Targeting the Neonatal Fc Receptor (FcRn) to Mediate Autoantibody Clearance in IgG-driven Autoimmune Disease

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INTRODUCTION

- Increased levels of pathogenic antibodies achieved after treatment with IVIG, plasma exchange, or rituximab, characteristic of autoimmune diseases can contribute to their therapeutic failure. A failure of such treatments can lead to a hyperthermia or purpura and other autoimmune manifestations. Surface-bound FcRn, the neonatal Fc receptor, is implicated in the pathogenesis of rheumatoid arthritis and systemic lupus erythematosus, leading to the identification of novel selective inhibitors of the FcRn system.

- A series of novel antibodies with low to moderate affinity for human FcRn were identified and affinity-matured by in vitro techniques. Antibodies were selected for further evaluation (Figure 1).

Table 1: Binding of Selected Anti-FcRn Antibodies to Human and Cynomolgus Monkey FcRn

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Human FcRn</th>
<th>Cynomolgus FcRn</th>
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<tbody>
<tr>
<td>mAb #1</td>
<td>1.1 ± 0.2</td>
<td>0.1 ± 0.01</td>
</tr>
<tr>
<td>mAb #2</td>
<td>0.9 ± 0.1</td>
<td>0.02 ± 0.005</td>
</tr>
<tr>
<td>mAb #3</td>
<td>0.7 ± 0.1</td>
<td>0.01 ± 0.005</td>
</tr>
<tr>
<td>mAb #4</td>
<td>0.5 ± 0.1</td>
<td>0.005 ± 0.001</td>
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</tbody>
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- Binding characteristics of each antibody were determined by surface plasmon resonance (ProteOn). The test antibody was incubated with human and cynomolgus monkey FcRn and the FcRn-blocking function of the test antibodies was measured at pH 6.0. Blocking of binding was assessed by subtracting the bound amount of the test antibody from the total amount of the test antibody. Blocking of binding was assessed by subtracting the bound amount of the test antibody from the total amount of the test antibody.

- These four IgG-blocking anti-FcRn antibodies significantly increased human IgG (IVIG) catabolism when administered to human transgenic FcRn mice (Figure 3). A model of FcRn (FCGRT, light and olive green; anti-FcRn, red) is shown in Figure 4.

- M281 was dosed i.v. at 5 mg/kg on days 1, 2, 3 or at 20 mg/kg on days 1, 3 (arrows) in cynomolgus monkey. Circulating endogenous IgG and albumin were detected by ECL (antibody group) or vehicle-PBS (negative control) treatment (Figure 5).

- M281 localizes in early endosomes following uptake by human endothelial cells and inhibits IgG, but not albumin, accumulation in endosomes.

- M281 potently inhibits collagen antibody-induced arthritis in human transgenic FcRn mice when dosed therapeutically.

REFERENCES


CONCLUSIONS

- M281 inhibits IgG-driven arthritis in human transgenic FcRn mice when dosed therapeutically.

- M281 may inhibit collagen antibody-induced arthritis in human transgenic FcRn mice when dosed therapeutically.

- M281 induces dose-dependent IgG clearance and target occupancy in IgG-driven autoimmune disease when dosed therapeutically.

- M281 significantly inhibits IgG-driven arthritis in human transgenic FcRn mice when dosed therapeutically.

- M281 potently inhibits IgG-driven arthritis in human transgenic FcRn mice when dosed therapeutically.