Seeing in the Dark: Improving Treatment for Diabetic Retinopathy

Bruce Berkowitz
Depts. Anatomy/Cell Biology and Ophthalmology
Cellular and Clinical Neurobiology Program
Wayne State University
Problem

• Current clinical methods only detect structural damage

• Not optimal for monitoring treatment response or drug discovery

Solution

• Predict a patients’ response to therapy earlier than is currently possible
  – More rapidly develop and evaluate treatments
Dynamic Contrast Enhanced MRI (DCE-MRI): Blood-Retinal Barrier

Gad (590 Da) is a MRI contrast agent
DCE-MRI: Validation

Movie Loop
(Post – Pre)

Control  BRB Damage

Accurate

- Mimic retinopathy: Vascular permeability factor / vascular endothelial growth factor (VPF / VEGF)
Retinal Oxygenation Response ($\Delta P_{O_2}$)

O$_2$ is a MRI contrast agent.

Preretinal Vitreous: Reflects inner retinal oxygenation.
$\Delta PO_2$: Method and Validation

$\Delta PO_2$ Image (Post – Pre)

Vitreous Only
100 mm Hg

0 mm Hg

Accurate

Adult rat eye

Preretinal
Midvitreous

Electrode
MRI

$\Delta PO_2$ (mm Hg)

79 88
63 63
Experimental Diabetes: Rats, Mice

Before Histopathology

Histopathology

• Subnormal retinal $\Delta$PO$_2$
  – Early event associated with histopathology in diabetes
ΔPO$_2$: Early Biomarker of Treatment Efficacy

- Correction of early subnormal retinal ΔPO$_2$
- predicted therapeutic efficacy
Overview of On-Going Studies

• Basic science
  – Transgenic mice
  – Prevention / Intervention

• Clinical trials

• Cell signaling factors
  – Protein kinase C βII

• Inflammatory factors
  – Nitric oxide
  – Cyclooxidasenase

• Oxidative stress factors
  – Superoxide dismutase

• Vasoactive factors
  – Endothelin-1
Acknowledgements

Laboratory
• Robin Roberts
• Dr. Yasuki Ito
• Hongmei Luan
• Jamie Peysakhov

Collaborators
• Dr. Tim Kern
• Dr. Renu Kowluru
• Dr. Robert Frank
• Dr. Gary Trick
• Dr. Paul Tofts
• Robin Berkowitz

NIH, JDRF, ADA, RPB, Merck, Pfizer

www.med.wayne.edu/anatomy/berkowitz