DNA-based gene therapies that require genome integration are limited by the size of the sequence they encode, number of proteins they can express, and the potential for uncontrolled proliferation. A recent wave of RNA-based gene therapies entering clinical trials has brought us closer to using mRNA as a potential therapeutic nucleic acid. Here, we report how mRNA can be used to engineer red blood cells with long-lasting protein expression to create an entirely new class of cellular medicines called Red Cell Therapeutics® (RCTs).

INTRODUCTION

- RCTs are a new class of allogeneic, off-the-shelf cellular therapies for the potential treatment of rare diseases, cancer, and autoimmune diseases (Figure 1).
- RCTs are engineered to express hundreds of thousands of copies of intracellular or membrane-bound therapeutic proteins, such as intracellular enzymes, co-stimulatory molecules and cytokines.
- Until now, the RED PLATFORM® has enabled the genetic engineering of donor-derived CD34+ hematopoietic stem cells (HSCs) using lentiviral-based DNA transduction. Here, we report on expanding RCT engineering methods via mRNA-based gene delivery.

CONCLUSIONS

- The results demonstrate that mRNA-based gene delivery using optimized electroporation can be used to generate an entirely new class of cellular therapy with sustained protein expression (Figure 7).
- Using mRNA-based gene delivery in RCTs demonstrated efficient co-expression of multiple membrane-bound or intracellular proteins.
- mRNA-based gene delivery enables tunable protein expression in RCTs.
- mRNA-based engineering of RCTs is scalable.

OBJECTIVES

- Expression of intracellular and/or membrane-bound therapeutic proteins using mRNA-based gene delivery.
- The expression of a single protein or combinations of multiple proteins using mRNA-based gene delivery.
- Tunable expression of therapeutic proteins.
- A scalable process.

Figure 1. The RED PLATFORM® Generates Allogeneic, Off-the-Shelf Cellular Therapies

Figure 2. Sustained Protein Expression for 9 Days Post mRNA Electroporation

Figure 3. Efficient Co-expression of Multiple Intracellular Therapeutic Proteins in RCTs

Figure 4. Efficient Co-expression of Multiple Extracellular Therapeutic Proteins in RCTs, Membrane Tethered Rituximab scFv and TRAIL

Figure 5. Tunable Control of Therapeutic Protein Expression in Each RCT

Figure 6. Efficient and Scalable Process for Generating mRNA-based Therapeutic RCTs

Figure 7. mRNA-Based Gene Delivery Can Be Used to Generate a New Class of Cellular Therapy With Sustained Protein Expression

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DISCLOSURES

All authors: Employment with and equity ownership in Rubius Therapeutics.

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