Annexon's C1q Series – Autoimmune Therapeutic Franchise

JULY 28, 2021

Welcome

Annexon's C1q Series - Autoimmune Therapeutic Franchise

Doug Love, Esq.

Chief Executive Officer

Annexon Biosciences

Forward-looking Statements

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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.

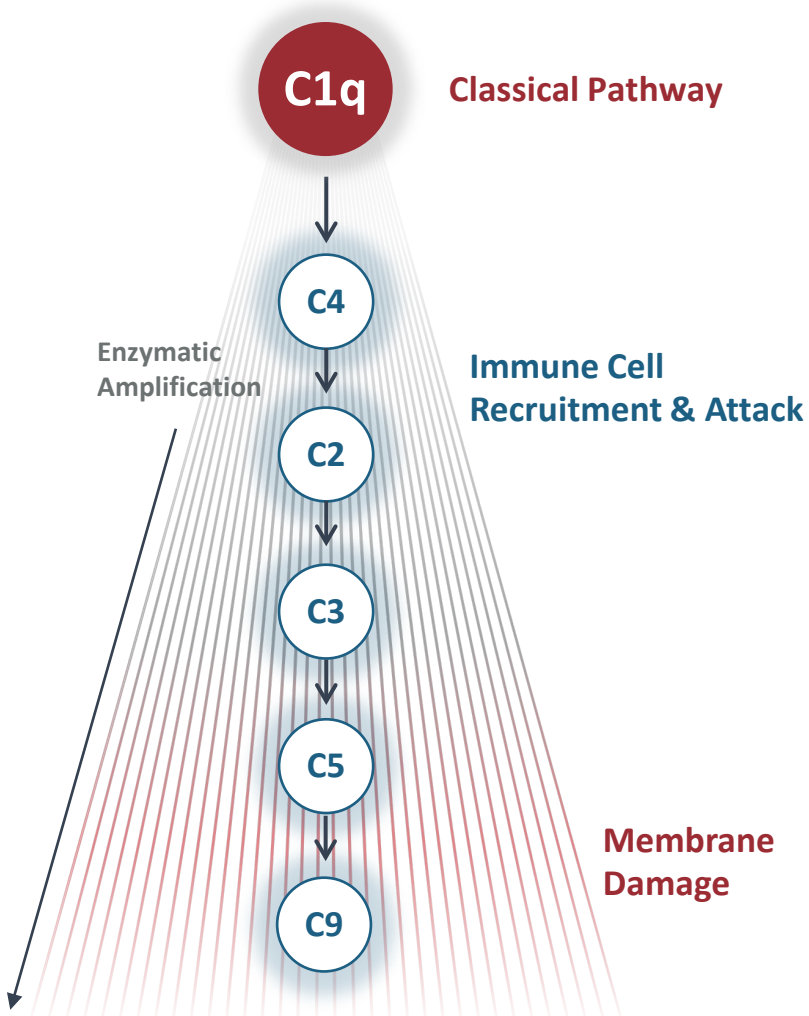
Forward-looking statements are not guarantees of future performance and are subject to risks and uncertainties that could cause actual results and events to differ materially from those anticipated, including, but not limited to, risks and uncertainties related to: our history of net operating losses; 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.

Agenda

TIME	TOPIC	PRESENTER
10:30-10:45am	**Annexon: Establishing a Class of New Complement Medicines**	Doug Love, CEO
10:45-11:00am	**Targeting C1q and the Classical Complement Pathway in Autoimmune Disease**	Ted Yednock, CSO
11:00-11:15am	**Pioneering a Precision Medicine Approach to Antibody-mediated Autoimmune Disorders**	Sanjay Keswani, CMO
11:15-11:35am	**Unmet Need in Lupus Nephritis** **KOL Perspective**	Mary Anne Dooley, MD Professor of Medicine, University of North Carolina Kidney Center
	ANX009 and the Role of Classical Complement in Lupus Nephritis	Ted Yednock, CSO
	ANX009 Clinical Program	Sanjay Keswani, CMO
11:35am-11:50am	**Multifocal Motor Neuropathy and the Role of Classical Complement** **KOL Perspective**	Hugh J. Willison, MD, PhD Professor of Neurology, University of Glasgow, Glasgow, Scotland
	ANX005 Clinical Program	Sanjay Keswani, CMO
11:50-12:15pm	**Q&A Session & Closing Remarks**	Doug Love, CEO

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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Rigorous Approach to Establishing a Class of New Complement Medicines

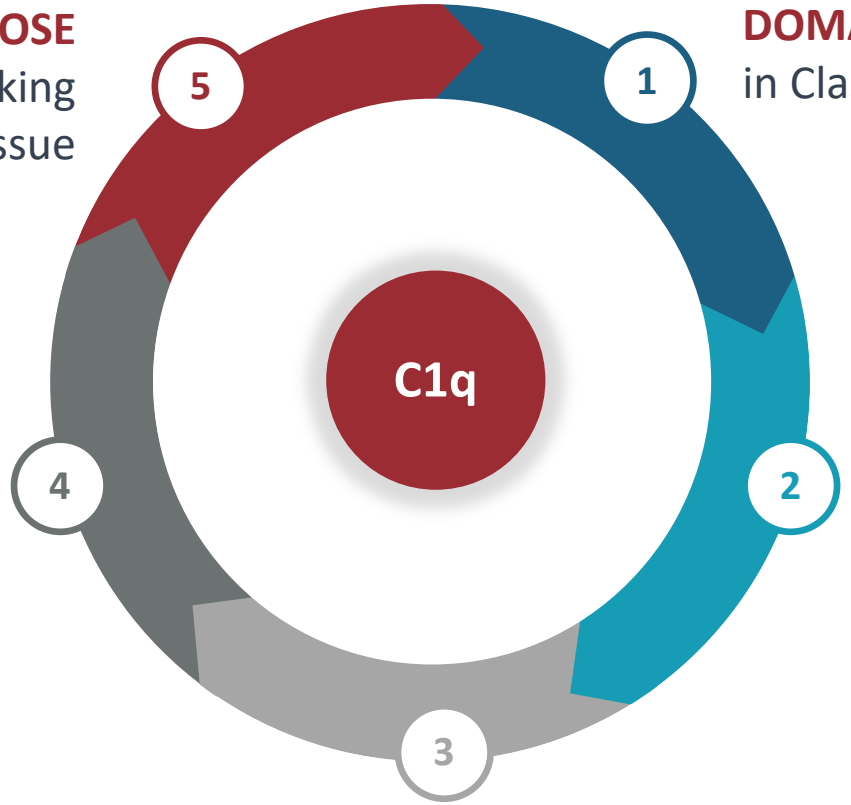
1 DOMAIN EXPERTISE
in Classical Complement Pathway

2 HIGHEST BIOLOGICAL RATIONALE
Indications with excess classical complement activity

3 DIVERSIFICATION
Parallel studies across autoimmune, neurodegeneration & ophthalmology

4 PRECISION MEDICINE
Leveraging biomarkers to select patients, set dose & assess impact

5 FIT-FOR-PURPOSE
drug candidates blocking complement in diverse tissue



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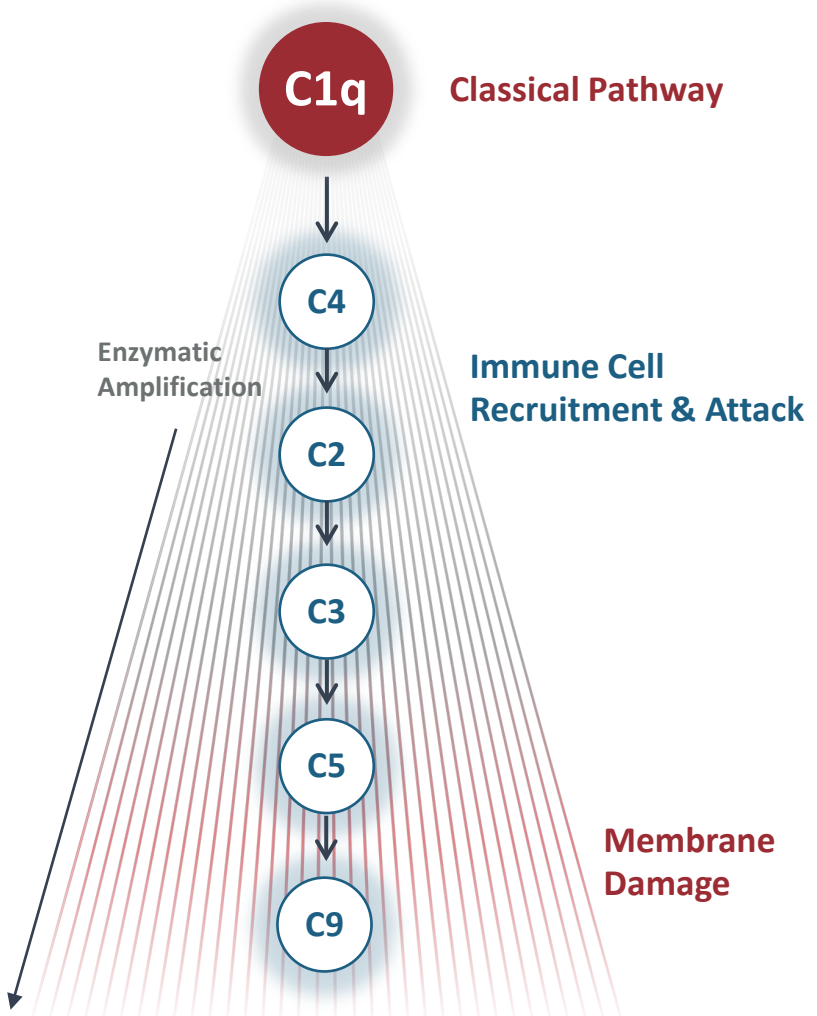
Strong Foundation Established for Our Classical Complement Platform



Treated ~200 subjects with 3 distinct drug candidates in autoimmune, neurodegeneration and ophthalmology indications

- ☑ **Consistent translation of preclinical data** to the clinic
- ☑ Drug candidates have been **well-tolerated**
- ☑ **Full C1q inhibition** in periphery, across BBB & in the eye
- ☑ **Full inhibition of downstream classical complement activity** through C3, C5 and C9
- ☑ **Demonstrated impact** on autoimmune & neurodegenerative disease processes, including **POC in GBS placebo-controlled trial**

7 mid-to-late stage clinical readouts anticipated over next 2 years

Annexon data on file

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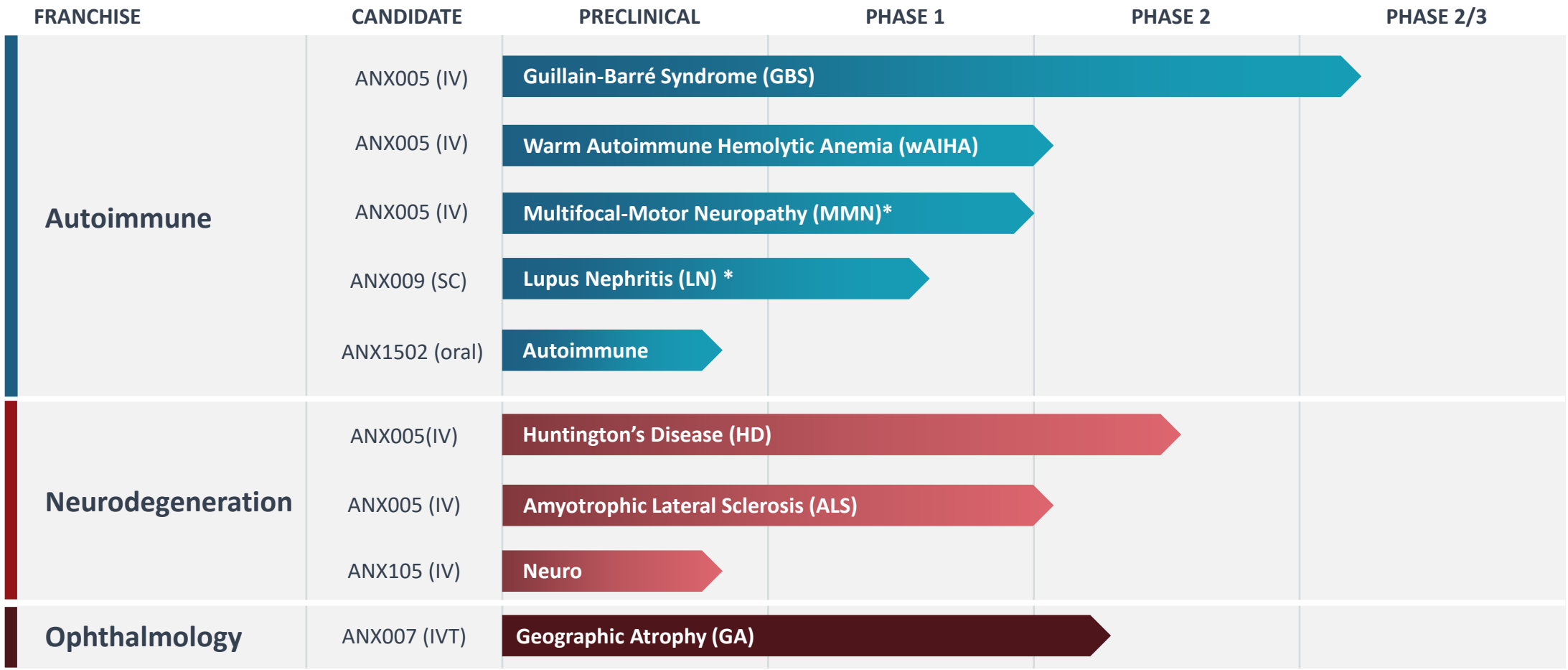
Broad & Deep Wholly Owned Classical Complement Pipeline

3 Therapeutic Franchises. 7 Clinical Trials. 5 Drug Candidates. 3 Clinical Candidates.



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

* Newly announced indications

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Line of Sight to Significant Additional Opportunities

Platform opportunity across breadth of mechanistically-related diseases

AUTOIMMUNE

wAIHA & LN

- **CAD** (Cold Agglutinin Disease)
- **Bullous Skin Diseases**
- **HIT** (Heparin-Induced Thrombocytopenia)
- **Rheumatoid Arthritis**
- **Crohn's Disease**

GBS & MMN

- **CIDP** (Chronic Idiopathic Demyelinating Polyneuropathy)
- **PMS** (Progressive Multiple Sclerosis)
- **ON** (Optic Neuritis)
- **MG** (Myasthenia Gravis)

NEURODEGENERATION

HD & ALS

- **FTD** (Frontal Temporal Dementia)
- **SMA** (Spinal Muscular Atrophy)
- **AD** (Alzheimer's Disease)
- **TBI** (Traumatic Brain injury)

OPHTHALMOLOGY

GA

- **GLA** (Glaucoma)

● Current Indications ● Sample Follow-on Indications

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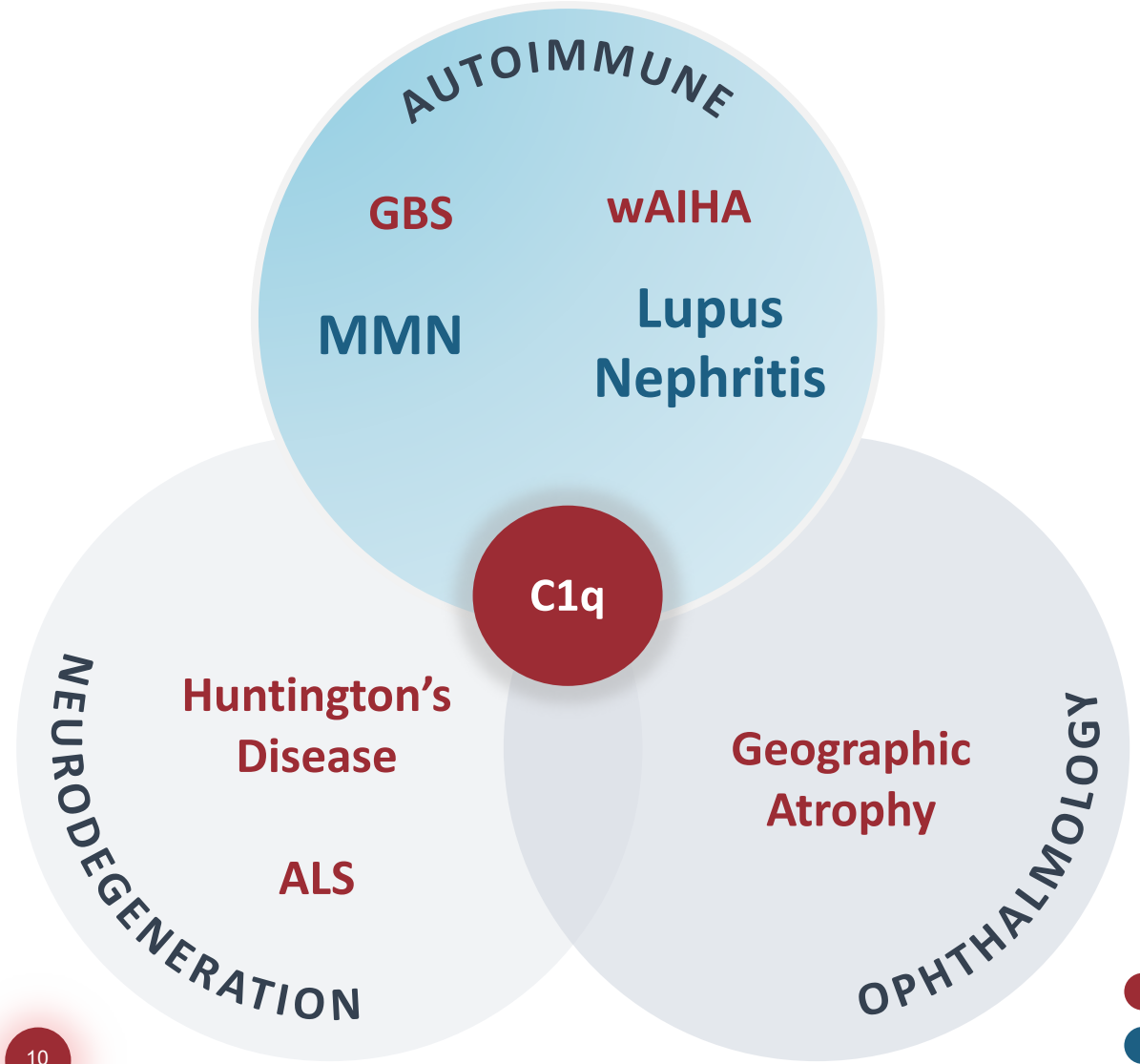
Autoimmune Franchise Strategically Expanded into Additional Potential High Value Indications



AUTOIMMUNE FRANCHISE EXPANSION

- **C1q-Mediated Diseases** - Strong scientific rationale & high unmet need
- **Precision-Medicine Approach in Lupus Nephritis**
- **Leveraging GBS POC Data in MMN** mechanistically related disease

Current Indications

New Indications

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Targeting C1q and the Classical Complement Pathway in Autoimmune Diseases

Ted Yednock, PhD

Chief Scientific Officer

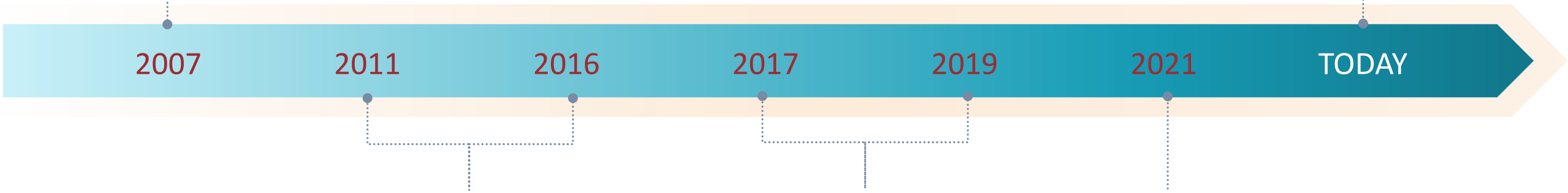
Annexon Biosciences

Annexon Pioneering New Generation of Complement Medicines for Multiple Classical Complement-Mediated Disorders

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

Expanding indications with ANX005 and **advancing pipeline** with additional fit-for-purpose therapeutics



Annexon developed ANX005 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

ANX005: initial **clinical POC in GBS** as lead antibody-mediated autoimmune indication

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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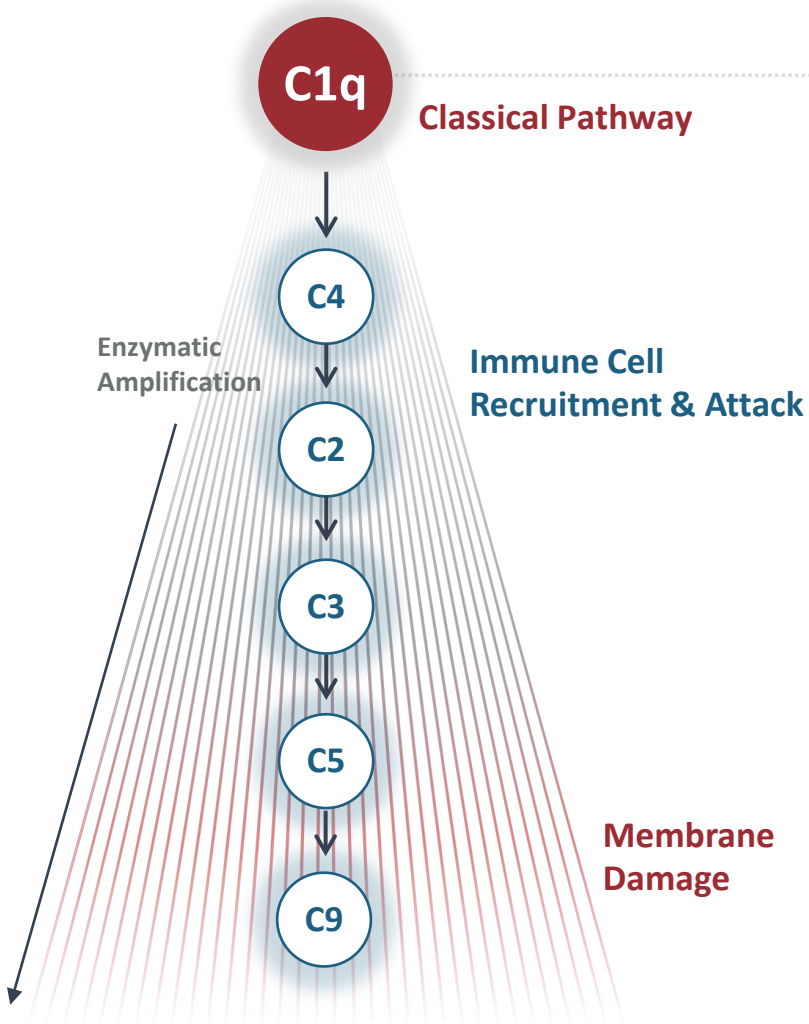
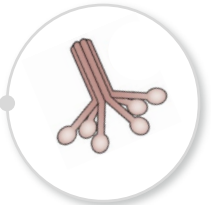
C1q Inhibition Stops Classical Complement Activity at the Start

Prevents downstream activation of all tissue-damaging components





C1q

- **Initiating molecule** of the classical complement cascade
- **Recognizes autoantibodies** bound to tissues in autoimmune disease
- **Initiates and focuses activity** of the classical cascade on the tissue surface
- **Independent opsonin** for macrophage attack
- **Pathway drives tissue damage** via macrophage recruitment, attack and membrane damage

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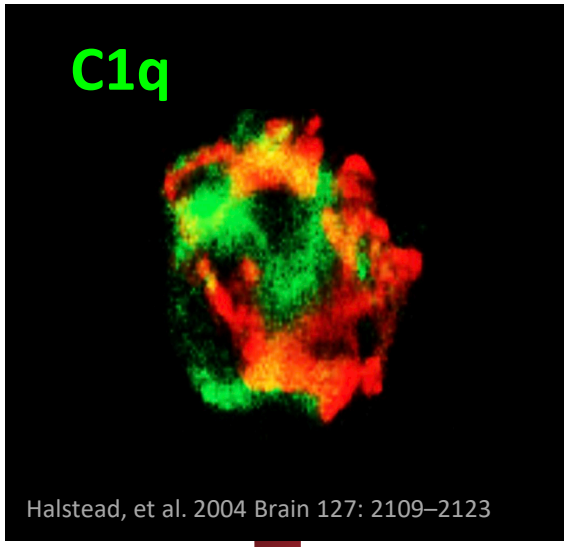
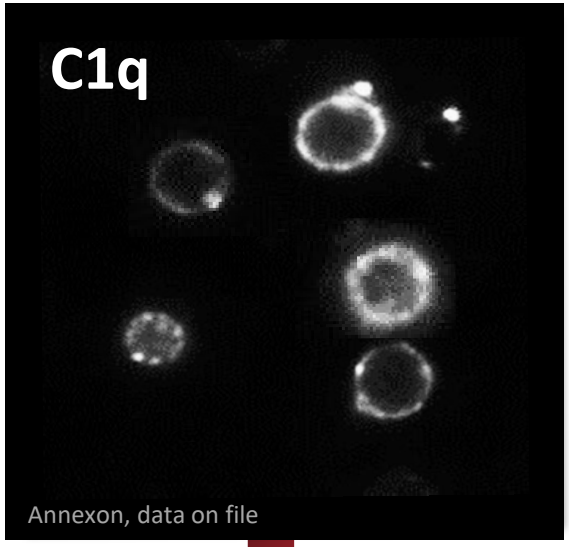
C1q Drives Tissue Damage in Numerous Antibody-Mediated Autoimmune Diseases

C1q binds to autoantibodies on tissue surfaces and anchors classical cascade activation

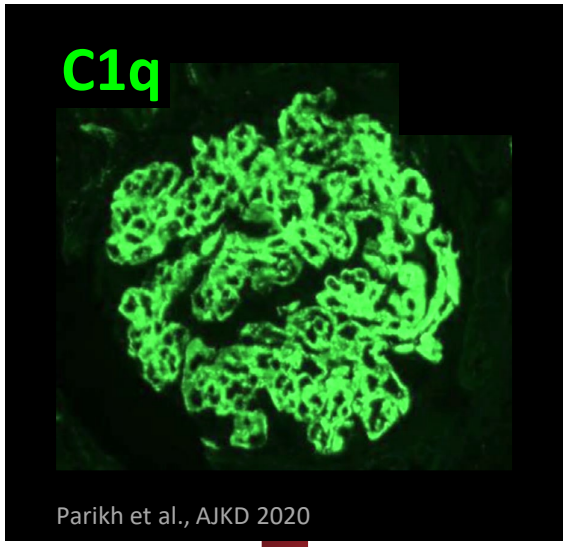
Neuromuscular junction



Red blood cells



Renal glomerulus



Neuromuscular

- GBS
- MMN

Hematology

- wAIHA
- Cold Agglutinin Disease

Nephrology

- Lupus Nephritis

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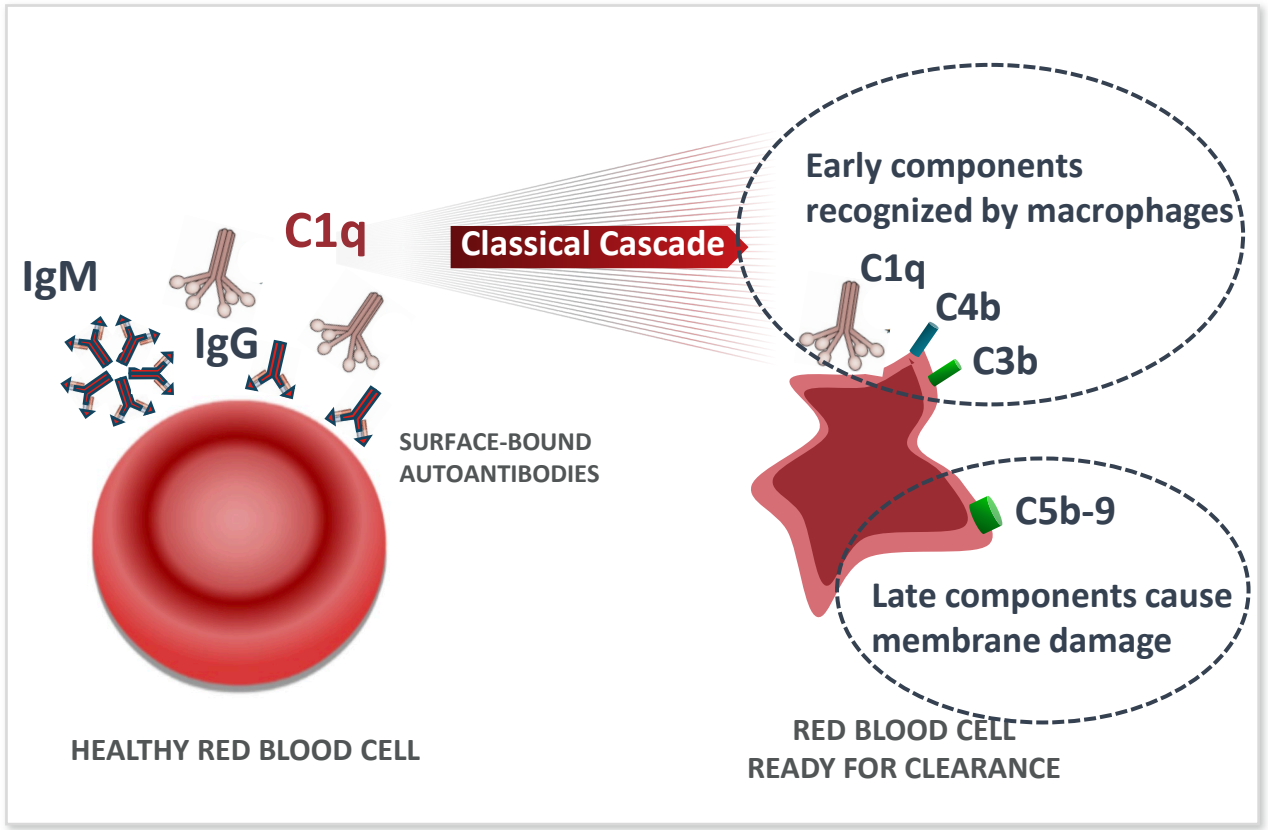
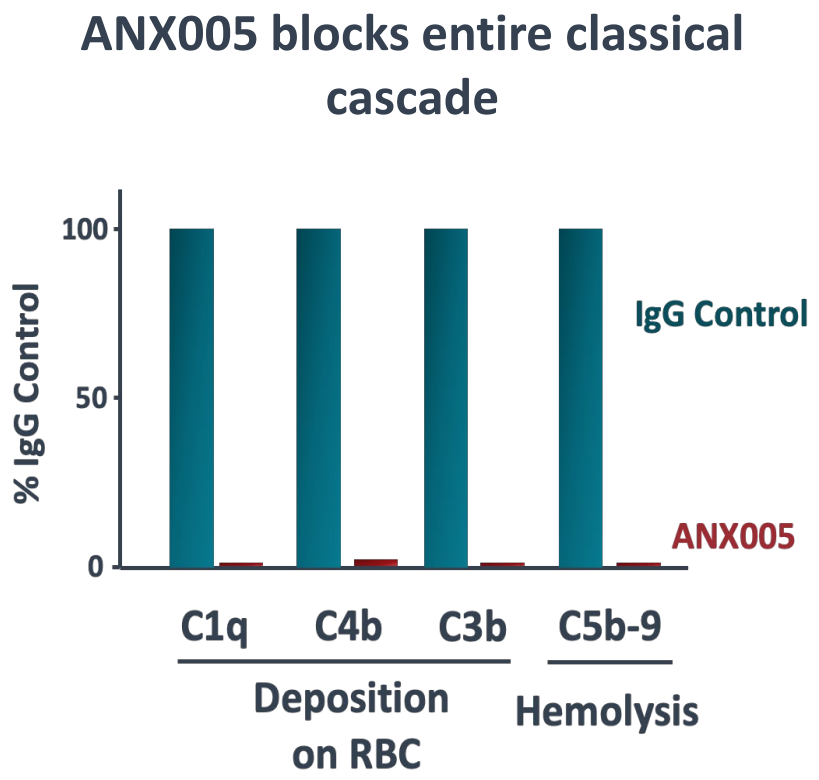
C1q is a Key Amplifier of IgM and IgG Antibody Damaging Activity

ANX005 inhibits the deposition of both early and late components of the classical pathway to block their distinct activities





Annexon, data on file

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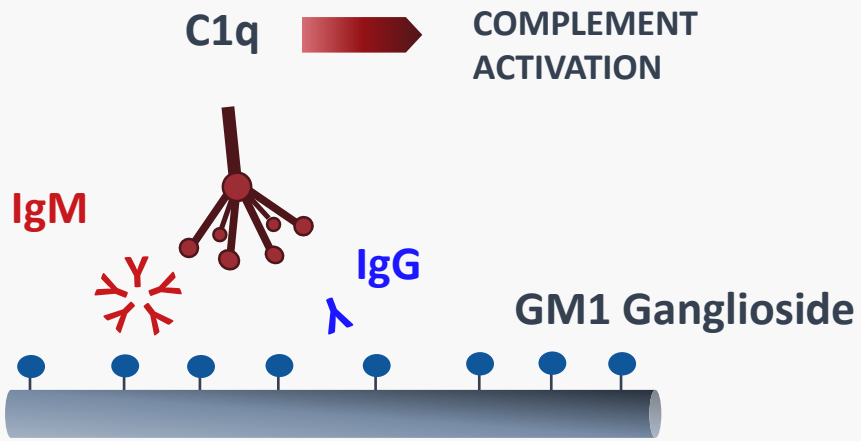
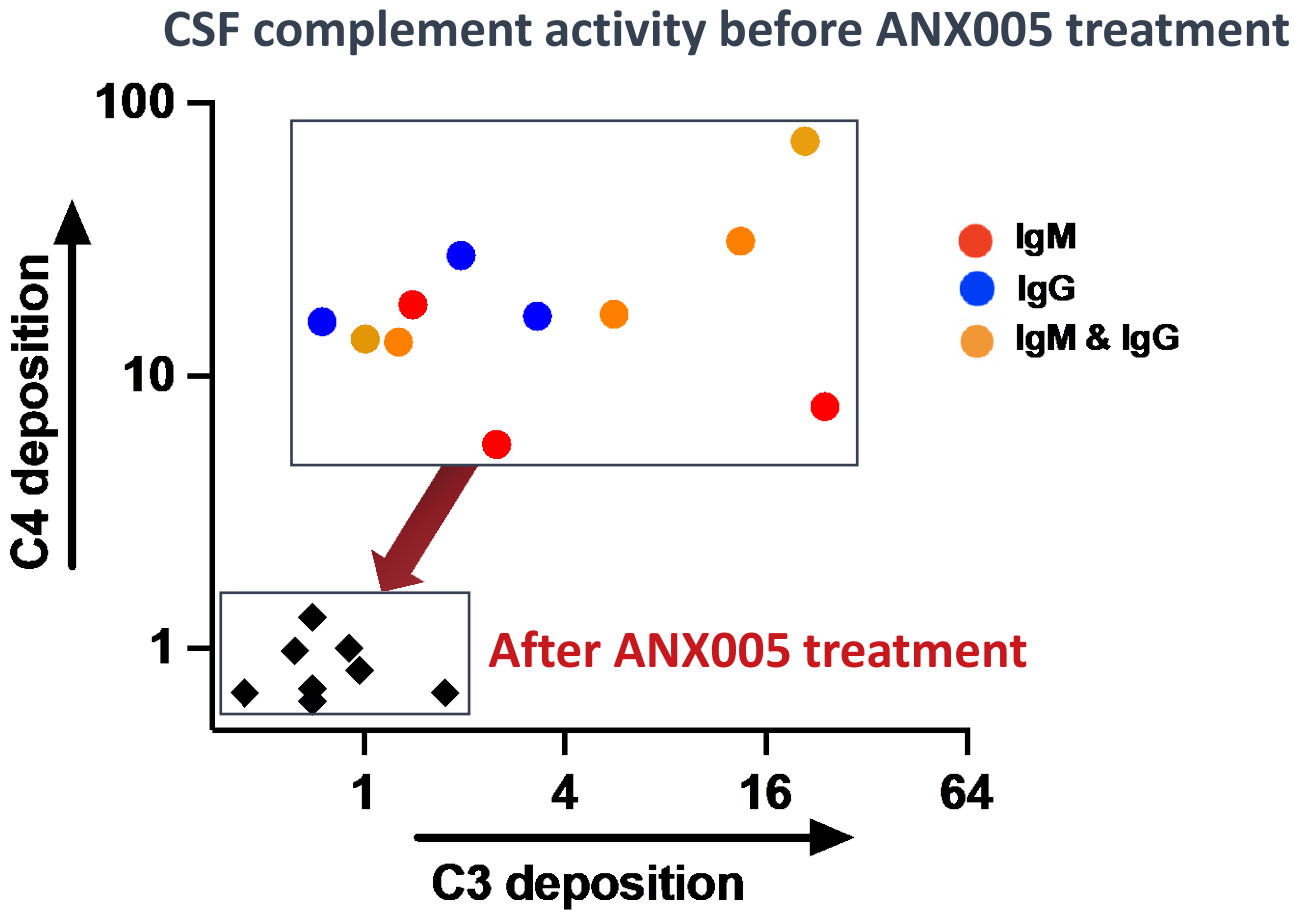
Treatment of GBS Patients with ANX005 Inhibits Both IgM and IgG Antibody-Mediated Complement Activity in the CSF





Platform presentation at 2021 PNS conference, Suri, et al., Annexon

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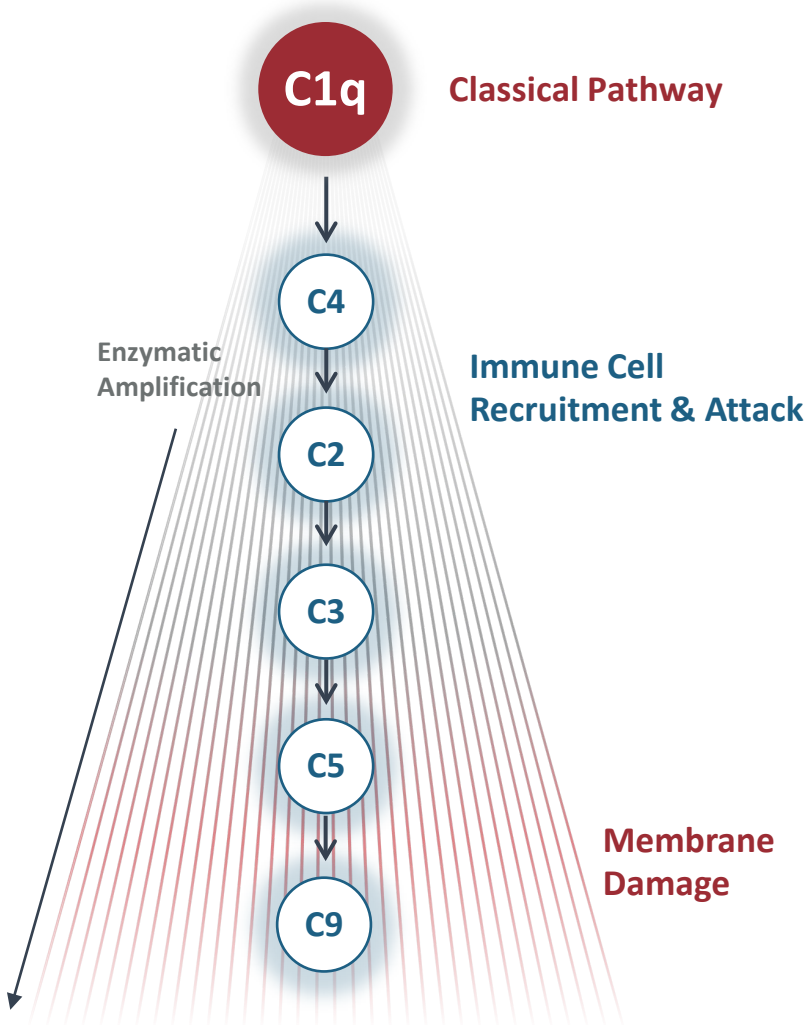
C1q Inhibition Stops Classical Complement Activity at the Start

Prevents downstream activation of all tissue-damaging components



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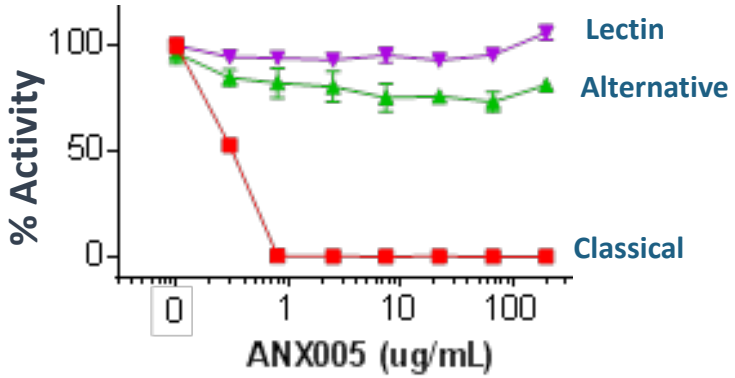
- **Targeting Enhanced Efficacy:** Shuts down all tissue-damaging components of classical pathway (C1q, C4, C3, C5, C9)[1]
- **Targeting Enhanced Safety:** Allows normal immune functions of lectin and alternative complement pathways[1]

ANX005: Selective inhibition of classical pathway activity[2]



[1]Annexon data on file
[2]Wieslab assay; Annexon data on file

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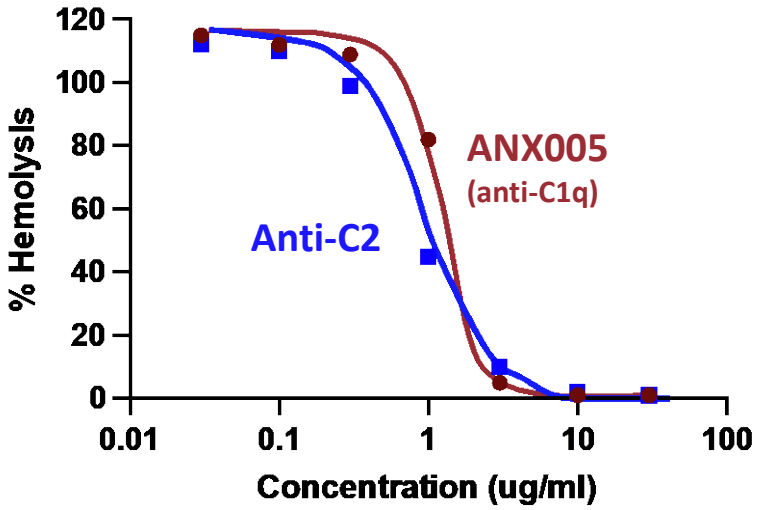
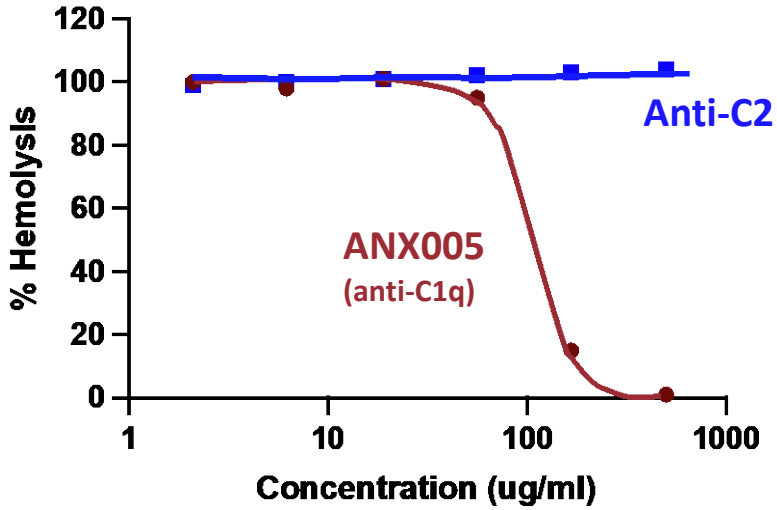
Important to Fully Inhibit Classical Pathway Activity at the Start

- ANX005 **blocks C1q binding to tissue surface** to stop pathway activation, **shutting down all tissue-damaging components** of classical pathway (C1q, C4, C3, C5, C9)
- **Anti-C1q effective with low and high complement activation conditions** - unlike downstream inhibitors that can be outpaced by mechanisms such as the "C2 bypass pathway[1]" and others[2]

Low Activation Condition
(Human serum 1:100)



High Activation Condition
(Human serum 1:3)



[1]Malhador, et al., J Immunol 2007; [2]C1s, C2, and C4: Annexon, data on file; C3 and C5: Mannes, et al., *Blood*, 2021

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Annexon Pioneering Expertise in Classical Complement Pathway

- **C1q binds to the tissue surface to drive** classical complement activation and **damage in IgM and IgG antibody-mediated autoimmune disease**
- **Blocking C1q at the top of the cascade is most effective** at fully stopping classical pathway
- **Anti-C1q inhibits all components of the classical pathway** with their distinct tissue damage activities (C1q, C4, C3, C5, C9)
- **C1q inhibition leaves lectin and alternative pathway in place** for normal immune functions
- **Anti-C1q effective with low and high complement activation conditions** – differentiated from downstream inhibitors

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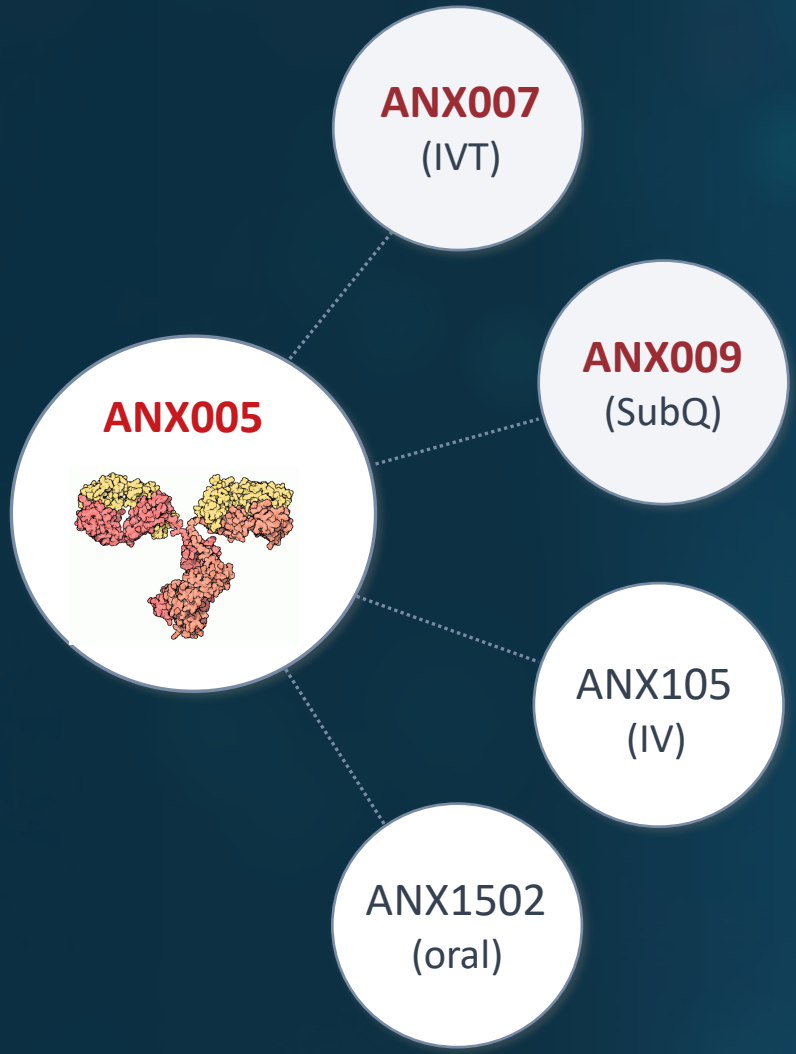
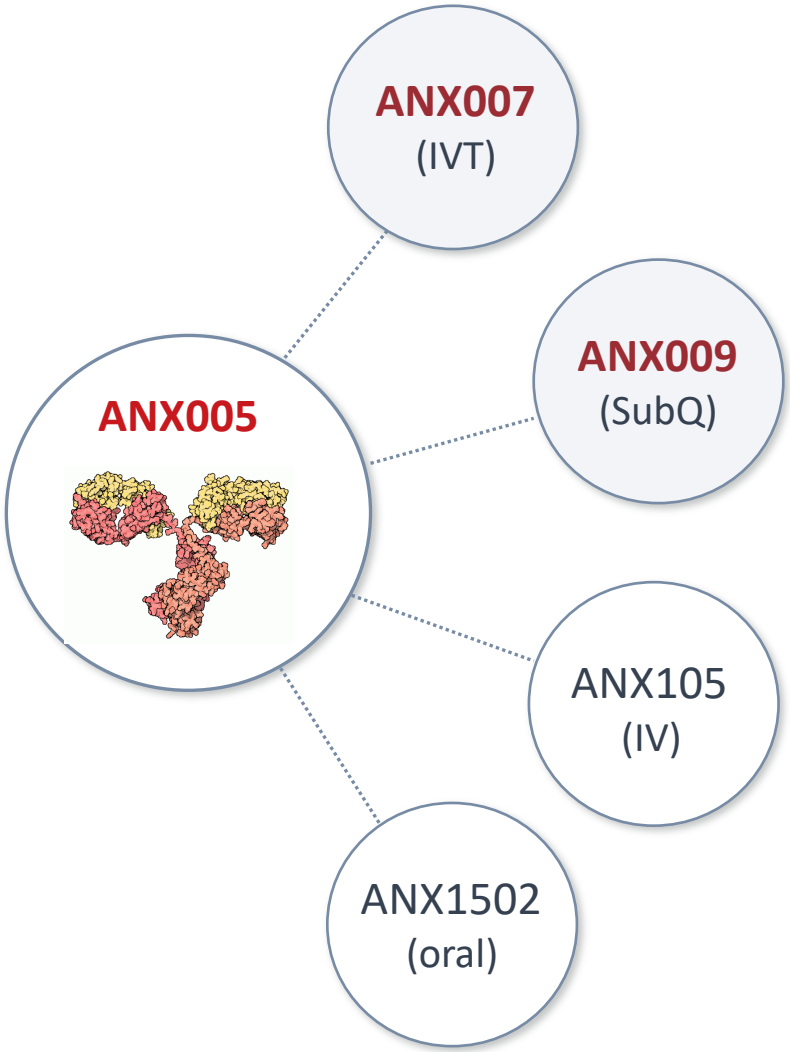


Overview of Annexon's Classical Complement Pathway Therapeutics

ANX005 First-in-Class Classical Complement Pathway Inhibitor at the Core of Drug Candidate Technology



ANX005: FIRST-IN-CLASS ANTI-C1Q THERAPEUTIC

- **Humanized anti-C1q mAb; mutated Fc tail**
- **7 pM binding affinity**; hinge stabilized IgG4 framework
- **Blood-brain penetration** – fully inhibits C1q and complement in serum and CSF
- Completely inhibits downstream classical cascade (e.g., C4, C3, C5-C9)
- Completed 4 week and 26 week tox in cyno (up to 200 mg/kg weekly)
- High yield GMP manufacturing process with Lonza
- **>100 patients dosed with ANX005**[1]; well-tolerated; transient skin rash at first dose

[1]Annexon data on file

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Building a Diverse Pipeline of New Complement Therapeutics

ANX009 (Fab)

- 2x weekly subcutaneous dosing
- Targeting vascular C1q

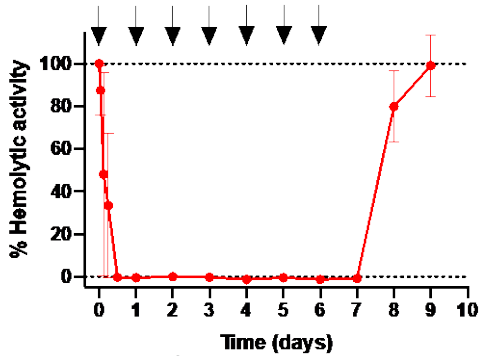
ANX105 (mAb)

- Enhanced dosing profile / PK
- Targeting systemic / CNS disease

ANX1502 (Small Molecule)

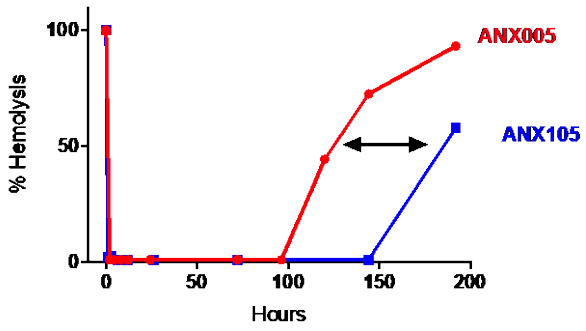
- Orally available small molecules
- Targeting daily dosing in autoimmune disease

Daily subcutaneous administration in nonhuman primates (*ex vivo* hemolysis)

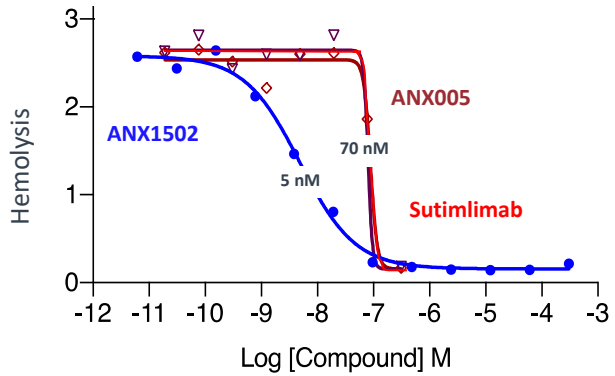


Annexon data on file

***Ex vivo* hemolysis following iv dosing at 15 mg/kg**



***In vitro* hemolysis**



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Leveraging Classical Complement Expertise into Innovative Pipeline for Multiple Indications

- **ANX005 is a high potency antibody** for use in in both neurodegenerative and autoimmune disorders
- **ANX009 Fab fragment** of ANX005 selectively targets C1q in the circulation for **blood based and vascular disease**
- **ANX105** is a modified version of ANX005 with enhanced dosing properties **for systemic autoimmune and neurological disorders**
- **ANX1502** is a small molecule **for oral dosing in autoimmune disorders**
- **Advancing ANX005** into POC studies for multiple indications with **expanding pipeline** of fit-for-purpose drug candidates

Pioneering a Precision Medicine Approach to Antibody-mediated Autoimmune Disorders

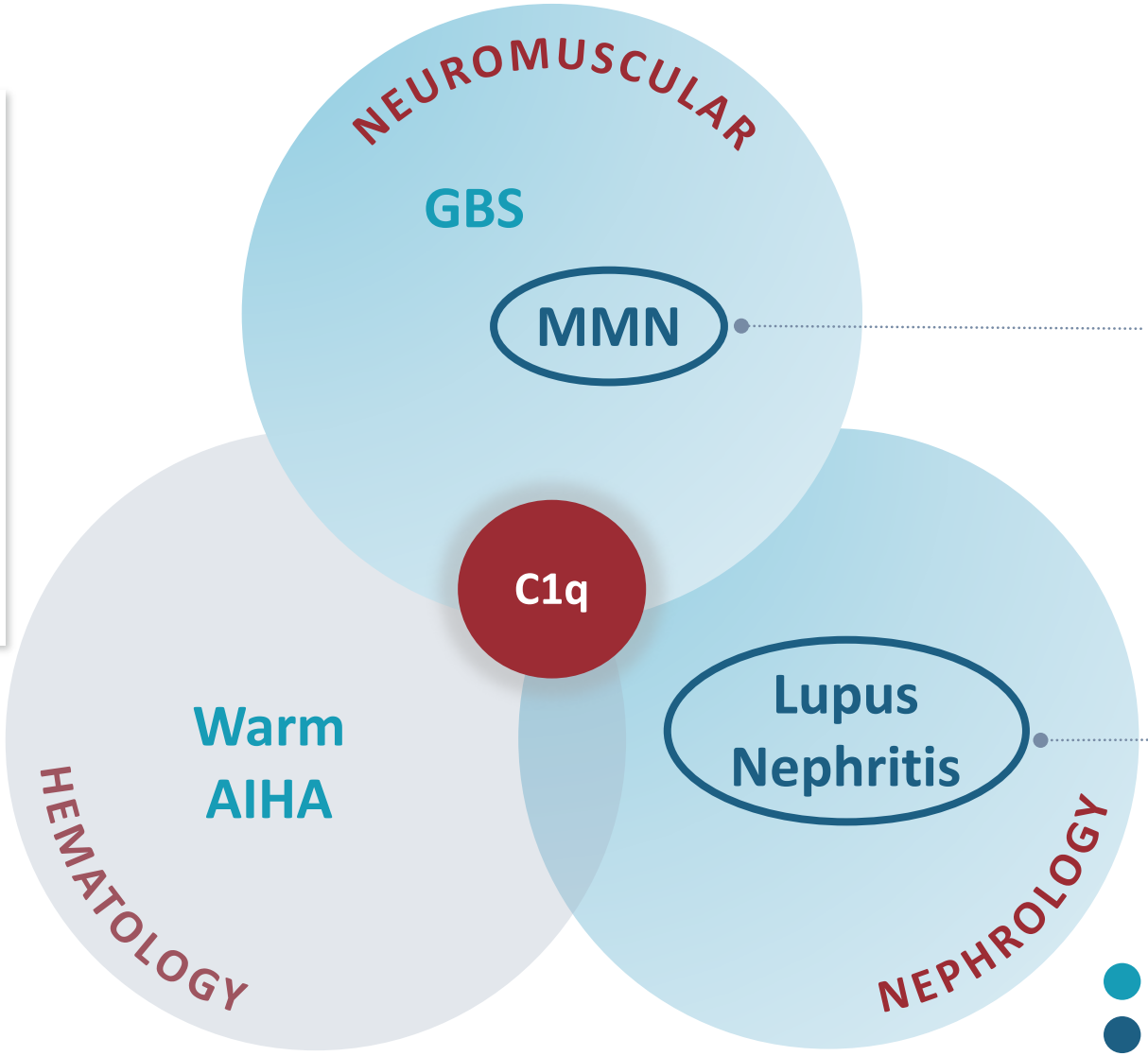
Sanjay Keswani, MD, FRCP (UK)

Chief Medical Officer

Annexon Biosciences

Broad Therapeutic Potential of Anti-C1q in Autoimmune Diseases

Demonstrated aberrant classical complement pathway activation in multiple autoimmune diseases with high unmet need



Leveraging GBS POC Data in mechanistically-related MMN

Precision-Medicine Approach in Lupus Nephritis

Current Beachhead Indications

New Indications

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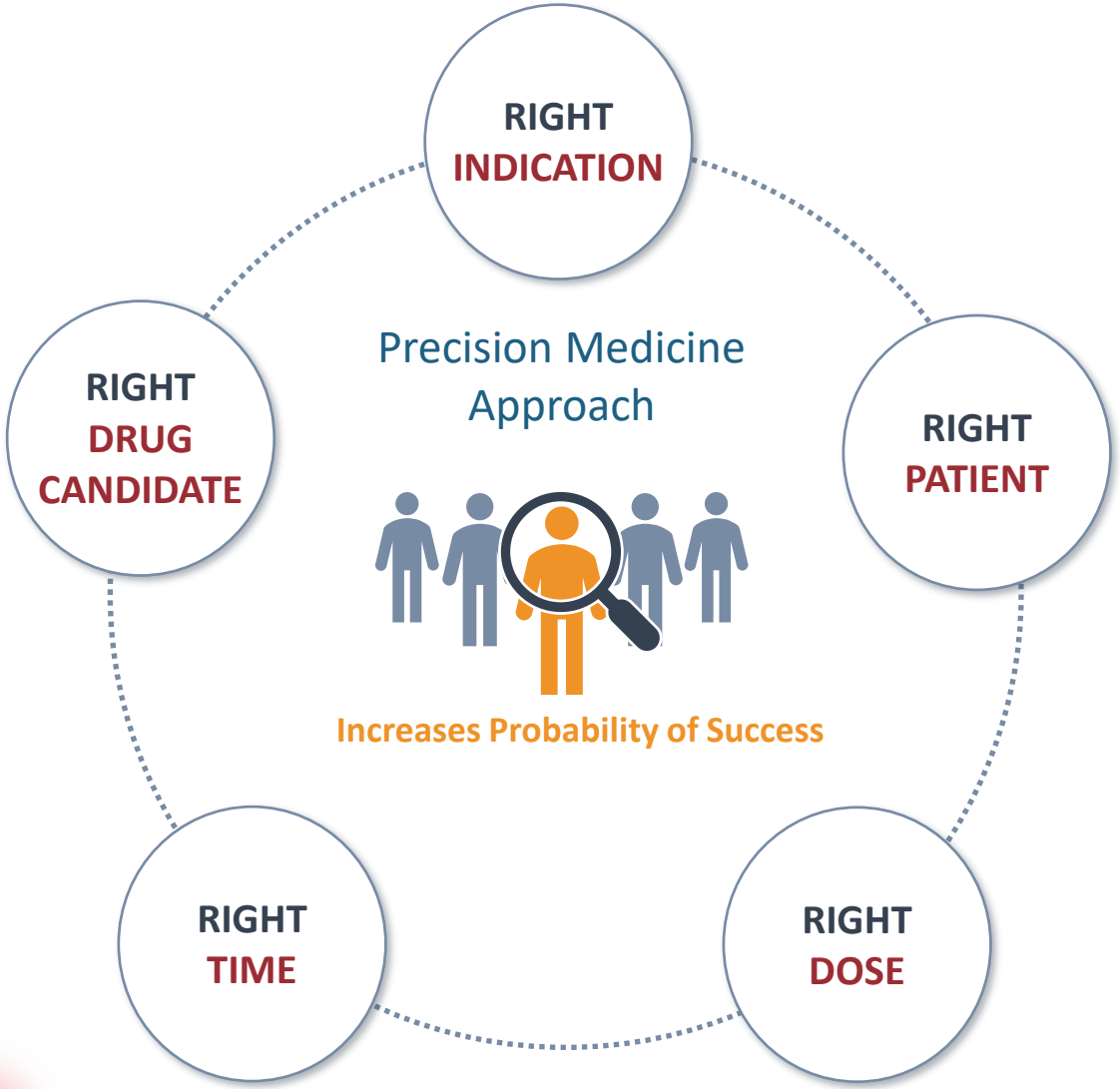
Precision Medicine Approach Underpins Annexon's Development Strategy in Autoimmunity



- Targeting **diseases driven by excess classical complement activation**
- Measuring excess classical complement activation with **established biomarkers**
- Enables **identification of patient indications and patients** that would respond best to anti-C1q therapeutic

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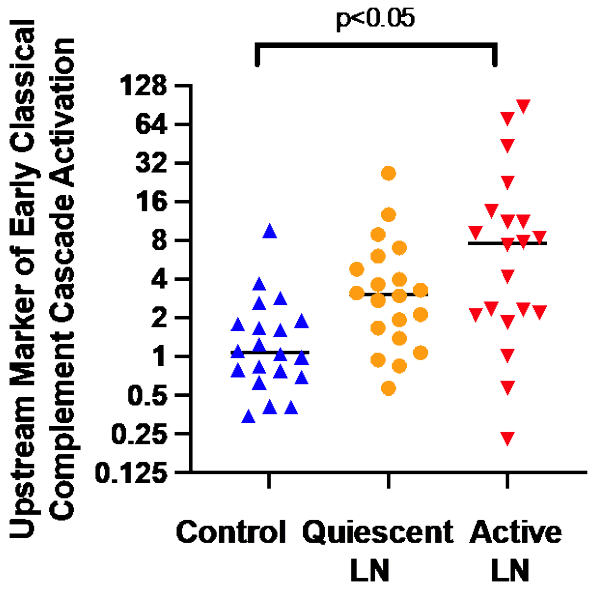
Established Biomarkers to Enhance Probability of Clinical Success

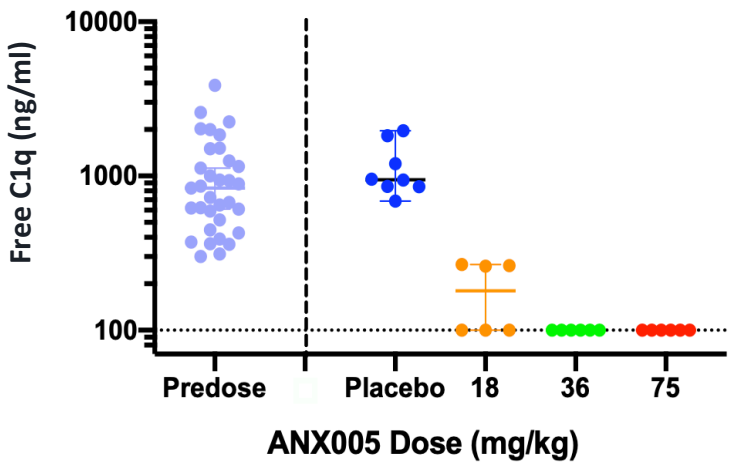
Leveraging classical complement and disease markers in patients

Indication and Patient Selection



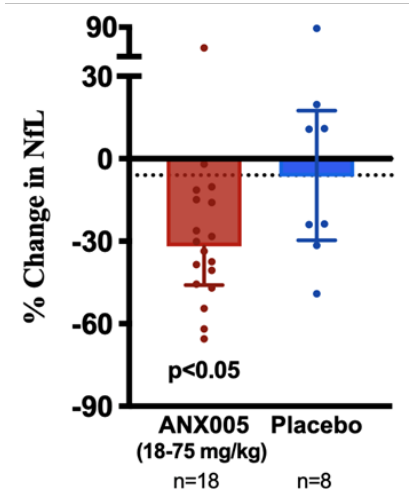
Higher Classical Complement Activation in Patients With Lupus Nephritis

Optimal Dose and Dosing Regimen



Dose-dependent decrease of CSF-free C1q in GBS Phase 1b

Objective Measures of Treatment Effect



NfL statistically reduced in GBS Phase 1b

Annexon data on file

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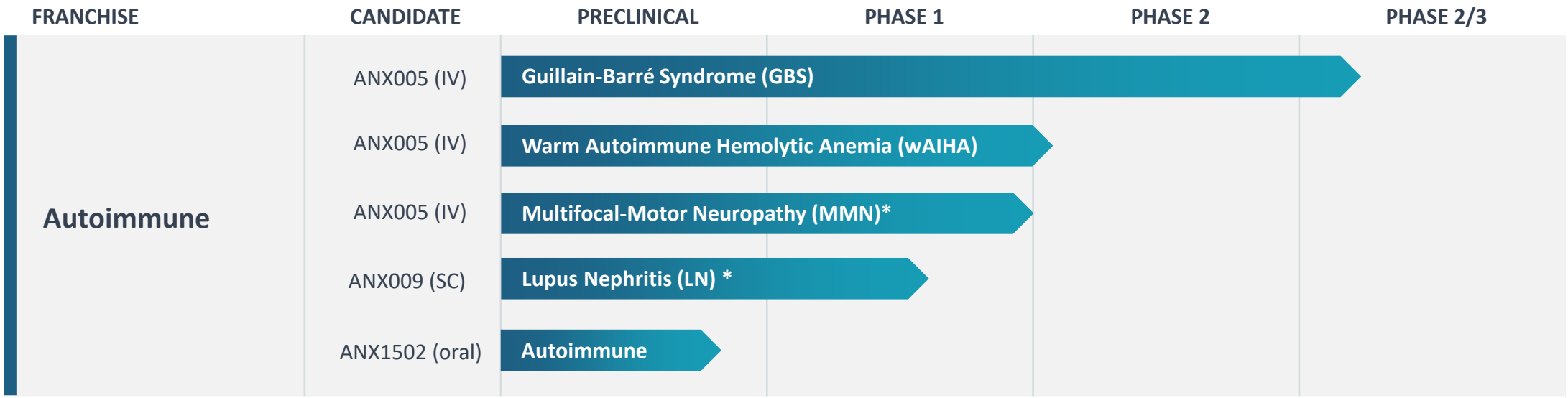
Annexon Pipeline in Antibody-mediated Autoimmune Disease

Expanding franchise of high PTS mechanistically-related indications



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

* Newly announced indications

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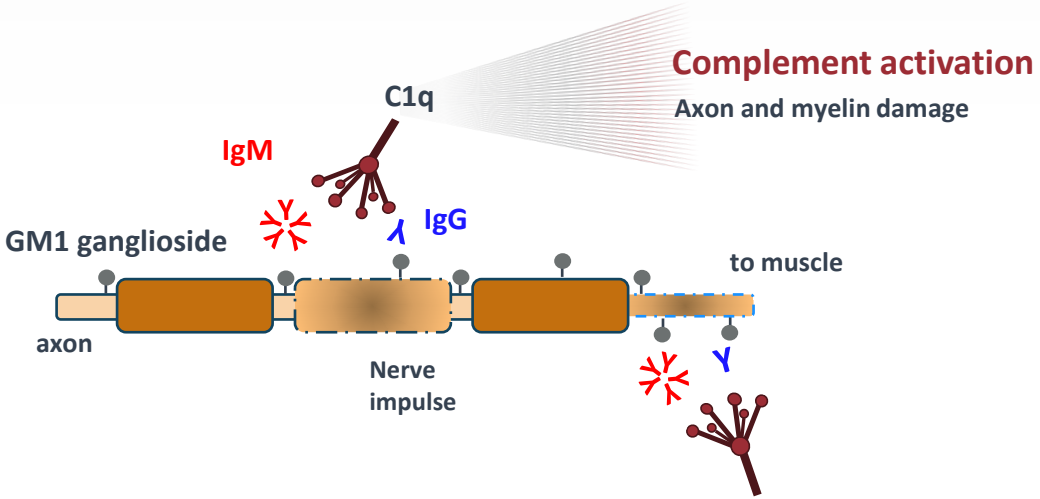
Guillain-Barré Syndrome, a Devastating Antibody-mediated Autoimmune Disease

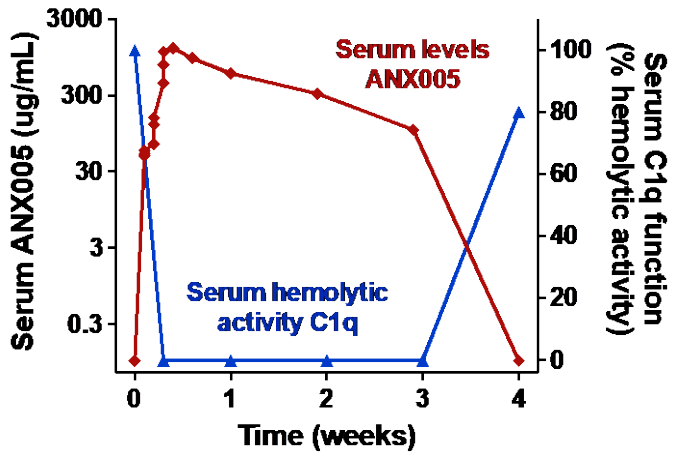
GBS is a severe disease resulting from autoantibody attack on peripheral nerves, triggering complement (C1q) and neurodegeneration



ANNEXON biosciences

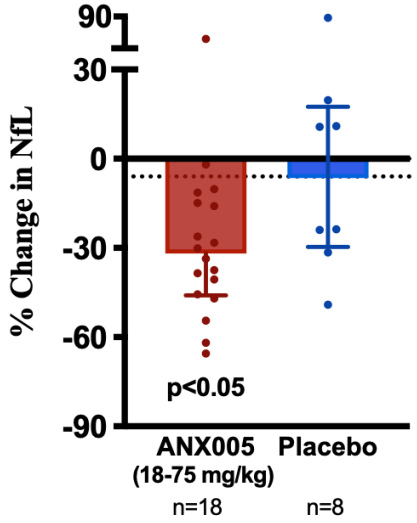
ANX005 POC Data Enabled Ongoing Phase 2/3 Trial in GBS

Full C1q Inhibition in Blood



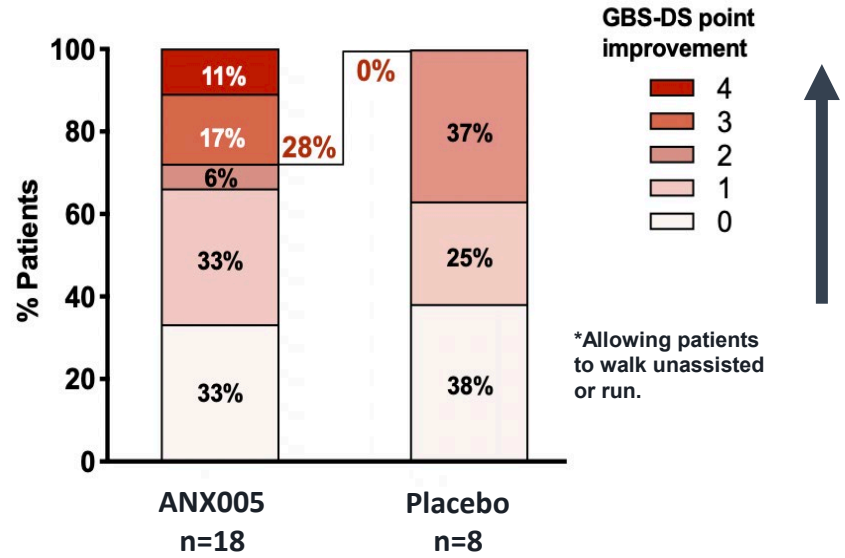
Data From a Patient Receiving 75 mg/kg (Target Ph 2/3 dose)

Significant Early NfL Reduction (Weeks 2-4)



High-Dose ANX005 (18-75 mg/kg) vs Placebo

28% of High-Dose Patients Improved by ≥3 pts on GBS-Disability Scale by Week 8*



High-Dose ANX005 (18-75 mg/kg) vs Placebo

Annexon data on file

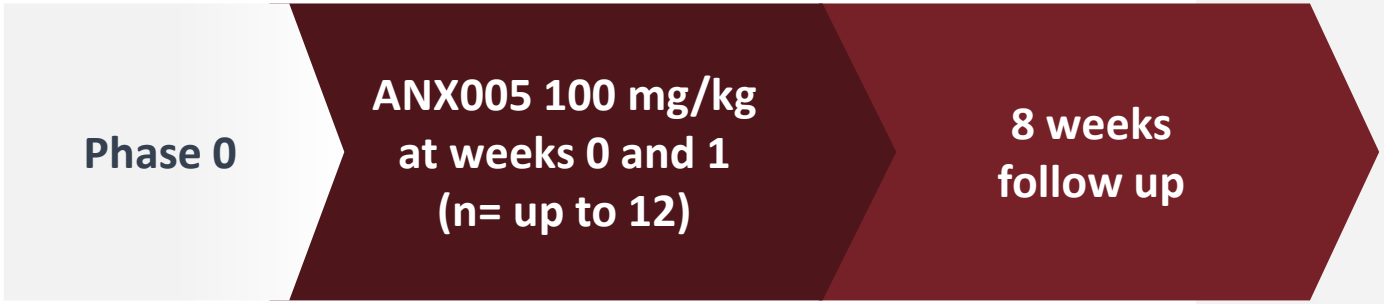
ANNEXON biosciences

Clinical POC in GBS Increases Confidence to Expand into Other Autoantibody-Mediated Diseases

- **ANX005 well-tolerated** at all doses (single and multiple doses)
- **Rapid and complete target engagement of C1q** in Blood and CSF
- **Early and statistical decline of NfL** indicative of reduced autoantibody-induced injury to peripheral nerves
- **Complete hemolysis inhibition (CH50)** enabling trials of autoantibody-induced hemolytic anemias (e.g., wAIHA, CAD)

ANNEXON biosciences

Precision Medicine Approach Underway in wAIHA Phase 0/2 Trial

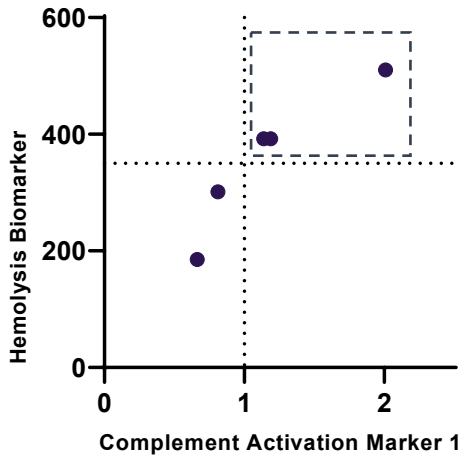


- **Open label trial** (n= up to 12)
- Using **Phase 0 'feeder' study to identify/select patients for Phase 2**
- **Objective endpoints:** safety, PK/PD, hemolysis markers, improvement in hemoglobin

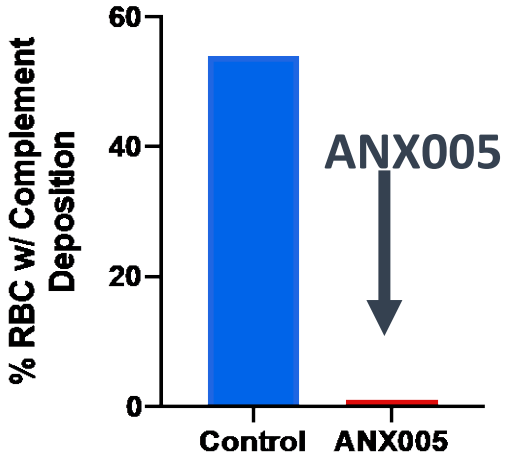
ANNEXON biosciences

Enriching for wAIHA Patients with Excess Classical Complement Activity In Vivo and In Vitro

Ongoing Phase 0:
Patient selection based on classical complement signature



ANX005 inhibits complement deposition on RBC with wAIHA patient serum *in vitro*



ACTIVITY FULLY INHIBITED BY ANX005

- **Detected complement-activating antibodies in 4 of 12 wAIHA patients** (consistent with literature ~30 %)
- **Activity fully inhibited by ANX005 *in vitro***

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Expansion into Mechanistically-related Autoimmune Diseases

- Lupus Nephritis
- MMN

Strong Rationale to Advance into Lupus Nephritis

- LN is an **autoantibody-mediated** disease
- **PACAs** are a specific autoantibody that drive aberrant classical complement activation and disease activity in LN patients
- **ANX009 uniquely targets** and inhibits PACA induced pathology
- Unique **precision medicine** approach to identify specific patient subset via established biomarkers of complement activity

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Strong Rationale to Advance into Multifocal Motor Neuropathy

- MMN disease caused by **anti-GM1 IgM autoantibodies** that activate the classical complement pathway
- In **MMN model, anti-C1q prevented nerve injury** induced by anti-GM1 IgM autoantibodies from patient sera
- **ANX005 blocked anti-GM1 IgM activity in GBS** patients
- **Leverage** existing KOL relationships, clinical endpoint **experience and disease understanding** in GBS

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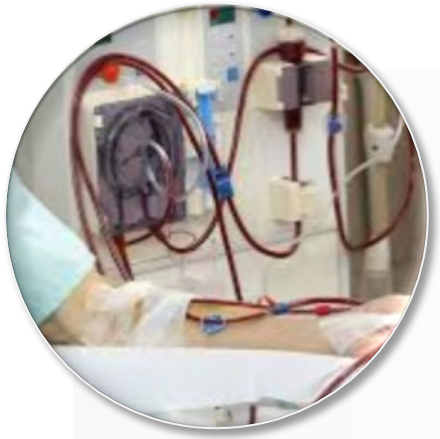
KOL Perspective: Unmet Needs in Lupus Nephritis

Mary Anne Dooley, MD

Professor of Medicine

University of North Carolina Kidney Center

Lupus Nephritis (LN) is a Severe Autoimmune Complication of SLE, with Chronic, Severe Life Impacts for Many



LN affects 130,000 people in G7, ~half within US

Half of SLE patients develop LN during the course of their disease[1]

85% of LN patients are women, presenting most often during childbearing years[2]

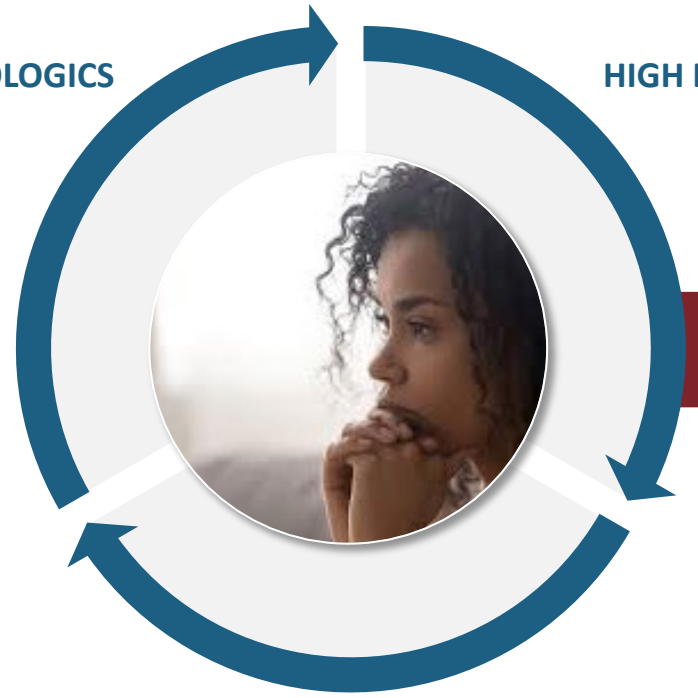
85% of children diagnosed with SLE will eventually develop LN[3]

30-70% of LN patients will progress to kidney failure[4]

Race and Socio-economic status impact patient outcomes[5]

1. Hahn, Bevra H. et al. Arthritis Care Research (2012); 64(6):797-808. 2. Moroni G, Vercelloni PG, et al. Ann Rheum Dis (2018); 77(9):1318-1325. 3. Brunner H, Gladman DD, et al. Arthritis Rheum. (2008); 58(2):556-62. 4. Parikh SV and Rovin BH. JASN (2016); 27(10):2929-2939. 5. Ward MM. J Rheumatol. 2009; 36:63-67.

Current Standard of Care for LN is Suboptimal, with 30-70% of LN Patients Progressing to Kidney Failure



CONTINUING DISEASE PROGRESSION

- Severe Fatigue
- Weight Gain
- ↑ HTN / CV Event Risk
- Progressive Kidney Damage
- Fertility & Pregnancy Risk
- Repeated Kidney Biopsy
- Weighting of Factors impacting LN Varies
- Infection
- Malignancy Risk
- Depression
- Economic Burden
- Dialysis Dependence
- Increased Mortality

ESRD

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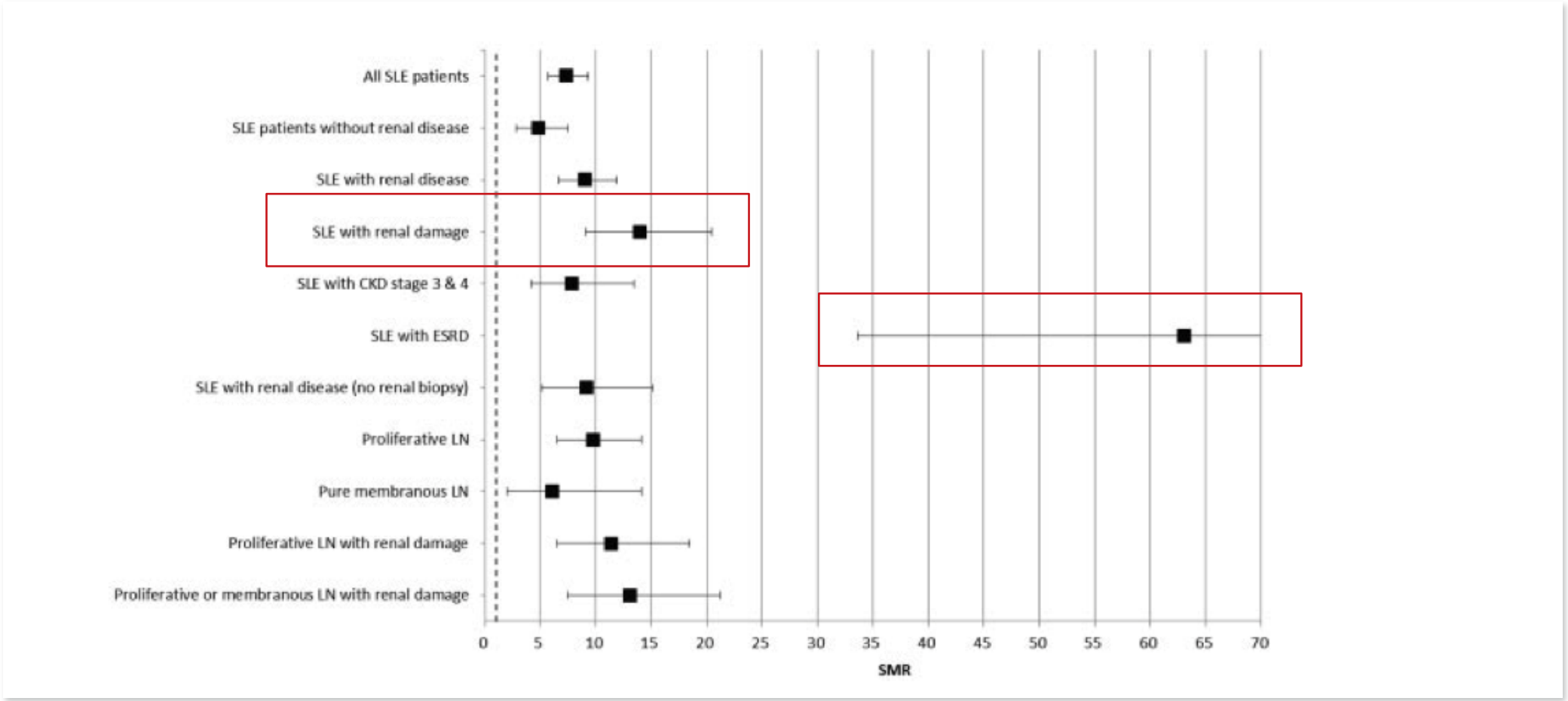
Lupus Nephritis Negatively Impacts Survival

Standardized Mortality Ratio



Mok et al, Arthritis Rheum 2013

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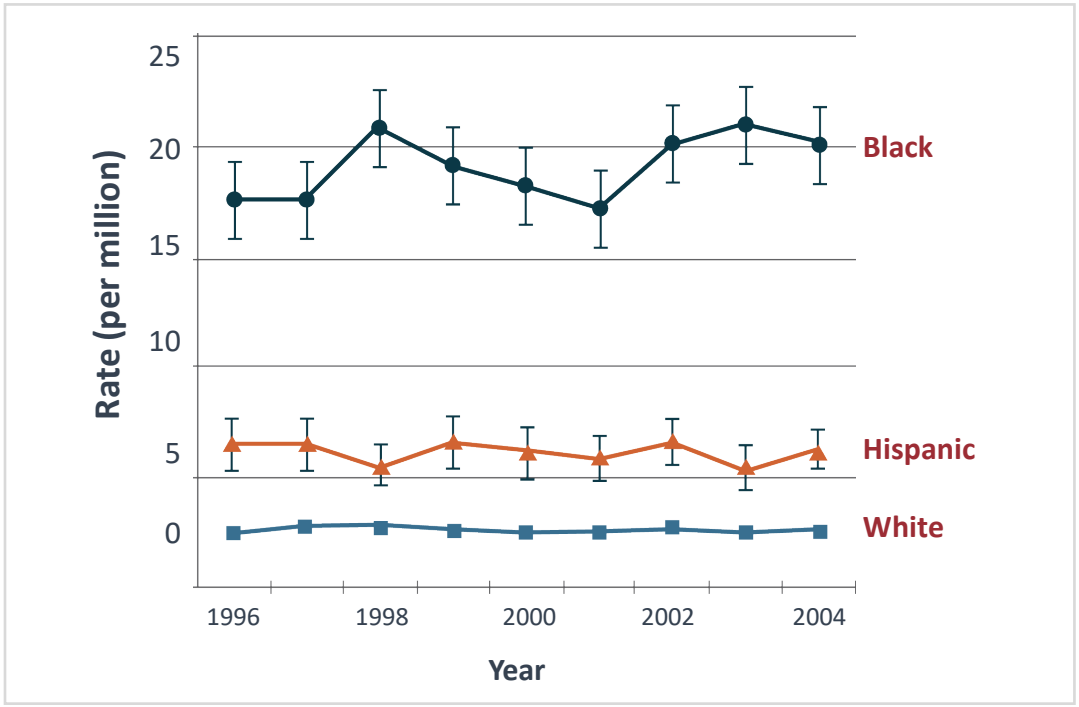
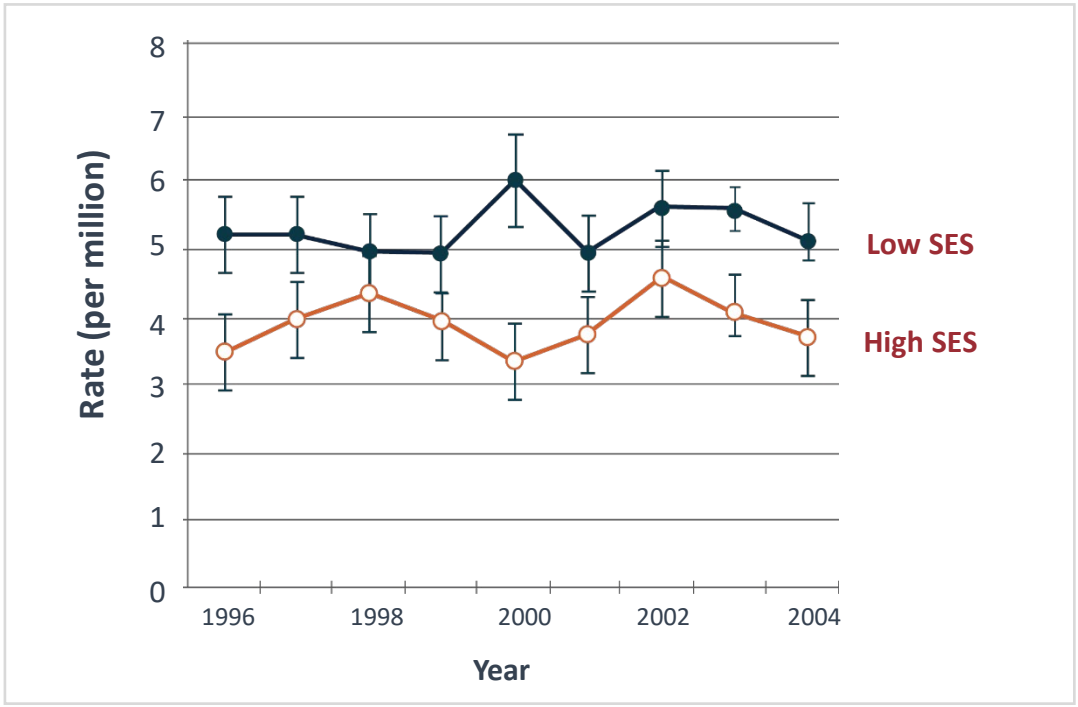
Lupus Nephritis Confers the Highest Risk of Mortality in Lupus Patients

ESRD Due to Lupus Nephritis Incidence by Race/Ethnicity



ESRD Due to Lupus Nephritis Incidence by Socioeconomic Status (SES)



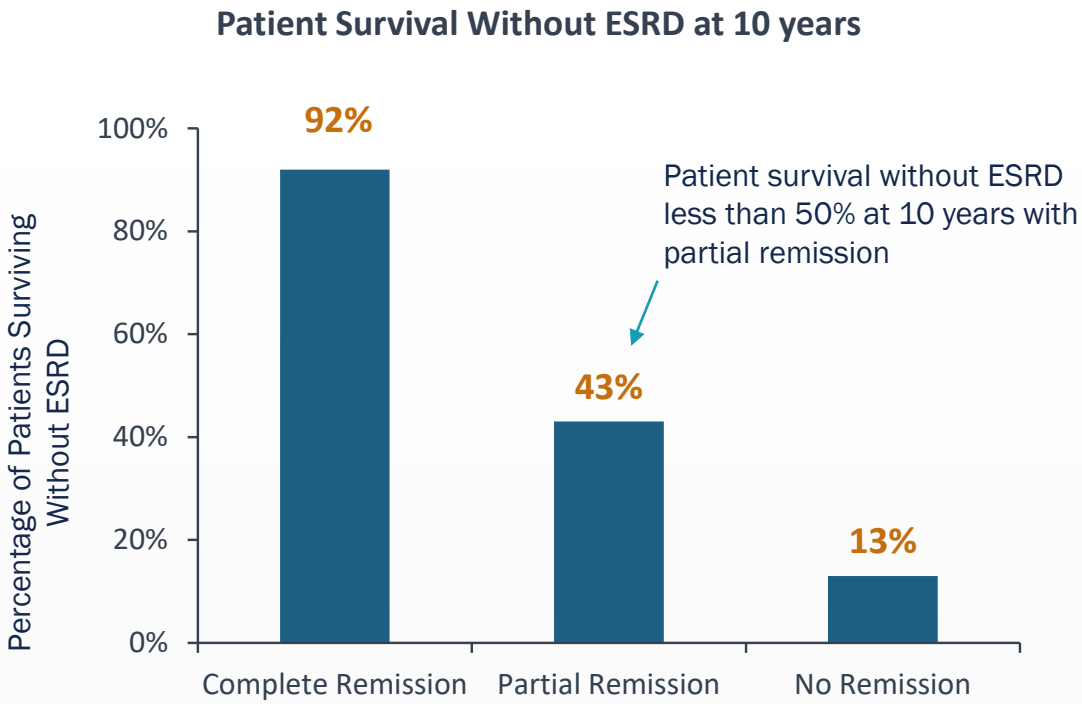
Patients aged ≥15 years with incidence of ESRD due to Lupus Nephritis were identified using the US Renal Data System, a national population-based registry of all patients needing chronic renal replacement therapy for ESRD. Incidence rates were age-, sex-, and race-adjusted to the composition of the US population. Mean age was 40.9 years, 82% of patients were female, 43% were white, 48% were black, 14.7% were Hispanic, 4.6% were Asian/Pacific Islander, 1.1% were Native American, and 2.7% were "other."

Ward MM. *J Rheumatol.* 2009;36:63-7.

There is Significant Need for Improved Treatments for LN to Help Preserve Kidney Function and Improve Long Term Outcomes

OPTIMAL GOALS OF THERAPY

- More effective treatment that achieves complete remission
- Minimize long term steroid use to reduce complications and toxicity from use
- Works rapidly to minimize damage to tissue
- Can be tailored to disease characteristics of the patient
- Reduces administrative and therapeutic burden
- Improve long-term renal and patient outcomes



Chen et al. Clin J Am Soc Neph. 2008; 3(1)

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Key Take-Aways

- **Lupus nephritis is a severe and life-threatening manifestation of SLE** characterized by inflammation and fibrosis, compromising kidney function
- **Current standard of care and immunosuppressive therapies carry significant toxicity** and fail to reduce disease burden in more than half of treated patients
- **The quality of life and socioeconomic burden of LN is considerable** for patients and families
- **There is significant unmet need** for new treatments to further improve outcomes in LN

ANX009 and the Role of Classical Complement in Lupus Nephritis

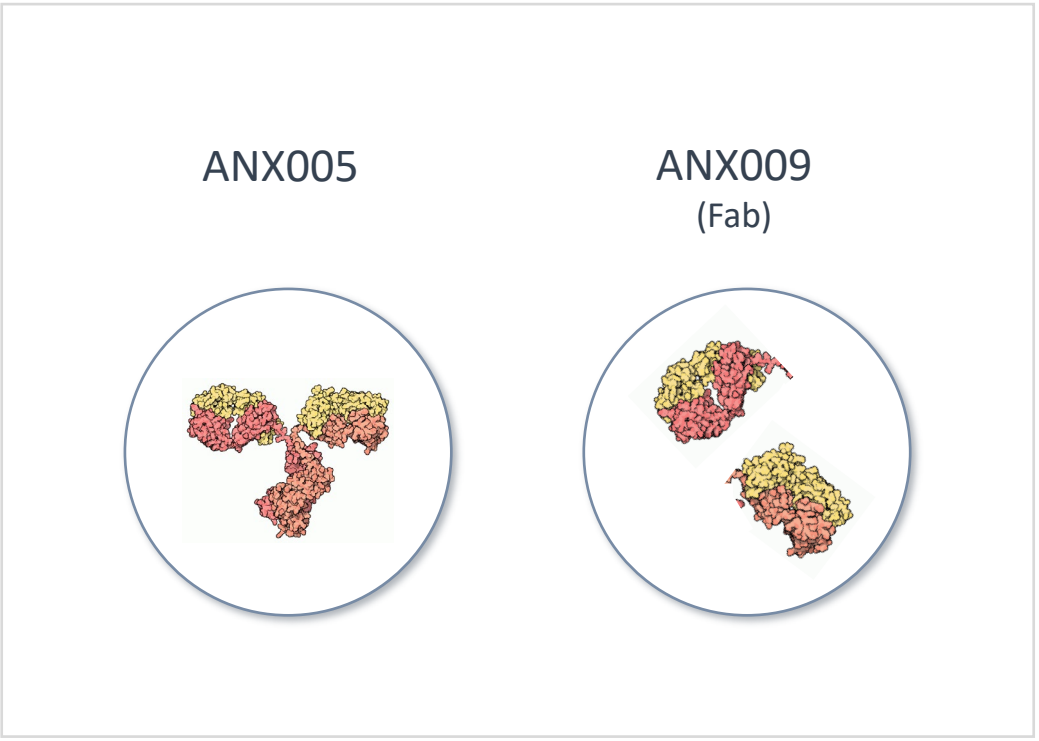
Ted Yednock, Ph.D

Chief Scientific Officer

Annexon Biosciences

ANX009: Differentiated Subcutaneous C1q Inhibitor

Tailored for Blood-Based and Vascular Autoimmune Diseases



Antibody diagram: https://pdb101.rcsb.org/motm/21

ANX009: SELECTIVELY TARGETS C1q IN THE CIRCULATION

- ANX005 Fab
- **Retains high affinity** (<10 pM) and potency of whole antibody
- Target-bound **drug remains attached to C1q in blood until C1q is replaced**
- Developing for **blood-based and vascular indications**
  - Hemolytic Anemias
  - Lupus Nephritis

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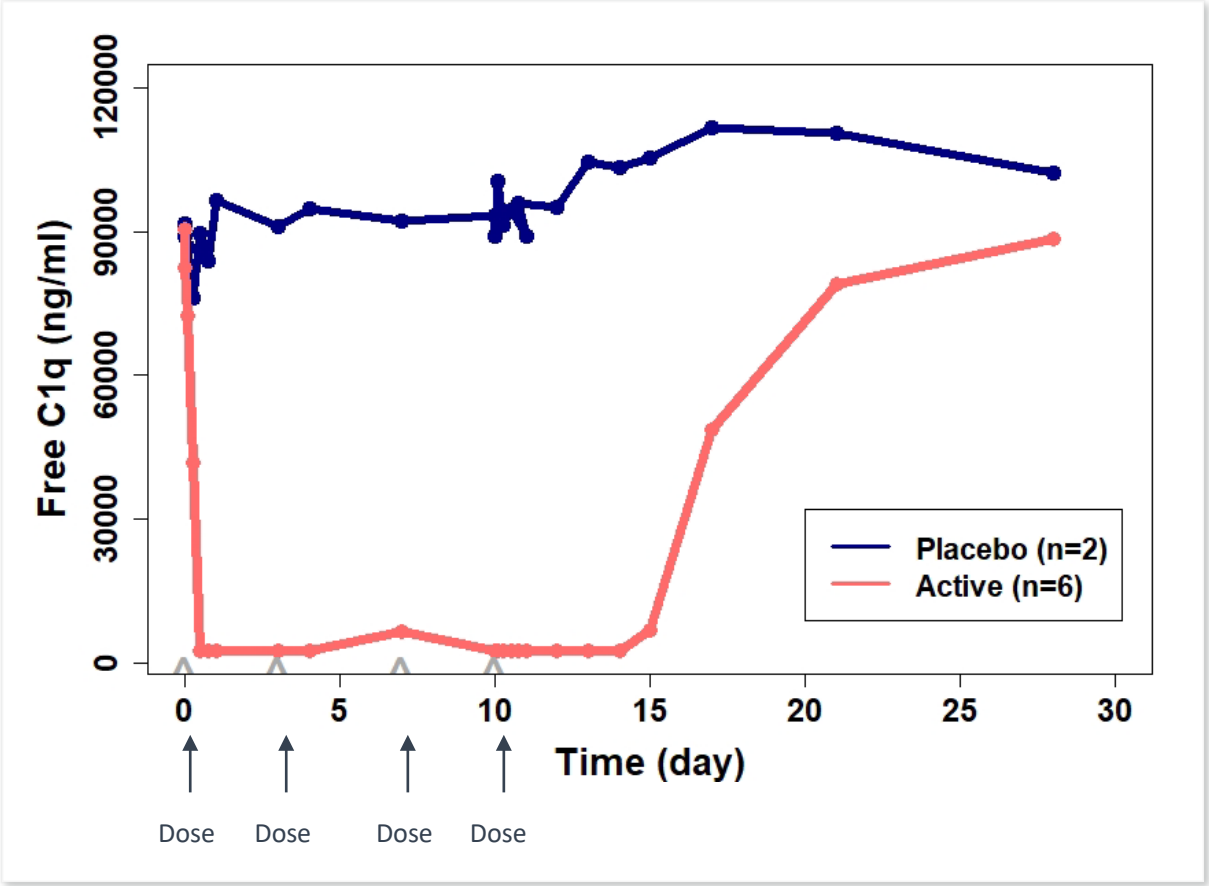
ANX009: Full Inhibition of Circulating C1q in Phase 1 Clinical Trial

Inhibition of C1q at highest dose of 750 mg supports twice weekly subcutaneous dosing

Free C1q Levels in Serum

Dosing 750 mg on days 0, 3, 7, and 10



Annexon data on file

- Dosing completed in 4 SAD and 2 MAD cohorts
  - **Clear dose response**
  - **Well-tolerated at all dose levels;** occasional mild, transient injection site reactions
- Target engaged for 4 days following last dose
  - **Supports 750 mg twice weekly subQ dosing**

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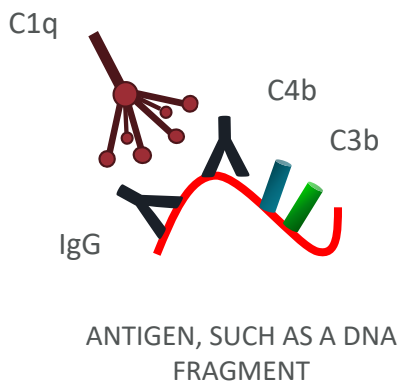
Rationale for C1q Precision Medicine Approach in Lupus Nephritis

Lupus Nephritis: Autoantibody-Mediated Disease with Unique C1q / Classical Complement Cascade Involvement

- Systemic Lupus Erythematosus (SLE) is driven by **autoantibodies against numerous self antigens** (including DNA)
- Autoantibodies activate classical complement in circulating **"immune complexes"** - become trapped in tissues, particularly kidney
- About 50% of SLE patients also develop **pathogenic anti-C1q antibodies (PACAs)**[1]
- **PACAs accumulate in the kidney and enhance C1q activation** of the classical complement cascade[2]
- **≥90% of SLE patients with active Lupus Nephritis (declining kidney function) have high PACA titers**[3]



[1]Sinico, et al., PNAS 2005; [2]Mannik, et al., Arthritis Rheum 1997; [3]Jourde-Chiche, et al., Clin Neiphrology 2012; Stojan and Petri Lupus, 2016; Trendelenburg, et al., Nehrol Dial Transplant 2006;

Annexon data on file

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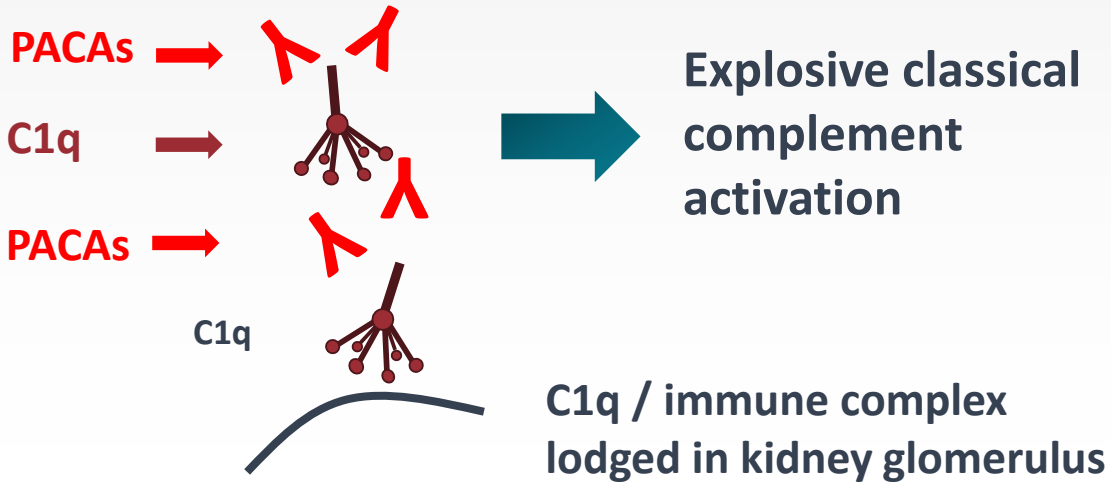
PACAs Drive Disease in Active Lupus Nephritis through Explosive Classical Complement Activation

Therapeutic anti-C1q unique among complement inhibitors for addressing this mechanism

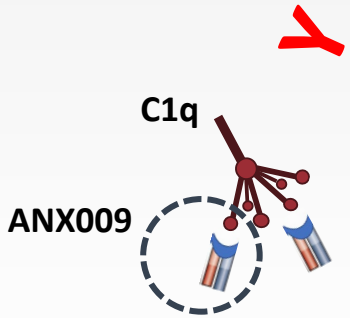
- PACAs **bind to the tail of C1q in immune complexes**
- **Recruit more C1q**, more PACAs, with more classical complement activation



Explosive classical complement activation

C1q / immune complex lodged in kidney glomerulus

- **ANX009** recognizes the head region of C1q and **blocks binding to immune complexes**
- **Prevents PACA binding and complement amplification**



ANX009 blocks C1q and prevents PACA binding

Kidney glomerulus

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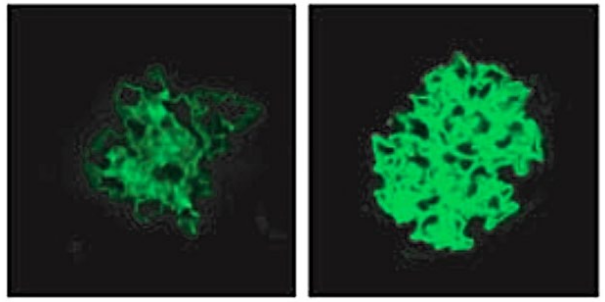
PACAs Exacerbate Disease in an Animal Model of Lupus Nephritis

- Animal model of LN with minimal baseline of disease
- **Administration of PACA greatly exacerbates disease**

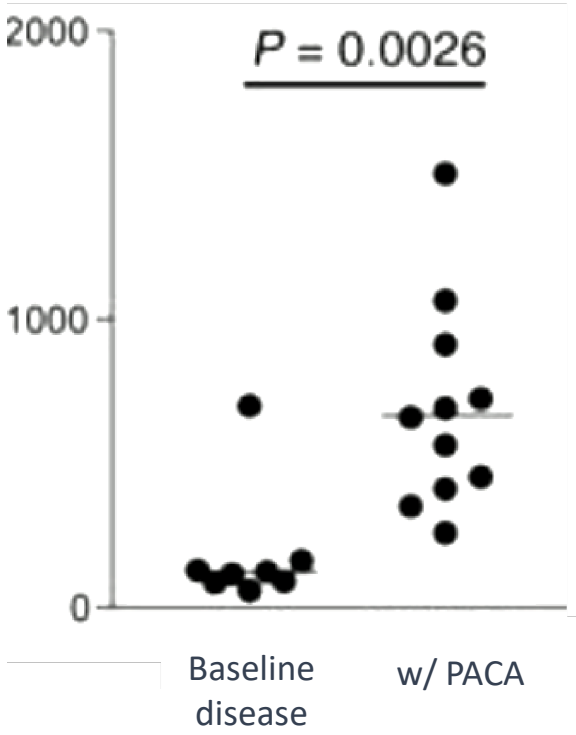
Complement deposition in the kidney
(glomerulus)

Baseline disease | Administer PACA



Large increase in complement activation/deposition

Kidney damage
(protein in the urine)



*Induced by injection of auto-reactive antibodies against kidney glomerular basement membrane antigens
Trouw et al. *J Clinical Investigation* (2004) 114:679

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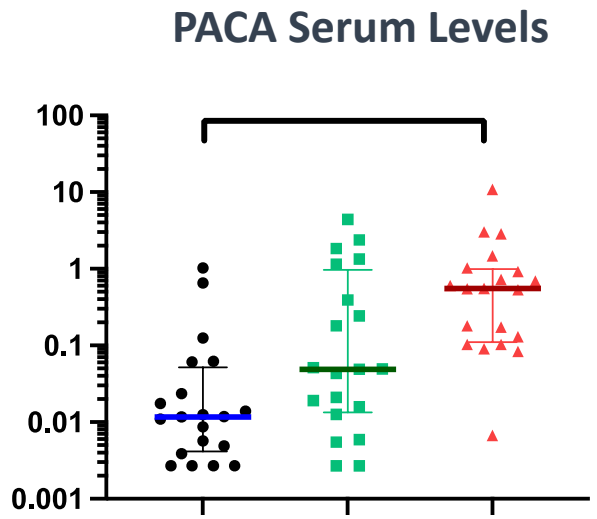
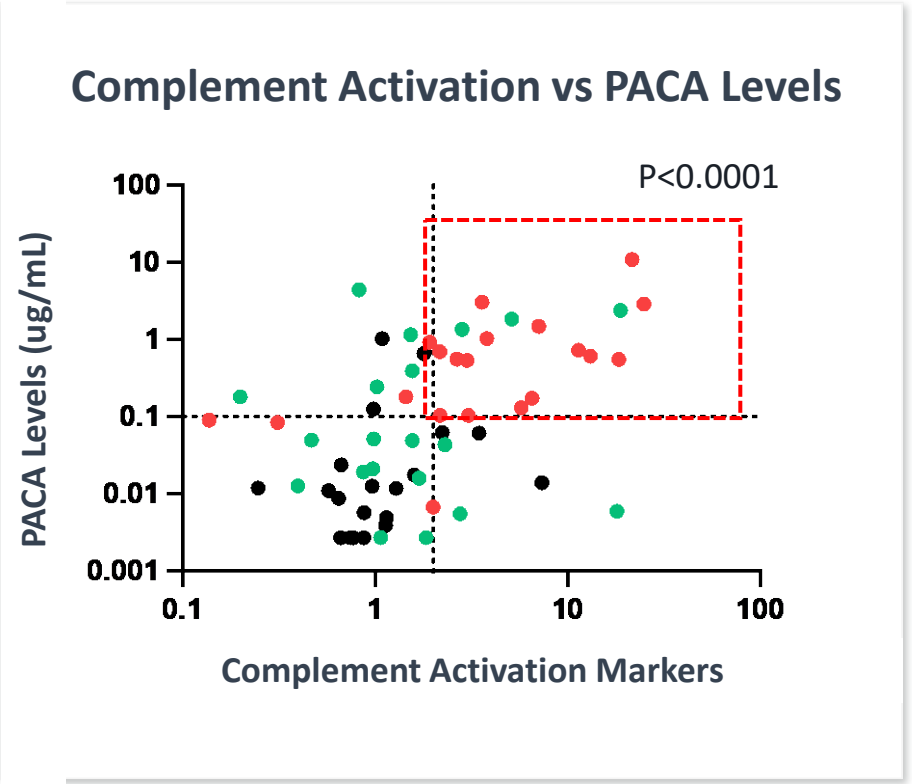
PACA Levels Correlate with Classical Complement Activation in Lupus Nephritis Patients

Consistent with Role as Key Driver of Excessive Complement Activation





PATIENTS WITH ACTIVE LN

- High PACA levels
- High Complement activation

Annexon data on file

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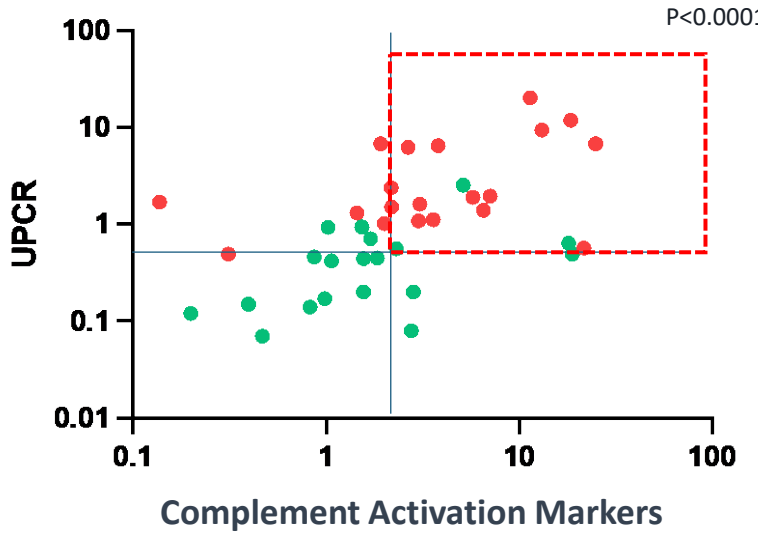
Classical Complement Activation Correlates with Disease Activity

Urinary Protein to Creatinine Ratio (UPCR)

Complement Activation vs UPCR



PATIENTS MOST LIKELY TO RESPOND TO ANX009 IN PHASE 1b STUDY

- High complement activation
- High UPCR

Annexon data on file

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ANX009, Tailor-Made for Lupus Nephritis, an Autoimmune Disease Driven by Complement Activation

- **C1q, itself, is attacked by pathogenic, activating autoantibodies in LN (PACAs)**
- PACAs are associated with **increased complement activity and disease activity**
- Strong therapeutic rationale to block C1q activity **– unique among complement inhibitors for this disease**
- **ANX009 specifically targets the vascular aspects of LN pathology** within the filtration unit of the kidney (glomerulus)
- **ANX009 well-tolerated and fully inhibited C1q**; FIH data support twice weekly subcutaneous dosing

ANX009 Clinical Program in Lupus Nephritis

Sanjay Keswani, MD, FRCP (UK)

Chief Medical Officer

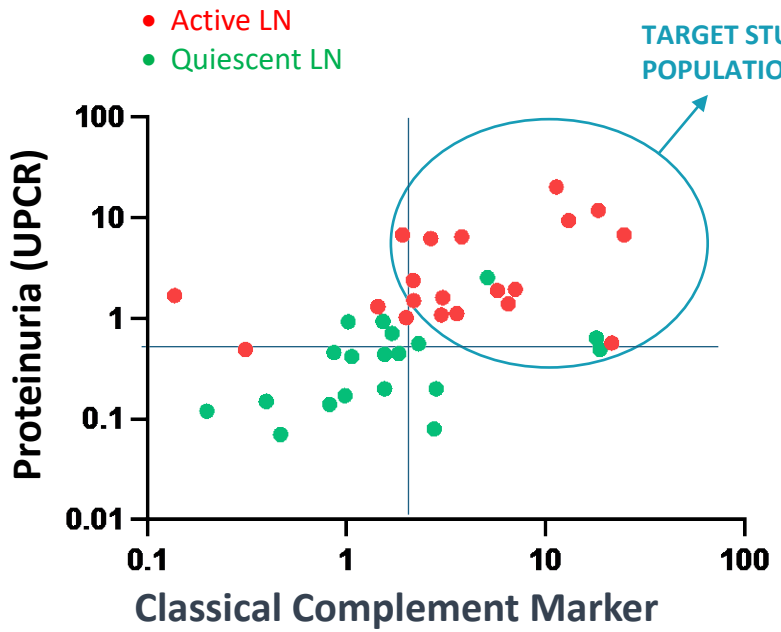
Annexon Biosciences

Annexon's Unique Precision Medicine Strategy in Lupus Nephritis

Phase 1b study provides mechanistic insight in LN population with classical complement activation

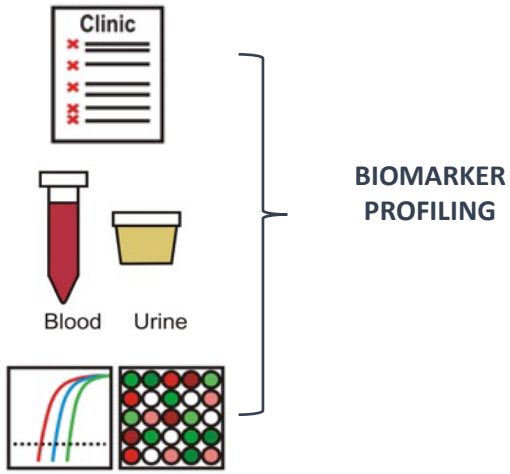
LN PATIENT BIOSAMPLE ANALYSIS:

Enables patient selection criteria



PHASE 1b STUDY:

Evaluates unique complement pathway & disease pathology markers to confirm therapeutic effect in enriched patient subset



LATE-STAGE TRIALS:

Confirms efficacy, safety and dosing paradigm in target patient subset

Samples courtesy of Dr. Maria Dall'Era, UCSF

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ANX009 Phase 1b Proof of Biology Trial in Lupus Nephritis

TRIAL DESIGN

- Open-label 1 month study with run-in and follow-up periods

TARGET PATIENT

- Smoldering disease
- Classical complement activity
- Proteinuria
- History of ISN/RPS Class III/IV (±V) proliferative LN on kidney biopsy
- Stable background therapy

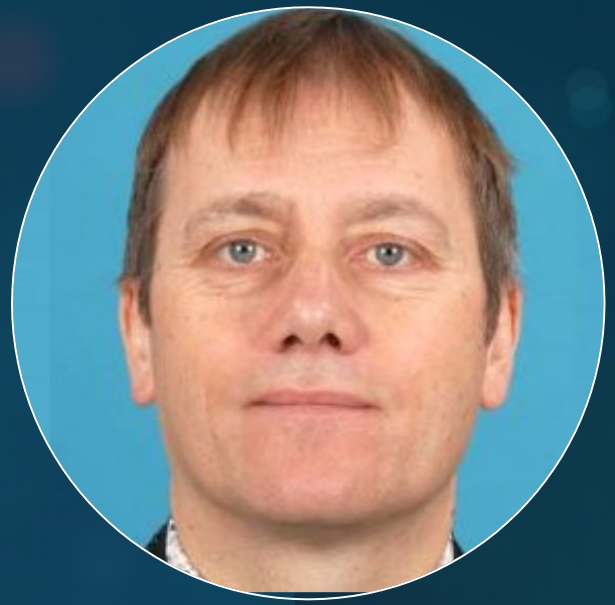
KEY OBJECTIVES

- Safety and tolerability
- Complement PD markers -> demonstrate anti-C1q blocks complement activation, amplification and downstream inflammation
- Exploratory markers of renal tissue damage and function

TIMELINE: INITIATE EARLY 2022

ANNEXON biosciences

KOL Perspective: Multifocal Motor Neuropathy & the Role of Classical Complement



Hugh Willison, MD, PhD.

Professor of Neurology, University of Glasgow

Honorary Consultant Neurologist, South Glasgow Hospitals University

NHS Trust Director, NHS Diagnostic Neuroimmunology Laboratory, Southern General Hospital

University of Glasgow

THE AWARDS 2020 | UNIVERSITY OF THE YEAR

Classical Complement in Multifocal Motor Neuropathy (MMN)

Hugh Willison, MD PhD

Professor of Neurology, University of Glasgow

Honorary Consultant Neurologist, South Glasgow Hospitals University

NHS Trust Director, NHS Diagnostic Neuroimmunology Laboratory Southern General Hospital

WORLD CHANGING GLASGOW

University of Glasgow

Strong Rationale for Anti-C1q Therapeutic in MMN

- ✓ **Pathogenic role for anti-GM1 IgM complement fixing antibodies in MMN**
- ✓ **ANX005 inhibited complement activation by anti-GM1 IgM antibodies and decreased nerve injury in patients with GBS**, a related autoimmune peripheral neuromuscular disease
- ✓ **Anti-C1q inhibited nerve injury in model of MMN by IgM autoantibodies from patient sera**
- ✓ **ANX005 stops classical pathway activation before it starts** by blocking C1q binding to tissue
- ✓ **High unmet medical need** with few available alternative treatments

MMN, a Devastating IgM Autoantibody Complement-Mediated Disease With High Unmet Need

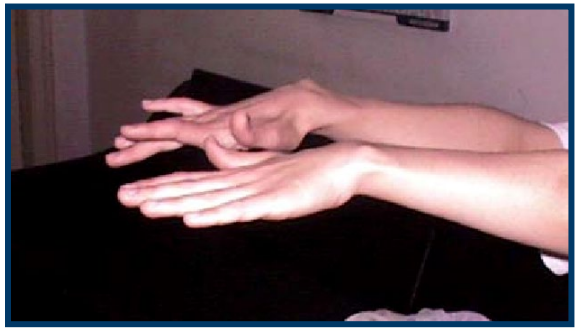
DISEASE OVERVIEW

Clinical Features:

- Slowly progressive asymmetrical distal limb weakness especially in upper limbs
- Prominent muscle wasting due to denervation atrophy over time

Pathophysiology:

- anti-GM1 IgM antibodies
- Motor conduction block
- Clear diagnostic criteria



Basta, et al., 2014

Prevalence:

- ~12K patients in US/EU
- Chronic lifelong disease, commonly affecting middle-aged men

Progressive disability despite IVIg SOC

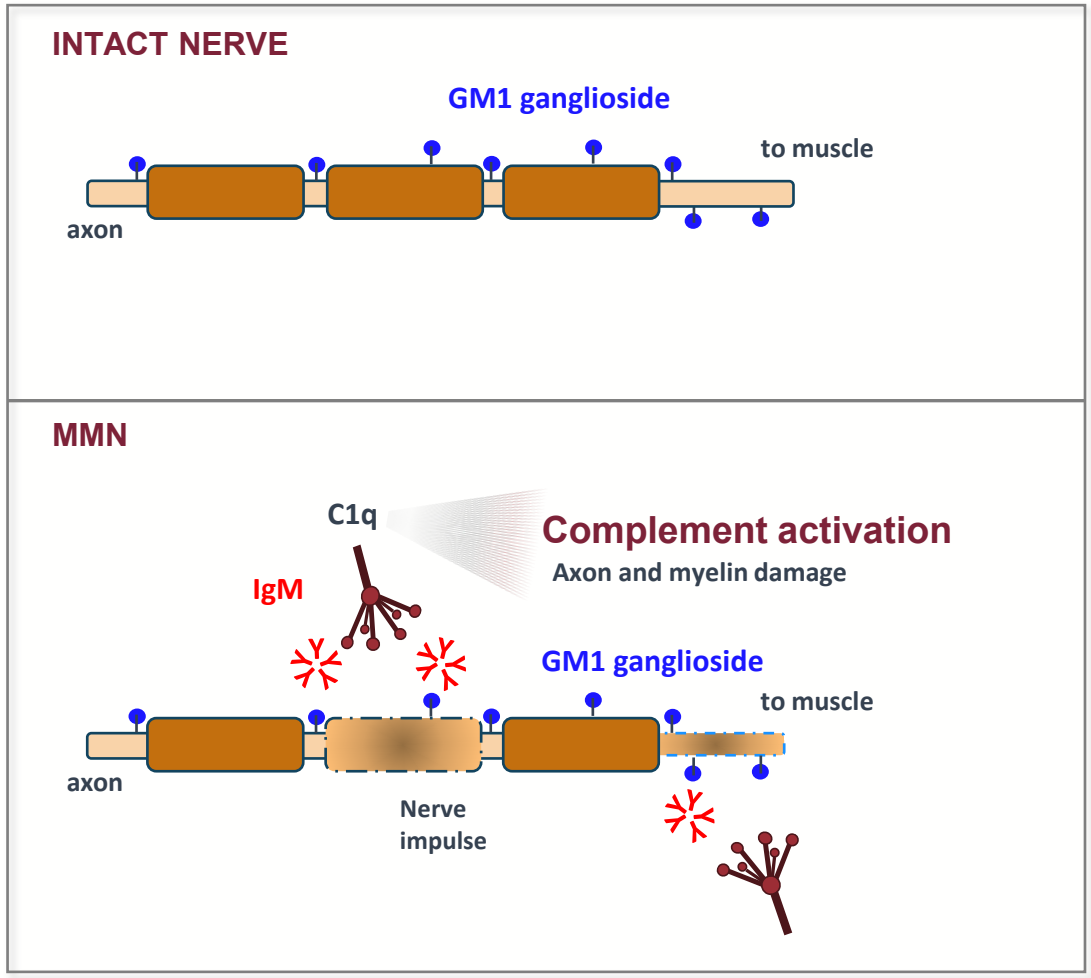
- Progressive nerve damage continues
- Life-long, time consuming treatment
- IVIg supply availability issues
- Side effects and biosafety
- Few alternative treatments

National Organization for Rare Diseases
https://rarediseases.org/rare-diseases/multifocal-motor-neuropathy/

IgM Autoantibodies Potently Drive Classical Complement Pathway Activity in MMN

IgM is a potent, proto-typical activator of C1q and the classical complement pathway

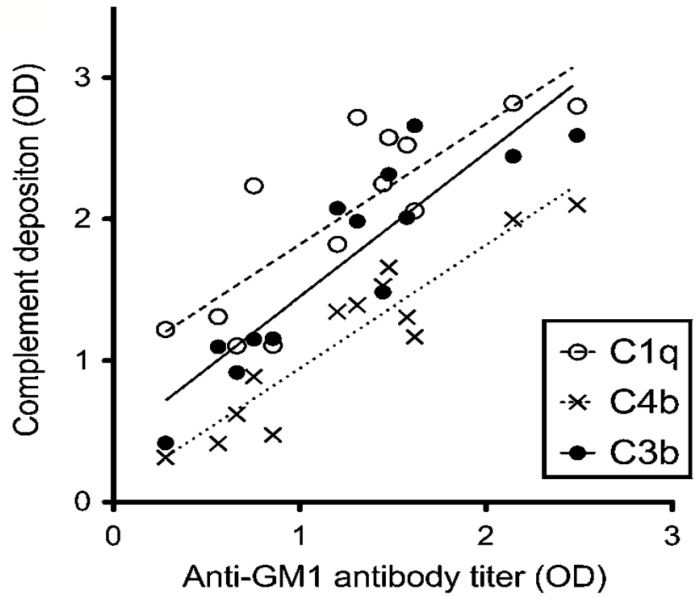
- Anti-GM1 IgM antibodies drive pathology in MMN[1]
  - Titers correspond with in-vitro complement-activating activity and disease severity
- C1q recruitment -> complement activation -> immune cell recruitment -> damage to nerve axon and myelin sheath



1. Vlam, Lotte et al., Neuroimmunology Neuroinflammation, 2015

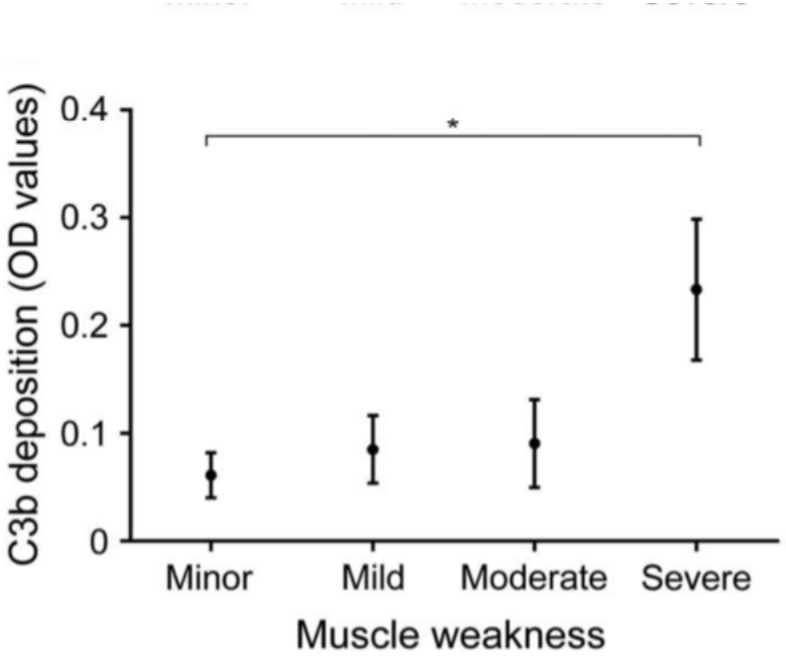
Anti-GM1 Classical Complement Activity In MMN Patient Sera Correlates with Anti-GM1 IgM Levels and Disease Severity

C1q, C4b and C3b deposition on GM1 *in vitro* correlates with anti-GM1 IgM titers



Yuki, et al., J Neurol Neurosurg Psychiatry 2011

Complement deposition on GM1 correlates with MMN disease severity

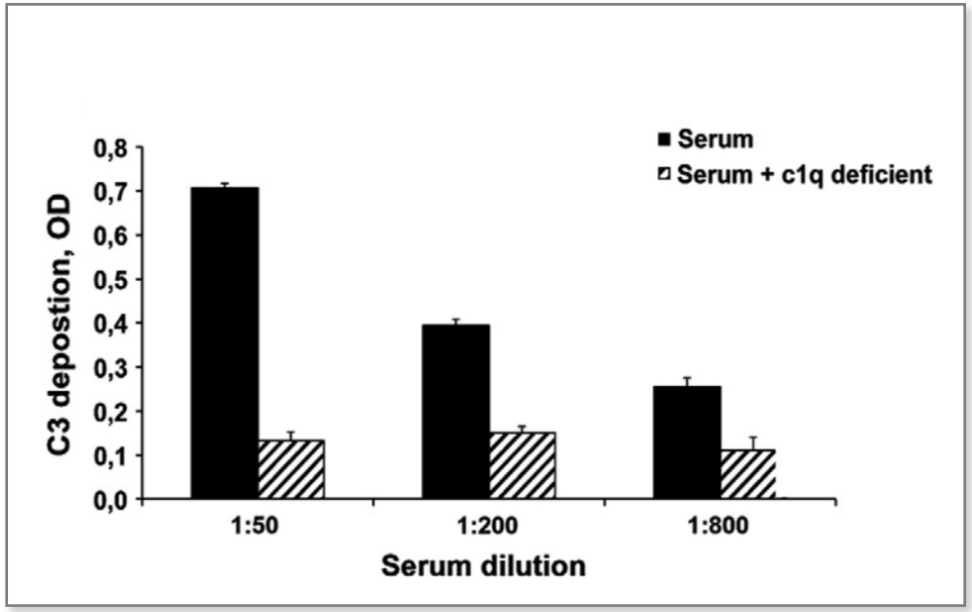


Vlam, et al., Neurology 2015

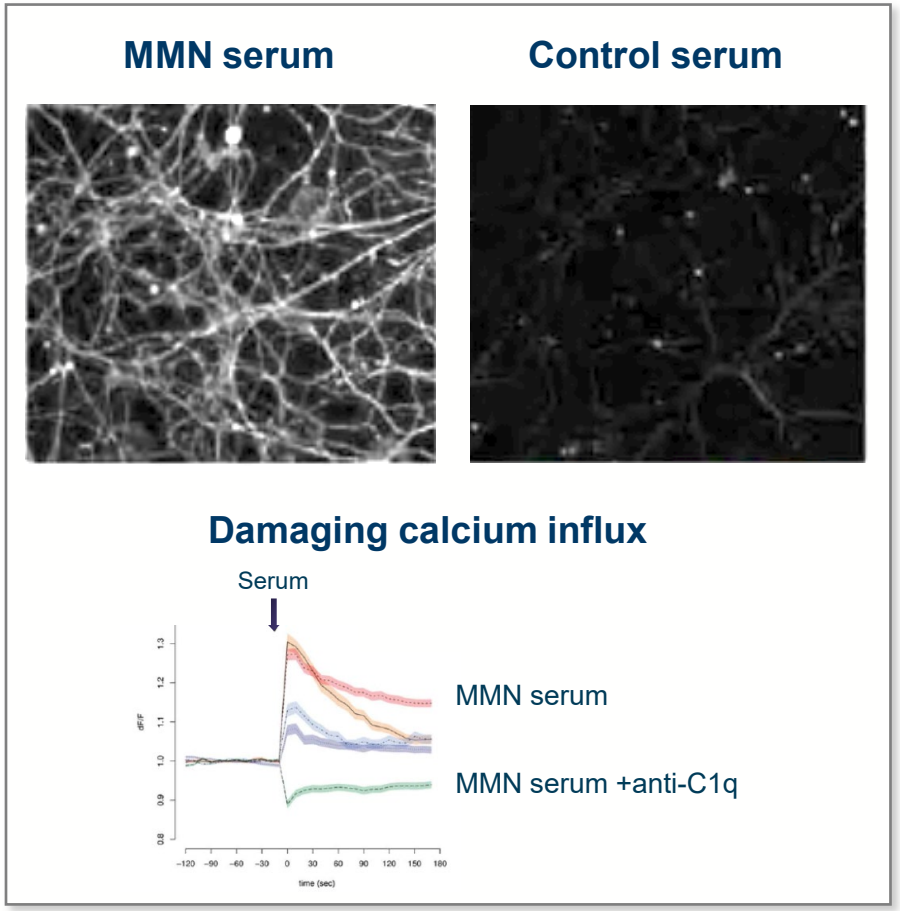
C1q Inhibition Blocks Nerve Damage in MMN Model

Blocks the effect of IgM reactive autoantibodies from MMN patient sera

Anti-GM1 IgM antibodies in a patient sera activates complement via C1q



Anti-C1q blocks neurotoxic calcium influx caused by IgM GM1antibodies



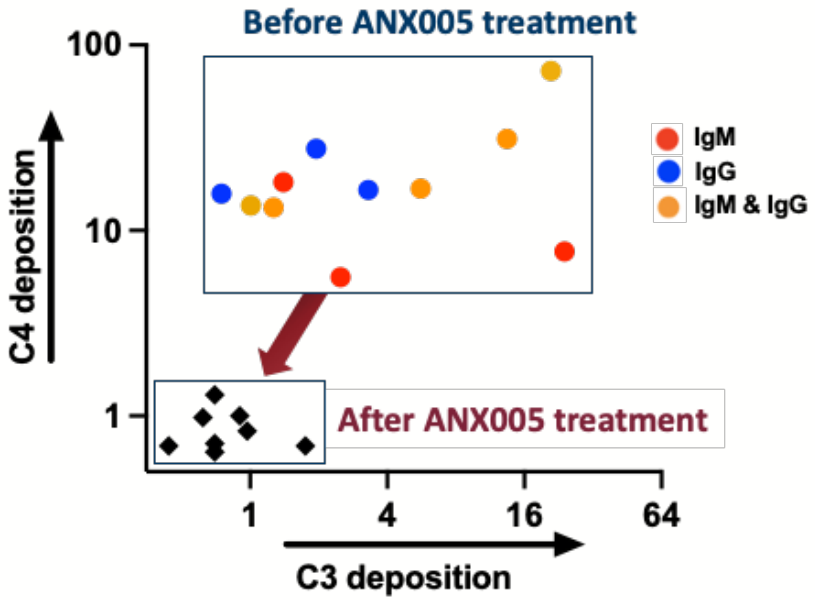
Piepers S et al., J Neuroimmunology 2010

Harschnitz, et al., Annals Neurol 2016

Treatment of GBS Patients with ANX005 Inhibits Anti-GM1 IgM and IgG Antibody-Mediated Complement Activity

ANX005 inhibits complement activation and deposition of downstream components

- With treatment in GBS patients, ANX005 inhibited complement activating activity of anti-GM1 IgM antibodies in vivo
- Titers of anti-GM1 IgM antibodies correlates with disease severity in MMN patients

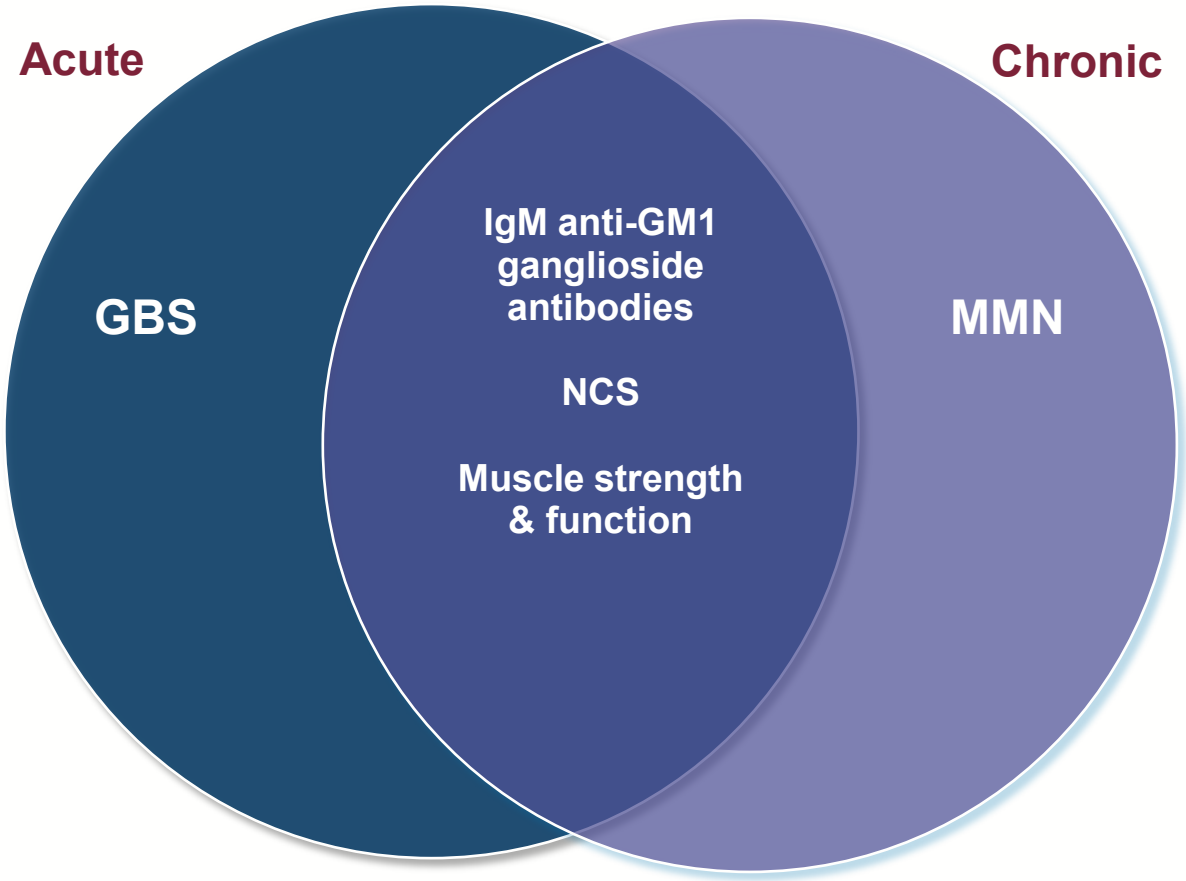


Platform presentation at 2021 PNS conference, Suri, et al., Annexon

Guillain-Barré Syndrome as Beachhead Indication for MMN

- Peripheral neuropathy with GM1-specific IgG and IgM antibodies in blood and CSF
- In GBS, nerve conduction studies (NCS) show features of demyelination and axonal damage
- Shared network of clinical experts in MMN and GBS
- Experience in measuring and analyzing neuromuscular disability by MRC & functional scores

Notable Overlap in Disease Pathology of MMN and GBS



MMN has Defined Clinical Endpoints and Regulatory Path

Clinical Endpoints:

- Muscle strength determination of pre-defined muscle groups
- Dynamometry on pre-defined / target muscle groups (e.g., grip strength, pinch grip)
- Guy's neurological disability score and MMN-Rasch built Overall Disability Scale
- 9-Hole Peg Test (hand function only)
- Reversible conduction block via serial nerve conduction studies
- IVIg retreatment

Hahn, Angelika F., et al, 2013. *Journal of the Peripheral Nervous System* 18(4):321–30.
Vanhoutte, Els K.,et al. 2013." *Neuromuscular Disorders* 23(11):924–33.

Summary of Key Takeaways

- ✓ MMN is a **devastating IgM autoantibody complement-mediated disease** with high unmet need, with **notable overlap in disease pathology to GBS**
- ✓ **C1q inhibition** was shown to **block nerve damage in MMN model**
- ✓ **ANX005 inhibited IgM and IgG** antibody-mediated complement activity **in GBS patients**
- ✓ C1q Inhibition **stops classical complement activity at the start**
- ✓ Ability to **translate operational experience** and biomarker research from GBS to MMN
- ✓ Clear **clinical and regulatory path**

ANX005 Clinical Program in Multifocal Motor Neuropathy

Sanjay Keswani, MD, FRCP (UK)

Chief Medical Officer

Annexon Biosciences

ANX005 Phase 2 Trial in Multifocal Motor Neuropathy (MMN)

TRIAL DESIGN

- Randomized, double-blind trial assessing efficacy of ANX005 vs. IVIg
- IVIg rescue provided

TARGET PATIENT

- "Early" MMN and documented response to IVIg (run-in period)

KEY OBJECTIVES

- Safety and tolerability
- MRC strength of pre-defined muscle groups
- Grip strength via hand dynamometry
- Patient function
- Need for IVIg retreatment

TIMELINE: INITIATE EARLY 2022

Q&A

ANNEXON biosciences

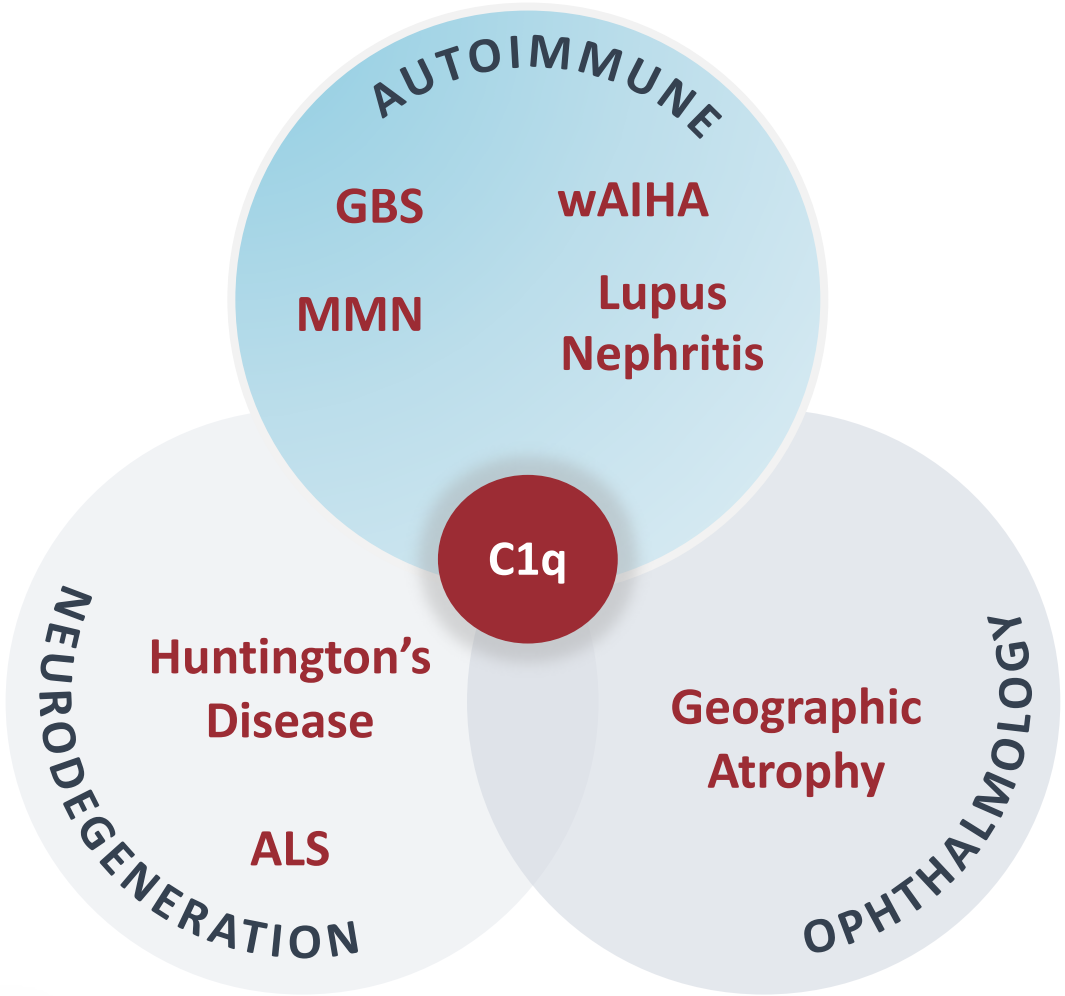
Closing Remarks

Doug Love, Esq.

Chief Executive Officer

Annexon Biosciences

Each of Annexon's Three Franchises Are Potentially Transformative, with Autoimmune Alone Significant



24 million Americans suffer from antibody-mediated autoimmune diseases, many of which are orphan or rare diseases with no or limited treatment options

NIH The Autoimmune Diseases Coordinating Committee. Progress in Autoimmune Diseases Research. Auth.experianidworks.com. Published March 2005. Accessed July 20, 2021

ANNEXON biosciences

Annexon is Well-Positioned to Drive Significant Value Over the Next 2 Years

- **Anti-C1q platform pioneering** a new class of complement medicines
- **Broad and deep applicability** across autoimmune and neurodegenerative diseases
- **Platform foundation established** with robust target engagement, POC data and 5 diverse drug candidates
- **Poised for significant value creation** with 7 mid to late-stage data sets anticipated over next 2 years
- **Winning team and well capitalized** to achieve milestones over next 2 years