Doctoral Dissertation Defense

DWANI D. PATEL

“The Development of Technologies for Early Intervention into Diabetic Retinopathy”

Thursday, May 20, 2021
9:00 am (CST)
Live Public Viewing:
https://mcw.hosted.panopto.com/Panopto/Pages/Viewer.aspx?id=5d62977b-a327-4bae-93c6-acf5011a053f

Committee in Charge:
Daniel M. Lipinski, MSc, DPhil (Advisor)
 John A. Corbett, PhD
 Joseph J. Carroll, PhD
 Iris S. Kassem, MD, PhD
 Thomas B. Connor, MD

Graduate School of Biomedical Sciences
Department of Cell Biology, Neurobiology, and Anatomy
Medical College of Wisconsin
GRADUATE STUDIES

Advanced Cell Biology
Techniques in Molecular Biology
Biology of Vision
Ethics and Integrity in Science
Research Ethics Discussion Series
Reading and Research
Cold Spring Harbor Laboratory, *Vision: A Platform for Linking Circuits, Perception and Behavior*
Dissertation
ABSTRACT

Diabetic retinopathy (DR) is a leading cause of blindness worldwide and affects over 7.7 million Americans today. Chronic hyperglycemia in diabetes contributes to dysfunction of microvascular endothelial cells (MVECs) and loss of retinal pericytes, resulting in irreversible damage to the small blood vessels that supply the retina. The long-term goal of this research is to develop technologies that enable the early diagnosis of DR and facilitate treatment in the pre-symptomatic stage of disease – before the onset of vision threatening complications.

The ability to monitor progression of retinal vascular diseases like DR in small animal models is often complicated by their failure to develop the end-stage complications which characterize the human phenotypes in disease. Interestingly, as micro-vascular dysfunction typically precedes the onset of retinal vascular and even some neurodegenerative diseases by decades, the ability to visualize and quantify hemodynamic changes (e.g. decreased flow or occlusion) in retinal vessels may serve as a useful diagnostic indicator of disease progression and as a therapeutic outcome measure in response to treatment. Nevertheless, the ability to precisely and accurately quantify retinal hemodynamics remains an unmet challenge in ophthalmic research. Firstly, we demonstrate the ability to modify a commercial fundus camera into a low-cost laser speckle contrast imaging (LSCI) system for contrast-free and non-invasive quantification of relative changes to retinal hemodynamics over a wide field-of-view in a rodent model. In the process, we also develop a custom and universal software for analyzing LSCI data.

We then describe the design and build of a custom LSCI system which can assess retinal vascular anatomy, quantify retinal hemodynamics, and measure physiological changes in response to retinal vascular dysfunction over a wide field-of-view and with high spatial and temporal resolution. The new system enables noncontact retinal LSCI which can generate reproducible, contrast-free maps of retinal blood flow at up to 590fps and under short exposure durations (>50µs). By applying this retinal LSCI system in vivo to study retinal anatomy and function in the context of laser-induced branch retinal vein occlusion (BRVO) and varied doses of volatile isoflurane anesthesia, we demonstrate that our retinal LSCI system may have broader applications for the diagnosis, study, and management of neurodegenerative conditions (i.e. mild cognitive impairment and Alzheimer’s disease) and systemic cardiovascular diseases (i.e. athero- and arteriosclerosis, coronary artery occlusion, and hypertension).

Finally, the ability to target MVECs and retinal pericytes for gene transfer may offer long-term solutions for restoring homeostasis in the retinal microvasculature and preventing disease progression. While recombinant adeno-associated viral (rAAV) vectors have been successfully used for mediating gene transfer to cells of the retina, their utility for targeting MVECs and pericytes has been limited by poor transduction efficiency. In subsequent projects, we apply strategies in rAAV capsid modification and a brute force library screening approach to isolate novel capsid mutant variants with greater tropism for MVECs and retinal pericytes. In doing so, we discuss challenges and alternative strategies in improving transduction of retinal MVECs and pericytes for the treatment of retinal vascular diseases.
CURRICULUM VITAE

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Education

Medical College of Wisconsin
Milwaukee, WI
Ph.D. student, Department of Cell Biology and Anatomy
Medical Scientist Training Program

Medical College of Wisconsin
Milwaukee, WI
M.D. candidate
Medical Scientist Training Program

University of Illinois at Urbana Champaign
Urbana, IL
B.S., Bioengineering with Honors
2011-2015

Research Experiences

Medical College of Wisconsin
Milwaukee, WI
Graduate Student, Advisor: Daniel M. Lipinski, MSc, DPhil
2017-Present
• Developing non-invasive and contrast free imaging techniques to quantify retinal hemodynamics over a wide field-of-view
• Identifying novel recombinant adeno-associated virus based vectors for gene delivery retinal microvascular endothelial cells and retinal pericytes

University of Illinois at Urbana Champaign
Urbana, IL
Undergraduate Student, Advisor: Rohit Bhargava, PhD
2011-2015
• Combing chemical imaging techniques such as surface-enhanced Raman spectroscopy with microscopy to study molecular dynamics in tumors and tumor microenvironment to enhance cancer diagnostics
Washington University in St. Louis  
St. Louis, MO

Amgen Scholars Program, Advisor: Alison Goate, DPhil  
2013-2014

- Understanding the molecular basis of Alzheimer’s disease to identify novel targets for therapy
- Determining the association between several susceptibility alleles identified through genome wide association studies and whole genome/exome sequencing with risk for late-onset Alzheimer’s disease

Publications


Invited Talks


Abstracts

Patel, D. Validating Laser Speckle Contrast Imaging as a Quantitative Tool for Measuring Retinal Vascular Function in Rodents. MCW Graduate School Symposium; 2019; Milwaukee, WI.

Patel, D. Validating Laser Speckle Contrast Imaging as a Quantitative Tool for Measuring Retinal Vascular Function in Rodents. 34th Annual MD/PHD National Conference; 2019; Copper Mountain, CO.
Patel, D. Validating Laser Speckle Contrast Imaging as a Quantitative Tool for Measuring Retinal Vascular Function in Rodents. ARVO Conference; 2019; Vancouver, BC.

Patel, D. Identification of Novel Retinal Pericyte-Targeting rAAV Vectors Through Directed Evolution. ASGCT Annual Meeting; 2018; Chicago, IL.

Patel, D. Short indel and G156S variants in CD33 show no association with Alzheimer’s Disease risk. Amgen Scholars Program Research Symposium; 2013; St. Louis, MO.

Honors
2020 David R. Pepperberg Travel Grant
2018 McPherson Eye Research Institute’s Vision Research Trainee Award
2015 Institutional Honors, University of Illinois at Urbana Champaign
2013 Amgen Scholar
2012 Engineering Travel Fellowship
2011-2015 Dean’s List, University of Illinois at Urbana-Champaign
2011-2012 Edmund J. James Scholar, University of Illinois at Urbana-Champaign

Professional Memberships
2018- Member, American Society of Gene & Cell Therapy
2019- Member, Association for Research in Vision and Ophthalmology

Extracurricular Activities
2015-2016 Saturday Clinic for the Uninsured, Student Volunteer
2015-2018 Greater Milwaukee Free Clinic, Student Volunteer
2017-2018 Greater Milwaukee Free Clinic, Schedule Coordinator
2016-2017 American Association of Physicians of Indian Origin MCW Chapter Treasurer
2017-2018 American Association of Physicians of Indian Origin MCW Chapter President
2018-2019 American Association of Physicians of Indian Origin – Milwaukee Chapter Board Member