**C3d-Targeted Factor H Achieves Potent Tissue-Directed Complement Inhibition and Disease-Modifying Efficacy Without Affecting Systemic Complement**

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**INTRODUCTION**

While systemic complement blockade is a therapeutic strategy for complement-driven diseases, effective inhibition is challenging due to high circulating concentrations and rapid turnover of complement effector proteins. Furthermore, because of complement’s essential role in innate and adaptive immunity, systemic blockade leads to increased infection risk. Consequently, substantial unmet needs remain for more effective and safer anti-complement therapies, particularly for chronic diseases. ADX-097, a humanized anti-C3 monoclonal linked to five fucosylated consensus repeats (FXA) of the complement AP inhibitor factor H (FhH), is designed to inhibit complement in diseased tissue while minimizing systemic blockade. After evaluating in vivo ADX-097 tissue targeting in skin, liver, and kidney diseases, we extensively characterized circulating and tissue PK and PD of ADX-097. ADX-097 surrogates, ADX-118, in C3H-/- mice that exhibit robust glomerular complement activation. We then examined ADX-097 efficacy in the rat Passive Heymann Nephritis (PHN) model of membranous nephropathy. We have further characterized C3d complement activation and C3d deposition by immunostaining in patient samples of renal, liver and skin diseases.

**TISSUE-TARGETING FUSION PROTEIN DESIGN**

ADX-097 targets tissue-deposited C3d, thus delivers fusion protein to disease tissue sites and inhibits pathogenic complement activation locally at disease tissue sites.

**METHODS & RESULTS**

**PASSIVE HEYMANN NEPHRITIS (PHN) MODEL:**

- ADX-097 administered as low as 0.3 mg/kg inhibited glomerular complement activation and significantly reduced urine protein-creatinine ratios, indicating potent disease-modifying efficacy. C3d-mediated tissue targeting drives ADX-097 potency as tissue target engagement and efficacy in PHN are achieved without affecting systemic complement activity. Furthermore, equimolar doses of a non-targeted inhibitor (FhFH-15) do not similarly reduce proteinuria.

**CONCLUSIONS**

Our data demonstrate the therapeutic potential of ADX-097 and show that C3d-mediated tissue targeting of FhH, in preclinical models results in potent, durable, and efficacious local AP complement blockade at low doses that avoid systemic complement inhibition.

**REFERENCES**

1. See Poster ABS & SDO for construct design and in vitro characterizations.
2. EDA. Anti mC3d induced tissue model of epitrochleal bullous acquired.

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<tr>
<th>Complement Activity (anti-mouse C3)</th>
<th>Drug Exposure (anti-hu FH)</th>
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**METHODS & RESULTS**

- A dose-response PK/PD study in C3H-/- mice showed that a single subcutaneous (SC) dose of 1 mg/kg ADX-118 (mouse surrogate of ADX-097) achieves >75% glomerular complement inhibition for at least 7 days without systemic complement blockade, while a 0.3 mg/kg dose still achieves approximately 50% glomerular inhibition.

**Factor H Knockout (C3H-/-) mice:**

- Loss of FcαR leads to uncontrolled complement activation.

**Passive Heymann Nephritis (PHN) model:**

- ADX-097 doses as low as 0.57 mg/kg inhibited glomerular complement activation and significantly reduced urine protein-creatinine ratios, indicating potent disease-modifying efficacy.

**C3d deposition in human liver diseases**

**Immunostaining of C3 Active Fragment and/or C3d Deposition in Human Disease Tissues**

- Bullous pemphigoid skin
- Normal skin
- C3 Activity
- C3d deposition

**Mice**

- C3 Activity
- C3d deposition

**Graphs and Tables**

- Glomerular Drug Exposure (RFU)
- Plasma Exposure (ug/ml)
- Plasma PK
- Plasma C3 (PD)
- Circulating Drug Exposure

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<thead>
<tr>
<th>Drug Exposure (mg/kg)</th>
<th>Plasma Drug Conc. (ug/ml)</th>
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<tr>
<td>ADX-097</td>
<td>ADX-097 mg/kg Fc-fH 1-5 mg/kg</td>
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<tr>
<td>0.57 (s.c.)</td>
<td>1 (i.v.)</td>
</tr>
<tr>
<td>0.17 (s.c.)</td>
<td>1 (s.c.)</td>
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<tr>
<td>1.7 (s.c.)</td>
<td>3 (s.c.)</td>
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**Tables**

- Plasma Drug Concentrations (ug/ml)
- Plasma PK
- plasma C3 (PD)
- Circulating Drug Exposure

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**Graphs**

- Glomerular C3 Activity
- Circulating Glomerular C3 Deposition
- Kidney harvested at defined timepoints
- Drug targeting and complement inhibition measured by immunofluorescence

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**Diagrams**

- In vitro characterization of ADX-097
- ADX-097 Biodistribution and Complement Inhibition in Rodent Disease Tissues

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**Additional Figures**

- Glomerular C3 Activity
- Circulating Glomerular C3 Deposition
- Kidney tissue collected
- High-Dose
- Mid-Dose
- Low-Dose

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**Graphs and Tables**

- ADX-097 Efficacy in PHN Model (Proteinuria Reduction)
- Day of study
- Pro:Cre (mg/mg)
- Normal Serum
- Anti-FX1A
- ADX-097 (SC)
- Fc-fH 1-5 (SC)

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