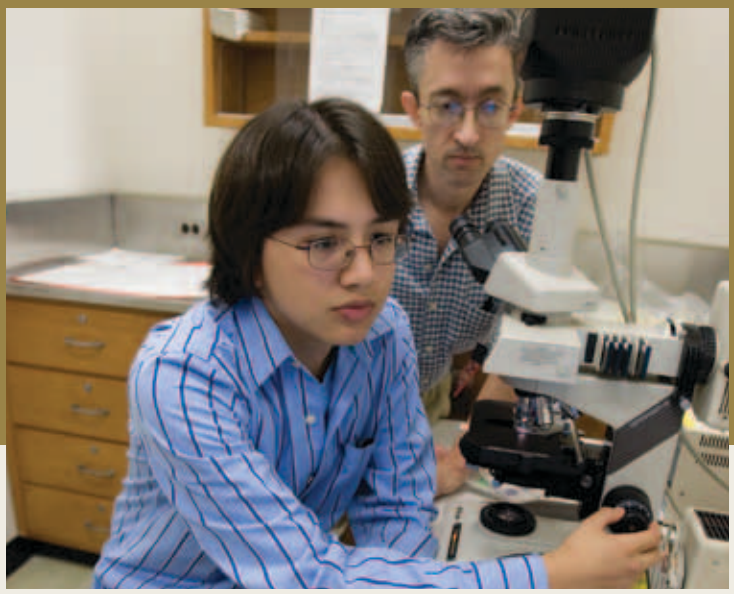
Kenneth Mitton

Associate Professor
Eye Research Institute



Regulating retinal development

Kenneth Mitton's laboratory investigates the biochemical events regulating genes in retinal development and disease, at the level of single genes, entire chromosomes and the genome.

According to Mitton, international genome sequencing projects show us that mammals have the same set of 26,000 genes. "I was fortunate to find the structure of one of these genes just before we entered the new century and the completion of the human genome sequence. Our genome encodes the protein building blocks required to construct our different cells and tissues," Mitton said. "These genes reside on our chromosomes written in a four-letter DNA base code named: A, C, G, and T. We can think of our genome as a 'human book,' with 3-billion characters (ACGT), telling 26,000 stories (genes), in 23 chapters (chromosomes). DNA is double stranded, with A pairing with T, and G pairing with C, on opposite strands. A copy of this 'best seller,' over 2 meters of DNA, resides in the nucleus of every cell."

Mitton's laboratory combines biochemical analysis and genome-wide bioinformatics analysis (computer based) for two major goals:

1) Finding new candidate genes to support clinical genetic diagnosis for more than 50 inherited retinal degenerative diseases. Researchers now know that the mouse has the same basic set of 26,000 genes as humans. Just as in humans, genes that become active during formation of the neural retina in the mouse make messenger RNA, produced by an enzymatic protein called RNA Polymerase-II. Using the sub-nano technology of DNA arrays, they can obtain all of the DNA regions that have the polymerase bound (active genes) and let them pair up with one of over five million DNA molecules synthesized on a DNA chip array. The molecules on the array are enough to map all of the control regions of 26,000 genes, which show researchers which genes are active and how their activity changes.

Using this method, Mitton and his colleagues have recently uncovered more than 700 gene activations as the neural retina completes development. In addition, more than 40 new candidate genes were uncovered for nine different retinal diseases, and the project is only halfway complete. They are also using this system to find alterations to gene expression in a new model of retinal disease in collaboration with Kim Drenser (Beaumont Hospital and the ERI) and a Swiss research group.

2) Analyzing genome-wide activation patterns in circulating blood cells, such as biomarkers, that can be developed into early warning medical tests for many diseases affecting fixed tissues such as atherosclerosis, various cancers, and AMD (age-related macular degeneration). Diseases and stresses that affect fixed tissues, even migraine attacks, have secondary effects on circulating white blood cells, altering their gene expression patterns.

Mitton and his coworkers have started pilot projects in collaboration with Beaumont Hospital's surgery department to use RNA-polymerase-II mapping to detect active genes in blood cells from patients with atherosclerosis and various cancers. This pilot development is almost complete, supported in part by a 2009 Beaumont - Oakland University Multidisciplinary Research Award, developing the processing methods for chip-on-chip analysis of blood cells. An initial genome-wide data set is expected in the near future. As for their retina projects, this new technology is expected to detect gene activations that escape expression microarray detection. These will form a source of novel biomarkers to develop safe clinical warning tests.

Representative Recent Publications

1. Simpanya MF, Wistow G, Gao J, David LL, Giblin FJ, Mitton KP. 2008. Expressed sequence tag analysis of guinea pig (Cavia porcellus) eye tissues for NEIBank. *Mol Vis* 14:2413-2427.

2. Mali RS, Peng GH, Zhang X, Dang L, Chen S, Mitton KP. 2008. FIZ1 is part of the regulatory protein complex on active photoreceptor-specific gene promoters in vivo. *BMC Mol Biol* 9:87.

3. Mali RS, Zhang X, Hoerauf W, Doyle D, Devitt J, Loffreda-Wren J, Mitton KP. 2007. FIZ1 is expressed during photoreceptor maturation, and synergizes with NRL and CRX at rod-specific promoters in vitro. *Exp Eye Res* 84:349-360.

4. Cheng H, Khanna H, Oh ECT, Hicks D, Mitton KP, Swaroop A. 2004. Photoreceptor-specific nuclear receptor NR2E3 functions as a transcriptional activator in rod photoreceptors. *Hum Mol Genet* 13:1563-1575.

5. Mitton KP, Swain PK, Khanna H, Dowd M, Apel IJ, Swaroop A. 2003. Interaction of retinal bZIP transcription factor NRL with Flt3-interacting zinc-finger protein Fiz1: possible role of Fiz1 as a transcriptional repressor. *Hum Mol Genet* 12:365-373.