RAPID, SCALABLE, COST-EFFECTIVE PROCESS FOR GENERATION OF STABLY INTEGRATED CHIMERIC ANTIGEN RECEPTOR (CAR) ENGINEERED T-CELLS BY "GENE WRITING": AN ALL RNA APPROACH, WITHOUT NEED FOR USE OF VIRAL VECTORS OR NUCLEASES

Madhusudan V. Peshwa, Tessera Therapeutics, Inc., Somerville, USA
mvpeshwa@tesseratx.com

Chimeric Antigen Receptor (CAR) engineered T-cell therapies have shown the ability to eradicate very advanced leukemias and lymphomas in advanced cancer patients. Since 2017 six CAR T-cell products have received marketing authorization in US & Europe and additional products have been approved in China, some of which are now also approved for earlier lines of therapy. Despite this excitement and CAR T-cell therapies becoming mainstream, significant challenges exist: (1) long-term survival has only been observed in fewer than half of the treated patients, potentially requiring re-treatment; (2) commercial challenges with economics of these therapies being in the range of $400,000 per patient; (3) supply chain limitations with availability of viral vectors and GMP quality of viral vector used as critical biological material in the manufacture of CAR T-cells, leading to approximately a 6-month long waiting list of patients to receive approved CAR T-cell therapies; and (4) from the perspective of a patient with rapidly advancing disease, the needle-to-needle time from initiation of treatment to receiving the final drug product can often be in the range of two months, which significantly limits the number of patients who get prescribed CAR T-cells even though they could potentially benefit. Efforts to address some of these challenges using allogeneic CAR T-cell therapies have progressed to early clinical trials but have failed to demonstrate efficacy on par with autologous CAR T-cells and need to address additional safety and regulatory challenges with the use of nucleases, resulting in double strand breaks with the potential for translocation within the genome of the administered drug product.

We have developed a manufacturing platform using RNA molecules for generation of stably integrated CAR T-cells, without need for lentivirus or nucleases that could potentially permit more rapid and cost-effective treatments with CAR T-cells. The platform utilizes Gene Writing by mobile genetic elements in creating CAR T-cells using the mechanism of target primed reverse transcription (TPRT) to write new genetic information into the genome and/or rewrite the genome to make substitutions, or small insertions and deletions. The process involves the use of a messenger RNA molecule encoding for the Gene Writer Protein along with another RNA molecule as Template that encodes specific changes to the genome (for example, a CAR molecule). Both molecules are delivered to a primary T-cells by non-viral delivery.

This presentation will describe the process used to generate CAR T-cells with Gene Writing and provide an overview of the critical attributes of the obtained drug product, including potency, as measured by the ability of the CAR T-cells to recognize and kill tumor cells in vitro. This presentation will further demonstrate the ability of Gene Writer CAR T-cells in effective control and clearance of pre-established tumors in preclinical animal models.