Cathepsin S Inhibitors for the Treatment of Inflammatory Bowel Disease

Therapeutic Area Partnerships Presentation

November 29, 2012
Cathepsin Cysteine Proteinases

Virobay possesses highly selective & potent (pM) lead molecules for these indications
Virobay Company Profile

- Virobay is a private drug discovery and development company in Menlo Park, California
- Celera spinout, founded in 2006; 20 year heritage
- Investors include: Alta Partners, Sutter Hill and TPG
- $30 million Series A, May 2006
  $16 million Series B, May 2010

1st generation cathepsin S inhibitor in clinic
Cathepsin K collaboration (odanacatib: NDA 2013)
2nd generation cathepsin S inhibitors; 2 Pre-IND
Vinyl sulfone inhibitors
Virobay Pipeline

- Liver Fibrosis VBY-376
- Pain VBY-036
- Autoimmunity VBY-285
- Dermatology VBY-891
- Renal Disease VBY-X
- Alzheimer’s Disease
- Oncology VBY-SSCI

Phase 0

Phase 1

Phase 2

Target

- Cathepsin B
- Cathepsin S
- CNS Penetrant

- Cathepsin S

- Cathepsin L
- CNS Penetrant
- Spectrum Selective
Cathepsin S Program

• Cathepsin S inhibitors are promising therapies for autoimmune diseases

• Virobay’s cathepsin S inhibitor program is at an advanced stage
  – Potent efficacy observed for the Virobay inhibitors
    • Autoimmune models (e.g. inflammatory bowel, psoriasis, atopic dermatitis)
    • Pain models
  – VBY-891 and VBY-036: Entry Into Human in Q1 2013
  – VBY-285: highly potent, highly selective inhibitor
    • Being developed for the treatment of autoimmunity
    • Non-CNS penetrant
    • PK characteristics suggest once daily oral dosing in humans

• Strong IP position
  – Issued patents covering broad chemical space
  – Established freedom to operate
# Inflammatory Bowel Disease

## Current Oral Therapies

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Efficacy in Crohn’s Disease</th>
<th>Efficacy in UC</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Yes</td>
<td>No</td>
<td>Not recommended for long term use</td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>Used in Mild – Moderate disease; Moderate efficacy</td>
<td>Used in Mild – Moderate disease; Moderate efficacy</td>
<td>Manageable</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Used in Moderate – Severe disease</td>
<td>Used in Moderate – Severe disease</td>
<td>Immunosuppression and Infections</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>Used in Moderate – Severe disease</td>
<td>Used in Moderate – Severe disease</td>
<td>Immunosuppression and Infections</td>
</tr>
</tbody>
</table>
VBY-285
An Attractive Compound Profile

• Extremely potent and highly selective covalent, reversible inhibitor
  – Cathepsin S $K_i = 10 \text{ pM}$ and cellular lip10 $IC_{50} = 22 \text{ nM}$
  – $\geq 200$ fold selective vs. cathepsins K, L, B, F

• Drug-like physicochemical, biochemical and $in\ vivo$ characteristics

• Clean 4-week GLP toxicology for molecules with similar templates

• Pharmacokinetic properties predict human once daily oral dosing

<table>
<thead>
<tr>
<th>Species</th>
<th>Terminal IV $T_{1/2}$ (hrs)</th>
<th>CL (mL/min/kg)</th>
<th>%F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>8.6</td>
<td>0.91</td>
<td>19</td>
</tr>
<tr>
<td>Mouse</td>
<td>3.8</td>
<td>25.2</td>
<td>22</td>
</tr>
</tbody>
</table>
Cathepsin S

*Multiple Roles*

**Cathepsin S**

- **Intracellular activity**
  - MHC class II-dependent antigen presentation
    - Inhibition blocks antigen presentation & prevents activation of CD4+ T cells

- **Extracellular activity**
  - Cleavage of fractalkine
    - sFKN: chemokine involved in nociception, lymphocyte chemotaxis
    - Inhibition blocks sFKN activation
  - Activates PAR-2 & PAR-4 proteolytically
    - Neurogenic inflammation and pain
  - Cleavage of extracellular matrix (ECM) proteins
Cathepsin S

Overexpressed in Inflammatory Bowel Disease

Normal Small Intestine  Crohn’s Disease

macrophages and dendritic cells

Cathepsin S
Expressed at high levels in diseased vs. normal tissue

Fractalkine Receptor (CX3CR1)
Expressed at high levels in diseased vs. normal tissue
Cathepsin S

Multiple Roles in IBD

- MHC class II-dependent antigen presentation
  - Inhibition blocks antigen presentation prevents activation of CD4+ T cells

MHC II is strongest susceptibility locus for IBD

MHC II (HLA-DR) upregulated on enterocytes in IBD

Intracellular activity
Cathepsin S
*Multiple Roles in IBD*

- Cleavage of fractalkine
  - sFKN: chemokine involved in nociception, lymphocyte chemotaxis
  - Inhibition blocks sFKN activation
- Activates PAR-2 & PAR-4 proteolytically
  - Neurogenic inflammation and pain
- Cleavage of extracellular matrix (ECM) proteins

**TNF-α + IFN-γ increases FKN release in epithelial cells from IBD patients**

**FKNR (CX3CR1) expression is upregulated in T-Cells from IBD patients**
Percentage of PAR2 positive mast cells is greatly increased in IBD patients

Cathepsin S injected into the colonic lumen induces pain and inflammation mediated by PAR2

- Cleavage of fractalkine
  - sFKN: chemokine involved in nociception, lymphocyte chemotaxis
  - Inhibition blocks sFKN activation

- Activates PAR-2 & PAR-4 proteolytically
  - Neurogenic inflammation and pain

- Cleavage of extracellular matrix (ECM) proteins
Cathepsin S Biology
Potential Involvement in IBD Pathogenesis?

**Intracellular activity**
- MHC class II-dependent antigen presentation
  - Inhibition blocks antigen presentation
  - Prevents activation of CD4+ T cells
  - MHC II is strongest susceptibility locus for IBD
  - MHC II (HLA-DR) upregulated on enterocytes in IBD

**Extracellular activity**
- Cleavage of fractalkine
  - Chemokine involved in nociception & lymphocyte chemotaxis
  - Inhibition blocks activation of sFKN
- Activates PAR-2 and PAR-4 proteolytically
  - Neurogenic inflammation and pain
- Cleavage of extracellular matrix proteins
Cathepsin S Inhibitors

Mouse Model of Inflammatory Bowel Disease (IBD)

• Colitis induced by adoptive transfer of CD4+ CD45RB$^{hi}$ T-cells
• Robust and reproducible
• High penetrance (>95%)
• Disease onset ~4-6 wks
• Lesions are chronic
  – Therapeutic treatment model
• Histological features of human Crohn’s disease
• Sulfasalazine & anti-TNF responsive

Normal proximal colon

Diseased proximal colon

Hyperplastic epithelium
Crypt microabscess

Inflammation

Mucosal ulcer

Hyperplastic epithelium

Normal medial colon

Diseased medial colon

All photos taken from the same part of the colon at the same magnification 100X
Cathepsin S Inhibitors

Efficacy in Mouse IBD Model: Colon Weight/Length

- VBY compounds dosed therapeutically
  - Treatment initiated ~5 weeks after primary T cell transfer
  - Mean weight loss per group ~10% prior to dosing
- Reduced body weight loss (data not shown)
- Restored colon weight/length ratio to normal levels

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Colon Weight/Pre-flush Length (g/cm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>VBY-301</td>
<td>0.035</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>VBY-306</td>
<td>0.040</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>0.045</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Normal Control</td>
<td>0.045</td>
<td></td>
</tr>
</tbody>
</table>

* indicates statistical significance.
**Cathepsin S Inhibitors**

**Efficacy in Mouse IBD Model: Medial Colon Histology**

VBY-306 improved histology score (medial segmental colon)

- REDUCED epithelial hyperplasia & edema
- REDUCED epithelial cell loss/damage
- REDUCED inflammatory infiltrate
- REDUCED erosions/ulcers
# Cathepsin S Inhibitors

**Efficacy in Multiple Autoimmune Diseases**

<table>
<thead>
<tr>
<th>Model</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory Bowel Disease CD4+CD45RB&lt;sup&gt;hi&lt;/sup&gt; T cell transfer</td>
<td>Significant Reversal</td>
</tr>
<tr>
<td>Psoriasis SDI&lt;sup&gt;TM&lt;/sup&gt; T cell transfer into SCIDS</td>
<td>Significant Reversal</td>
</tr>
<tr>
<td>Atopic Dermatitis NcNga Spontaneous model</td>
<td>Significant Reversal</td>
</tr>
<tr>
<td>Delayed Type Hypersensitivity Human PBMC/Tetanus Toxoid into SCID mice</td>
<td>Significant Inhibition of Paw Swelling</td>
</tr>
<tr>
<td>RR – EAE PLP immunized SJL mice</td>
<td>Significantly inhibited relapses and improved body weight</td>
</tr>
</tbody>
</table>
# Virobay Cathepsin S Inhibitors

## Summary of Efficacy in Pain Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Efficacy on Hyperalgesia</th>
<th>Efficacy on Allodynia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory</td>
<td>Reversal</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Chronic inflammatory</td>
<td>No effect</td>
<td>Reversal</td>
</tr>
<tr>
<td>Partial nerve ligation</td>
<td>Reversal</td>
<td>Reversal</td>
</tr>
<tr>
<td>Full nerve ligation</td>
<td>Reversal</td>
<td>Reversal</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>Not assessed</td>
<td>Reversal</td>
</tr>
<tr>
<td>Chemotherapy induced neuropathy</td>
<td>Not assessed</td>
<td>Reversal</td>
</tr>
<tr>
<td>Post-surgical pain</td>
<td>Reversal</td>
<td>Reversal</td>
</tr>
</tbody>
</table>

No tolerance, no sedation, no respiratory depression, no effects on GI transit times
Cathepsin S Program

• Cathepsin S inhibitors: promising therapy in autoimmune diseases

• VBY-285 – clinical candidate
  – Is a highly potent and highly selective cathepsin S inhibitor
  – Is being developed for the treatment of autoimmunity
  – PK characteristics suggest once daily oral dosing in humans

• Structurally similar cathepsin S inhibitors
  – Potent efficacy in several models of autoimmunity
    • Inflammatory bowel disease
    • Psoriasis and atopic dermatitis
  – Potent efficacy in pain (multiple models)

• Strong IP position
  – Issued patents covering broad chemical space with
  – Established freedom to operate
Virobay Partnerships

Virobay As a Partner

- Extensive knowledge
  - Protease & cathepsin biology
  - Medicinal chemistry
  - Translational medicine
- Extensive, unique databases
  - SARs and crystal structures
  - Facilitate drug discovery
- Experienced team & model
  - Rapid and flexible
  - Cost-efficient development
  - Clinical proof-of-concept

Virobay Seeks in a Partnership

- A highly collaborative partner
- Autoimmunity expertise
- Upfront, milestones & royalties
- Financial support for Virobay to conduct Phase 2 proof-of-concept
- Drug product manufacture
- Clinical development for NDA

Chemical templates & biological expertise necessary to create and de-risk a new generation of therapeutics