Forward-looking Statements

This presentation and accompanying oral presentation contain "forward-looking" statements about Annexon, Inc. and our industry that involve substantial risks and uncertainties. All statements other than statements of historical facts, including statements regarding our clinical and preclinical programs, timing and commencement of future nonclinical studies and clinical trials and research and development programs, timing of clinical results, strategic plans for our business and product candidates, including additional indications which we may pursue, our financial position and anticipated milestones, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "focus," "goal," "intend," "may," "objective," "plan," "positioned," "potential," "predict," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

Forward-looking statements are not guarantees of future performance and are subject to risks and uncertainties that could cause actual results and events to differ materially from those anticipated, including, but not limited to, risks and uncertainties related to: our history of net operating losses; our ability to obtain necessary capital to fund our clinical programs; the early stages of clinical development of our product candidates; the effects of COVID-19 or other public health crises on our clinical programs and business operations; our ability to obtain regulatory approval of and successfully commercialize our product candidates; any undesirable side effects or other properties of our product candidates; our reliance on third-party suppliers and manufacturers; the outcomes of any future collaboration agreements; and our ability to adequately maintain intellectual property rights for our product candidates. These and other risks are described in greater detail under the section titled "Risk Factors" contained in our Annual Report on Form 10-K and Quarterly Reports on Form 10-Q and our other filings with the Securities Exchange Commission (SEC). All forward-looking statements in this presentation speak only as of the date of this presentation. Except as required by law, we undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise.

This presentation concerns drugs that are under clinical investigation, and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). These are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

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Agenda / Executive Summary

- **Scientific Rationale**
  - Classical complement pathway implicated in Neurodegenerative (Huntington's Disease) and Autoimmune (Guillain-Barre Syndrome) Diseases
  - Classical complement pathway is implicated in Geographic Atrophy; drusen and other breakdown products of photoreceptor digestion activate C1q and the classical pathway

- **Laboratory Evidence**
  - Animal and human pathology specimen show classical complement activation
  - Inhibition of C1q is protective against retinal damage and maybe neuroprotective
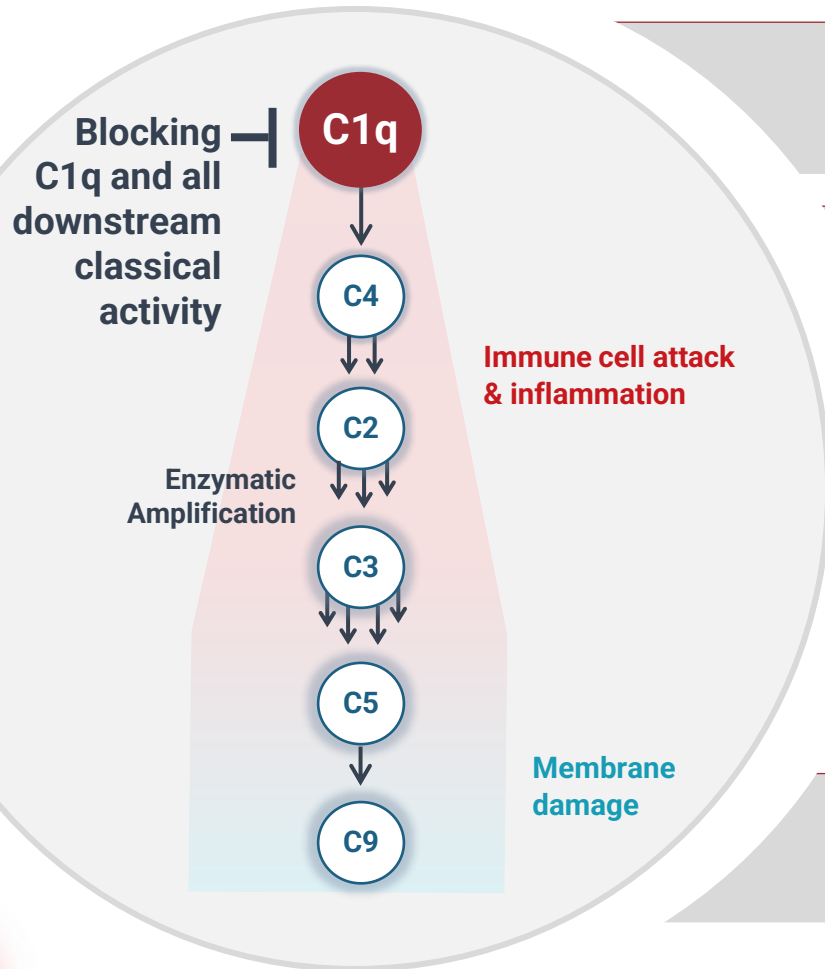
- **Human Experience**
  - ANX007 good target engagement >29 days
  - Phase 1 studies demonstrate favorable safety profile

- **ARCHER Clinical Trial**
  - Randomization stratified for lesion location and size
  - Phase 2 data anticipated in 1st half 2023

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Annexon Pioneering a Powerful Approach to Classical Complement Inhibition

Classical Complement Pathway

Blocking C1q and all downstream classical activity ⊣ **C1q**

↓

C4

Immune cell attack & inflammation

↓↓

C2

Enzymatic Amplification

↓↓↓

C3

↓↓↓

C5

↓

Membrane damage

C9

Complement Inhibition Clinical & Commercially Validated

Next Generation Approach Blocking Both Up & Downstream Classical Complement

Unique Clinical Benefit Demonstrated in Autoimmune & Neurodegenerative Trials

5 'fit-for-purpose' Clinical Candidates in Autoimmune, Neurodegenerative & Ophthalmic Trials

Positioned for Significant Value Creation -- Several Upcoming Clinical Milestones & 2H 2025 Runway

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C1q: A Key Driver of Complement-Mediated Disease

Initiator of aberrant or excess complement activity in autoimmune and neurodegenerative diseases

Key Takeaways

- C1q is initiating molecule in classical complement cascade

- C1q binds tissue surfaces to **anchor and amplify** complement activation and drive disease

- **C1q marks cells and synapses for elimination by microglia and tissue macrophages**
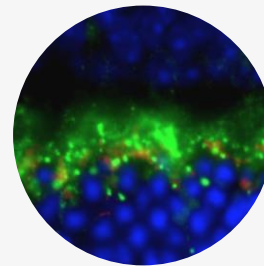
Initiator: C1q Binding to Tissues in Disease
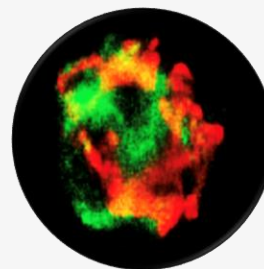
Autoimmune
Guillain-Barré Syndrome
C1q Targeting the Neuromuscular Junction[1]
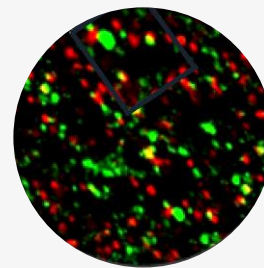
Neurodegeneration
Huntington's Disease
C1q Targeting Striatal Synapses[2]

Ophthalmologic
Geographic Atrophy
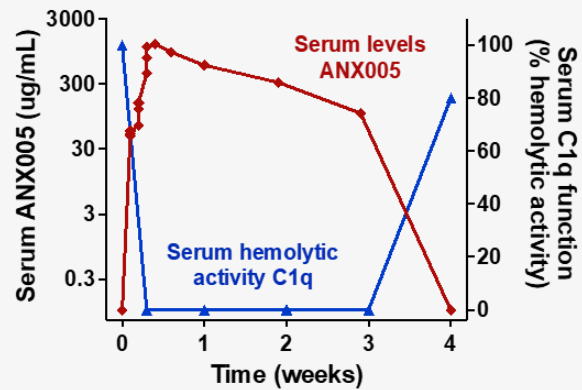**C1q Targeting Photoreceptor Synapses[3]**

[1] Halstead, et al. 2004 Brain 127: 2109–2123 [2] Jia, et al, 2018 Mol Neurodegen 14:45

[3] C1q bound to photoreceptor synapses in aged mice: Annexon data on file

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Annexon's Lead Candidates Demonstrate Robust Target Engagement in Body, Brain and Eye in Clinical Trials

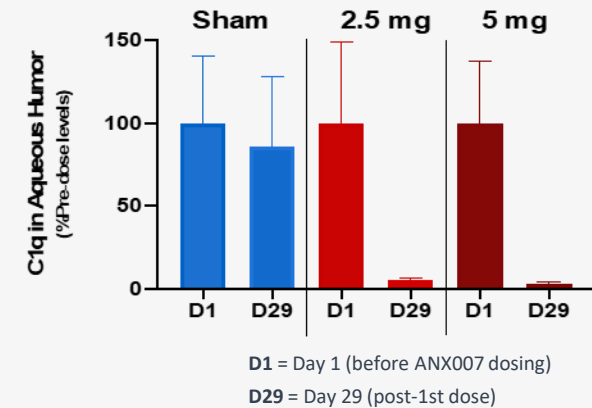## C1q Body Inhibition

ANX005 Full C1q Inhibition in Serum

Serum levels ANX005

Serum hemolytic activity C1q

Serum ANX005 (ug/mL)

Serum C1q function (% hemolytic activity)

Time (weeks)

Autoimmune

C1q Brain Inhibition

ANX005 Full C1q Inhibition in CSF

CSF C1q and ANX005

CSF C1q (ng/ml)

CSF ANX005 (ng/ml)

Weeks

n=13

Neuro
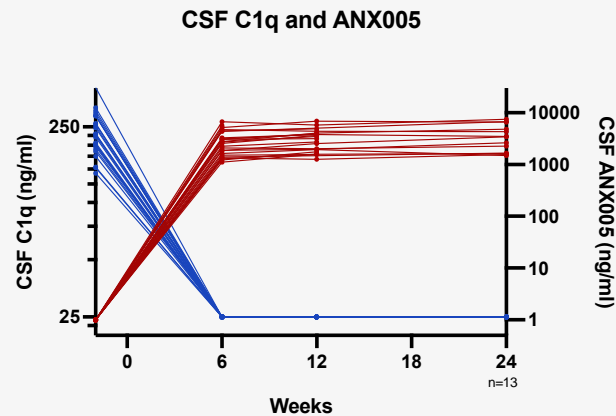
C1q Eye Inhibition

ANX007 Full C1q Inhibition in Aqueous Humor

Sham   2.5 mg   5 mg

C1q in Aqueous Humor (%Pre-dose levels)

D1   D29   D1   D29   D1   D29

D1 = Day 1 (before ANX007 dosing)
D29 = Day 29 (post-1st dose)

Ophthalmology

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Upstream Classical Complement Inhibition Associated with Clinical Benefit

Guillain-Barré Syndrome

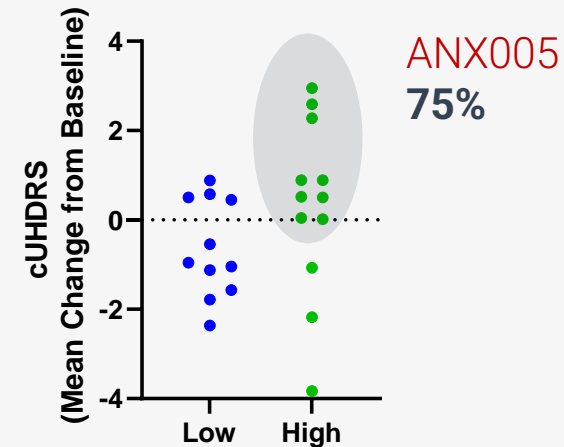Patients achieving **≥3 point improvement** in 8 weeks

ANX005
28%

Placebo
0%
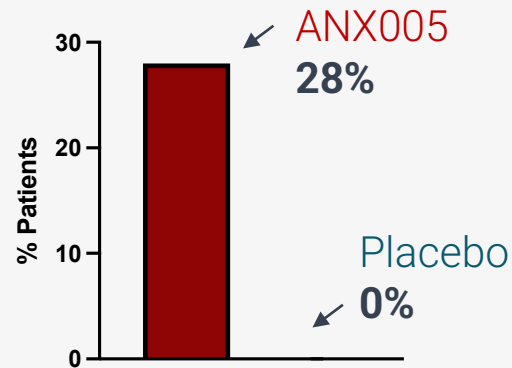
GBS Disability Scale
Patients improved from being bed bound to walking unassisted

Huntington's Disease

75% of patients with high baseline complement activity maintained improvement at week 36

ANX005
**75%**

Composite Unified Huntington's Disease Rating Scale

Annexon data on file.
GBS Disability Scale and composite Unified Huntington's Disease Rating Scale are accepted regulatory endpoints.

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Why target C1q in Geographic Atrophy?

- **Complement pathway** confirmed as a **key driver of disease**
  - **Polymorphisms** in 6 different complement genes
  - **Clinical trials** show inhibition of amplification loop (C3) and MAC (C5) slow progression of disease

- **Why and how is complement system activated** in geographic atrophy (GA)?
  - In age and disease, C1q tags synapses on photoreceptor cells
  - Drusen and other photoreceptor breakdown products activate C1q
  - C4 (classical pathway upstream of C3) is found at leading edge of GA lesion
  - In animal models, C1q inhibition slows atrophy and preserves function
  - **C1q and classical pathway activation is result of substrate-based activation**
  - C1q inhibition stops enzymatic cascade and may offer neuroprotection

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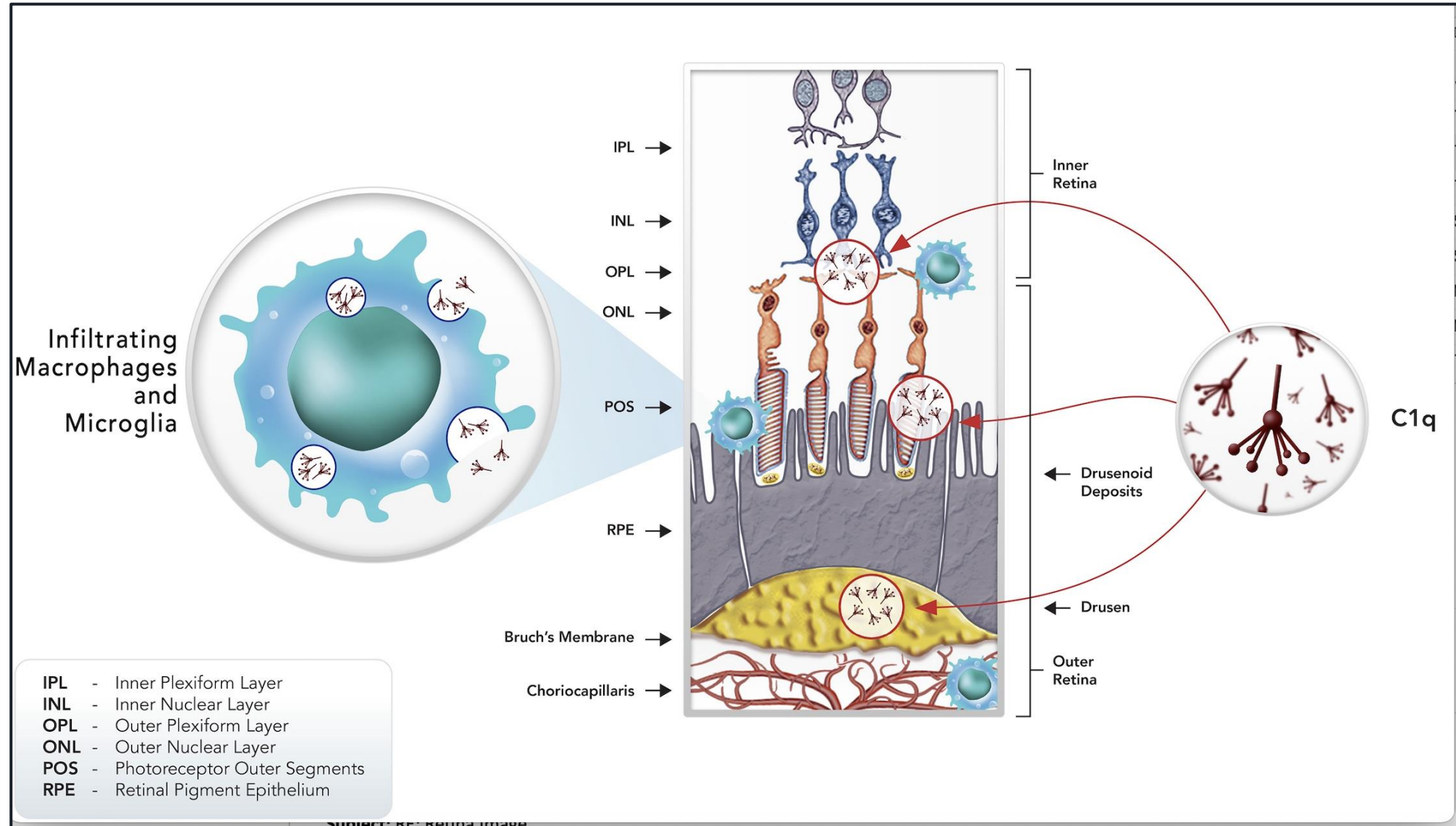biosciences

Why target C1q in GA?
Aberrant Substrate-Based Complement Cascade
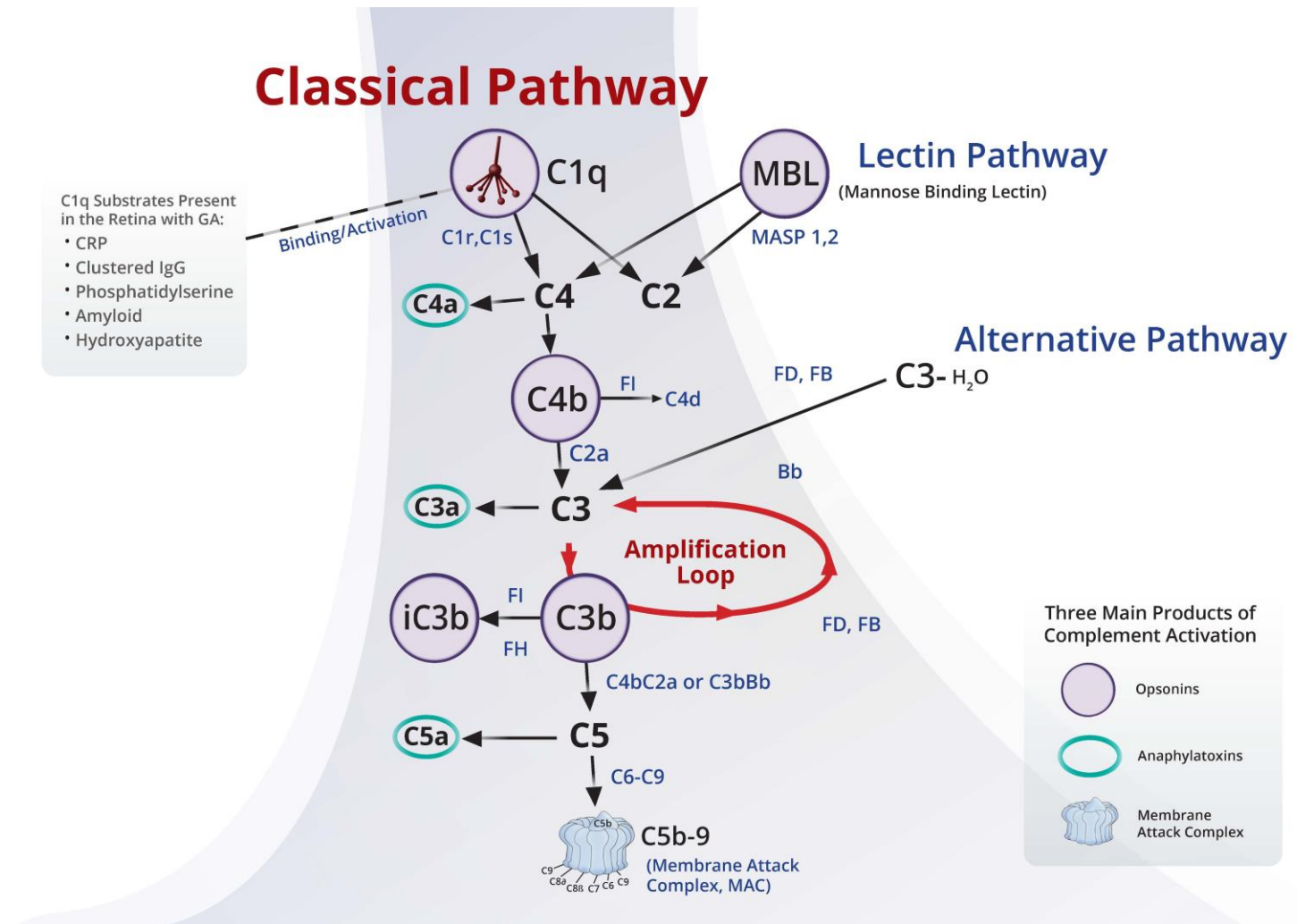
Katsche et al. Scientific Reports 2018
Law and Dodds. Protein Science 1997
*Chirco and Potemp. Front Immunology 2018*

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Why target C1q in GA?
C1q Present in All Layers of the Outer Retina

Infiltrating Macrophages and Microglia

IPL - Inner Plexiform Layer
INL - Inner Nuclear Layer
OPL - Outer Plexiform Layer
ONL - Outer Nuclear Layer
POS - Photoreceptor Outer Segments
RPE - Retinal Pigment Epithelium

IPL
INL
OPL
ONL
POS
RPE
Bruch's Membrane
Choriocapillaris

Inner Retina
Drusenoid Deposits
Drusen
Outer Retina

C1q

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Why target C1q in GA?
Anti-C1q Differentiated from Other Approaches

C1q, C4b and C3b are the major opsonins of the classical pathway for macrophage and microglial cell attack
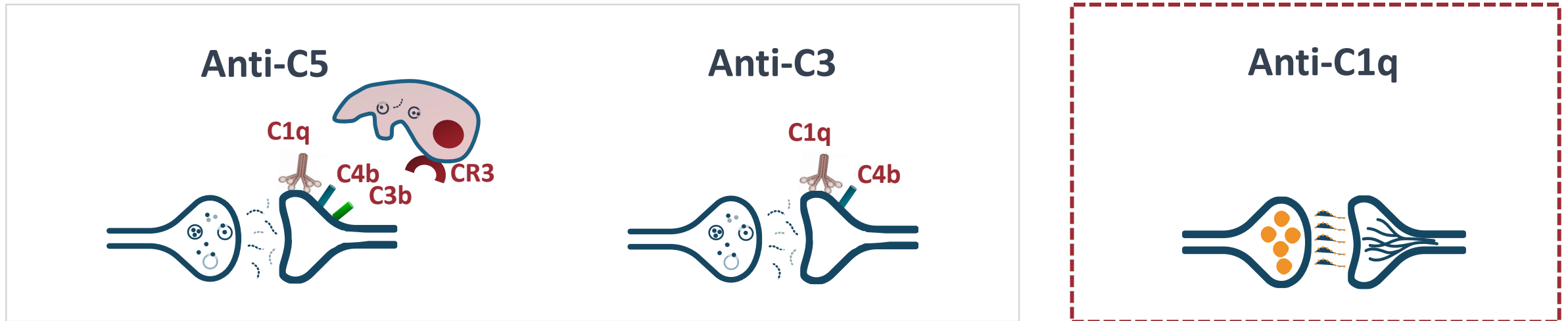
Selective inhibition of classical pathway allows alternative and lectin pathways to continue homeostatic functions

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Why target C1q in GA?
C1q Accumulates with Age and in GA

C1q accumulation on photoreceptor cell synapses in mouse retina

C1q accumulation on drusen in human retina with GA
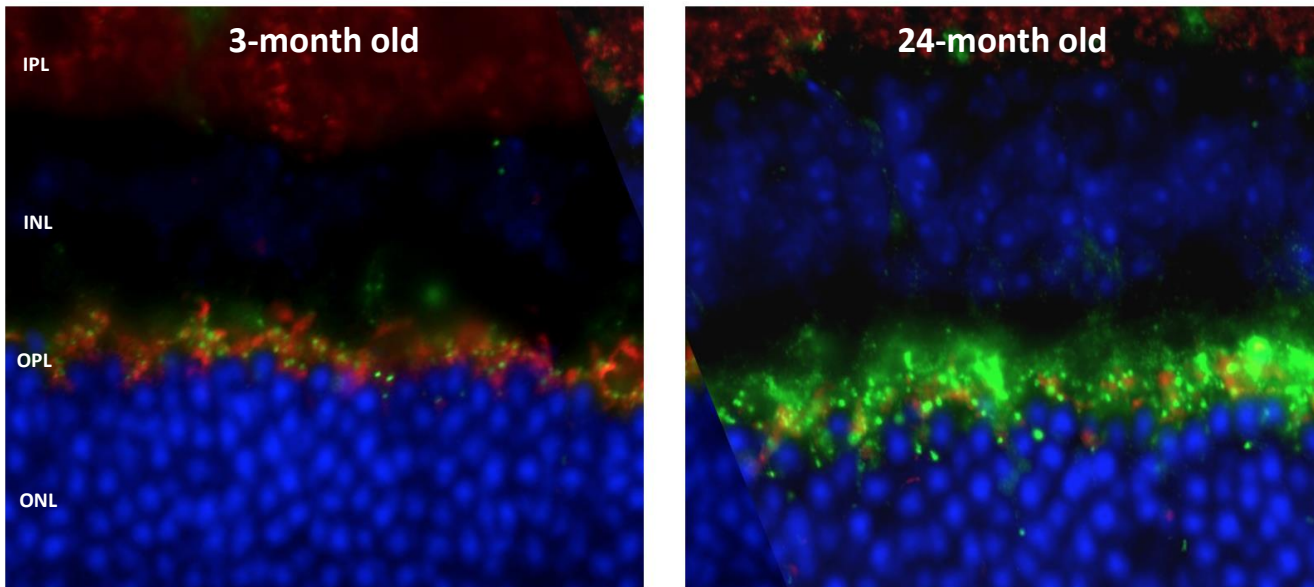
Data on File, Annexon Biosciences

Synapses **C1q** **Nuclei**
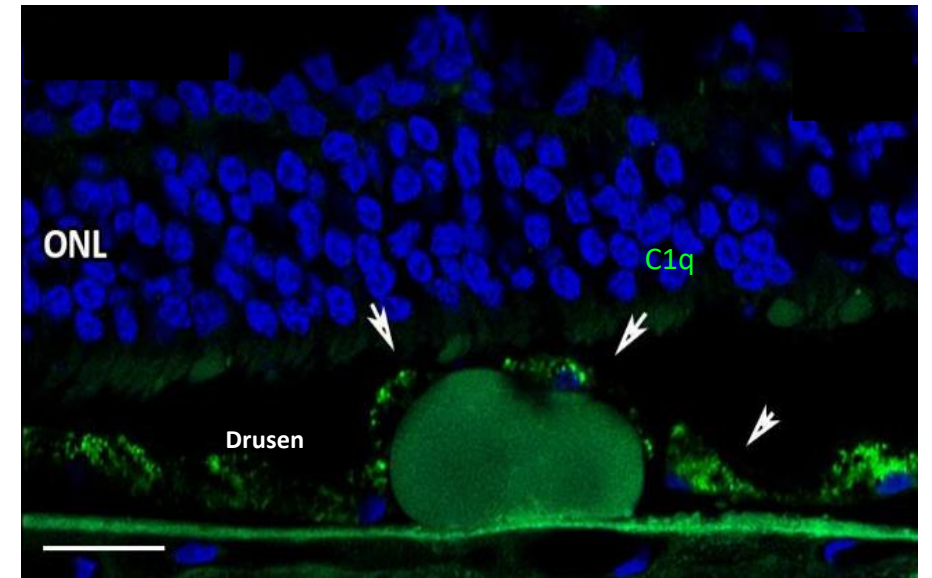
Human retinal micrograph: Jiao, et al., Mol Neurodegener. 2018 08 20;13(1):45

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C4 Accumulation Support Classical Complement Cascade in GA

- 67% of photoreceptor cells (outer segments) show early stage accumulation of complement C4

- 26% show accumulation of C3 (see white arrows)

GA (86 yr GA patient) – 1.2 mm from lesion edge
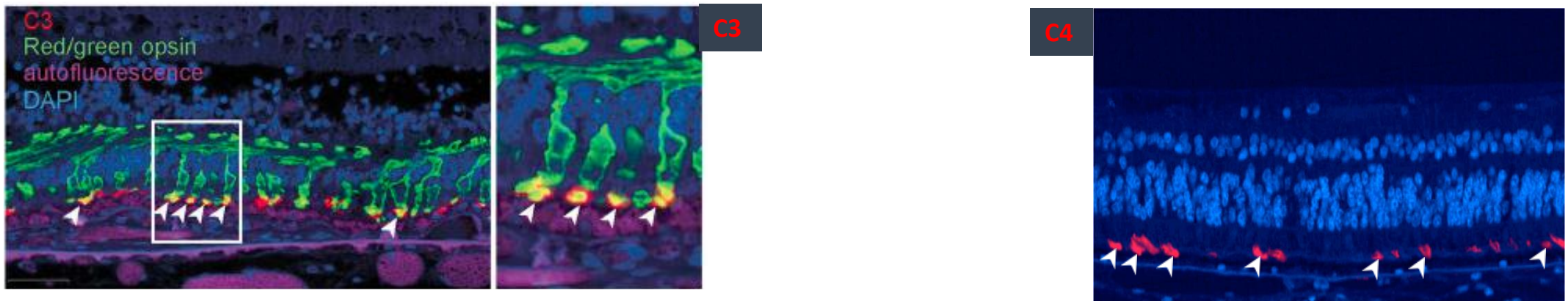
C3 and C4 staining on photoreceptor outer segments (POS)

	Mean age (±SD)	Donors	Total eyes	C3+ POS	C4+ POS
AMD	85.9 (±5.1)	13	19	5/19 (26%)	12/18 (67%)
Control	76.4 (±8.4)	9	13	0/11 (0%)	1/13 (8%)

Katschke et a., Sci Reports 2018

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New Data: Light Damage Model of Photoreceptor Degeneration

- To examine expression and tissue localization of complement proteins in synapses of mice retina exposed to damaging light

- To determine the potential therapeutic benefit of classical complement inhibition in the light damage model of photoreceptor degeneration

Mouse (Balb/c, albino)

White Light

Photoreceptors

RPE
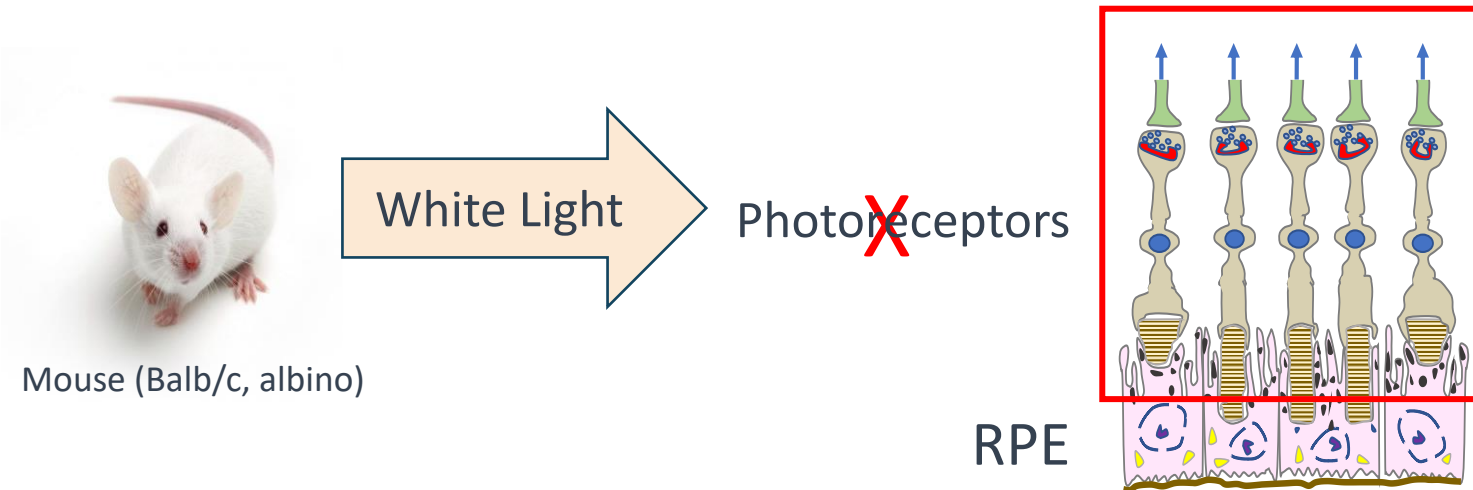
- Overactivation of visual transduction cascade in photoreceptor cells
- Photoreceptor oxidative stress
- Direct photoreceptor death

Light Damage Model of Photoreceptor Degeneration – 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 the 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 one day prior light exposure. Tissue was assessed at Day 3 and 5 after treatment

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Blocking C1q Protects Photoreceptors in Light Damage Mouse Model

Increased C1q Expression on Photoreceptor Synapses and Cell Bodies

Naive **Light Damage**

Photoreceptor cell bodies
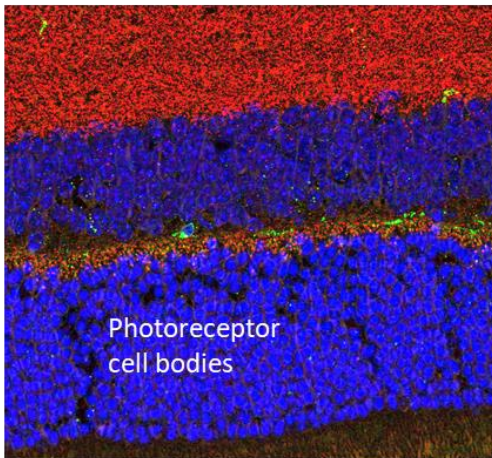
Photoreceptor cell bodies

Synapses **C1q**
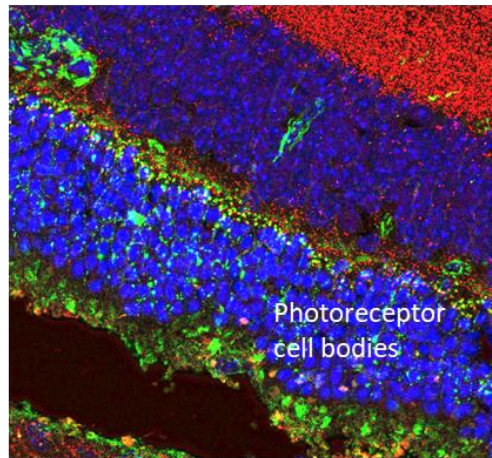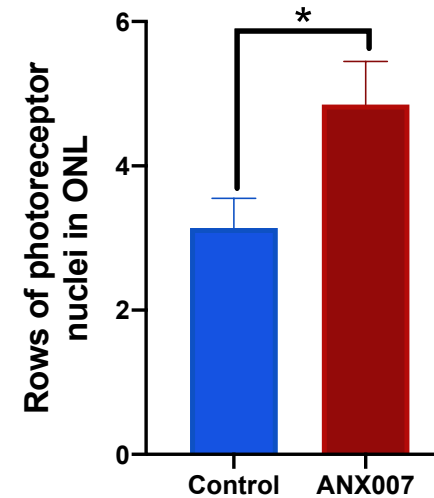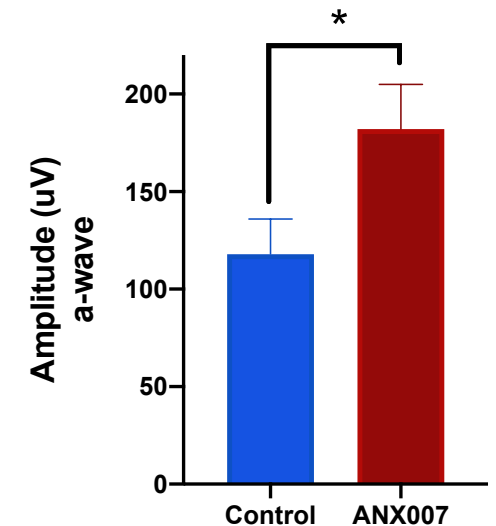
Annexon data on file

Anti-C1q Protects Photoreceptors & Retinal Function in Light damage Model

Anti-C1q Protects Photoreceptor Cells / Retinal Thickness
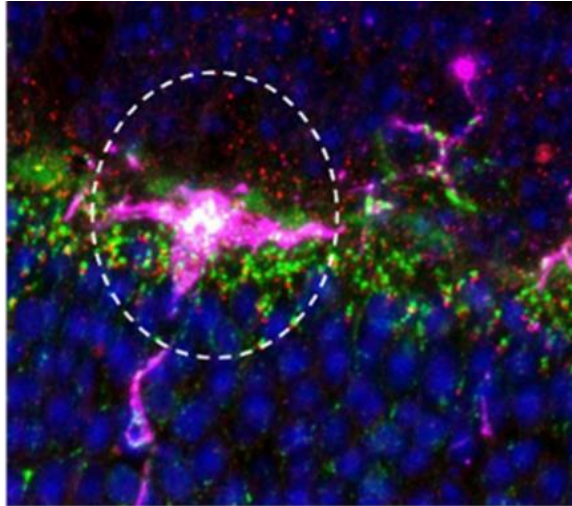
Protects Retinal Function

Rows of photoreceptor nuclei in ONL — Control, ANX007 *

Amplitude (uV) a-wave — Control, ANX007 *

Jiao,, et al., 2018 Mol Neurodegener 13(1):45
$* p < 0.05$

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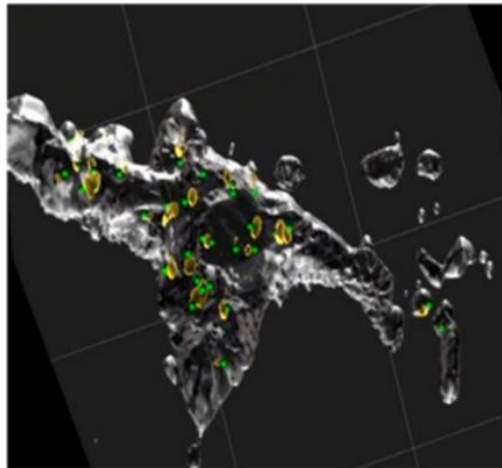# Microglial Cell Engulfment of C1q-Tagged Photoreceptor Synapses

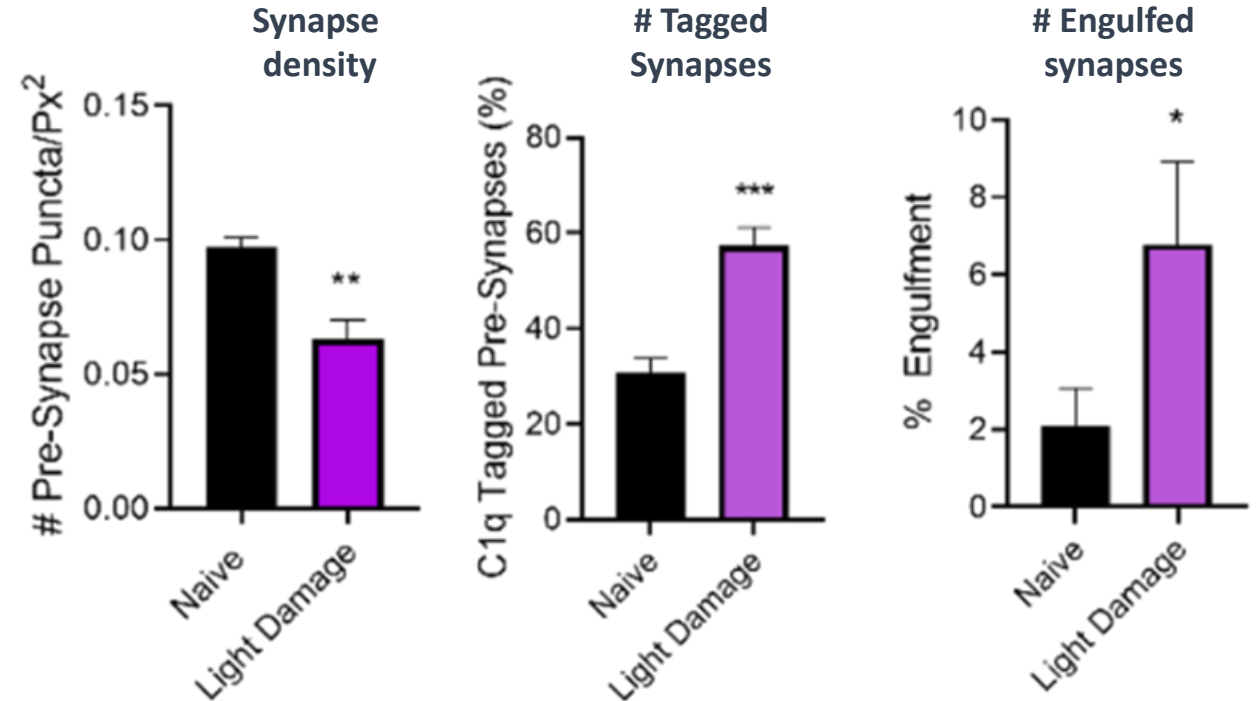**Microglial infiltration of OPL**

Microglia/C1q/BSN

**High resolution 3D surface rendering**

Engulf. C1q-Synapse

Microglial cell engulfment of C1q tagged synapses in light damaged retina

Synapse density

\# Pre-Synapse Puncta/Px^2 — Naive, Light Damage **

\# Tagged Synapses

C1q Tagged Pre-Synapses (%) — Naive, Light Damage ***

\# Engulfed synapses

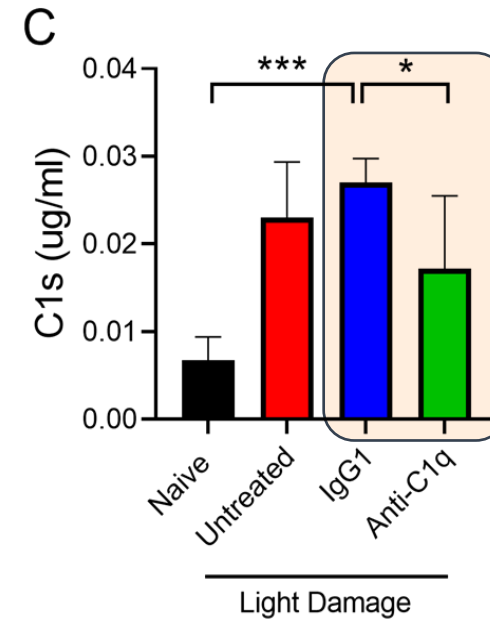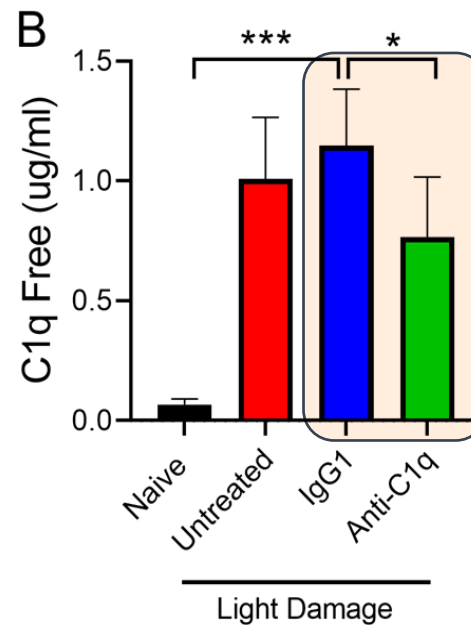% Engulfment — Naive, Light Damage *

* ≤ 0.05; ** ≤0.01; *** ≤0.001

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

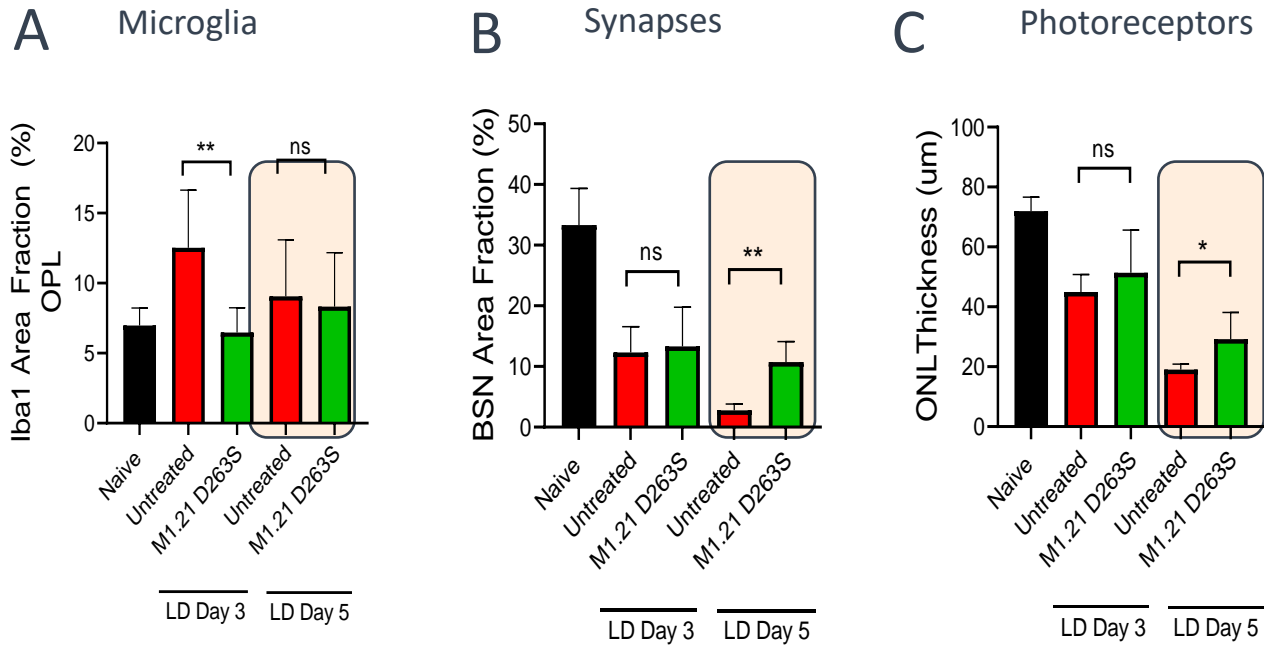**Measurable drug levels in retina lysates**
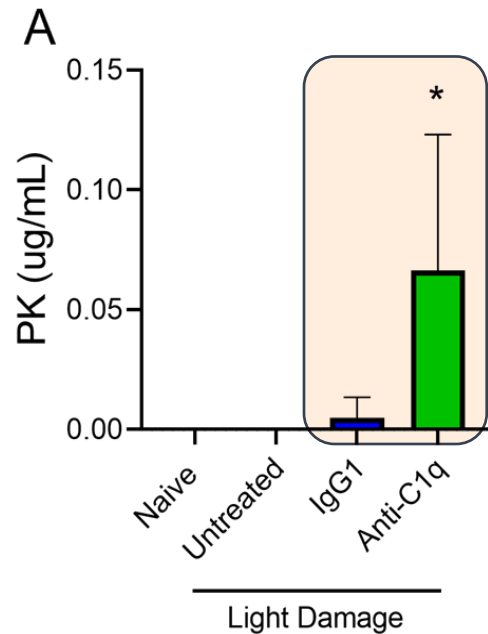
Significant decrease in C1q, C1s and C3d levels upon anti-C1q treatment

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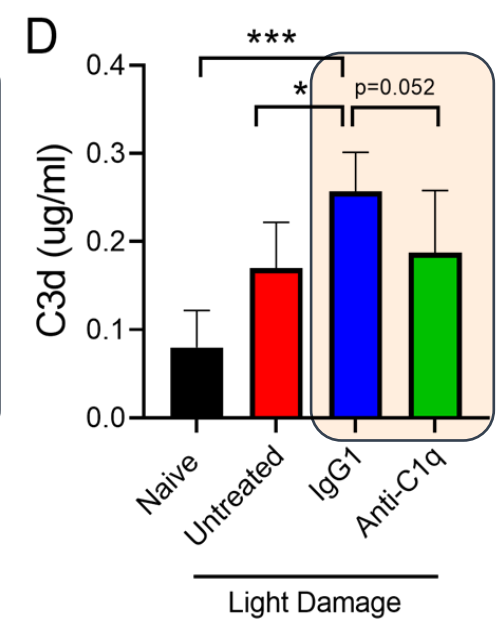
Anti-C1q Reduces Neurodegeneration in Light Damage Mouse Model
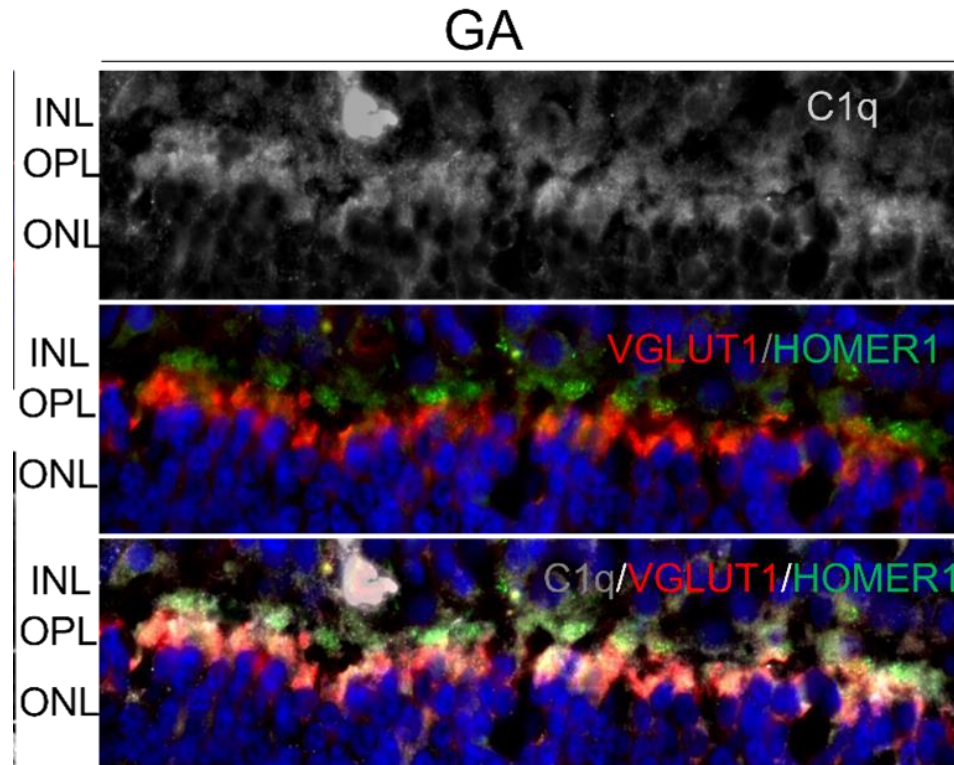

A — Microglia

B — Synapses

C — Photoreceptors

* ≤ 0.05; ** ≤0.01; *** ≤0.001

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

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C1q Deposition on Photoreceptor Synapses in Human GA Retina

Triple immunolabelling for C1q (grey), presynaptic marker VGLUT1 (red) and postsynaptic marker HOMER1 (green) 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*

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Other Evidence of Neuroprotection: C1q Drives Synapse Loss in Genetic Mouse Model of Glaucoma
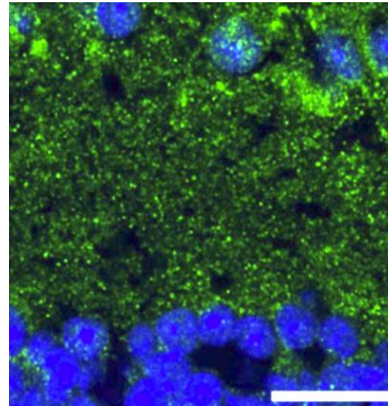
DBA/2J Mouse model of glaucoma

- Spontaneous disease with retinal degeneration and loss of optic nerve
- As with human disease, IOP correlates with progression

C1q accumulation on synapses prior to axonal damage or neuronal loss

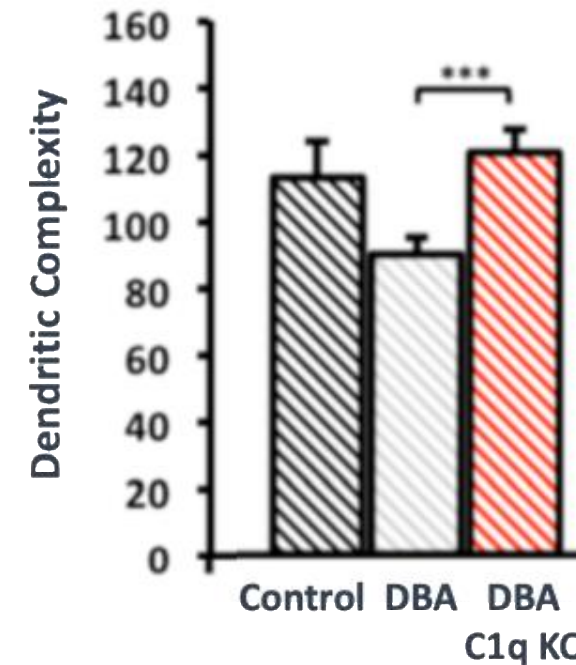**Protection of Synapses with C1q Inhibition**
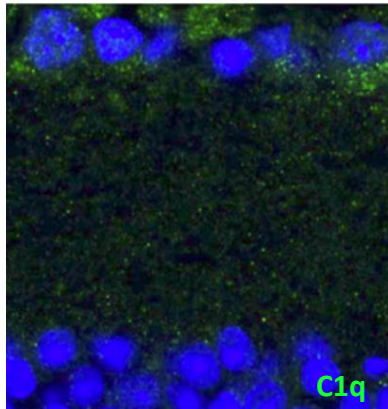
Control mice   DBA/2J mice

Inner Plexiform Layer (IPL)

C1q

Stevens and Barres, Cell 2007

Williams, et al., Molecular Neurodegeneration, 2016

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C1q Inhibition Protects Neurons in Both Chronic and Acute Mouse Models of Glaucoma / C1q Also Present in Human Glaucoma

Protective in both chronic and acute models of glaucoma

C1q KO protected optic nerve integrity at 12 months of age[1]

Anti-C1q protected against acute optic nerve damage[2]

[1]Howell J Clin Invest
[2]Annexon data
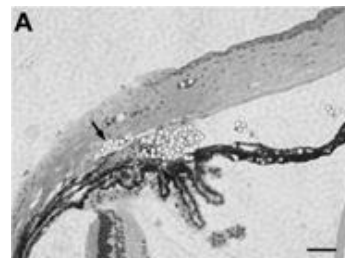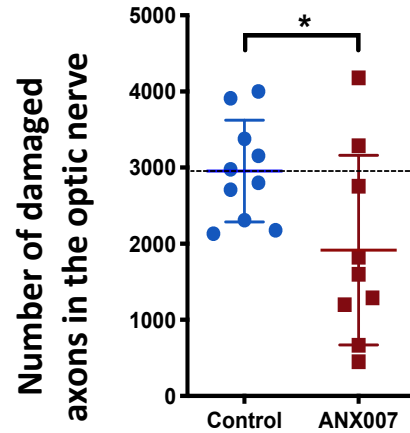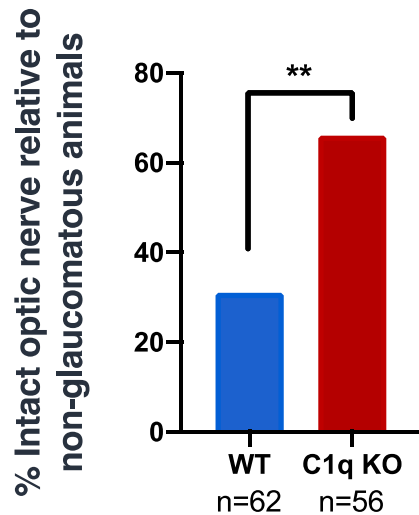
C1q deposition in 34/34 glaucoma patients

Control   **Glaucoma**

C1q staining within synapse layer (IPL)

C3b staining within synapse layer (IPL)

Tezel IOVS 2010

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ANX007 is Designed to Inhibit C1q
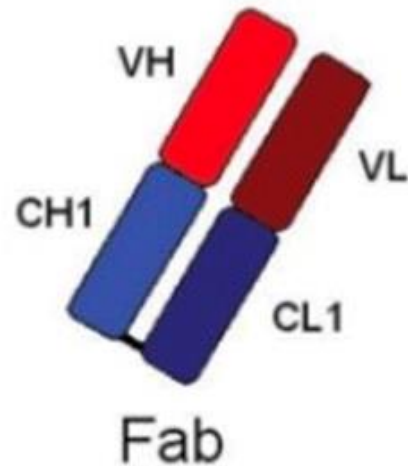
- Recombinant humanized antigen binding fragment (Fab) of a monoclonal antibody

- Composed of one VH and CH1 segment of an IgG1 heavy chain covalently linked to one kappa light chain

- Molecular weight - ~48 kDa

- Binds to the complement protein C1q via its antigen binding domain

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ANX007 Reduces C1q Levels in Retina of Non-Human Primates
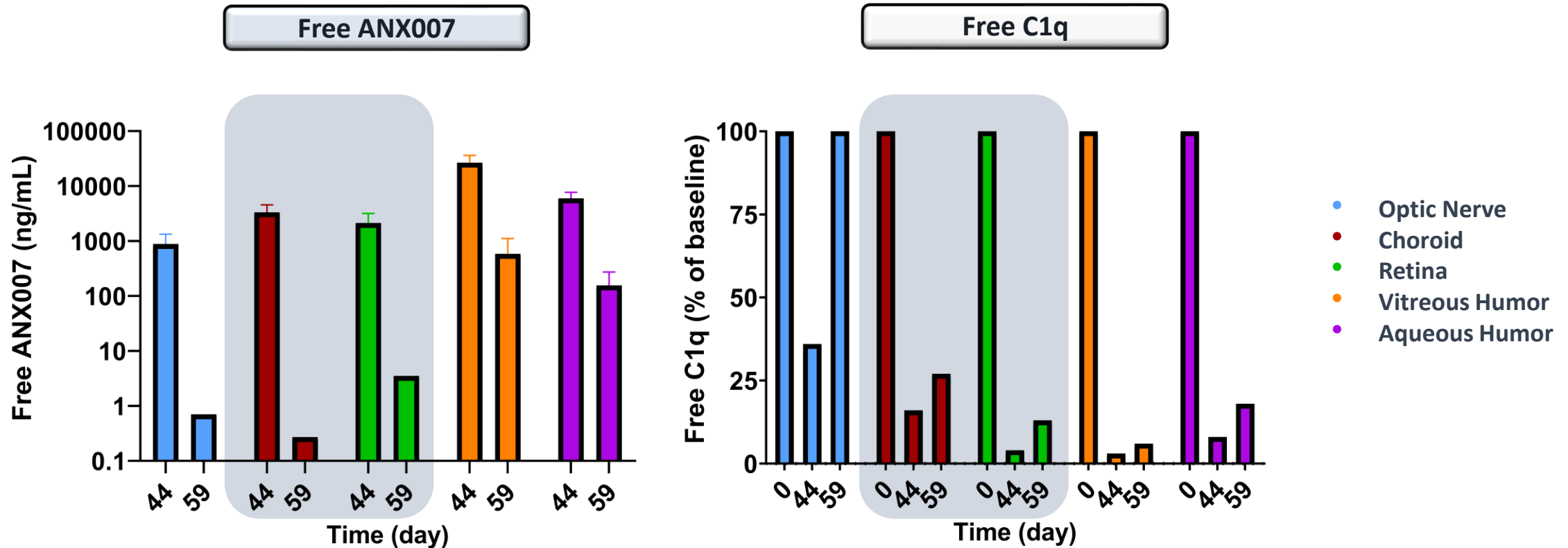
Two doses of 5 mg ANX007 administered IVT 28 days apart in cynomolgus monkeys
- *Day 44* = 15 days post-last dose
- *Day 59* = 30 days post-last dose

Grover A, et al. IOVS 2021;62:ARVO E-Abstract 219

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Phase 1 Studies Assessing the Safety and Tolerability of ANX007 in Those With Glaucoma

ANX007-GLA-01 phase 1a study

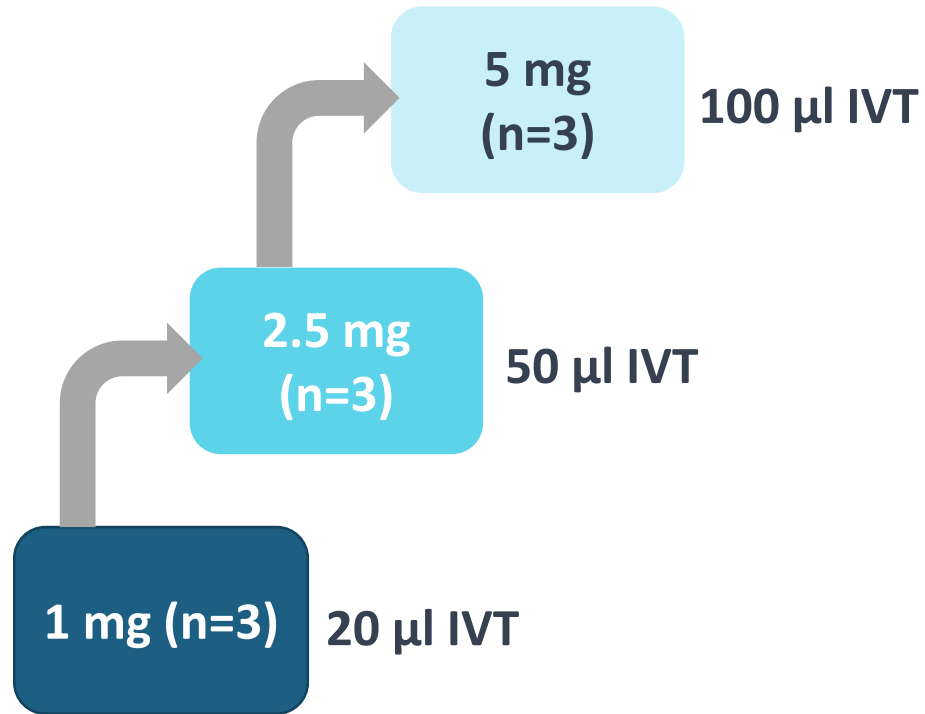5 mg (n=3)   100 µl IVT

2.5 mg (n=3)   50 µl IVT

1 mg (n=3)   20 µl IVT

- Single ascending doses in participants with glaucoma
- Follow-up through 8 weeks

ANX007-GLA-02 phase 1b study

Screening

Randomized

5 mg IVT (n=7)

2.5 mg IVT (n=6)

Sham (n=5)

Dosing day 1 AH sample at baseline

Dosing day 29 AH sample prior to dose

Follow-up through 12 weeks
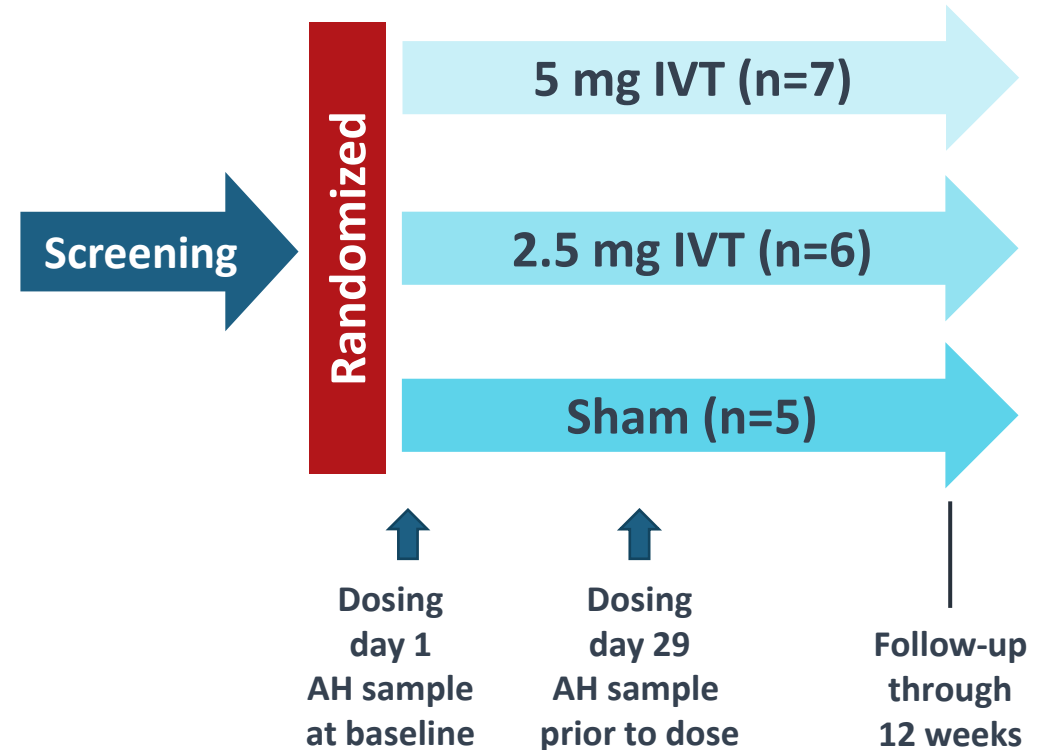
- Two monthly doses in participants with glaucoma
- AH samples were also collected to assess PK/PD

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ANX007 Effectively Inhibits C1q in Phase 1b Patients

Full inhibition at low and high doses support monthly or less frequent dosing

ANX007 DATA SUMMARY

- **ANX007 well-tolerated** at all dose levels

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

Free C1q Levels in Aqueous Humor

Sham 2.5 mg 5 mg

C1q in Aqueous Humor (%Pre-dose levels)

D1 = Day 1 (before ANX007 dosing)

D29 = Day 29 (post-1st dose)

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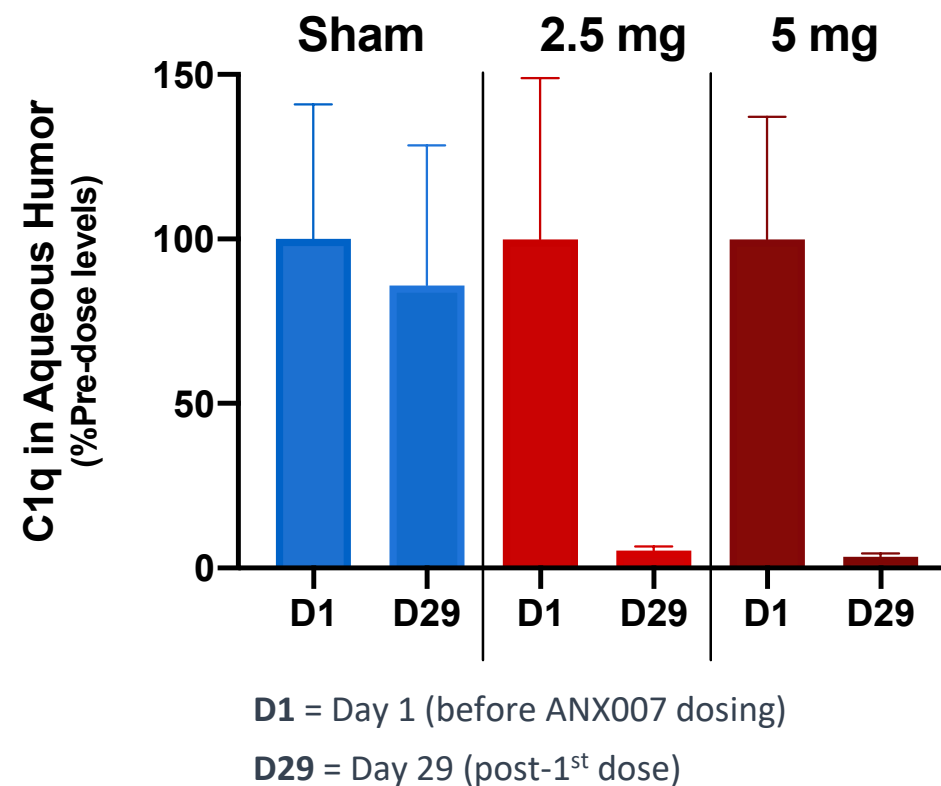
ARCHER Study:
Ongoing Phase 2 Study Evaluating Effect of ANX007 in GA
Data Anticipated 1st Half 2023

Randomization*

2:2:1:1

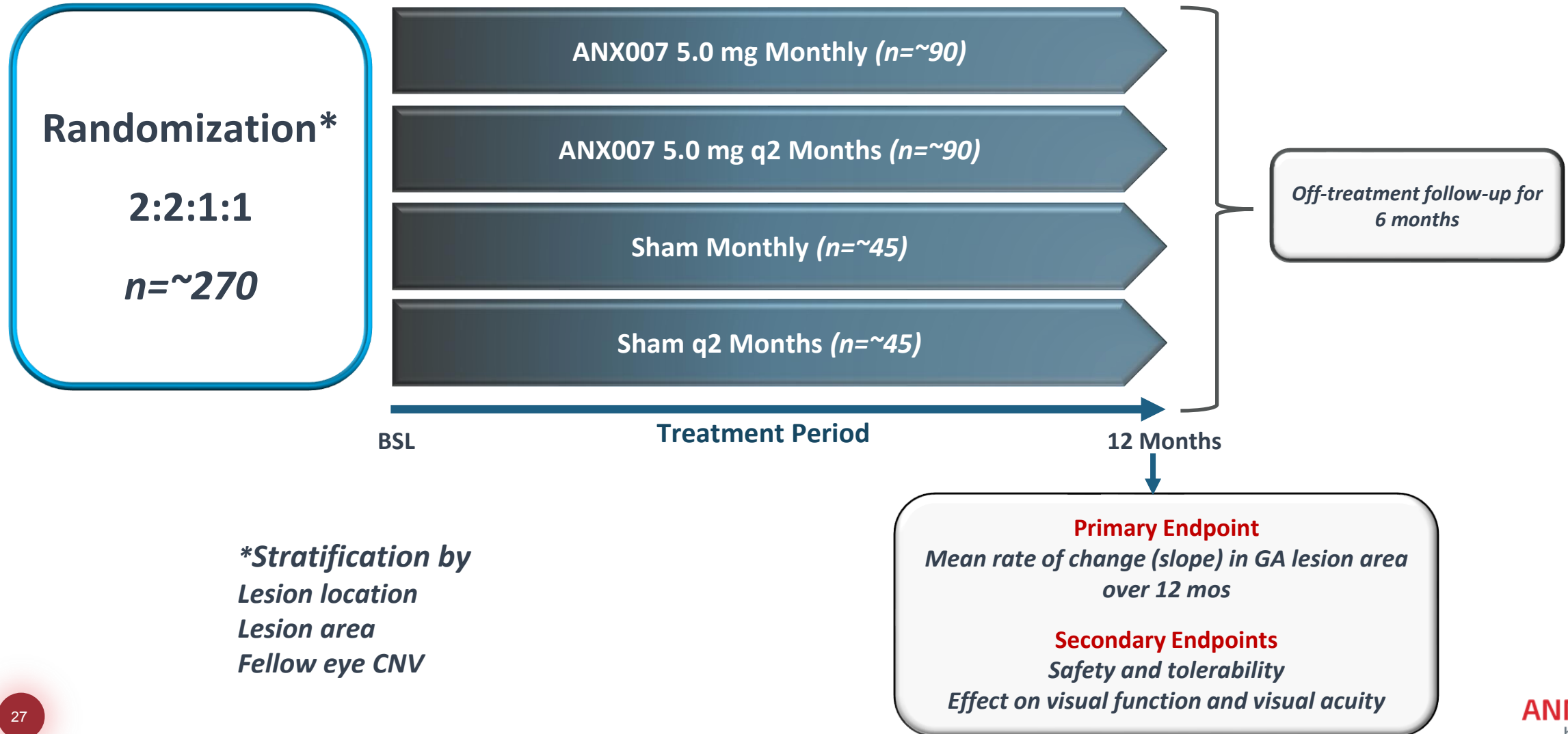*n=~270*

ANX007 5.0 mg Monthly *(n=~90)*

ANX007 5.0 mg q2 Months *(n=~90)*

Sham Monthly *(n=~45)*

Sham q2 Months *(n=~45)*

Off-treatment follow-up for 6 months

BSL

Treatment Period

12 Months

***Stratification by
Lesion location
Lesion area
Fellow eye CNV***

Primary Endpoint
Mean rate of change (slope) in GA lesion area over 12 mos

Secondary Endpoints
*Safety and tolerability
Effect on visual function and visual acuity*

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Conclusion

- **Scientific Rationale**
  - Classical complement pathway implicated in Neurodegenerative (Huntington's Disease) and Autoimmune (Guillain-Barre Syndrome) Diseases
  - Classical complement pathway is implicated in Geographic Atrophy. Drusen and other breakdown products of photoreceptor digestion activate C1q and the classical pathway

- **Laboratory Evidence**
  - Animal and human pathology specimen show classical complement activation
  - Inhibition of C1q is protective against retinal damage and maybe neuroprotective

- **Human Experience**
  - ANX007 good target engagement >29 days
  - Phase 1 study demonstrate favorable safety profile

- **ARCHER Clinical Trial**
  - Randomization stratified for lesion location and size
  - Ph 2 data anticipated in 1st half 2023

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