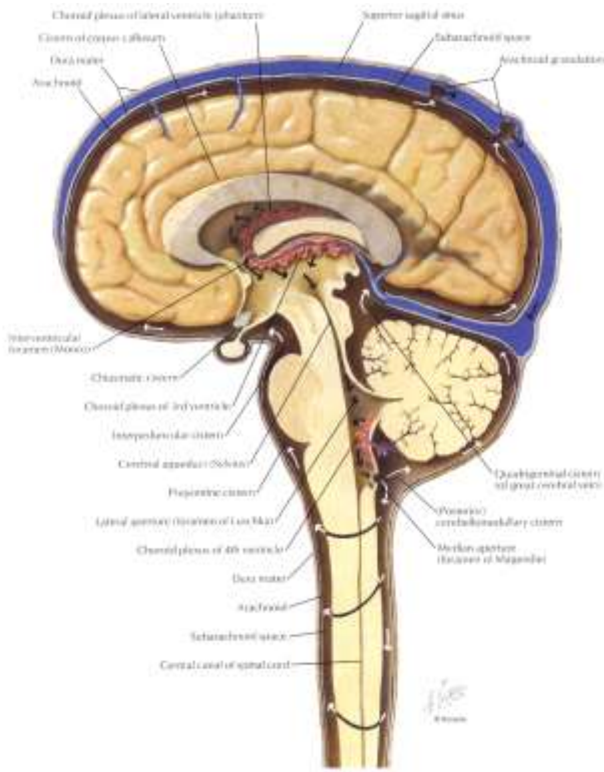
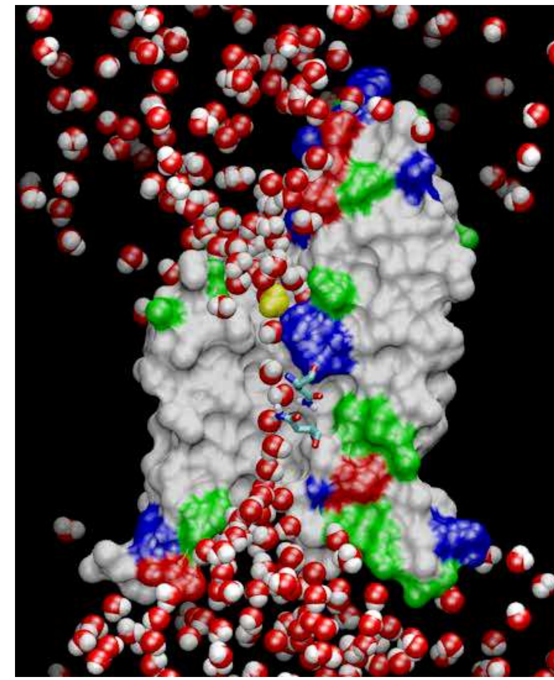
Water Biology and Mediicne: from aquaporins to aquaphotomics





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Dept. of Pharmacology
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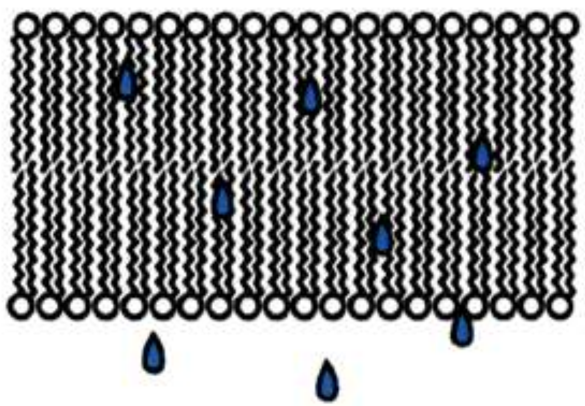
since 1917
Keio University School of Medicine
医学部開設100年記念

Water permeabilities of plasma membrane vesicles

Membrane	P_f (μm/s)	E_A (kcal/mol)	Mercurial sensitivity	Reference
Planar lipid bilayer	1–104	10.8–14.9	–	[25]
Toad bladder apical membranes (–ADH)	4	11.0	–	[24]
Hog gastric vesicles	2.8	15.1	–	[26]
Human placenta	19	13.9	–	[27]
Brain synaptosomes	45	18	–	[22]
Rat small intestine	60	13.3	–	[21]
Rabbit proximal tubule	166	n.d.	+	[28]
Rabbit erythrocytes	530	4.6	+	[29]
Rat proximal tubule	760	3.1	+	[30]
Toad bladder apical membrane (+ADH)	450	n.d.	+	[23]
Rat collecting duct endosomes	300	3.8	n.d.	[31]
Toad bladder endosomes	1000	3.9	+	[32]

Transmembrane water permeability

Bilayer Diffusion



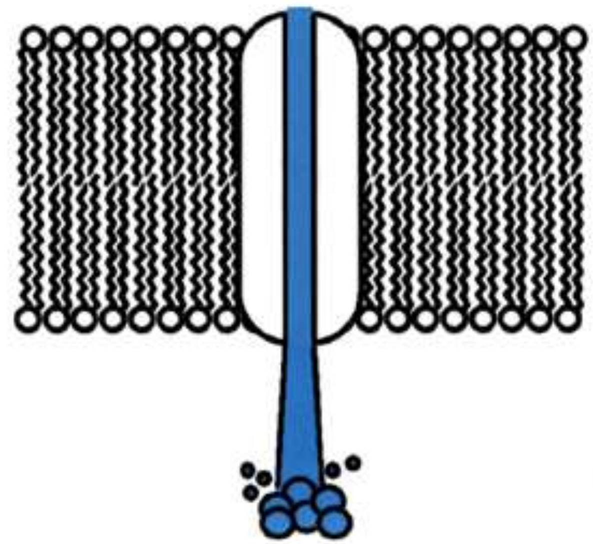
All biological membranes

Low capacity

No known inhibitors

E_a 10 kcal/mol

Water Channels



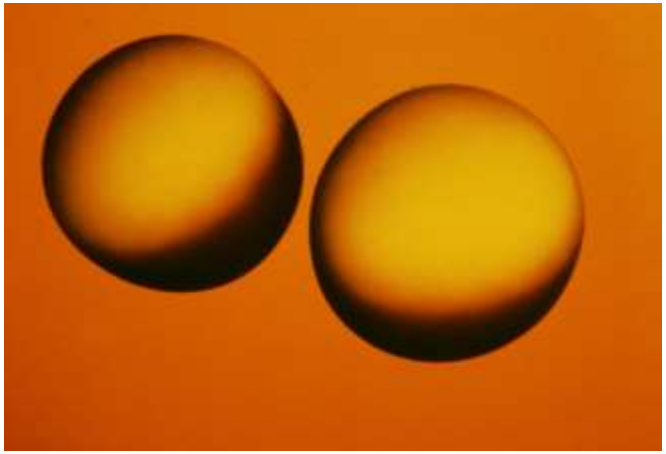
Renal tubules, secretory glands, red cells

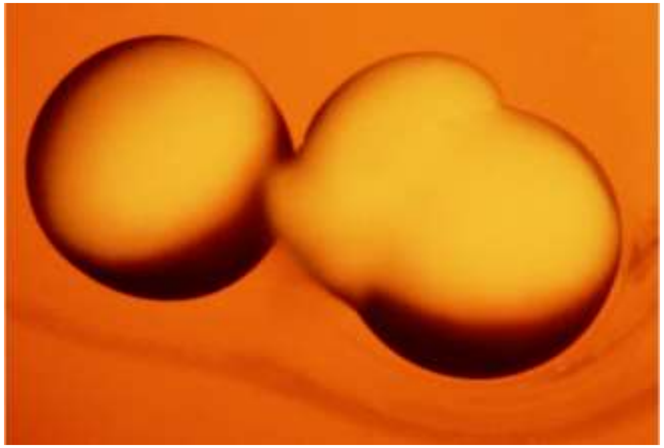
High capacity for H_2O, not H_3O^+

Reversibly inhibited by Hg^{++}

E_a 5 kcal/mol

Discovery of Aquaporin-1
Functional expression

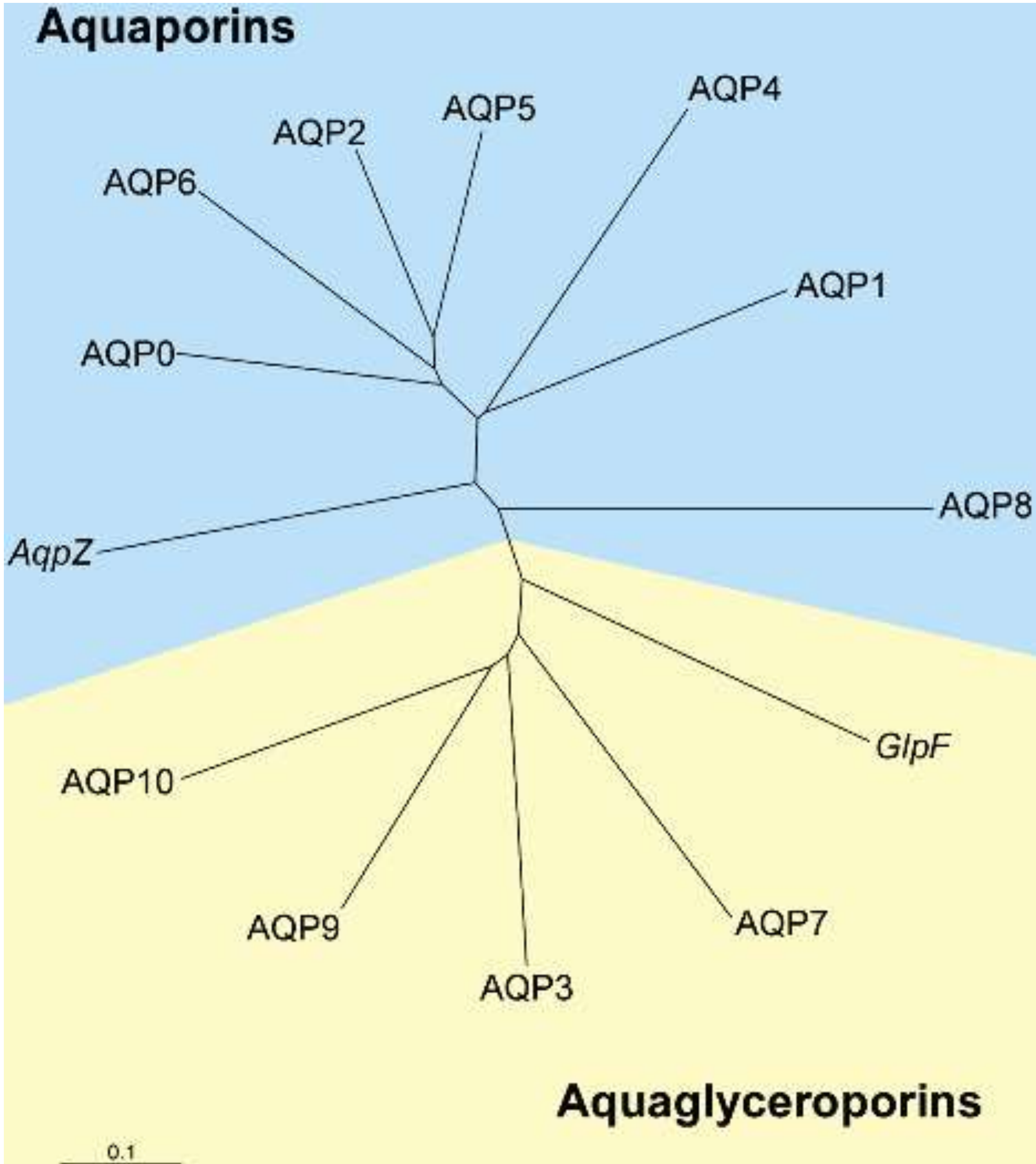




Hypo-osmolar swelling
Hg^{++} inhibited, no currents

Preston *et al., Science* 1992

Human Aquaporin Repertoire



Body Distribution of 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

Source: Masato Yasui, MD, PhD/Johns Hopkins Medicine

(Yasui, *JAMA*, 2004)

Clinical relevance of aquaporins

schizophrenia

Brain edema

Cataract

Mood disorders

Malaria infection

Dry eye

glaucoma

Obesity

DM

Dry mouth

Dry skin

Lung edema

DI

Polycystic kidney

Skin regeneration

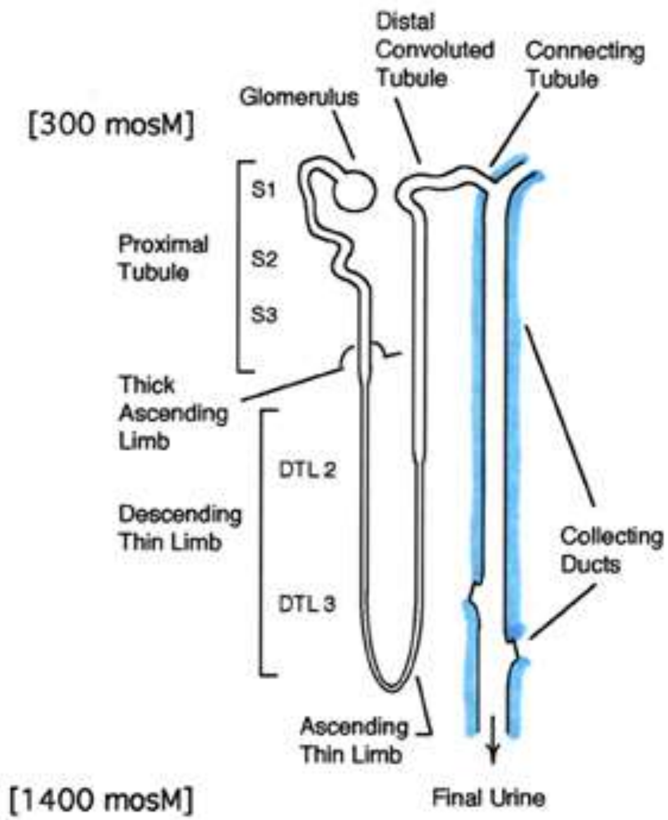
Toxemia of pregnancy

Cell Biology:

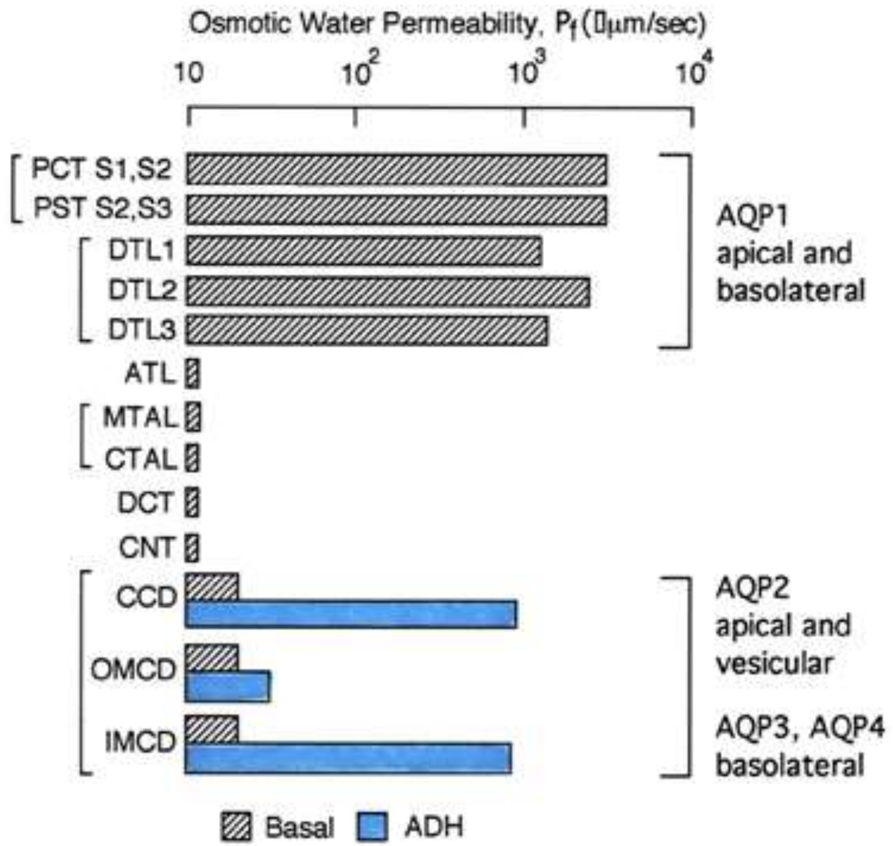
- Secretion/absorption
- Epithelial regeneration
- Tumor Growth
- Vascular regeneration
- Cell cycle

AQP2—A regulated water channel

cDNA cloned by homology
(Fushimi *et al., Nature,* 1993)

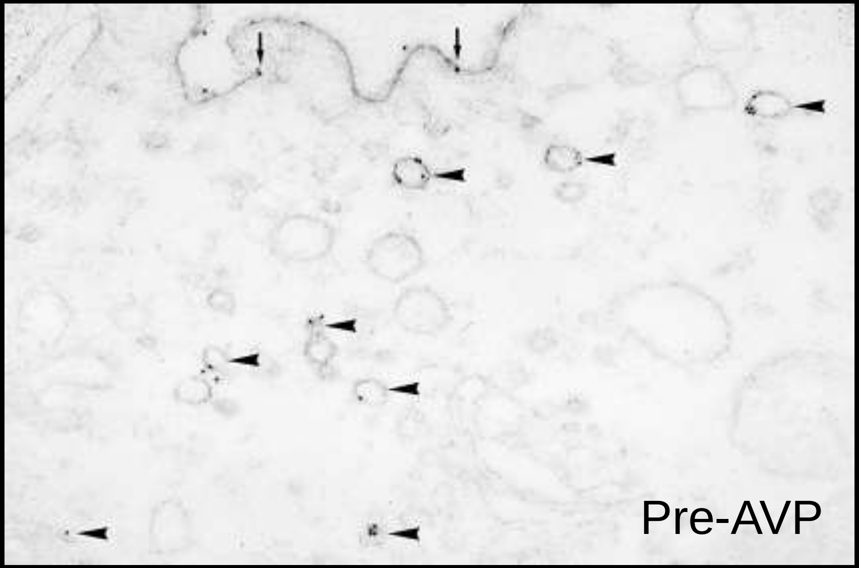


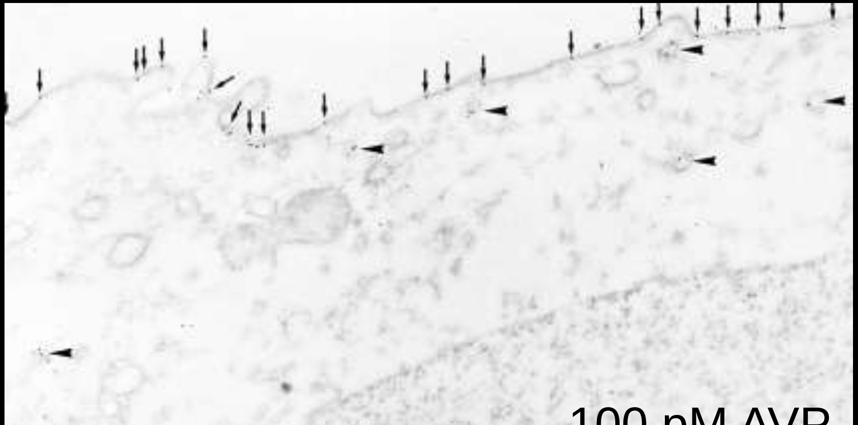
AQP2 localization in kidney
(Nielsen *et al., Proc Natl Acad Sci,* 1993)



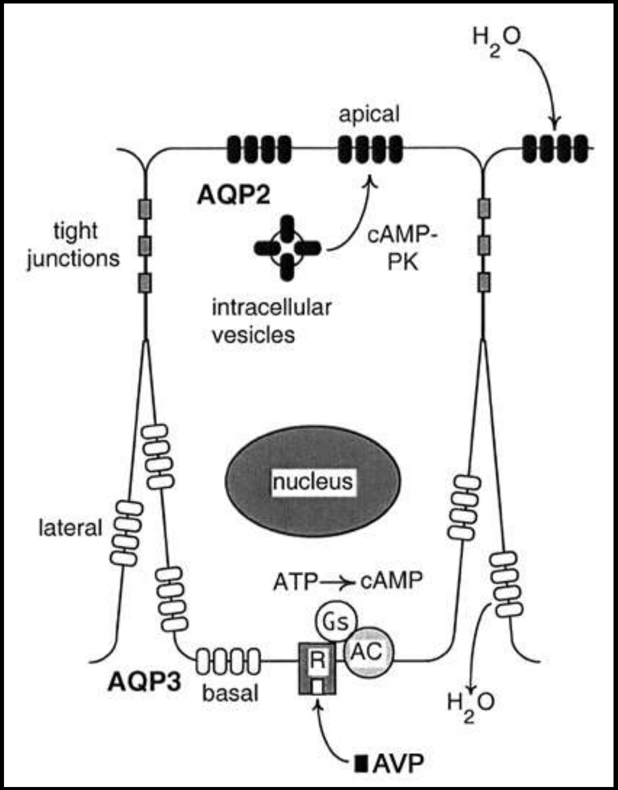
AQP2—Acute regulation by AVP

Isolated renal collecting ducts





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



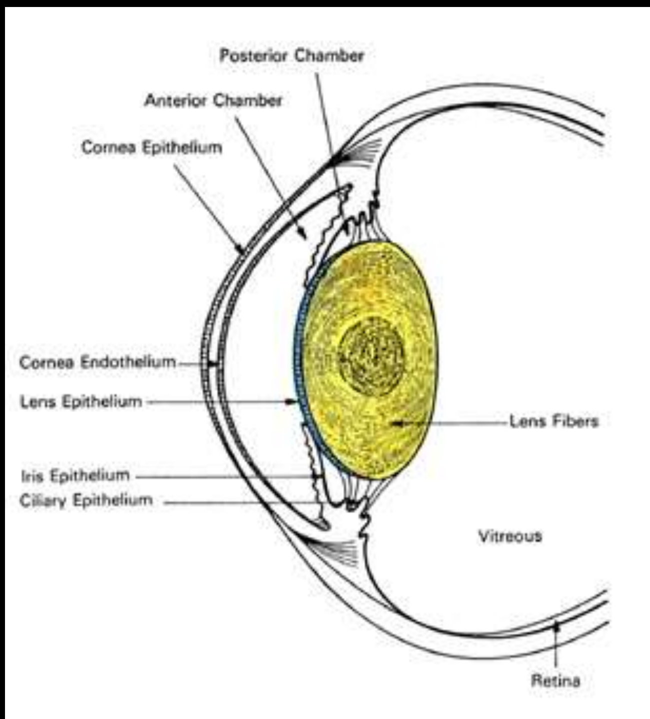
Inherited defects (rare)
- Nephrogenic DI (severe)

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

AQP0 and Cataracts

Major intrinsic protein (MIP)

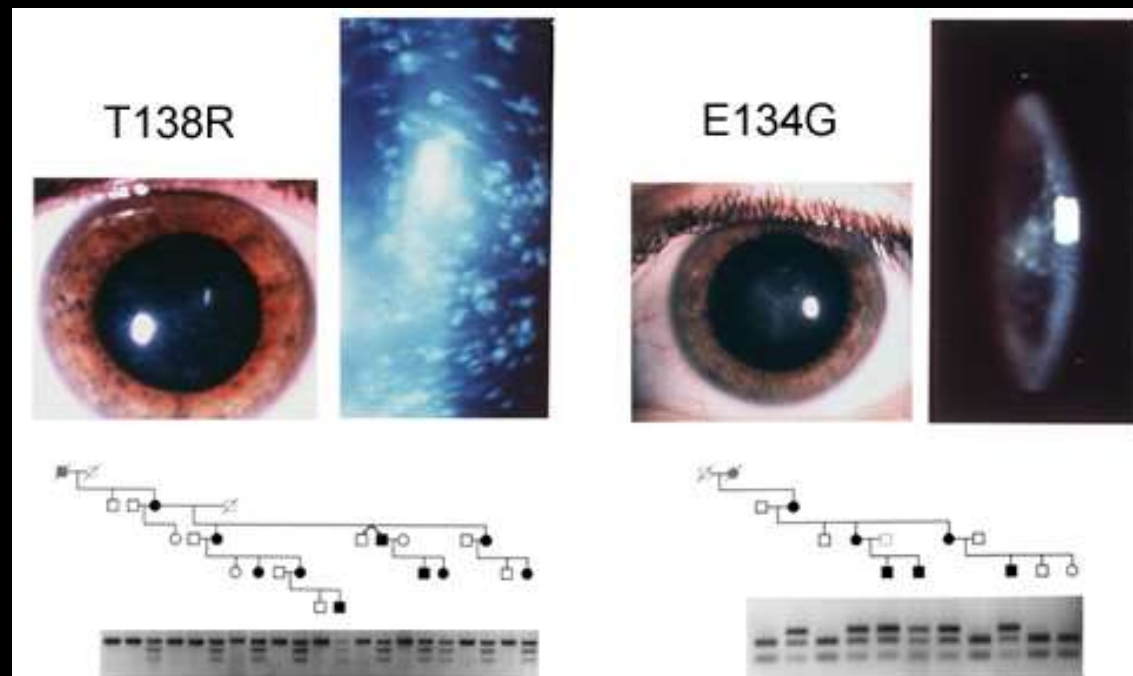
- Lens fiber cells



Importance in neonatal lens development?

Human AQP0 mutations

- Congenital cataracts
- Dominant inheritance
  - T138R—Multifocal opacities
  - E134G—Unilamellar cataract

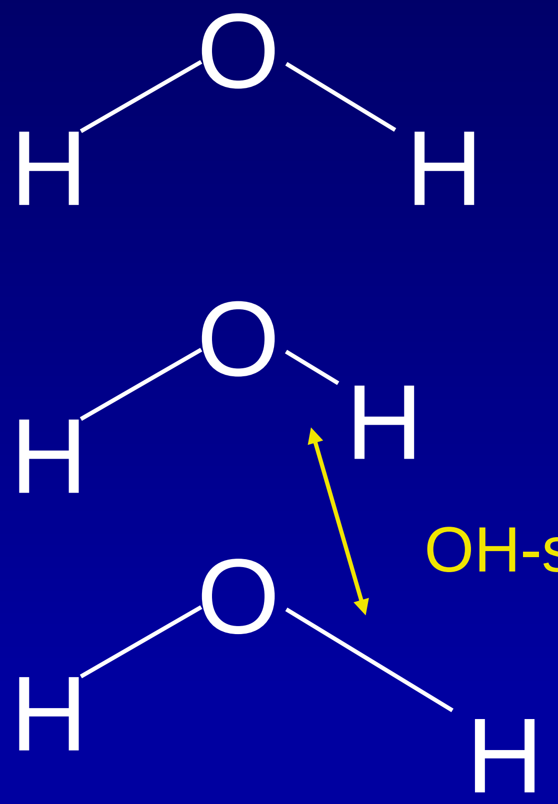


Berry *et al., Nature Genetics,* 2000
Francis *et al., Human Mol Genetics,* 2000

Coherent anti-Stokes Raman scattering (CARS)

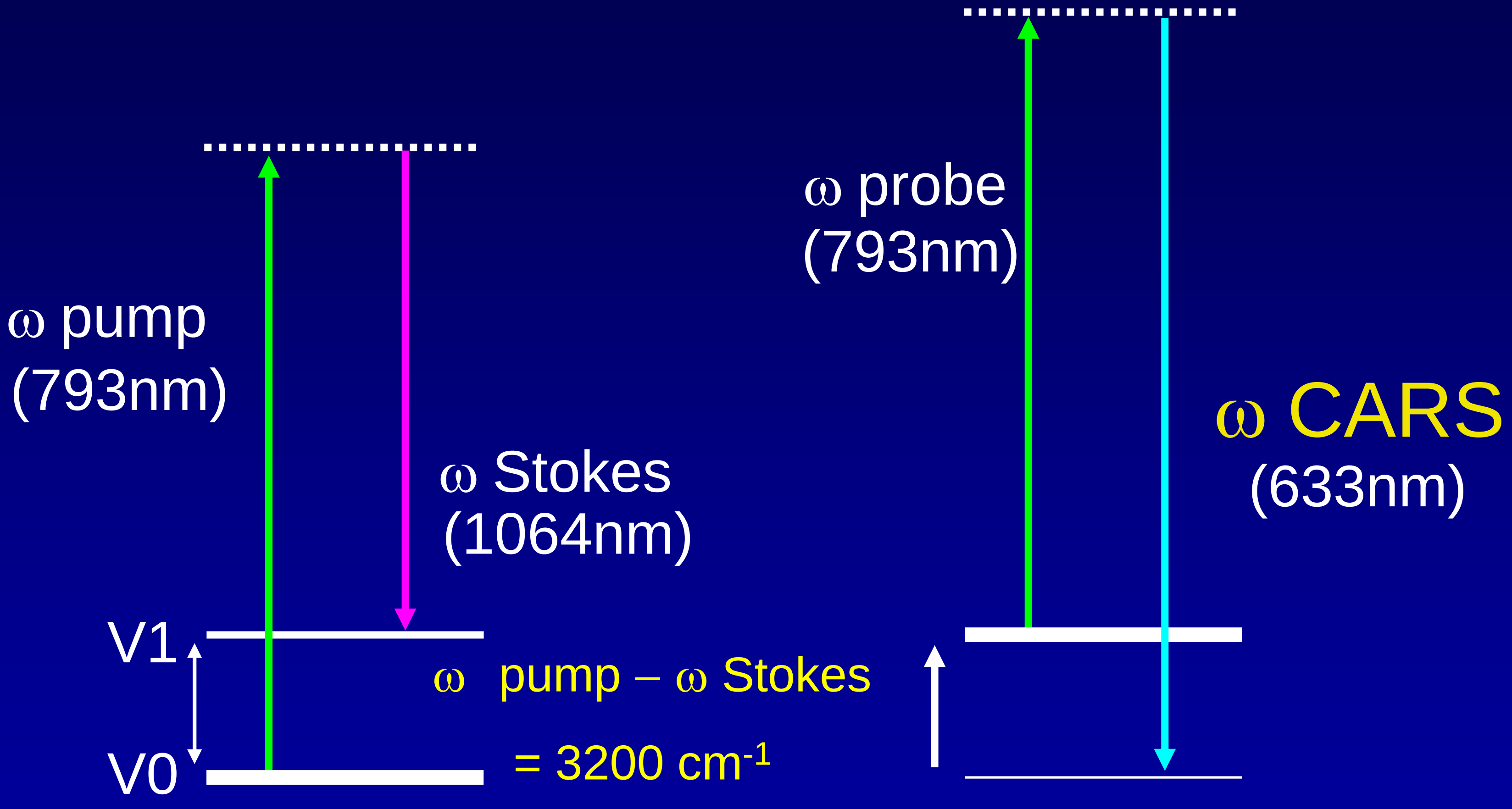
Imaging specific molecular vibration

H_2O molecule



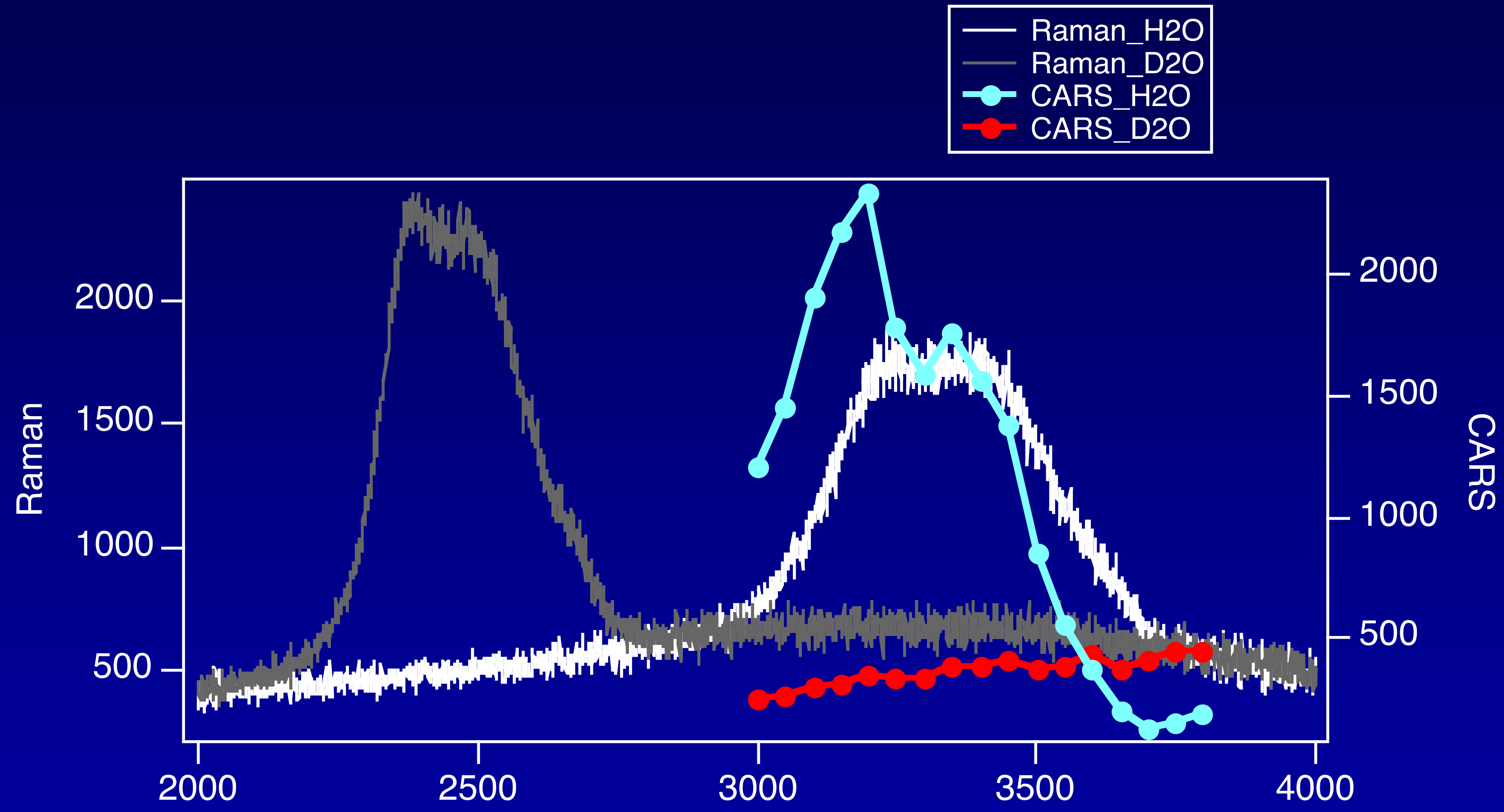
OH-stretching vibration

Energy diagram for OH CARS



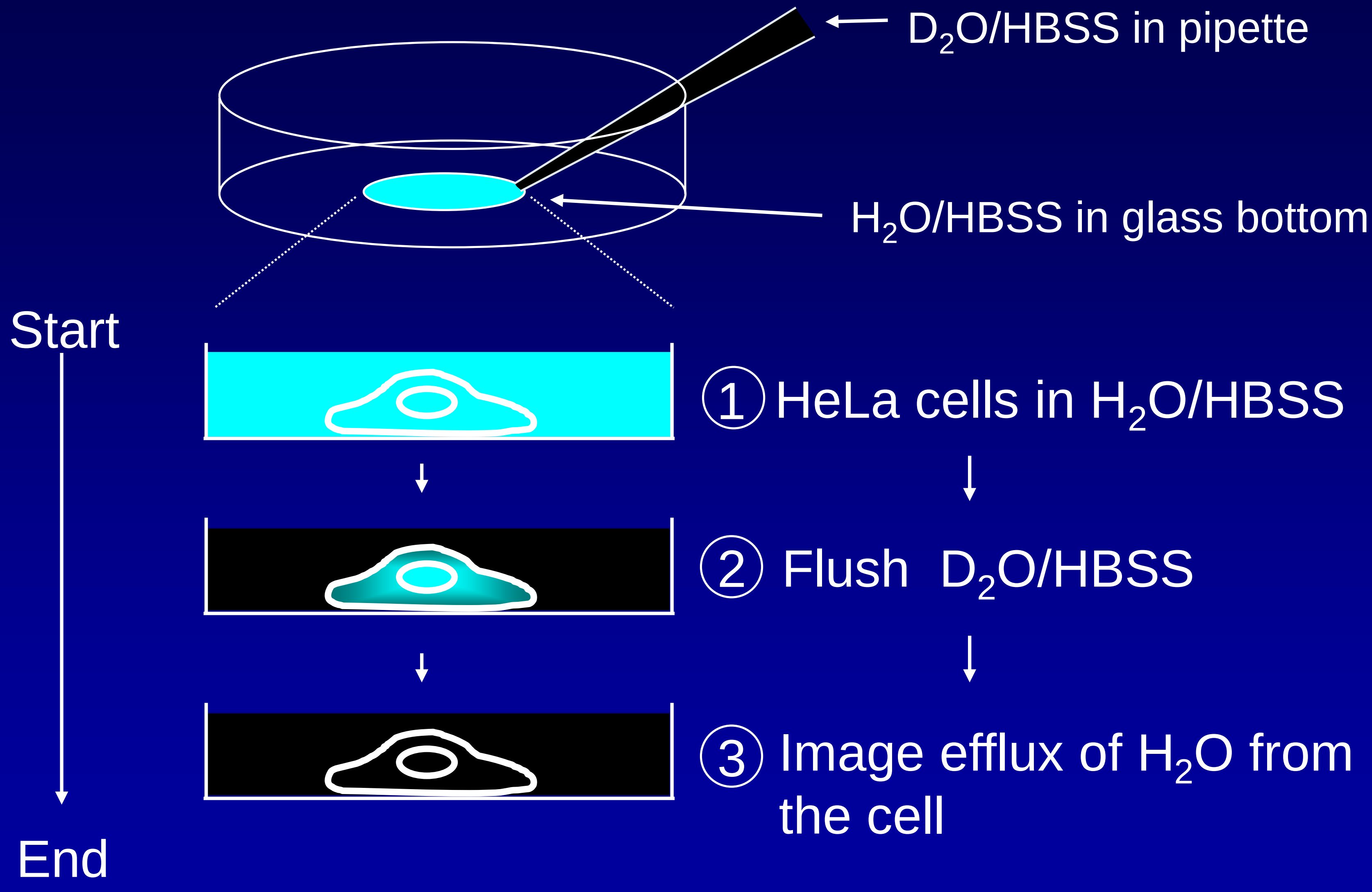
Raman shift for OH-stretch vibration= 3200 cm^{-1}

CARS signals from H_2O and D_2O

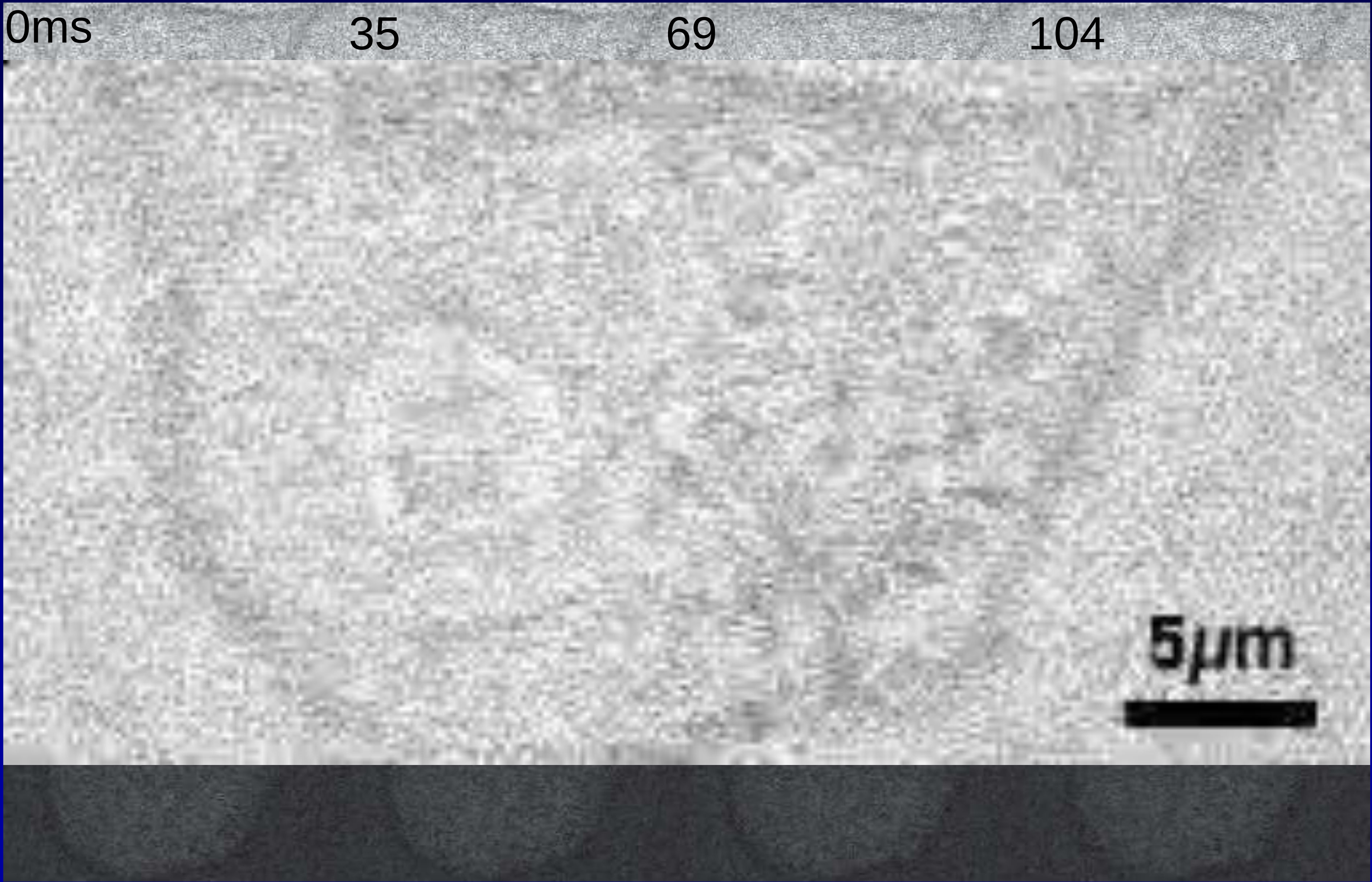


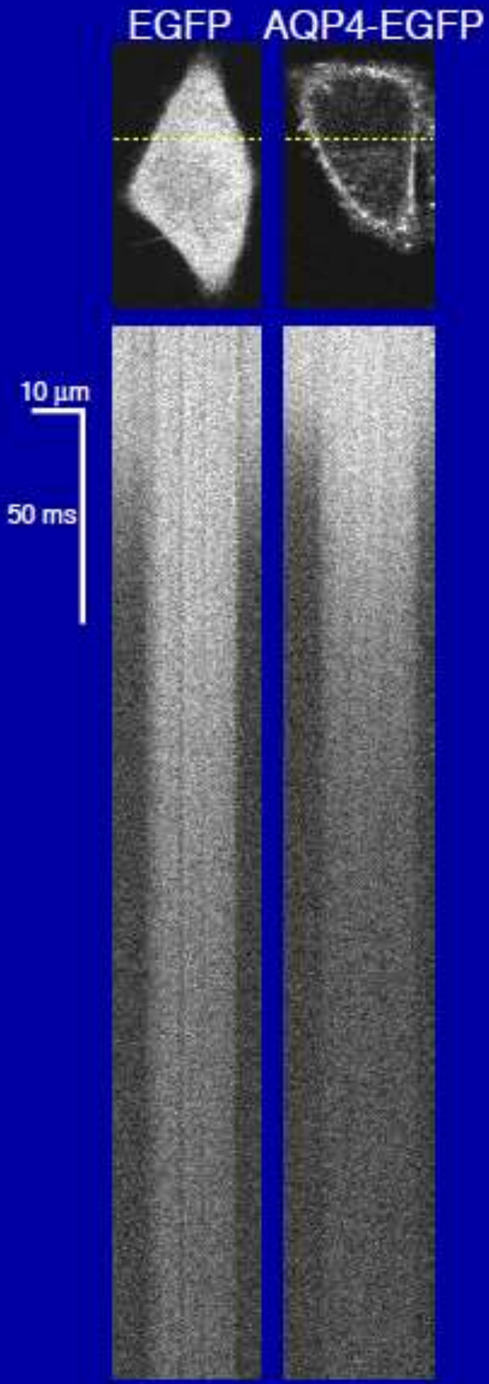
Detection of H_2O, but not D_2O (deuterium oxide)

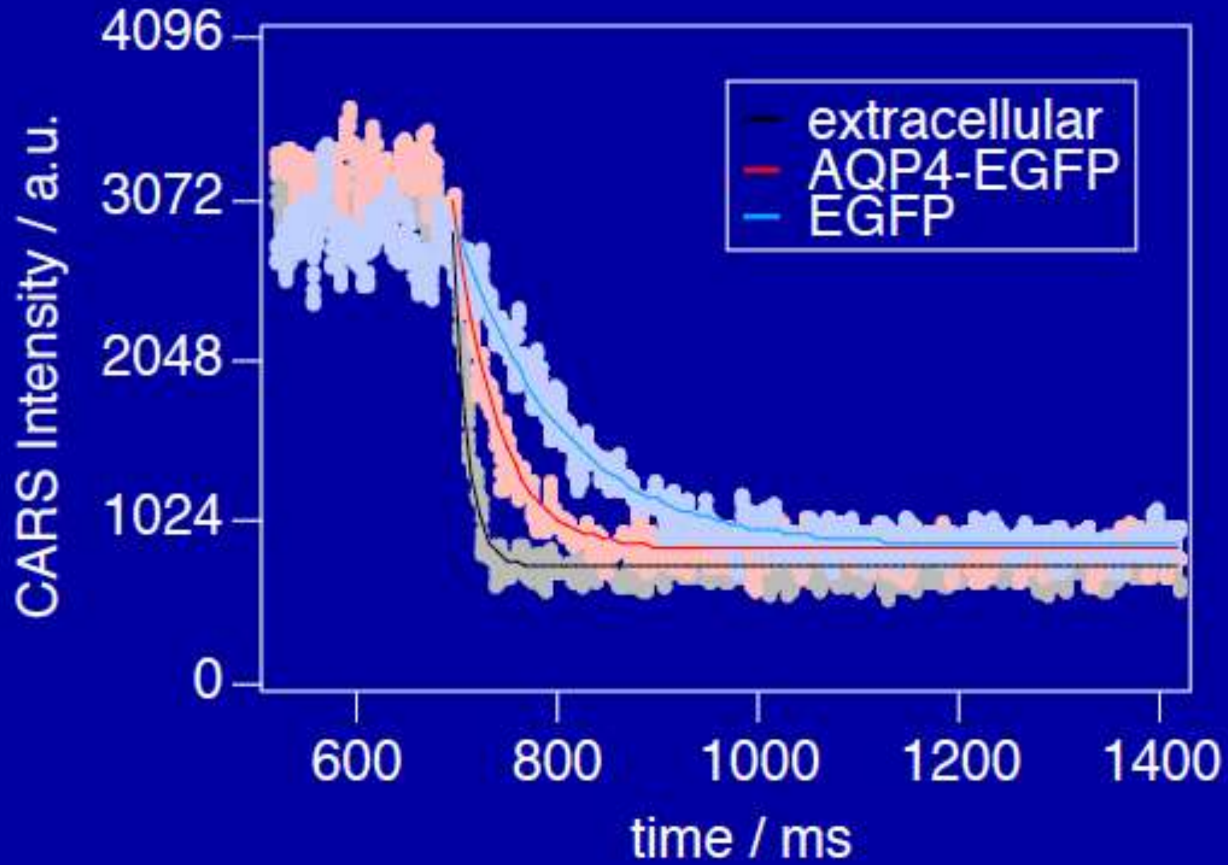
Experimental procedure for flushing isotonic D_2O/HBSS



Frame by frame pictures of H_2O efflux from single cell

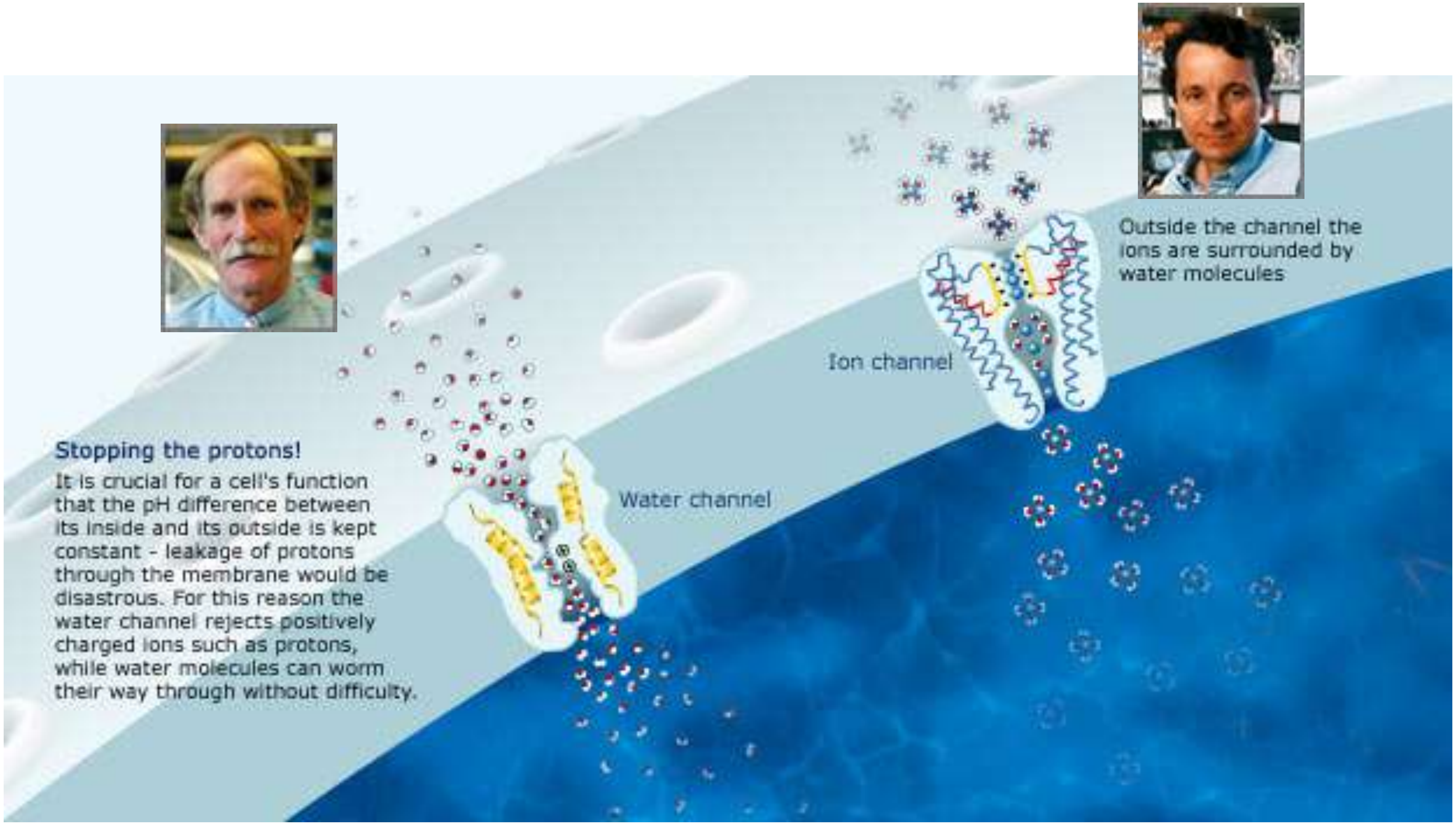




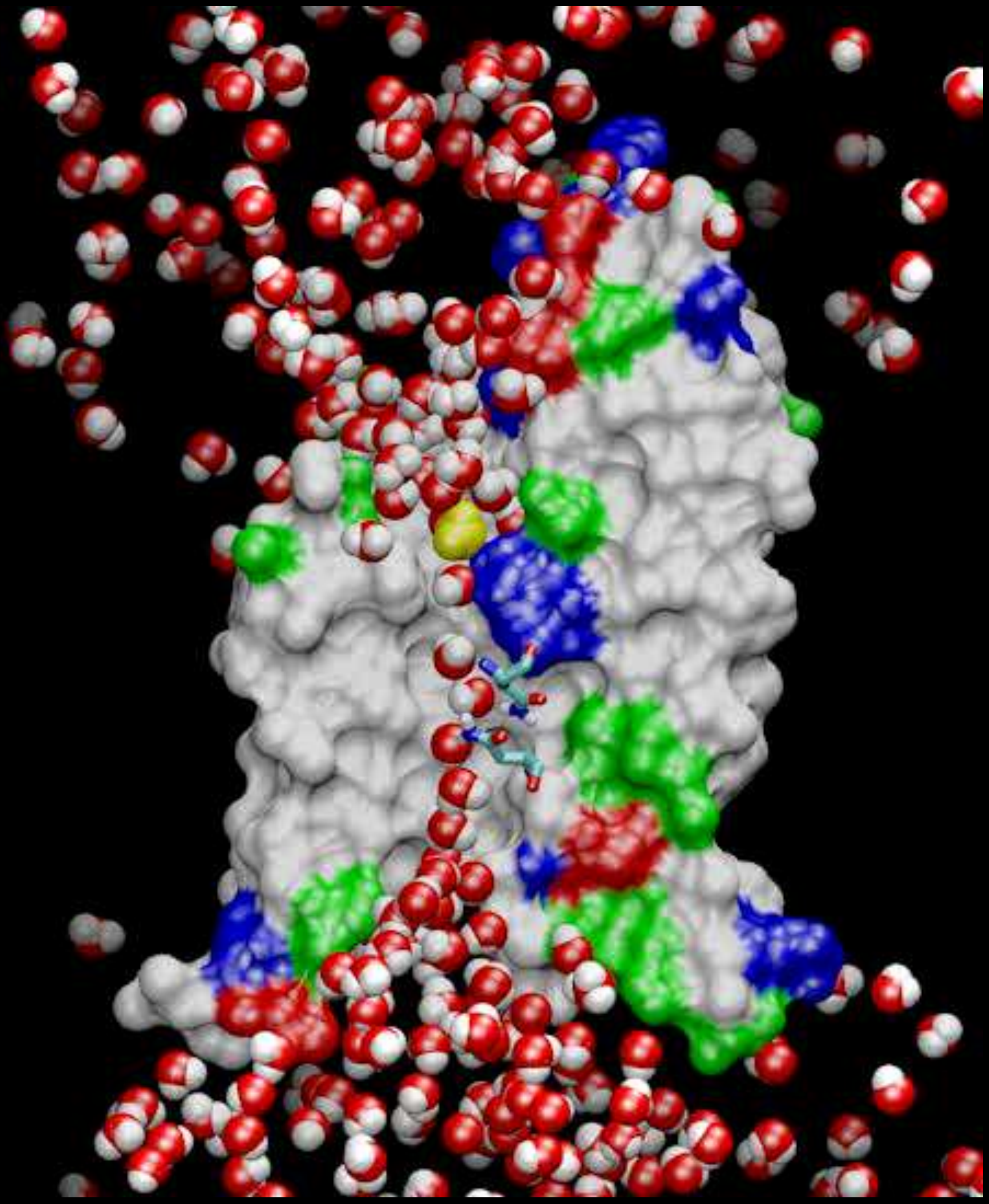


(Ibata *et al*, *Biophys. J*. 2011)

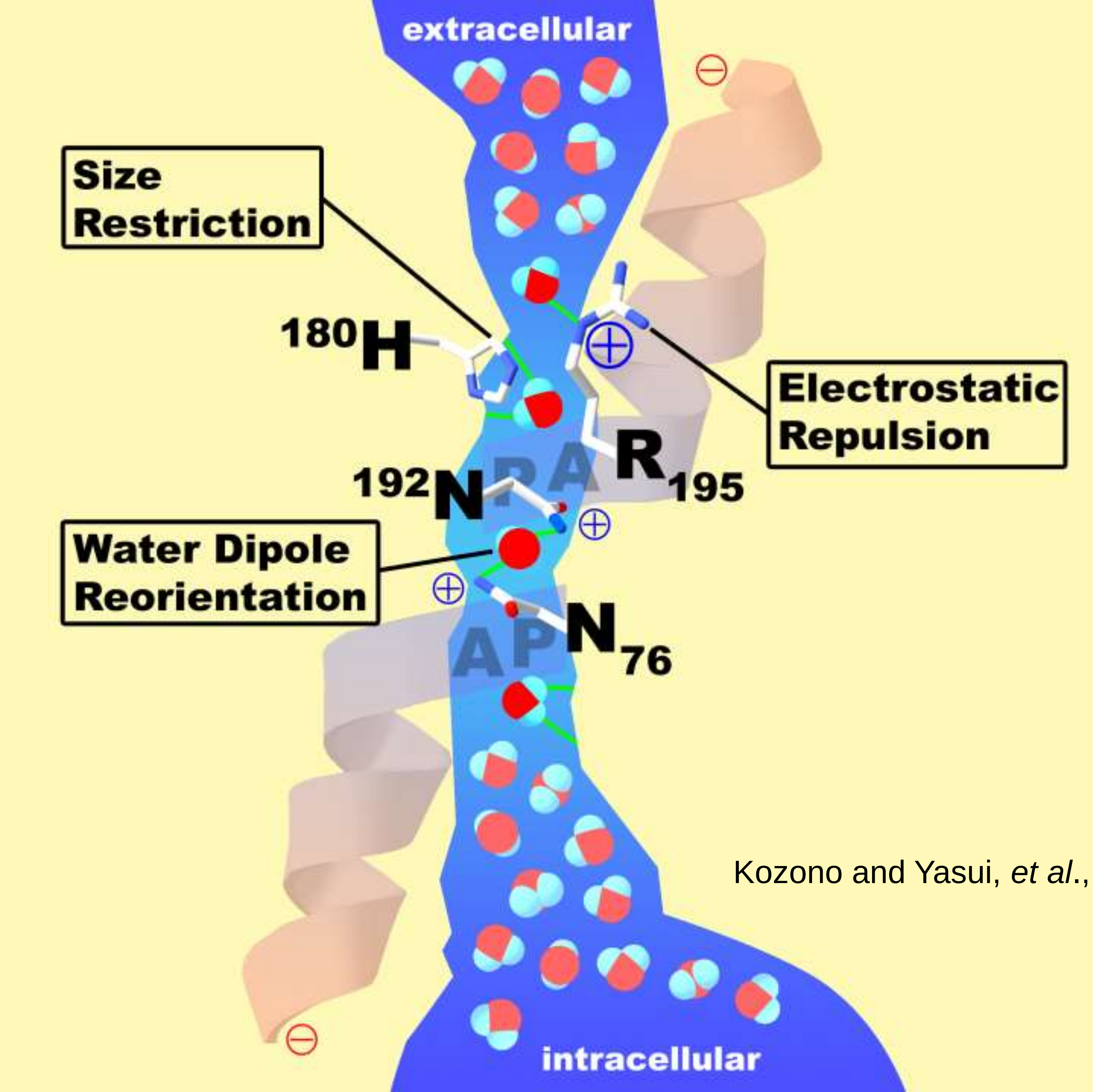
Structure and Function



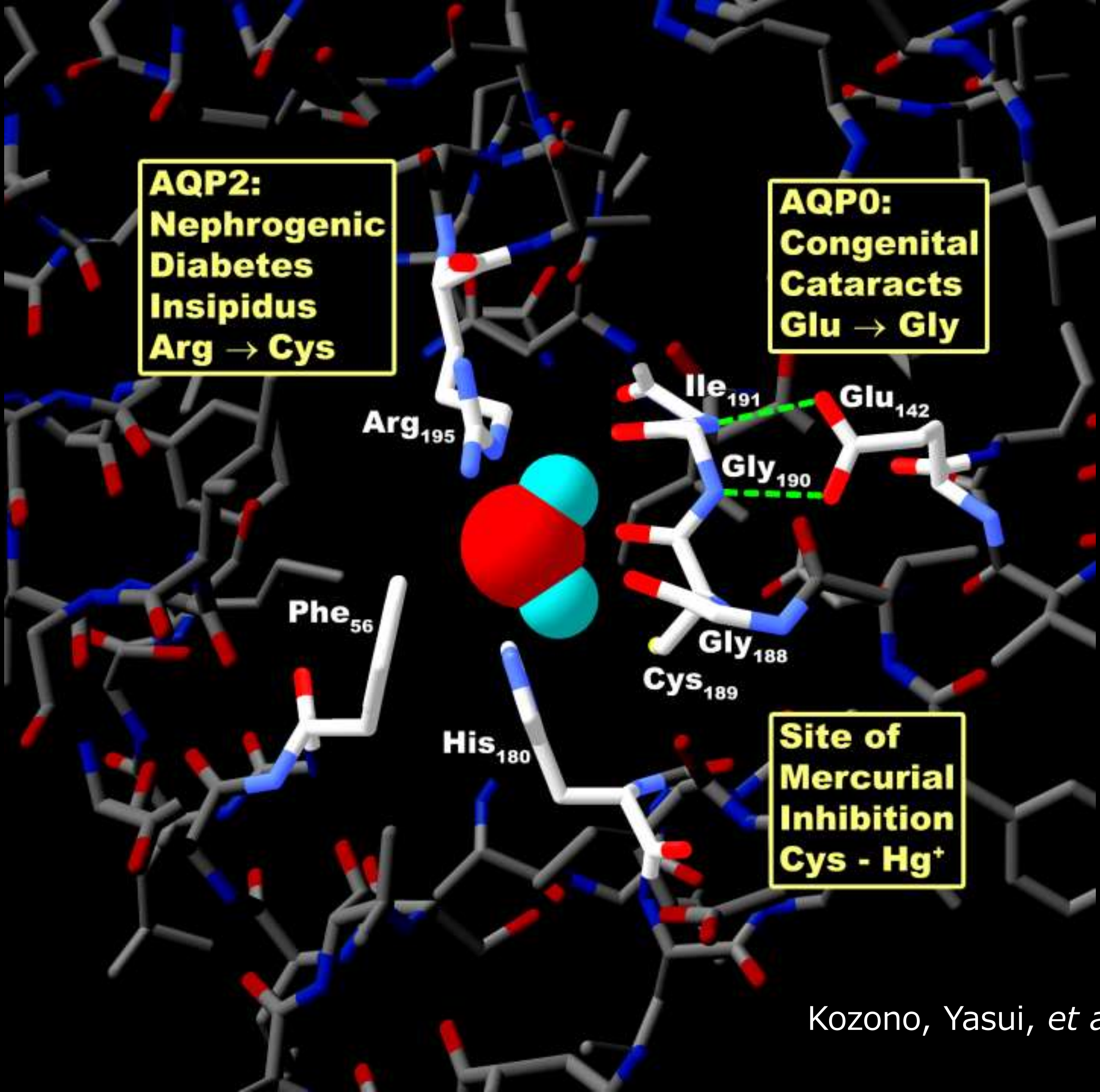
The Nobel Foundation (2003)



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

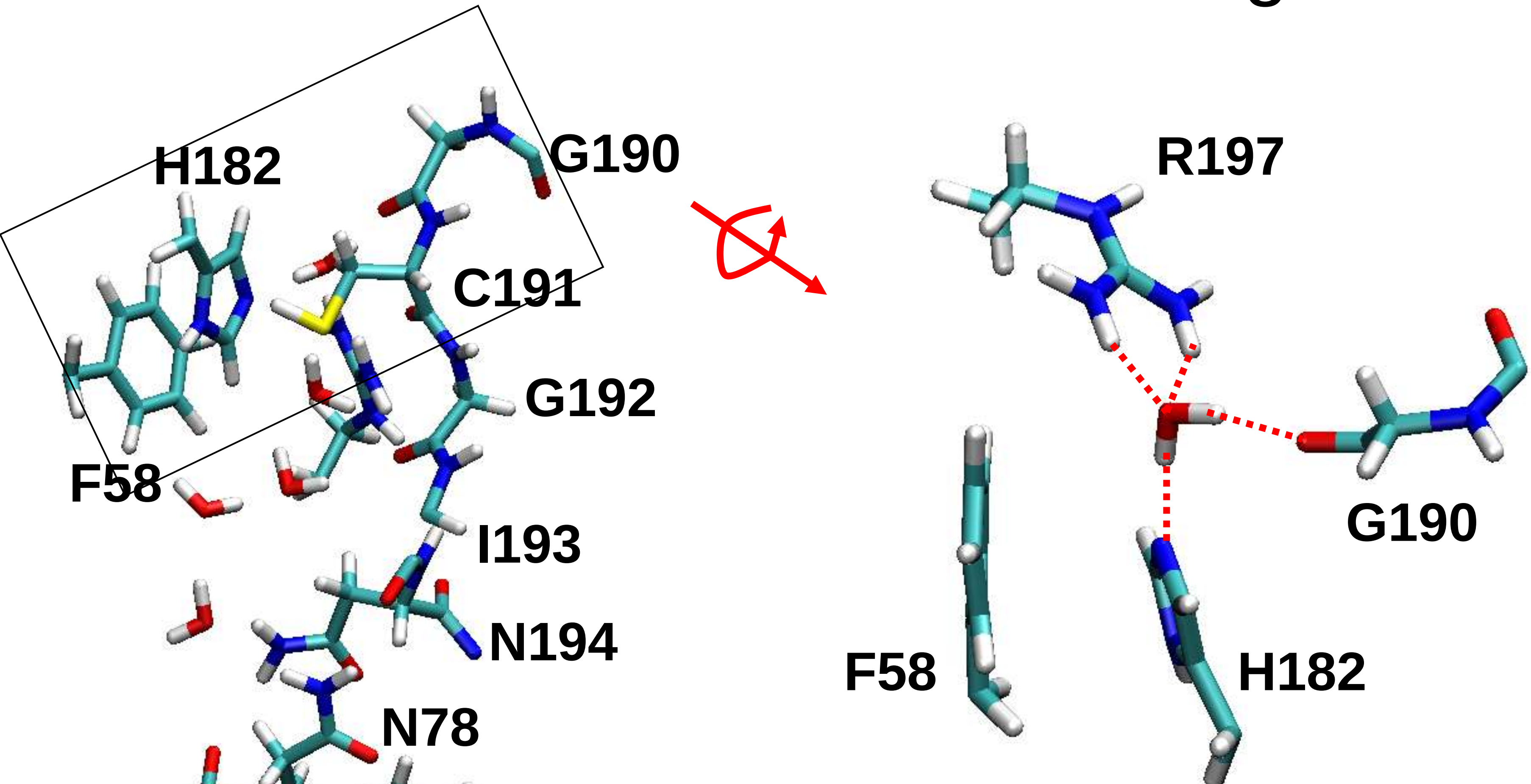


Kozono and Yasui, *et al*., JCI 2002



Kozono, Yasui, *et al*., 2002

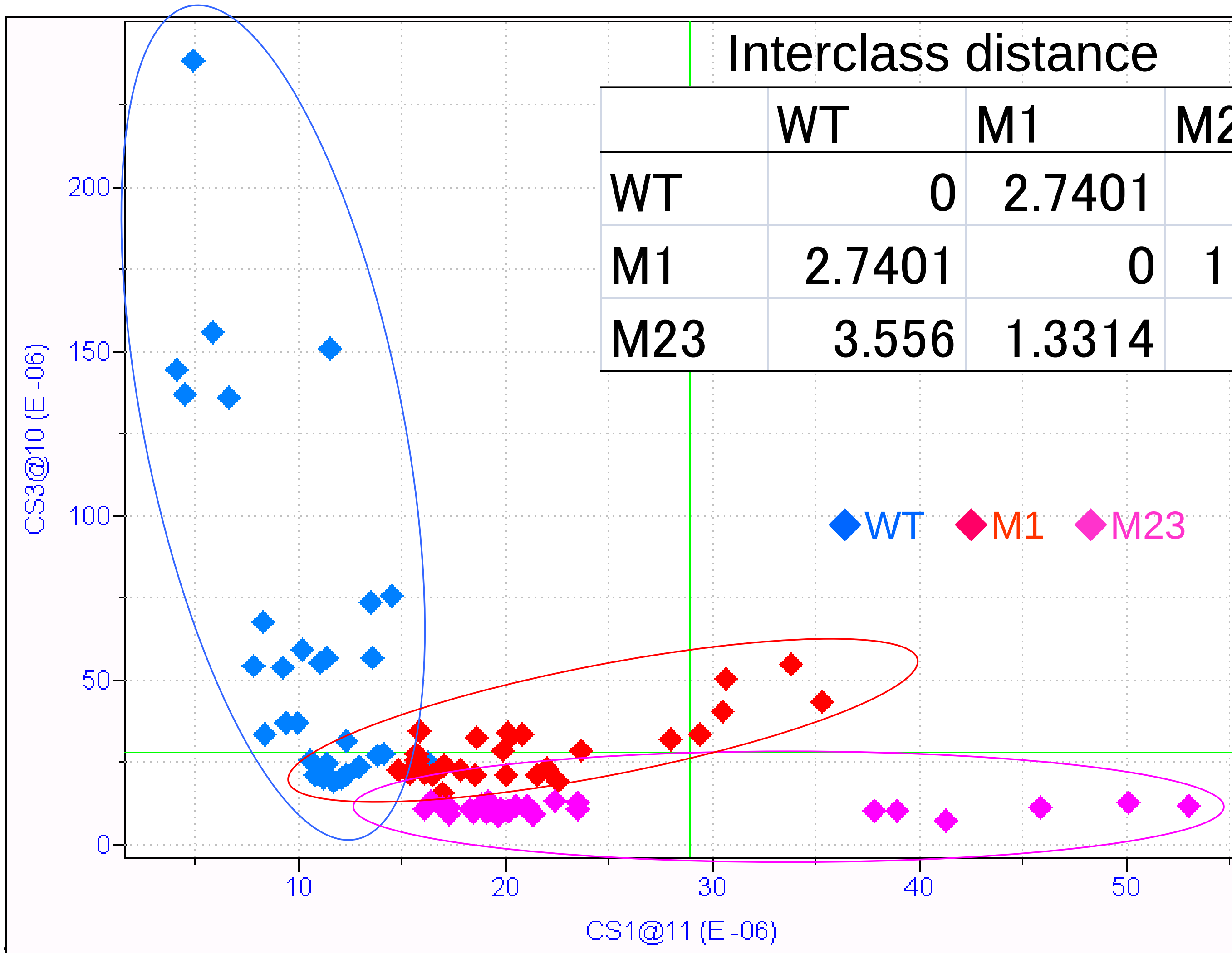
The orientation and hydrogen bonding of water molecule at ar/R region



Isolation from other water molecule

Interrupts proton conduction

SIMCA (1300-1600nm, transform : MSC)

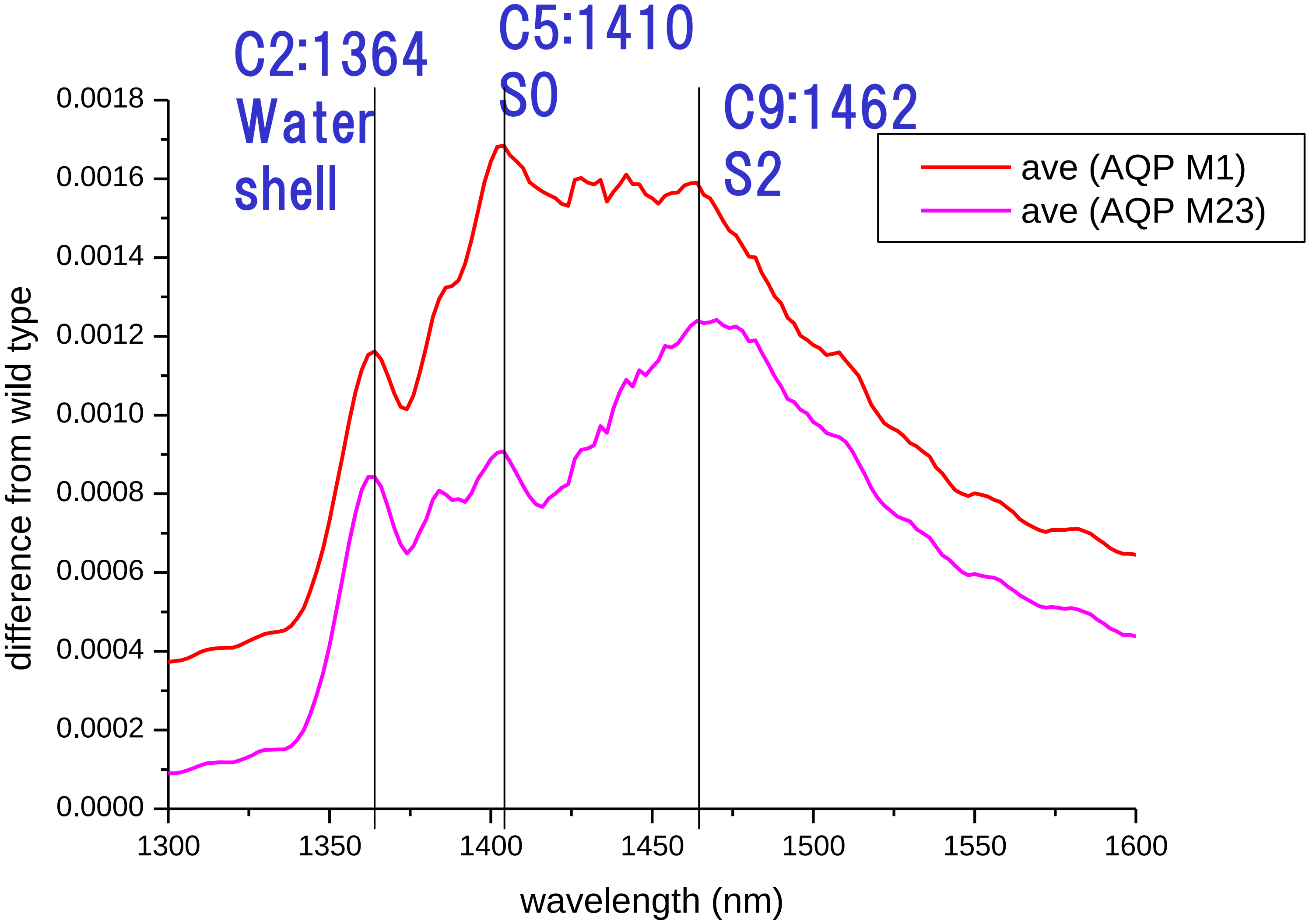


Interclass distance

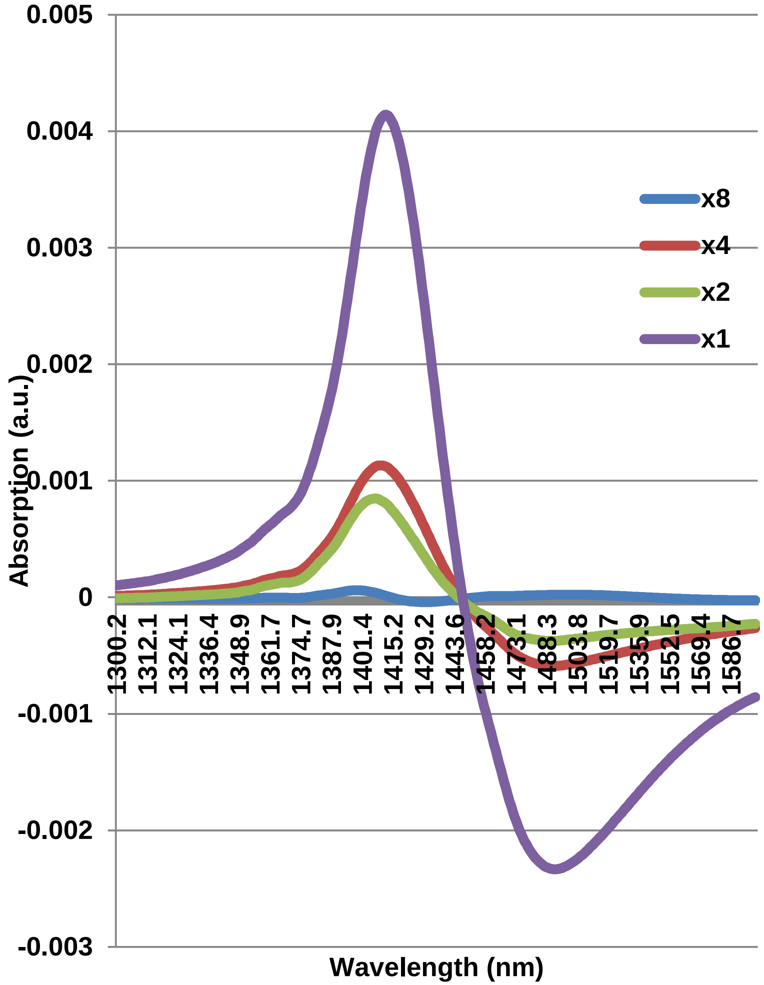
	WT	M1	M23
WT	0	2.7401	3.556
M1	2.7401	0	1.3314
M23	3.556	1.3314	0

(Tsenkova & Yasui, unpublished)

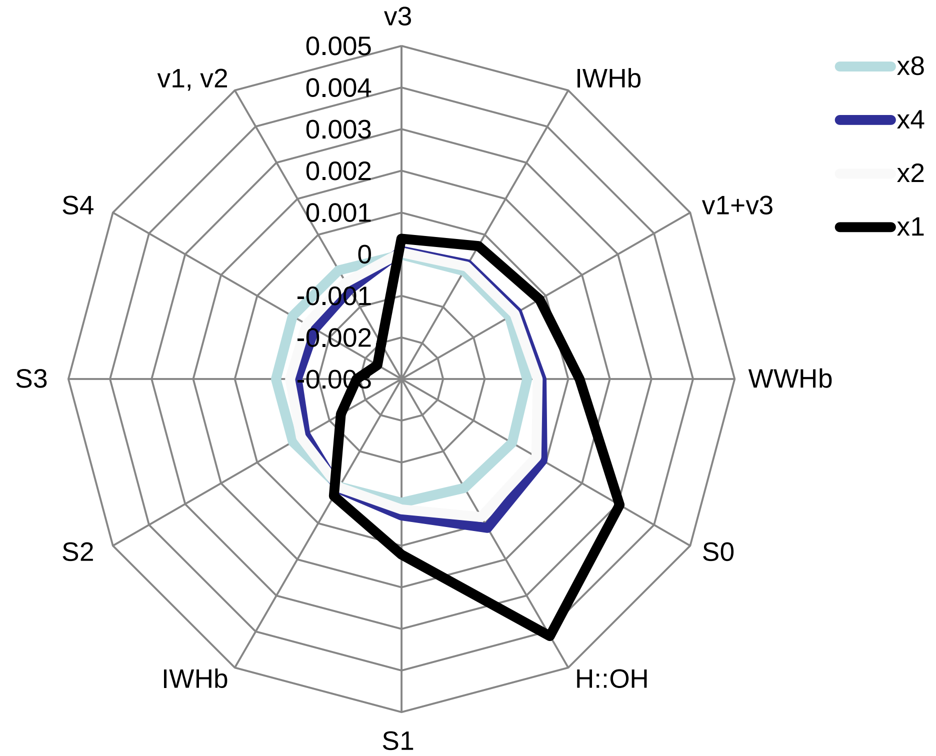
Difference spectra from Wild type



Difference spectra
WT (AQP4$^+$) – KO (AQP4$^-$)

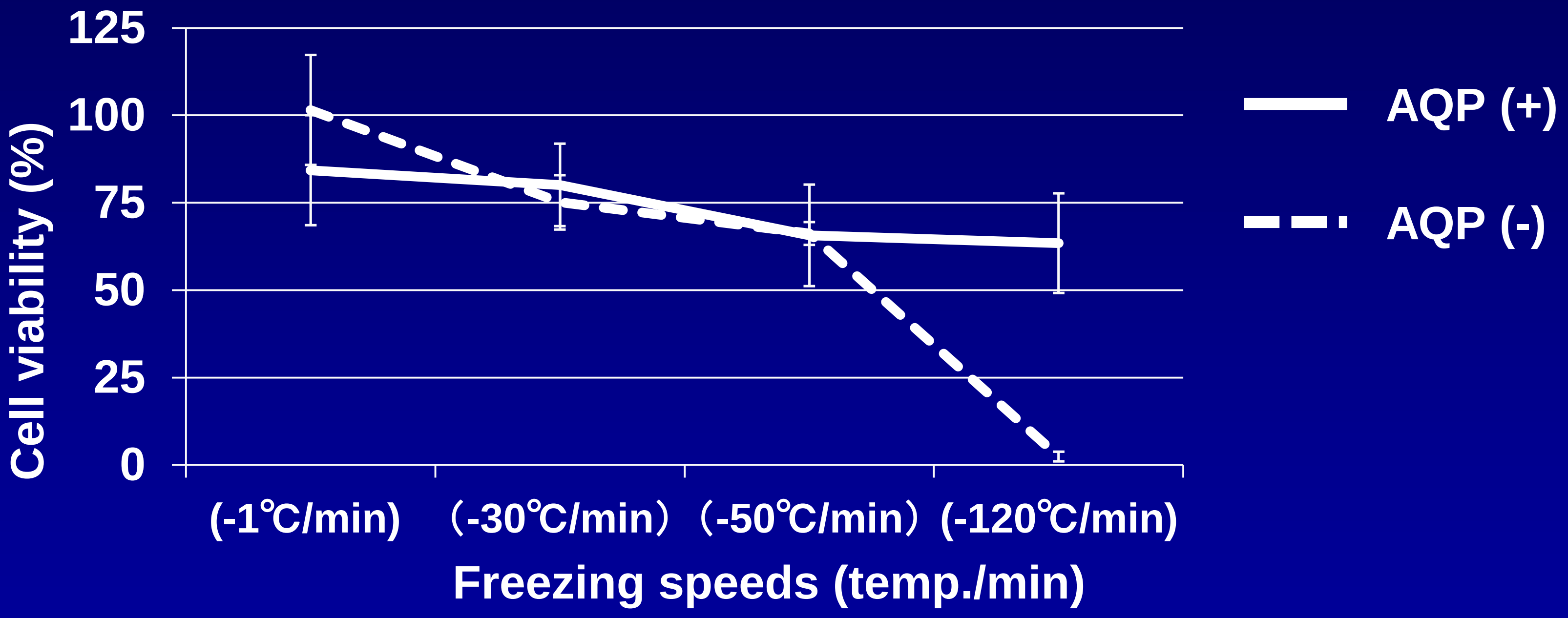


AquaGram of difference spectra (WT-KO)



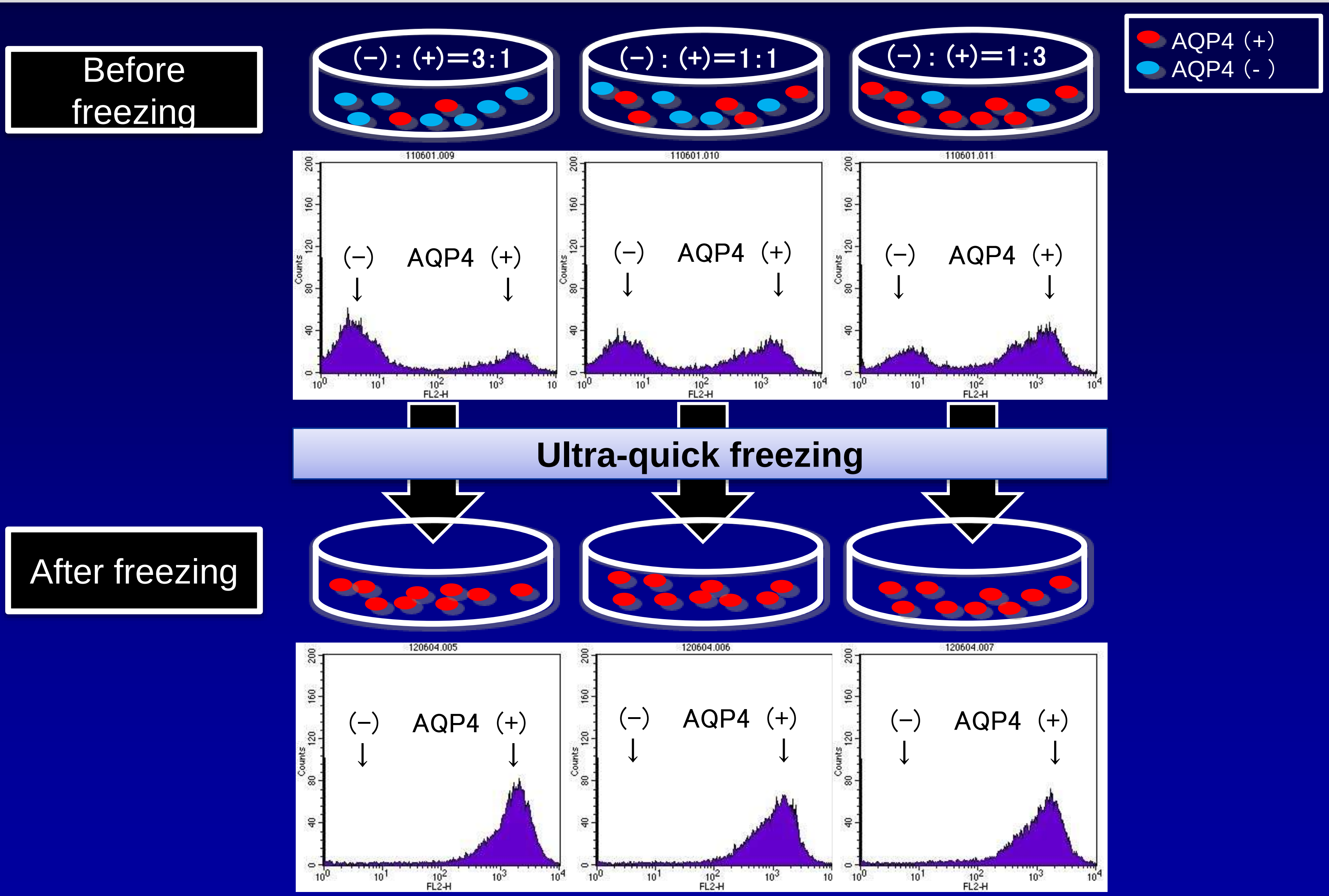
Difference spectra WT and KO was indicated the positive band around 1409nm and negative band around 1491nm (left figure). (right figure). AquaGram of Difference spectra WT (AQP4+) and KO (AQP4-) (right figure). These data shown the increased

Effects of AQP expression on cryopreservation



(Kato *et al*., *PLoS One*, 2014)

Anti-freezing effects of AQP



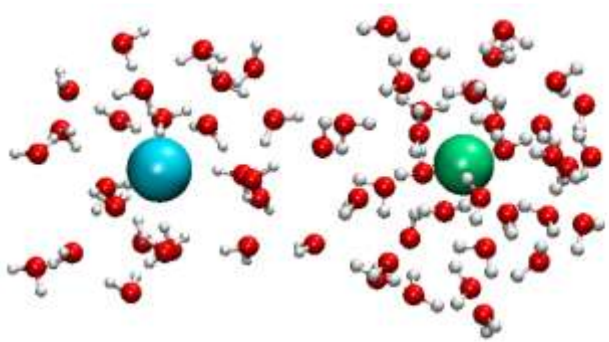
(Kato *et al*., *PLoS One*, 2014)

Aquaphotomics Team at Keio Univ.
: from basic to clinical applications

Project leader: Dusan Kojic

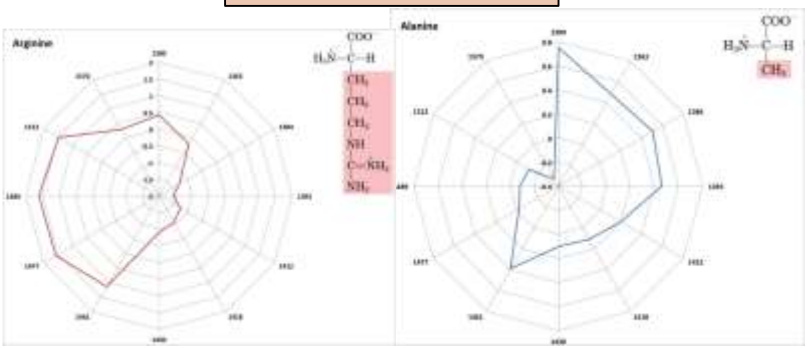
KEIO Aquaphotomics projects: from basic to clinical application

electrolytes



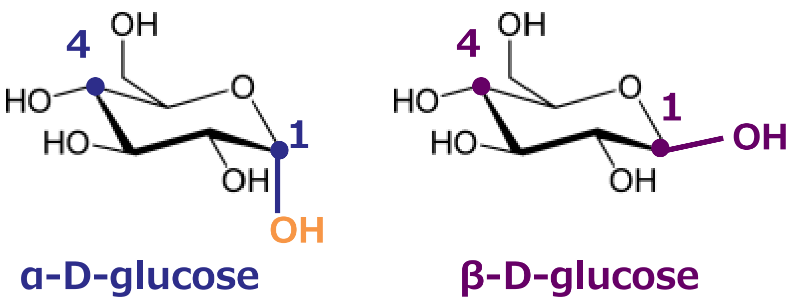
by Kojic

amino-acids



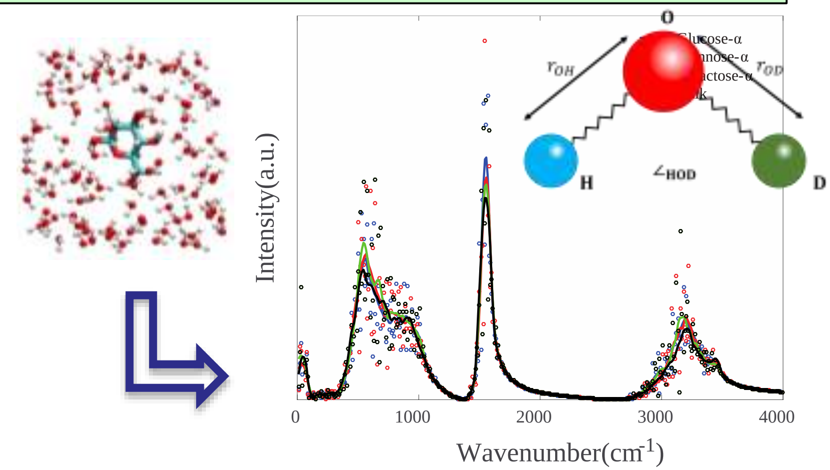
by Nakajima and Kojic

sugars



by Tanaka, Iijima, et al.

Ab-initio or flexible MD simulation



by Tomobe, Nakamura and Yasuoka

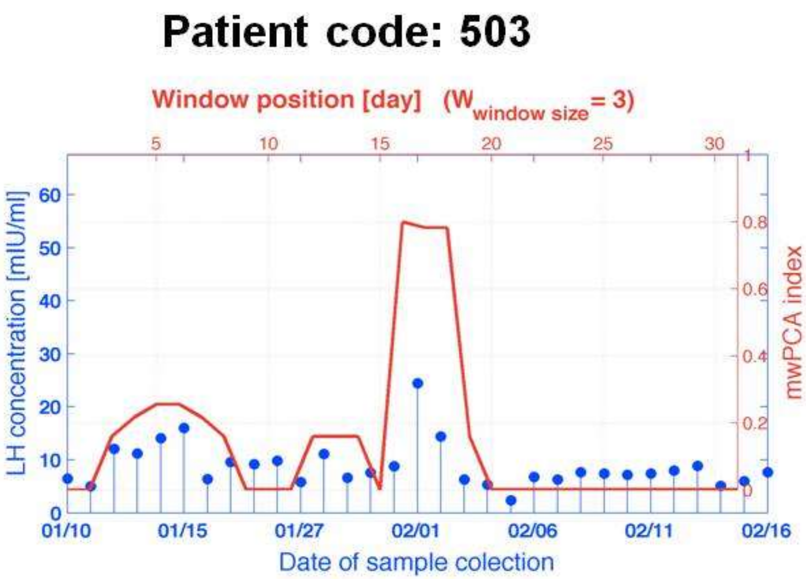
Clinical Applications

Prediction of ovulation in Panda : Kinoshita *et al. Sci. Rep.* 2012

Prediction of Ovulation in Women

Diagnosis of Prostate Cancer

10 healthy women



Relation to LH

(Unpublished)

Biomarkers :

1. Plasma PSA
2. Urine PCA

200 urine samples have been collected and analyzed from patients whose PSA is between 4 and 20, and taken biopsy at Keio Hospital

By Kojic, Tanaka, Iijima, etc.

Dept. of Pharmacology, Keio Univ. School of Medicine