Ophthalmology Times

Research Scholar Honoree Program

The Effects of Brimonidine on Retinal Pigment Epithelial Cells and Muller Cells Exposed to Amyloid-Beta 42 Peptide *In Vitro*

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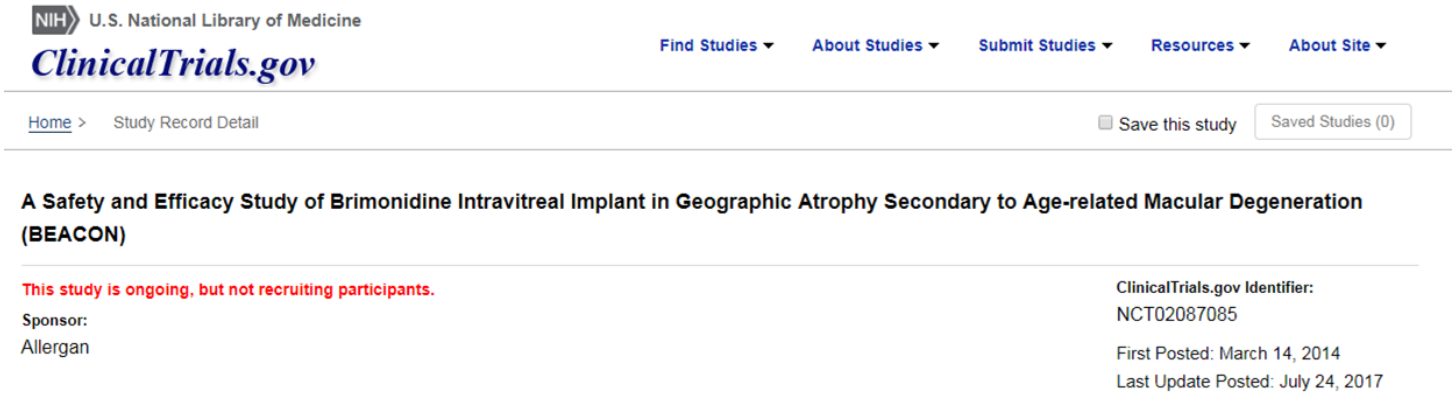
FINANCIAL DISCLOSURES

SWT, RG, KT, MCK: None relevant to presentation.

BDK: Allergan (Consultant)



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A Safety and Efficacy Study of Brimonidine Intravitreal Implant in Geographic Atrophy Secondary to Age-related Macular Degeneration (BEACON)

This study is ongoing, but not recruiting participants.

Sponsor:
Allergan

ClinicalTrials.gov Identifier:
NCT02087085

First Posted: March 14, 2014
Last Update Posted: July 24, 2017

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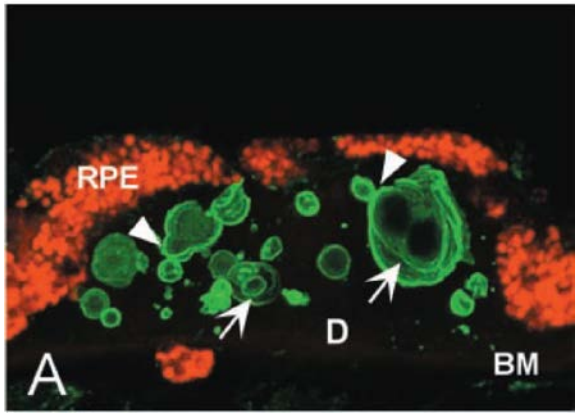
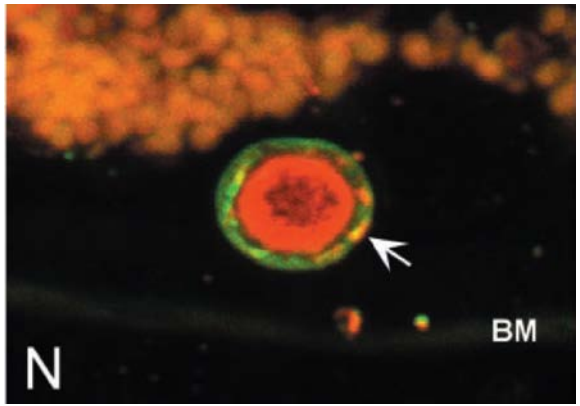
Kuppermann BD, Patel SS, Boyer DS, et al. Invest Ophthalmol Vis Sci. 2017;58(8):1924-1924.

Amyloid-Beta (Aβ) and Drusen





Johnson LV, Leitner WP, Rivest AJ, Staples MK, Radeke MJ, Anderson DH. Proc Natl Acad Sci U S A. 2002 Sep 3;99(18):11830-5.

Our Question:

What are the effects of **brimonidine** on **retinal pigment epithelial cells (RPE)** and **Muller cells (MIO)** exposed to **Aβ42 peptide** *in vitro*?

Methods

ROS

Membrane Potential

Cell Viability

Brimonidine 50 ug / 4 mL

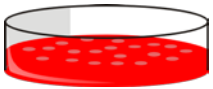
12 hours

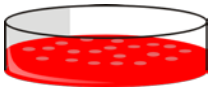
Amyloid-β42

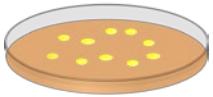
24 hours

Assays

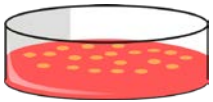
Retinal Pigment Epithelium

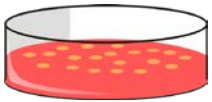


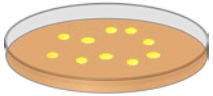




Muller Cells







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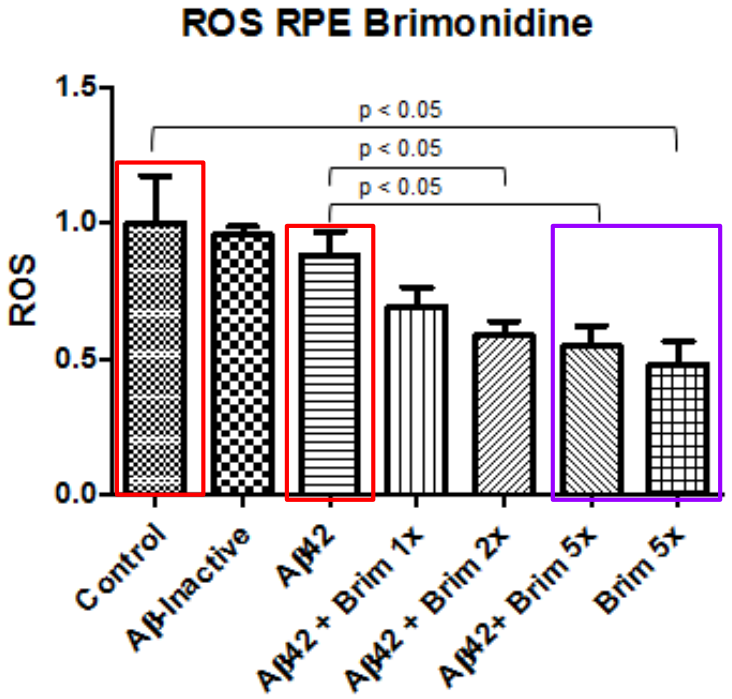
Ramírez C, Cáceres-del-Carpio J, Chu J, Chu J, Moustafa MT, Chwa M, Limb GA, Kuppermann BD, Kenney MC. J Ocul Pharmacol Ther. 2016 Mar;32(2):102-8.

Brimonidine reduces ROS production in RPE cells

Aβ42 did not increase ROS production in RPE cells.

High dose (5x) brimonidine strongly reduced ROS production in the presence of Aβ42.



Brimonidine reduces ROS production in Muller Cells

Aβ42 did not increase ROS production in Muller cells.

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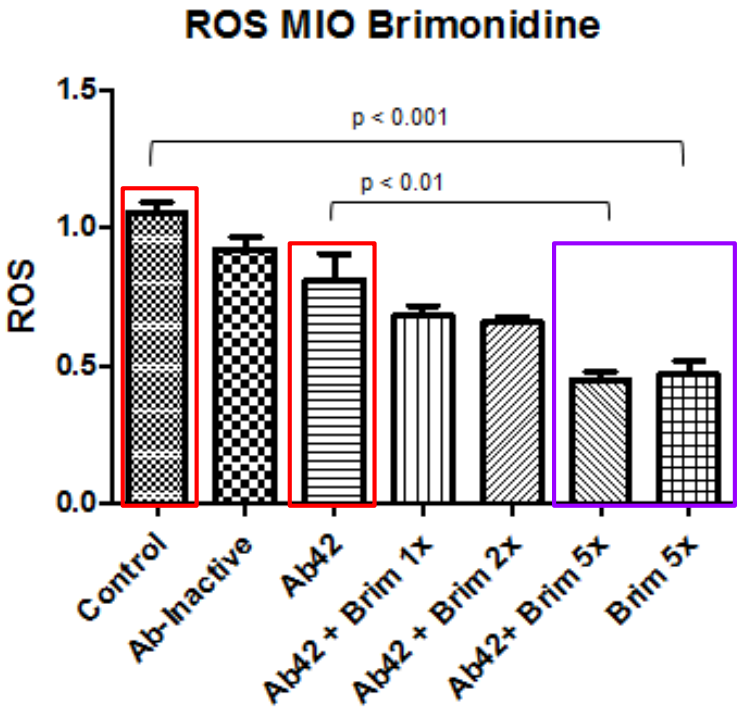


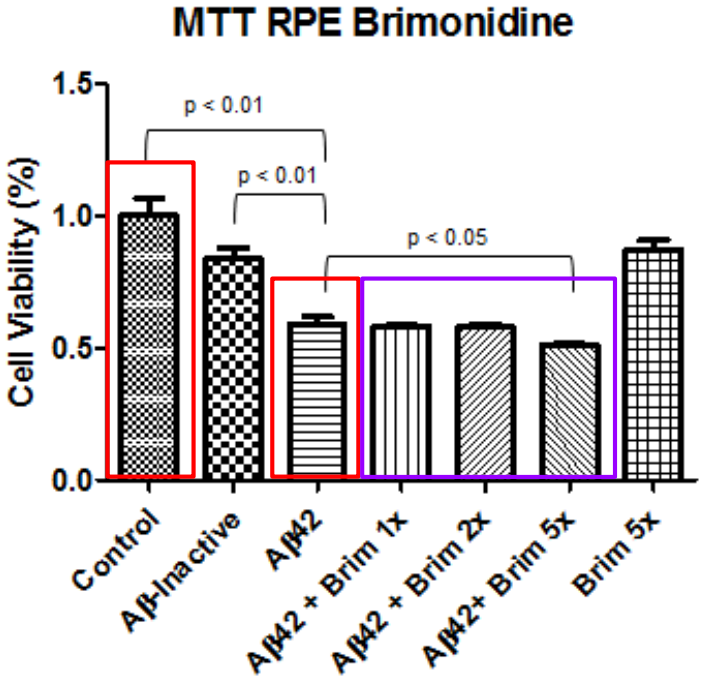
Scorecard: Brimonidine and Aβ42 Peptide

	Reactive Oxygen Species	Cell Viability	Membrane Potential
Retinal Pigment Epithelium	Protective		
Muller Cells	Protective		

Brimonidine did not rescue cell viability in RPE cells

Aβ42 was reduced cell viability in RPE cells.

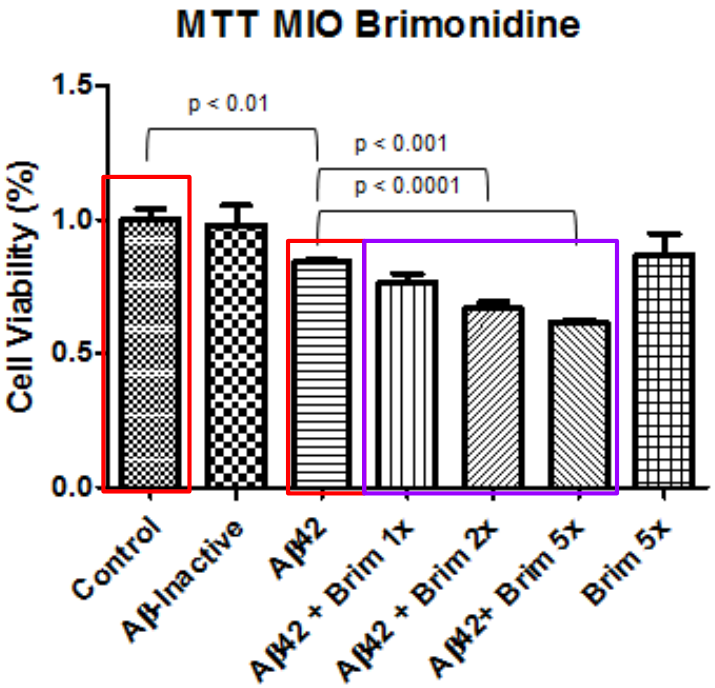
Brimonidine did not rescue cell viability in Aβ42 treated cells.



Brimonidine did not rescue cell viability in Muller Cells

Aβ42 decreased cell viability in Muller cells.

Brimonidine did not rescue cell viability in Aβ42 treated cultures.



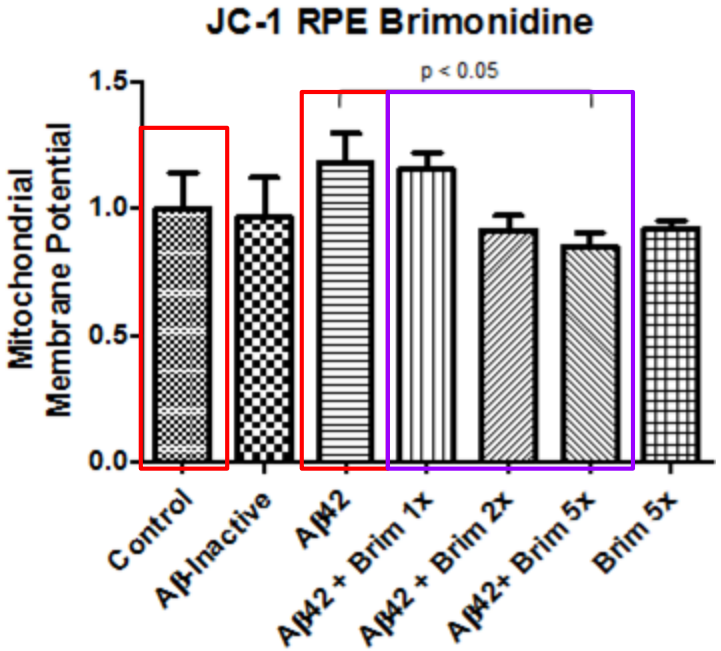
Scorecard: Brimonidine and Aβ42 Peptide

	Reactive Oxygen Species	Cell Viability	Membrane Potential
Retinal Pigment Epithelium	Protective	Not Protective	
Muller Cells	Protective	Not Protective	

Brimonidine reduced membrane potential in RPE cells treated with Aβ42

Aβ42 did not affect mitochondrial membrane potential.

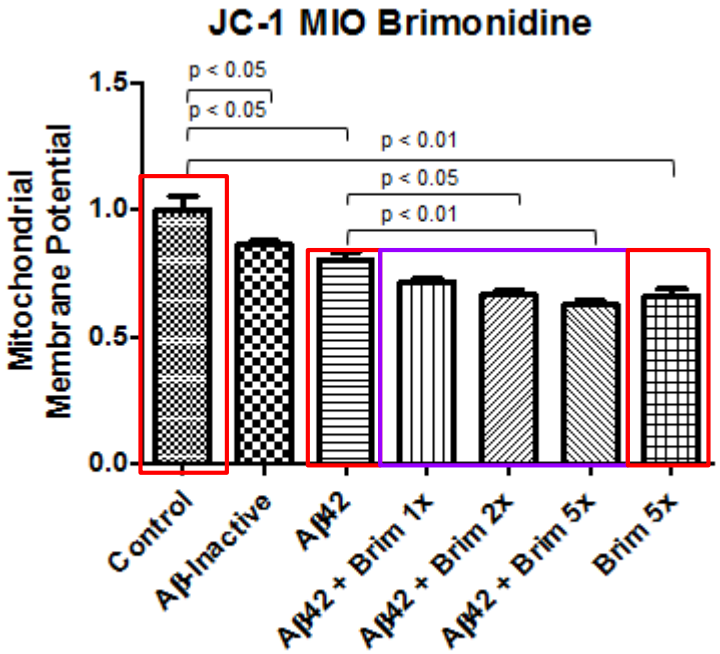
Brimonidine reduced mitochondrial membrane potential in Aβ42 treated cultures.



Brimonidine had a synergistic toxic effect on membrane potential in Muller cells treated with Aβ42

Membrane potential was reduced by addition of both amyloid peptide and brimonidine.

Brimonidine had a toxic synergistic effect with Aβ42 on the membrane potential of Muller cells.



Scorecard: Brimonidine and Aβ42 Peptide

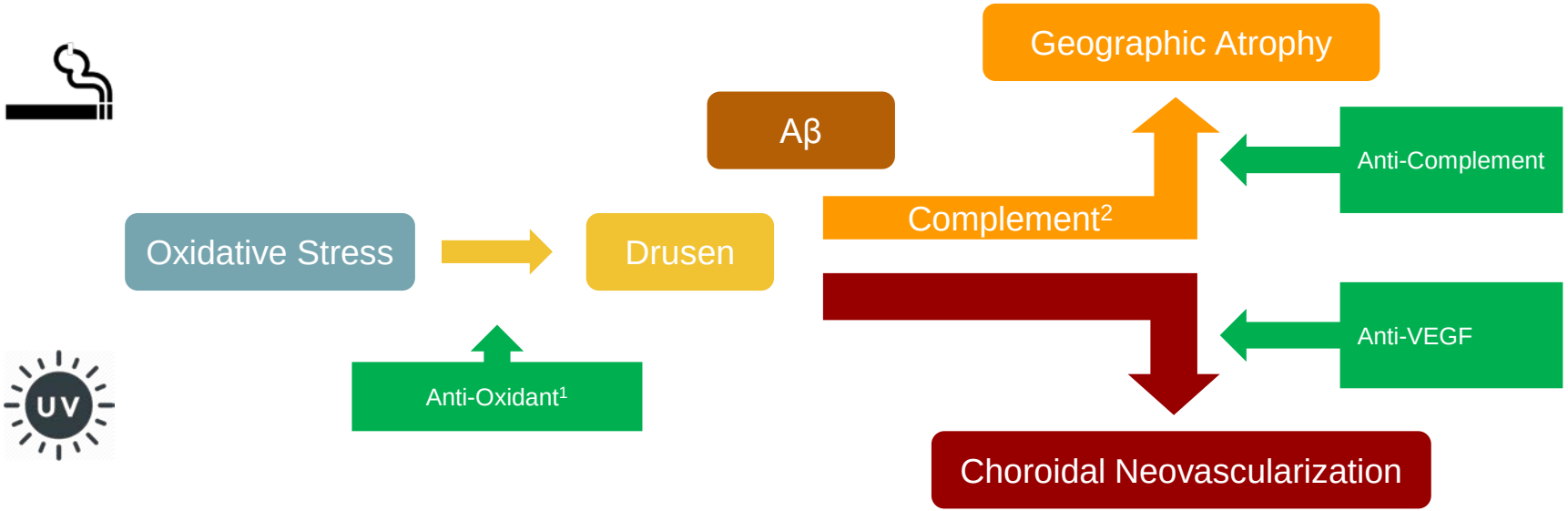
	Reactive Oxygen Species	Cell Viability	Membrane Potential
Retinal Pigment Epithelium	Protective	Not Protective	Not Protective
Muller Cells	Protective	Not Protective	Not Protective

How does this data fit compared to previous cellular toxicity studies?

	Hydroquinone		Amyloid-Beta	
	No Treatment	Brimonidine	No Treatment	Brimonidine
Cell Viability				
RPE	harmful	protective	harmful	not protective
Muller	harmful	protective	harmful	not protective
Membrane Potential				
RPE	harmful	protective	no effect	not protective
Muller	harmful	protective	harmful	not protective
Reactive Oxygen Species				
RPE	harmful	protective	no effect	protective
Muller	harmful	protective	no effect	protective

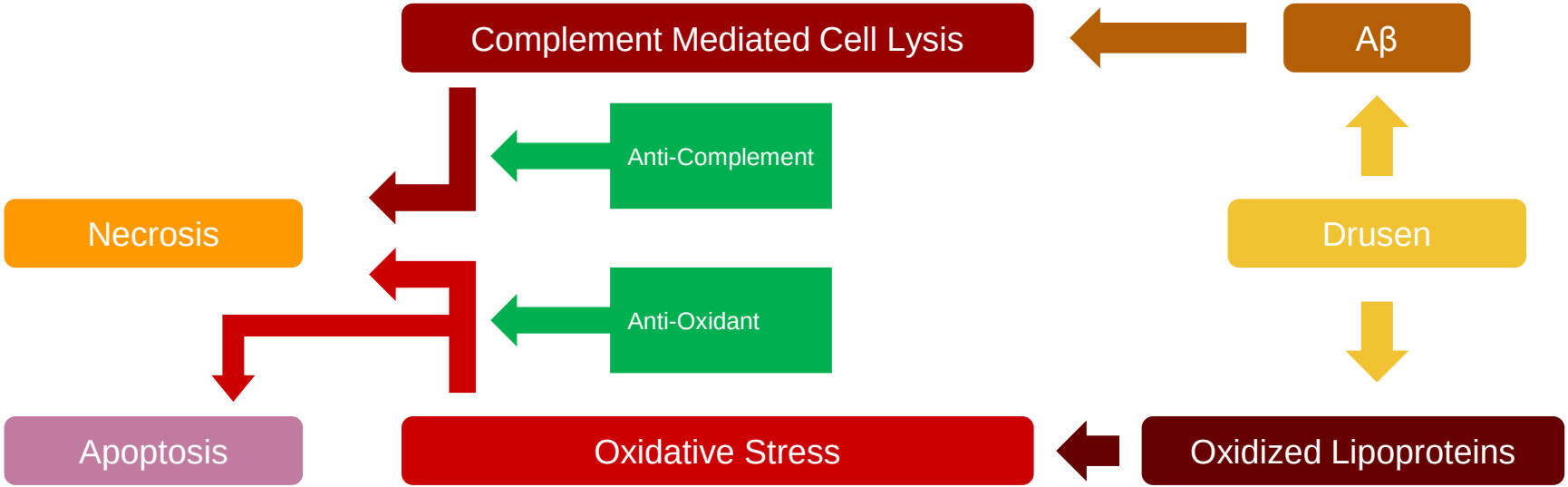
Ramírez C, Cáceres-del-Carpio J, Chu J, Chu J, Moustafa MT, Chwa M, Limb GA, Kuppermann BD, Kenney MC. J Ocul Pharmacol Ther. 2016 Mar;32(2):102-8.

How does this fit into our understanding of pathology in AMD?



1. Beatty S, Koh H, Phil M, Henson D, Boulton M. 2000;45(2):115-134.
2. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. Retina. 2017 May;37(5):819-835

How does this data fit with our model of cell death in Geographic Atrophy?



Conclusions

- Brimonidine **reduces ROS production** in both RPE and Muller cells.
  - Brimonidine **reduces ROS production** in both RPE and Muller cells **even in the presence of Aβ42.**
  - Findings are consistent with the literature:
    - protective against neuronal excitotoxicity.[1]
    - protective against oxidative stress.[2]

1. Lee D, Kim KY, Noh YH, Chai S, Lindsey JD, Ellisman MH, Weinreb RN, Ju WK. PLoS One. 2012;7(10)
2. Ramírez C, Cáceres-del-Carpio J, Chu J, Chu J, Moustafa MT, Chwa M, Limb GA, Kuppermann BD, Kenney MC. J Ocul Pharmacol Ther. 2016 Mar;32(2):102-8.

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Conclusions

- Brimonidine **does not rescue cell viability** in RPE and Muller cells exposed to Aβ42.

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Limitations

- Amyloid-Beta is only **one subcomponent** of drusen, and therefore only representative of a small component of toxicity in macular degeneration.
- Results are reflective of responses from cells of **glial** and **pigment epithelial** lineage but not **neuronal** lineage.

Future Directions

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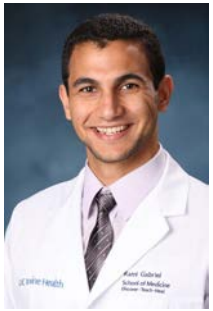
- This *in vitro* model can be applied towards:
  - investigating the pathways to cell death in AMD
  - evaluating the therapeutic effect of other agents aimed at treating geographic atrophy
    - Lampulizumab (Roche, anti-CFD)
    - Zimura (Ophthotech, anti-C5)
    - CLG561 (Alcon, anti-properdin)
    - APL-2 (Apellis, anti-C3)

My Role in This Research

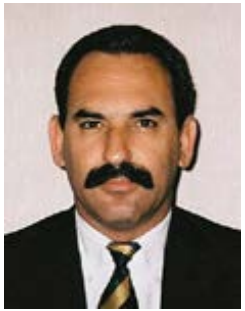
- ☐ Conception and design of the work/project
- ☐ ~~Acquisition of data~~
- ☐ Analysis and interpretation of data
- ☐ Creation and/or critical review of the presentation

Acknowledgements



Rami Gabriel

Kunal Thaker



Baruch Kuppermann

Cristina Kenney

UC Irvine Health

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Thank You!

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