

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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UBM

# FINANCIAL DISCLOSURES

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

BDK: Allergan (Consultant)

## 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.**

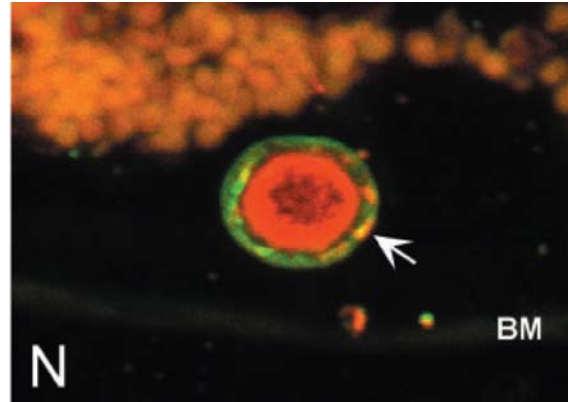
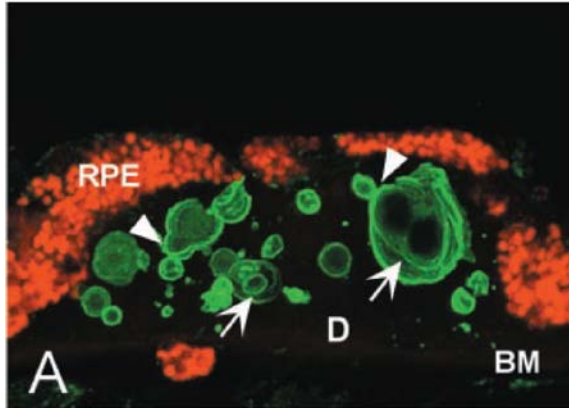
Sponsor:  
Allergan

ClinicalTrials.gov Identifier:  
NCT02087085

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# Amyloid-Beta ( $A\beta$ ) and Drusen



# Our Question:

What are the effects of **brimonidine** on **retinal pigment epithelial cells (RPE)** and **Muller cells (MIO)** exposed to **A $\beta$ 42 peptide** *in vitro*?

# Methods

Brimonidine  
50 ug / 4 mL



12 hours

Amyloid-  
 $\beta$ 42

24 hours

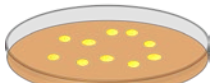
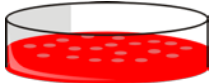
ROS

Membrane Potential

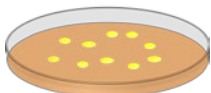
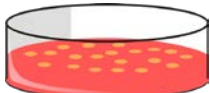
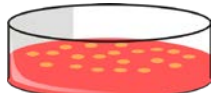
Cell Viability

Assays

Retinal  
Pigment  
Epithelium



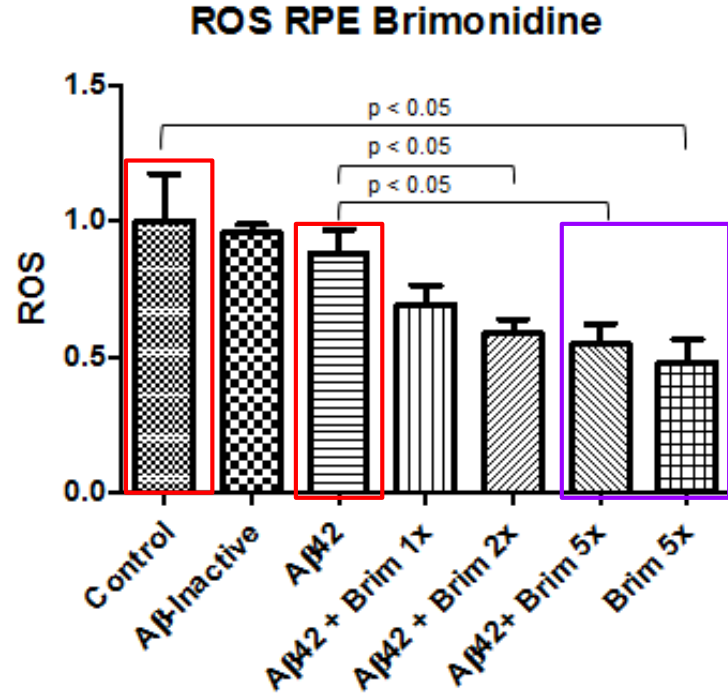
Muller  
Cells



# Brimonidine reduces ROS production in RPE cells

A $\beta$ 42 did not increase ROS production in RPE cells.

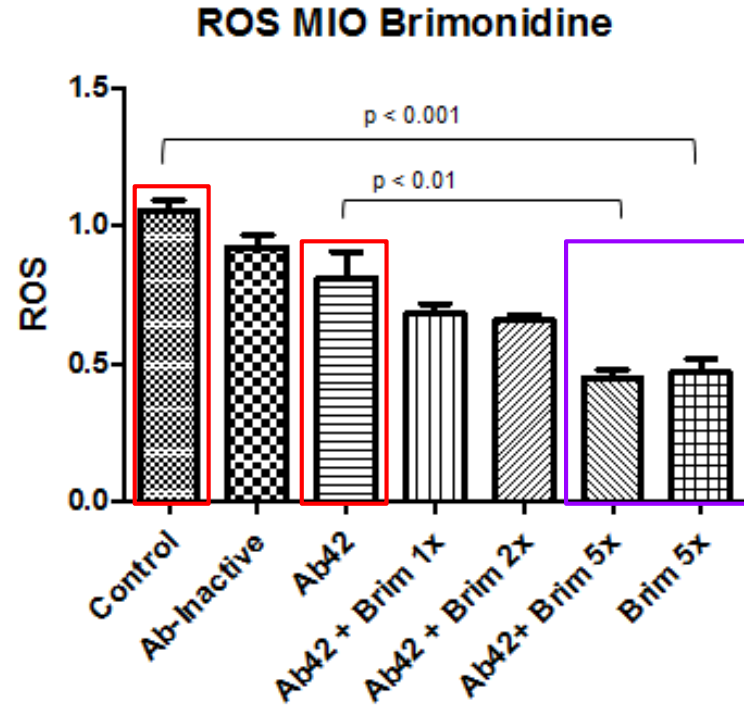
High dose (5x) brimonidine strongly reduced ROS production in the presence of A $\beta$ 42.



# Brimonidine reduces ROS production in Muller Cells

A $\beta$ 42 did not increase ROS production in Muller cells.

High dose (5x) brimonidine strongly reduced ROS production in the presence of A $\beta$ 42.





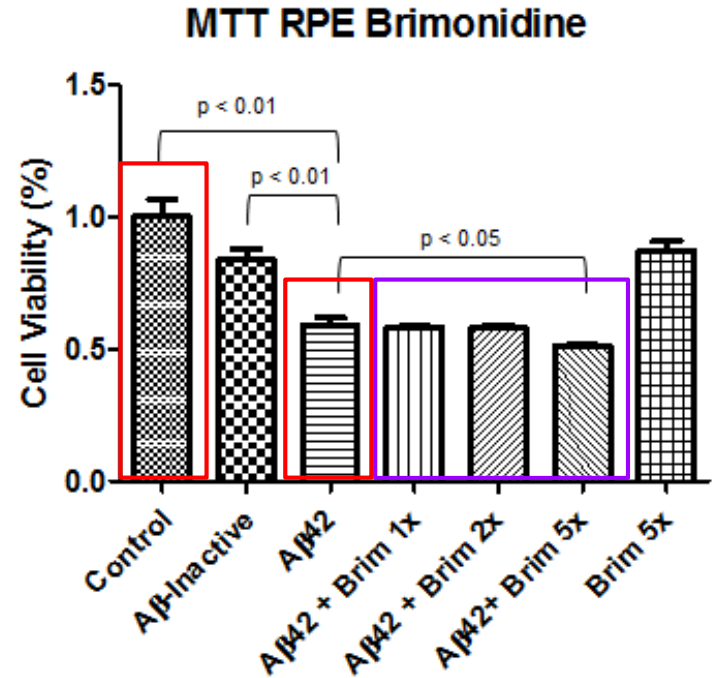
# Scorecard: Brimonidine and A $\beta$ 42 Peptide

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

# Brimonidine did not rescue cell viability in RPE cells

A $\beta$ 42 was reduced cell viability in RPE cells.

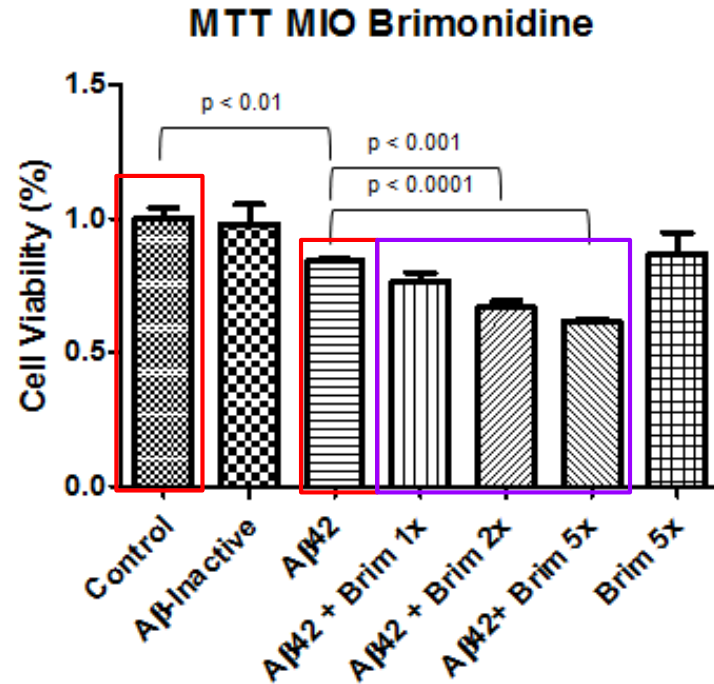
Brimonidine did not rescue cell viability in A $\beta$ 42 treated cells.



# Brimonidine did not rescue cell viability in Muller Cells

A $\beta$ 42 decreased cell viability in Muller cells.

Brimonidine did not rescue cell viability in A $\beta$ 42 treated cultures.



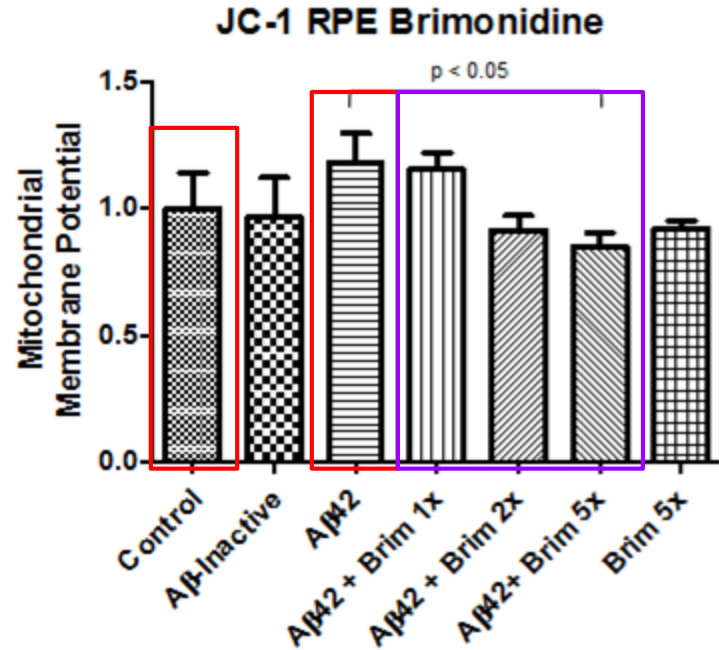
# Scorecard: Brimonidine and A $\beta$ 42 Peptide

	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 A $\beta$ 42

A $\beta$ 42 did not affect mitochondrial membrane potential.

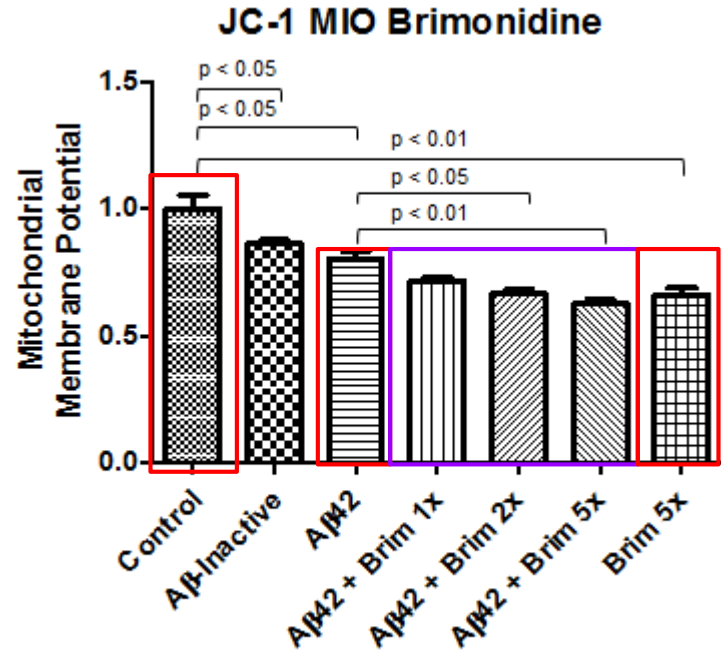
Brimonidine reduced mitochondrial membrane potential in A $\beta$ 42 treated cultures.



## Brimonidine had a synergistic toxic effect on membrane potential in Muller cells treated with A $\beta$ 42

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

Brimonidine had a toxic synergistic effect with A $\beta$ 42 on the membrane potential of Muller cells.



# Scorecard: Brimonidine and A $\beta$ 42 Peptide

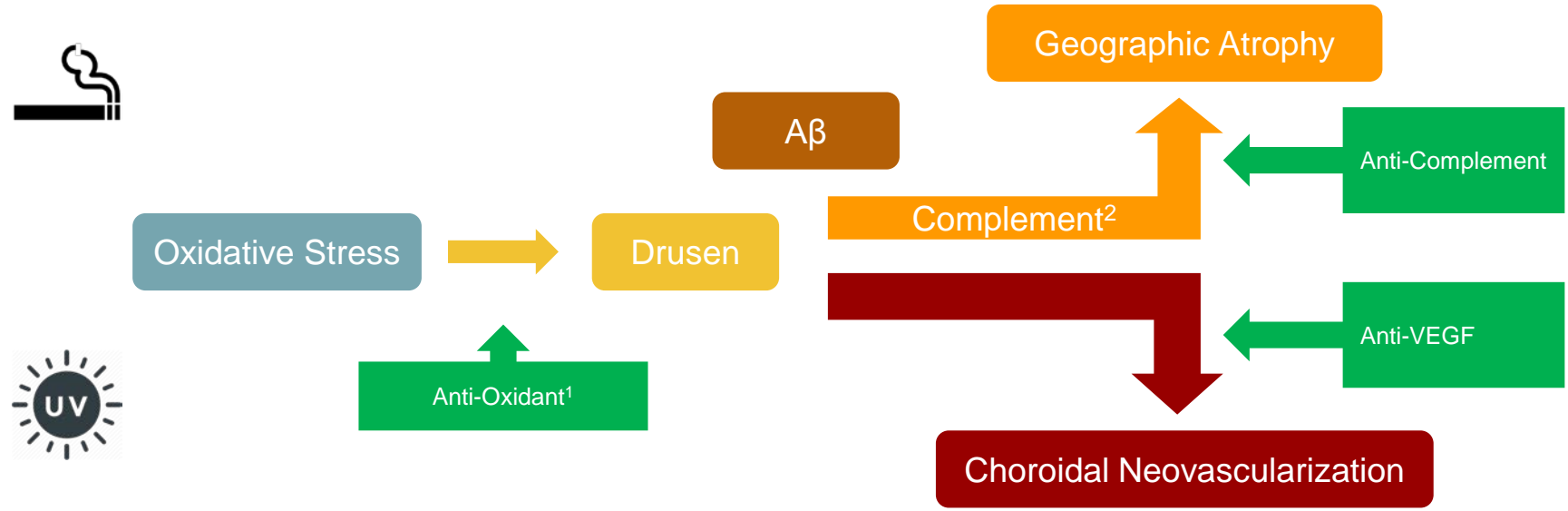
	Reactive Oxygen Species	Cell Viability	Membrane Potential
Retinal Pigment Epithelium	Protective	Not Protective	Not Protective
Muller Cells	Protective	Not Protective	Not Protective

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

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

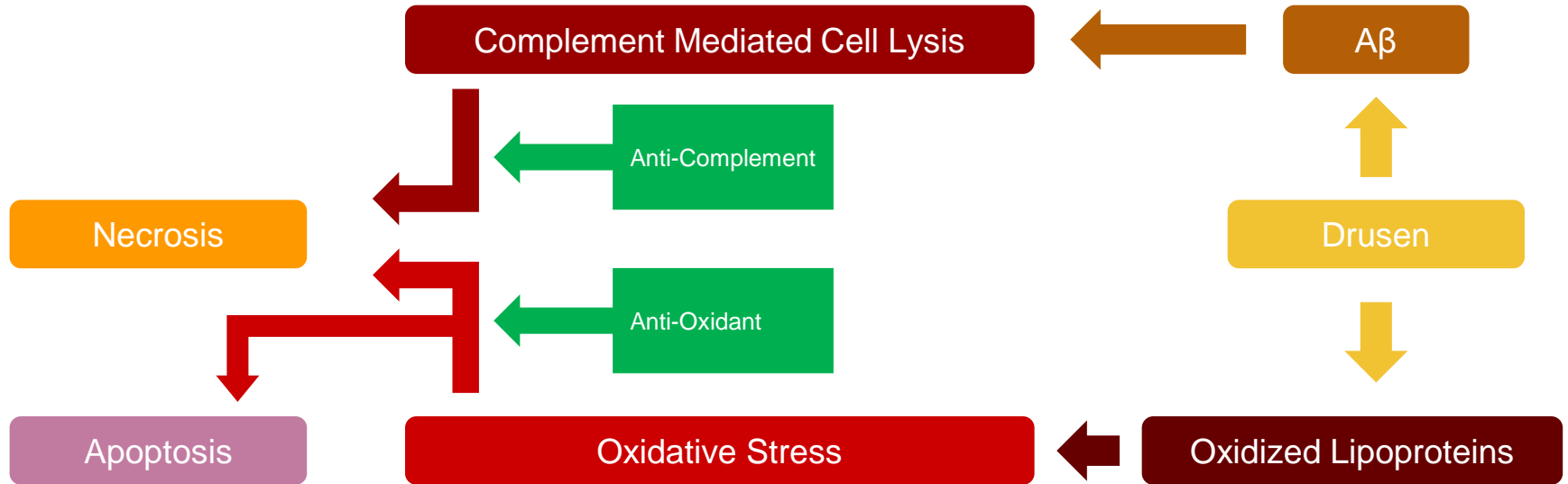


# How does this fit into our understanding of pathology in AMD?



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 A $\beta$ 42.**
  - Findings are consistent with the literature:
    - protective against neuronal excitotoxicity.<sup>1</sup>
    - protective against oxidative stress.<sup>2</sup>

# Conclusions

- Brimonidine **does not rescue cell viability** in RPE and Muller cells exposed to A $\beta$ 42.

# 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

- 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



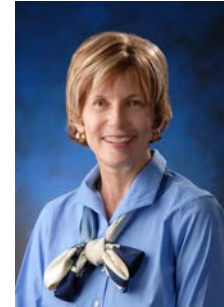
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# Thank You!