2021 PNS ANNUAL MEETING

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Intravenous Administration of ANX005, an Anti-C1q Therapy, Reduced CSF Antibody-Driven Complement Activity in Early-Stage Guillain-Barré Syndrome

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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 the results and analysis of the results of our Phase 1b study conducted in GBS patients and underlying hypotheses, 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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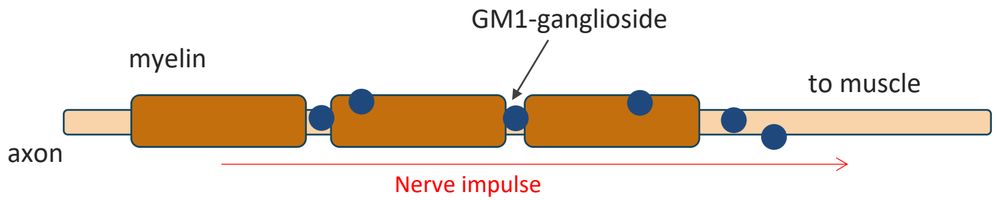
This presentation concerns drugs that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). These are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

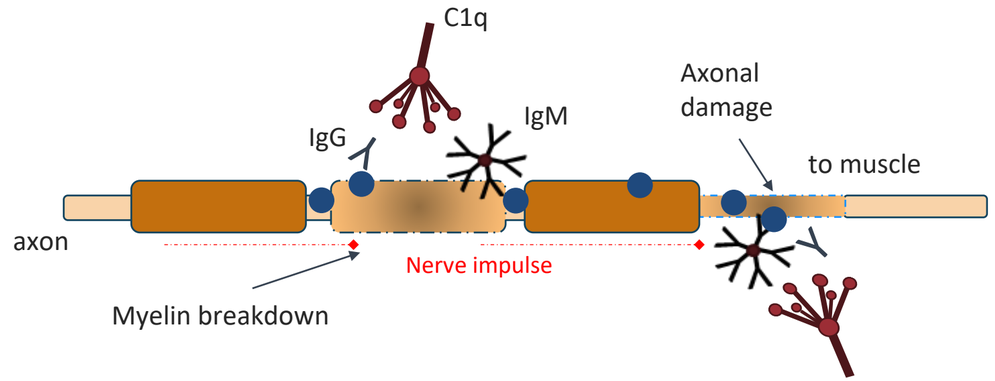
Guillain-Barré Syndrome (GBS)

- Acute antibody-mediated autoimmune disease
- Rapidly progressive muscle weakness, impaired mobility, respiratory distress
- Autoantibodies (IgM, IgG, IgA) target an array of gangliosides on peripheral nerves & nerve roots
- Hypotheses: In early stage GBS
  - Increased blood-CSF permeability allows entry of autoreactive antibodies & complement components
  - Peripheral nerve roots, being bathed in CSF, are subjected to classical complement-mediated damage

Intact nerve



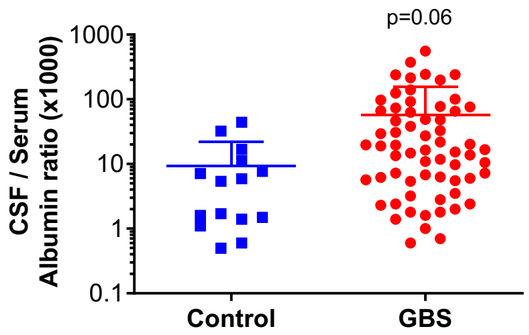
GBS



- Pathogenic antibody (IgG/IgM) binding
- C1q recruitment -> complement activation
- Damage to nerve axon (AMAN) or insulating myelin (AIDP)

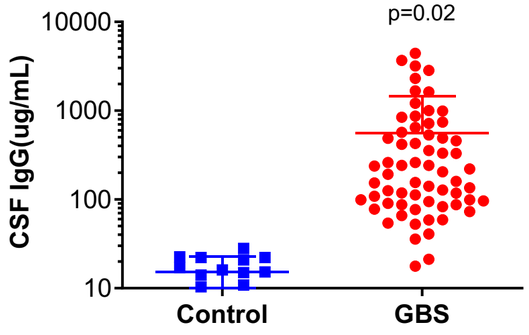
Increased Blood-CSF Permeability in GBS Associated with Increased IgG and IgM Antibody Levels in the CSF

Average Albumin Quotient = 60

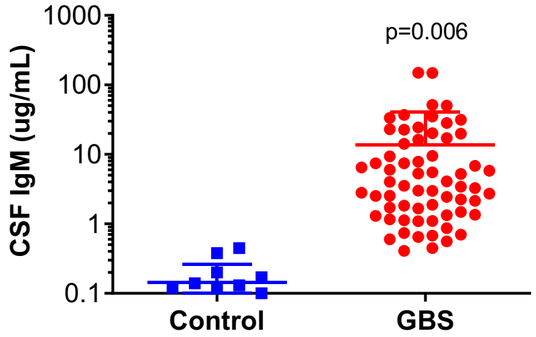


Control value < 10

36x increase in IgG



96x increase in IgM



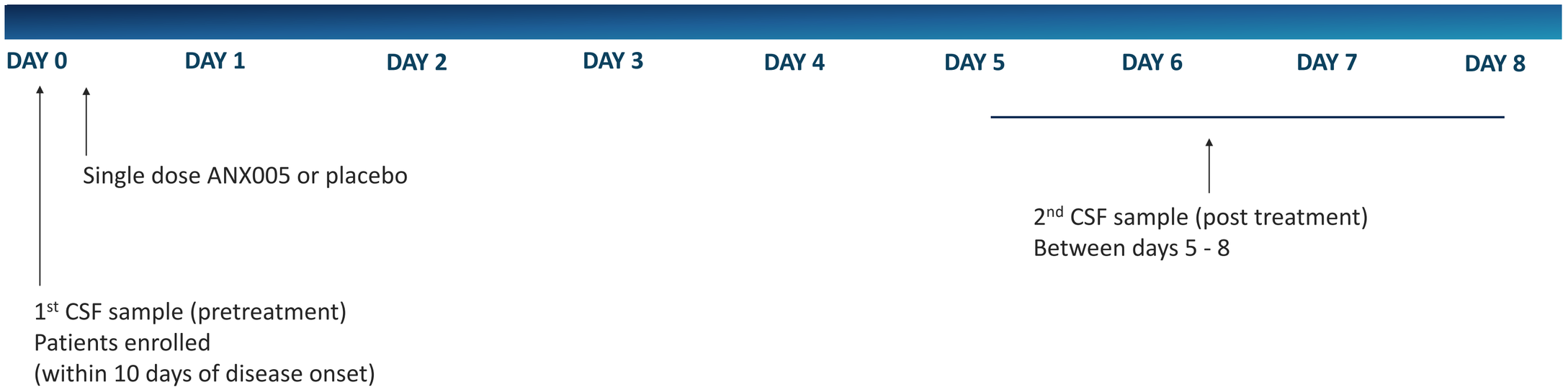
Relative to antibody levels in control CSF

Increase in CSF albumin along with IgG and IgM indicated that the blood-CSF barrier is open to proteins of a wide range of sizes in GBS

Annexon Phase 1b Study Design

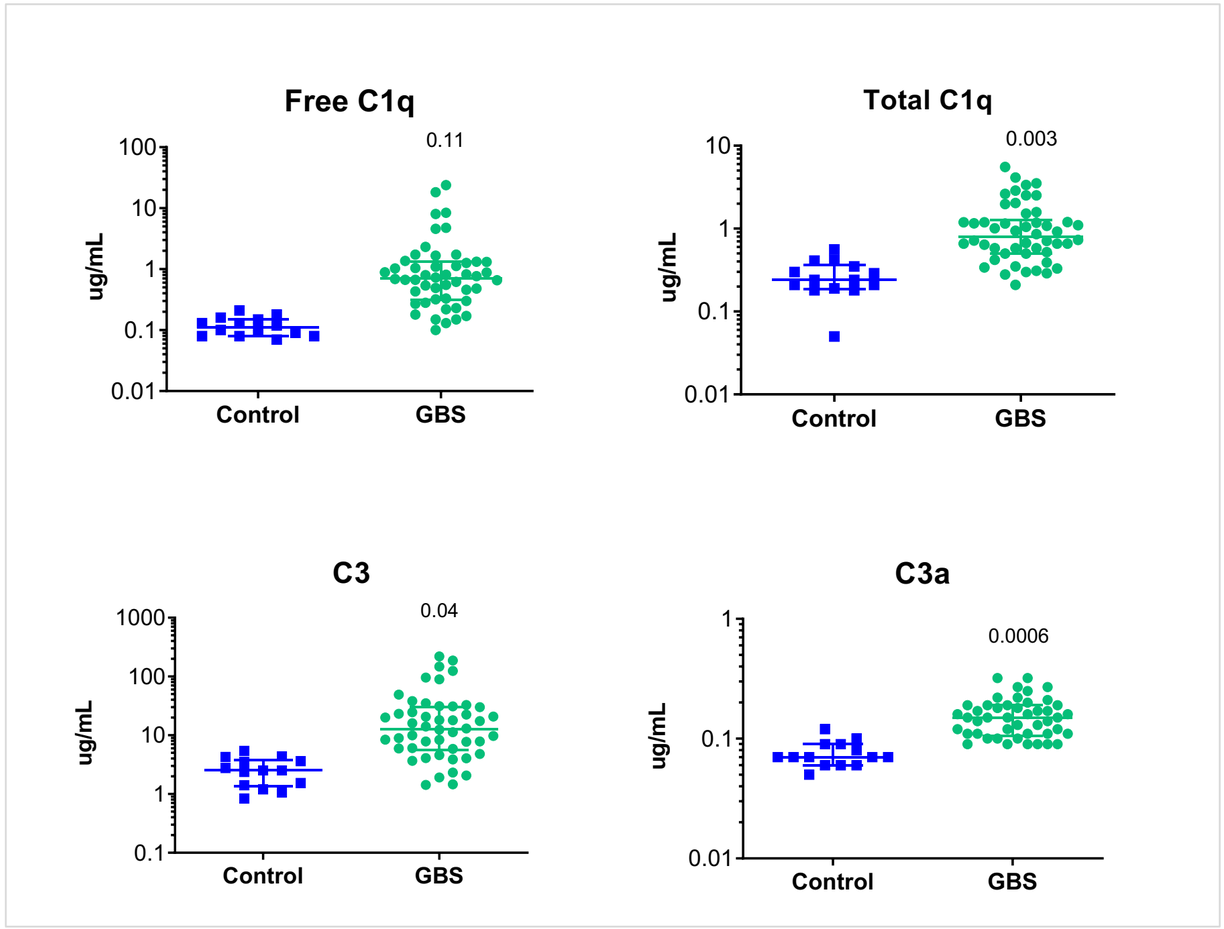
Annexon GBS Phase 1b study (top-line results presented 2020 PNS meeting)

- 38 patients treated with ANX005 (anti-C1q)
- 12 placebo patients



Significant Elevation of Complement Proteins & Activation Fragments in CSF of GBS Patients vs. Controls

Annexon Phase 1b Study

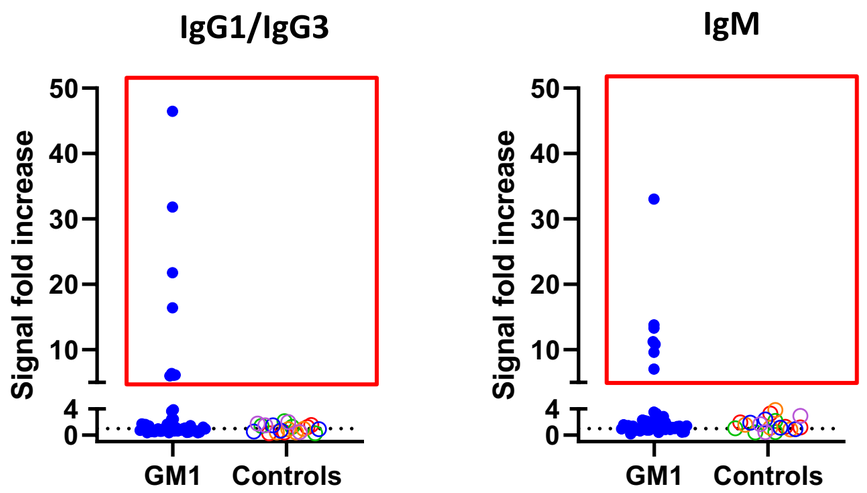


Was found to correlate with blood-CSF barrier permeability

GBS Patients Had Elevated Levels of Both IgM and IgG Anti-GM1* Antibodies in Their CSF

Results consistent with published serum results from lipid arrays

CSF Antibodies against GM1



GM1 specific antibodies

11/50 (22%) patients
(3 IgG, 4 IgM and 4 Both)

Cut point

- **>5-fold** above non-ganglioside coated well
- > control subject CSF on GM1 coated wells

Reactivity with other Gangliosides:

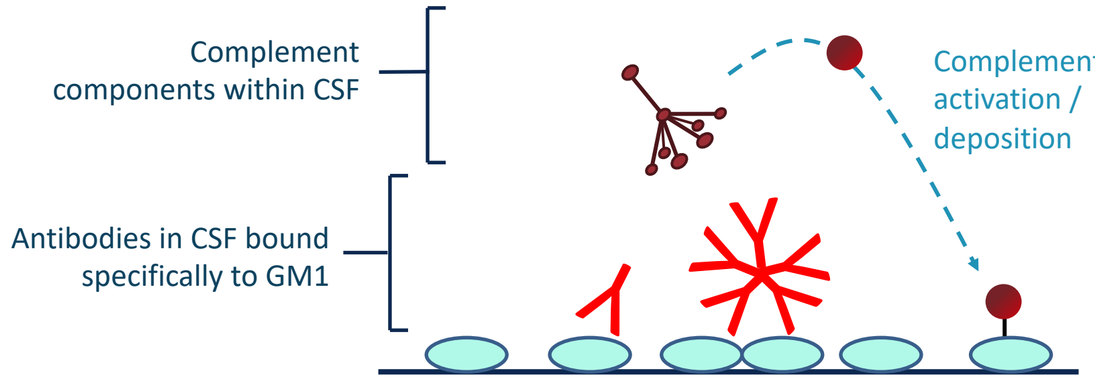
GM1 (22%) > GD1a (10%) > GD1b (10%) = Bov. G (10%) > GQ1b (2%)
Did not look at ganglioside combinations or other ganglioside / lipids

*GM1 is only one of the peripheral nerve components recognized by autoantibodies in GBS patients. We focused on antibodies against this one antigen to more generally understand complement activity.

Evaluated Ability of Anti-GM1 Antibodies within CSF to Activate Complement in an *Ex Vivo* Assay (Endogenous / No Additional Complement)

Focused on the 11 patients with GM1 reactivity

Diluted CSF sample added to GM1 coated plate

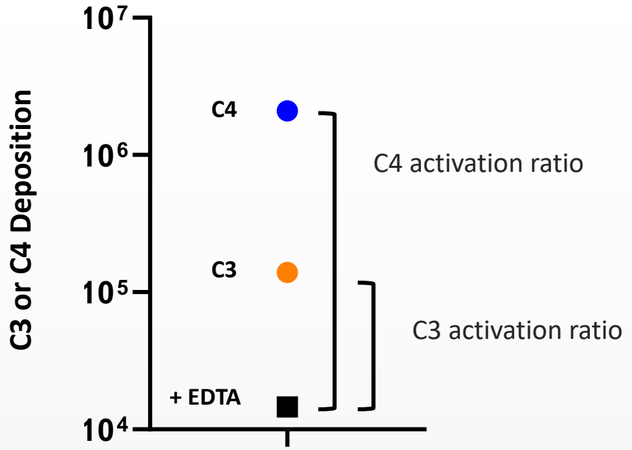


GM1 vs control ganglioside

Detect complement deposition bound C3, C4 fragments (resulting from activation)

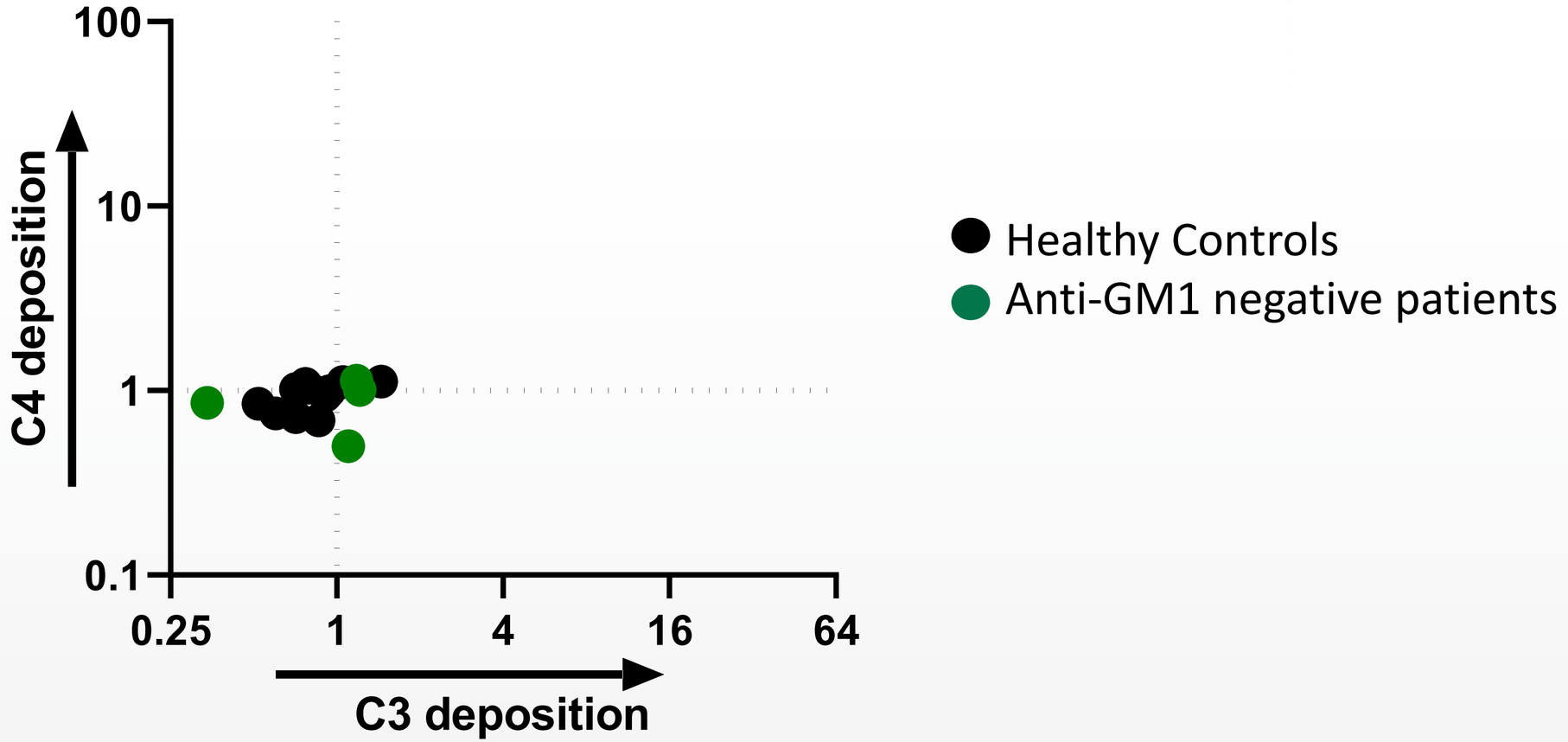
C4 and C3 specific activation ratios:

Positive signal / signal with classical complement inhibition (EDTA)

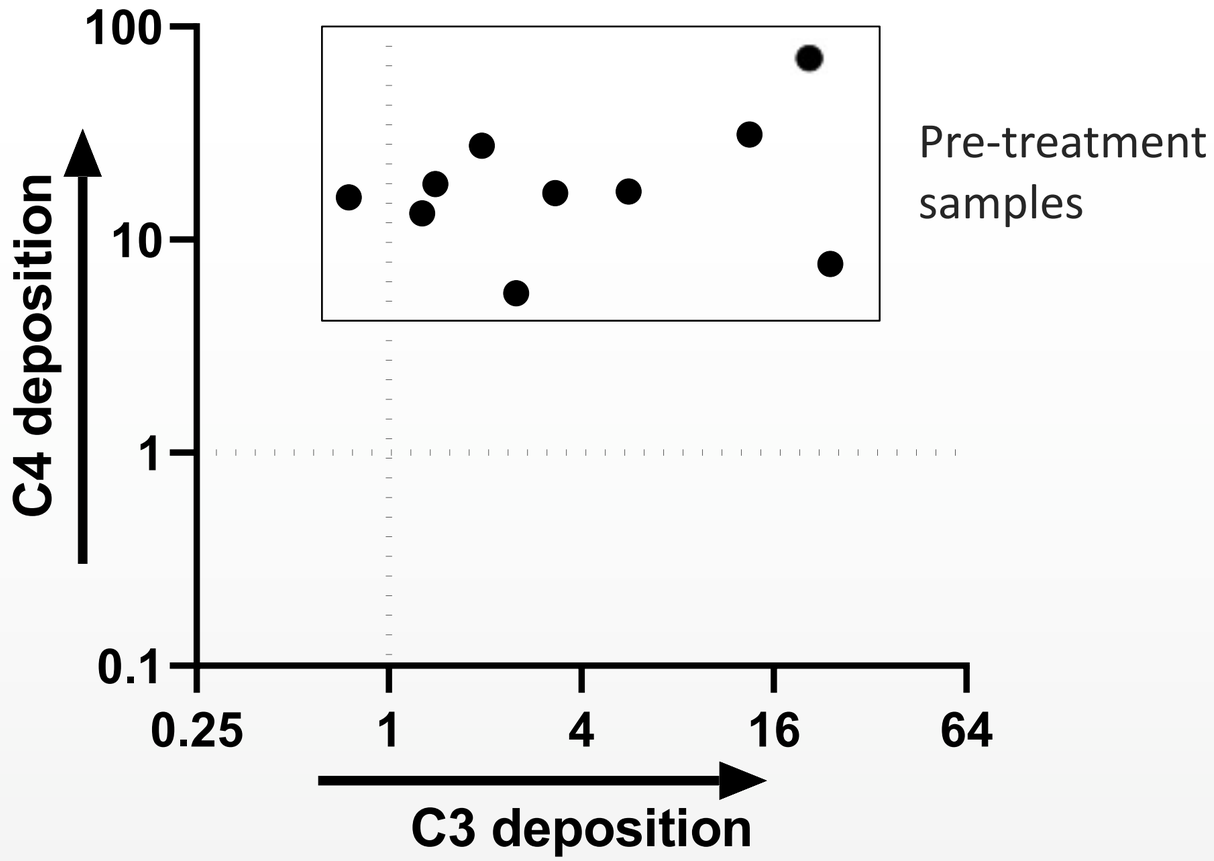


Complement deposition w/ CSF from anti-GM1+ patient

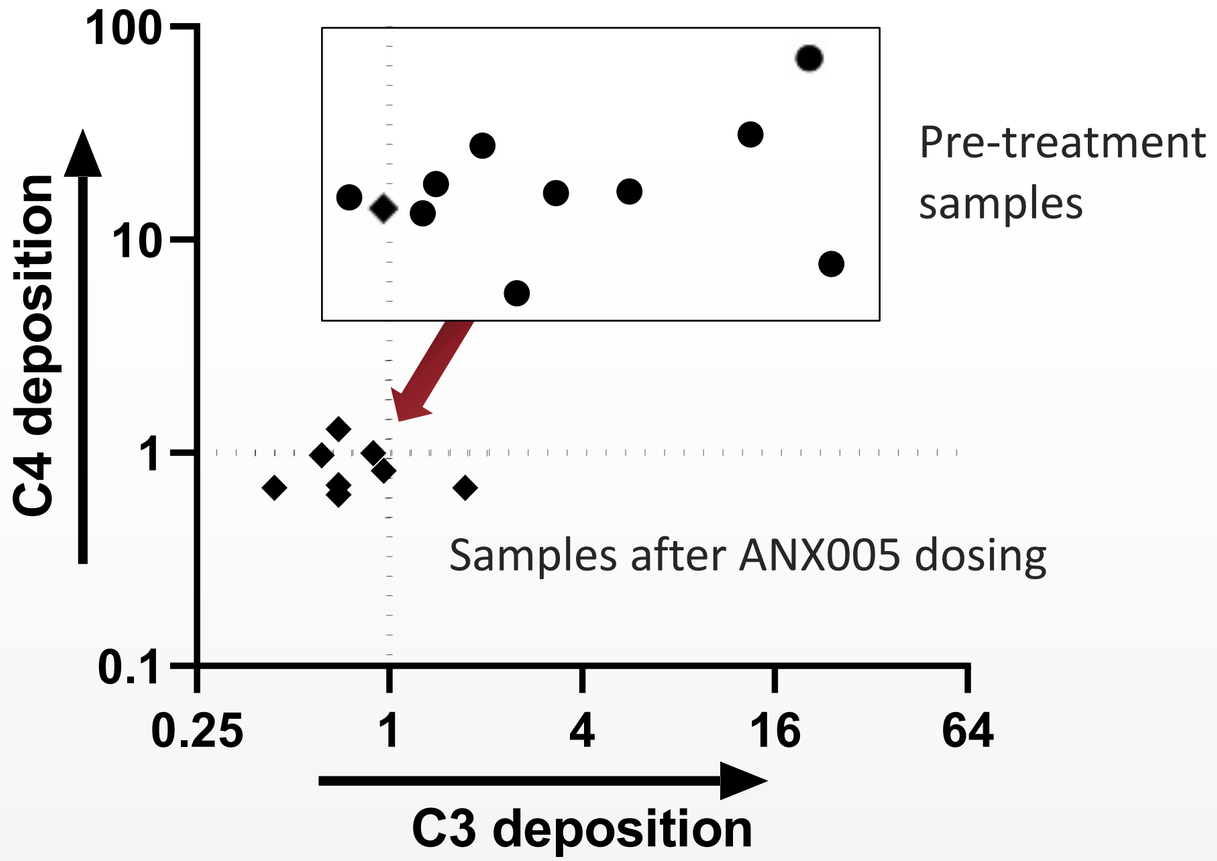
CSF Anti-GM1 Mediated Complement Activation is Not Observed in Healthy Controls or GBS Patients Lacking Autoantibodies



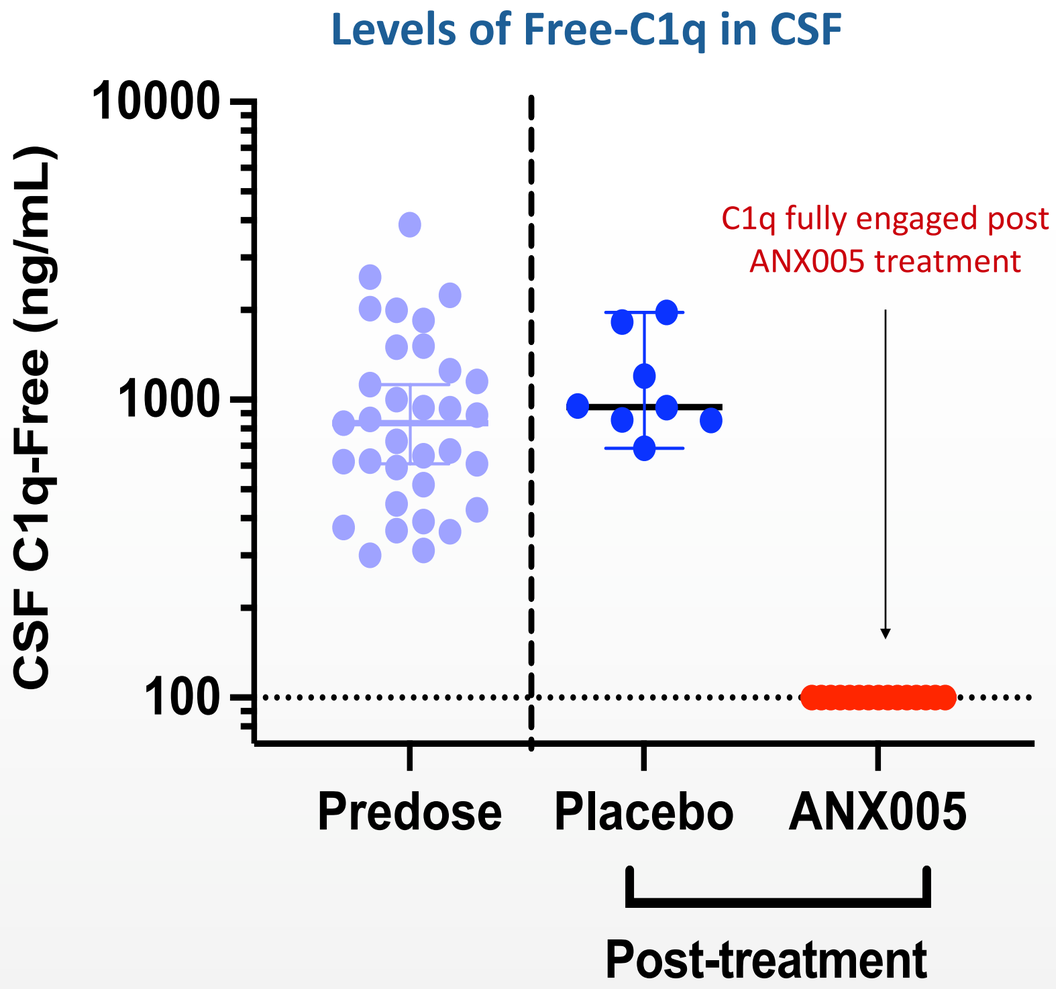
All Anti-GM1+ CSF Samples Showed Complement Deposition



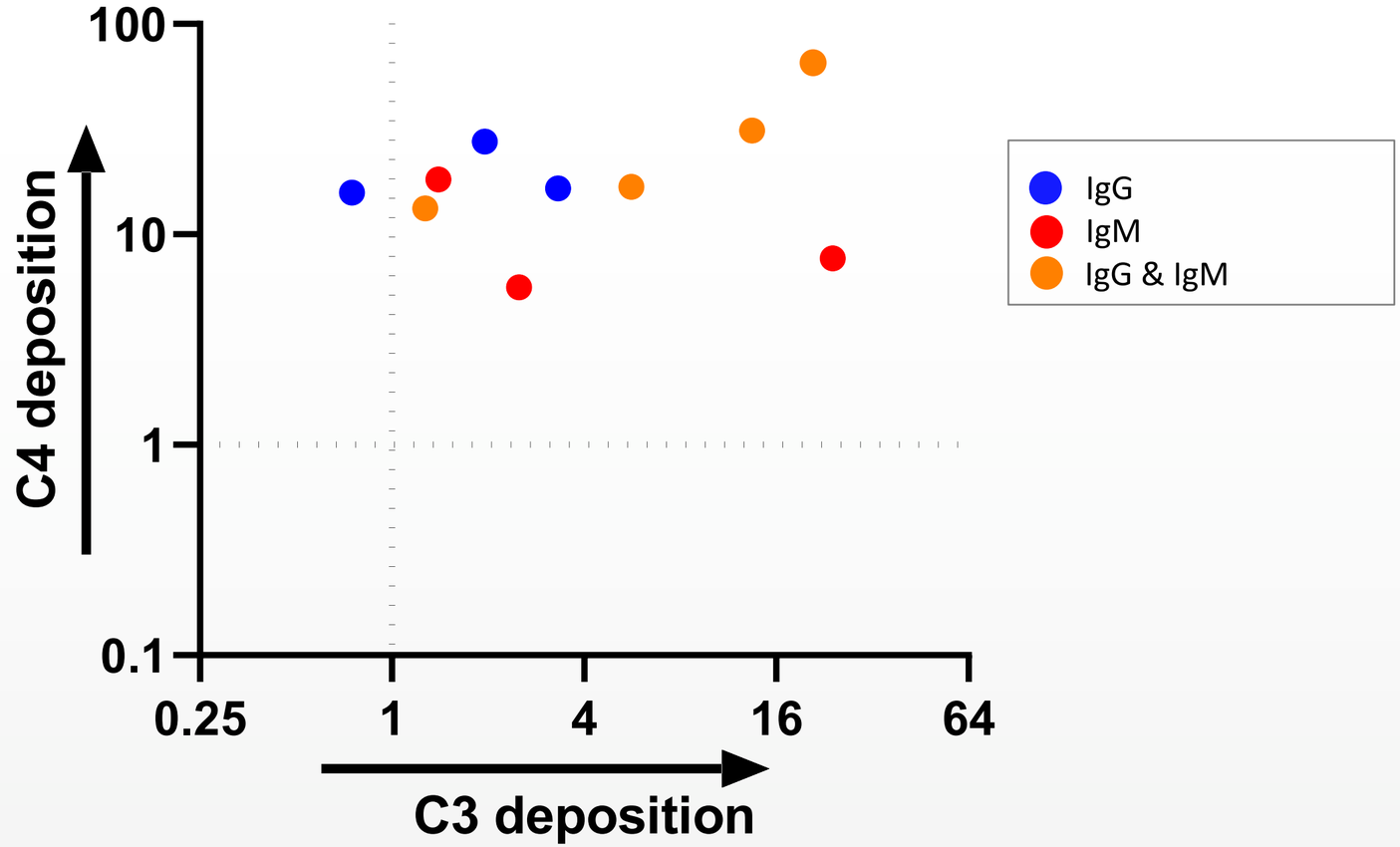
Complement Deposition was Lowered in Patients Treated with ANX005



Inhibition of Complement Activity Consistent with Full C1q Target Engagement Observed in CSF

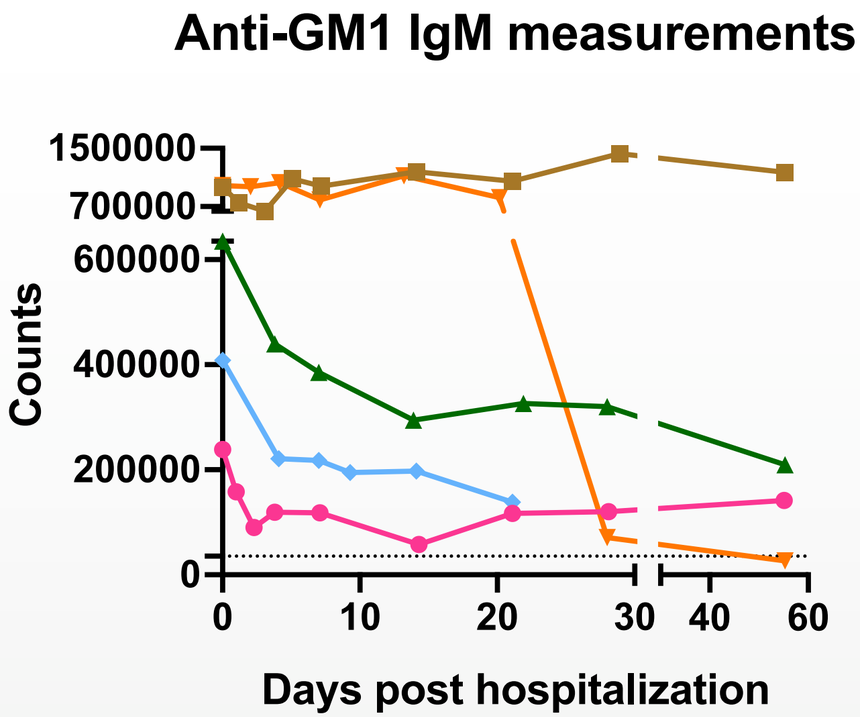


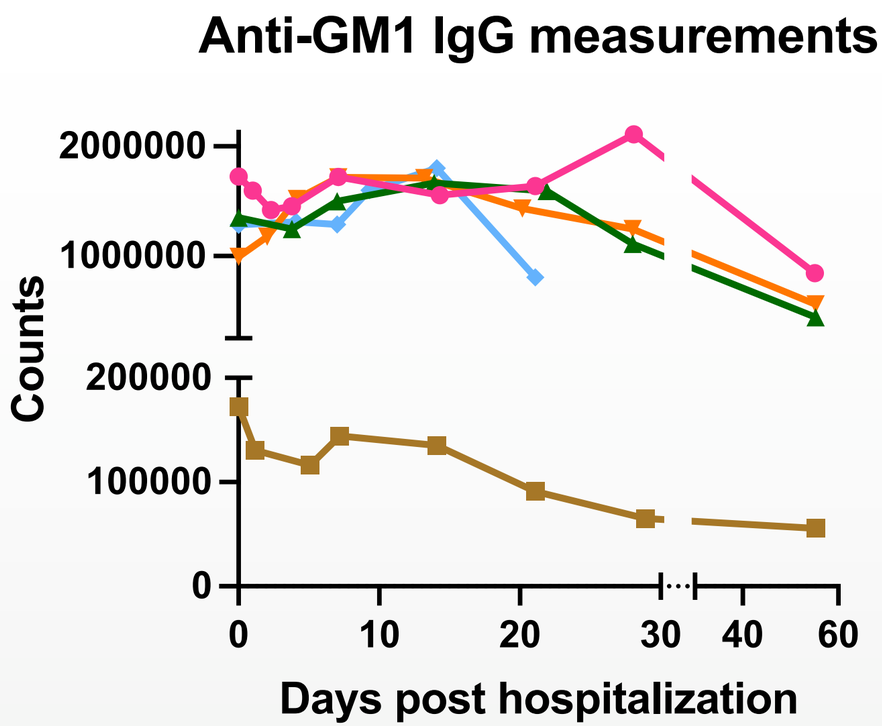
Patients with a Combination of Anti-GM1 IgG & IgM Have the Most Robust C3 and C4 Deposition



Patients with Anti-GM1 Antibodies in Their CSF also Had GM1-Specific Antibodies in Their Plasma*

Anti-GM1 IgM levels better reflect the time course of the disease, while anti-GM1 IgG levels persisted longer





*Focused on the 5 patients with highest CSF titers of anti-GM1

Dotted lines-median signal from healthy plasma controls

Conclusions

- IgM and/or IgG antibodies against GM1 were observed in the CSF of 22% of patients, but not in controls – consistent with increased blood-CSF permeability
- CSF from these patients triggered complement deposition specifically on GM1-coated plates – highest in those with both IgM and IgG anti-GM1
- Complement activation was reduced following patient treatment with ANX005 (unlike placebo), consistent with full engagement of C1q by the anti-C1q therapy
- Results support the hypothesis that IgM and IgG autoantibodies induce complement-mediated damage of peripheral nerve roots, which is amenable to classical complement inhibition

Thank You