Docket #: S25-455

A Toolkit for Lineage-Specific Expression via Targeted Knock-Ins in Hematopoietic Stem Cells

Stanford scientists have developed a platform to engineer hematopoietic stem cells (HSCs) to express a genetic payload in specific cell lineages.

Despite advances in genome editing, precise control of transgene expression remains a major challenge for therapeutic applications. Current strategies rely on synthetic promoters, safe harbor loci, or exogenous regulatory elements that often fail to reproduce endogenous gene regulation. There is a need for approaches that harness native regulatory elements to achieve lineage-specific transgene expression.

The Porteus lab at Stanford has developed a toolkit for lineage-specific expression in hematopoietic stem and progenitor cells using CRISPR/Cas9-mediated targeted knock-ins. Rather than relying on viral promoters or random integration, this system enables precise knock-in of therapeutic payloads, reporters or other functional elements into endogenous lineage-specific loci, allowing transgene expression to be controlled by native regulatory elements. As hematopoietic stem and progenitor cells differentiate, transgene expression is activated only within the target lineage. The toolkit includes validated target loci, guide RNAs, donor templates, optimized editing and differentiation protocols, and assays to confirm lineage-restricted expression for applications in lineage tracing, disease modeling, and targeted gene therapy.

Stage of Development: *In vitro*

Applications

- Commercialized kits for tracking cellular differentiation, drug discovery, and disease modeling

Advantages

- Enables safer therapies by restricting transgene expression to specific cell lineages, thereby reducing off-target expression and associated toxicity
- Accelerates next-generation CAR-T and immunotherapy development
- Versatile platform with broad commercial potential

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