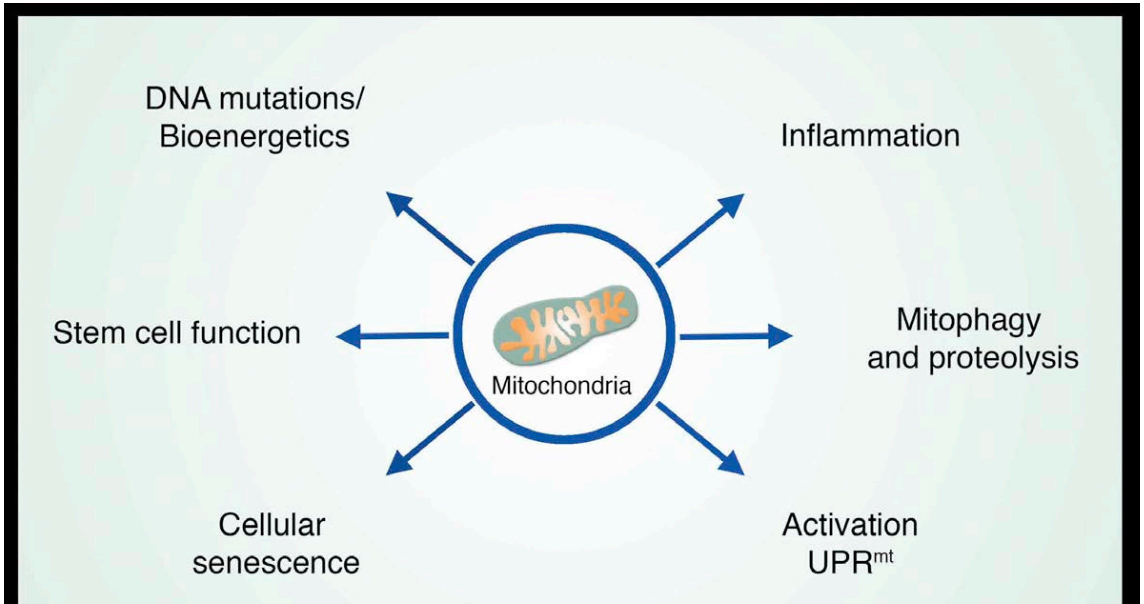
Mitochondrial dysfunction in benign prostatic hyperplasia

Don DeFranco, PhD



Sun, Youle, Finkel (2016). Mol. Cell

University of Pittsburgh

O'Brien Urology Research Center

George M. O'Brien
Urology Research Center
UNIVERSITY OF WISCONSIN–MADISON

UMASS BOSTON

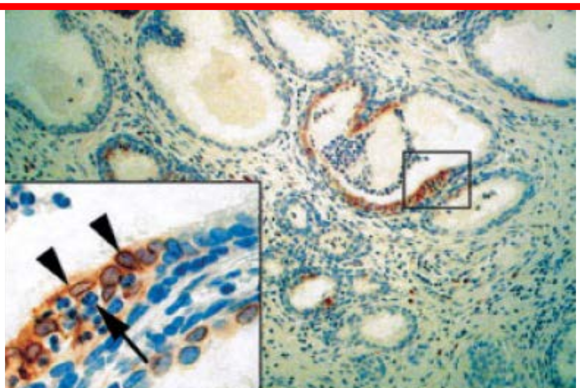
UTSW

NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

PIND
Pittsburgh Institute for Neurodegenerative Diseases

TREATMENT FOR BPH/LUTS

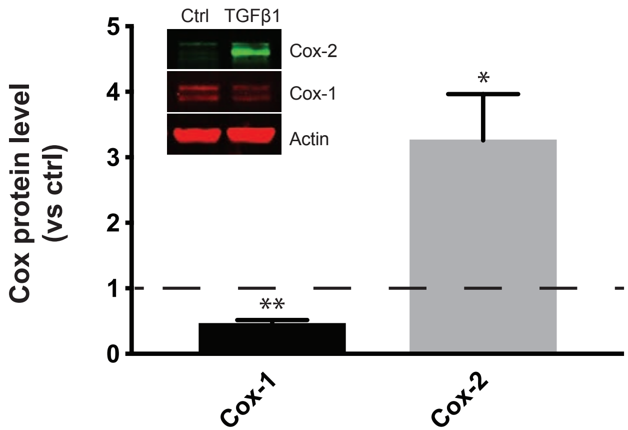
- α-adrenergic blockers treat the symptoms of BPH/LUTS
- 5α-reductase (5AR) inhibitors decrease prostate size
- TURP may need to be performed if drug treatments fail
- **Increased Cox-2 expression in inflammatory vs non-inflammatory BPH**
- Combination therapies: 5ARi + **NSAIDs** (mixed results, beneficial effects not long lasting) – **Why?**

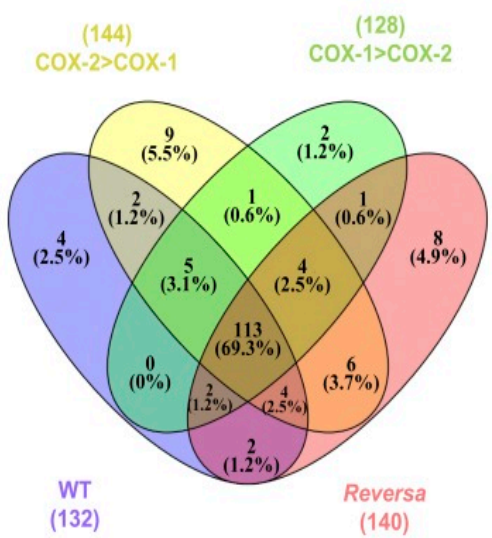


Focal areas of Cox-2 overexpression in BPH (Damber Lab, 2004)

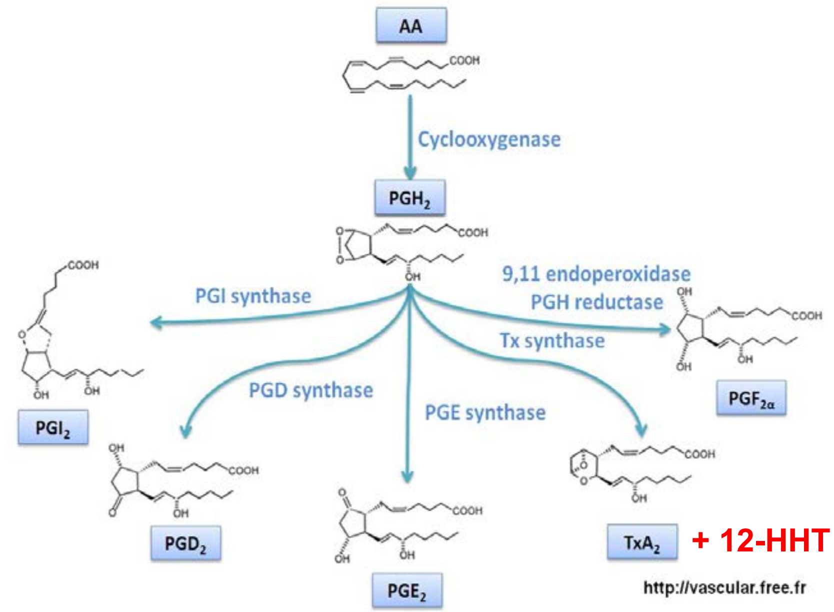
Reciprocal Regulation of Cox-1 and Cox-2

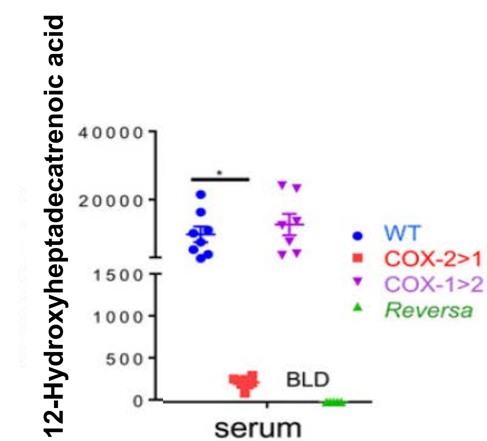
BPH-1 Cells





COX-1 vs COX-2 in MΦ:
Differential gene expression
(Li X et al., (2018) J. Lipid Res.)





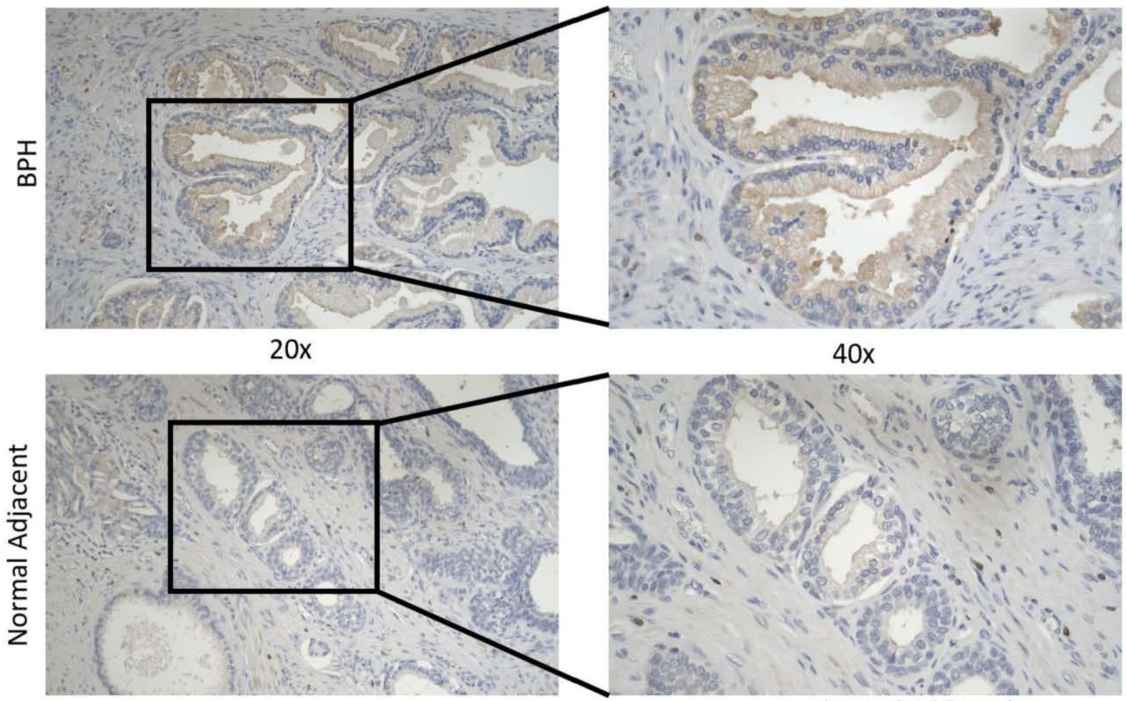
Genomic and lipidomic analyses differentiate the compensatory roles of two COX isoforms during systemic inflammation in mice[1,2]

Xinzhi Li,* Liudmila L. Mazaleuskaya,† Laurel L. Ballantyne,* Hu Meng,† Garret A. FitzGerald,† and Colin D. Funk[3,*]

COX-1 IHC in Human Prostate

BPH vs. Normal Adjacent (n=8)

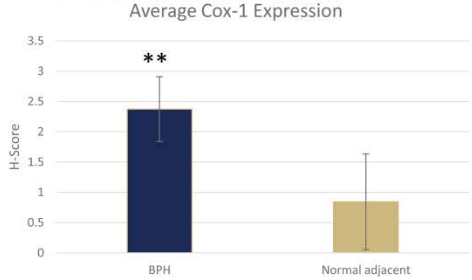
		Race		Cancer Status	
	Age	Caucasian	African American	Gleason score =6	Cancer Free or Non-Prostatic Cancer
Average	65 ± 9.13	50%	50%	50%	50%
Range	53-78				



Statistically significant increase in COX-1 expression in BPH compared to normal adjacent tissue.

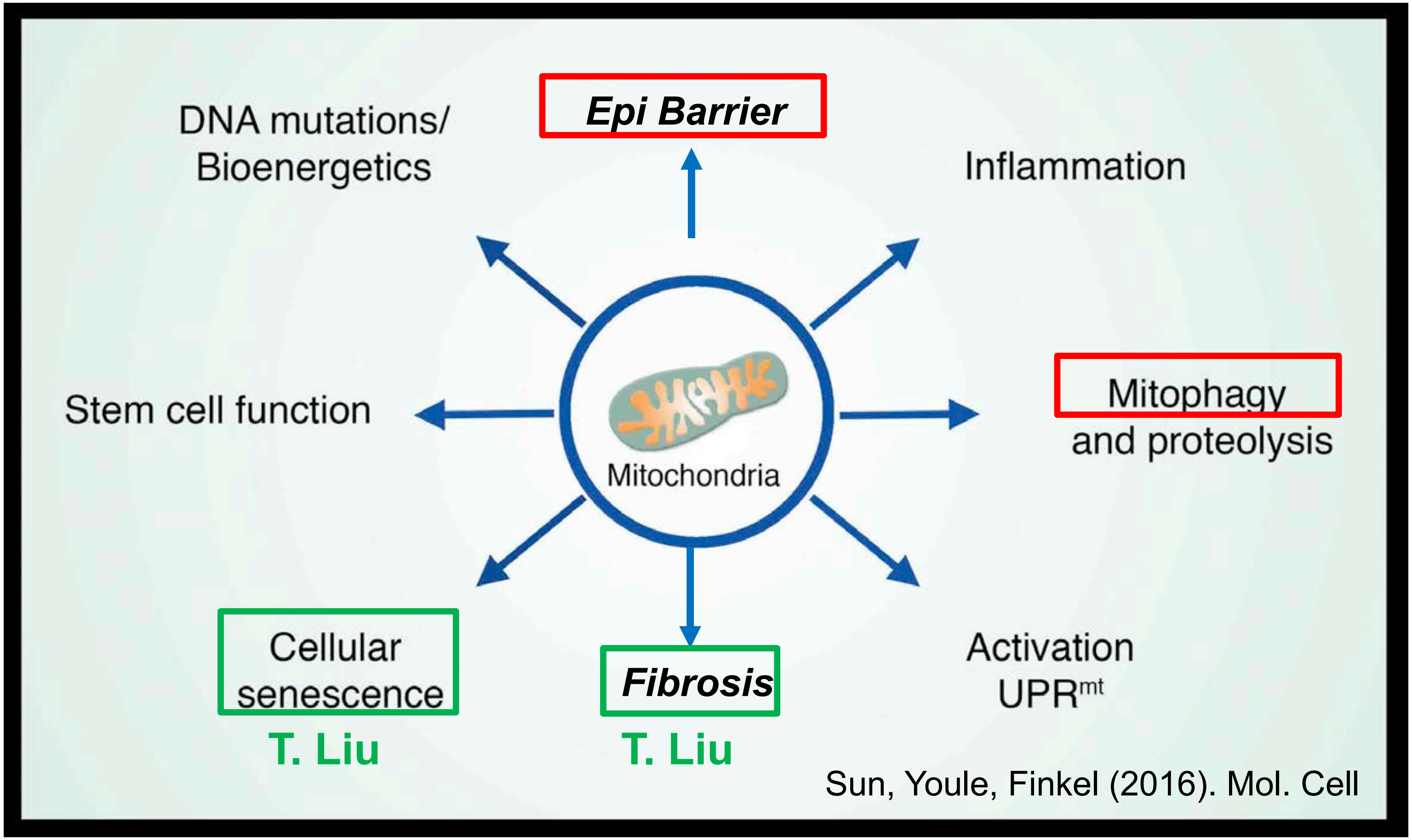
Summary of results

	H Score	Students T test
BPH	2.375 ± 0.5345	
Normal Adjacent	0.84375 ± 0.7898	P= 0.00004



Physiologic or Pathophysiologic Regulators of COX-1?

Age-dependent gradual mitochondrial dysfunction: Is this relevant to BPH progression?



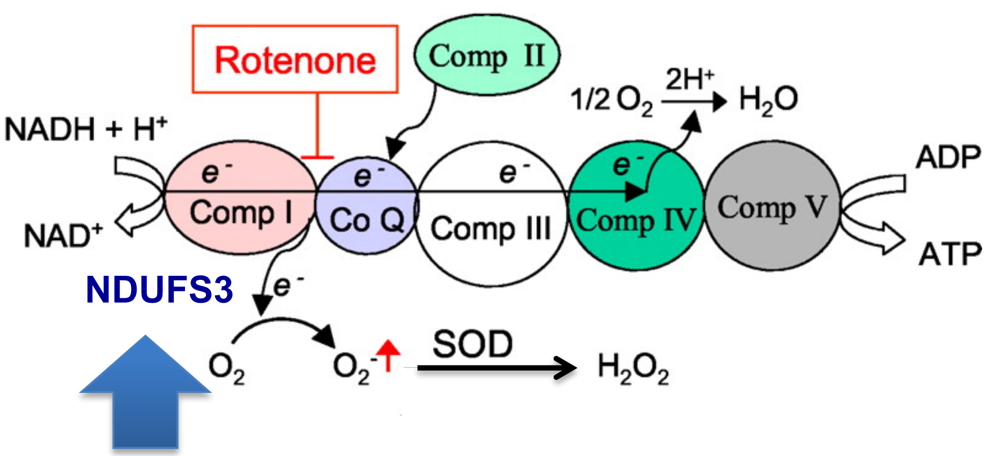
Focus on ETC Complex I: Dysfunction associated with human diseases

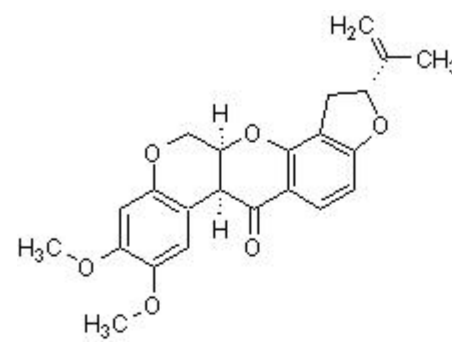
Rotenone: an inhibitor of complex I of the mitochondrial respiratory chain

- ❑ Leading to a blockade of oxidative phosphorylation with limited ATP production;

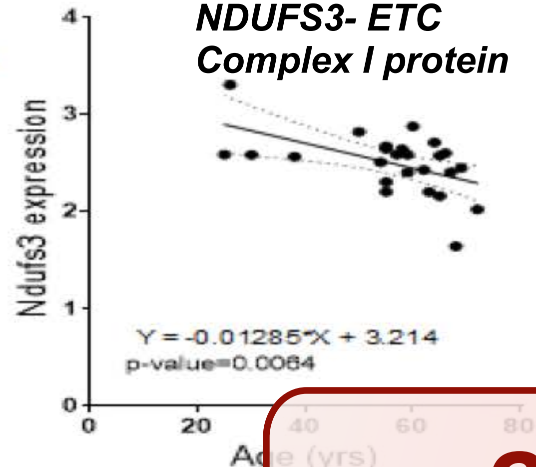
- ❑ Incomplete electron transfer to oxygen could cause the formation of ROS.

Rotenone exposure has been shown to correlate with the occurrence of several Parkinson's disease (PD)-like symptoms in humans. Chronic administration of rotenone has been used to create experimental animal models of PD.

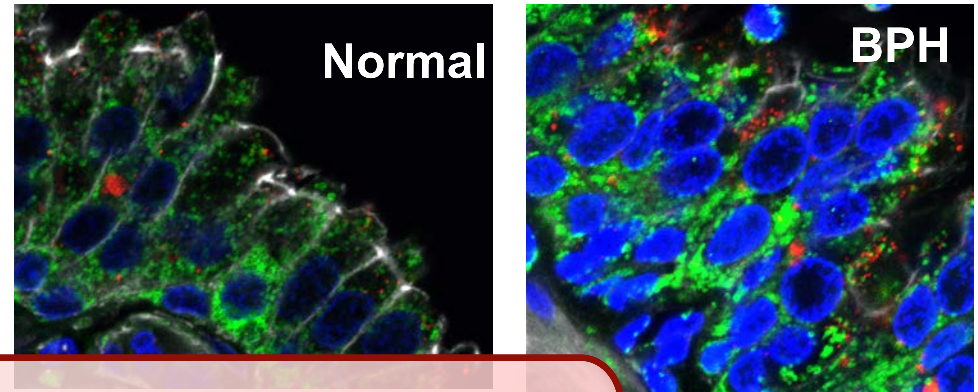




Hypothesis: Age-dependent decline in mitochondrial ETC Complex I activity contributes to BPH pathogenesis

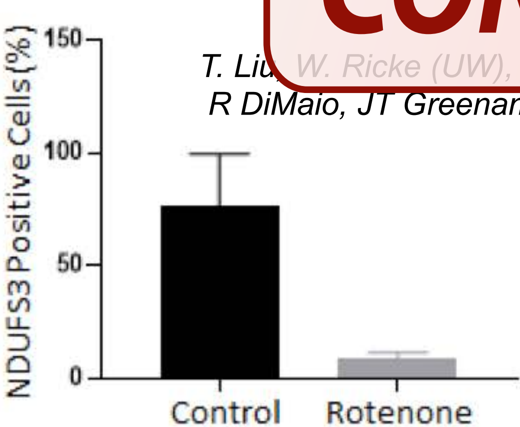


Age-dependent decline in NDUFS3 in human prostate (T. Liu, UWisconsin)

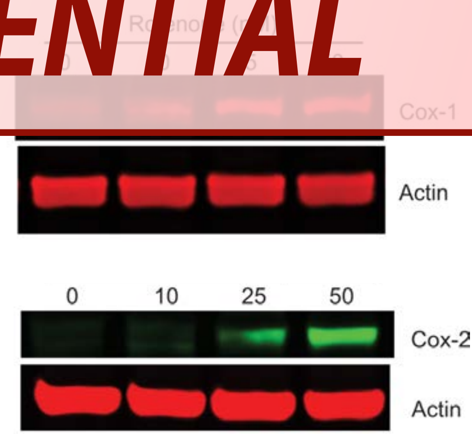


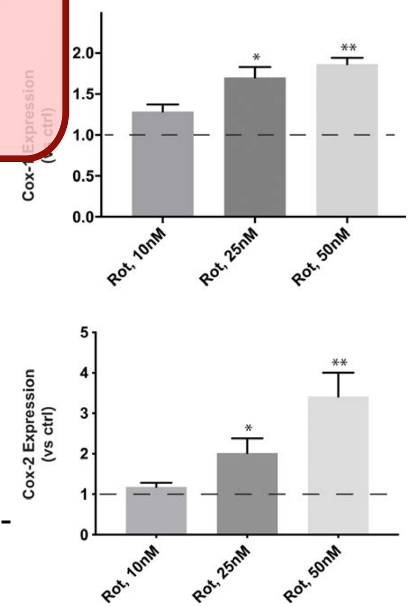
TOM 20 IIF (D. Stolz) in BPH tissue
Compensatory increase in mito mass?

T. Liu, W. Ricke (UW),
R DiMaio, JT Greenamyre (Pitt)



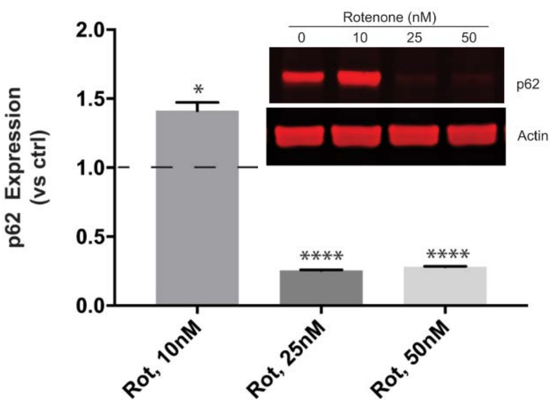
Repression of NDUFS3 in prostates of rotenone-treated rats

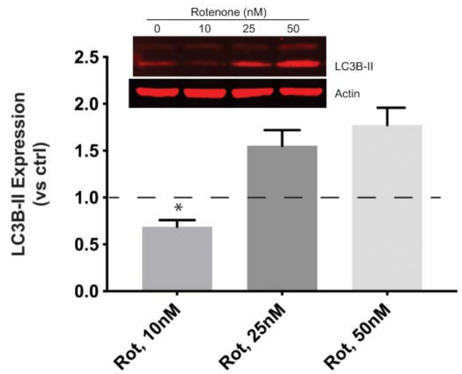


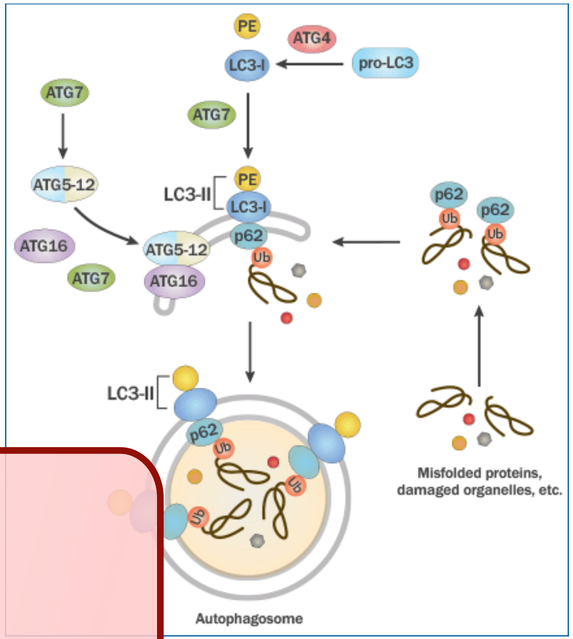


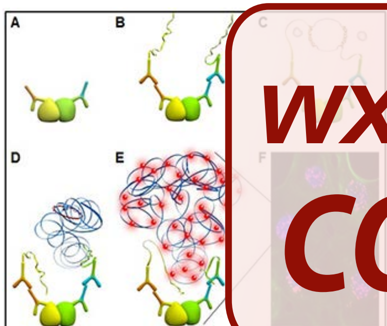
Rotenone induction of COX-1 & COX-2 in RWPE-1 Cells (K. He)

ROTENONE DISRUPTS AUTOPHAGIC FLUX (MITOPHAGY?) IN PrECs









MITOPHAGY ASSESSMENT

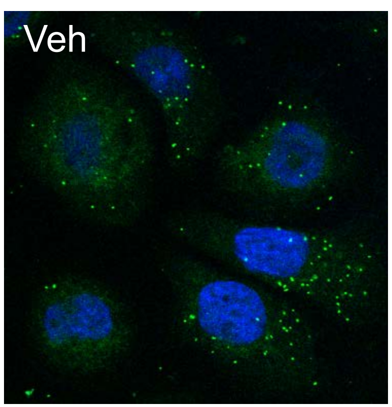
Proximity Ligation Assay

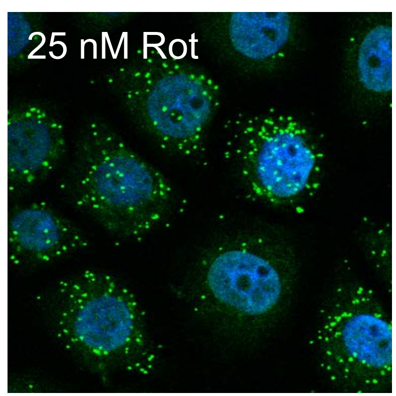
Tom20 & p62 Colocalization

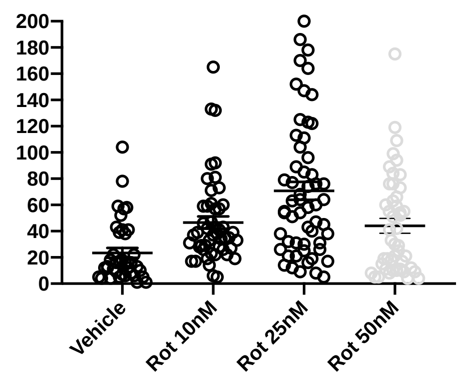
RWPE-1 Cells

K. He & R. DiMaio

Diversion of p62 to damage mito?

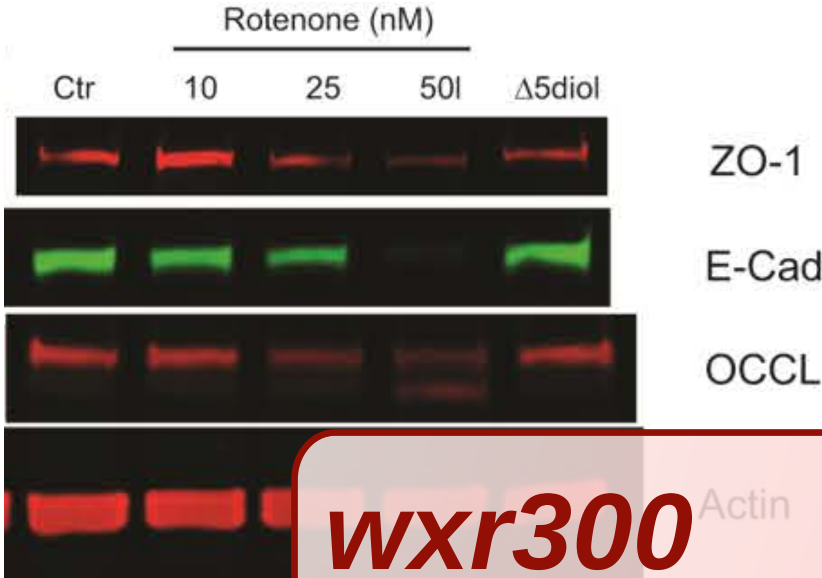


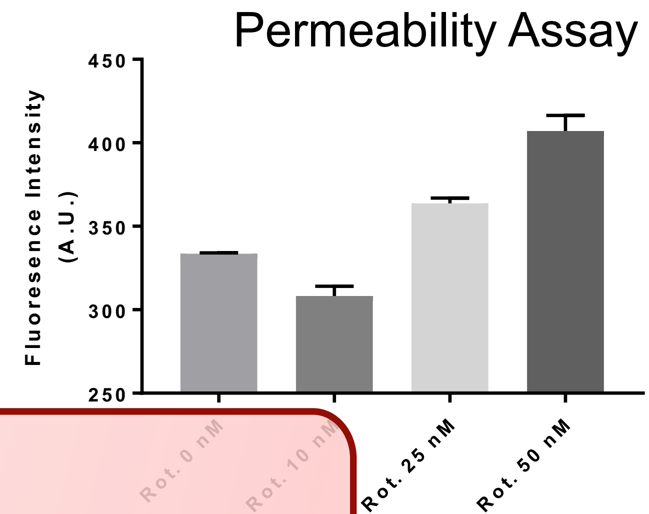


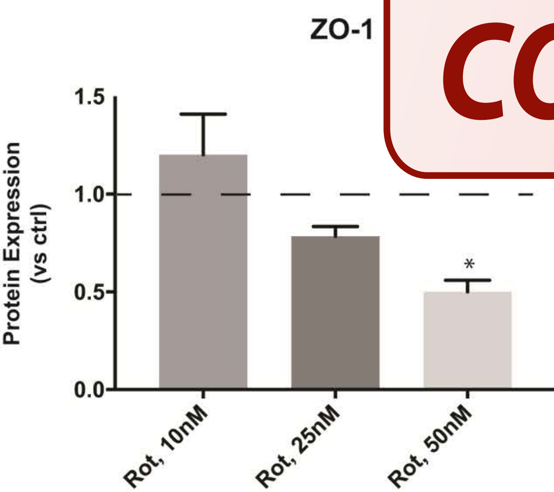


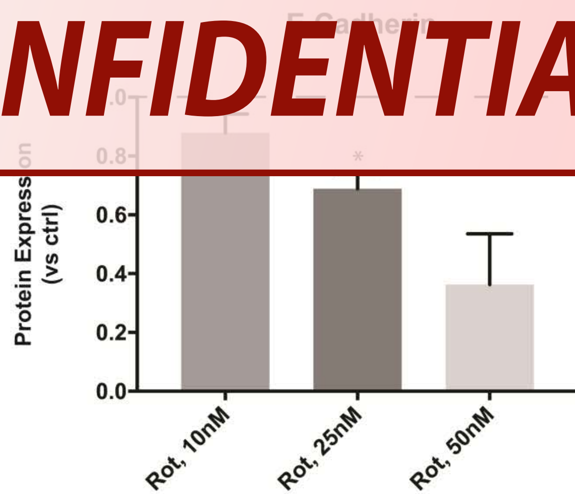
Rotenone Effects on Cell Junction Proteins In RWPE-1 Cells

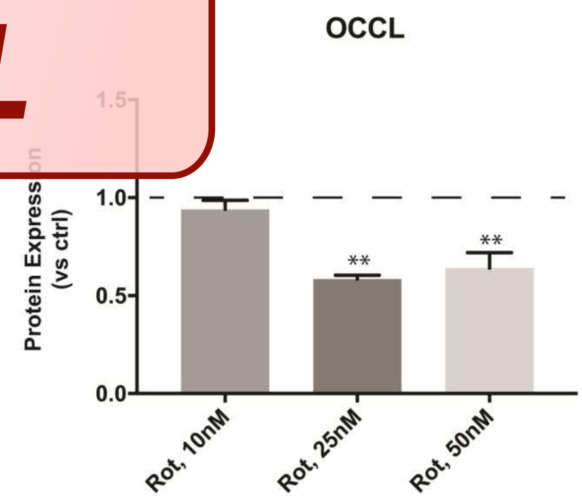
Kai He







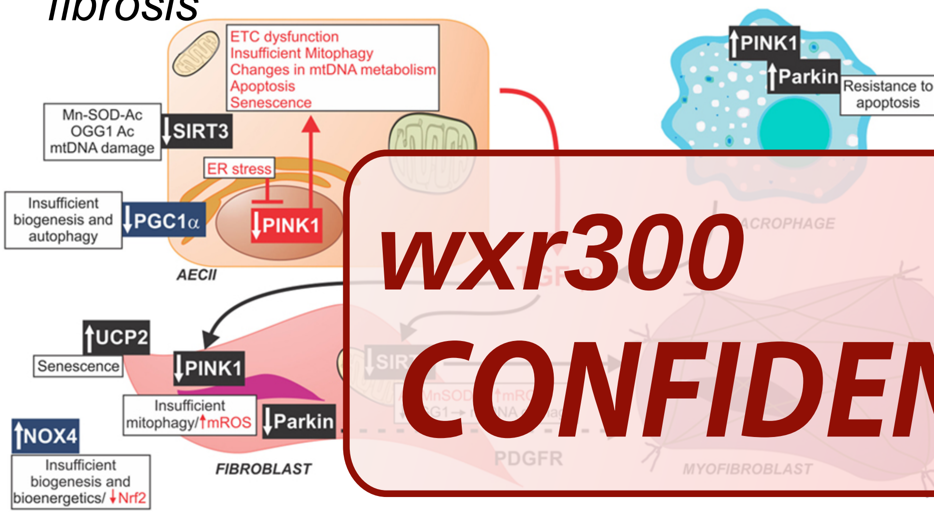




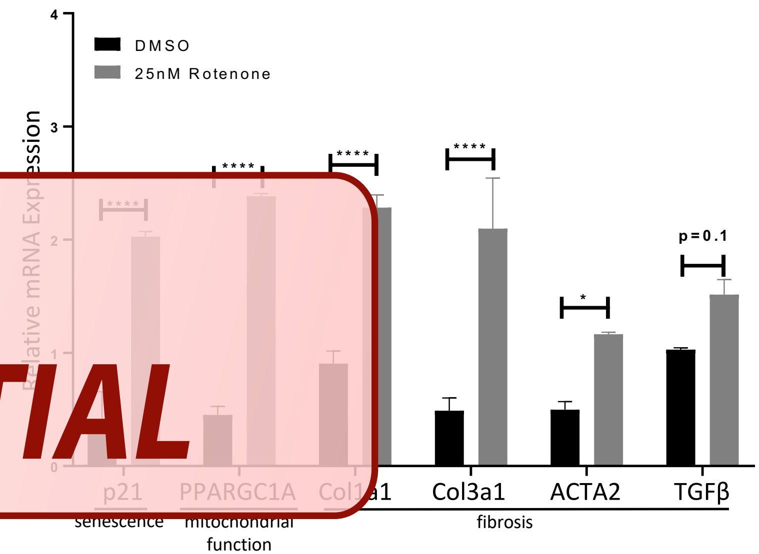
In Vivo Rat Study (Neuroniol Dis 2018): Rotenone treatment induced intestinal hyperpermeability and disrupted expression of ZO-1, Occludin, Claudin-1)

Does mitochondrial dysfunction contribute to prostatic fibrosis?

Lessons from idiopathic pulmonary fibrosis



BhPrS1 Cells (T. Liu, W. Ricke)



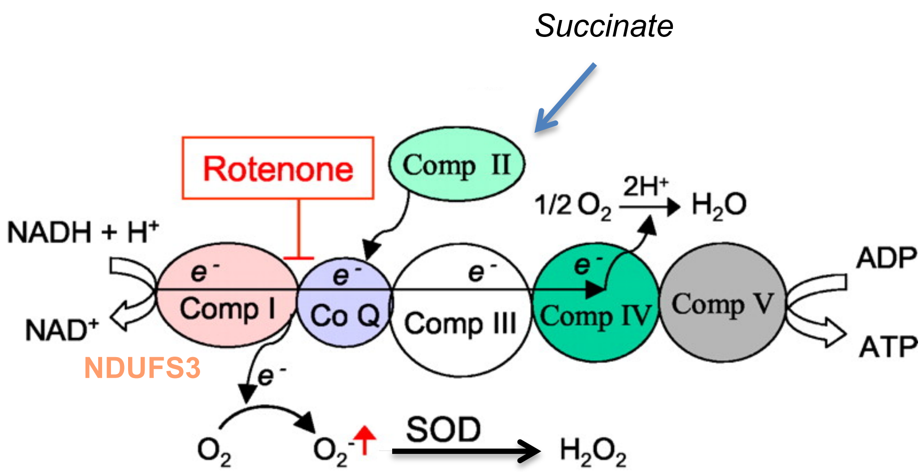
Zank DC et al., (2018) Front. Med.
Idiopathic Pulmonary Fibrosis: Aging, Mitochondrial Dysfunction, and Cellular Bioenergetics

FUTURE DIRECTIONS

Is mitochondrial (ETC Complex I) dysfunction (or altered mitophagy) associated with the BPH progression?

Complex-I Alteration and Enhanced Mitochondrial Fusion Are Associated With **Prostate** Cancer Progression.
Philley JV, et al., J Cell Physiol. 2016 Jun;231(6):1364-74. PMID: 26530043

"Respiratory Complex I-mtDNA mutations (in the NADH ubiquinone oxidoreductase chain 4 gene), MFN2, and IMMT proteins were detected in the circulating exosomes in serum of men with benign prostate hyperplasia (BPH) and progressive PCa!



Can drugs that "restore" mitochondrial function reverse various phenotypes observed with in vitro and in vivo models of prostatic epithelial cell dysfunction, inflammation, or LUTS?

University of Pittsburgh
O'Brien Urology Research Center

Acknowledgments

George M. O'Brien Urology Research Center
UNIVERSITY OF WISCONSIN–MADISON

Univ of Pittsburgh O'Brien Center

DeFranco Lab

Kai He
Chandler Hudson
Caroline Madigan

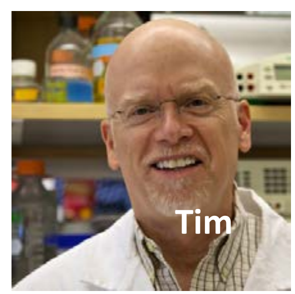
Zhou Wang
Laura Pascal
Naoki Yoshimura
Rajiv Dhir
Pooja Srivastava

Univ. Wisconsin O'Brien Center

Will Ricke - PI
Emily Ricke
Teresa Liu – K12 Scholar
Liv Myklebust – CAIRIBU Research Training and Development Awardee

Pittsburgh Institute for Neurodegenerative Diseases

Tim Greenamyre
Roberto Di Maio



PIND
Pittsburgh Institute for Neurodegenerative Diseases

NIDDK: U54 DK112079

NIH National Institute of Diabetes and Digestive and Kidney Diseases