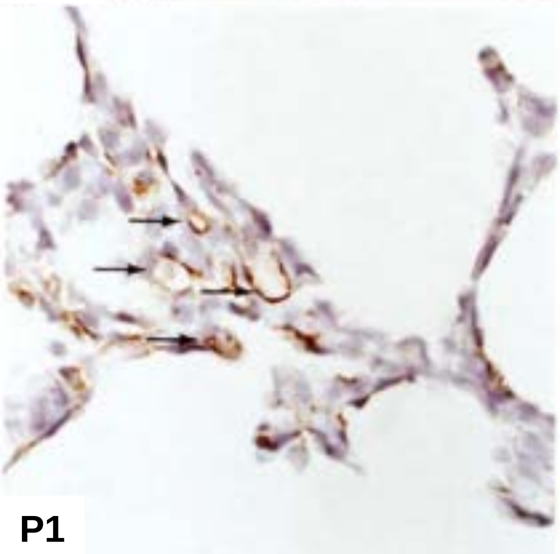
J Clin Invest 97, 1996



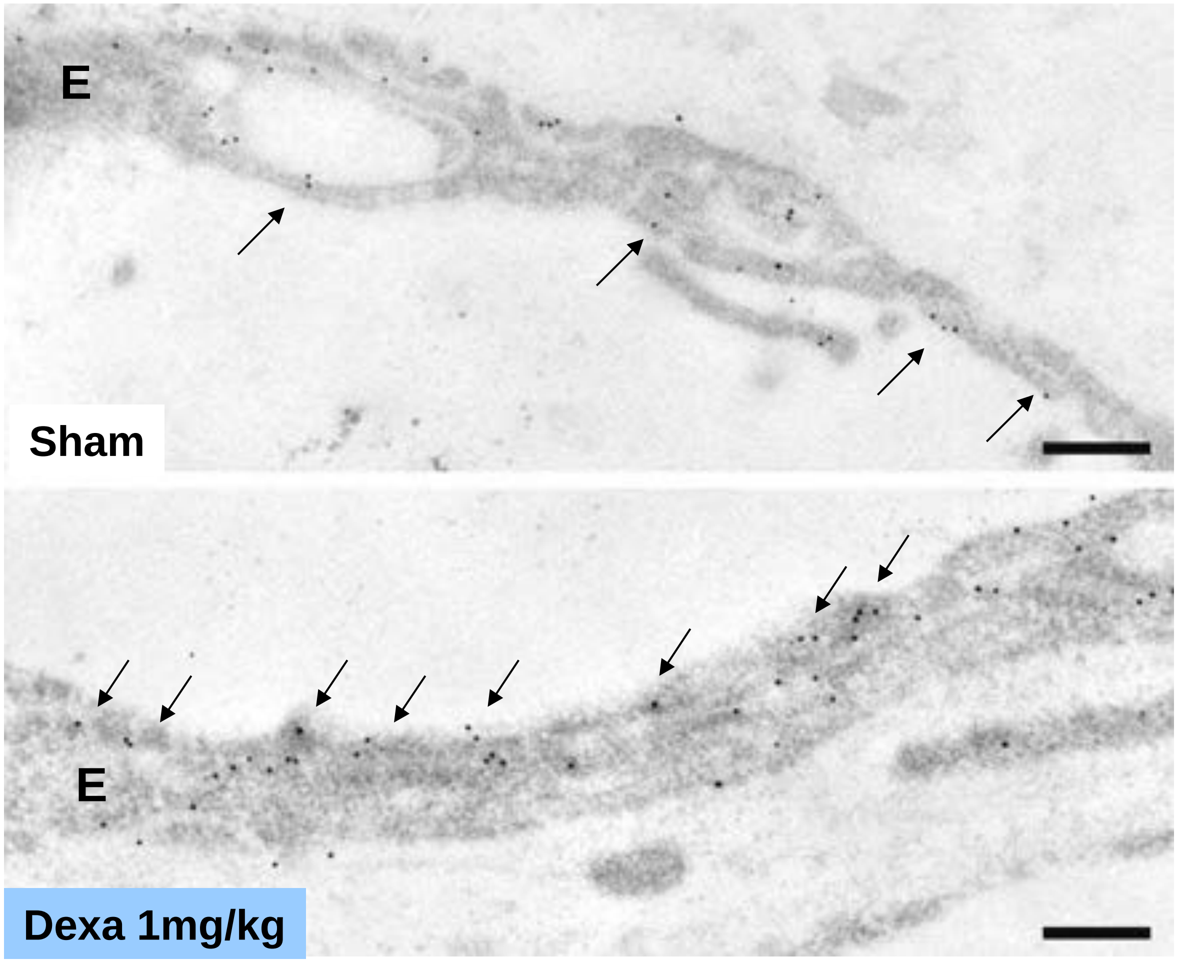


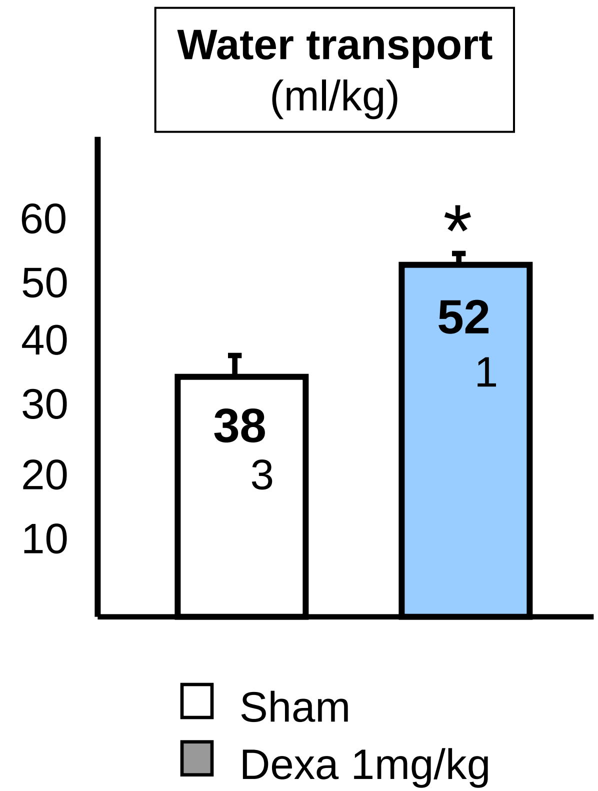
saline or betamethasone (0.35 mg/kg)





Glucocorticoids upregulate AQP1 in peritoneal capillaries



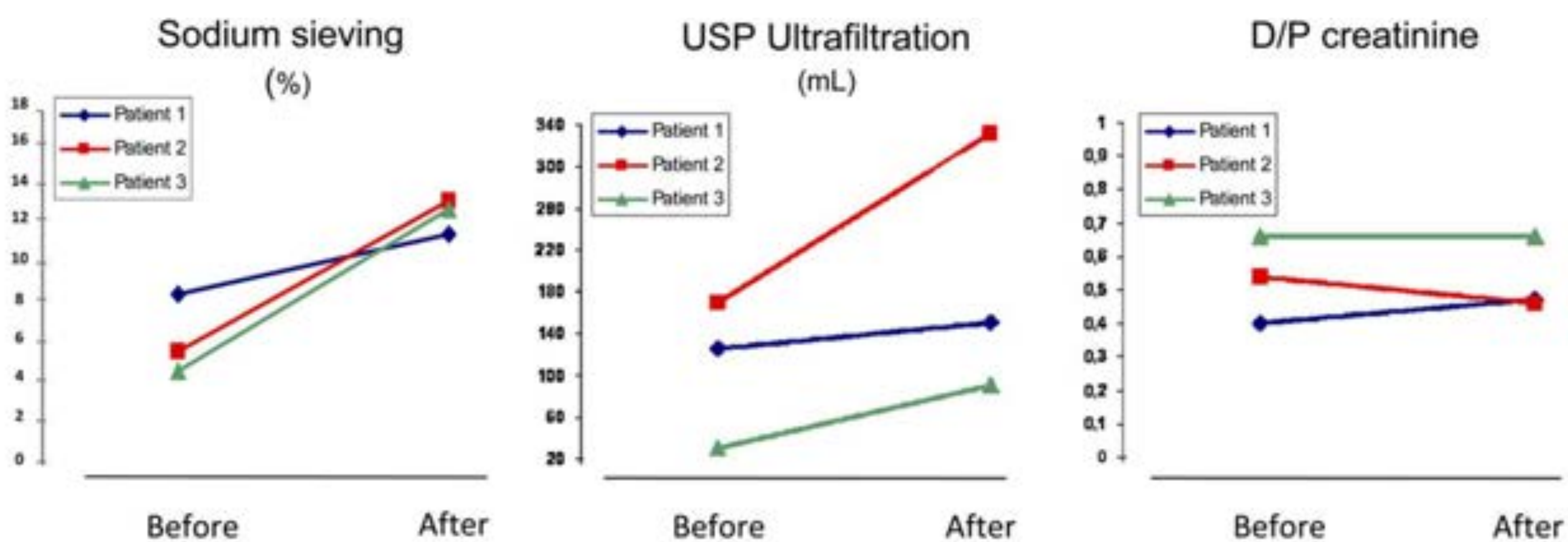


Stoenoiu et al. JASN 14: 555-65, 2003

Nephrol Dial Transplant (2011) 26: 4142–4145

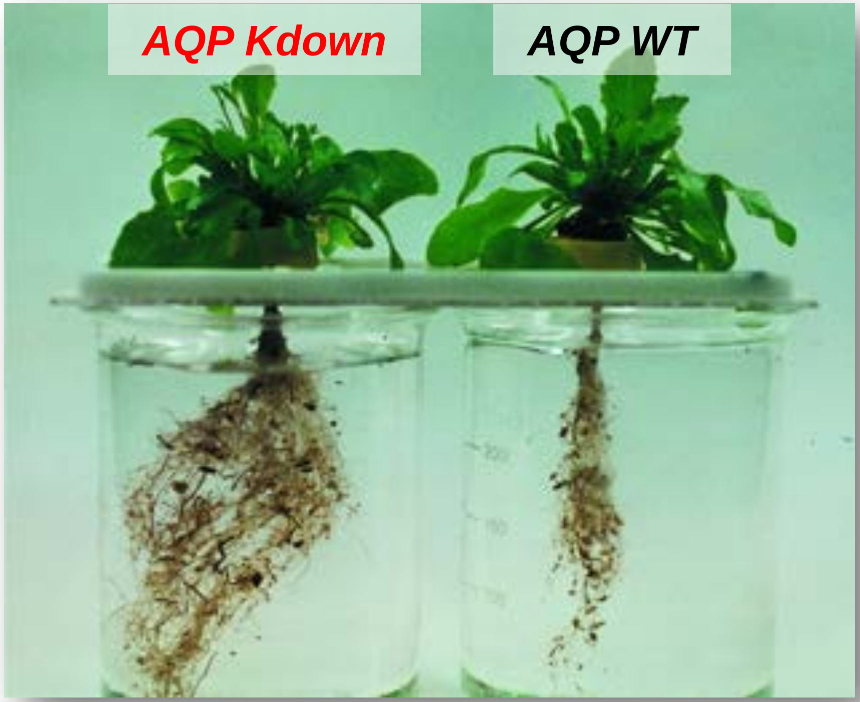
High-dose steroid treatment increases free water transport in peritoneal dialysis patients

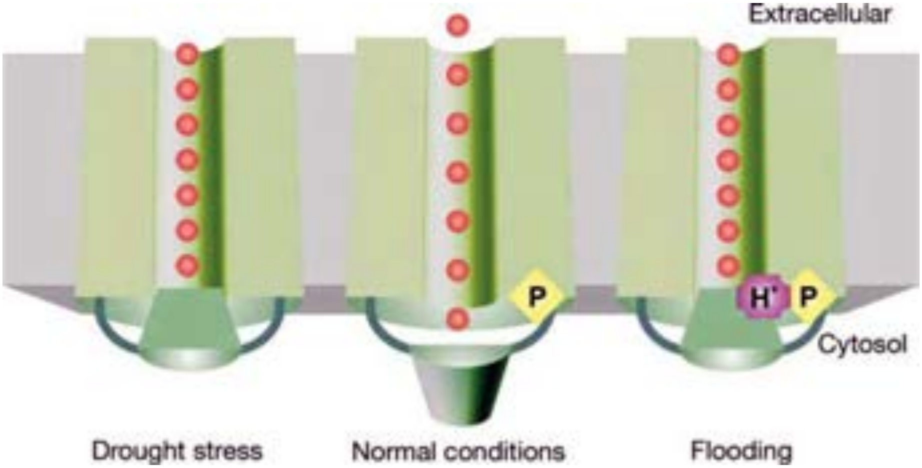
Javier de Arteaga[1,2], Fabian Ledesma[1,2], Gabriela Garay[1,2], Carlos Chiurchiu[1,2], Jorge de la Fuente[1,2], Walter Douthat[1,2], Pablo Massari[1,2], Sara Terryn[3] and Olivier Devuyst[3,4]



Gating AQP1 to improve water transport ?

Aquaporins Role in Plants: Gating Mechanisms





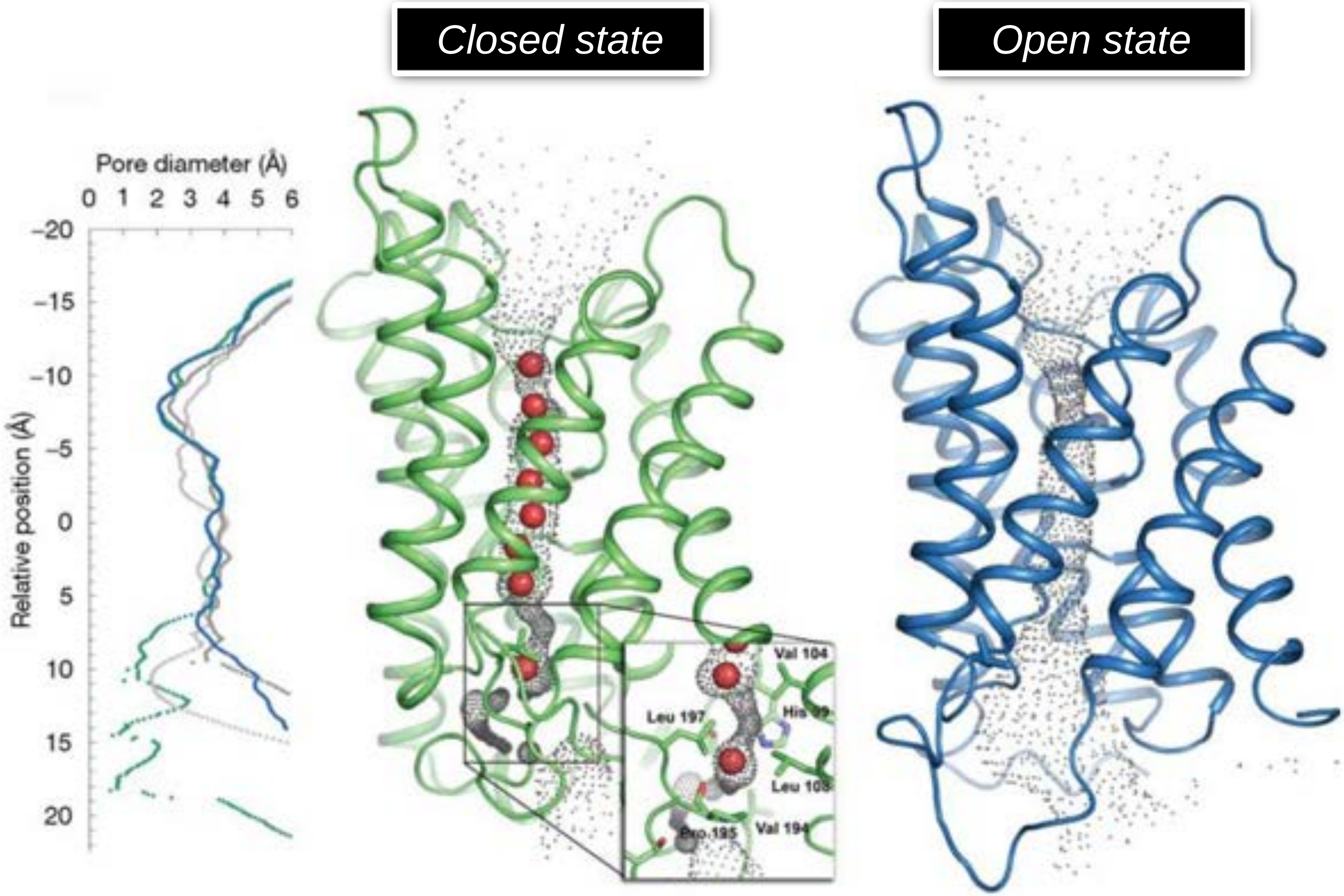
Fluctuations in water supply: regulation of AQPs in plants

Drought stress → dephosphorylation of two conserved serine → channel closure

Flooding (acidification)→ protonation of a conserved histidine → channel closure

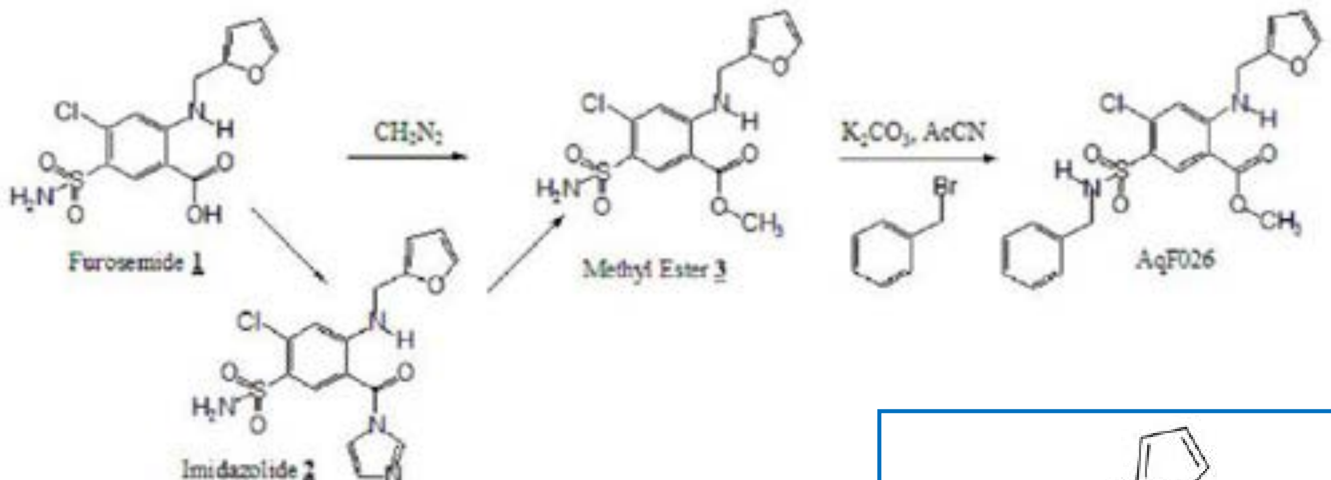
Tournaire-Roux et al, *Nature* 2003; Chaumont et al, *Biol Cell* 2005; Tornroth-Horsefield et al, *Nature* 2006

The gating of plant AQP involves loop D

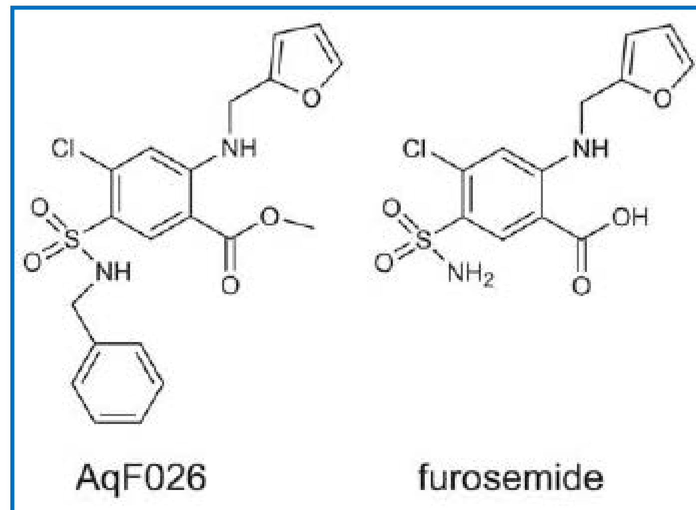


Tornroth-Horsefield et al, *Nature* 2006

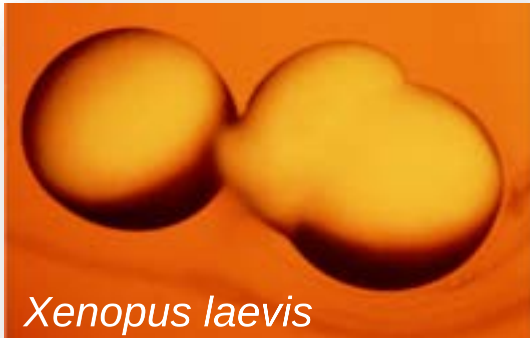
Chemical library screen: Aryl sulfonamides – AqF026

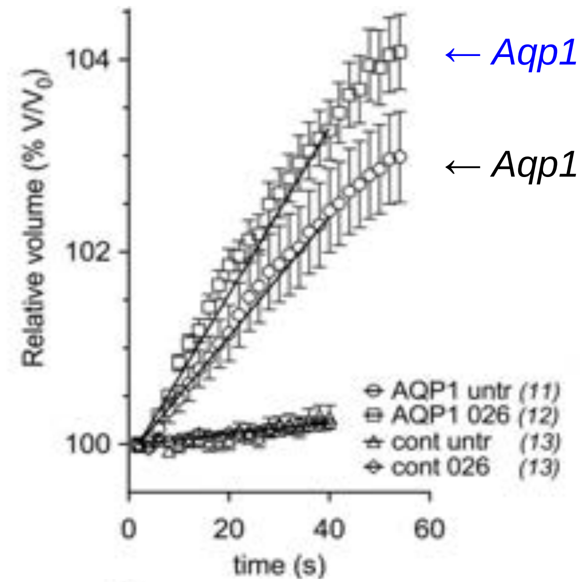


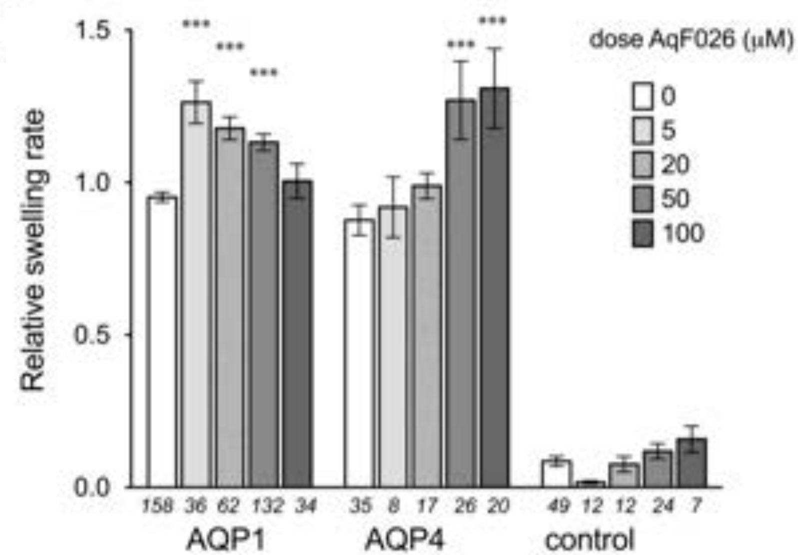
Distinctive sulfhydryl-linked
aromatic ring
of AqF026 vs. furosemide

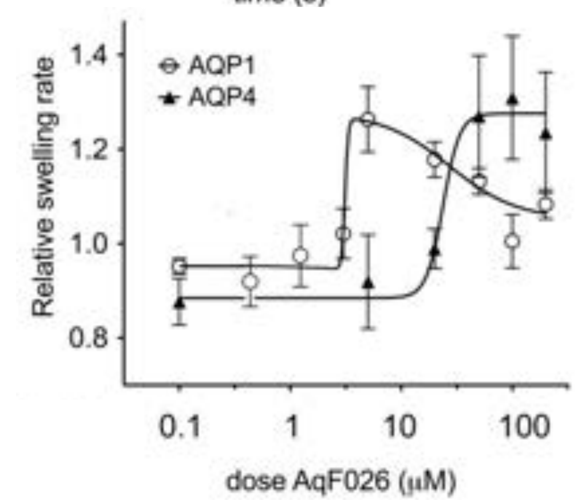


Effect of AqF026 on transport water *in vitro*



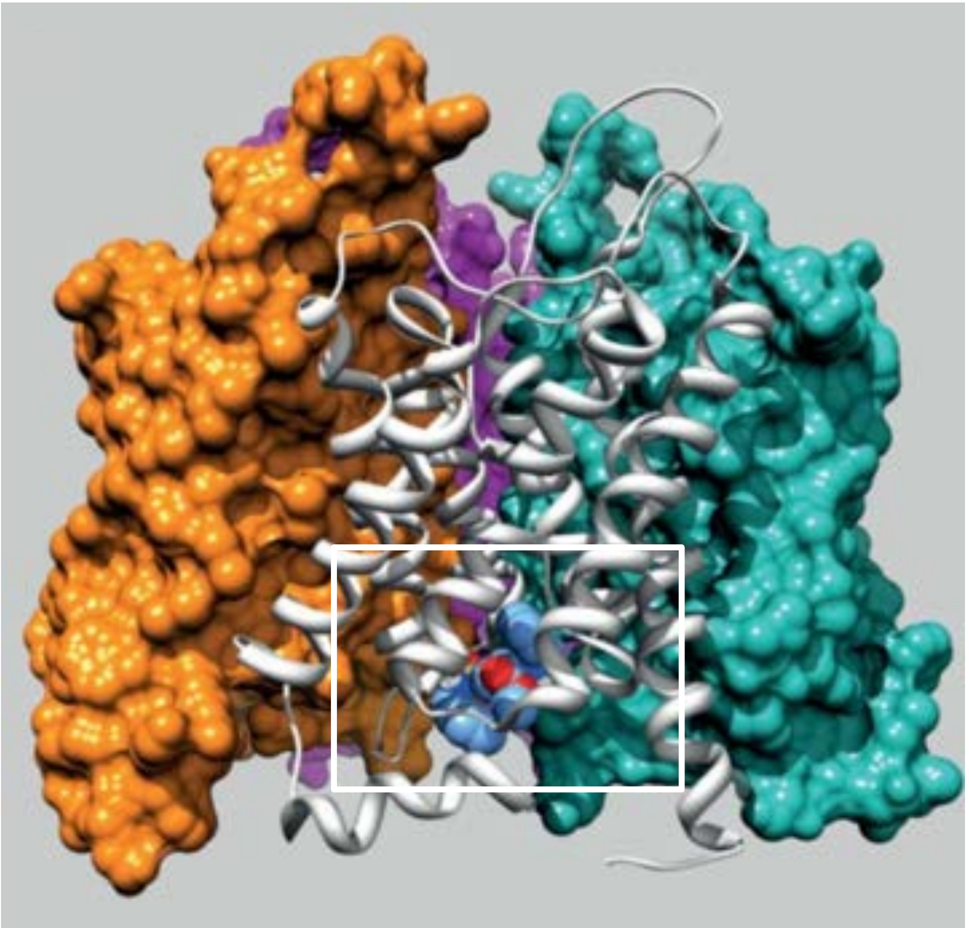


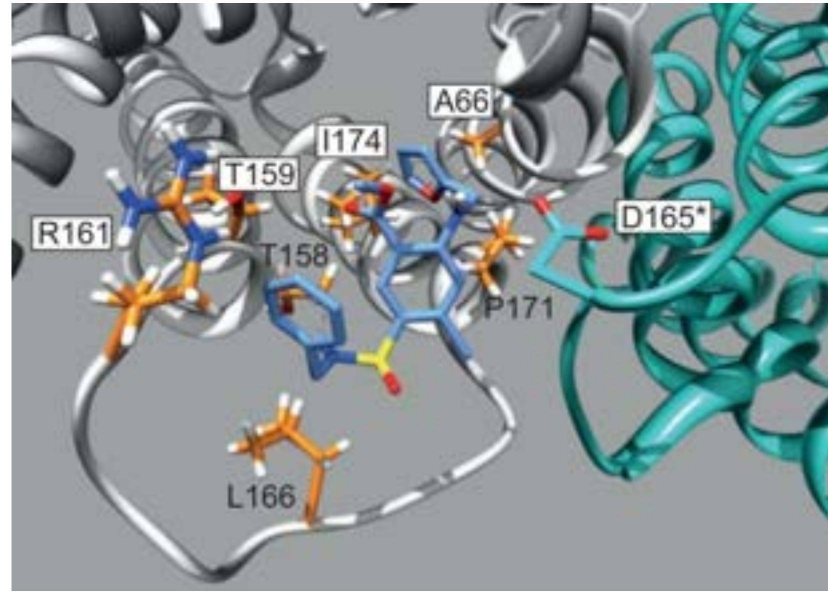




Potentiation of water transport : maximal at 5-20 µM for AQP1 (>50-100 µM for AQP4) with EC_{50} at 3.3 µM

Docking model suggests the binding of AqF026 to residues in the loop D domain

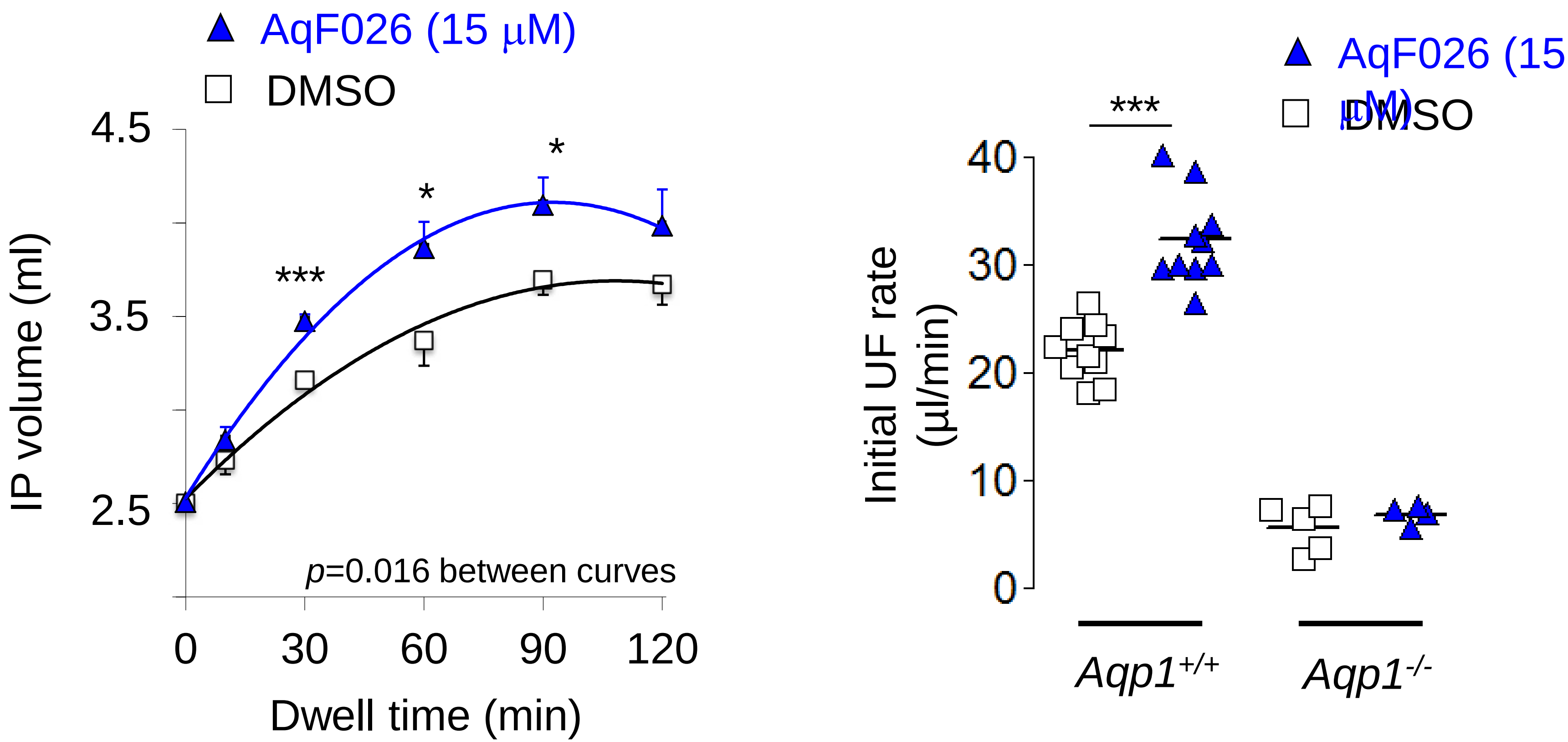




The binding site involves residues (Arg161, Thr159) located in the cytosolic D loop.

J Am Soc Nephrol **24:** 1045–1052, 2013

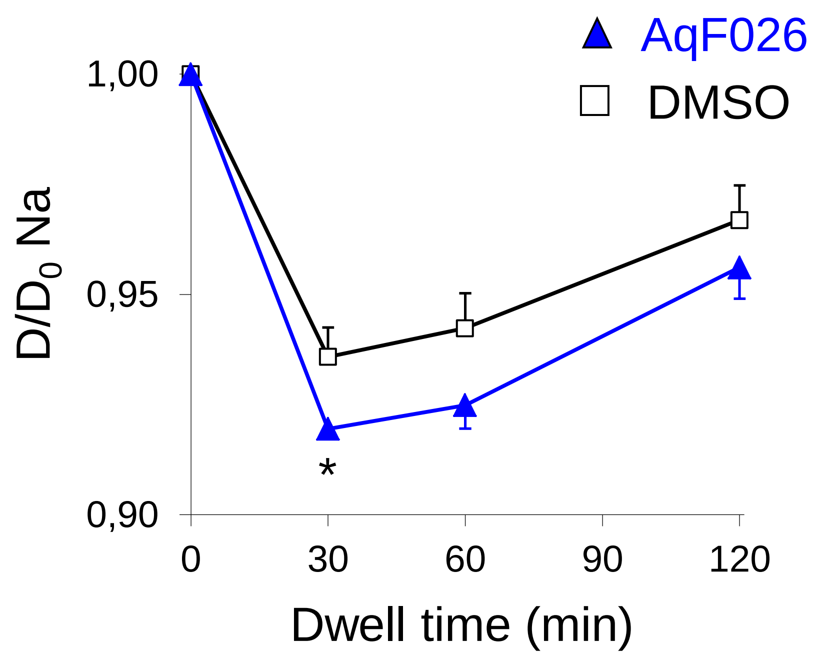
In vivo effect of AqF026: IPV curves and initial UF rate

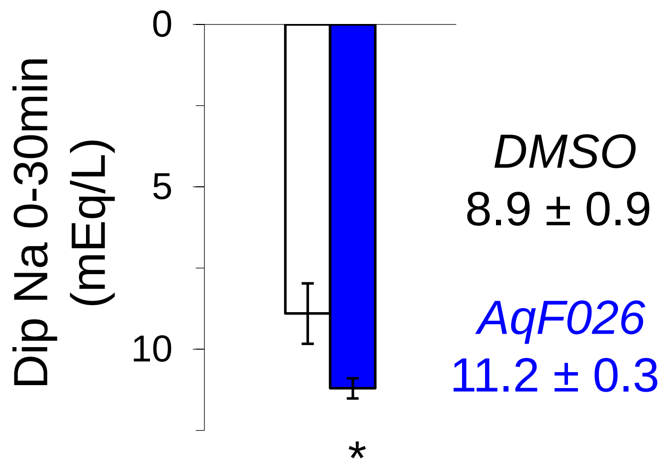


1. AqF026 increases initial UF rate by ~50%
2. AqF026 has no effect on the initial UF rate in *Aqp1*-null mice

J Am Soc Nephrol **24:** 1045–1052, 2013

In vivo effect of AqF026 on the sodium sieving





AqF026 increases the sodium sieving,
reflecting the enhanced free-water transport through AQP1

AqF026 15 µM, data are mean ± SEM; n=10 for each group

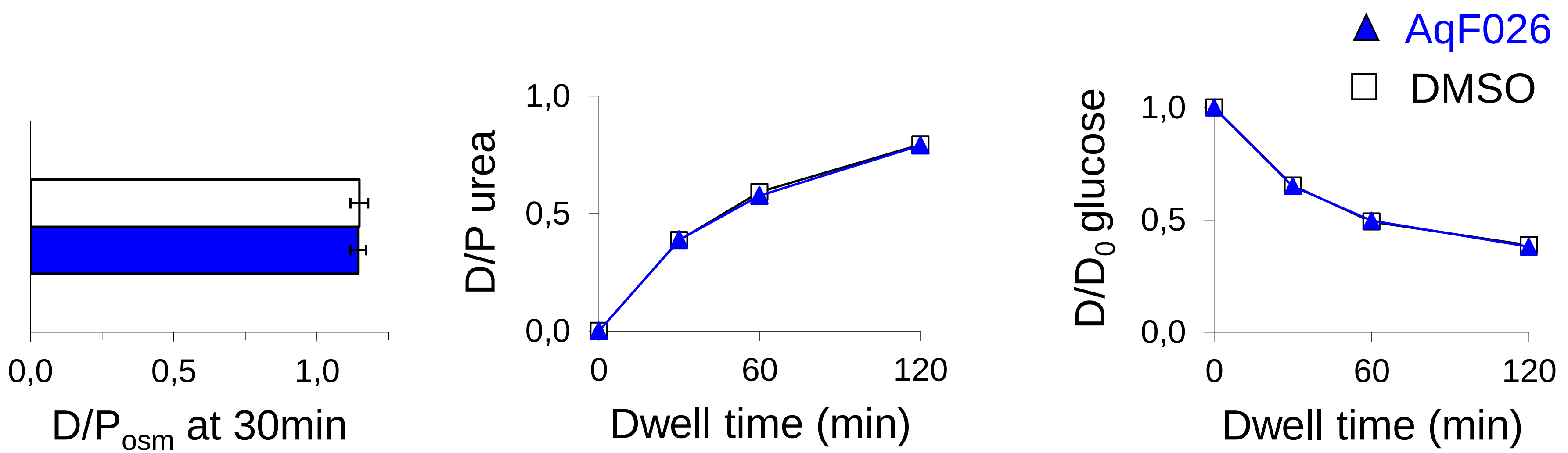
J Am Soc Nephrol **24:** 1045–1052, 2013

AqF026: No Effect on Osmotic Gradient and Solute Removal

Group (n)		Net UF (µl/g BW)	D/Posm at 30min	MTAC urea (µl/min)
Aqp1$^{+/+}$	DMSO (16)	37.2±1.3	1.14±0.03	35.0±2.3
Aqp1$^{+/+}$	026 (16)	**42.8±1.4***	1.15±0.03	34.2±1.7
Aqp1$^{-/-}$	DMSO (6)	15.7±1.9***	1.28±0.02	35.5±3.6
Aqp1$^{-/-}$	026 (6)	15.6±1.6	1.27±0.03	36.4±7.0

+15%

increase in net UF after a 2-h dwell



Tolerance of AqF026

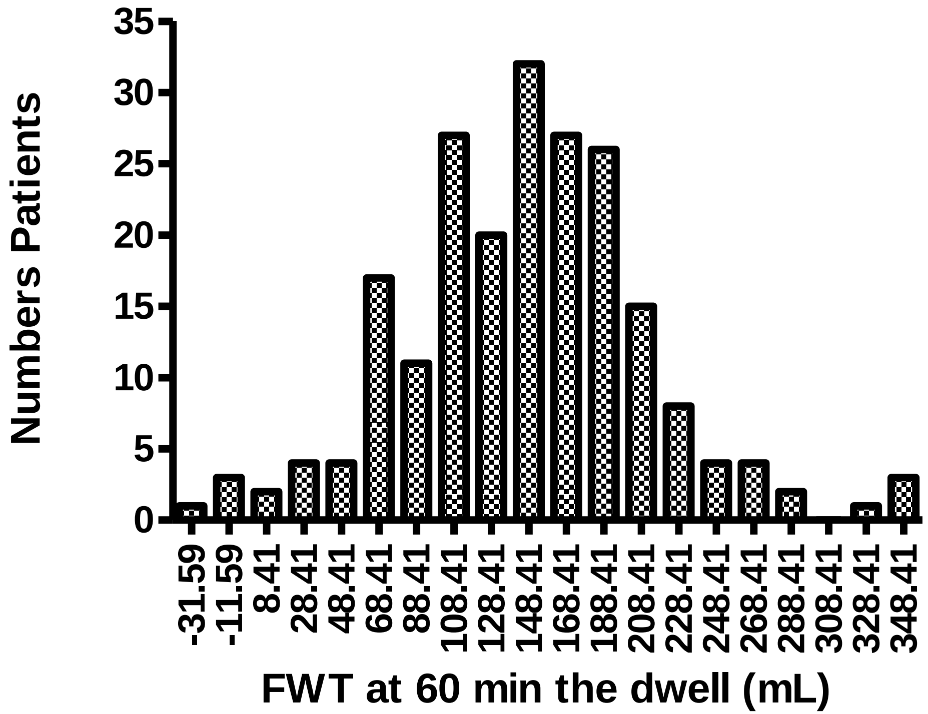
- Well-established safety index of loop diuretics during acute or chronic administration
- No overt tissue or organ toxicity under the conditions tested
- No diuretic effect; biological screening:

	n/group	Normal values (SV129)	DMSO	AqF026
AST (UI/L)	6	71–201	180 ± 30	132 ± 9
ALT (UI/L)	6	45–84	12 ± 1	13 ± 1
LDH (UI/L)	9	2212-3150	978 ± 115	804 ± 89

Mazzaccara et al, *PLOS one* 2008

Genetic influence on water transport ?

Distribution of Water Transport in PD Patients



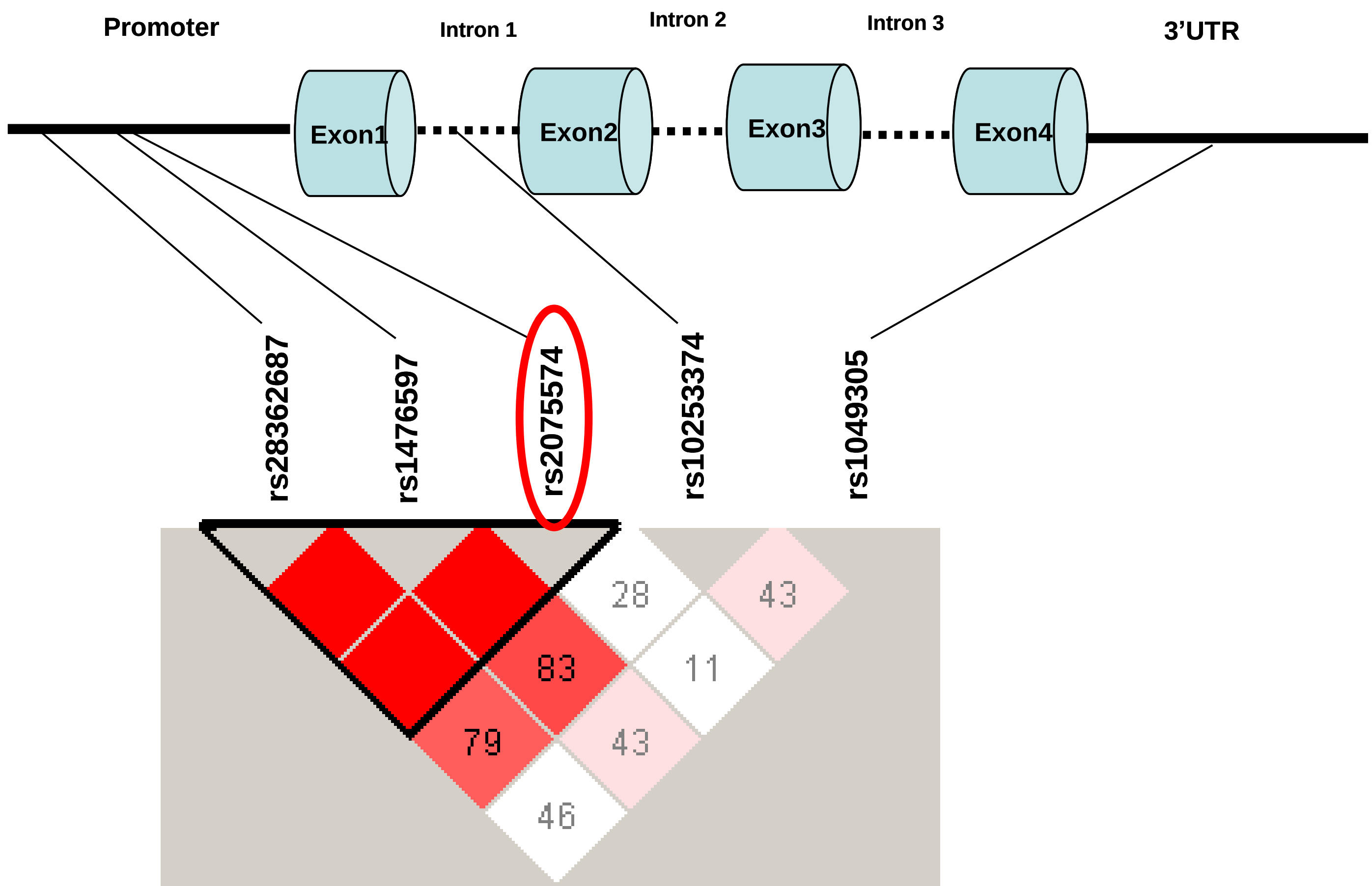
Amsterdam data – SPA test
60 min – hypertonic dwell
Incident PD patients, n=211

Clinical variables account for only ~ 20% of the variability:
→ Variations in water channels ?

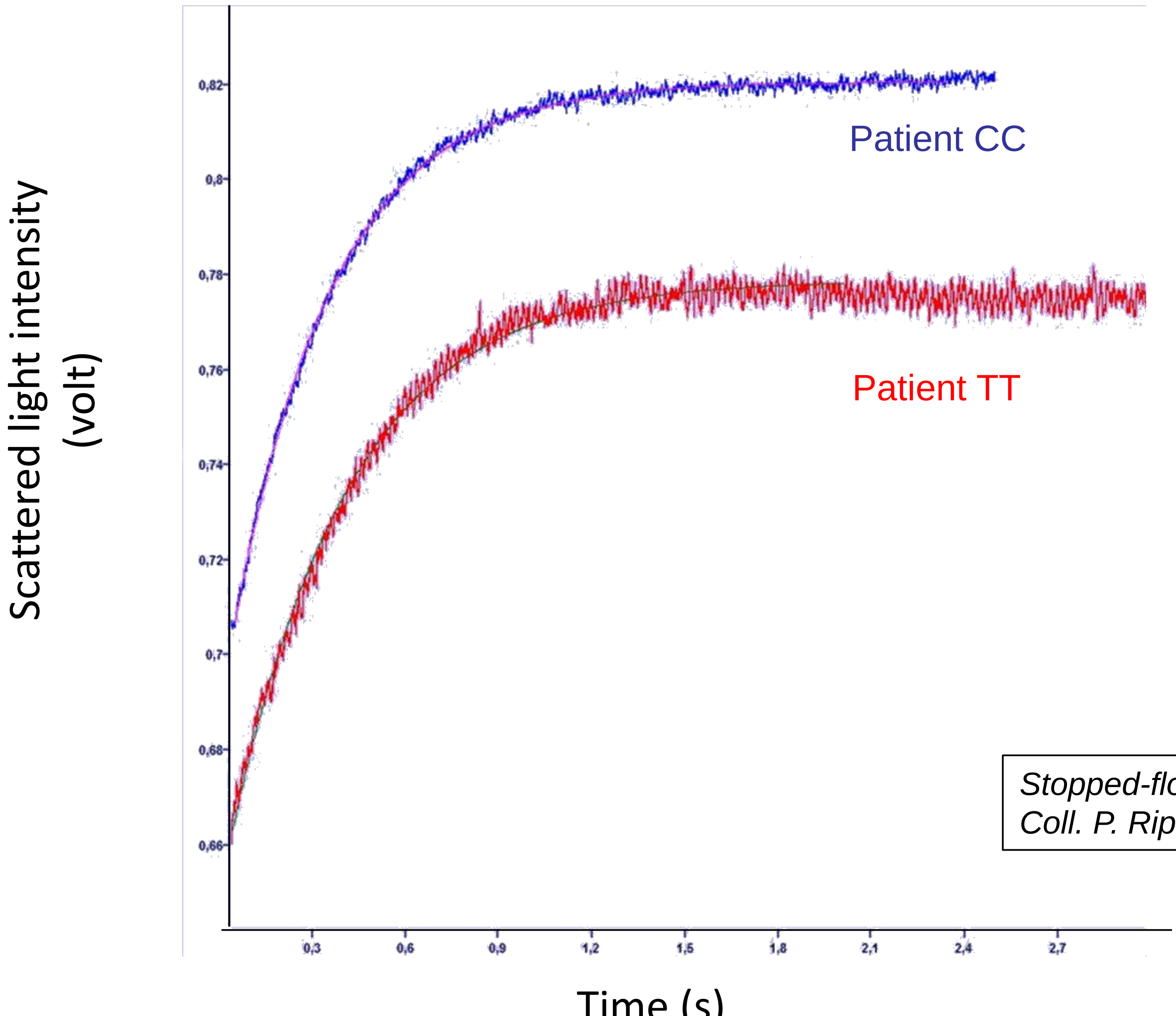
Influence of variants in *AQP1* on Water transport and PD Outcome

- Multicentric association study
  - UCL – KUL – CHC Liège: N=215
  - NECOSAD – AMC Amsterdam: N=500
  - Replication: UK and Spain cohorts
- Initial water flow, small solute transport
- Survival : technique and patient

AQP1 Haplotype

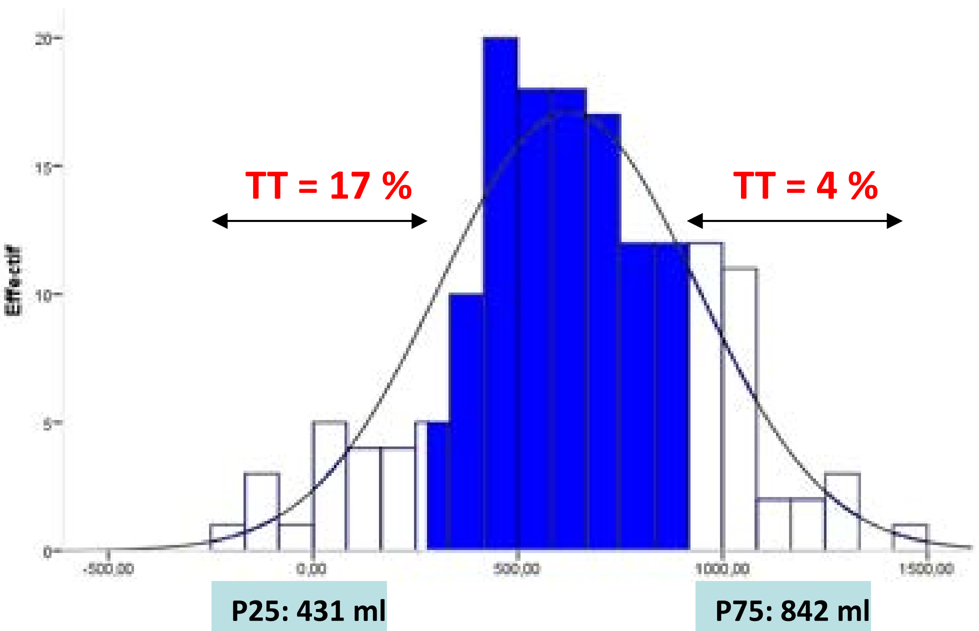


AQP1 Genotype: Water transport in erythrocytes



Stopped-flow scattering
Coll. P. Ripoche, Paris

AQP1 Genotype and Transport

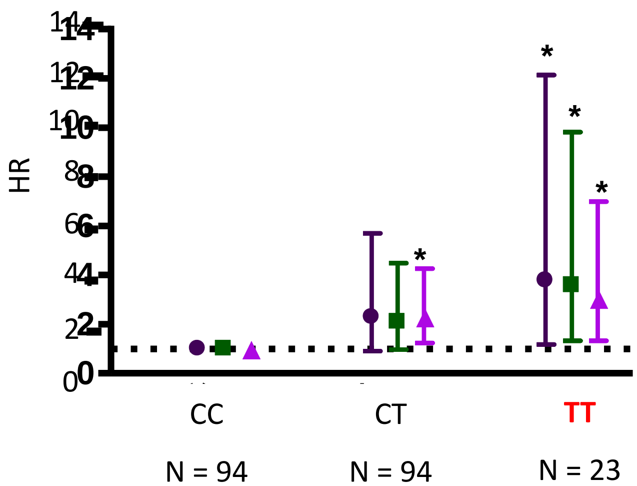


Ultrafiltration volume (ml)

rs2075574	CC N = 94	CT N =94	TT N = 23	P-value
Transport parameters				
UF Mean (Std)	588 (338)	673 (309)	483 (266)	0.02
Sieving Na Mean (Std) (n=155)	0.05 (0.03)	0.05 (0.02)	0.04 (0.03)	0.046
D/P creat 4 hours Mean (Std)	0.72 (0.12)	0.73 (0.11)	0.76 (0.12)	NS

AQP1 Genotype: Influence on Survival

Cohort UCL – KUL (N=211)

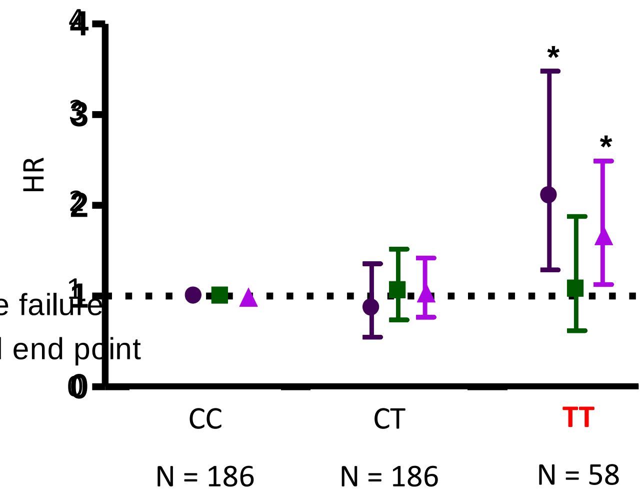


Death

Technique failure

Combined end point

Cohort NECOSAD – AMC (N=430)



Death

Technique

Combined

	Death (33 events)*		Technique failure (41 events) **		Combined end point (65 events) ***	
rs2075574	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
CC (n = 94)	1		1		1	
CT (n = 94)	2.28 (0.91-5.70)	0.08	2.09 (0.97 – 4.49)	0.06	2.30 (1.24-4.26)	0.01
TT (n = 23)	3.78 (1.18 – 12.14)	0.03	3.59 (1.32-9.82)	0.01	3.04 (1.33-6.98)	0.01

* Adjusted for age, gender, CVE and diabetes
** Adjusted for age, gender, CVE, diabetes, UF, DPcreat and DDo gluc 4h
***Adjusted for age, gender, CVE, diabetes, UF, DPcreat and DDo gluc 4h

General Conclusions

- *Water requires specific carriers, which have been acquired through evolution*
  - → *>1000 genes coding for carriers in mammalian genomes*
  - → *Teological reason: control & regulation*

- *Essential role of AQP1 – archetype of water channel*
  - → *kidney, lung, endothelium : peritoneal dialysis*

- *Importance of adequate animal models*
  - → *Mechanistic studies & drug development - testing*

- *Advances in structure – regulation mechanisms*
  - → *therapeutic implications & individual predictions*

Acknowledgements

UCL Brussels - Nephrology

J. Ni, J. Morelle
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T. Nishino

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Extramural Grant Program

But man has in him the silence of the sea

R. Tagore

Thank you for your attention

End

Acknowledgements

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Modulating AQP1 (increasing water transport): Always beneficial ?

- AQP1 in endothelial cells: migration and angiogenesis

  → *Angiogenesis – peritonitis – long-term exposure*

- AQP1 in peritoneal macrophages: motility and phagocytosis

  → *Host defense – peritonitis*

- Interaction endothelial cells – circulating leukocytes

AqF026, *a Novel Agonist of the Water Channel Aquaporin-1*

- AqF026 increases water transport across AQP1 *in vitro*
- *In silico* modelling and site-directed mutagenesis support interaction between AqF026 and residues in the loop D domain of AQP1
- Application of AqF026 to the mouse model of PD demonstrates the efficacy of the AQP1 agonist to increase water transport *in vivo*
- AqF026 has potential therapeutic value for clinical situations based on osmotic water transport:

  → *Peritoneal dialysis, edema, angiogenesis, alterations of AQP1*

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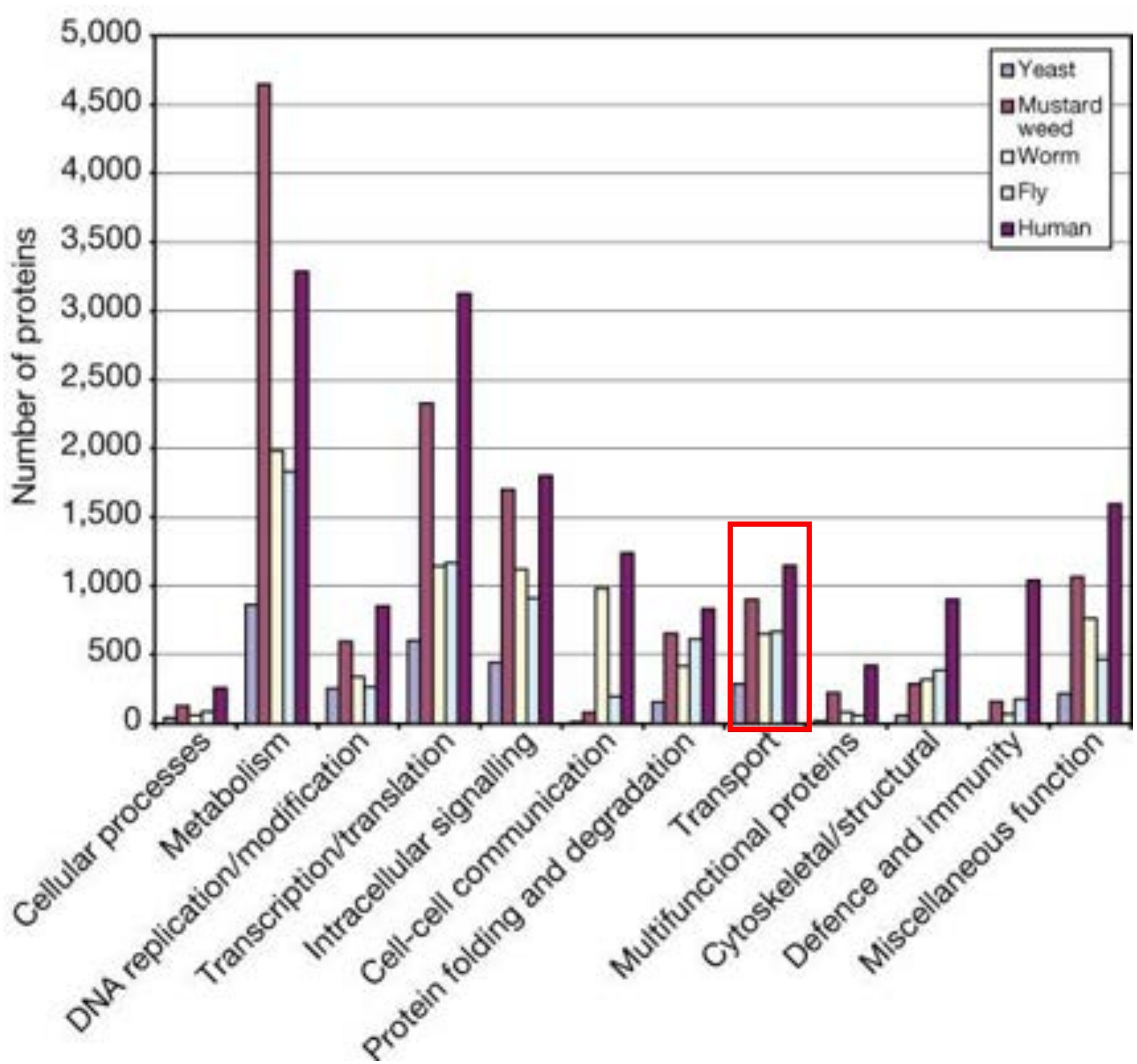
S. Shpun, J. Hoffmann, U. Katz

JOHNS HOPKINS
MEDICINE


Universität Zürich[UZH]




The human genome contains > 1,000 genes for transport proteins



Nature **409**:860-921, 2001

Quantitative visualization of passive transport across bilayer lipid membranes

John M. A. Grime*[†], Martin A. Edwards*[†], Nicola C. Rudd[†], and Patrick R. Unwin[†‡]

Significantly, the permeation coefficient decreased with acyl tail length contrary to previous work and to Overton's rule. The reasons for this difference are considered, and we suggest that the applicability of Overton's rule requires re-evaluation.

PNAS | September 23, 2008 | vol. 105 | no. 38 | 14277–14282

PNAS

LETTER

Passive transport across bilayer lipid membranes: Overton continues to rule

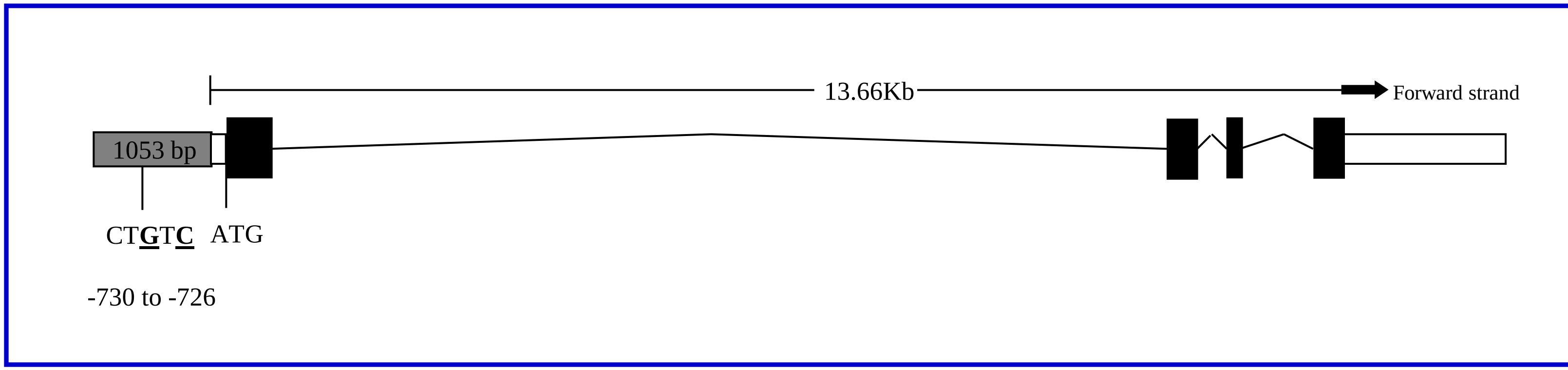
According to Overton's rule, membrane permeability (P_M) of a molecule increases with its hydrophobicity. Experiments with a series of carboxylic acids now suggest the opposite: the most hydrophilic acid exhibited the highest P_M (1).

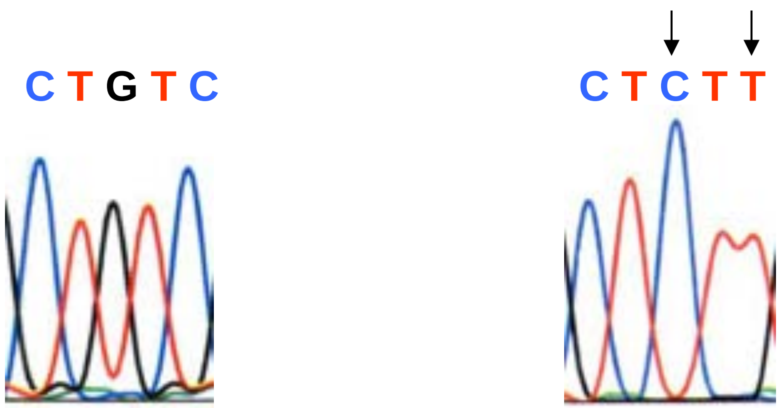
The experiments, however, do not justify this conclusion

Andreas Missner[a], Philipp Kügler[b,c], Yuri N. Antonenko[d], and Peter Pohl[a,1]

PNAS | December 30, 2008 | vol. 105 | no. 52 | E123

CTGTC *Motif* in the Promoter of *AQP1*





Wild-type ***Mutant***

Maréchal C et al. 2010, unpublished

Nephrol Dial Transplant. 2011 Dec;26(12):4142-5.

High-dose steroid treatment increases free water transport in peritoneal dialysis patients.

de Arteaga J, Ledesma F, Garay G, Chiurchiu C, de la Fuente J, Douthat W, Massari P, Terryn S, Devuyst O.

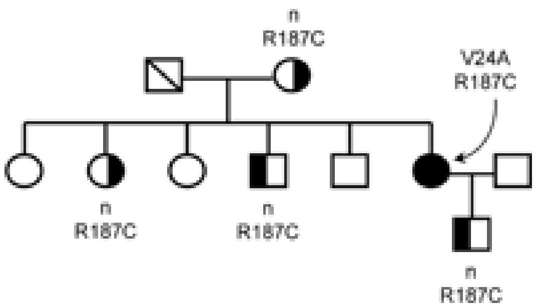
Abstract

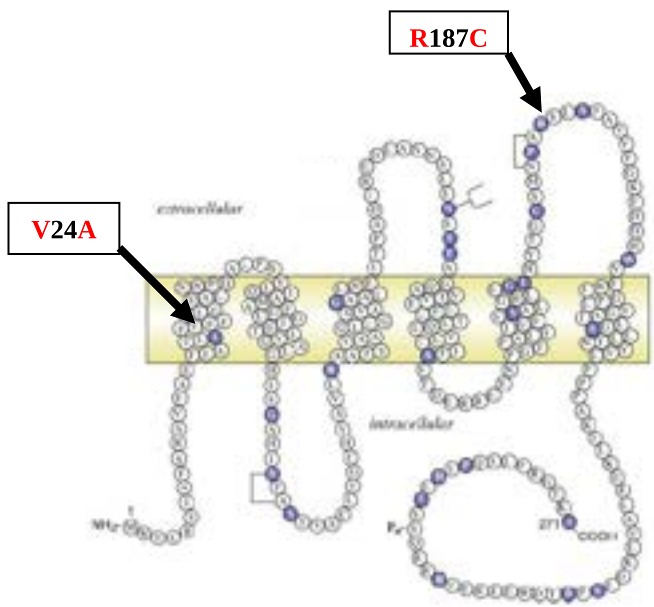
The water channel aquaporin-1 (AQP1) is the molecular counterpart of the ultrasmall pore that mediates free water transport during peritoneal dialysis (PD). Proof-of-principle studies performed in rats have shown that treatment with corticosteroids upregulates the expression of AQP1 in the peritoneal capillaries, causing a significant increase in free water transport. Whether such a beneficial effect could be observed in end-stage renal disease patients treated by PD remains unknown. Peritoneal transport parameters were evaluated in three patients on PD, shortly before and after living-donor renal transplantation and treatment with high-dose methylprednisolone (1.0-1.2 g/m(2)). As compared with pre-transplantation values, the post-transplantation test revealed an ~2-fold increase in the sodium sieving and ultrasmall pore ultrafiltration volume, suggesting an effect on AQP1 water channels. In contrast, there was no change in the parameters of small solute transport. The direct involvement of AQP1 in these changes is suggested by the expression of glucocorticoid receptors in the human peritoneum and the presence of conserved glucocorticoid response elements in the promoter of the human AQP1 gene.

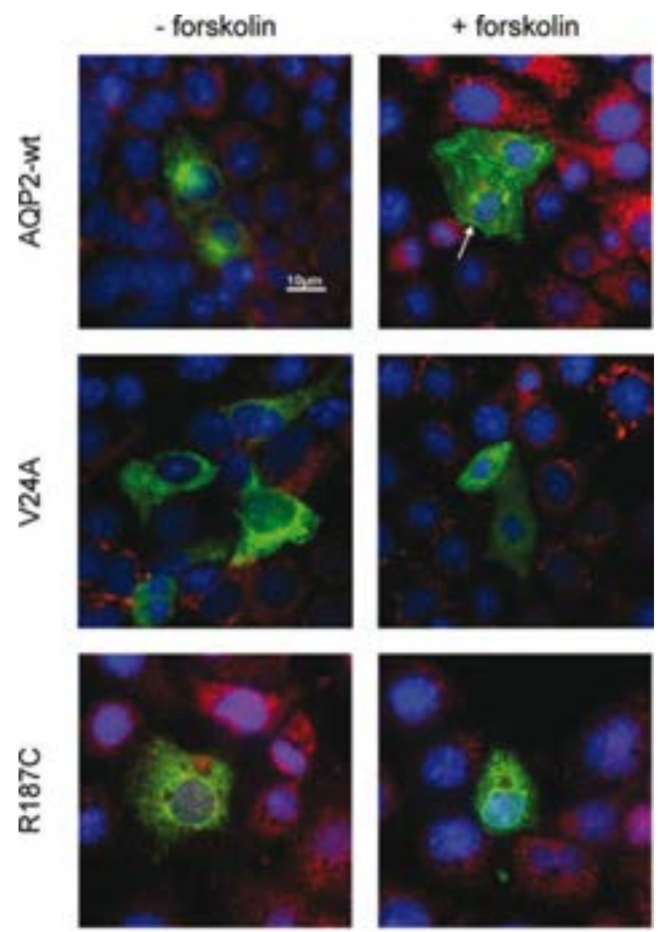
Sylvie, 39 year-old

- Urinates 15 L/day
- Needs to drink : 15-20 L/day
- Difficult scolarity, multiple hospitalizations (dehydration)

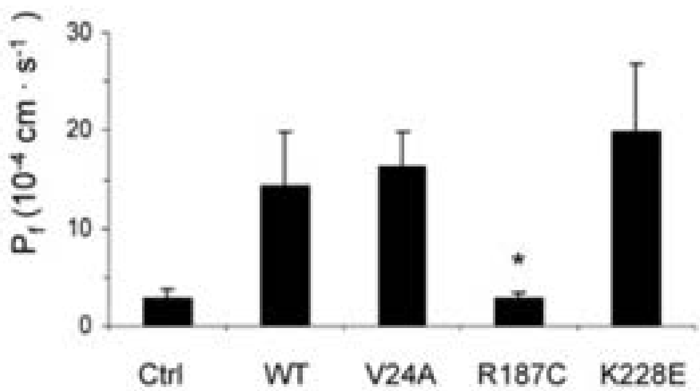
→ Asks for handicap recognition

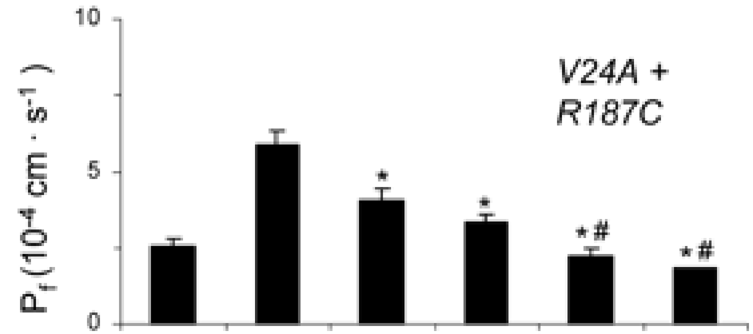






Compound heterozygous: combination of two mutations



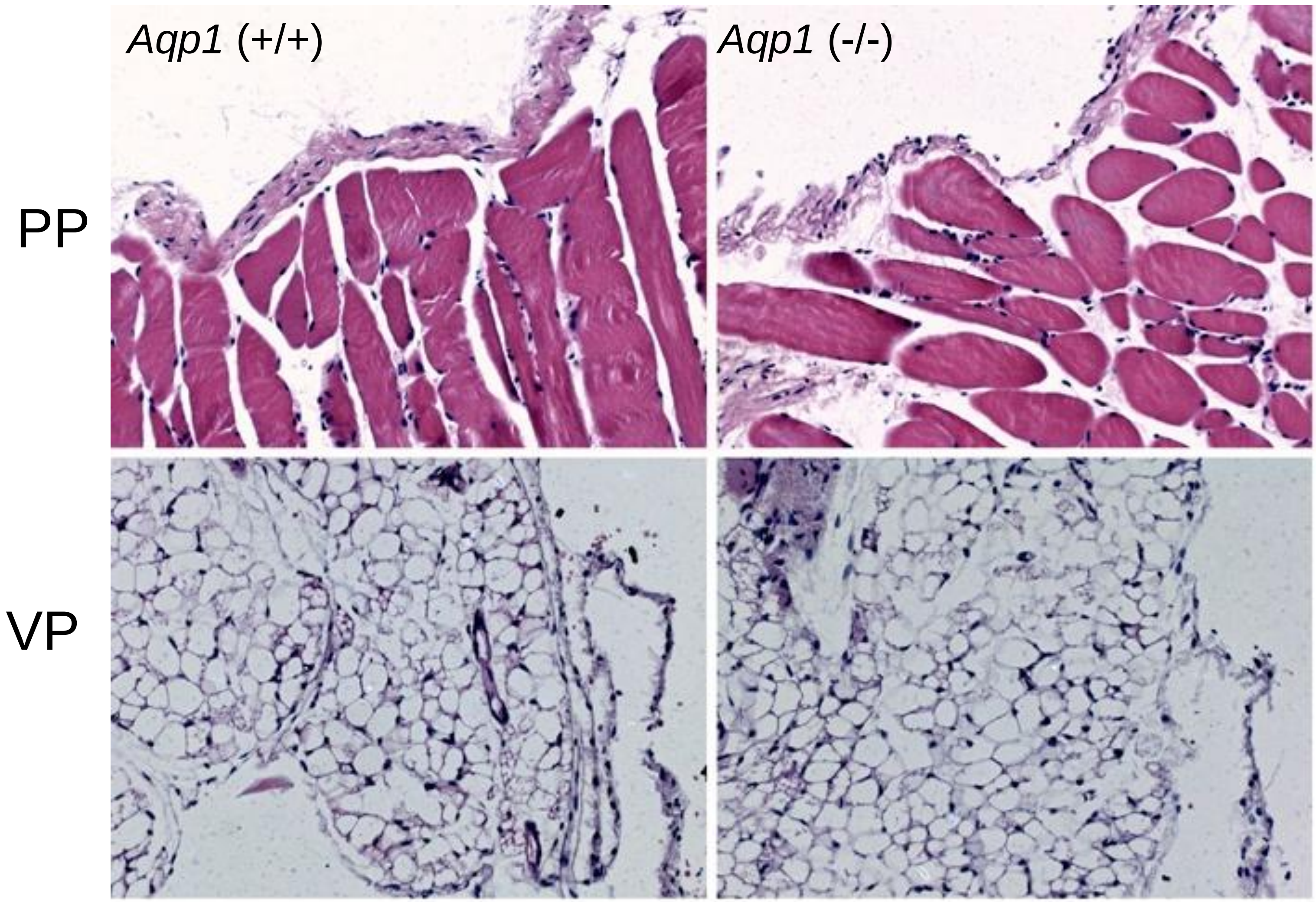


mutant	0	5	5	5	5	5
R187C	0	0	2.5	5	7.5	10

→ Combined effect : decreased water transport *in vitro*

Leduc-Nadeau A et al. J Physiol 588: 2205-18, 2010

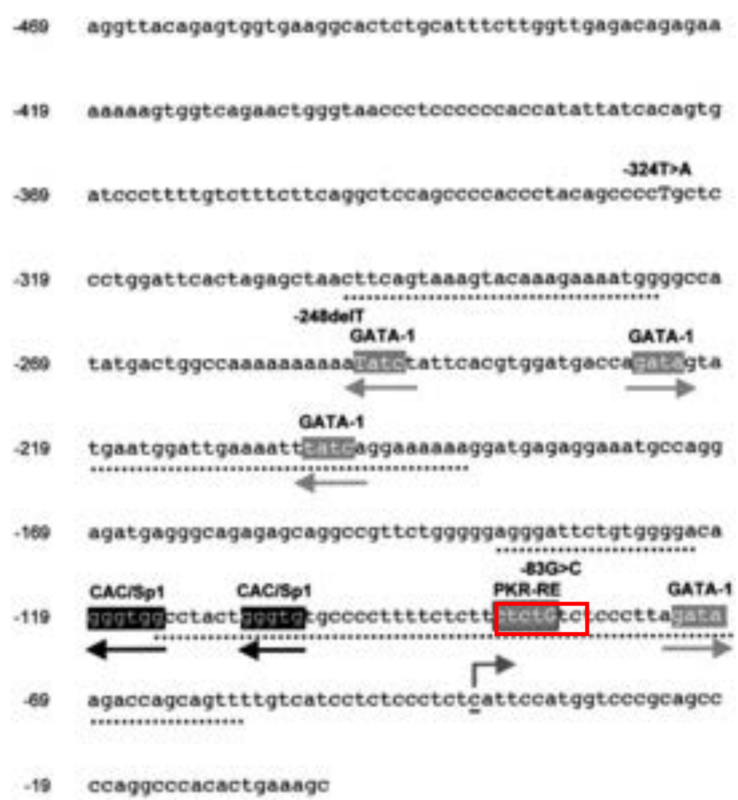
Peritoneal Structure in *Aqp1* Mice: Morphology

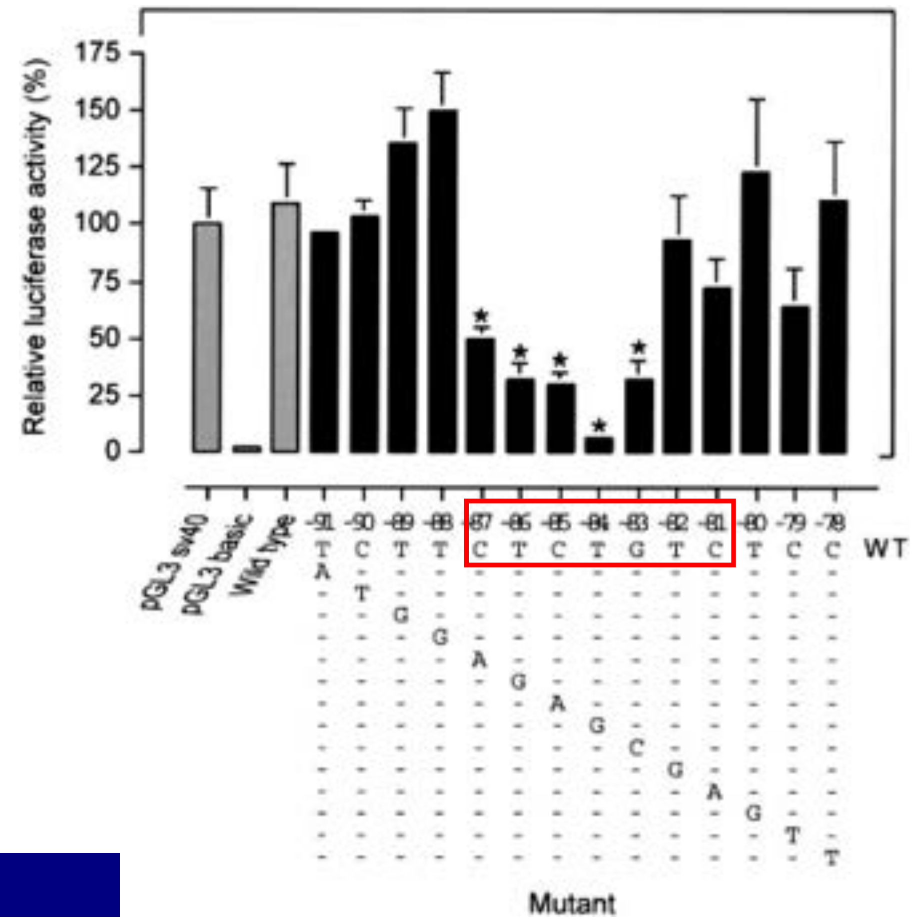


Disruption of a novel regulatory element in the erythroid-specific promoter of the human *PKLR* gene causes severe pyruvate kinase deficiency

Richard van Wijk, Wouter W. van Solinge, Claus Nerlov, Ernest Beutler, Terri Gelbart, Gert Rijksen, and Finn C. Nielsen

Blood 2003; 101: 1596-1602



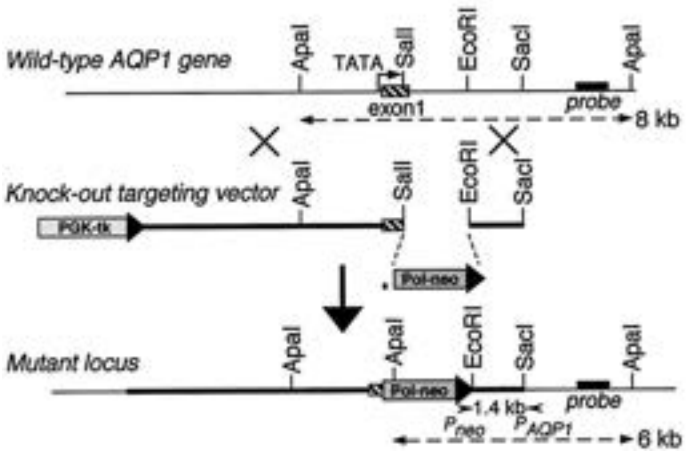


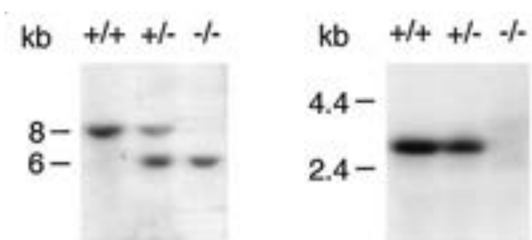
CTCTG, core binding motif of a regulatory element for PKLR

J Biol Chem. 1998 Feb 20;273(8):4296-9.

Severely impaired urinary concentrating ability in transgenic mice lacking aquaporin-1 water channels.

Ma T, Yang B, Gillespie A, Carlson EJ, Epstein CJ, Verkman AS.

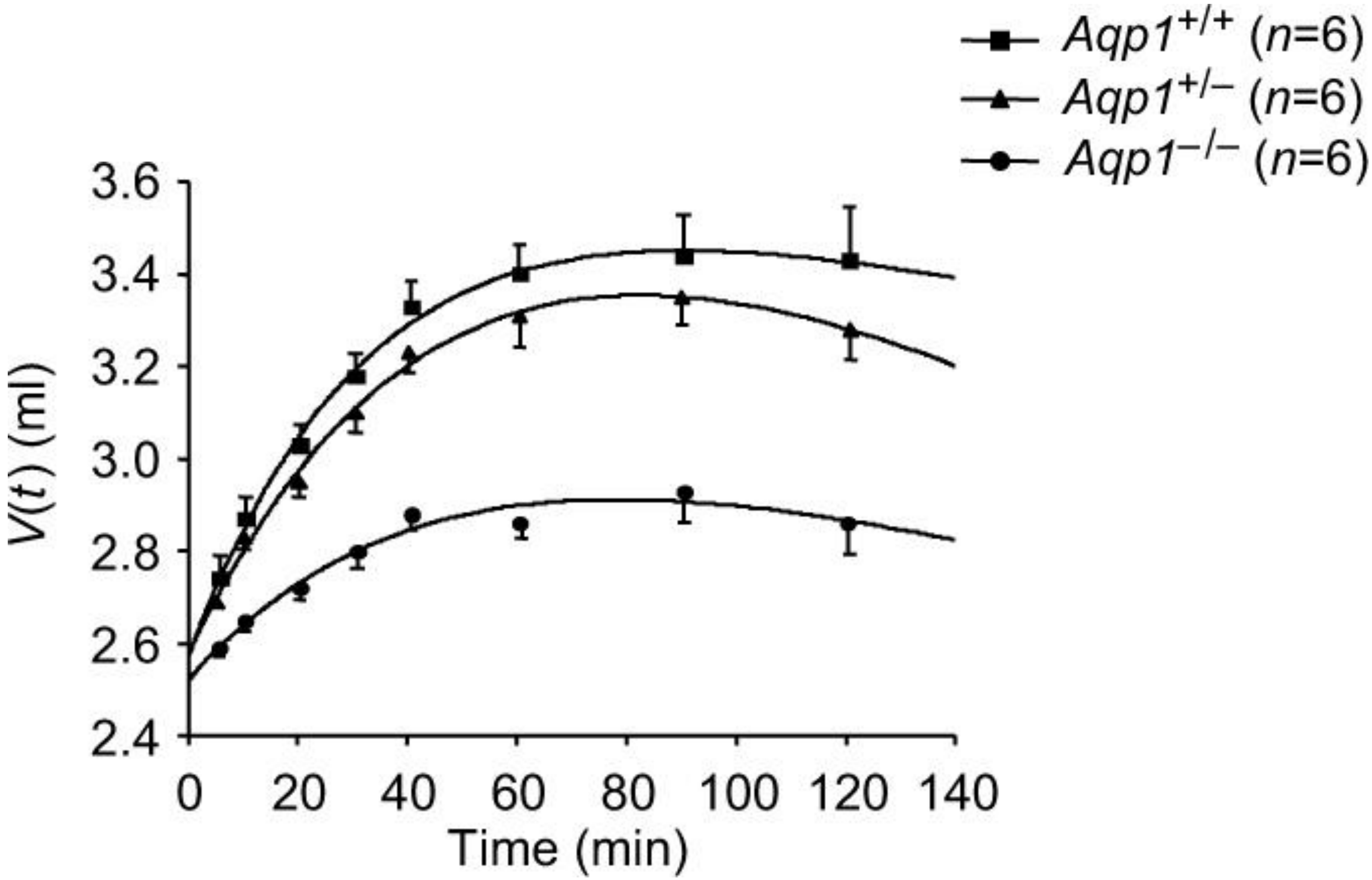




- Diabetes insipidus - nephrogenic
- ↓ water permeability across lung capillaries
- ↓corneal water permeability
- ↓cerebrospinal fluid production

→ Transport across the peritoneal membrane ?

Intraperitoneal volume during PD



Ni et al. Kidney Int 69, 2006

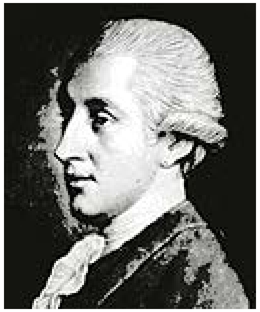
Steroid Induction of AQP1: PET after Living Donor Transplantation

Parameter	Before → After
Sodium sieving (D/P sodium, T30-T0)	**-8 → -16**
Ultrafiltration USP (mL)	**108 → 190**
D/P creatinine	**0.53 → 0.53**

- N=3, living related kidney transplantation (F11y, M52y, M5y)
- Methylprednisolone, 1mg/m2
- MiniPET, before and 22 days after transplant

Nephrol Dial Transplant. 2011; 26:4142-5

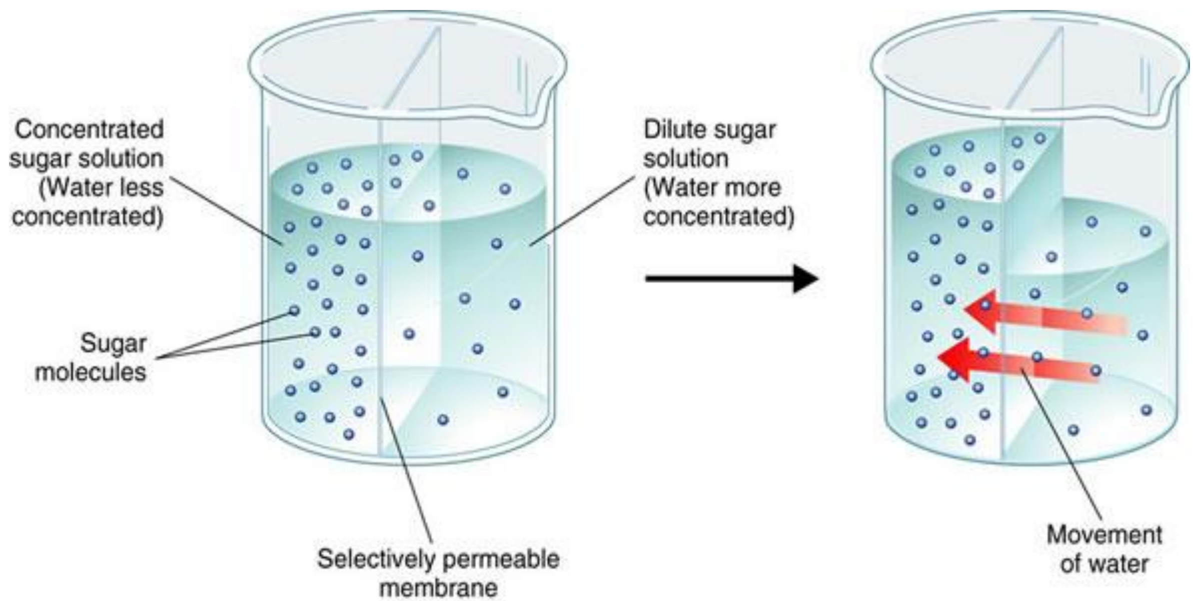
Early Formulations of Water Transport

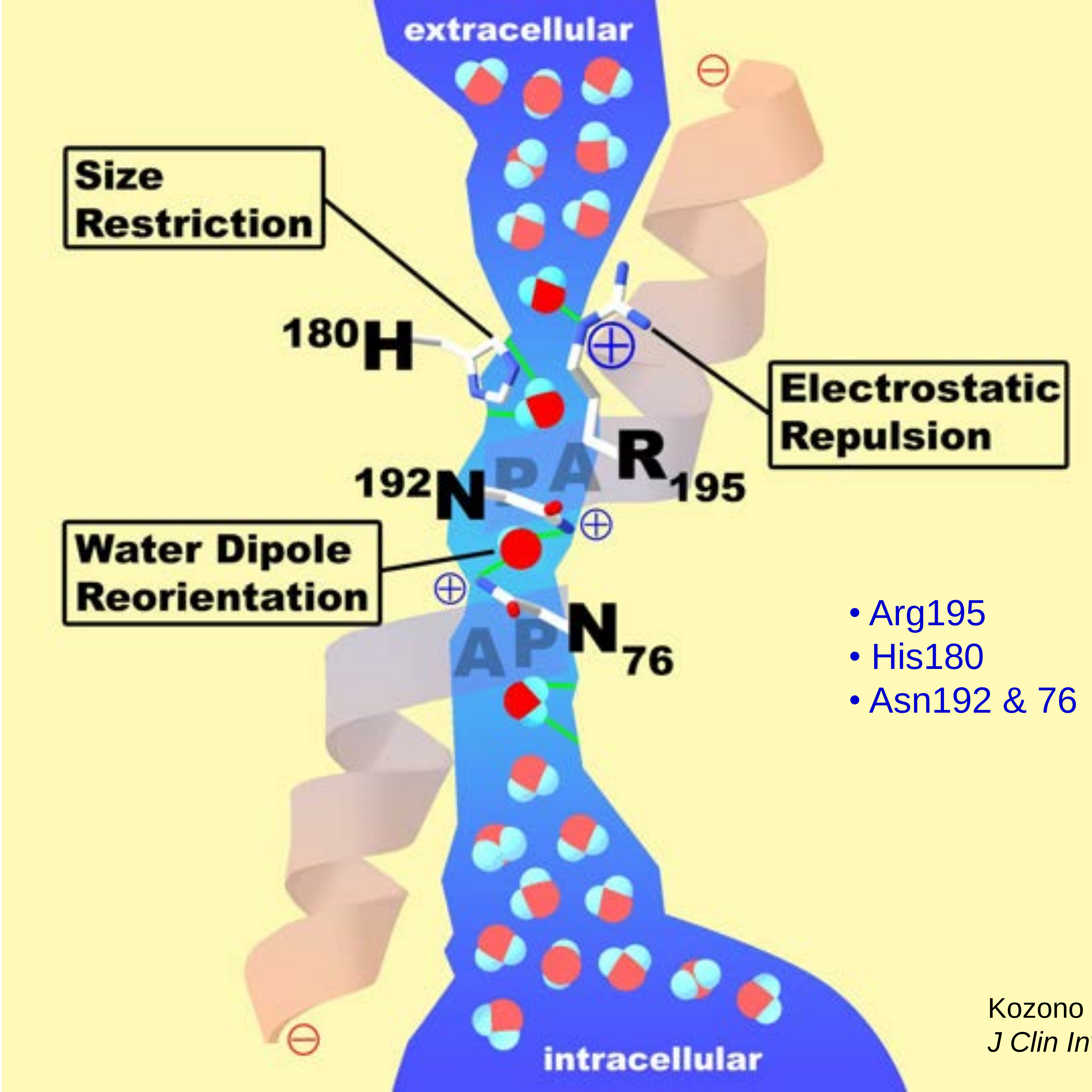


• **William Hewson (1773)** : lysis of red blood cells
→ Fluid-containing vesicles that shrink or swell depending on the nature of the bathing fluid

• **Karl von Nägeli (PD, University of Zurich 1855)**
→ osmosis in plant cells

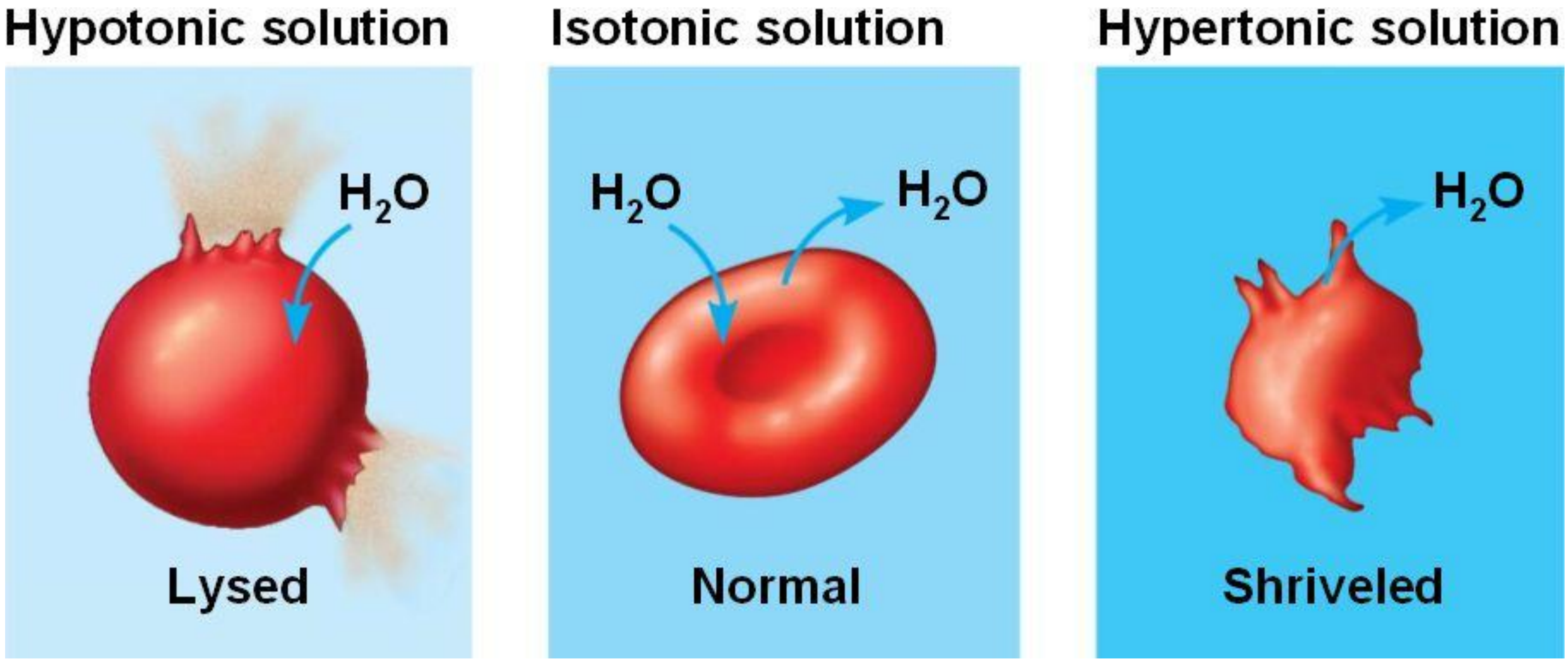
• **Jakobus van‘t Hoff (1887)** : cells thought as osmometers
→ change in volume governed by bathing fluid composition
(Nobel Prize Chemistry 1901)


Concentrated sugar solution (Water less concentrated)
Sugar molecules
Dilute sugar solution (Water more concentrated)
Selectively permeable membrane
Movement of water



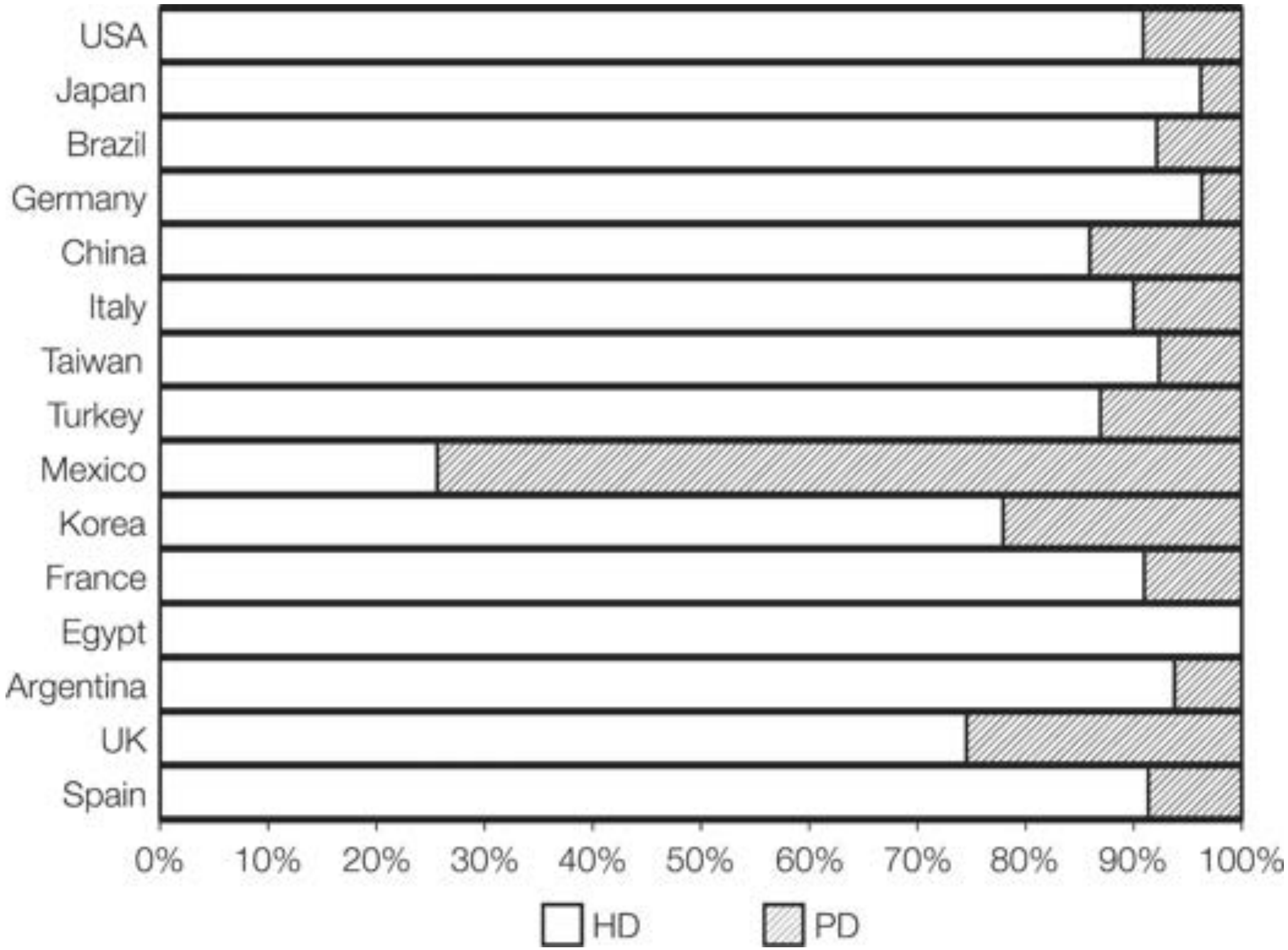
- Arg195
- His180
- Asn192 & 76

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



Hypotonic solution
Isotonic solution
Hypertonic solution
H_2O
H_2O
H_2O
H_2O
Lysed
Normal
Shriveled

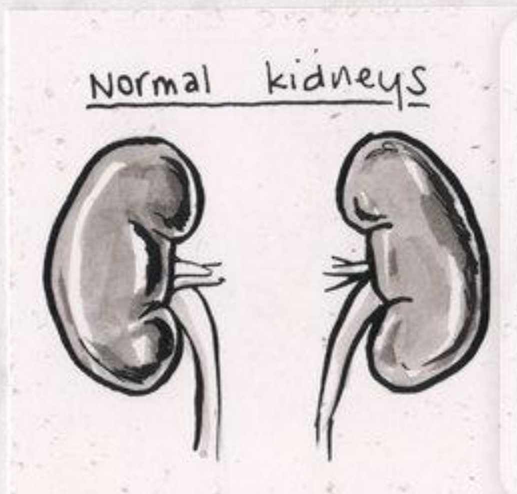
Comparison of HD and PD patient numbers in the 15 countries with the highest dialysis patient populations.



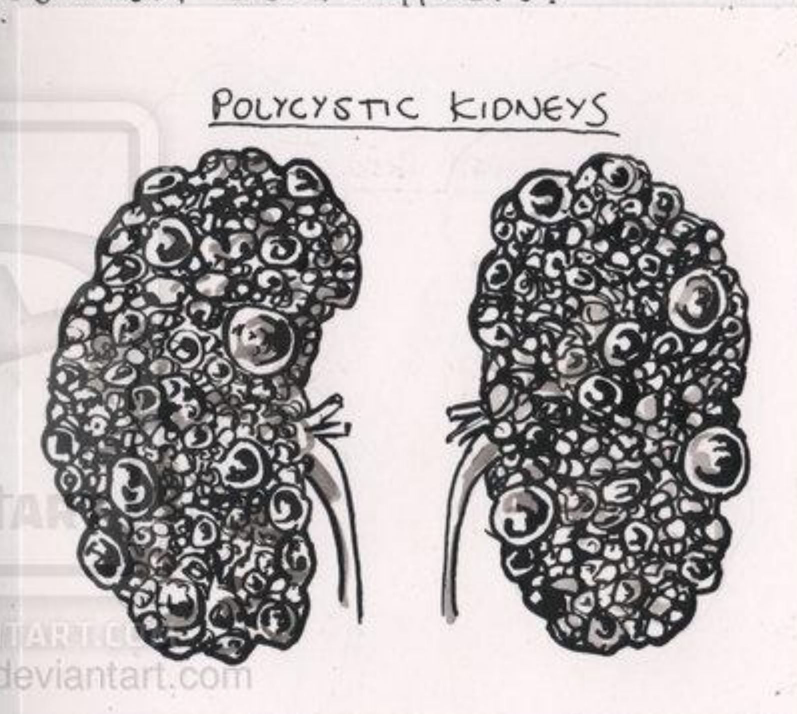
Grassmann A et al. Nephrol. Dial. Transplant. 2005;20:2587-2593

NDT Nephrology Dialysis Transplantation

In 1995 I was diagnosed with POLYCYSTIC KIDNEY DISEASE. It was not a great surprise. It's a genetic condition, often hereditary. My mum's father



had it, she and both her sisters had/have it, my brother and I have it, three of my cousins have it. It usually begins to affect you as you get older. Over the years cysts grow on the kidneys, causing them to grow in size and their function to gradually cease. High-blood pressure, infected cysts and urine infections are common side-affects.



Eventually I will need dialysis or a transplant. I'll cross that bridge when I come to it.


The
BEGINNING
IS
NEAR.
LEIGHTON

Distribution of Human Aquaporins

Aquaporin	Permeability	Tissue distribution
AQP0	Water (low)	Lens
AQP1	Water (high)	Red blood cell, kidney, lung, vascular endothelium, brain, eye
AQP2	Water (high)	Kidney, vas deferens
AQP3	Water (high), glycerol (high), urea (moderate)	Kidney, skin, lung, eye, colon
AQP4	Water (high)	Brain, muscle, kidney, lung, stomach, small intestine
AQP5	Water (high)	Salivary gland, lacrimal gland, sweat gland, lung, cornea
AQP6	Water (low), anions ($NO_3^- > Cl^-$)	Kidney
AQP7	Water (high), glycerol (high), urea (high), arsenite	Adipose tissue, kidney, testis
AQP8[‡]	Water (high)	Testis, kidney, liver, pancreas, small intestine, colon
AQP9	Water (low), glycerol (high), urea (high), arsenite	Liver, leukocytes, brain, testis
AQP10	Water (low), glycerol (high), urea (high)	Small intestine

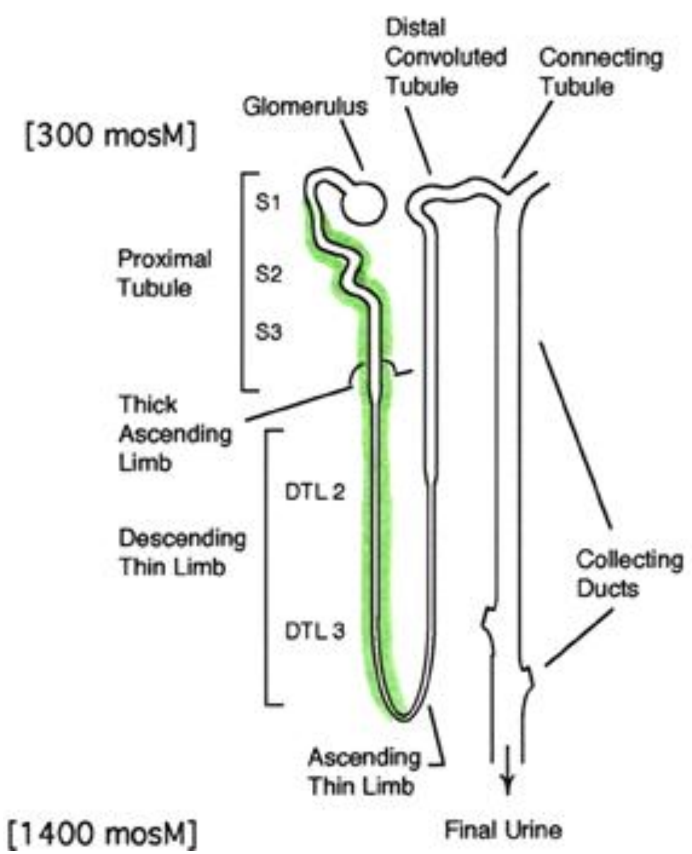
King et al. Nat Rev Mol Cell Biol 2004

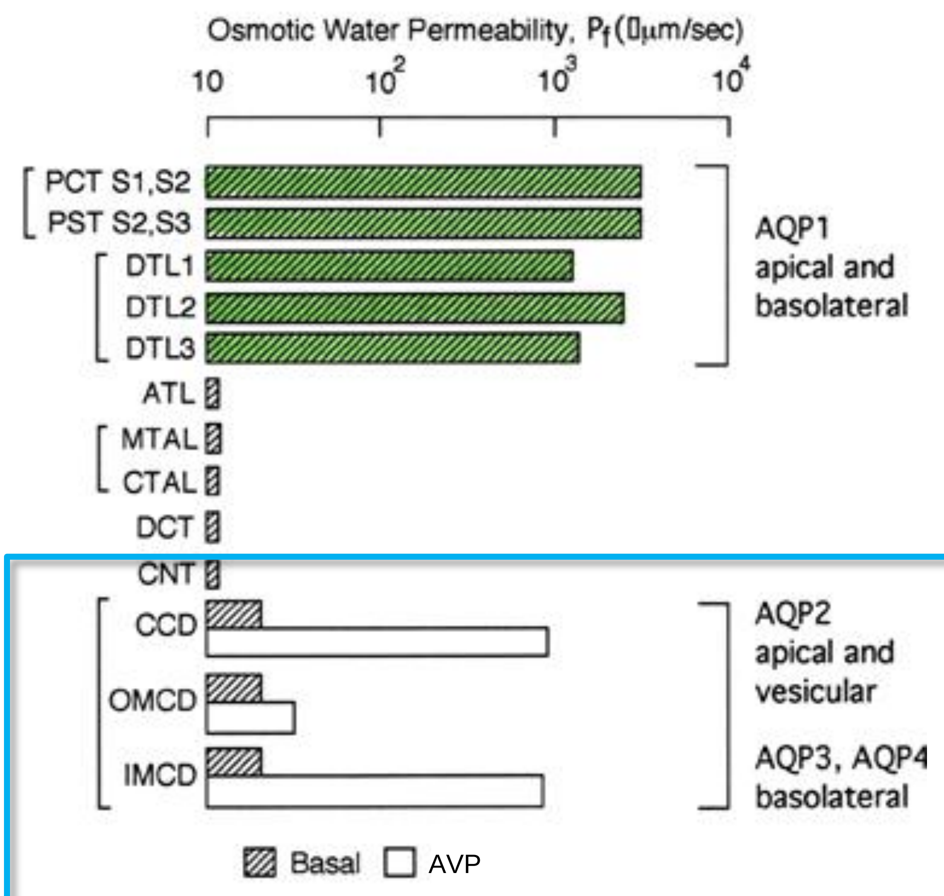
A quoi ça rime, l'Aquaporine ?

Théâtre

Sylvie Déthiollaz
Vivienne Baillie Gerritsen

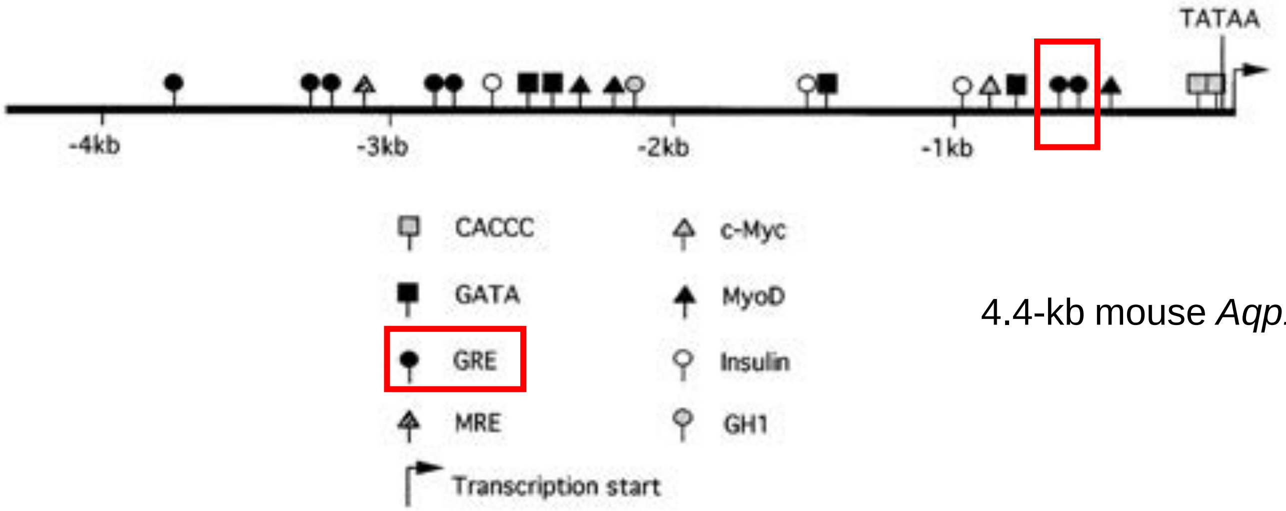
Localization of Aquaporins & Water Permeability in Kidney



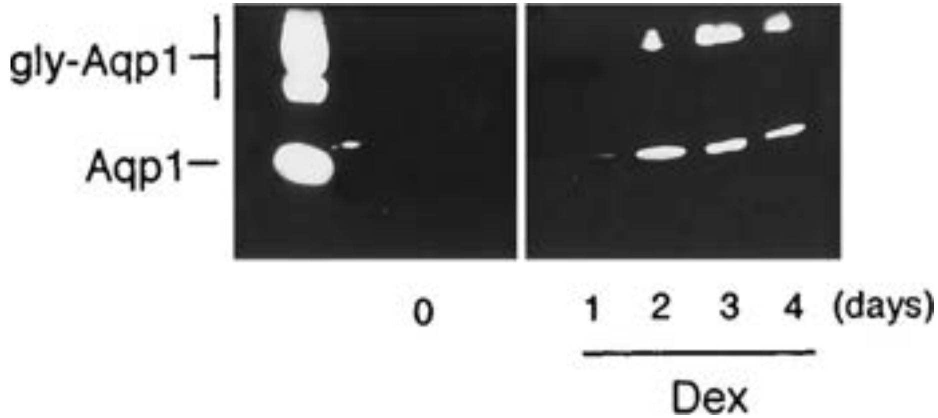


Nielsen *et al., J Cell Biol,*1993

AQP1 Expression : Glucocorticoid Induction



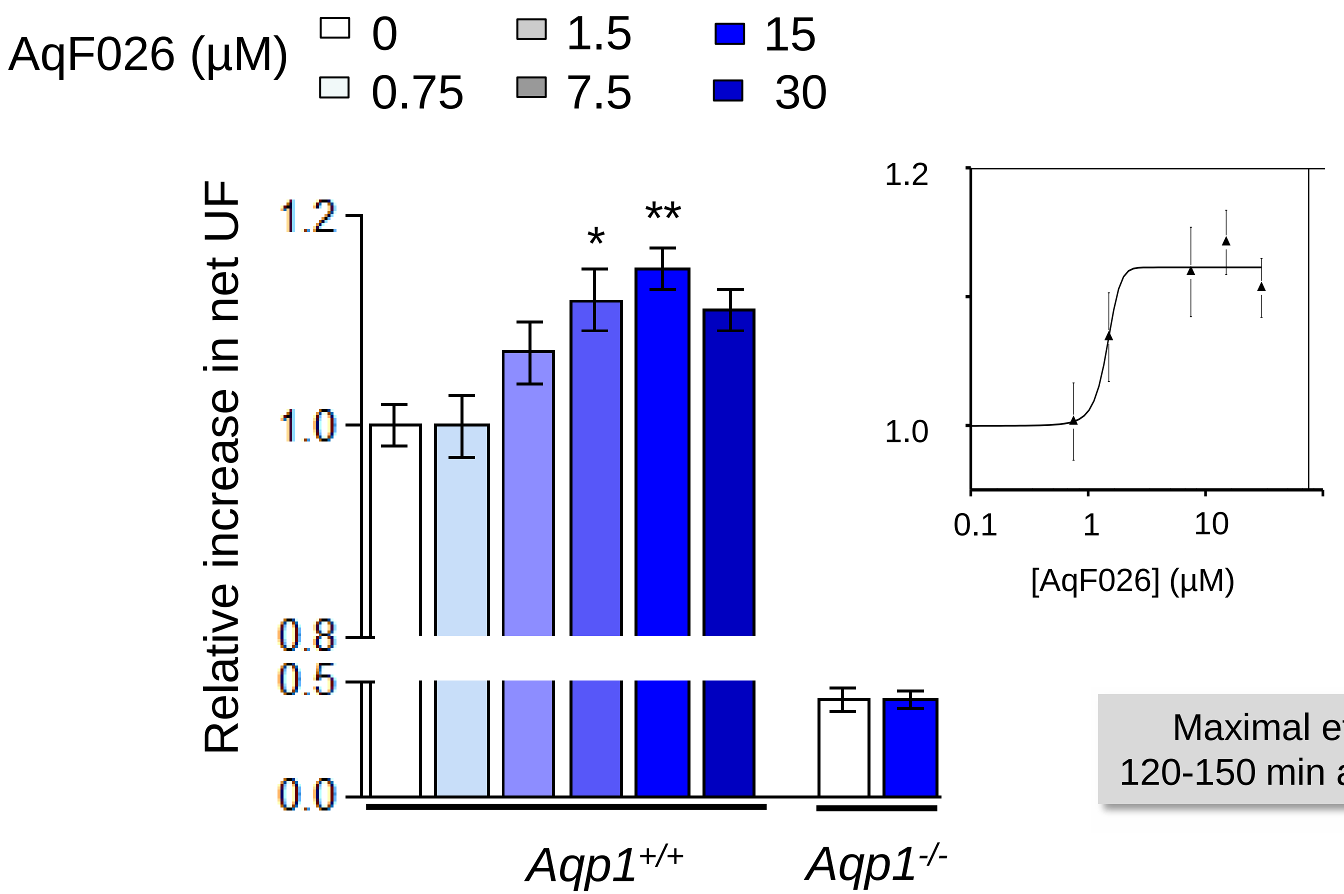
4.4-kb mouse *Aqp1*



MEL cells
1μM Dexa

Moon C. et al. AJP 273: C1562, 1997

In vivo Effect of AqF026: Dose-response



Maximal effect
120-150 min after i.v.

The effect of AqF026 is dose-dependent, with a maximal response observed for a concentration of 15 µM and an EC_{50} value of 4.2 µM