Engineered Stem Cell Antibody Paired Evasion 1 (ESCAPE-1): Paired HSC epitope engineering and upregulation of fetal hemoglobin for antibody-mediated androgenous stem cell therapy conditioning for the potential treatment of hemoglobinopathies


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Introduction

A major hurdle to the successful application of antigen-enhanced hematopoietic stem cell transplantation (HSCT) therapy is a potential treatment for a variety of these enigmatically including sickle cell disease and beta-thalassemia. Antigenic effects associated with use of the donor hematopoietic cells set can be minimized, but treatment of the graft versus host disease.

Our engineered naive cell antibody paired escape (ESCAPE) strategy (Figure 1) consists of multiple base edited epitopes that induce a therapeutic effect at the paracrine region of adjacent cells. This therapeutic strategy allows for the development of an antithetical therapy that is minimally toxic to the body or patient. The ESCAPE strategy allows the combination of multiple epitopes that can be used to deliver a variety of anti-rejection treatments simultaneously.

We report here the use of multiplexed engineered naive cell antibody paired escape (ESCAPE-1) strategy for the delivery of therapeutic agents to hematopoietic stem cells (HSCs) and precursors of HSCs.

In vitro characterization of lead CD117 edit and anti-CD117 mAb

Lead anti-CD117 antibody mAb-7 did not recognize the lead CD117 variant (Figure 2A). While mAb-7 treatment mimicked complete SCF withdrawal and enforced CD117-edited cells in vitro (Figure 2B), mAb-7 treatment generated highly potent mAb that did not produce major cell destabilization in vitro (Figure 2C).

In vivo characterization of lead CD117 edit and anti-CD117 mAb

Base editing of CD171 in CD34+ cells did not alter long-term engraftment and multilineage reconstitution in rodent model (Figure 3A). mAb-7 selectively depleted unedited cells from the bone marrow of mice transplanted with hCD34+ cells (Figure 3B).

Figure 1. ESCAPE strategy

Gene editing with Adenine Base Editors (ABE)

A ABE compatible CD171 antigen engineering and antibody screening

Base edited CD171 enables engineered HSCs to selectively escape antibody binding

Figure 4. Engineered CD171 antigen screening, (A) Schematic of antibody binding strategy. CD171 mAb binding to CD171 engineered HSCs expressing the erythroid and granulocytic lineages. mAb binding was detected using fluorescein isothiocyanate (FITC)-labeled goat anti-human secondary antibody. No binding to unedited HSCs. (B) Antibody screening. 180 mAb clones were identified and affinity rankings were determined for 180 mAb clones.

Multiplex editing

Figure 5. Base editing enabled highly efficient multiplex editing of both CD171 and HBG1/2 primary CD34+ HSPCs

Conclusions

We have developed Engineered Stem Cell Antibody Paired Evasion (ESCAPE) strategy, wherein a base-edited CD171 antigen and anti-CD171 mAb pair enables edited cells to evade recognition by the intact body, thus selectively depleting unedited cells. This anti-rejection strategy is dependent on multiplexed antigen engineering allowing for broad, cell type-specific depletion.

References and Disclosures

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