Weill Cornell Medicine

Transient Modified-RNA Expression of Activation Factor Promotes Adult Hematopoietic Stem Cell Expansion

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Background & Unmet Need

- Hematopoietic Stem Cell (HSC) transfer and transplantation is a life-saving treatment for many diseases, including cancers and blood disorders
- Human mobilized peripheral blood (mPB) is the most accessible source of Hematopoietic Stem and Progenitor Cells (HSPCs)
- However, there can be insufficient numbers of available transplantable mPB HSPCs following extraction or following ex-vivo genetic therapy
- Moreover, mPB HSPCs are much less proliferative than HSPCs from other sources, such as cord blood, and are less likely to respond to current expansion protocols
- **Unmet Need:** Activation methods for mPB-derived HSPC robust expansion for successful stem cell transplants resulting with full recovery and reconstitution of blood and immune systems

Technology Overview

- **The Technology:** A method for ex-vivo activation of HSPC expansion using a modified-RNA to overexpress master transcription regulator Fli-1
- **The Discovery:** The inventors have discovered a master transcriptional regulator for HSPC activation, Fli-1, which can direct HSPC regenerative expansion from a quiescent non-cycling state
- Fli-1 mediates the crosstalk between HSPCs and their niche and sensitizes them to expansionary regenerative signals
- Treatment with modified RNA to induce over-expression of Fli-1 or downstream activation factors can prime HSPCs for robust expansion
- **PoC Data:** Human adult mPB HSPCs treated with Fli-1 modified-RNA had increased expansion and superior engraftment capacity in vivo matching that of neonatal cord blood-derived HSPCs

Inventors:
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Lior Zangi

Patents:
Provisional Filed

Publications:
Itkin et al. *BioRxiv*. 2023. (preprint)

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Technology Applications

- Ex-vivo, pre-transplantation expansion of adult bone marrow or peripheral blood mobilized HSPCs
- Use for patients with poorly-mobilizing mPBs (e.g. due to genetic factors, diabetes, immunotherapy, chemotherapy)
- Pre-engraftment expansion of HSCs following successful genetic therapy for gene replacement (e.g. beta-thalassemia)

Technology Advantages

- Increased adult HSPC activation and expansion
- Expanded HSCs successfully engraft when transplanted displaying higher numbers of repopulating cells
- Transient expression using Fli-1 modified-RNA technology limits the risk of tumorigenesis or stem cell exhaustion associated with constitutive expression of activation factors

Supporting Data / Figures

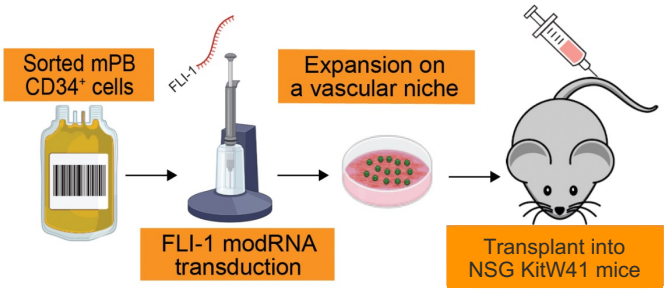

Figure 1: Summary diagram of HSPC expansion and transplantation from mobilized peripheral blood.

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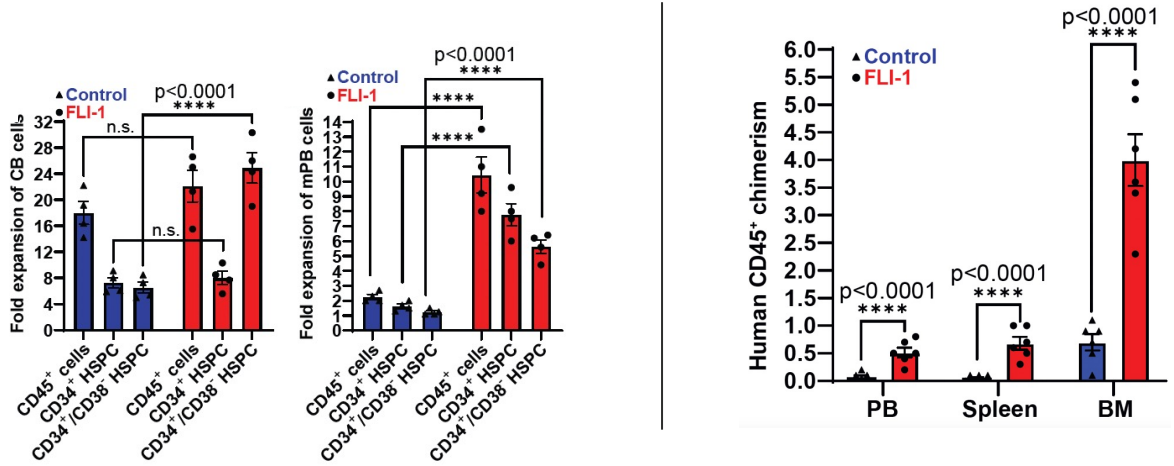

Figure 2: Left: Adult mPB HSPCs treated with Fli-1 mod-RNA demonstrate similar expansion capacity as cord blood-derived HSPCs. **Right:** Chimerism is higher in mice with transplanted mPB HSPCs treated with Fli-1 mod-RNA, indicating higher engraftment levels.

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