**Key findings**

- Therapeutic blockade of E-selectin significantly enhanced survival to repeated rounds of high-dose chemotherapy in mice.
- GMI-1271 administration during chemotherapy both:
  - Accelerated neutrophil recovery
  - Reduced intestinal mucositis leading to increased mouse survival.

**Background**

The problem with chemotherapy

Oncotaxis target rapidly dividing cells, including malignant cells and also normal progenitors needed to replenish:

- the blood and immune system.
- mucosal surfaces lining the respiratory and gastrointestinal tracts.

... resulting in neutropenia - increased susceptibility to infections - together with intestinal ulceration providing a portal of entry for bacteria. Upto 20% of AML and high grade lymphoma patients will die from their cancer therapy and their disease (Pommier, HC, 2005).

**Blocking E-selectin - a possible solution**

Selectins are a family of classic leukocyte adhesion molecules.

E-selectin (CD62E) is expressed on endothelial cells following inflammation and is involved in recruiting and activating leukocytes.

**Hematopoietic Stem Cells are regulated by their niches**

Hematopoietic Stem Cells (HSC) have two conflicting roles:

2. Cycle to replenish the blood and immune system.  

These decisions are largely determined by the microenvironment (niche) in which the HSC reside.

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**Experiment outline**

Studies were performed in mice using two treatment regimens (chemotherapy or radiation), and endpoints were compared:

- Chemotherapy: mice received repeated rounds of the anti-metabolite prototype 5-fluorouracil (5-FU).
- Radiation: mice received repeated rounds of the anti-metabolite prototype 5-fluorouracil (5-FU).

Using this regimen, median survival for wildtype mice was 48 days. In contrast, 80% of E-selectin gene-deleted mice (E-/-) survived >40 days (Fig 1).}

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**Absence or therapeutic blockade of E-selectin during chemotherapy...**

- Increases overall mouse survival

**Likely mechanism**

**Accelerated Neutrophil Recovery**

GMI-1271 administration increases the proportion of HSC able to survive each round of chemotherapy, (see Fig 6). Increased numbers of surviving HSC help accelerate subsequent bone marrow and blood recovery post-chemotherapy.

**... accelerates & sustains neutrophil recovery**

- % mice able to recover normal neutrophil counts over repeated rounds of 5-FU

**... alleviates intestinal mucositis and therapy-related weight loss**

- Chemotherapy-induced mucositis is significantly reduced in E-selectin mice

**Likely mechanism**

Alleviating chemotherapy-mucositis

Mucositis is now thought to be exacerbated by infiltrating inflammatory cells. Our data show that:

- E-selectin expression is upregulated in damaged intestine
- GMI-1271 administration blocks recruitment of inflammatory macrophages to damaged intestine.

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**Conflict of Interest Disclosure**

- Jody Magnani is an employee of GlycoMimetics.
- GlycoMimetics funded parts of this work involving their compound (GMI-1271).