John S. Penn, Ph.D.

Phyllis G. and William B. Snyder Endowed Professor
Vice Chairman
Department of Ophthalmology and Visual Sciences
Office: MCN B3307

Associate Dean for Faculty Affairs
Office: Light Hall 331

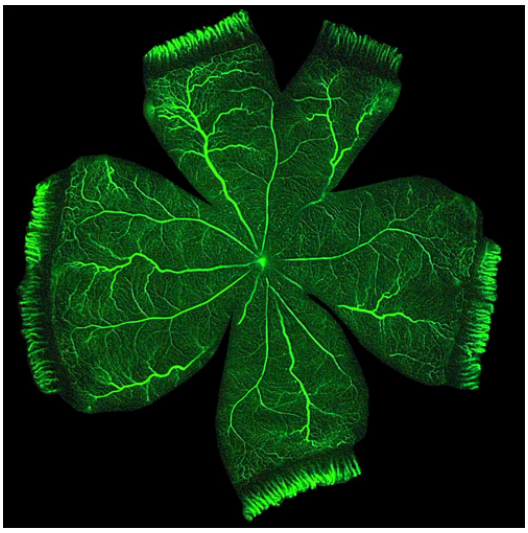
Professor, **Cell & Developmental Biology**, **Molecular Physiology & Biophysics**, Medical Education & Administration

Preceptor, Graduate Programs in **Pharmacology** and **Neuroscience**

PhD 1984, Kasha Institute of Molecular Biophysics, Florida State University

Penn Lab Website
email: john.s.penn@vumc.org or john.penn@vanderbilt.edu
phone: 615.936.1456

Research Interests



This image illustrates the retinal vasculature of a 20-day old rat using isolectin staining. The method allows for high resolution study of vascular architecture.

The large majority of irreversible blindness in the US is caused by pathology of the blood vessels of the eye. Penn's long-standing interest is in the molecular basis of retinal vascular disease. The over-arching goal of his research is to characterize the processes involved in retinal vascular inflammation and angiogenesis, and to begin to develop preventive strategies based on understanding gained from *in vitro* and *in vivo* studies. The Penn lab has the capability to isolate and culture a variety of primary cells from retinal tissue of several species, including retinal vascular endothelial cells, choroidal endothelial cells, retinal Müller glia, retinal pericytes, retinal microglia and retinal pigment epithelial cells – all of which are involved in vascular diseases of the retina. In addition, the lab uses a battery of *in vivo* models of vascular diseases of the eye including rodent models of retinopathy of prematurity, neovascular age-related degeneration and diabetic retinopathy. Using these *in vitro* and *in vivo* tools, Penn's research program focuses on pro-inflammatory and pro-angiogenic molecular signaling in the retina. In his research, Penn places an emphasis on both drug target identification and on development of novel pharmaco-therapeutics and methods of drug delivery to the eye.

Penn has been continuously funded by the National Eye Institute of NIH for 33 years. He currently serves on the advisory boards of three prominent foundations supporting eye research, and he is President of the International Society for Eye Research. Penn's lab currently holds 18 contracts with pharmaceutical companies to develop novel drugs for eye diseases.

NFAT and retinal vascular homeostasis: The Penn lab currently has multiple projects directed at understanding the role of the transcription factor, NFAT, in diabetic retinopathy pathogenesis. First, we are investigating NFAT's regulation of extracellular matrix expression in the development of basement membrane thickening – a hallmark of diabetic retinopathy. Second, we are characterizing the role of NFAT in the response of photoreceptors to diabetes-relevant stimuli. Finally, we are determining NFAT isoform specificity in early pathogenic events related to retinal cytokine induction under diabetic conditions.

Epoxygenated lipids and their products in retinal vascular inflammation: Epoxide lipids generated by Cytochrome P450 epoxygenases are anti-inflammatory, but their levels are limited by the soluble epoxide hydrolase enzyme. We are testing the hypothesis that epoxide levels are decreased in the diabetic retina due to altered expression of the enzymes that regulate them, and therefore elevating their levels would be beneficial for the early treatment of diabetic retinopathy. Similarly, the lipid epoxide-derived endocannabinoids that are selective for cannabinoid receptor 2 (CB2) binding are also potently anti-inflammatory. We are characterizing their roles in diabetic retinopathy and the efficacy associated with elevating their endogenous levels.

Novel biomarker imaging and drug delivery methods: The properties of the eye allow for unique opportunities to image biomarkers *in vivo.* We are designing novel RNA-based molecular beacons and contrast agents to better understand early disease processes, and as a first step in developing targeted strategies for delivery of novel therapeutic agents.

Available Projects

- Characterize the specific mechanisms by which NFAT-c2 exerts its anti-inflammatory bioactivity in retinal disease
- Characterize the efficacy and mechanism of action of endocannabinoids in inflammatory retinal disease
- Define the role of photoreceptors in promoting vascular inflammation in the diabetic retina
- Determine the utility of hypoxia probes RNA-based molecular beacons for ophthalmic use

Publications

Uddin, M.I., Jayagopal, A., Wong, A., McCollum, G.W., Wright, D.W. and **Penn, J.S.** (2018) Real-time imaging of VCAM-1 mRNA in TNF-α activated retinal microvascular endothelial cells using antisense hairpin-DNA functionalized gold nanoparticles. *Nanomed.* 14(1):63-71.

Capozzi, M.E. and **Penn, J.S.** (2018) Palmitic acid induces Müller cell inflammation that is potentiated by co-treatment with glucose. *Nature Sci Rep.* 2018 Apr 3;8(1):5459.

Uddin, M.I., Kilburn, T.C., Yang, R., McCollum, G.W., Wright, D.W. and **Penn, J.S.** (2018) Targeted imaging of VCAM-1 mRNA in a mouse model of laser-induced choroidal neovascularization using antisense hairpin DNA-functionalized gold nanoparticles. *ACS Mol Pharm.* 3;15(12):5514-5520.

Cao, J., Yang, R., Smith, T.E., Evans, S., McCollum, G.W., Pomerantz, S.C., Petley, T., Harris, I.R. and **Penn, J.S.** (2019) Human umbilical tissue-derived cells secrete soluble VEGFR1 and inhibit choroidal neovascularization. *Mol Ther Meth Clin Dev.* 2019 May 22(14):37-46.

Capozzi, M.E., Savage, S.R., McCollum, G.W., Hammer, S.S., Yang, R., Bretz, C.A. and **Penn, J.S.** (2020) Peroxisome proliferator-activated receptor-β/δ mediates retinal leukostasis via CCL8 and CXCL10. *Exp Eye Res.* 2020 Jan;190:107885.