

CLAIMS

1. A cell genetically modified to produce a chimeric polypeptide receptor comprising (i) an extracellular recognition domain, (ii) at least one protease cleavage site, and (iii) an intracellular transcription factor, and further genetically modified to comprise a polynucleotide encoding a gene product comprising at least one exosomal polypeptide and a protein of interest, in which binding of the extracellular recognition domain to its target induces proteolytic cleavage of the at least one protease cleavage site and endogenous transcription by the intracellular transcription factor of the polynucleotide encoding the gene product.
2. A cell according to Claim 1, in which the protein of interest is an antibody, a single-chain antibody, a bispecific T cell engager (BiTE), a receptor, a cytokine such as an interleukin, an enzyme such as caspase, granzyme, Cas, Cas9, a checkpoint inhibitor, a costimulation inhibitor, an RNA-binding protein, a membrane transporter such as NPC-1, a splicing factor, a protein associated with cellular organelles, a lysosomal enzyme, a transcription factor, a mitochondrial proteins, an intracellular protein, an antiviral protein, an antibacterial protein.
3. A cell according to Claim 1 or 2, in which when the protein of interest is an RNA-binding protein the cell is further genetically modified to comprise an RNA cargo molecule selected from the group consisting of mRNA, sgRNA, shRNA, miRNA, shRNA, siRNA, lncRNA, ncRNA, piRNA, piwiRNA, circRNA, tRNA, rRNA, crRNA and any combination thereof.
4. A cell according to Claim 1, 2 or 3, in which the cell is an effector immune cell.
5. A cell according to Claim 3 or 4, in which the cell is a T cell, a cytotoxic CD8⁺ T cell, a CD4⁺ T cell, a regulatory T cell, a natural killer (NK) cell, a B cell, a plasma cell, a dendritic cell (DC), a macrophage, a monocyte, a neutrophil, an epithelial cell, an endothelial cell, a microglia, an astrocyte, a neuron, a stem cell, a bone marrow derived mesenchymal stromal cell or a Wharton's jelly derived MSC.
6. A cell according to any preceding claim, in which the extracellular recognition domain of the chimeric polypeptide receptor is an antibody, a single-chain fragment, a single-chain

antibody, a nanobody, a peptide, a ligand for a receptor, an adhesion molecule, a receptor, an interleukin receptor, an extracellular matrix component, or any combination thereof.

7. A cell according to any preceding claim, in which the at least one protease cleavage site is at least one of an S1, an S2 and/or an S3 cleavage site.

5 8. A cell according to any preceding claim, in which the chimeric polypeptide receptor is a chimeric Notch polypeptide comprising from N-terminus to C-terminus and in covalent linkage:

(i) an extracellular recognition domain that is not naturally present in a Notch receptor polypeptide;

10 (ii) a Notch regulatory region which comprises a Lin 12-Notch repeat, an S2 proteolytic cleavage site, and a transmembrane domain comprising an S3 proteolytic cleavage site;

(iii) an intracellular transcription factor that is heterologous to the Notch regulatory region,

15 in which binding of the extracellular recognition domain to its target induces cleavage at the S2 and S3 protease cleavage sites, thereby releasing the intracellular transcription factor which activates transcription of the polynucleotide.

9. A cell according to Claim 8, in which the Notch regulatory region further comprises a heterodimerization domain comprising the S2 proteolytic cleavage site.

20 10. A cell according to Claim 7, in which the S1 proteolytic cleavage site is a furin-like protease cleavage site comprising the amino acid sequence Arg-X-(Arg/Lys)-Arg, where X is any amino acid.

11. A cell according to any preceding claim, in which the chimeric polypeptide receptor comprises at least one linker.

25 12. A cell according to any preceding claim, in which the polynucleotide further comprises a transcriptional control element, responsive to the transcription factor, operably linked to a coding sequence.

13. A cell according to any preceding claim, in which the cell is genetically modified to produce at least two types of fusion polypeptides, in which at least one of the (i) extracellular

recognition domain, the (ii) protease cleavage site, and the (iii) intracellular transcription factor differ between the fusion polypeptides, optionally in which the extracellular recognition domains of the fusion polypeptides are different from one another.

14. An extracellular vesicle (EV) produced by a cell according to any preceding claim,
5 optionally in which the EV is an exosome.
15. A pharmaceutical composition comprising a cell according to any of Claims 1 to 13.
16. A cell according to any of Claims 1 to 13 or a pharmaceutical composition according to Claim 15 for use in medicine.