Role of C1q Inhibition in the Treatment of Geographic Atrophy Secondary to Age-related Macular Degeneration

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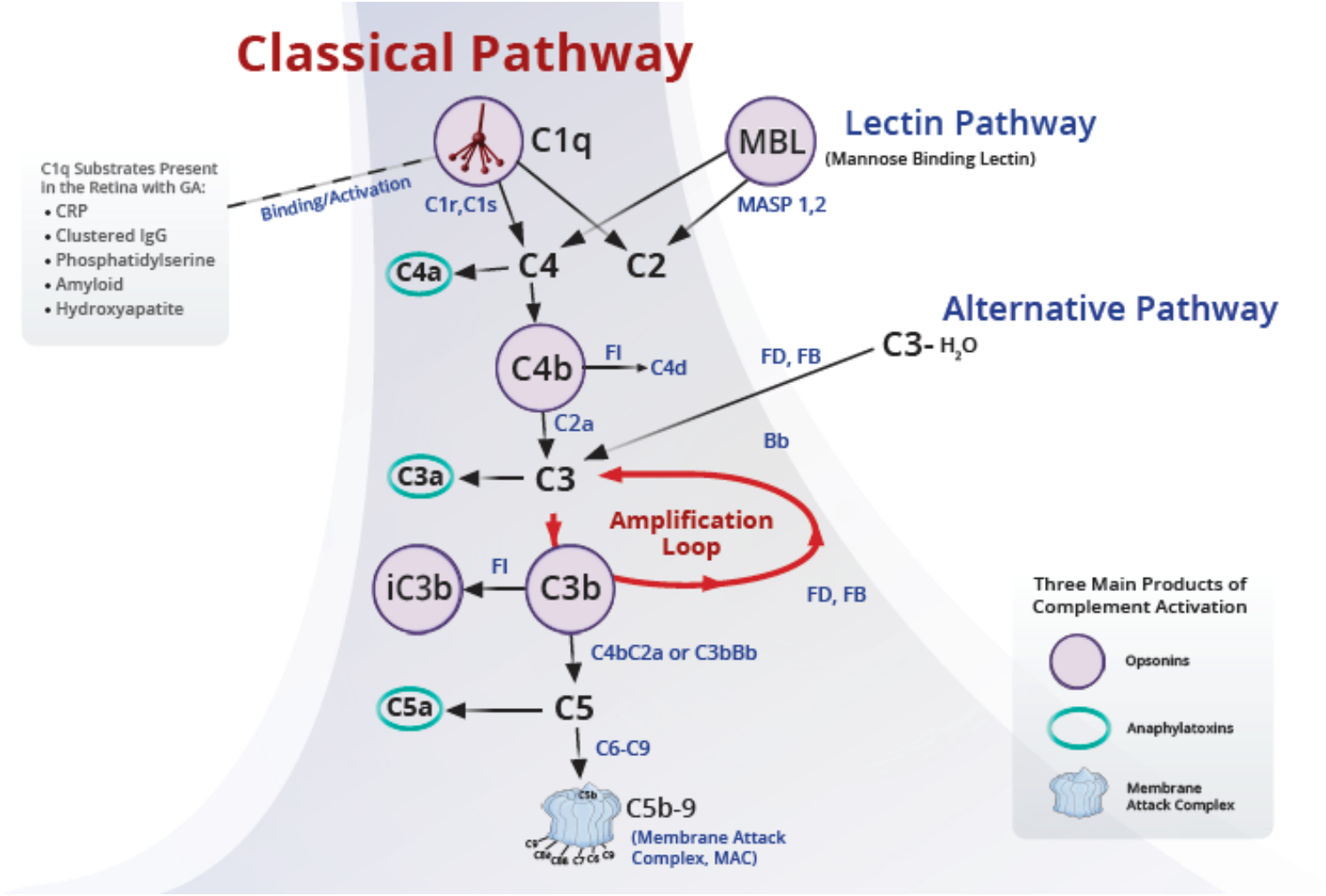
C1q and Classical Complement Pathway

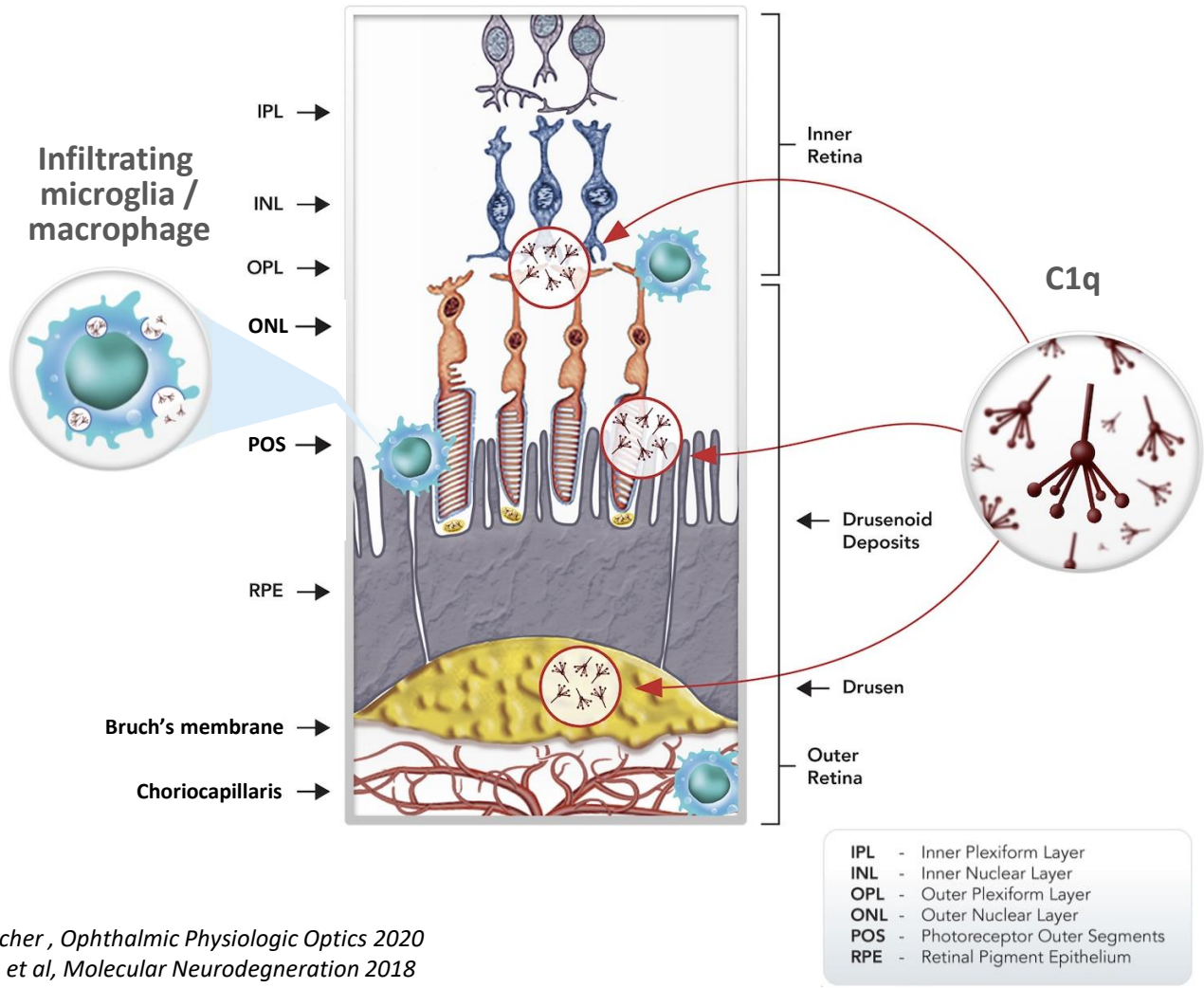


Selective inhibition of C1q and the classical cascade allows immune functions of lectin and alternative complement pathways to continue without disruption

Katsche et al. Scientific Reports 2018
Law and Dodds. Protein Science 1997
Chirco and Potemp. Front Immunology 2018

C1q and Classical Cascade are Key Drivers in Geographic Atrophy

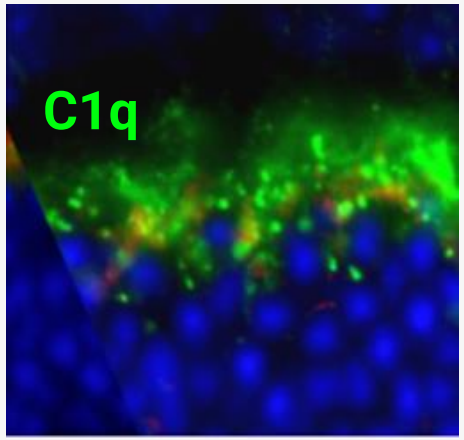
- **High local expression of C1q in retina by infiltrating macrophages**
  - Macrophages in OPL, POS, RPE, choroid express high levels of C1q
- **C1q and activated complement components deposited in multiple layers of outer retina**
- **Blocking C1q / classical pathway protects photoreceptor cells and function in photoreceptor damage models**
  - *Blocks all tissue-damaging components of classical pathway (C1q, C4, C3, C5, C9)*
  - *Maintains immune functions of lectin and alternative complement pathways*



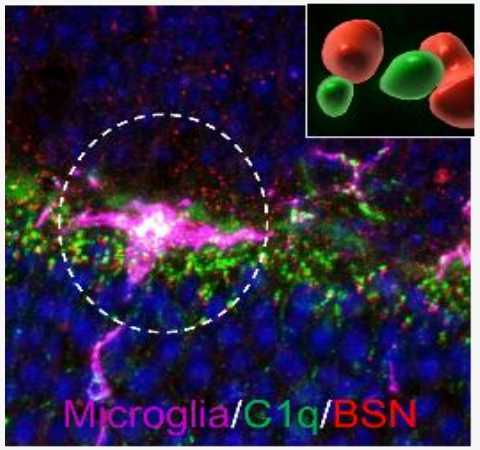
Fletcher , Ophthalmic Physiologic Optics 2020
Jiao et al, Molecular Neurodegeneration 2018

C1q Accumulates with Age and Disease in GA

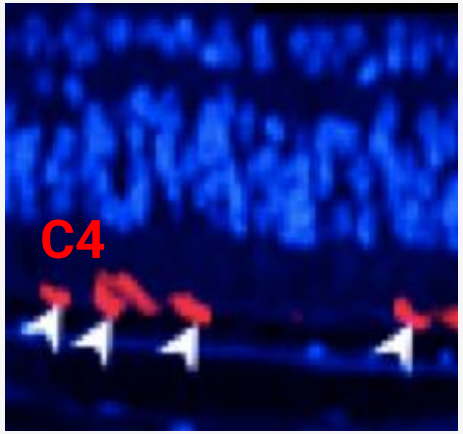
C1q activated within multiple layers of outer retina in GA



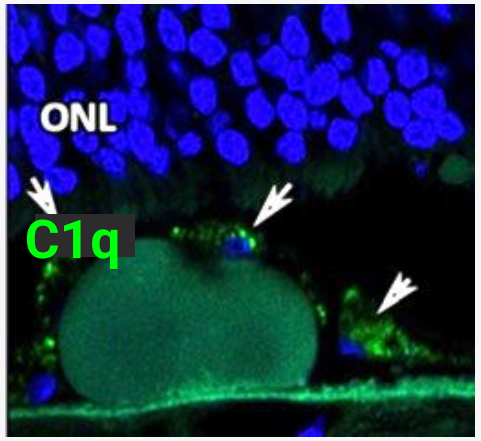
C1q on synapses of photoreceptor cells in aged mice[1]



Microglia engulfing C1q labeled photoreceptors in mouse model of retinal damage[1]



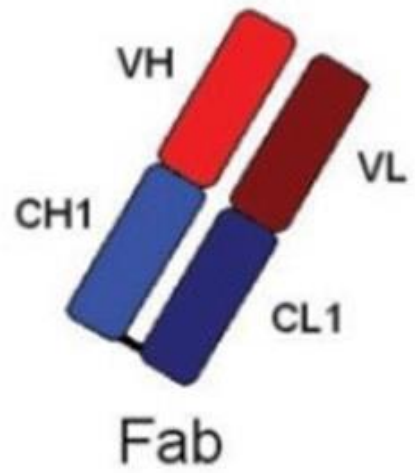
Downstream C4 deposited on photoreceptor cell outer segments in GA patients[2]



C1q on Drusen in GA patients[3]

[1]Annexon data on file; [2]Katschke, 2018; [3]Jiao, 2018

ANX007 is Designed to Inhibit C1q



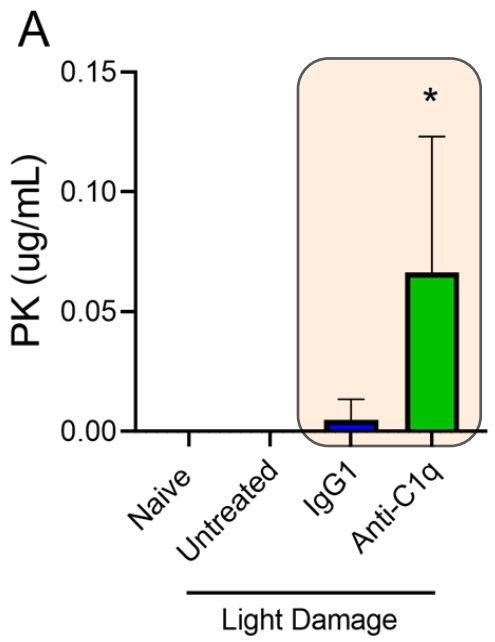
- Recombinant humanized IgG1 antigen binding fragment (Fab)
- High affinity (10 pM) against substrate-binding head groups of C1q
- Molecular weight - ~48 kDa

Methods

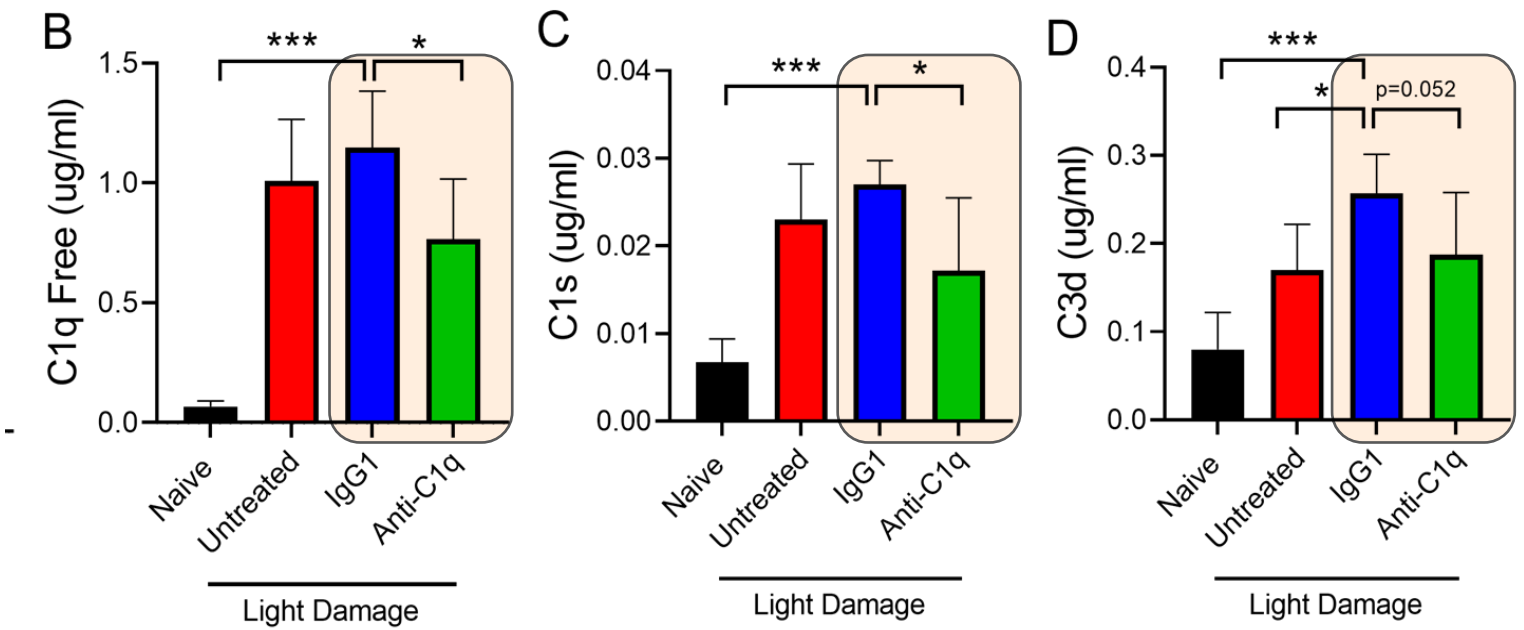
Light Damage	• Balb/c mice were exposed to white light to cause retinal damage and observed at Day 1, 3 and 7 post light exposure • Acute: 25K Lux for 4hs; Mild: 5K Lux for 30min
Complement Signature	• Classical complement component levels were measured in retinal lysates by standard sandwich ELISA
C1q deposition on synapses and microglia engulfment	• C1q expression in tissue was assessed by Immunofluorescence (IF) and Confocal Microscopy • Microglia engulfment of synapses was assessed using IMARIS software
C1q inhibition	• C1q activity was pharmacologically blocked by intravitreal injection of a C1q inhibitory antibody (ANX-M1.21) one day prior to light exposure • Tissue was assessed at Day 3 and 5 after treatment by ELISA and IHC
Human Tissue Procurement	• Retina specimens from GA patients were procured from the San Diego Eye Bank

Intravitreal Administration of Anti-C1q Reduces Retinal Complement Levels in a Light Damage Mouse Model

Measurable drug levels in retina lysates

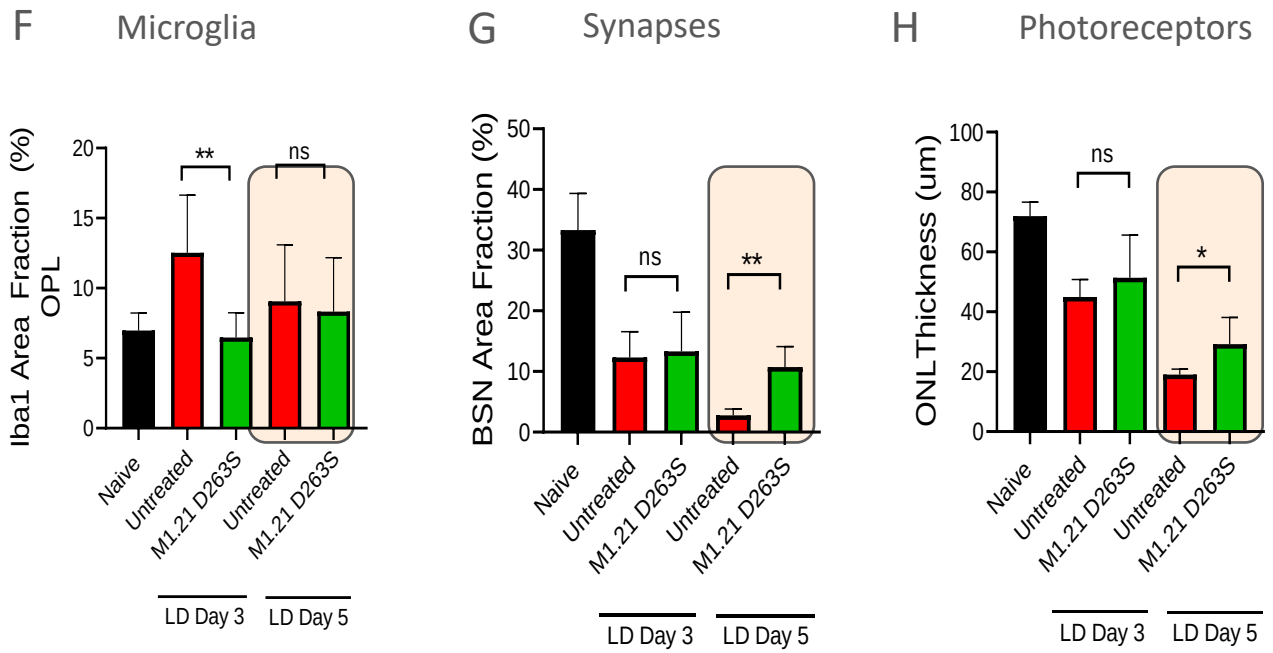


Significant decrease in C1q, C1s and C3d levels upon anti-C1q treatment



ANNEXON biosciences

Anti-C1q Reduces Neurodegeneration in a Light Damage Model

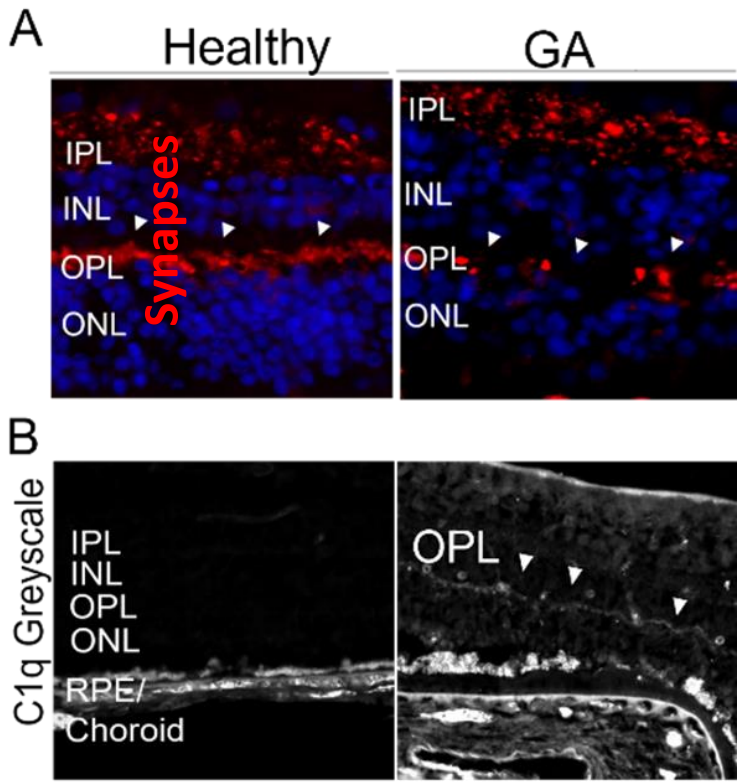


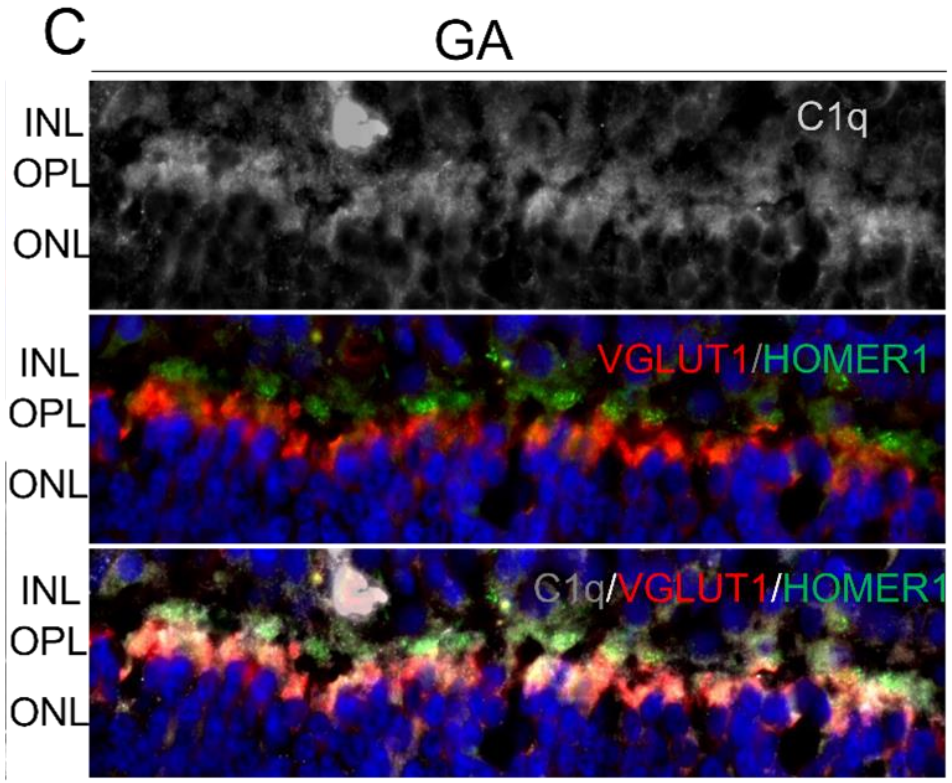
Preliminary immunofluorescence data shows –

- Reduced microgliosis in the OPL at Day 3 post treatment
- Significant preservation of photoreceptor synapses and cell bodies at Day 5 post treatment

Annexon data on file

C1q Expression and Deposition on Photoreceptor Synapses in Human GA Retina





IF showing reduced immunoreactivity for pre-synaptic marker VGLUT1 (A, red) and increased labelling for C1q (B, grey scale) in photoreceptor synaptic layer OPL, confirming synaptic loss and C1q accumulation occurring in GA retina

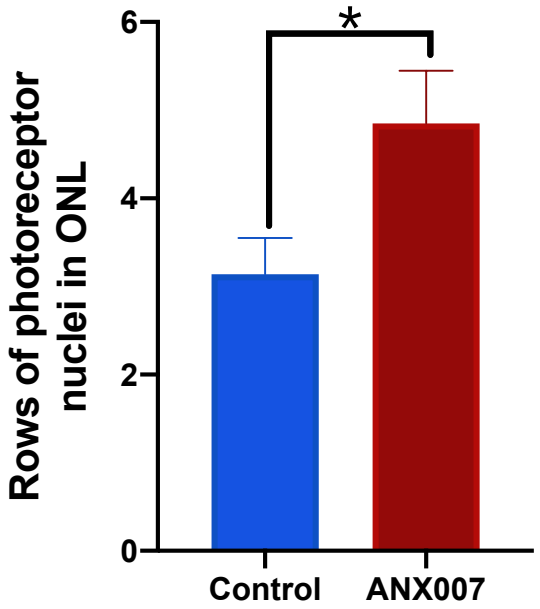
Triple immunolabelling for C1q (grey), presynaptic marker VGLUT1 (red) and postsynaptic marker (HOMER1) confirming co-localization of C1q with photoreceptor synapses in human GA donor retina

Retina specimens from GA patients were procured from the San Diego Eye Bank

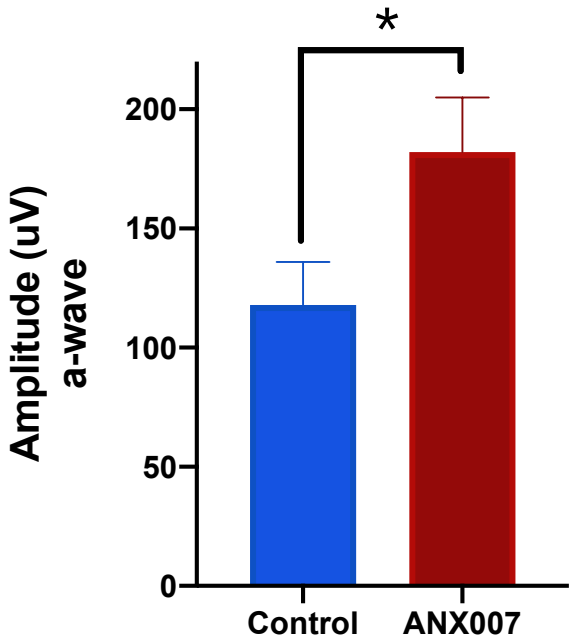
ANX007 Provides Neuroprotection in a Mouse Model

Intravitreal Administration of ANX007 Protects Photoreceptor Cells and Retinal Function

Anti-C1q Protects Photoreceptor Cells / Retinal Thickness



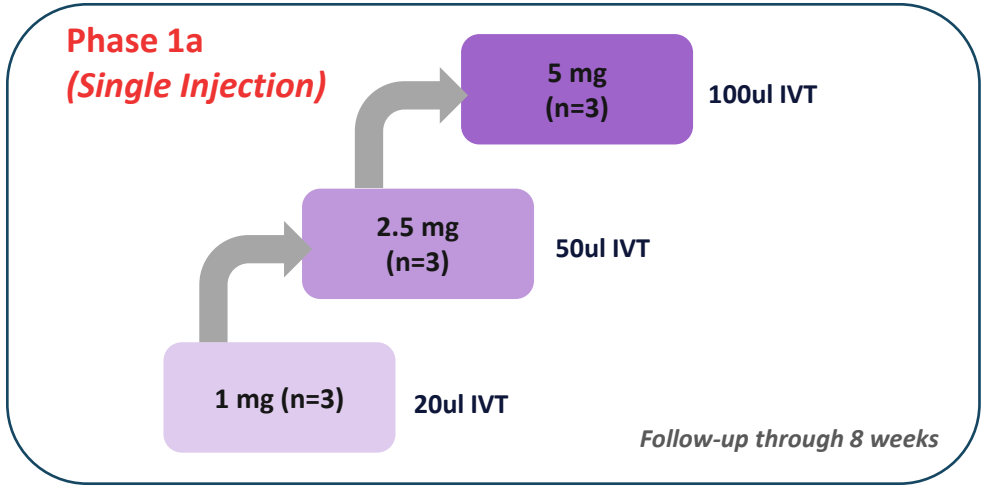
Protects Retinal Function

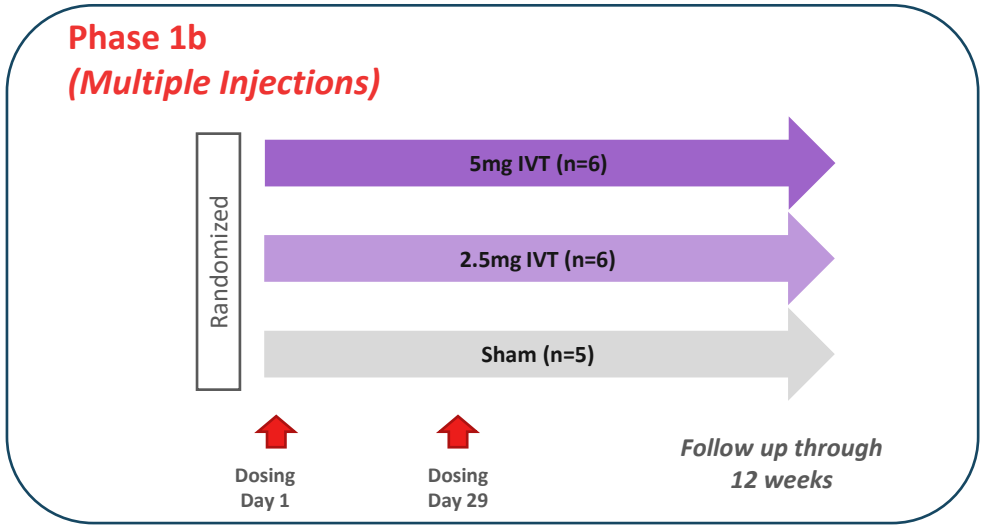


** p < 0.05;*

Jiao et al., 2018 Mol Neurodegener 13(1):45

Phase 1 Studies in Glaucoma



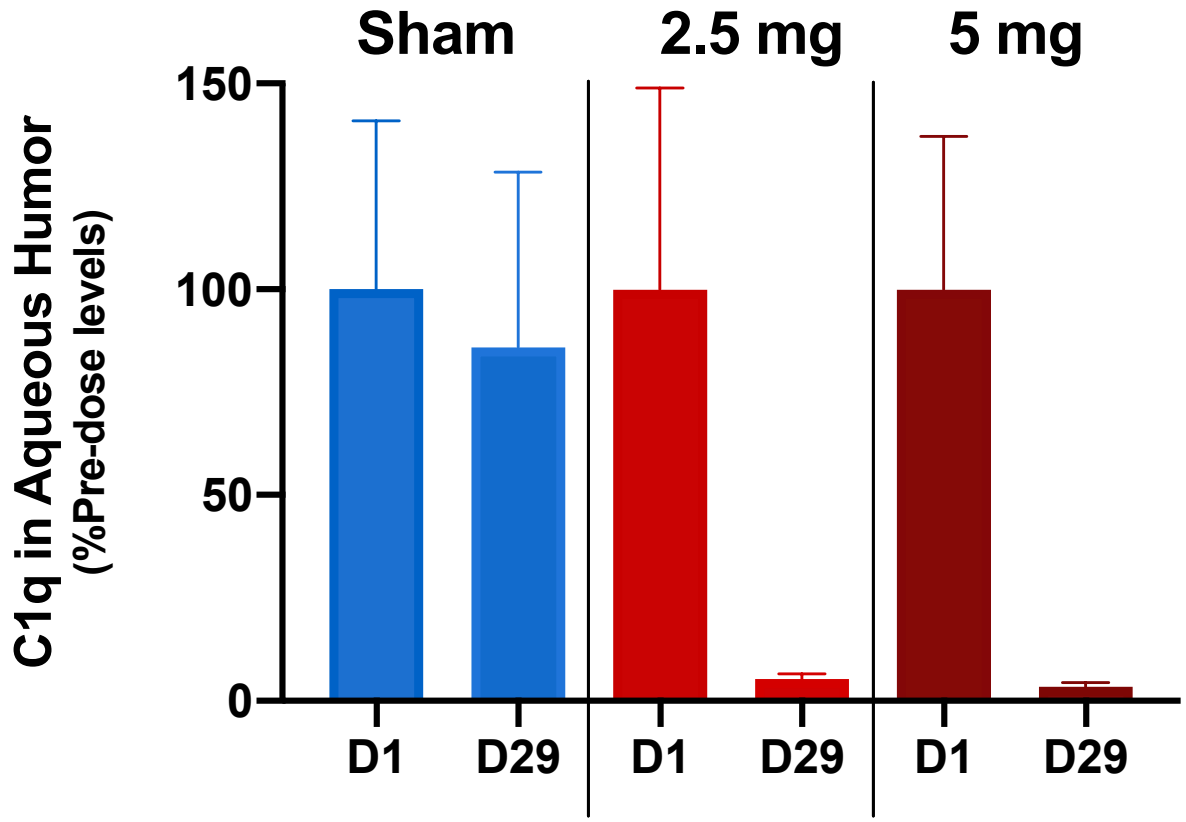


SUMMARY

- Repeat doses, in patients with Primary Open-Angle Glaucoma *(n=17)*
- Well-tolerated at all dose levels
  - No SAEs or severe TEAEs
  - All AEs were mild in severity and resolved
  - Ocular TEAEs (ocular irritation, subconjunctival hemorrhage or conjunctival hyperemia) consistent with other IVT administered treatments

Data on File, Annexon Biosciences

ANX007 Effectively Inhibits C1q



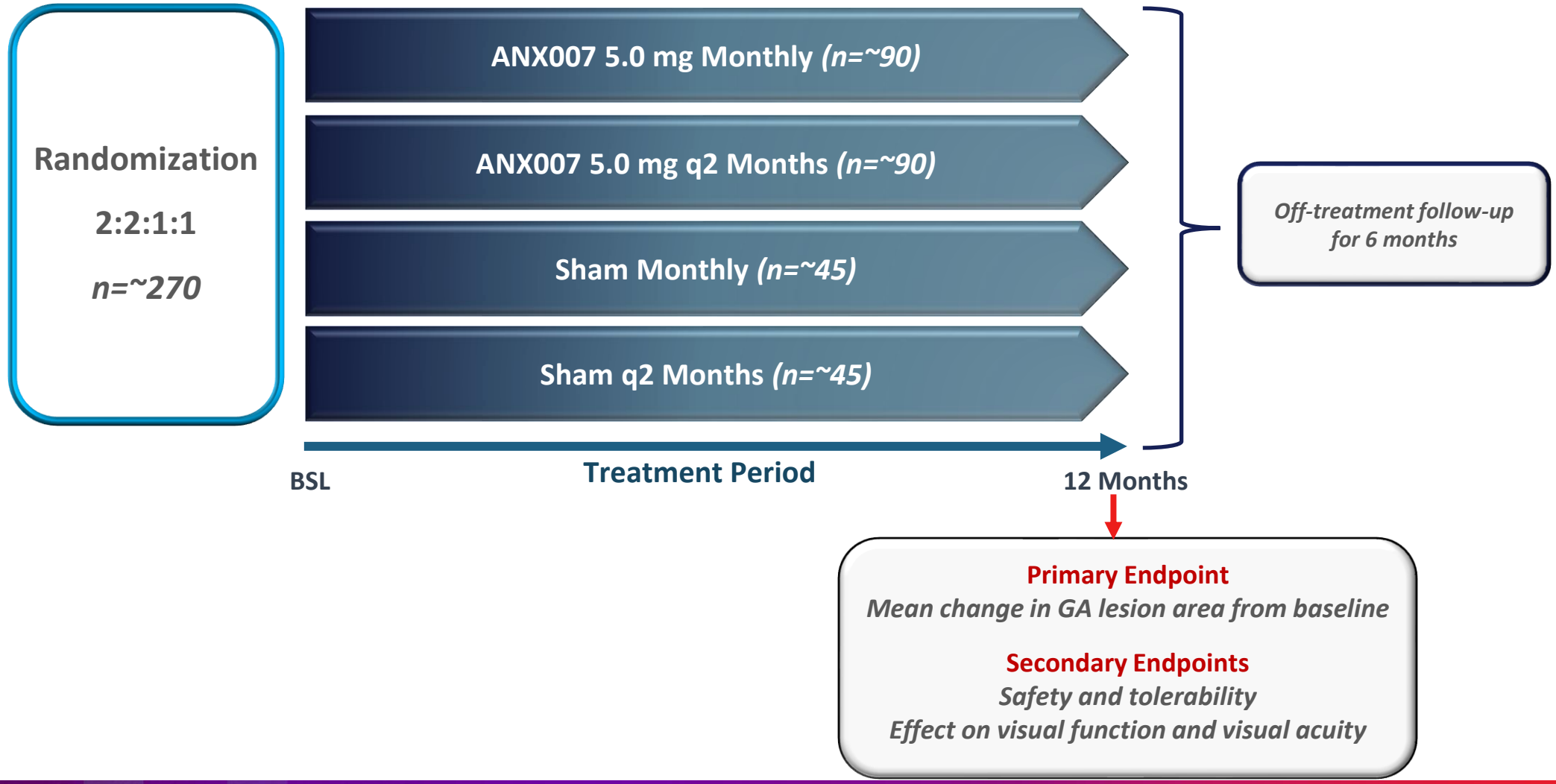
D1 *= Day 1 (before ANX007 dosing)*

D29 *= Day 29 (post-1st dose)*

Single intravitreal injection ***inhibited C1q in aqueous humor for at least 29 days*** at both doses

Data on File, Annexon Biosciences

The ARCHER Study: *Ongoing Phase 2 Study Evaluating Effect of ANX007*



Summary

- C1q, the initiating molecule of the classical complement cascade, has been implicated in neurodegenerative diseases, including GA
- Anti-C1q treatment reduces retinal complement levels, decreases inflammation and reduces neurodegeneration in the light damage model
- ANX007 is designed to inhibit C1q while allowing immune functions of lectin and alternative complement pathways to continue
- IVT ANX007 was well- tolerated in Phase 1 studies in glaucoma
- ***Enrollment completed for*** ARCHER study evaluating GA lesion growth rate following IVT ANX007 (5 mg q1 month or q2 months) compared to sham