BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Paul L. Kaufman, MD

POSITION TITLE: Ernst H. Bárány Professor of Ocular Pharmacology, Department Chair Emeritus

eRA COMMONS USER NAME (credential, e.g., agency login): PLKAUFMA

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tufts University, Medford, MA	None	1963	Chemistry-Biology
New York Univ. School of Med - New York	MD	1967	Medicine
Columbia Univ. Bellevue Hosp.-NY (Med. Int.)		1968	Medicine
National Cancer Inst., NIH, Bethesda, MD		1970	Biometry/Epidemiology
Washington Univ. Barnes Hosp.-St. Louis, MO		1973	Ophthalmology Residency
Seeing Eye/NIH Special Fellow, Uppsala, Sweden	None	1975	Ocular Pharmacology

A. Personal Statement

My laboratory has conducted aqueous humor dynamics studies in nonhuman primates for over 30 years. The research done in my laboratory has been of critical importance to understanding the regulation of intraocular pressure, the pathophysiology of glaucoma, and the development of new glaucoma medications. Our studies have enhanced understanding of ocular hydrodynamics and methods for therapeutic manipulation of the outflow pathways. In addition, we are the leader in the field for using gene therapy with viral vectors to over-express products in the anterior segment of the eye to lower intraocular pressure which will potentially be relevant for glaucoma therapy. I have a qualified staff and collaborators that will enable us to make significant progress on the proposed studies. Techniques utilizing monkey and pig organ-cultured anterior segments have been established in my laboratory for assessing effects of agents on trabecular outflow in vitro. We have adapted techniques such as spectral domain OCT for assessing retinal integrity and nerve fiber layer thickness in a variety of species including nonhuman primates. In addition, my laboratory also utilizes sophisticated imaging technologies to investigate the role of various ocular structures in the development of presbyopia, and how that may relate to glaucoma.

B. Positions and Honors.

Positions and Employment

1975-2004 Asst, Assoc, Full Prof, Dep't of Ophthalmol & Vis Sci (Acting Chair 92)
1975-2004 Director, Glaucoma Service, UW-Madison
1992-95, 98-03 Councilor/Pres Elect/Pres, Int Soc Eye Res
1993-2008 Trustee, Pres. & Exec VP, ARVO
2004-2014 Peter A. Duehr Professor and Chairman, Dept Ophthalmology Vis Sci, Univ Wisconsin
2007-2012 Editor-in-Chief, Invest. Ophthalmol. Vis. Sci
2010-present Ernst H. Bárány Professor of Ocular Pharmacology

Other Experience, Professional Memberships, Honors

(1973-75) Seeing Eye and NIH Special Res Fellowships; (1979-84) NIH Res Career Devel Award; (1980-83) Glau Program Planning Panel, NAEC-NEI; (1981-84) Phys & Pharm Section Comm., ARVO; (1982-85) Vis Sci A1 Study Section, NIH; (1985-86) Fogarty Senior Int Fellowship; (1985) Alcon Res. Inst. Award; Ed Boards (Curr Eye Res, 1980-94; J Glaucoma, 1991-98); (1983-95) Treatment Effects Monitoring/Adv Comm., Glaucoma Laser Trial, NEI; (1991-94) Nat Adv Eye Council, NEI; (1992-date) Sci Adv Board, Glaucoma Foundation (NY); (1993-98; 2002-07) Data & Safety Monitoring Committee, Early Management of Glaucoma Trial, NIH-NEI and Swedish Med. Res. Council; (1994-2001 (Chair, 1998-2001) Sci Adv Comm, Glaucoma Res. Foundation (SF); (1994-98) Scientific Advisory Board, Merck Institute; (1995-2000) Sci Adv Comm, Alcon Res. Institute;(1998-2010) Glaucoma Advisory Board, Pharmacia & Upjohn/Pfizer; (1997-2001) Sci Adv Board, Proneuron Biotechnology, Inc; (1997-2007) Sci Adv Comm, Gullstrand Foundation; 1998-2000 Res

Comm, Am Glau Soc; (2000) Mol Dev Cell Neurosci Working Group, CSR, NIH; (2003) Honorary doctorate from Uppsala University; (2004-date) Board of Directors, Glaucoma Foundation, NY; (2004) AIGS award best glaucoma paper of 2003; (2006) Helen Keller Fndn/Pfizer Ophthalmics Res Award in Glaucoma (Liu PI); (2006) ISER Bárány prize; (2007) ARVO Distinguished Service Award; 2009 honoree, Am Glau Society; (2009) The Glaucoma Foundation Robert Ritch Award for Excellence and Innovation in Glaucoma; (2010) WARF Named Professorship (Ernst H. Bárány Professor of Ocular Pharmacology); (2010) Editor, Adler's Physiology of the Eye; (2008-2012) Editor-in-Chief, IOVS; (2013) ARVO Joanne Angle Service Award; (2013) AAO Distinguished Service Award; (2017) ARVO Friedenwald Award.

Patents: Cytoskeletal Active Agents for Glaucoma Therapy; US Patent #s 5,798,380, 6,110,912, 6,586,425; 8/25/1998, 8/29/2000, 7/1/2003 (Expires 2/21/2016); Inventors: Paul L. Kaufman, Benjamin Geiger. Method for Treating Glaucoma (Caldesmon); Patent # PCT/US2005/005428; 2/18/2005 (Expires 2/18/2025); Inventors PL Kaufman, B Geiger, T Borrás, AD Bershadsky. Method for Treating Glaucoma (C3); Patent # PCT/US2005/005427; 2/18/2005 (Expires 2/18/2025); US Patent # 7,083,783; 08/01/2006; Inventors PL Kaufman, X Liu.

C. Contribution to Science

1) How the trabecular meshwork (TM) effects fluid outflow from the eye. Total iris removal and ciliary muscle disinsertion techniques were developed in live non-human primates to distinguish outflow facility responses due to iris or ciliary muscle contraction from those due to direct effects of a drug on the TM. Removing the iris had no effect on the large and acute facility-increasing action of pilocarpine, whereas disinserting the ciliary muscle from its attachment to the scleral spur and TM completely abolished the effect. Neither the iris nor the ciliary muscle was involved in epinephrine's outflow facility increasing effect, indicating that epinephrine's effect was directly on the TM. cAMP delivered intracamerally was also effective, whereas 5'-AMP was not, consistent with a b-adrenergic pathway. Disrupting the actin cytoskeleton with intracameral cytochalasin B or D dramatically increased outflow facility, subthreshold doses of epinephrine and cytochalasin B were facility-effective and the potentiation was dose-dependent throughout the subthreshold range for each drug. The actin filament stabilizer phalloidin at least partly inhibited epinephrine's facility-increasing effect. Thus, there was a b-adrenergic regulation of the contractile machinery of the TM cells and of the TM as a whole. Rho kinase / myosin light chain kinase inhibitors that targeted actomyosin contractility, and marine macrolides such as latrunculins that primarily targeted actin filament assembly, increased facility in live monkeys and humans. Intracameral injection of nitric oxide (NO) donating compounds or cGMP increased outflow facility in the live monkey, identifying another signaling pathway by which mechanical and perhaps other perturbations of the TM (e.g., distension caused by small alterations of IOP) are translated into the cytoskeletal alterations that produce homeostatic compensatory alterations of outflow facility to maintain IOP at some "preset" target level. RK inhibitors and an NO-donating compound have reached phase 3 clinical trials for glaucoma therapy. In essence, I opened and developed these entire fields over a generation of work that has been of critical importance in understanding the regulation of IOP, the pathophysiology of glaucoma, and the development of new glaucoma medications.

Refs:

a) Kaufman PL, Bárány EH: Loss of acute pilocarpine effect on outflow facility following surgical disinsertion and retrodisplacement of the ciliary muscle from the scleral spur in the Cynomolgus monkey. Invest Ophthalmol 15:793-807, 1976.
b) Robinson JC, Kaufman PL: Phalloidin inhibits epinephrine's and cytochalasin B's facilitation of aqueous outflow. Arch Ophthalmol 112:1610-1613, 1994.
c) Tian B, Kaufman PL, Volberg T, Gabelt BT, Geiger B: H-7 disrupts the actin cytoskeleton and increases outflow facility. Arch Ophthalmol 116:633-643, 1998.
d) Heyne GW, Kiland JA, Kaufman PL, Gabelt BT: Effect of nitric oxide on anterior segment physiology in monkeys. Invest Ophthalmol Vis Sci 54:5103-5110, 2013. PMC3729238.

2) Uveoscleral outflow (Fu), Ciliary Muscle ECM regulation of Fu, rationale for FU, FU as a lymphatic pathway
The uveoscleral outflow pathway (through the ciliary muscle, choroid and sclera) in primates had been discovered and partially characterized by Anders Bill in the 1960s, but neither its function nor its "regulators" were understood. In the 1980s, when it became apparent that PGF2a was a potent ocular hypotensive agent in primates and in man, much effort was spent trying to determine its mechanism of action. We demonstrated

that the drug dramatically enhanced uveoscleral outflow in non-human primates by upregulating MMP synthesis and release, with consequent remodeling of the extracellular matrix, in the ciliary muscle. Further, iatrogenically induced ocular inflammation had precisely the same effect, presumably mediated by release of PGF2α, and thus establishing the uveoscleral pathway as a back-up aqueous outflow system that could "turned up" when needed to protect the eye from severe ocular hypertension when the trabecular meshwork pathway was inflamed or obstructed by inflammatory debris, and to remove extravasated protein from the eye. This latter function mimicked a lymphatic system, and in essence predicted the subsequent discovery by others of a lymphatic pathway within the ciliary muscle. Our work greatly facilitated the development of PGF2α analogues into the most commonly prescribed glaucoma medication world-wide.

Refs:
a) Crawford K, Kaufman PL: Pilocarpine antagonizes prostaglandin induced ocular hypotension in monkeys: Evidence for enhancement of uveoscleral outflow by prostaglandin. Arch Ophthalmol 105:1112-1116, 1987.
b) Gabelt BT, Kaufman PL: Prostaglandin increases uveoscleral outflow in the Cynomolgus monkey. Exp Eye Res 49:389-402, 1989.
c) Gaton DD, Sagara T, Lindsey JD, Gabelt BT, Kaufman PL, Weinreb RN: Increased matrix metalloproteinases 1, 2, and 3 in the monkey uveoscleral outflow pathway following topical prostaglandin F isopropyl ester treatment. Arch Ophthalmol 119:1165-1170, 2001.
d) Sagara T, Gaton DD, Lindsey JD, Gabelt BT, Kaufman PL, Weinreb RN: Collagen type I is reduced in the ciliary muscle of inflamed monkey eyes. Invest Ophthalmol Vis Sci 40:2568-2576, 1999.

3) Gene transfer to the TM/SC/CM. More recently, we have concentrated on bypassing the patient as part of the delivery system via a gene transfer approach targeting the same pathways, to avoid patient noncompliance issues. We accomplished the first successful transfer and expression of a foreign gene into glaucoma-relevant tissues of the live primate eye, specifically transducing the TM, nonpigmented ciliary epithelium, retinal ganglion cells, and also the retinal pigment epithelium, with a β-gal gene HSV construct. Adenoviral vectors encoding a cDNA for either caldesmon (a protein which physiologically uncouples actin from myosin) or the C3 exotoxin from Clostridium (which inhibits the Rho cascade) dramatically increase outflow facility in the monkey organ cultured anterior segment. FIV or scAAV vectors injected into the anterior chamber will transduce GFP into the TM in live monkeys, with strong clinically visible GFP expression for at least 2 years, with only a mild transient inflammatory reaction at the outset. Lentiviral vectors will transduce the TM of the live monkey over 360 degrees for at least several months following a single injection into Schlemm's canal, with no clinically apparent inflammatory reaction. However, the inability of any vectors thus far to transduce a functional cytoskeletal gene into the TM of live monkeys has been limiting. We are investigating the basis and workarounds for this phenomenon. Recently, lentiviral vector delivery of the prostaglandin F synthase gene to the anterior segment of the live monkey eye produced a 5-month reduction in IOP, presumably by increasing uveoscleral outflow in the same manner as the small molecule PGF2a analogues. This was the first instance where a functional gene was shown to have an effect on IOP in the live primate. These studies opened up new approaches to understanding basic physiologic mechanisms and devising new therapeutic approaches relevant to glaucoma.

Refs:
a) Barraza RA, Rasmussen CA, Loewen N, Cameron JD, Gabelt BT, Teo W-L, Kaufman PL, Poeschla EM: Prolonged transgene expression with lentiviral vectors in the aqueous humor outflow pathway of non-human primates. Human Gene Ther 20:191-200, 2009. PMC3726241
b) Buie LK, Rasmussen CA, Porterfield EC, Ramgolam VS, Choe VW, Markovic-Plese S, Samulski RJ, Kaufman PL, Borrás, T: Self-complementary AAV virus (scAAV) safe and long-term gene transfer in the trabecular meshwork of living rats and monkeys. Invest Ophthalmol Vis Sci 51:236-248, 2010. PMC2869048
c) Aktas Z, Tian B, McDonald J, Yamamoto R, Larsen C, Kiland JA, Kaufman P, Rasmussen CA: Application of canalopasty in glaucoma gene therapy: where are we? J Ocular Pharm Ther 30:277-282, 2014. PMC3991989
d) Lee ES, Rasmussen CA, Filla MS, Slauson SR, Peters DM, Kaufman PL, Gabelt BT, Brandt CR: Prospects for lentiviral vector mediated prostaglandin F synthase gene delivery in monkey eyes *in vivo*. Curr Eye Res 39:859-870, 2014. PMC4134385

4) Presbyopia. Presbyopia, the age-related loss of accommodation (the ability to focus on near objects), is the world's most common ocular affliction. Age-related loss of lenticular deformability was long regarded as "explaining" presbyopia, and as the sole factor/target in designing accommodating intraocular lenses (AIOLs). However, we have shown that: rhesus monkeys develop presbyopia on essentially the same time scale relative to life span as humans; ciliary muscle mobility is restricted by progressively inelastic posterior attachments; ciliary muscle contractility is maintained throughout life but the posterior restriction makes the contraction progressively isometric; the restriction can be partly alleviated by enzymatic lysis of the posterior (intermediate) vitreous zonule with resulting increased mobility of the contracting ciliary muscle and the lens; the zonular apparatus is vastly more complex than previously thought; there is a highly complex sensori-motor regulation of focus that depends on different parts of the ciliary muscle and zonular apparatus as intermediaries between the retina and the lens; the ability to stimulate ciliary muscle contraction via a mid-brain electrode, allowing movement of all parts of the accommodative apparatus to be recorded and analyzed in real time, is critical in unraveling the physiology and pathophysiology of primate accommodation; high resolution ultrasound biomicroscopy (UBM) enables these analyses and insights; the movement at the ora serrata and more posteriorly through the choroid all the way back to the optic nerve head may provide insights into the pathophysiology of glaucomatous optic neuropathy; the in vivo imaging has been remarkably predictive of structural findings by scanning electron microscopy; these same changes apply to the human and non-human primate accommodative apparatus and their aging; the new findings may explain the poor performance and limited accommodative amplitude provided by current AIOLs, which assume that the ciliary muscle and zonular movements necessary for lens movement and deformation are equal to those in the young eye. AIOL designs are now beginning to take the reduced mobility into account and incorporating compensatory strategies.

Refs:
a) Neider MW, Crawford K, Kaufman PL, Bito LZ: *In vivo* videography of the rhesus monkey accommodative apparatus. Age-related loss of ciliary muscle response to central stimulation. Arch Ophthalmol 108:69-74,1990.
b) Tamm E, Croft MA, Jungkunz W, Lütjen-Drecoll E, Kaufman PL: Age-related loss of ciliary muscle mobility in the rhesus monkey. Role of the choroid. Arch Ophthalmol 110:871-876, 1992.
c) Lütjen-Drecoll E, Kaufman PL, Wasielewski R, Ting-Li L, Croft MA: Morphology and accommodative function of the vitreous zonule in human and monkey eyes. Invest Ophthalmol Vis Sci 51:1554-1564, 2010. PMC2829378
d) Croft MA, McDonald JP, Katz A, Lin T-L, Lütjen-Drecoll E, Kaufman PL: Extralenticular and lenticular aspects of accommodation and presbyopia in human vs. monkey eyes. Invest Ophthalmol Vis Sci 54:5035-5048, 2013. PMC3726241

List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/paul.kaufman.2/bibliography/40355214/public/?sort=date&direction=ascending.

D. Research Support.

ACTIVE

Foundation Fighting Blindness, Gund-Harrington Initiative 8/1/16 to 7/21/19
Bioengineering Micro-Patterned Scaffolds for Human Pluripotent Stem Cell-Based Photoreceptor Replacement Therapies
The grant is aimed at developing a human pluripotent stem cell-based therapeutic for photoreceptor replacement to treat a broad range of inherited outer retinal degenerative diseases.
Kaufman laboratory allocated $200,000 for milestone #3, which runs in years 2 to 3 of the grant.
Gamm (PI) Kaufman (co-PI)

NIH/NEI 1R01EY02359 01/01/16-12/31/19
Extralenticular aspects of accommodation and presbyopia
Identifying and quantifying the roles played by the anterior and posterior attachments of the ciliary muscle, choroid and zonules in accommodative function and its aging
Role: PI

NIH/NEI P30 EY016665 (Brandt) 07/01/05-08/31/21
Core grant for vision research

The major goal of this proposal is to provide funding for four core services for the Visual Sciences Community on Campus: 1) Gene Therapy/Quantitative Molecular Biology 2) Pathology and *In vivo* Imaging 3) Animal and Eye Organ Culture and 4) Biostatistics.
Role: Director of Animal and Organ Culture Core

Stein Innovation Award
Research to Prevent Blindness (PI: Kaufman) 08/01/15 – 12/31/18
Develop viral vectors with therapeutic proteins attached and investigate delivery methods for them as a novel therapeutic approach for glaucoma
Role: PI

Stein Innovation Award 1/1/17–7/30/19 1.0 calendar
Research to Prevent Blindness (PI: Hongrui)
Develop sensors to place in that eye to monitor pressure. ($20,212 total)
Overlap: None

Lions Eye Bank of Wisconsin Award 7/1/17–6/30/18 0.1 calendar
Lions Eye Bank Research Award (PI: Kaufman) ($50,000 total)
Overlap: None

NIH/NEI 01EY027752 (Brandt) 4/1/17-3/31/22 0.6 calendar
Microbial actin disruptors for glaucoma gene therapy $290,137
The overall goal of this project is to carry out a side-by-side comparison of several microbial actin-disrupting proteins using an FIV based viral vector system to determine the optimal protein or proteins for glaucoma gene therapy. We will clone these genes into a FIV based vector and quantify their ability to disrupt actin filaments in cultured trabecular meshwork cells and to increase outflow facility in our monkey eye organ culture system.

Pending
MSN206194 (PI: Piwnica-Worms) 10/01/18-10/31/21 0.6 calendar
MD Anderson Cancer Center/NIH $150,000 total direct costs per year
Membrane Permeant Peptides for Imaging Cell Function
Investigations into developed a probe for detecting apoptosis (programed cell death) in retinal ganglion cells

Pending
Partnerships for Innovation (PI:Kaufman) 08/1/18-07/31/21 0.3 calendar
National Science Foundation $750,000
Advancing Glaucoma in the 21st Century
Overlap:None