Introduction

- The inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn’s disease (CD) have a high unmet medical need with no current curative therapies; the majority of patients with both diseases require life-long treatment to prevent disease progression. UC and CD are characterized by disease-specific upregulation of matrix metalloproteinase 9 (MMP9). MMP9 can exert pathogenic effects both by degrading extracellular matrix (ECM) proteins and participating in tissue destruction and by activating or releasing growth factors and cytokines from the ECM or cell surface. Previous attempts to target MMPs with broad-spectrum or semi-selective inhibitors in oncology and inflammatory diseases have been unsuccessful, partly due to their lack of specificity.

- We developed a highly MMP9-selective inhibitory antibody and evaluated the therapeutic potential of MMP9 inhibition in a preclinical model of IBD.

Methods

- Immunohistochemistry was used to demonstrate MMP9 induction at disease focus in both human UC and CD as well as in colons of DSS-exposed mice. We evaluated the efficacy of a therapeutically-dosed MMP9-specific monoclonal antibody (AB0046) in a mouse DSS-induced colitis model of IBD (run at Biomodels, LLC). To evaluate colitis severity histologically, a board-certified veterinary pathologist, blinded with respect to study groups, evaluated 5–8 H&E-stained FFPE step sections of colon tissue from each mouse. Representative IHC images of were selected based on group average disease (body weight loss, endoscopy, histology). Serum protein analysis was by Myriad RBM (Rodent MAPv2.5). Statistical significance was assessed by a one-way ANOVA with Dunnett’s Multiple Comparison post test. P value designations are as follows: * < 0.05, ** < 0.01, *** < 0.001, **** < 0.0001.

Mouse DSS-induced colitis study design:

<table>
<thead>
<tr>
<th>Group</th>
<th>AB0046 (20 mg/kg)</th>
<th>Day 6</th>
<th>Day 9</th>
<th>Day 12</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% DSS</td>
<td></td>
<td>Day 5</td>
<td>Day 9</td>
<td>Day 12</td>
<td>Day 14</td>
</tr>
</tbody>
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Results

Figure 1. MMP9 Expression in Human UC and CD

Figure 2. MMP9 Expression in Human Ulcerative Colitis and Mouse DSS-Induced Colitis

Figure 3. Efficacy of Anti-MMP9 Antibody on In-Life Measurements

Figure 4. Efficacy of Anti-MMP9 Antibody on Histological Disease

Figure 5. Anti-MMP9 Treatment Reduces Serum Disease Markers

Conclusions

- MMP9 is highly expressed in human IBD, and in mouse DSS-exposed colons. The ability of MMP9 to degrade basement membrane and to activate or release pro-inflammatory factors from the ECM make this protein a compelling therapeutic target in IBD. Treatment of established DSS-induced colitis with an MMP9-specific monoclonal antibody resulted in improvement in clinical measures of disease, histopathology, as well as in systemic markers of inflammation. These data suggest that an MMP9 specific monoclonal antibody is a promising therapeutic strategy for treatment of IBD.

- Gilead Sciences has developed a humanized MMP9-selective monoclonal antibody that is currently in a Phase 1b clinical trial in UC.

Disclosure: All authors are employees of Gilead Sciences, Inc.