Docket #: S18-457

Controlling Blood Stem Cell Differentiation with Small Molecules and Gene Therapy Targeting GABA Signaling

While conventionally known for its function as an inhibitory neurotransmitter, GABA signaling was recently discovered to have a significant role in fate determination of blood stem cells. Control of the differentiation of hematopoietic stem cells (HSCs) or megakaryocyte progenitors (MkPs) can be achieved by inhibition or activation of GABA receptors. Thus, pharmacologic or genetic manipulation of GABA signaling can offer therapeutic benefit to patients with serious blood disorders.

Stage of Development
Preclinical, in vivo data is available. Robust regulation of HSC and MkP differentiation has been demonstrated with pharmacologic agents (agonists or antagonists) and gene editing of GABRR1.

Applications

- Manipulation of hematopoiesis as a treatment for patients with blood disorders
    - Thrombocythemia patients can be depleted of platelets using GABA antagonists
    - Thrombocytopenia patients can be augmented with platelets using GABA agonists
- Genetic knockout or overexpression of GABRR1 to inhibit or promote MkP differentiation
    - Gene therapy for patients with bleeding or clotting disorders
    - High-efficiency in vitro generation of megakaryocytes and platelets

Advantages

- GABA is one of the most well-studied endogenous chemicals and numerous potent drugs targeting GABA receptors have been developed
- Control of GABA signaling, whether by reagents or gene editing, is a novel and differentiated method of manipulating HSC and MkP differentiation

Publications

- F. Zhu, M. Feng, R. Sinha….I.L. Weissman The GABA receptor GABRR1 is expressed on and functional in hematopoietic stem cells and megakaryocytic progenitors *PNAS* Sept., 10, 2019.

Patents

- Published Application: WO2020231935
- Published Application: 20220218753
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