STOPPING Complement-Driven Diseases

AT THE START

- **Spotlight on ANX007 – Inhibition of C1q for GA**

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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.

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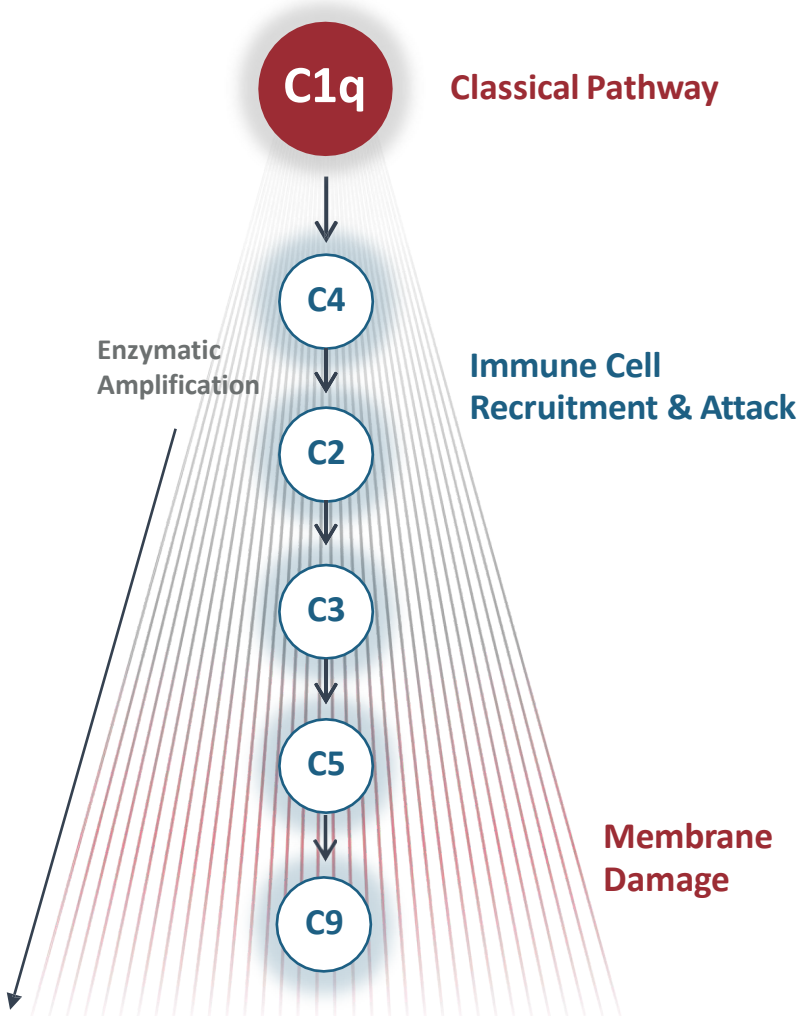
This presentation concerns drugs that are under clinical investigation, and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). These are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness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

Agenda / Executive Summary

- **Scientific Rationale**
  - 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
- **Human Experience**
  - Phase 1 study show good safety profile and good target engagement
- **ARCHER Clinical Trial**
  - Ongoing with results expected in 2023

Pioneering a Class of New Complement Medicines by Stopping C1q and Classical Complement at the Start



- **Targeting Enhanced Efficacy & Safety** by blocking downstream inflammation & tissue damage at the start
- **Pluri-Potential Across 3 Therapeutic Areas** - autoimmune, neurodegeneration & ophthalmology
- **Multiple Delivery Solutions** to fully inhibit the cascade with diverse routes of administration

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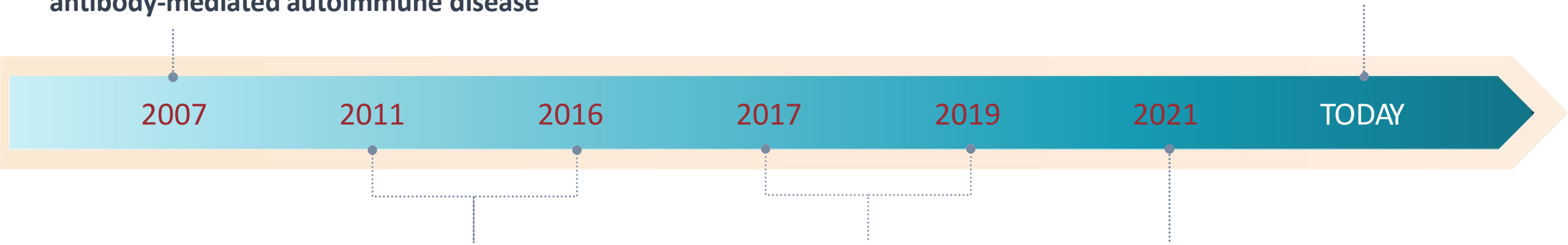
Annexon: Unique Domain Expertise in the Classical Pathway

Annexon co-founder **Ben Barres discovered that C1q drives synapse loss and disease progression** in neurodegenerative disorders

C1q also known to drive tissue damage in **antibody-mediated autoimmune disease**

Advancing Diverse Portfolio with biomarker-led development & multiple fit-for-purpose therapeutics



Annexon developed ANX005 (IV) and other classical pathway inhibitors (C1q, C1s, C2, C4)

Demonstrated **importance of inhibiting C1q at the top of the pathway**, blocking activity before it starts in the PNS, CNS & eye

ANX005: clinical **POC in GBS**, including full target engagement in periphery & centrally, and NfL reduction

ANX007: Full target engagement in the eye with intravitreal administration in glaucoma patients

ANX009: Full target engagement in the blood space with subcutaneous administration in healthy volunteers

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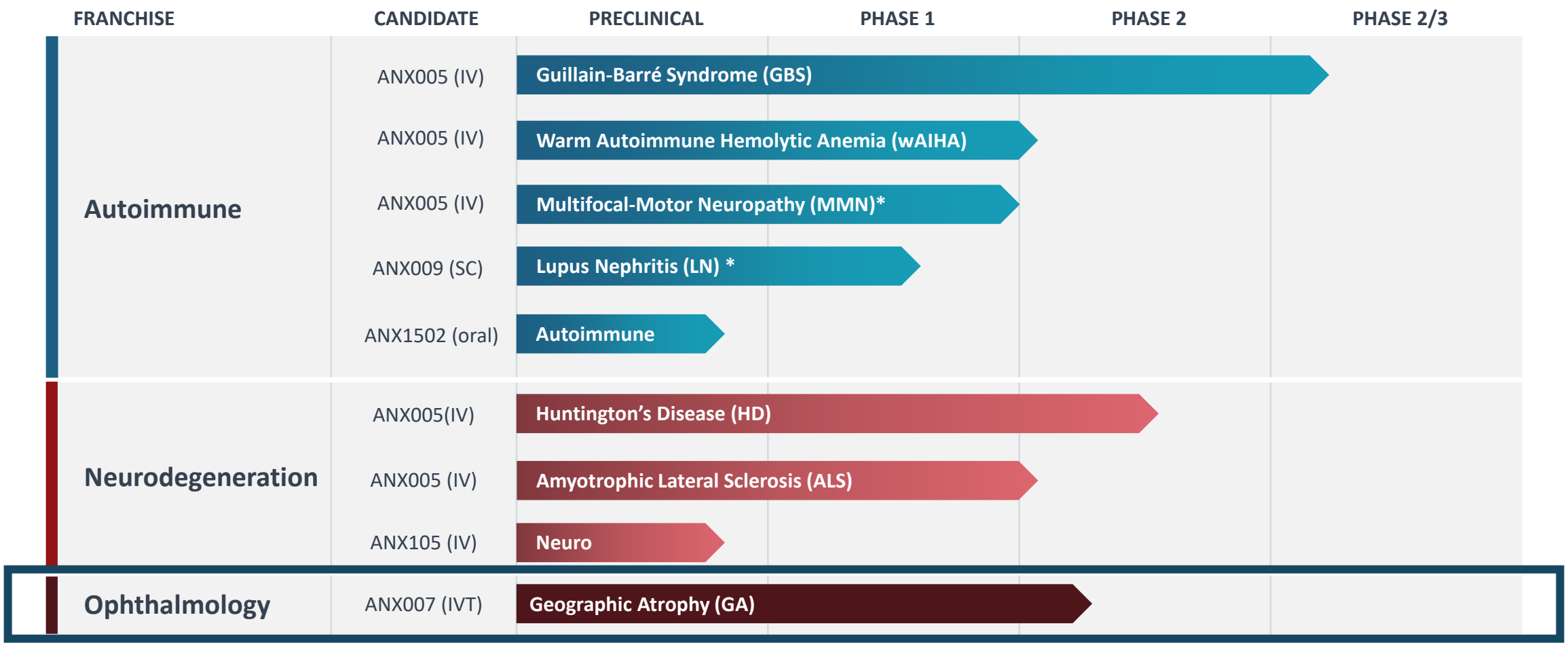
Broad & Deep Wholly Owned Classical Complement Pipeline

3 Therapeutic Franchises. 3 Clinical Candidates. 7 Clinical Readouts in next 2 years



IV, intravenous; IVT, intravitreal; SC, subcutaneous.

* Newly announced indications

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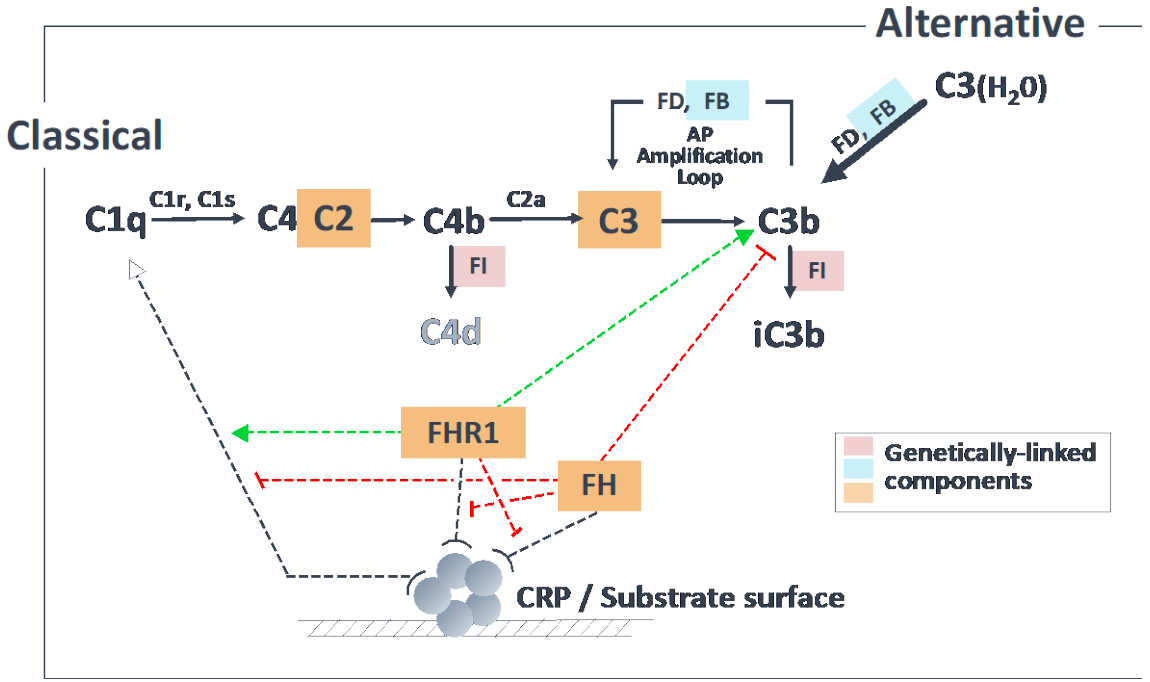
Strong Human Genetic Link between Complement and GA

At least six GA-related polymorphisms impact activity of the complement system

- Functional consequence of polymorphisms associated with AMD
  - FH: ↓ substrate binding, ↑ C activation, ↑ *risk*
  - Factor I: ↓ activity, ↑ C activation, ↑ *risk*
  - Factor B: ↓ activity, ↓ C activation, ↓ *risk*
  - C2: *Impact not definitively characterized*
  - C3: ↓ FH binding, ↑ C activation, ↑ *risk*
  - CFHR1/3 deletion: ↑ FH binding, ↓ C act, ↓ *risk*
- All modulate complement activation, but do not indicate how it is activated
  - Have focused on alternative pathway because C3 is the initiating molecule of the alternative pathway / AP amplification
  - However, C3 is the central component of all three pathways



Complement genetics: Tan et al. Human Genomics (2016) 10:23
CFHR1 and CRP: Csincsi, et al., *J Immunol* 2017; 199:292-303

C1q in AMD: Mohlin et al., Molecular Immunology 89 (2017) 84–99; CRP and AMD: *Chirco and Potempa 2018 Front. Immunol. 9:539;* Katschke et a., *Sci Reports* 2018, Genentech

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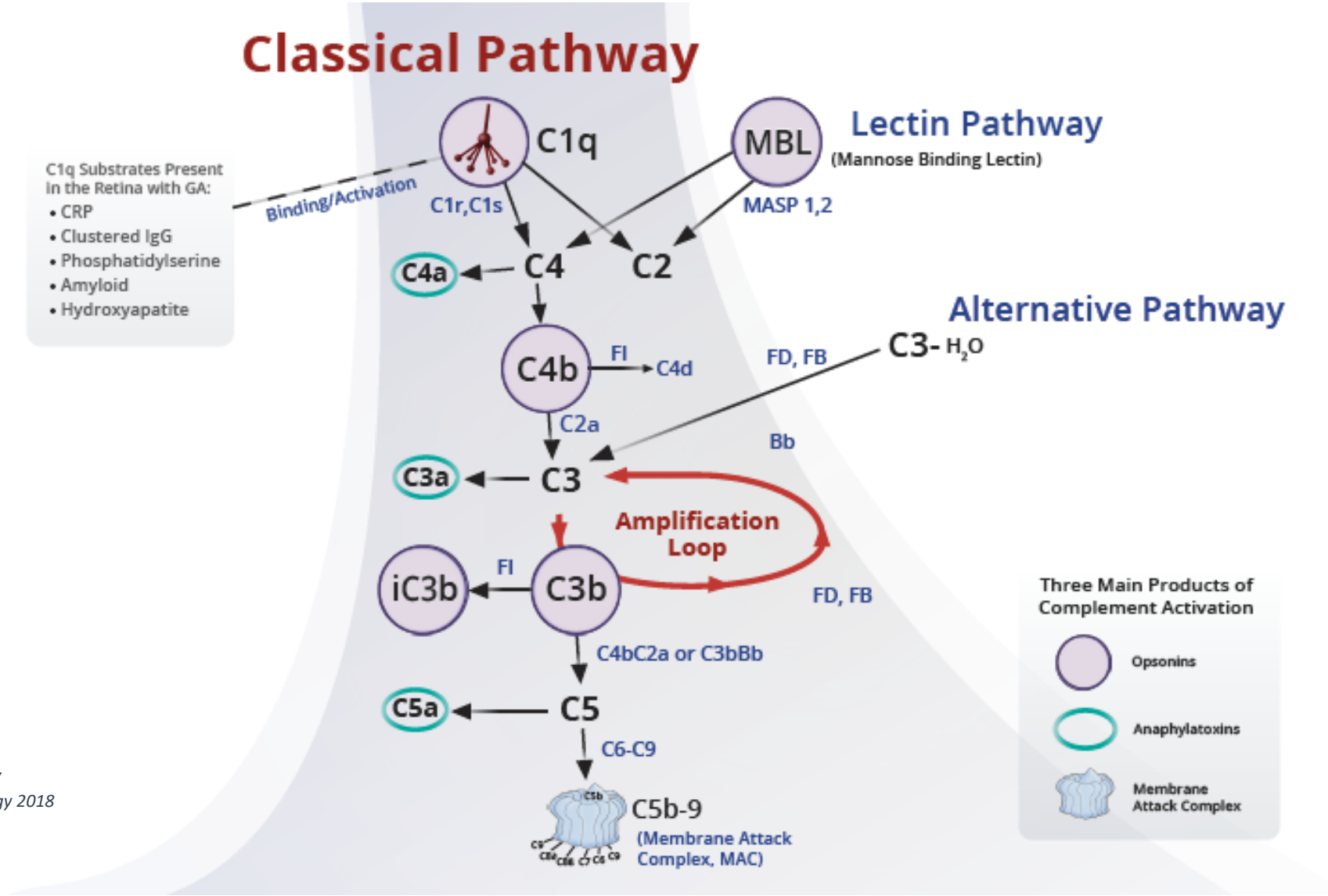
C1q and Classical Complement Pathway



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

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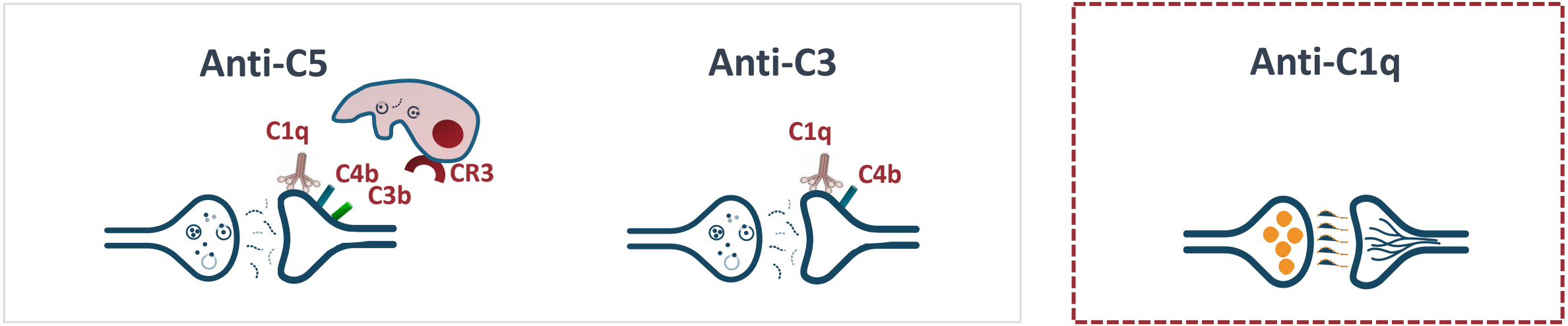
Anti-C1q Differentiated from Other Approaches

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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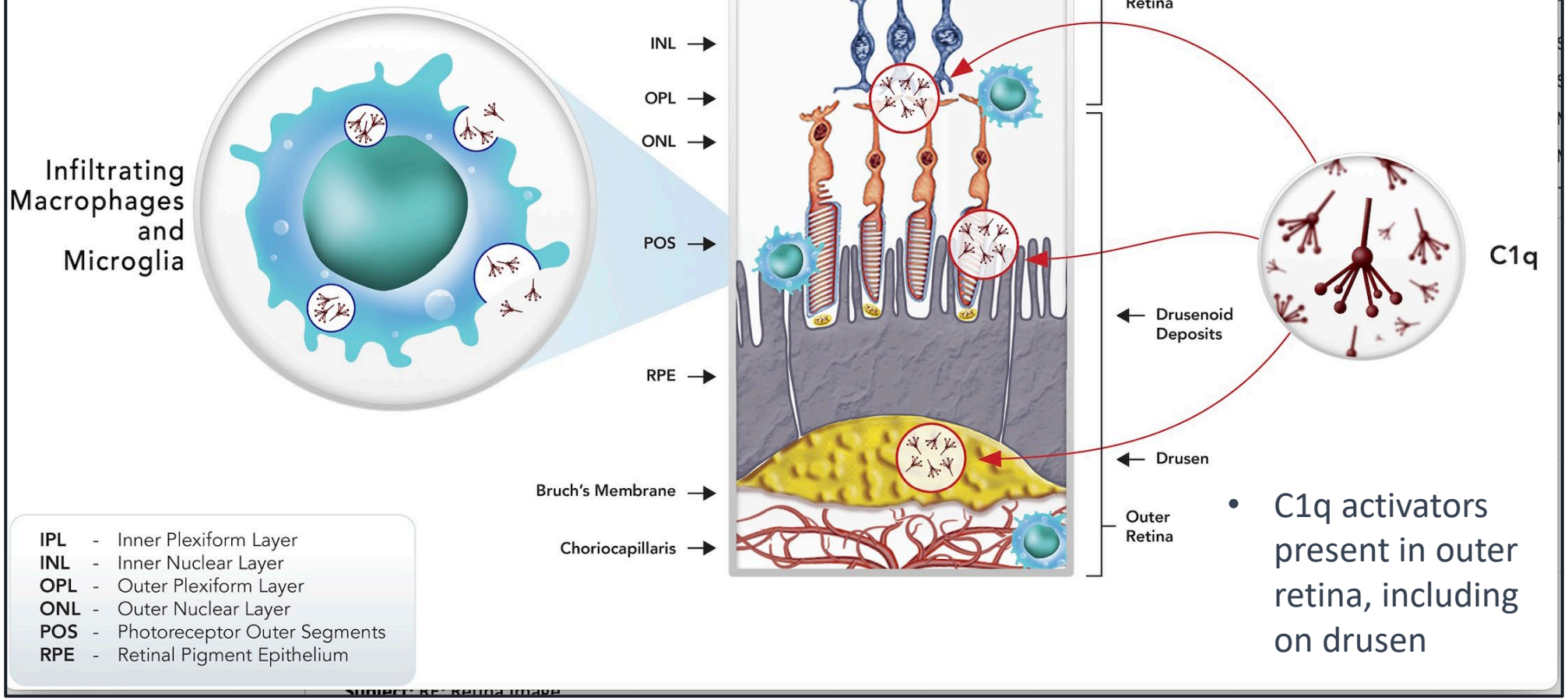
C1q and Classical Cascade are Key Drivers in Geographic Atrophy

- C1q present in all layers of the outer retina
  - Source: macrophages and microglia



- C1q activators present in outer retina, including on drusen

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

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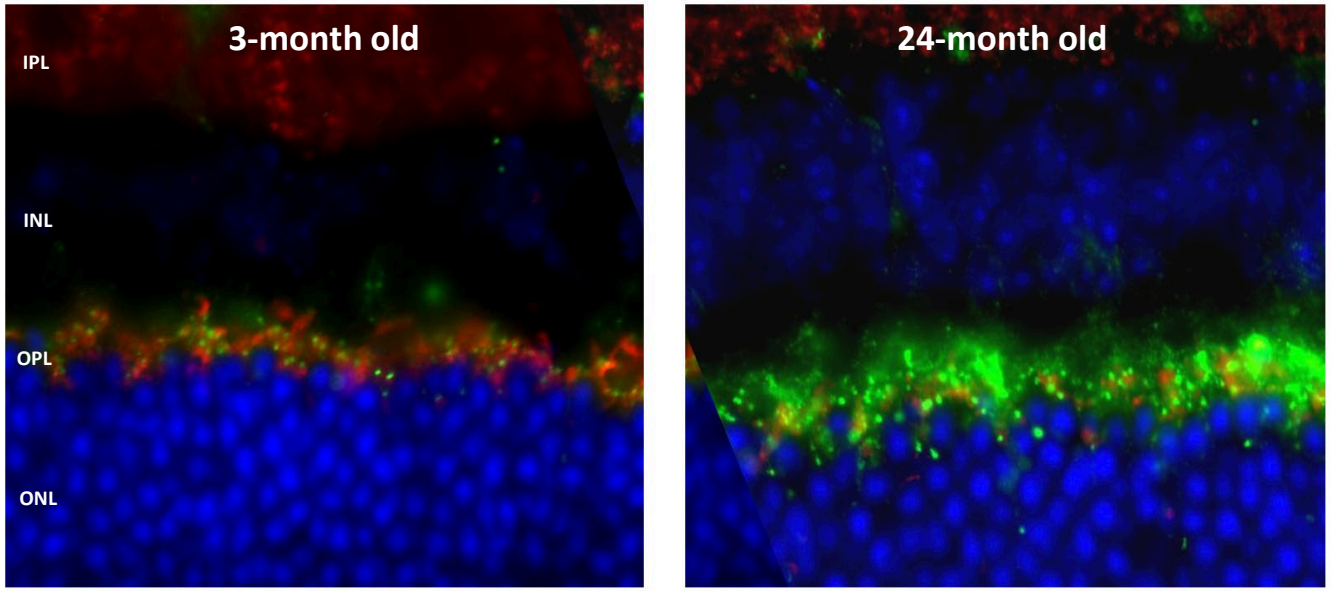
Why target C1q in GA?

- Human genetics point to the **complement pathway** as a **key driver of disease**
  - **Polymorphisms** in 6 different complement genes
  - **Role of C3 reinforced** by APL-2 data

- Annexon data and data from other labs indicate that **C1q and classical pathway** are well **positioned to drive substrate-based C3 activation**:
  - C1q and many other complement components / activation products found in drusen below photoreceptor cells
  - C1q tags synapses on photoreceptor cells with both age and disease
  - C4 (classical pathway upstream of C3) deposited on photoreceptor outer segments at leading edge of GA lesion
  - C1q inhibition slows atrophy and improves function in photo-oxidative retinal degeneration animal model

C1q Accumulates with Age in Geographic Atrophy

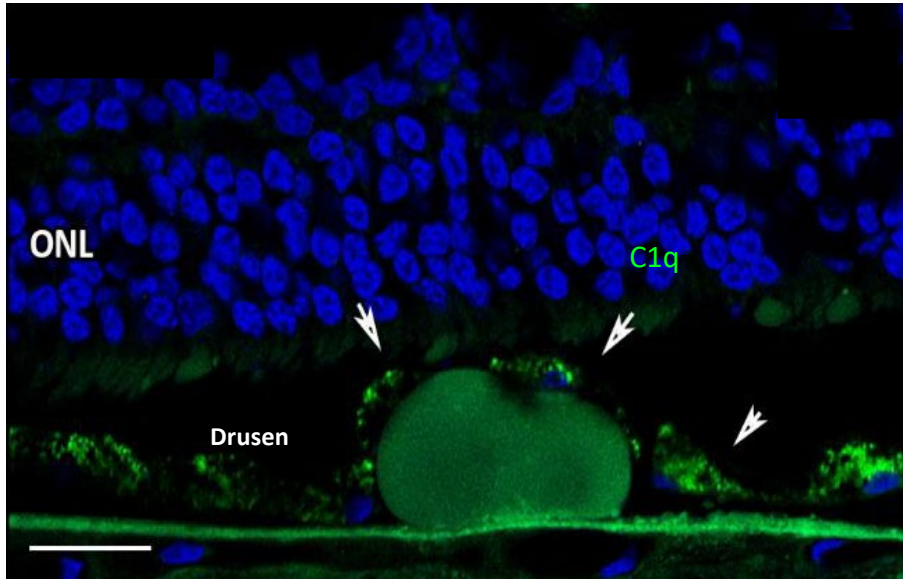
C1q accumulation on photoreceptor cell synapses in mouse retina



Data on File, Annexon Biosciences

Synapses C1q Nuclei

C1q accumulation on drusen in human retina with GA



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

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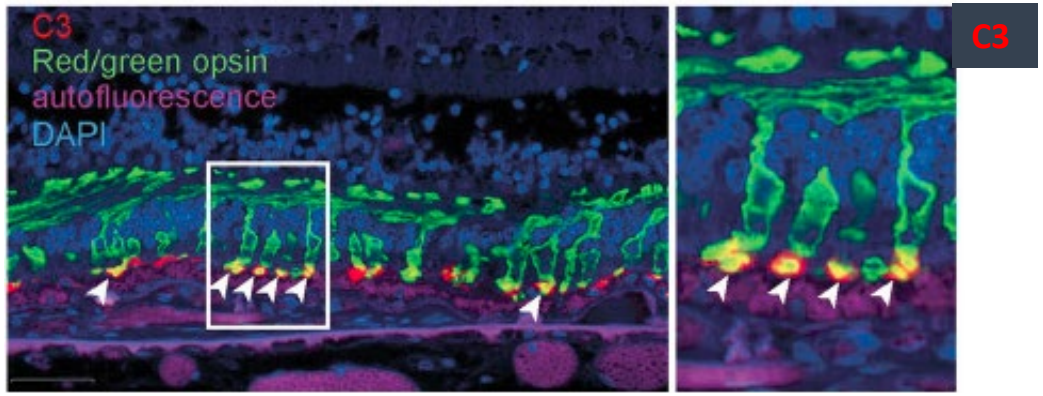
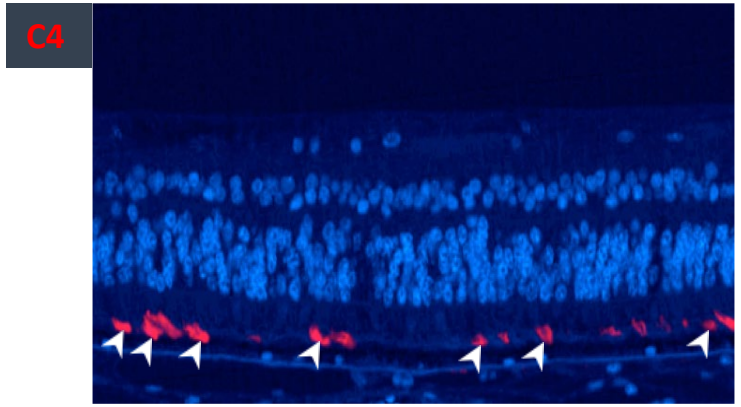
C3 and C4 accumulation on photoreceptor cells support a role for classical complement cascade in GA

- 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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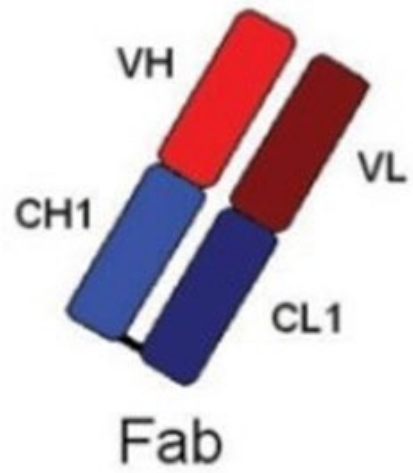
ANX007 is Designed to Inhibit C1q

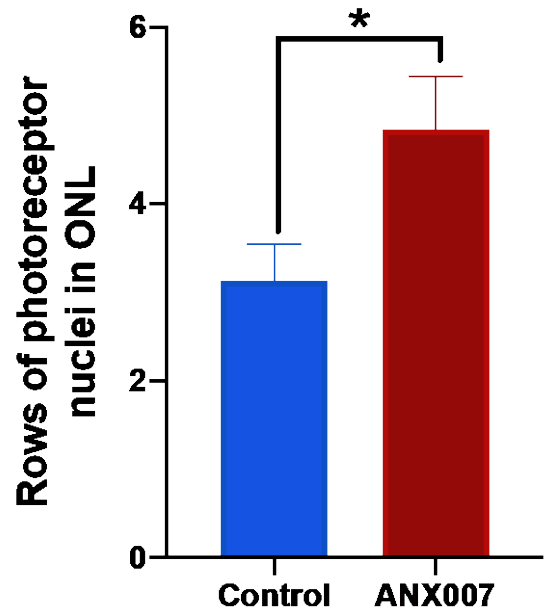


- Recombinant humanized antigen binding fragment (Fab) of a monoclonal antibody
- Composed of one VH and CH1 segment of an IgG1 heavy chain covalently linked to one kappa light chain
- Molecular weight - ~48 kDa
- Binds to the complement protein C1q via its antigen binding domain

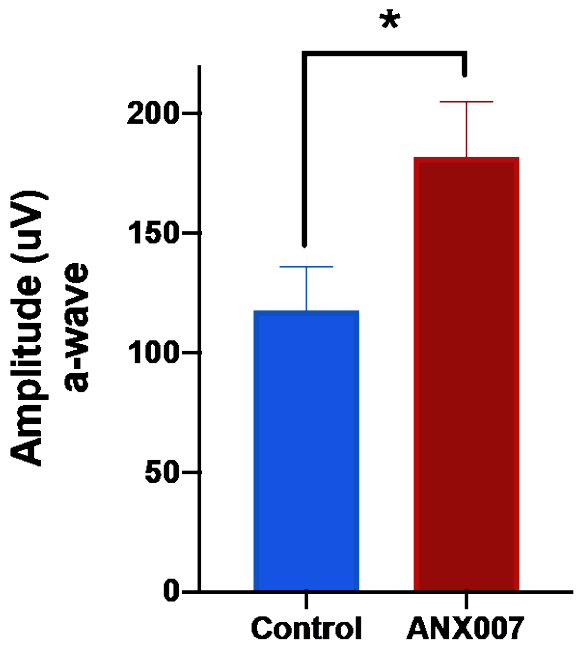
ANX007 Provides Neuroprotection in a Mouse Model

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

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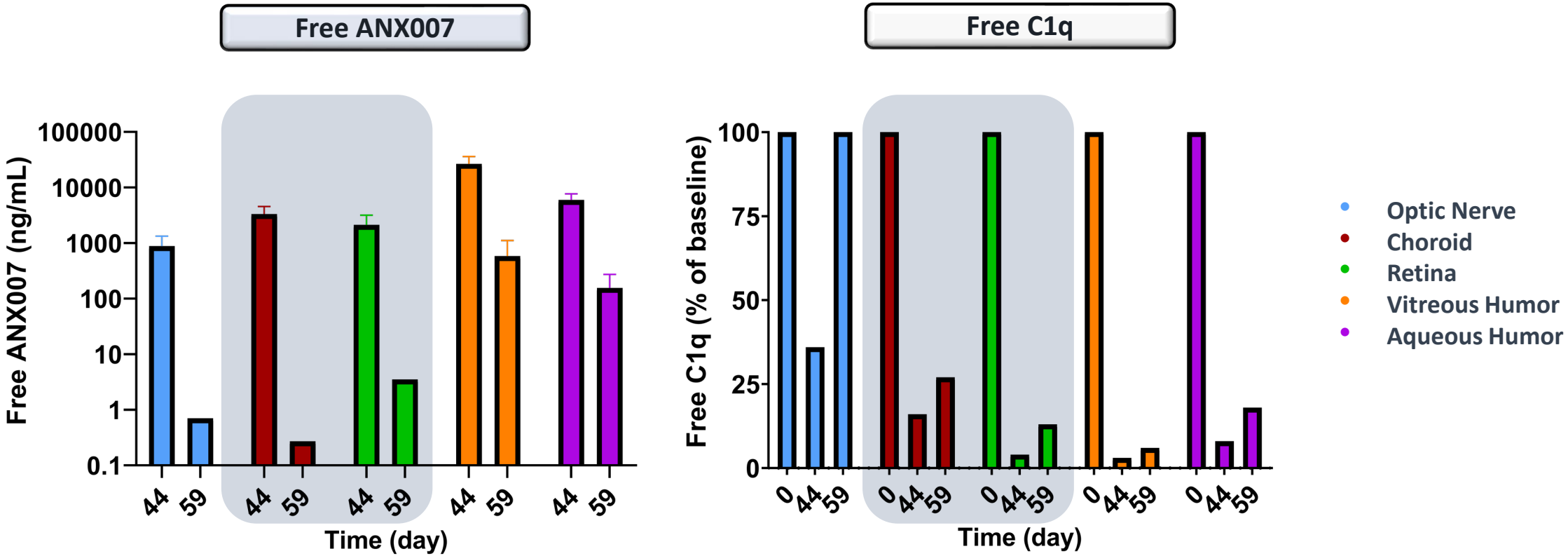
ANX007 Reduces C1q Levels in Retina of Non-Human Primates



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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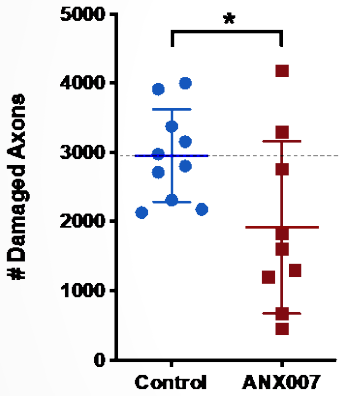
Blocking C1q Protects Against Neurodegeneration

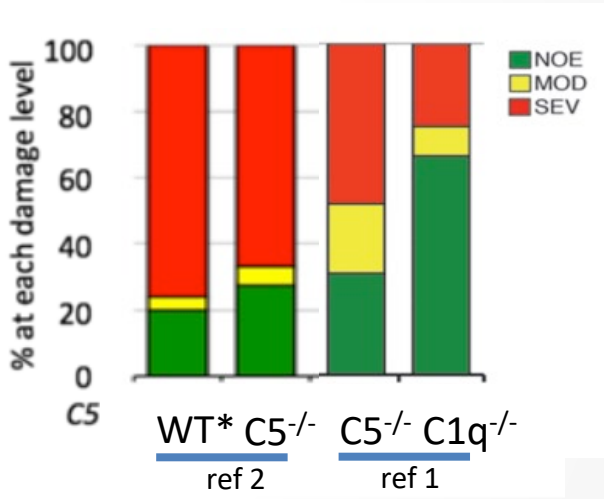
Glaucoma
Protects Optic Nerve Damage

Decreased optic nerve damage w/ ANX007



Bead-induced mouse model of glaucoma
Annexon, data on file

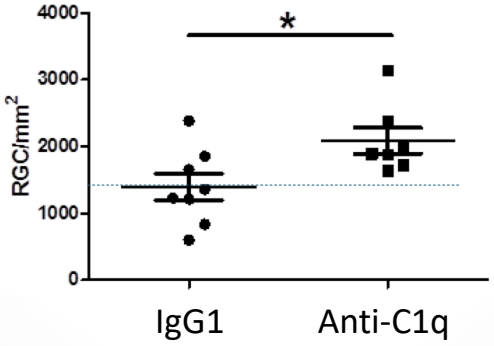
C1q deficiency protects optic nerves in chronic mouse model



[1]Howell, et al., 2011 J Clin Invest 121:1429
[2]Howell, et al., 2013 J Neuroinflam 10:76

Optic Neuritis
Protects Nerve Loss

Decreased nerve damage w/ ANX005



Unpublished data
Jing Jin and Peter Calabresi,
Johns Hopkins

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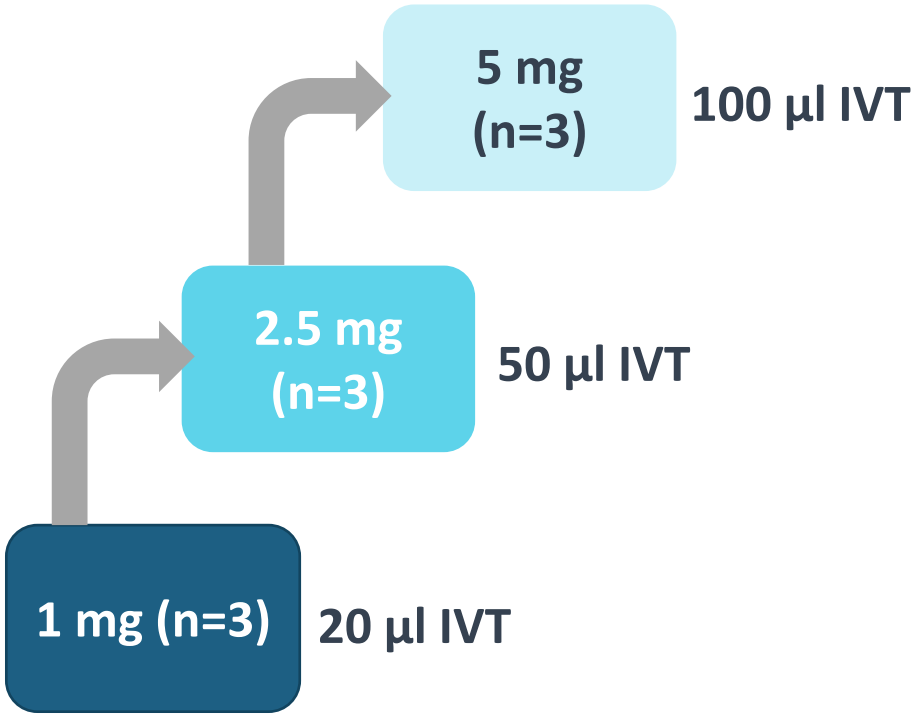
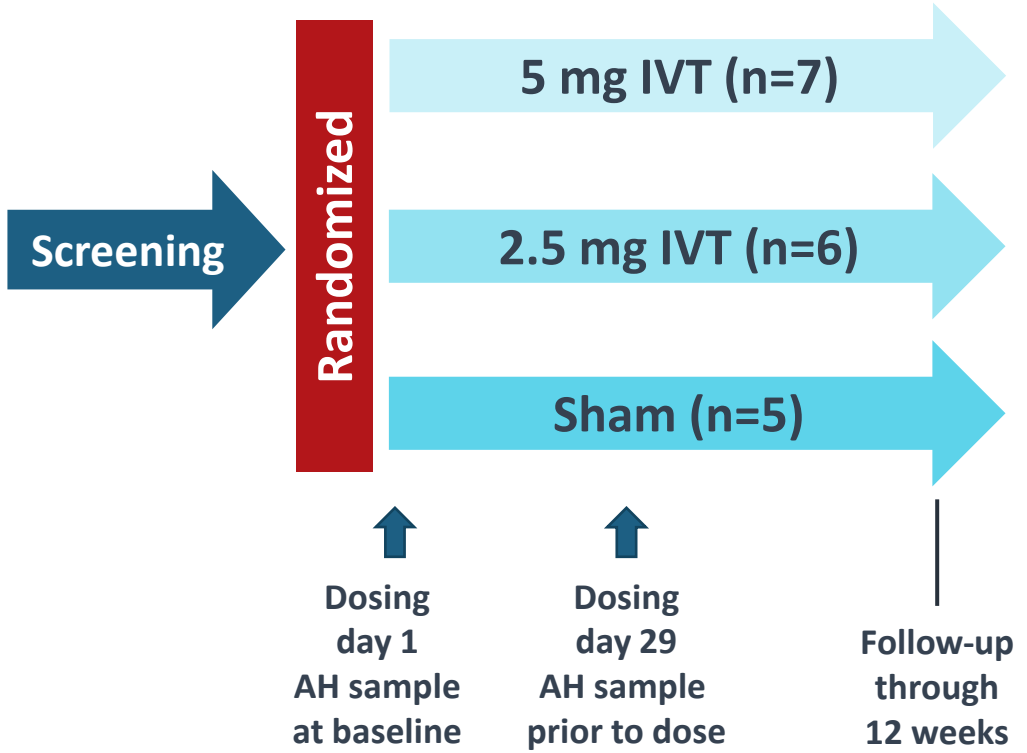
Phase 1 Studies Assessing the Safety and Tolerability of ANX007 in Those With Glaucoma

ANX007-GLA-01 phase 1a study



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

ANX007-GLA-02 phase 1b study



- Two monthly doses in participants with glaucoma
- AH samples were also collected to assess PK/PD

AH, aqueous humor; IVT, intravitreal; PD, pharmacodynamics; PK, pharmacokinetics.

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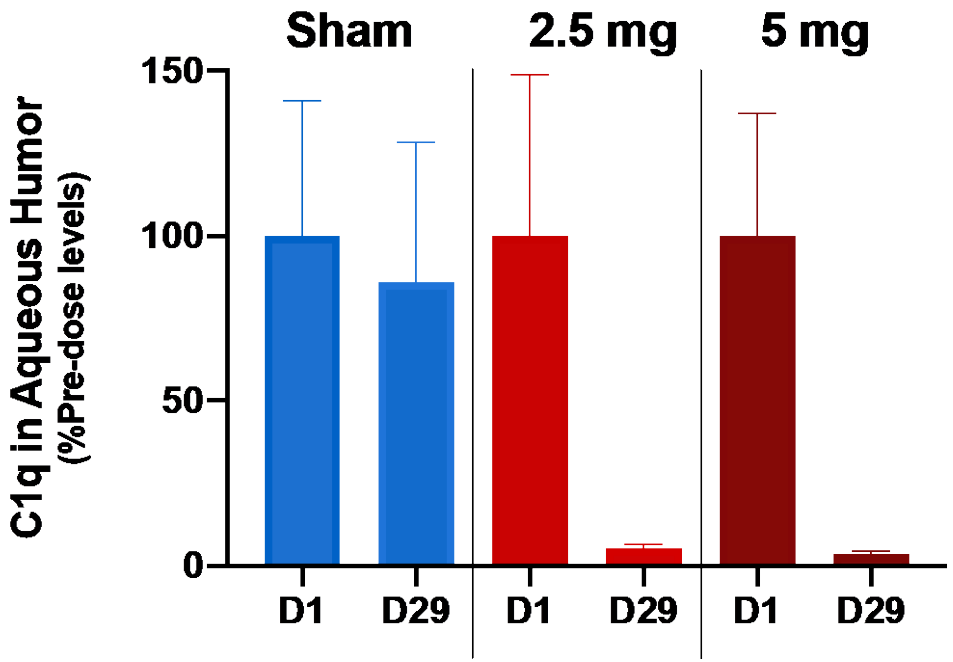
ANX007 Effectively Inhibits C1q in Phase 1b Patients

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

Free C1q Levels in Aqueous Humor



D1 = Day 1 (before ANX007 dosing)

D29 = Day 29 (post-1st dose)

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
- Repeat doses, N = 17

Annexon data on file

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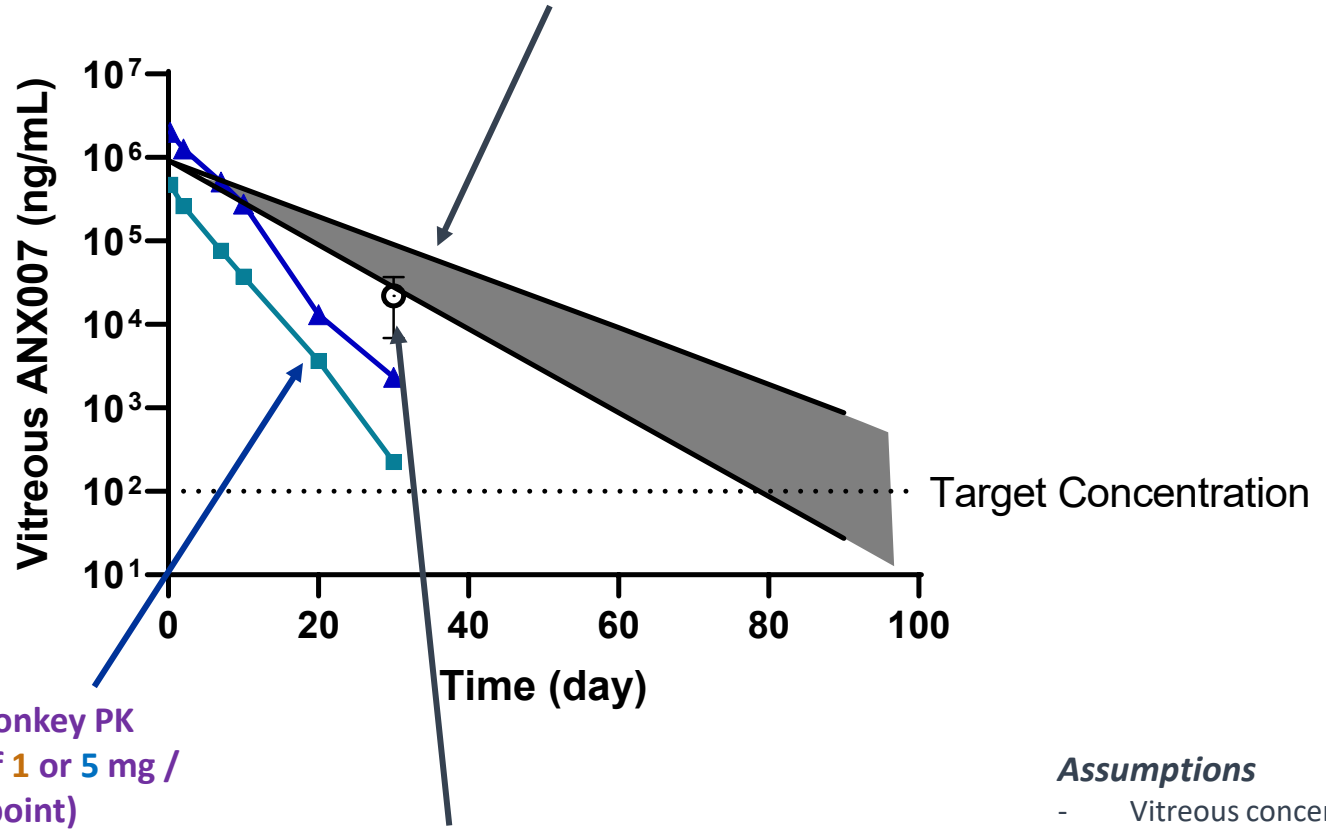
C1q Inhibition in Vitreous Projected to be Maintained for at Least 2 Months

Projected ANX007 PK in human vitreous following a 5 mg dose based on observed data from cynomolgus monkey



Observed cynomolgus monkey PK following a single dose of 1 or 5 mg / eye (mean of n=2 / timepoint)

Calculated vitreous concentration, based on observed aqueous PK in ANX007 phase 1b glaucoma study (n=3, mean ± SE)

Assumptions

- Vitreous concentrations are 4x aqueous concentrations based on observed cynomolgus monkey data
- Human ocular half life is 3x cynomolgus monkey ocular half life based on published data from other IVT-administered Fabs (*Xu et al, IOVS 2013 54(3):1616-24)*

Data on File, Annexon Biosciences

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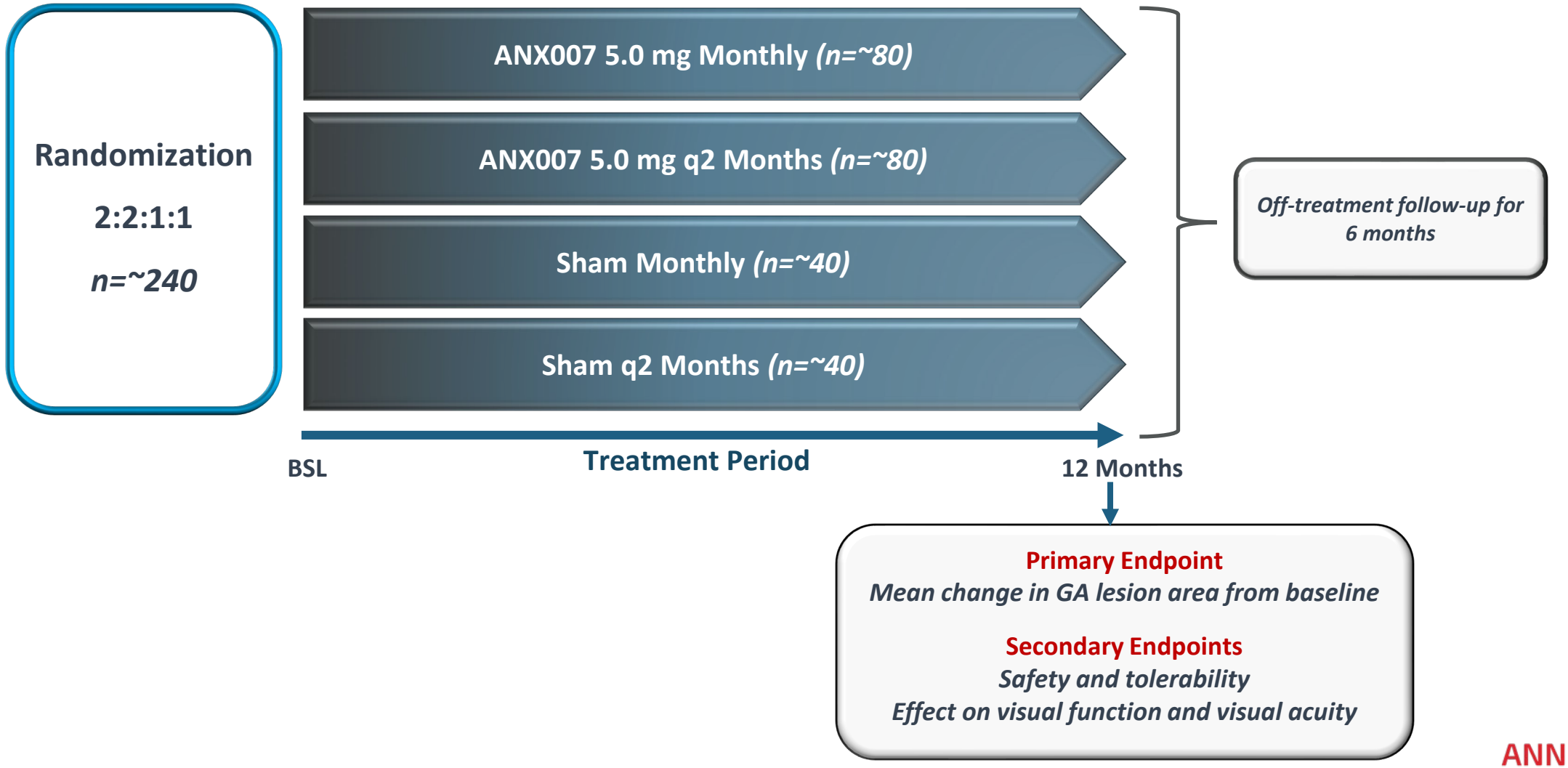
The ARCHER Study: *Ongoing Phase 2 Study Evaluating Effect of ANX007*



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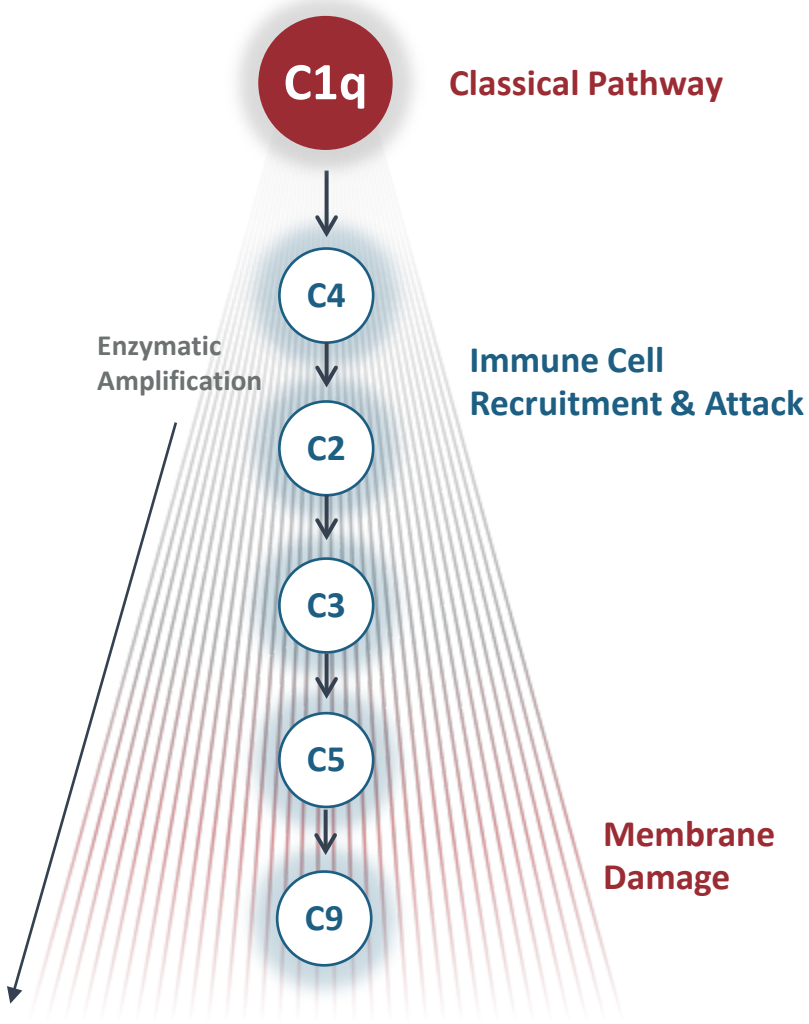
C1q Inhibition by ANX007 Stops Classical Complement Activity at the Start

Prevents downstream activation of all tissue damaging components



- **Broad therapeutic potential:** Deposition of C1q and its activation products in retina associated with aging and disease (e.g., AMD, glaucoma)
- **C1q activated by pathological hallmarks of disease:** Includes drusen (CRP) and photoreceptor degradation products
- **Only anti-C1q fully blocks the classical complement pathway:** blocks upstream cellular infiltration / attack, as well as C3 & C5 activity via classical pathway
- **Early platform promise:** blocking C1q improves outcomes in models of eye and brain disease

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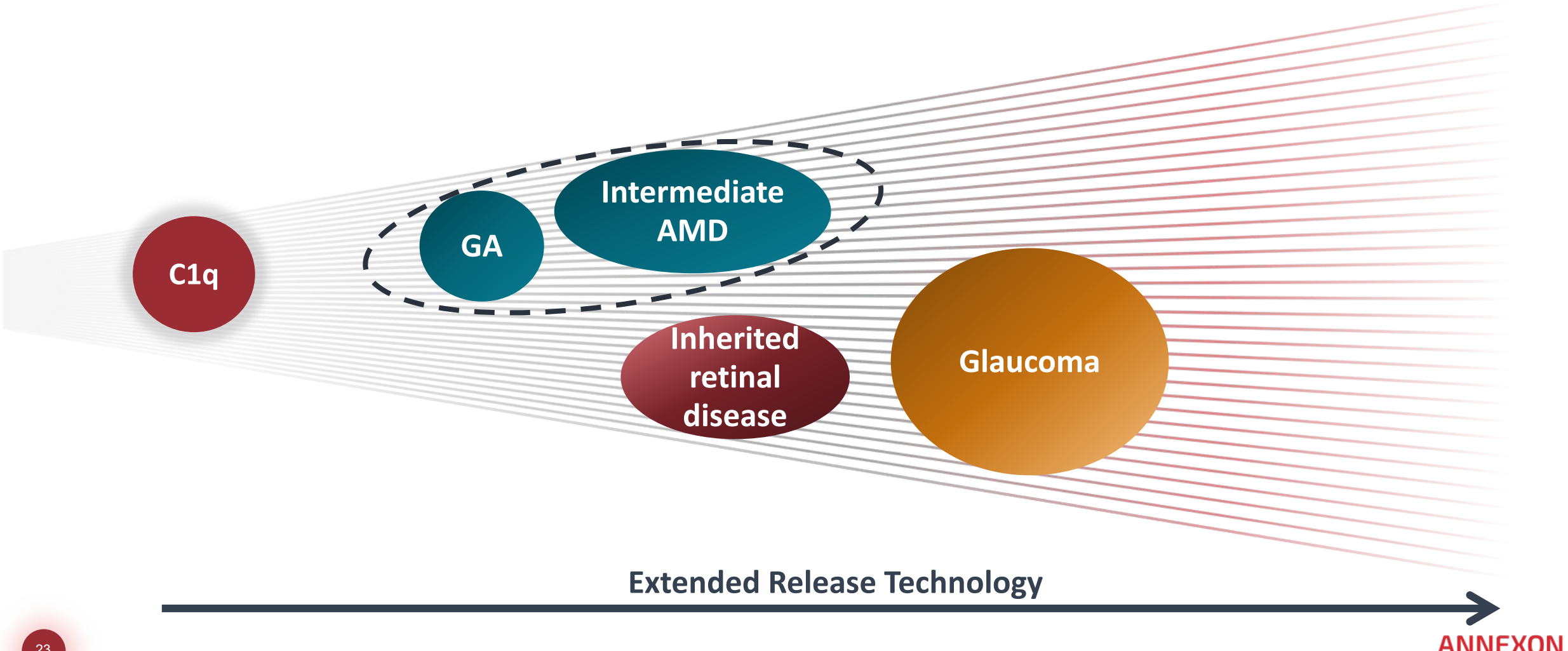
Looking Ahead for Additional Ophthalmology Opportunities



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