Stanford

Douglas Vollrath

Associate Professor of Genetics and, by courtesy, of Ophthalmology

CONTACT INFORMATION

- **Alternate Contact**

  Ashley Tzu En Chen - Administrative Associate

  Email tzuenc@stanford.edu

Bio

ACADEMIC APPOINTMENTS

- Associate Professor, Genetics
- Associate Professor (By courtesy), Ophthalmology
- Member, Bio-X
- Member, Wu Tsai Neurosciences Institute

ADMINISTRATIVE APPOINTMENTS

- Regular Member, NIH Biology of the Visual System Study Section, (2017-2021)
- Board of Scientific Counselors, National Eye Institute-NIH, (2008-2013)

BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS

- Scientific Advisory Board, Foundation Fighting Blindness (2009 - present)

PROFESSIONAL EDUCATION

- BS, University of Wisconsin-Madison , Biochemistry (1981)
- PhD, Stanford University , Biochemistry (1988)
- MD, Stanford University , Medicine (1989)

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Work in the Vollrath laboratory is focused on understanding processes in the eye that are relevant to human health and disease. The eye is an organ particularly amenable to genetic analysis because its accessibility facilitates detection and characterization of a variety of disease states, yet such diseases rarely impair life span or fertility. We frequently start with genes known to be important in the eye because of their association with ocular disease phenotypes, and then investigate molecular mechanisms by uncovering pathways and processes relevant to normal eye function and pathogenesis.

RPE mitochondrial dysfunction is thought to play a causative role in retinal degenerative diseases such as mitochondrial retinopathy and age-related macular degeneration. As a test of this hypothesis, we generated mice with an RPE-selective postnatal loss of mitochondrial oxidative phosphorylation (OXPHOS). OXPHOS-deficient RPE cells are surprisingly long-lived, but lose critical epithelial characteristics through cellular dedifferentiation and, later, an epithelial to mesenchymal-like transition. OXPHOS-deficient RPE cells initiate a stress response that includes dependence upon the HGF/c-Met pathway, upregulation of aerobic glycolysis, activation of the mTOR signaling pathway, and cellular hypertrophy. Activation of mTOR and subsequent dedifferentiation can also be triggered by acute chemical oxidative damage to the RPE in vivo. For both chronic metabolic and acute oxidative RPE stress, the consequences for adjacent photoreceptors are profoundly negative, resulting in a gradual or rapid (respectively) retinal degeneration. Strikingly, treatment of animals with the mTOR inhibitor, rapamycin, blunts RPE dedifferentiation and hypertrophy and preserves photoreceptor numbers and function for both stressors. We would like to understand the mechanism of mTOR-mediated RPE dedifferentiation and determine whether this new in vivo RPE stress response is activated in human retinal disease.

Phagocytosis is an example of a basic process that we study. Every morning in mammalian eyes, the distal portion of the light sensing outer segments of photoreceptors are phagocytized by adjacent cells of the retinal pigment epithelium (RPE). Phagocytosis is balanced by new synthesis at the proximal end of the outer segment. Together, these two processes lead to constant turnover of outer segments and serve to repair light- and oxygen-induced damage. The daily ‘big breakfast’ of outer segment material, summed over the life of an animal, distinguishes the post-mitotic RPE cell as the most phagocytic cell in the body. Photoreceptor degeneration in mutant rats and mice with defective RPE phagocytosis demonstrates that this process is essential for the normal functioning of the mammalian retina. By genetic analysis of these mutant rodents, we identified the receptor tyrosine kinase, MERTK, as a critical part of the phagocytic mechanism. We also identified mutations in the human MERTK gene in individuals with a retinal degenerative disease known as retinitis pigmentosa. We have elaborated our understanding of the mechanism of phagocytosis by demonstrating that MERTK acts locally, at the site of phagocytosis, to promote ingestion of bound outer segment tips. MERTK does so by triggering a striking redistribution of myosin II from the cell periphery to sites of ingestion. We are continuing to investigate the mechanism of RPE phagocytosis with an emphasis on identifying new protein components and understanding its circadian regulation.

Teaching

COURSES

2019-20

- Advanced Genetics: GENE 205 (Win)
- Genetics and Developmental Biology Training Camp: DBIO 200, GENE 200 (Aut)

2018-19

- Advanced Genetics: GENE 205 (Win)
- Genetics and Developmental Biology Training Camp: DBIO 200, GENE 200 (Aut)

2017-18

- Advanced Genetics: GENE 205 (Win)
- Genetics and Developmental Biology Training Camp: DBIO 200, GENE 200 (Aut)

2016-17

- Genetics and Developmental Biology Training Camp: DBIO 200, GENE 200 (Aut)

STANFORD ADVISEES

Doctoral Dissertation Reader (AC)

Nikki Teran

Postdoctoral Faculty Sponsor

Ming Chen

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Genetics (Phd Program)

Publications

PUBLICATIONS

- **Highly Differentiated Human Fetal RPE Cultures Are Resistant to the Accumulation and Toxicity of Lipofuscin-Like Material.** *Investigative ophthalmology & visual science*
  Zhang, Q., Presswalla, F., Calton, M., Charniga, C., Stern, J., Temple, S., Vollrath, D., Zacks, D. N., Ali, R. R., Thompson, D. A., Miller, J. M.
  2019; 60 (10): 3468–79

- **Genetic analyses of human fetal retinal pigment epithelium gene expression suggest ocular disease mechanisms.** *Communications biology*
  Liu, B., Calton, M. A., Abell, N. S., Benchorin, G., Gloudemans, M. J., Chen, M., Hu, J., Li, X., Balliu, B., Bok, D., Montgomery, S. B., Vollrath, D.
  2019; 2: 186

- **Abnormal mTORC1 signaling leads to retinal pigment epithelium degeneration** *THERANOSTICS*
  Huang, J., Gu, S., Chen, M., Zhang, S., Jiang, Z., Chen, X., Jiang, C., Liu, G., Radu, R. A., Sun, X., Vollrath, D., Du, J., Yan, et al
  2019; 9 (4): 1170–80

- **Method for measuring extracellular flux from intact polarized epithelial monolayers** *MOLECULAR VISION*
  Calton, M. A., Beaulieu, M. O., Benchorin, G., Vollrath, D.
  2018; 24: 425–33

- **Assessment of Murine Retinal Function by Electroretinography** *BIO-PROTOCOL*
  Benchorin, G., Calton, M. A., Beaulieu, M. O., Vollrath, D.
  2017; 7 (7)

- **Treatment of retinitis pigmentosa due to MERTK mutations by ocular subretinal injection of adeno-associated virus gene vector: results of a phase I trial.** *Human genetics*
  Ghazi, N. G., Abboud, E. B., Nowilaty, S. R., Alkuraya, H., Alhommadi, A., Cai, H., Hou, R., Deng, W., Boye, S. L., Almaghamsi, A., Al Saikhan, F., Al-Dhibi, H., Birch, et al
  2016; 135 (3): 327-343

- **Gene Therapy for MERTK-Associated Retinal Degenerations.** *Advances in experimental medicine and biology*
  LaVail, M. M., Yasumura, D., Matthes, M. T., Yang, H., Hauswirth, W. W., Deng, W., Vollrath, D.
  2016; 854: 487-493

- **The mTOR Kinase Inhibitor INK128 Blunts Migration of Cultured Retinal Pigment Epithelial Cells.** *Advances in experimental medicine and biology*
  Calton, M. A., Vollrath, D.
  2016; 854: 709-715

- **Tyro3 Modulates Mertk-Associated Retinal Degeneration.** *PLoS genetics*
  Vollrath, D., Yasumura, D., Benchorin, G., Matthes, M. T., Feng, W., Nguyen, N. M., Sedano, C. D., Calton, M. A., LaVail, M. M.
  2015; 11 (12): e1005723

- **Intrastriatal Transplantation of Retinal Pigment Epithelial Cells for the Treatment of Parkinson Disease: In Vivo Longitudinal Molecular Imaging with (18)F-P3BZA PET/CT.** *Radiology*
  Bu, L., Li, R., Liu, H., Feng, W., Xiong, X., Zhao, H., Vollrath, D., Shen, B., Cheng, Z.
  2014; 272 (1): 174-183

- **PRPF4 mutations cause autosomal dominant retinitis pigmentosa** *HUMAN MOLECULAR GENETICS*
  Chen, X., Liu, Y., Sheng, X., Tam, P. O., Zhao, K., Chen, X., Rong, W., Liu, Y., Liu, X., Pan, X., Chen, L. J., Zhao, Q., Vollrath, et al
  2014; 23 (11): 2926-2939

- **A Novel Homozygous BEST1 Mutation Correlates with Complex Ocular Phenotypes** *OPHTHALMOLOGY*
  Sheng, X., Chen, X., Zhao, K., Liu, Y., Vollrath, D., Zhao, C.

2013; 120 (7): 1511-+

- **Targeted Sequencing of 179 Genes Associated with Hereditary Retinal Dystrophies and 10 Candidate Genes Identifies Novel and Known Mutations in Patients with Various Retinal Diseases** *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*
  Chen, X., Zhao, K., Sheng, X., Li, Y., Gao, X., Zhang, X., Kang, X., Pan, X., Liu, Y., Jiang, C., Shi, H., Chen, X., Rong, et al
  2013; 54 (3): 2186-2197
- **Amyloid Fibril Formation by the Glaucoma-Associated Olfactomedin Domain of Myocilin** *JOURNAL OF MOLECULAR BIOLOGY*
  Orwig, S. D., Perry, C. W., Kim, L. Y., Turnage, K. C., Zhang, R., Vollrath, D., Schmidt-Krey, I., Lieberman, R. L.
  2012; 421 (2-3): 242-255
- **Tyrosine-Mutant AAV8 Delivery of Human MERTK Provides Long-Term Retinal Preservation in RCS Rats** *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*
  Deng, W., Dinculescu, A., Li, Q., Boye, S. L., Li, J., Gorbatyuk, M. S., Pang, J., Chiodo, V. A., Matthes, M. T., Yasumura, D., Liu, L., Alkuraya, F. S., Zhang, et al
  2012; 53 (4): 1895-1904
- **An ENU-Induced Mutation in the Mertk Gene (Mertk(nmf12)) Leads to a Slow Form of Retinal Degeneration** *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*
  Maddox, D. M., Hicks, W. L., Vollrath, D., LaVail, M. M., Naggert, J. K., Nishina, P. M.
  2011; 52 (7): 4703-4709
- **mTOR pathway activation in age-related retinal disease** *AGING-US*
  Zhao, C., Vollrath, D.
  2011; 3 (4): 346-347
- **Generation of Cre Transgenic Mice with Postnatal RPE-Specific Ocular Expression** *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*
  Iacovelli, J., Zhao, C., Wolkow, N., Veldman, P., Gollomp, K., Ojha, P., Lukinova, N., King, A., Feiner, L., Esumi, N., Zack, D. J., Pierce, E. A., Vollrath, et al
  2011; 52 (3): 1378-1383
- **mTOR-mediated dedifferentiation of the retinal pigment epithelium initiates photoreceptor degeneration in mice** *JOURNAL OF CLINICAL INVESTIGATION*
  Zhao, C., Yasumura, D., Li, X., Matthes, M., Lloyd, M., Nielsen, G., Ahern, K., Snyder, M., Bok, D., Dunaief, J. L., LaVail, M. M., Vollrath, D.
  2011; 121 (1): 369-383
- **Focus on Molecules: MERTK** *EXPERIMENTAL EYE RESEARCH*
  Strick, D. J., Vollrath, D.
  2010; 91 (6): 786-787
- **Candidate genes for chromosomes 6 and 10 quantitative trait loci for age-related retinal degeneration in mice** *MOLECULAR VISION*
  Ogando, D. G., Dahlquist, K. D., Alizadeh, M., Kunchithapautham, K., Li, J., Yu, N., LaVail, M. M., Rohrer, B., Vollrath, D., Danciger, M.
  2010; 16 (111-13): 1004-1018
- **Rescue of Glaucoma-Causing Mutant Myocilin Thermal Stability by Chemical Chaperones** *ACS CHEMICAL BIOLOGY*
  Burns, J. N., Orwig, S. D., Harris, J. L., Watkins, J. D., Vollrath, D., Lieberman, R. L.
  2010; 5 (5): 477-487
- **Mertk Drives Myosin II Redistribution during Retinal Pigment Epithelial Phagocytosis** *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*
  Strick, D. J., Feng, W., Vollrath, D.
  2009; 50 (5): 2427-2435
- **Rapid and stable knockdown of an endogenous gene in retinal pigment epithelium** *HUMAN GENE THERAPY*
  Paskowitz, D. M., Greenberg, K. P., Yasumura, D., Grimm, D., Yang, H., Duncan, J. L., Kay, M. A., LaVail, M. M., Flannery, J. G., Vollrath, D.
  2007; 18 (10): 871-880
- **A novel His158Arg mutation in TIMP3 causes a late-onset form of Sorsby fundus dystrophy** *AMERICAN JOURNAL OF OPHTHALMOLOGY*
  Lin, R. J., Blumenkranz, M. S., Binkley, J., Wu, K., Vollrath, D.
  2006; 142 (5): 839-848
- **Temperature sensitive secretion of mutant myocilins** *EXPERIMENTAL EYE RESEARCH*
  Vollrath, D., Liu, Y.
  2006; 82 (6): 1030-1036

- **phi C31 integrase confers genomic integration and long-term transgene expression in rat retina** *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*
  Chalberg, T. W., Genise, H. L., Vollrath, D., Calos, M. P.
  2005; 46 (6): 2140-2146

- **Reversal of mutant myocilin non-secretion and cell killing: implications for glaucoma** *HUMAN MOLECULAR GENETICS*
  Liu, Y. H., Vollrath, D.
  2004; 13 (11): 1193-1204

- **MERTK arginine-844-cysteine in a patient with severe rod-cone dystrophy: Loss of mutant protein function in transfected CeRs** *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*
  McHenry, C. L., Liu, Y. H., Feng, W., Nair, A. R., Feathers, K. L., Ding, X. L., Gal, A., Vollrath, D., Sieving, P. A., Thompson, D. A.
  2004; 45 (5): 1456-1463

- **An RCS-like retinal dystrophy phenotype in Mer knockout mice** *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*
  Duncan, J. L., LaVail, M. M., Yasumura, D., Matthes, M. T., Yang, H. D., Trautmann, N., Chappelow, A. V., Feng, W., Earp, H. S., Matsushima, G. K., Vollrath, D.
  2003; 44 (2): 826-838

- **Mertk triggers uptake of photoreceptor outer segments during phagocytosis by cultured retinal pigment epithelial cells** *JOURNAL OF BIOLOGICAL CHEMISTRY*
  Feng, W., Yasumura, D., Matthes, M. T., LaVail, M. M., Vollrath, D.
  2002; 277 (19): 17016-17022

- **Molecular and clinical evaluation of a patient hemizygous for TIGR/MYOC** *ARCHIVES OF OPHTHALMOLOGY*
  Wiggs, J. L., Vollrath, D.
  2001; 119 (11): 1674-1678

- **Correction of the retinal dystrophy phenotype of the RCS rat by viral gene transfer of Mertk** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Vollrath, D., Feng, W., Duncan, J. L., Yasumura, D., D'Cruz, P. M., Chappelow, A., Matthes, M. T., Kay, M. A., LaVail, M. M.
  2001; 98 (22): 12584-12589

- **Mutations in MERTK, the human orthologue of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa** *NATURE GENETICS*
  Gal, A., Li, Y., Thompson, D. A., Weir, J., Orth, U., Jacobson, S. G., Apfelstedt-Sylla, E., Vollrath, D.
  2000; 26 (3): 270-271

- **Age-dependent prevalence of mutations at the GLC1A locus in primary open-angle glaucoma** *AMERICAN JOURNAL OF OPHTHALMOLOGY*
  Shimizu, S., Lichter, P. R., Johnson, A. T., Zhou, Z. H., Higashi, M., Gottfredsdottir, M., Othman, M., Moroi, S. E., Rozsa, F. W., Schertzer, R. M., Clarke, M. S., SCHWARTZ, A. L., Downs, et al
  2000; 130 (2): 165-177

- **Mutation of the receptor tyrosine kinase gene Mertk in the retinal dystrophic RCS rat** *HUMAN MOLECULAR GENETICS*
  D'Cruz, P. M., Yasumura, D., Weir, J., Matthes, M. T., Abderrahim, H., LaVail, M. M., Vollrath, D.
  2000; 9 (4): 645-651

- **A cellular assay distinguishes normal and mutant TIGR/myocilin protein** *HUMAN MOLECULAR GENETICS*
  Zhou, Z. H., Vollrath, D.
  1999; 8 (12): 2221-2228

- **Characterization of the murine TIGR/myocilin gene** *MAMMALIAN GENOME*
  Abderrahim, H., Jaramillo-Babb, V. L., Zhou, Z. H., Vollrath, D.
  1998; 9 (8): 673-675

- **Loss-of-function mutations in the LIM-homeodomain gene, LMX1B, in nail-patella syndrome** *HUMAN MOLECULAR GENETICS*
  Vollrath, D., Jaramillo-Babb, V. L., Clough, M. V., McIntosh, I., Scott, K. M., Lichter, P. R., Richards, J. E.
  1998; 7 (7): 1091-1098

- **CONSTRUCTION OF HUMAN Y-CHROMOSOMAL HAPLOTYPES USING A NEW POLYMORPHIC A-TRANSITION TO G-TRANSITION** *HUMAN MOLECULAR GENETICS*
  Seielstad, M. T., Hebert, J. M., Lin, A. A., Underhill, P. A., Ibrahim, M., Vollrath, D., CAVALLISFORZA, L. L.

1994; 3 (12): 2159-2161

- **TANDEM ARRAY OF HUMAN VISUAL PIGMENT GENES AT XQ28** *SCIENCE*
  Vollrath, D., Nathans, J., Davis, R. W.
  1988; 240 (4859): 1669-1672

- **SEPARATION OF LARGE DNA-MOLECULES BY CONTOUR-CLAMPED HOMOGENEOUS ELECTRIC-FIELDS** *SCIENCE*
  Chu, G., Vollrath, D., Davis, R. W.
  1986; 234 (4783): 1582-1585