NGM621 is a Potent Inhibitory Anti-Complement C3 Antibody in Development for Treatment of Geographic Atrophy

Alexander Loktev, Iris Ngan, Kalyani Mondal, Yan Wang, Jian Luo, Darrin Lindhout, Bin Fan, Raj Haldankar, Jie Tang, Husam Younis, David Shen, Hui Tian, and Zhonghao Liu

NGM Biopharmaceuticals, South San Francisco, CA, USA
Financial Disclosures:

All authors are employees of NGM Biopharmaceuticals, South San Francisco, CA, USA
Geographic Atrophy (GA) is an Advanced Form of AMD

• GA is characterized by progressive and irreversible loss of photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris
• GA is typically bilateral and lesion enlargement results in irreversible blindness
• GA affects ~5 million people globally and ~ 1 million people in the US
• Currently there are no effective treatments for GA
Complement Activation is Associated with Development of Advanced AMD

Variants in the complement pathway account for the majority of the known genetic risk for AMD
Pathological Dysregulation of Complement System Provides Rationale for Total Complement Inhibition for Treatment of GA

- Pathological activation of complement system is strongly implicated in development and progression of GA secondary of AMD

Unsuccessful late stage clinical trials with alternative pathway complement inhibitors in GA provide rationale for developing inhibitors of all complement activation pathways

- Preclinical retinal degeneration models show greatest benefit from inhibition of both classical and alternative complement pathways

Katschke et al. Sci. Reports 2018
NGM621 Targets Complement C3, Blocking All Three Pathways of Complement Activation

Inhibition at C3 may provide superior efficacy for treatment of GA

- Phagocytosis
- Tissue recruitment
- Ag presentation

Anti-C5 Abs do not block all activities mediated by C3b / C3a

- Inflammation
- Chemotaxis
- Vascular permeability

Membrane Attack Complex (MAC)

Cell lysis

Classical Pathway

Lectin Pathway

Alternative Pathway

Factor B

Factor D

Alternative pathway inhibitors do not block classical/lectin pathway

NGM621

C2

C4

C3b

C5

C3a

C5a

C5 convertase
Discovery and Engineering of NGM621: A Potent Anti-Complement C3 Antibody

NGM Hybridoma Antibody Discovery Platform

- NGM621 is a humanized monoclonal antibody selected for
  - High affinity binding to intact C3 determined by surface plasmon resonance (SPR)
  - Complete and potent inhibition of C3a release in biochemical assay
  - Completed and potent inhibition of complement activation via alternative and classical pathways in hemolytic assays
- Fc receptor effector function eliminated
- Inhibitory activity is identical for common C3 SNPs (A80G and P292G)
- Favorable biophysical properties
  - High solubility and low viscosity
  - Excellent long-term stability

![Binding by SPR](image)

![C3a Release Assay](image)

![Complement Hemolytic Assays](image)
NGM621 Binds to Intact Human and Cynomolgus Monkey C3 with High Affinity

Binding affinity between NGM621 and human or cynomolgus monkey C3 measured by SPR at 37°C
• During complement activation, and inactivation by host factors, C3 is sequentially proteolyzed into fragments C3a, C3b/iC3b, C3c and C3d
• C3 fragments play role physiological functions including inflammation, activation of adaptive immune system, opsonization, phagocytosis and cell lysis
• NGM621 is >100 fold selective for intact C3 over C3b and other C3 proteolytic products
NGM621 Potently Inhibits Classical and Alternative Complement Activation Pathways

- Canonical hemolytic assays allow for functional analysis of complement inhibitors
- C3 concentration in vitreous humor of GA patients was reported to be 150 nM (Loyet, K. M., et al., 2012)

**NGM621 Inhibition of Classical Pathway (CP) Hemolytic Assay**
- C3 depleted human serum supplemented with **150 nM human C3**
- Lysis of sheep erythrocytes coated with anti-sheep IgM
- Requires Mg++ and Ca++

**NGM621 CP IC₅₀ = 74.1 nM**

**NGM621 Inhibition of Alternative Pathway (AP) Hemolytic Assay**
- C3 depleted human serum supplemented with **150 nM human C3**
- Lysis of rabbit erythrocytes
- Requires Mg++ and chelation of Ca++

**NGM621 AP IC₅₀ = 37 nM**
Intravitreally Administered NGM621 Inhibits LPS-mediated Complement Activation in Cynomolgus Monkey

• Durability and in vivo efficacy of NGM621 after intravitreal injection (IVT) in Cynomolgus Monkey eye was assessed based on inhibition of C3a release, a proximal product of complement C3 proteolysis
• C3a protein concentration was measured in aqueous humor (AH) samples
• In the healthy eye baseline levels of C3 proteolysis and C3a production are low
• A carefully optimized low dose of LPS was used to transiently activate complement

Testing NGM621 in vivo Activity in the Eye of Cynomolgus Monkeys

Treatment groups (n=12 eyes per treatment group)
• Vehicle or NGM621 8 mg/eye
• AH samples collected prospectively

C3a concentration in AH samples were measured by ELISA and normalized to baseline (day -3) concentration

NGM621 Inhibits Complement Activation up to 4 Weeks in Cynomolgus Monkey Eyes

AH C3a (fold change from baseline)

<table>
<thead>
<tr>
<th></th>
<th>Day 22</th>
<th>Day 23</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>NGM621 8 mg/eye</td>
<td><strong>0.5</strong></td>
<td><em>2.0</em></td>
<td><em>4.0</em></td>
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**p<0.01, *p<0.05

LPS IVT
NGM621: A Potent Anti-Complement C3 Antibody

**NGM621 Molecule Attributes**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Value</th>
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<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Humanized IgG1 monoclonal antibody</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Binds &amp; inhibits Complement C3</td>
</tr>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>~150 kDa</td>
</tr>
<tr>
<td><strong>Affinity (Biacore binding)</strong></td>
<td>$K_D = 0.34 \text{ nM}$, &gt;100 specific to C3 over C3b</td>
</tr>
<tr>
<td><strong>Potency (hemolytic assays)</strong></td>
<td>AP $IC_{50} = 37\text{nM}$; CP $IC_{50} = 74\text{nM}$ (150 nM C3 concentration)</td>
</tr>
<tr>
<td><strong>Effector Function</strong></td>
<td>2-point mutations in the Fc region eliminate effector function</td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td>15mg, 100ul IVT dose (150 mg/mL)</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Liquid</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>IVT Injection</td>
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- Currently completing the first-in-human open-label single dose (SD) and multidose (MD) Phase 1 study of 15 GA patients (NCT04014777)
- Favorable safety and tolerability supports continued development of the maximum tolerated dose in Phase 2b study in GA
- Preclinical evidence suggest anti-angiogenic effect of C3 inhibition – see ARVO Abstract/Video Presentation # B0268
Thank you!

Contact information:
Zhonghao Liu: zlui@ngmbio.com