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Ongoing Research Projects:

Our research focuses on the physiology and pharmacology of mammalian lens membrane transporters, with specific emphasis on aquaporins, glucose transporters, and Vitamin C transporters and their relation to lens cataract and transparency.

Publications

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Kushmerick, C., **Varadaraj, K**. and Mathias, R.T. 1998. Effect of lens Major Intrinsic Protein on glycerol permeability and metabolism. J. Membrane Biol., 161:9-19.

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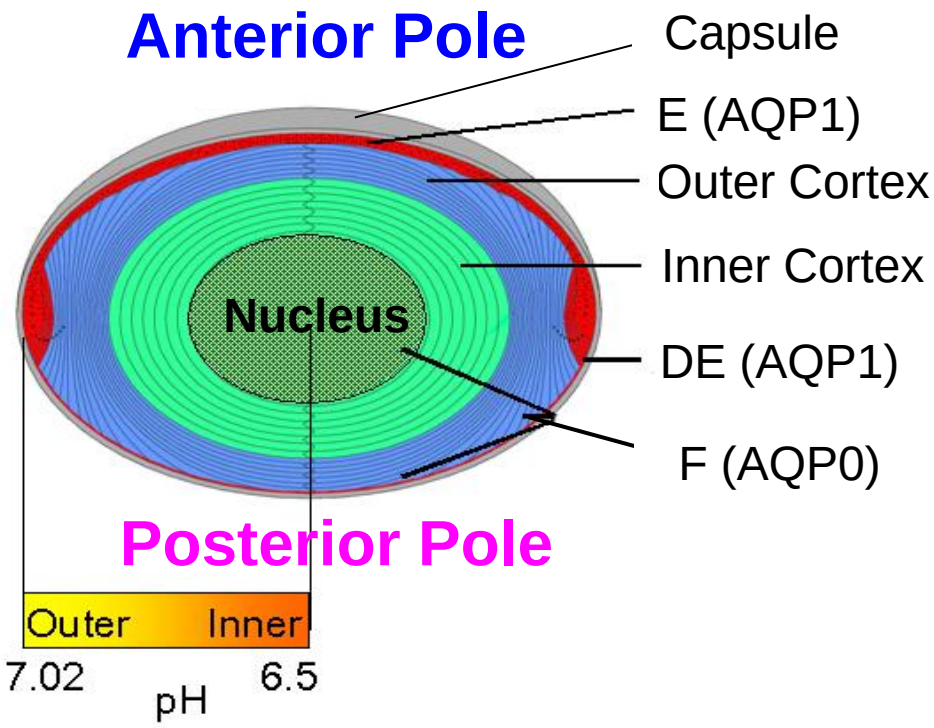
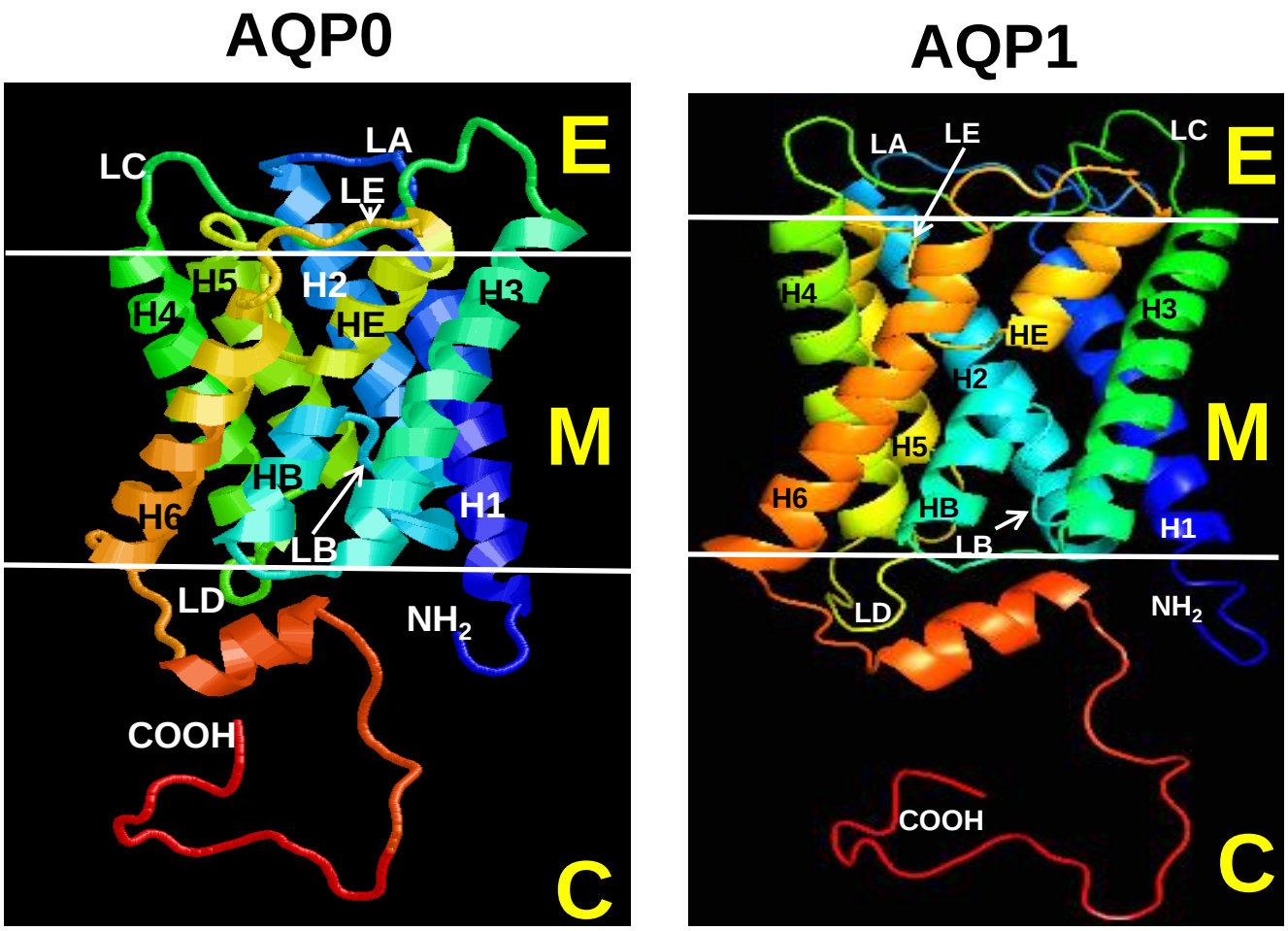
Mammalian Lens



E - Anterior Epithelial cells; F - Fiber cells; DE - Differentiating Equatorial Epithelial cells; AQP - Aquaporin

Lens Aquaporins

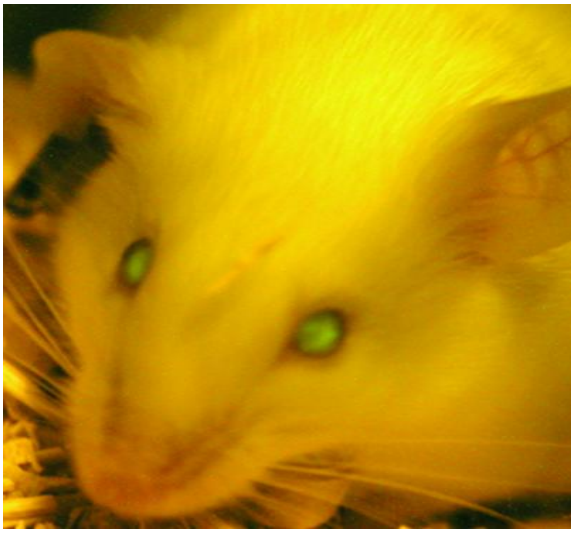


Three dimensional models of wild type mouse AQP0 (a) and human AQP1 (b) proteins predicted using 3D-JIGSAW (version 2.0 (Bates and Sternberg, 1999; Bates et al., 2002; Contreras-Moreira and Bates, 2002). The figure was produced using PyMOL (Delano, 2002). A monomer is rendered in cartoon showing the folds, helix assignment, and the location in the membrane; Membrane-spanning helices are denoted as H1–H6, loops as LA–LE, and the two pore helices formed by loops B and E as HB and HE, respectively. E, extracellular space; M, membrane; C, cytoplasm, NH2, amino terminus; COOH, carboxy terminus.

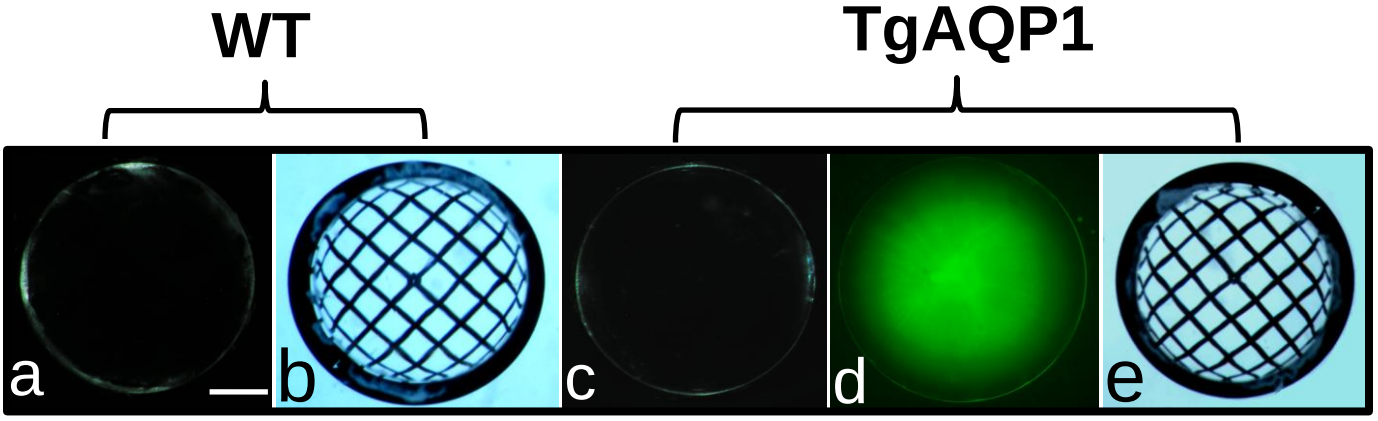
AQP0 is expressed in the lens fiber cells and AQP1 in the anterior epithelial cells.

Genetically Engineered mice

TgAQP1



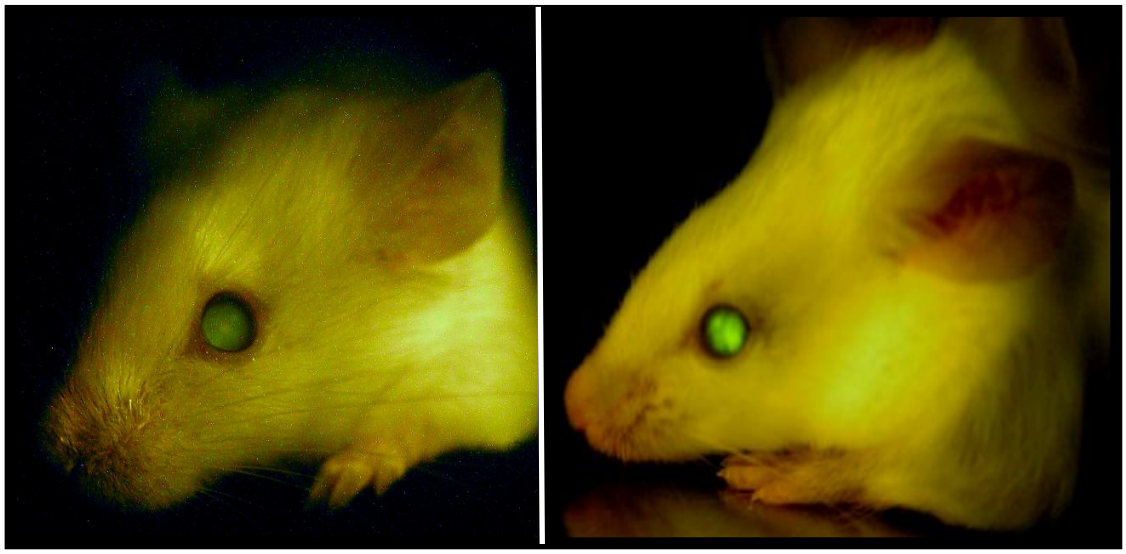
Transgene AQP1 with EGFP Tag expressed in the lens fiber cells of wild type mouse



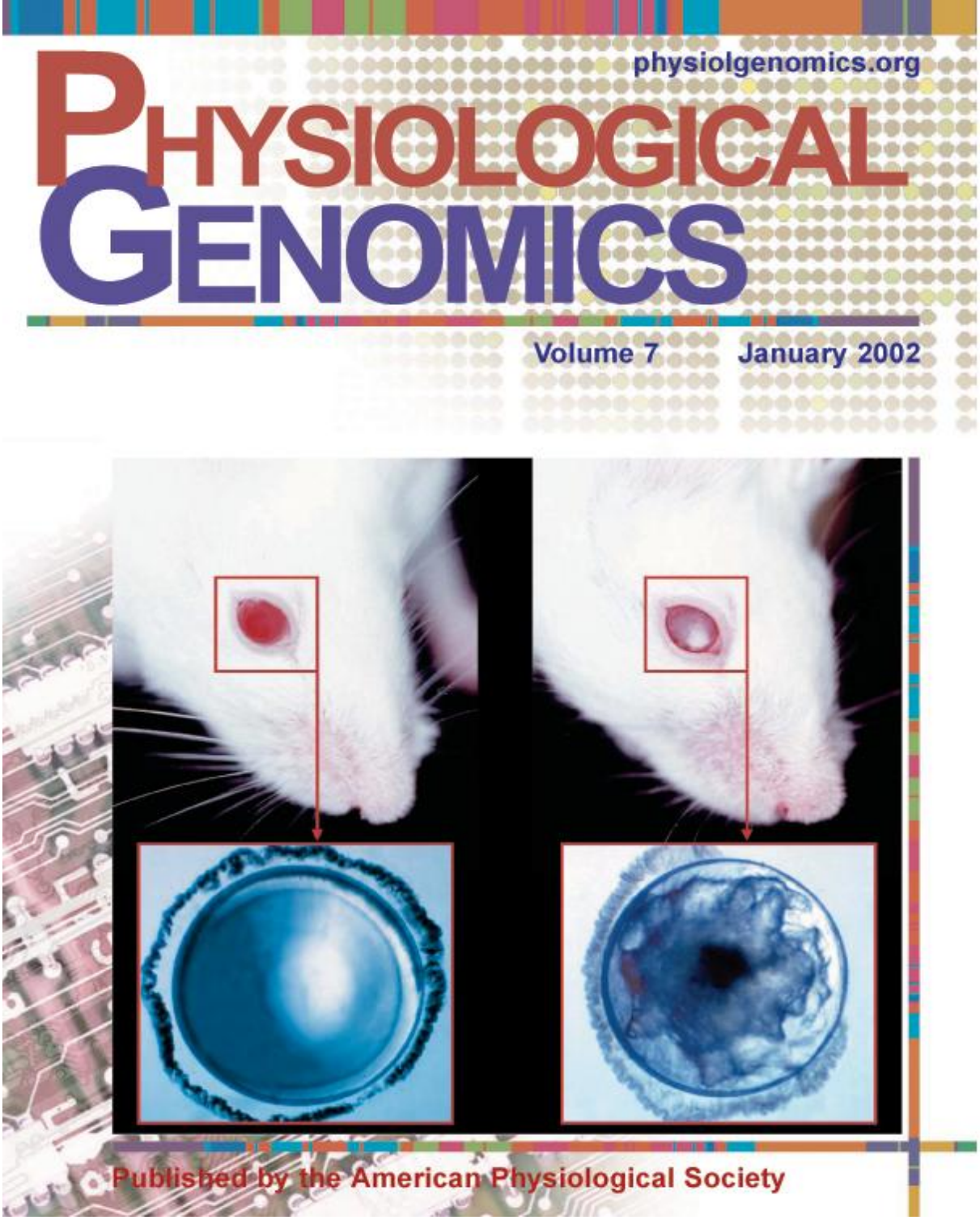
Lens transparency of WT and TgAQP1 lenses. (a) and (b), WT; (c-e), TgAQP1. (a), (b), (c) and (e), light microscopic images of lenses; (d), epifluorescent image of lens expressing AQP1-EGFP chimeric protein observed using EGFP fluorescent filter; (b) and (e), lenses focusing grid. Bar, 275 μm.

Genetically Engineered AQP0 Knockout Mice Expressing AQP1 Transgene Tagged with EGFP

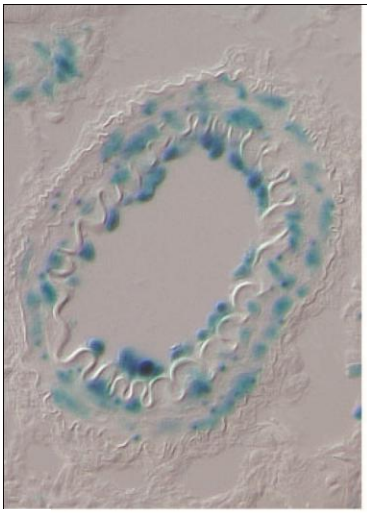
$TgAQP1^{+/-}AQP0^{+/-}$ **$TgAQP1^{+/+}AQP0^{-/-}$**

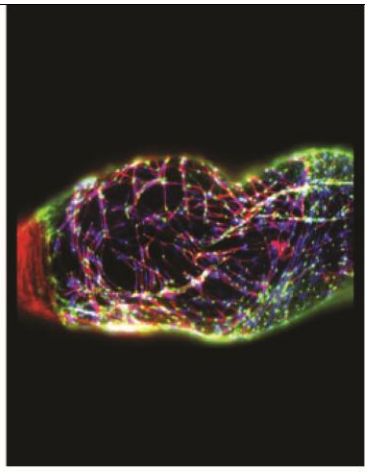


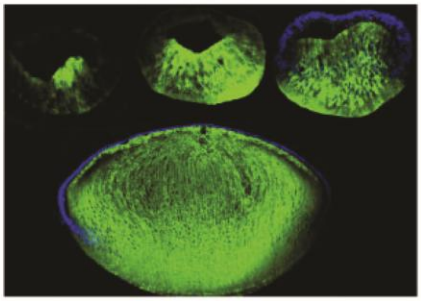
Expression of AQP1-EGFP chimeric protein. Fluorescent eyes show the levels of AQP1-EGFP chimeric protein expression in lenses of (a) heterozygous ($TgAQP1^{+/-}/AQP0^{+/-}$) and (b) homozygous ($TgAQP1^{+/+}/AQP0^{-/-}$) AQP1 transgenic AQP0 knockout mice.

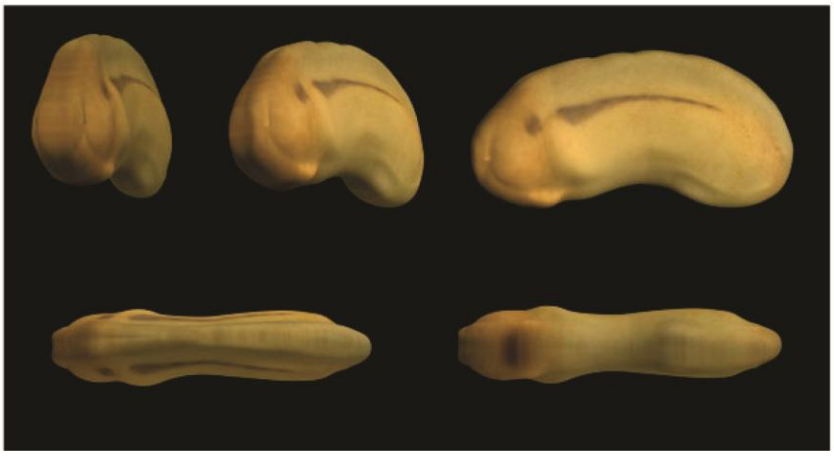


Shiels A, Bassnett S, **Varadaraj K**, Mathias R, Al-Ghoul K, Kuszak J, Donoviel D, Lilleberg S, Friedrich G, Zambrowicz B. Optical dysfunction of the crystalline lens in aquaporin-0-deficient mice. Physiol. Genomics, 2001, 7(2):179-186.



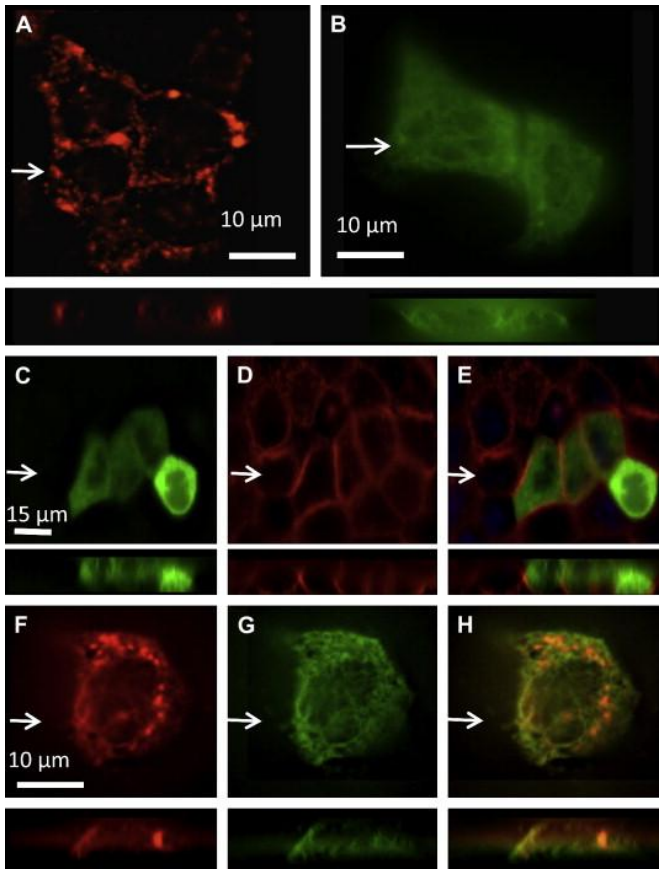


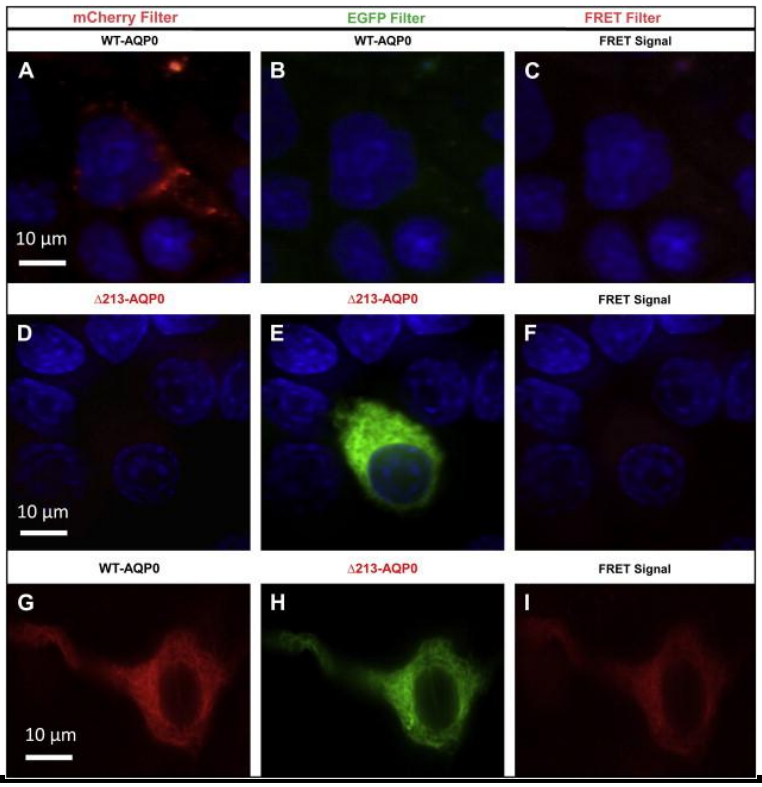




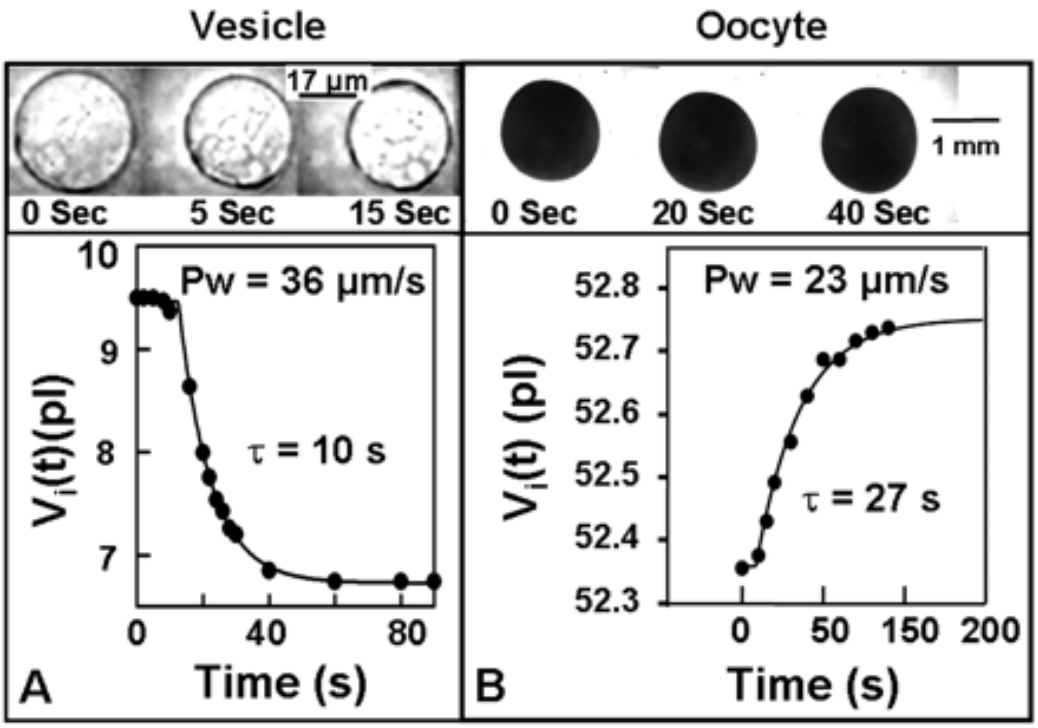
DD ArtPix is a picture gallery of images related to papers published recently in *Developmental Dynamics.* Dev. Dyn. 236:1115–1125, 961–970, 1093–1105, DOI: 10.1002/dvdy.21125, 236:1036–1043.

Varadaraj K, Kumari SS, Mathias RT. Functional expression of aquaporins in embryonic, postnatal, and adult mouse lenses. Dev. Dyn., 2007, 36(5):1319-1328.

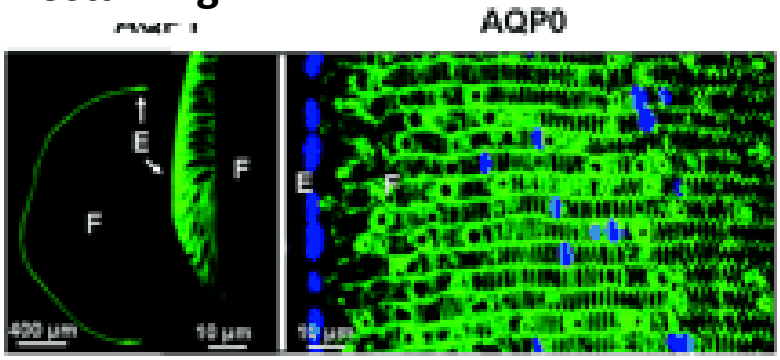




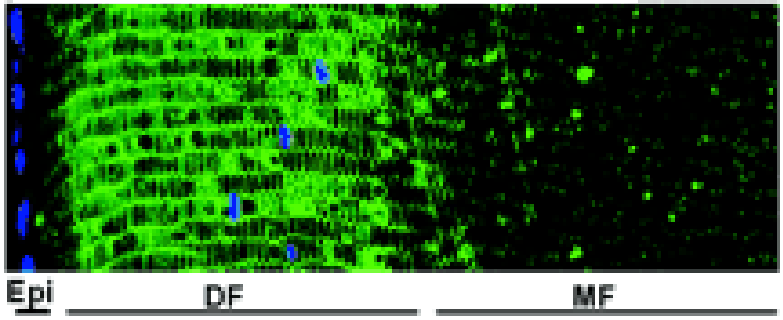
Varadaraj K, Kumari SS, Patil R, Wax MB, Mathias RT. Functional characterization of a human aquaporin 0 mutation that leads to a congenital dominant lens cataract. Exp. Eye Res., 2008, 87(1):9-21.



Immunostaining



E- Epithelial Cells; F- Fiber Cells; Blue- Nuclei



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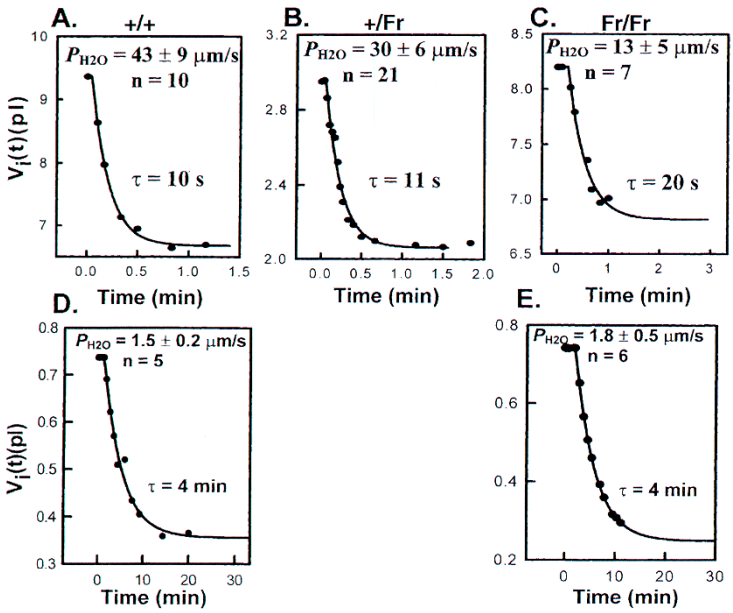

Fig. 7. The water permeability (p_{H2O}) of fiber cell membrane and lipids from wild-type (+/+) mouse lenses and heterozygous (+/Fr) and homozygous (Fr/Fr) Cat^{Fr} mutant mouse lenses. Each panel shows a typical result and gives the mean ± SD from *n* vesicles. The Cat^{Fr} mouse synthesizes a mutant form of MIP that is poorly translocated to the fiber cell membrane. This mutation has no significant effect on the p_{H2O} of fiber cell lipids (panel *D* and *E*), however, the systematic reduction in the amount of MIP present in +/+, +/Fr, and Fr/Fr mouse lenses results in a systematic decrease in p_{H2O}.

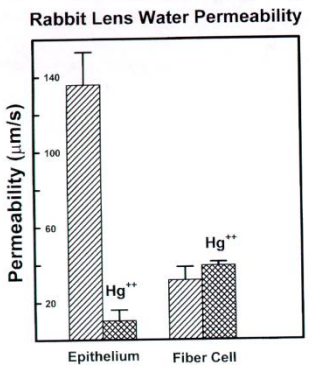

Fig. 5. A comparison of epithelial and fiber cell membrane water permeabilities. Lens epithelial cells have a relatively large water permeability that is blocked by Hg^+ whereas fiber cells have a smaller, Hg^+-insensitive water permeability. These data are consistent with CHIP28 (AQP1) being the epithelial membrane water channel and MIP being the fiber cell membrane water channel.

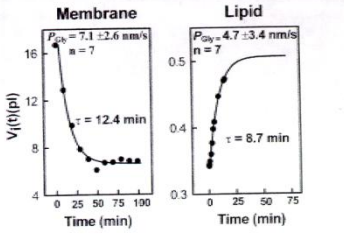

Fig. 6. The glycerol permeability (p_{Gly}) of fiber cell membrane and lipids from the outer cortex of the rabbit lens. Each panel shows a typical result and gives the mean ± SD from *n* vesicles. As described in Theory, each vesicle was first observed to swell in an isosmotic solution containing glycerol, then, if the vesicle survived, observed to reshrink in an isosmotic solution with the glycerol removed. There was no systemic difference in the values of p_{Gly} determined from swelling or reshrinking, hence a typical response of each is illustrated. The majority of fiber cell membrane glycerol permeability appears to be mediated by the lipid matrix.

consistent with MIP being the fiber cell membrane water channel and AQP1 being the epithelial cell membrane water channel. Moreover, the presence of protein medi-

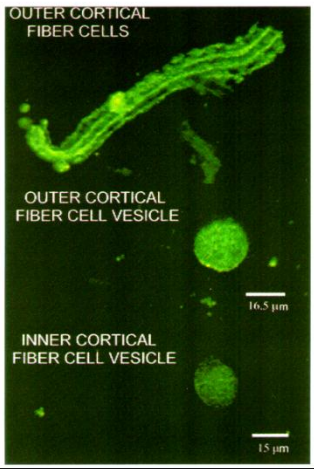

Fig. 3. Fiber cells and fiber cell membrane vesicles stained positively for MIP. These rabbit lens cells or vesicles were incubated with a mouse monoclonal antibody against an epitope on the C-terminus of bovine MIP (a gift from Dr. P. FitzGerald). They were then exposed to FITC-labeled anti-mouse IgG and the resulting fluorescence is shown.

Varadaraj K, Kushmerick C, Baldo GJ, Bassnett S, Shiels A, Mathias RT. The role of MIP in lens fiber cell membrane transport. J. Membr. Biol., 1999, 170(3):191-203.