Novel compositions and methods for targeted replacement of endogenous T-cell receptor with a chimeric antigen receptor

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TECHNOLOGY DESCRIPTION

This invention is a method for targeted and high-efficiency replacement of the endogenous T-cell receptor (TCR) with a chimeric antigen receptor (CAR) by introducing a Cas9 and guide RNA (gRNA) ribonucleoprotein (RNP) that targets a genomic break to the endogenous T-cell receptor alpha constant chain (TRAC) locus. The depletion of TCR-positive cells by magnetic beads enriches the cells which have both the CAR knockin and TCR knockout. Also cells, which are modified successfully by homology-directed-repair (HDR) through minimizing non-homologous-end-joining (NHEJ)-mediated TCR knockout by the selection of gRNA targets that do not disrupt protein-coding regions, are enriched. A set of HDR templates, which use recombinant adeno-associated virus (rAAV) or ssDNA/dsDNA Cas9 “shuttle” hybrid templates, is adapted along with selected gRNA targets that stimulate high-efficiency HDR with reduced disruption of endogenous TCR expression in the absence of HDR.

PATENT STATUS

Country	Type	Number	Dated	Case
Australia	Published Application	WO 2021/183884	09/16/2021	2020-206
Canada	Published Application	WO 2021/183884	09/16/2021	2020-206
China	Published Application	WO 2021/183884	09/16/2021	2020-206
Israel	Published Application	WO 2021/183884	09/16/2021	2020-206
Japan	Published Application	WO 2021/183884	09/16/2021	2020-206
Rep Of Korea	Published Application	WO 2021/183884	09/16/2021	2020-206
Mexico	Published Application	WO 2021/183884	09/16/2021	2020-206
Brazil	Published Application			2020-206
European Patent Office	Published Application			2020-206
Patent Cooperation Treaty	Published Application	WO 2021/183884	09/16/2021	2020-206

Additional Patent Pending

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OTHER INFORMATION

CATEGORIZED AS

- Medical
  - Disease: Autoimmune and Inflammation
  - Disease: Cancer
  - Gene Therapy
  - Therapeutics

RELATED CASES

2020-206-0

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