Inhibition of Chemokine Receptors CCR1 and CCR6 as Promising Therapies for Autoimmune Diseases Such as Rheumatoid Arthritis and Psoriasis


Overview of Presentation

- Why target the chemokine system?
  - Selective blockade – minimize side effects
  - Orally administered treatment

Chemokine receptor CCR1

- Selectively blocks CCR1-mediated recruitment of monocytes/macrophages and osteoclasts

Chemokine receptor CCR6

- Selectively block CCR6-mediated recruitment of Th17 cells to sites of inflammation

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CCR1 Inhibition in Rheumatoid Arthritis: Scientific Rationale

- Blocks recruitment of activated macrophages to synovium
  - CCR1 signals actively secreted by inflammatory cells and synoviocytes
  - Macrophage is major producer of TNF/Inflammatory cytokines, and proteases
- Prevent bone destruction through effect on osteoclast maturation, mobility, and activity

CCR1 Antagonist for Rheumatoid Arthritis

- ChemoCentryx developed a CCR1 antagonist (CCX354) and tested a dosing regimen with PD coverage assessment in a Phase-1 study
- ChemoCentryx conducted a Phase-2 Proof of Principle (CARAT-2) study in subjects with rheumatoid arthritis that showed significant reductions in clinical endpoints, including ACR20 and bone resorption markers
- GSK in-licensed CCX354 and two “back up” compounds
- ChemoCentryx has developed a superior, novel CCR1 antagonist: CCX9588

Disclosures

- All authors are employees of ChemoCentryx Inc.
Inflammatory Bowel Disease

Excellent pharmacokinetic and safety profile

Why target the chemokine system?

Humanized CCX9588 is Phase 1

Psoriasis

Orally administered treatment

Selectively blocks CCR6

Selectively blocks CCR1

Th17 cells are prominent

We have developed the "next generation" CCR1 antagonist

Rheumatoid Arthritis

Chemokine receptor CCR1

Multiple Sclerosis

Migration Signal (Fluorescence)

Different chemical scaffold

1000

2000

3000

4000

Control

CCX9588 (5 nM)

CCX9588 (10 nM)

CCCL15/Lipotrexin (M)

Migration Signal

(0.2 µM; CCR6+ to Affected Tissue

Potency against human CCR1

| Cells       | Chemokine Ligand | Binding IC50 Buffer | Calcium Flux IC50 Buffer | Chemotaxis A2
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Monocytes</td>
<td>CCL15/MCP-1</td>
<td>2 nM</td>
<td>1 nM</td>
<td>0.2 µM</td>
</tr>
<tr>
<td></td>
<td>CCL4/MIP-1</td>
<td>-</td>
<td>10 nM</td>
<td>0.4 µM</td>
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<tr>
<td></td>
<td>CCL20/MIP-2</td>
<td>2 nM</td>
<td>1 nM</td>
<td>0.2 µM</td>
</tr>
<tr>
<td></td>
<td>CCL22/MIP-3</td>
<td>-</td>
<td>10 nM</td>
<td>0.2 µM</td>
</tr>
</tbody>
</table>

CCX9588 is highly selective for CCR1

Little-to-no activity (IC50 > 10,000 nM) for following chemotactic receptors: CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, C3aR, C5aR, Duffy, and CXC/CRK

Summary of Next Generation CCR1 Antagonist CCX9588

- We have developed the "next generation" CCR1 antagonist
  - 100-times more potent than clinical compound CCX354
  - Excellent pharmacokinetic and safety profile
  - Different chemical scaffold

- CCX9588 is Phase-1 ready

CCR6 as a Key Regulator of Th17 Biology

- All Th17 cells express CCR6
- Th17 cells are prominent in human autoimmune diseases
  - Psoriasis
  - Rheumatoid Arthritis
  - Multiple Sclerosis
  - Inflammatory Bowel Disease
- Human genetic studies and the clinical success of anti-IL-17 and anti-IL-12/IL-23 biologicals (e.g., brodalumab and ustekinumab) have confirmed the importance of this pathway in human disease

CCX9588: In Vitro Safety and Pharmacokinetic Properties Suitable for Human Studies

<table>
<thead>
<tr>
<th>In vitro Safety</th>
<th>PK</th>
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</thead>
<tbody>
<tr>
<td>P450 (IC50)</td>
<td>Species</td>
</tr>
<tr>
<td>3A4</td>
<td>Mouse</td>
</tr>
<tr>
<td>2D6</td>
<td>Rat</td>
</tr>
<tr>
<td>2C19</td>
<td>Dog</td>
</tr>
<tr>
<td>2C9</td>
<td>F (%)</td>
</tr>
<tr>
<td>1A2 induction</td>
<td>not done</td>
</tr>
<tr>
<td>2B6</td>
<td>No</td>
</tr>
<tr>
<td>3A4 induction</td>
<td>No</td>
</tr>
<tr>
<td>1A2</td>
<td>No</td>
</tr>
<tr>
<td>2B6</td>
<td>No</td>
</tr>
<tr>
<td>CCR6 (patch clamp IC50)</td>
<td>40 µM</td>
</tr>
</tbody>
</table>

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- Why target the chemokine system?
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CCR6-Mediated Recruitment of Th17 Cells to Affected Tissue

Recruitment of CCR6-positive, IL-17-producing cells to site of injury/infection

Therapeutic Premise: CCR6 inhibition will prevent recruitment of CCR6-positive, IL-17-producing cells to the affected sites and will break the vicious cycle of inflammation
CCR6 – Competitive Landscape

- CCR6 has been a highly desirable and impossible target to crack
  - Numerous companies have tried unsuccessfully to find small molecule leads
- ChemoCentryx is the first company to identify bona fide small molecule CCR6 antagonists
  - Potencies currently in the ~20 nM range (chemotaxis)
  - Good selectivity and DMPK profiles
- ChemoCentryx success in finding chemical leads resulted from two unique factors:
  - Unique screening methodology (RAM™ screening)
  - Unique compound collection
- We are currently validating the target with animal models and the research tool compound CCX9664
  - Animal models of psoriasis and arthritis

Evaluation of CCR6 Coverage Requirements

As a rule, goal is to maintain >90% receptor coverage at all times

CCX9664 is a potent CCR6 antagonist suitable for rodent studies

Animal Models Used With CCX9664

- Mouse models of disease
  - Psoriasis-like models
    - IL-23 induced dermal inflammation
  - Imiquimod-induced psoriasis-like skin inflammation
  - Arthritis
    - Collagen-induced arthritis
- In these models, CCX9664 was dosed orally to maintain >90% receptor coverage at trough

CCX9664 is Protective in an Imiquimod-induced Model of Psoriasis-like Skin Inflammation

CCX664 is Protective in an Imiquimod-induced Model of Psoriasis-like Skin Inflammation

- Imiquimod: CCX9664

Vehicle

Imiquimod: CCX9664

Day

Imiquimod: Vehicle

Imiquimod: CCX9664

Skin Thickness

CCL20 mRNA in skin

Imiquimod: CCX9664

Skin Thickness

CCX9664: A Research Tool Compound for In Vivo Studies

<table>
<thead>
<tr>
<th>Assay</th>
<th>Media</th>
<th>Cell</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotaxis CCL20/MIP-βa</td>
<td>Baf3 A/2</td>
<td>L1.2A/2</td>
<td>880 nM</td>
</tr>
<tr>
<td>Chemotaxis CCL20/MIP-βa</td>
<td>Baf3 A/2</td>
<td>L1.2A/2</td>
<td>30 nM</td>
</tr>
<tr>
<td>Chemotaxis CCL20/MIP-βa</td>
<td>Baf3 A/2</td>
<td>L1.2A/2</td>
<td>24 nM</td>
</tr>
<tr>
<td>Mouse CTX CCL20/MIP-βa</td>
<td>Baf3 A/2</td>
<td>L1.2A/2</td>
<td>127 nM</td>
</tr>
</tbody>
</table>
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