SHIP Inhibitors and Uses Thereof

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Uses of a SHIP1/2 Inhibitor

- Promote blood cell recovery after myeloablative or myelosuppressive therapies (Chemotherapy, radiation)
- Therapy for hematologic cancers (MM, AML, CML, ALL) and breast cancer
- Mobilize blood stem/progenitors cells for transplantation
- To facilitate allogeneic transplantation: reduce BM graft rejection, reduce GvHD
SHIP1 as an diagnostic for IBD

- Identified SNPs in SHIP1 indicative of colon disease (IBD, Crohn’s, ulcerative colitis)
- Under expression of SHIP1 in peripheral blood mononuclear cells indicative of IBD
SHIP1 inhibition promotes blood cell recovery after myelosuppressive therapies (chemotherapy, radiation)
Enhancing Blood Cell Production

In the US today...

• 1.5 Million new cancer cases in 2010
• Half of all cancer patients receive chemotherapy or radiation
• After Chemotherapy, patients are given treatment to mobilize blood cell production

• Treatments currently available for Blood Cell production are proteins, which:
  1. Are costly to produce and difficult to store
  2. Must be injected
SHIP inhibition promotes recovery of all major blood cell types

Brooks et al JI 2010

Brooks et al submitted
Therapy for hematologic cancers (MM, AML, CML, ALL) and breast cancer
Multiple Myeloma

In the US today...

- 20,180 new cases of Multiple Myeloma will be diagnosed this year
- In the same time period, an estimated 10,650 deaths will occur from this debilitating disease
- An estimated 69,598 people are living with or are in remission from MM
- Five year survival rate is 35%
- Treatments have improved, but there is still no cure
SHIP1 Inhibition Induces Programmed Cell Death in AML Cells

Brooks et al JI 2010
SHIP1 Inhibition Is Also Cytotoxic for Multiple Myeloma Cells

Brooks et al JI 2010
SHIP Inhibition Abrogates Multiple Myeloma Growth In Vivo

Fuhler et al. Molecular Medicine 2012
Pan-SHIP1/2 inhibitors

Fuhler et al Molecular Medicine 2012
SHIP Inhibition Abrogates Multiple Myeloma Growth In Vivo

Vehicle

3AC

4 weeks Post challenge
Pan-SHIP1/2 inhibitors are also cytotoxic for MM cells
Pan-SHIP1/2 inhibitors are cytotoxic for breast cancer cells

Fuhrer et al Molecular Medicine 2012
Mobilize blood stem/progenitors cells for transplantation
SHIP1 inhibition mobilizes hematopoietic stem/progenitor cells.

**3AC**

**Vehicle**

- **c-Kit**
- **Sca1**

![Box plots](chart.png)

Frequency of Live

- **Day 4**
- **Day 6**
- **Day 8**
- **Day 10**
- **Vehicle**

**Significance:**
- *: p < 0.05
- **: p < 0.01
SHIP1 inhibition mobilizes functional hematopoietic stem/progenitor cells that radioprotect a lethally irradiated mouse and repopulate all major blood cell lineages.

Radioprotection

Repopulation
SHIP1 inhibition induces G-CSF (Neupogen equivalent) and represses SDF1 production in vivo.
To facilitate allogeneic bone marrow transplantation:
• reduce BM graft rejection
• reduce GvHD
SHIP Inhibition Increases Myeloid Immunoregulatory (MIR) Cell Numbers

Brooks et al JI 2010
SHIP Inhibition Increases T Regulatory Cell Numbers In Vivo
SHIP1 Inhibition Increases Immunoregulatory Function In Vivo

Mouse

Human

Brooks et al JI 2010
SHIP1 Inhibition Enhances Engraftment of ….
Diagnostic for Inflammatory Bowel Disease

- Identified SNPs in SHIP1 (INPP5D) indicative of colon disease (IBD, Crohn’s, ulcerative colitis)

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<th>Exon</th>
<th>Chr pos</th>
<th>SNP</th>
<th>Nuc</th>
<th>Exp % (n)</th>
<th>CD % (n)</th>
<th>UC % (n)</th>
<th>Healthy % (n)</th>
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<td>8 (6)</td>
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Diagnostic for Inflammatory Bowel Disease

- Underexpression of SHIP1 (INPP5D) in peripheral blood mononuclear cells is indicative of a colon disorder.

As especially can be seen in the comparison of subjects in experiment 2, P5-P8 for Crohn’s patients and C3-C5 for healthy controls, SHIP1 activity is less in the Crohn’s patients than in the healthy controls.
Current research:
Analogs of 3AC that are more soluble and more potent have been identified

Analogs of the SHIP1/2 inhibitory compounds have been identified with improved solubility and potency

The above analogs will be tested in a wide variety of in vivo models for:
1. Cancer: Multiple myeloma, breast cancer and leukemia
2. Blood cell recovery
3. Stem cell mobilization
4. Allogeneic BMT