

Technology Disclosure Form

Instructions:

Please submit a copy of (a) MS Word version of this Technology Disclosure Form; and (b) a copy of PDF version of this Technology Disclosure Form **fully signed** by all inventors to Enterprise Division.¹

A. Technology Disclosure Details

1. Technology Title:

New Chimeric Antigen Receptors for Monocytes/Macrophage and Uses Thereof

2. RI Name:

IMCB

3. RI TD Number:

2024-020

4. Purpose of Technology Disclosure (TD) Submission

This technology disclosure form is submitted for the purpose of (please tick only 1 box):

☒ For Evaluation

☐ For recording purpose

5. Keywords:

(List all keywords relevant to this technology. Separate each keyword by a comma (,))

Chimeric, antigen, receptor, monocyte, macrophage, toll-like-receptor 4, TLR4, 4-1BB

6. Brief Summary of Technology:

Insert figure(s) of technology (if necessary)

Monocytes were engineered to express chimeric antigen receptor (CAR-M) targeting tumor surface proteins and efficiently reduced human tumor burden in an *in vivo* humanized mouse model. CAR construct schematic is as follows:



where TM: transmembrane domain; TIR: Toll/Interleukin-1 receptor domain.

Specifically, the present invention discloses a Chimeric Antigen Receptor (CAR) construct comprising an antigen binding domain, a hinge region, a transmembrane domain, and an intracellular domain connected in sequence; wherein the intracellular domain comprises at least one costimulatory signaling domain, comprising a TLR4 TIR signaling domain and a 4-1BB signaling domain connected in sequence; wherein the TLR4 TIR signaling domain is constructed to be positioned adjacent to the transmembrane domain.

¹ Portfolio OICs to edit according to RI's requirement before providing TD form to inventors.

As described below, the intracellular domain of the CAR construct in the present invention combines TLR4 TIR and 4-1BB in a specific sequence (i.e., TLR4 TIR closer to the transmembrane domain, while 4-1BB closer to the C-terminus of the CAR protein construct), which enables effective recruitment of both MyD88-NF- κ B and IRF3 via efficient homodimerization of TLR4 TIR. Simultaneously, the CAR construct maintains robust activation of 4-1BB. These synergistic mechanisms promote M1 polarization of macrophages, significantly enhancing anti-tumor efficacy, particularly against solid tumors.

7. Problem Statement:

Cancer is one of the leading causes of mortality worldwide, accounting for nearly 10 million deaths in 2020 [<https://www.who.int/news-room/fact-sheets/detail/cancer>]. Lung and colorectal cancers are among the most commonly diagnosed types [<https://www.cancer.gov/about-cancer/understanding/statistics>]. Traditional cancer treatments have primarily included surgery, chemotherapy, radiation, or a combination of these approaches. While surgical resection can be curative in selected cases, most patients with advanced solid tumors are not candidates for surgery and thus require additional treatment modalities such as radiation or chemotherapy. A significant limitation of cytotoxic chemotherapy drugs is their lack of specificity, which causes them to attack both normal and tumor cells, leading to potentially severe side effects. The emergence of chimeric antigen receptor (CAR)-T cell immunotherapy offers a promising new approach for cancer treatment. However, to extend the benefits of immunotherapy to a broader range of solid tumor types, further advancements are necessary to overcome critical barriers, including immunosuppression and the challenges of targeted delivery.

Currently, there are about 124 clinical trials registered on ClinicalTrials.gov (accessed on 1st July 2024) evaluating various CAR-T constructs for solid tumor treatment. However, the challenges for CAR-T cell therapy in eradicating solid tumours are substantial. Solid tumours can be difficult for CAR-T cells to infiltrate, and the tumour microenvironment can recruit myeloid-derived suppressor cells (MDSCs) that disrupt the cytotoxic capabilities of effector T cells (Ma, Das et al. 2023, PMID: 37998743).

Given these limitations, we propose that CAR-monocytes/macrophages (CAR-M) could be a more effective solution. CAR-M therapy leverages the natural abilities of macrophages to infiltrate solid tumours and modulate the tumour microenvironment (TME), potentially overcoming the barriers faced by CAR-T cell therapy (Zhang, Yang et al. 2023, PMID: 37388769).

In animal models, it had been shown that CAR-M can reduce tumour growth and potentially modulate the tumour microenvironment (Lei, Yu et al. 2024, PMID: 38012418). Early results from a phase 1 clinical trial demonstrated that CAR-M trafficked into solid tumour, modulated the TME and possibly led to expansion of tumour reactive T cells (Reiss, Yuan et al. 2022, doi: 10.1158/1538-7445.SABCS21-OT1-03-01). Although the best response observed in these studies was disease stabilization (Annunziata, Ghobadi et al. 2020, doi: 10.1200/JCO.2020.38.15_suppl.3014), the findings are promising. In terms of adverse effects following CAR-M infusion, two separate clinical trials showed that only low-grade cytokine release syndrome occurred, which resolved without further treatment (Annunziata, Ghobadi et al. 2020, Reiss, Yuan et al. 2022). Additionally, other trials investigating the adoptive transfer of M1-activated macrophages reported that the treatment was well-tolerated by patients, with clinical side effects primarily limited to fever and flu-like symptoms (Sloas, Gill et al. 2021 PMID: 34899748).

8. Detailed Description of Technology:

(Please also attach a detailed written description and figure(s) of your technology.)

We developed a CAR construct with an scFv targeting PD-L1 and intracellular domains associated with M1 polarization pathways. As a proof of concept, we expressed this CAR construct in THP-1 cells, a monocyte cell line, to create CAR-THP-1 cells. We then evaluated the anti-tumour effects of CAR-THP-

1 in a human immune system humanized mouse model. These humanized mice were created by engrafting immunodeficient NOD/SCID IL2R $\gamma^{-/-}$ (NIKO) mice with human CD34 $^{+}$ pluripotent stem cells (Costa, Ye et al. 2017, PMID: 28765218), resulting in mice with approximately 50-60% human immune cell chimerism after 12 weeks. The human immune cells in these mice comprised about 50% CD3 $^{+}$, 30% CD19 $^{+}$, and 10% CD14 $^{+}$ (Fig. 1A).

As an example, for the use of our new CAR construct in treating solid cancers, we subcutaneously engrafted a lung cancer cell line, A549, which expresses PD-L1, into the right flank of these humanized mice. After one week, the mice were divided into three groups: no treatment (Ctrl), wildtype THP-1 cells (THP-1), and CAR-THP-1 cells (CAR-THP-1). Tumour dimensions were measured over the course of one month. Notably, compared to the control group, the tumour volume in the CAR-THP-1 group was significantly lower starting from day 21 ($90.4 \pm 45.6 \text{ mm}^3$, $n=12$ vs $188.6 \pm 62.2 \text{ mm}^3$, $n=8$, multiple t-tests with Benjamini-corrected p-value: <0.05) (Fig. 1B).

On day 28, the mice were sacrificed, and tumours were harvested and weighed (Fig. 1C). In line with the observed reduction in tumour volume, the weights of tumours retrieved from humanized mice receiving CAR-THP-1 cells ($0.6 \pm 0.3 \text{ g}$, $n=12$) were significantly lower than those from mice receiving wildtype THP-1 cells ($1.3 \pm 0.6 \text{ g}$, $n=15$, one-way ANOVA with Tukey's post hoc test, p-value: 0.006) and those from the control group ($1.8 \pm 0.5 \text{ g}$, $n=8$, one-way ANOVA with Tukey's post hoc test, p-value: <0.0001) (Fig. 1D).

CAR-THP-1 work synergistically with human T cells. Having demonstrated that CAR-THP-1 cells targeting PD-L1 effectively reduced tumour burden in humanized mice engrafted with the lung tumour cell line A549 by approximately 67% (Fig. 1D), we next sought to determine if CAR-THP-1 cells can exhibit their anti-tumour effect independently or require additional human immune cells, we conducted an experiment using immunodeficient NIKO mice engrafted with A549 cells. The mice were divided into two groups: no treatment (Ctrl) and treatment with CAR-THP-1 cells (CAR-THP-1). Tumour dimensions were measured over the course of one month. No significant differences in tumour volume were observed between the two groups (Fig. 2A). Similarly, no significant differences in tumour weights were noted on day 28, when the mice were sacrificed (Fig. 2B and C). This data suggests that CAR-THP-1 cells alone are insufficient to control tumour growth and require the presence of other human immune cells to be effective.

Given the crucial roles of T cells in tumour eradication, we investigated the contributions of CD4 $^{+}$ and CD8 $^{+}$ T cells to the CAR-THP-1 mediated anti-tumour effect. We engrafted A549 cells into humanized mice and divided them into four groups: no treatment (Ctrl), CAR-THP-1 cells (CAR-THP-1), CAR-THP-1 cells with an anti-CD4 depleting antibody (CAR-THP-1 + aCD4), and CAR-THP-1 cells with an anti-CD8 depleting antibody (CAR-THP-1 + aCD8). After one month, tumours were harvested and analysed. The results showed that a significant reduction in tumour weight was observed only in the group treated with CAR-THP-1 cells alone (Fig. 3A and B). This data suggests that the anti-tumour effects of CAR-THP-1 cells require the presence of both CD4 $^{+}$ and CD8 $^{+}$ T cells, indicating that CAR-THP-1 cells work synergistically with these T cell subsets to mediate their anti-tumour activity.

CAR-THP-1 shifted macrophage polarization towards M1 in the TME. Having identified the cellular components responsible for the anti-tumour effects of CAR-THP-1 cells, we next sought to elucidate the mechanism by which CAR-THP-1 cells interact with T cells. Given the pivotal role macrophages play in modulating the TME, we aimed to determine the polarization state of macrophages within the TME. To this end, we extracted tumour-infiltrating lymphocytes (TILs) from tumours retrieved from humanized mice engrafted with A549 cells, either untreated or treated with CAR-THP-1 cells for one month. The extracted TILs were analysed by flow cytometry for the expression of species markers (huCD45, mouse CD45.1), macrophage markers (CD14, CD16, CD68), an M0 marker (CD11b), an M1 marker (CD80), and an M2 marker (CD206).

t-SNE analysis of these markers, followed by FlowSOM clustering, revealed that the cells could be organized into at least seven distinct groups. The clusters with high contributions from CD11b, CD80,

and CD206 were highlighted (Fig. 4A). When breaking down the t-SNE analysis by treatment group, we found that in humanized mice that received no treatment, the majority of macrophages were in the cluster with high CD206 expression. In contrast, macrophages from humanized mice that received CAR-THP-1 treatment mostly fell into the CD11b and CD80 clusters (Fig. 4B). This was further validated at the individual mouse level, where the expression of CD11b (1472 ± 1357 , $n=9$ vs 147 ± 102 , $n=7$, t-test p-value: 0.002, Fig 4C) and CD80 (586 ± 323 , $n=9$ vs 168 ± 124 , $n=7$, t-test p-value: 0.006, Fig 4D) were significantly higher in the CAR-THP-1 group compared to the untreated group. Conversely, CD206 expression (135 ± 106 , $n=9$ vs 370 ± 153 , $n=7$, t-test p-value: 0.003, Fig. 4E) was significantly lower in the CAR-THP-1 group compared to the untreated group.

These findings suggest that CAR-THP-1 cells induce a shift in macrophage polarization towards an M1 phenotype within the TME, which may facilitate their interaction with T cells and contribute to their anti-tumour effects.

CAR-THP-1 reduced PD-1 expression on CD4 and CD8 T cells in the TME. Given the crucial roles of both CD4⁺ and CD8⁺ T cells in the CAR-THP-1 mediated anti-tumour response, we next examined the phenotype of these T cells within the TILs. We found no major differences in the percentages of effector memory, central memory, naïve, and regulatory T cells for both CD4⁺ and CD8⁺ TILs between treatment groups. However, the percentage of CD4⁺ T cells expressing programmed cell death protein 1 (PD-1) was significantly reduced in the CAR-THP-1 group compared to the control group ($47.9 \pm 8.3\%$, $n=9$ vs $68.0 \pm 7.6\%$, $n=7$, t-test p-value: 0.003, Fig. 5A). Similarly, the percentage of CD8⁺ T cells expressing PD-1 was also significantly lower in the CAR-THP-1 group ($36.6 \pm 11.4\%$, $n=9$ vs $61.7 \pm 11.2\%$, $n=7$, t-test p-value: 0.007, Fig. 5B).

Our results show that PD-1 expression in tumour-infiltrating T cells was reduced in tumours retrieved from humanized mice treated with CAR-THP-1. This finding aligns with clinical observations in lung cancer patients, where lower PD-1 expression on CD8⁺ lymphocytes is associated with longer overall survival (Mazzaschi, Madeddu et al. 2018, PMID: 29074606). This suggests that CAR-THP-1 cells may enhance the anti-tumour immune response by modulating PD-1 expression on TILs, thereby contributing to improved tumour control and potentially better clinical outcomes.

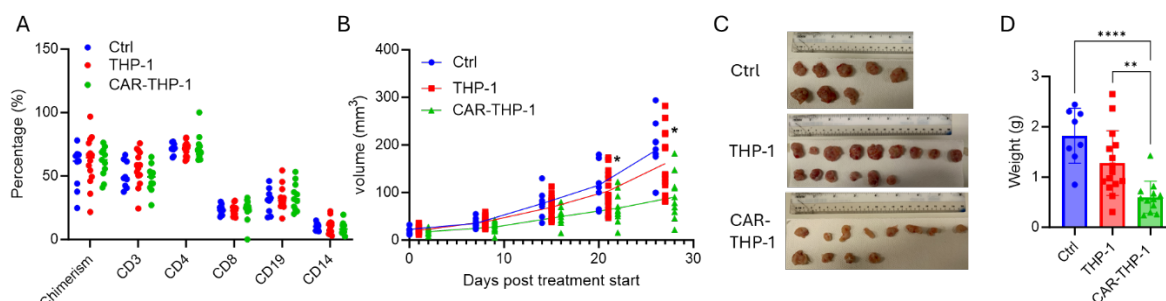


Figure 1: CAR-THP-1 Reduced Lung Tumour Burden In Humanized Mice. Immunodeficient NOD/SCID IL2Rγ^{-/-} (NIKO) mice were engrafted with human CD34⁺ pluripotent stem cells to generate humanized mice. (A) At week 12, human cell chimerism was assessed by flow cytometry, determined as the percentage of human CD45⁺ cells within the total lymphocyte population (human CD45⁺ and mouse CD45.1⁺). The percentages of human T cells (CD3⁺), B cells (CD19⁺), and monocytes (CD14⁺) were identified within the human CD45⁺ cell population, while human CD4⁺ and CD8⁺ cells were determined as the percentage of positive cells within the CD3⁺ subset. (B) One million A549 lung tumour cells were engrafted into the flank of 12-week-old humanized mice. After one week, the mice were divided into three groups: no treatment (Ctrl), intravenously injected with 10 million wild-type THP-1 cells (THP-1), and injected with 10 million CAR-THP-1 cells (CAR-THP-1). Tumour dimensions were monitored weekly for 28 days. (C-D) After 28 days, tumours were retrieved from the indicated groups (C) and weighed (D). Each dot represents one individual mouse, with bar plots showing the mean $\pm$ SD. **: $p < 0.01$; ****: $p < 0.001$.

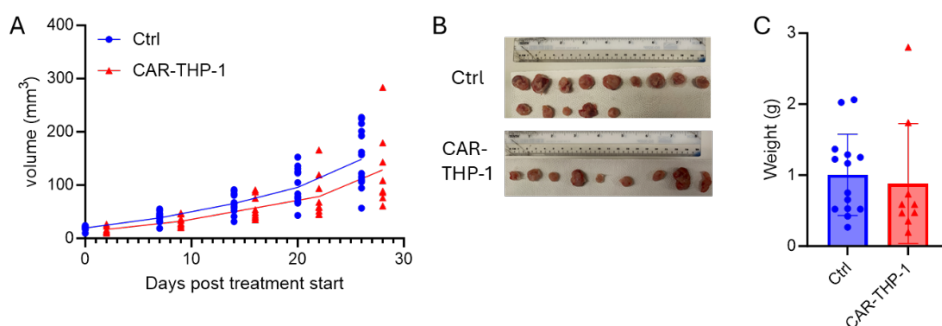


Figure 2: CAR-THP-1 Requires Other Human Immune Cells For Anti-tumour Activity. (A) Twelve-week-old immunodeficient NOD/SCID IL2Rγ^{-/-} (NIKO) mice were engrafted with one million A549 lung tumour cells. After one week, the mice were divided into two groups: untreated controls (Ctrl) and those injected with 10 million CAR-THP-1 cells (CAR-THP-1). Tumour dimensions were tracked weekly for 28 days. (B-C) At the end of the 28-day period, tumours were harvested from the respective groups (B) and weighed (C). Each dot represents an individual mouse, with bar plots indicating the mean ± SD.

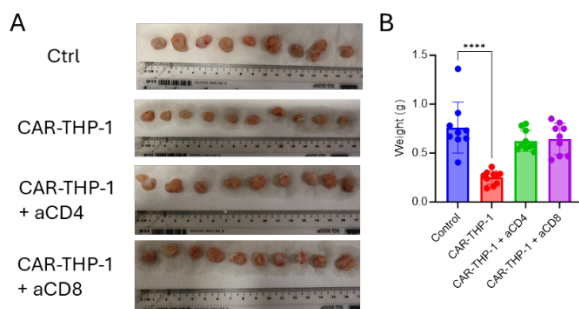


Figure 3: CAR-THP-1 Works Synergistically With Human T Cells To Reduce Tumour Burden. Twelve weeks old humanized mice were engrafted with one million A549 lung tumour cells. After one week, the mice were divided into four groups: no treatment (Ctrl), intravenously injected with 10 million CAR-THP-1 cells (CAR-THP-1), injected with 10 million CAR-THP-1 and a CD4 depleting antibody (CAR-THP-1 + aCD4), and injected with 10 million CAR-THP-1 and a CD8 depleting antibody (CAR-THP-1 + aCD8). (A-B) After 28 days, tumours were retrieved from the indicated groups (A) and weighed (B). Each dot represents one individual mouse, with bar plots showing the mean ± SD. ****: p<0.001.

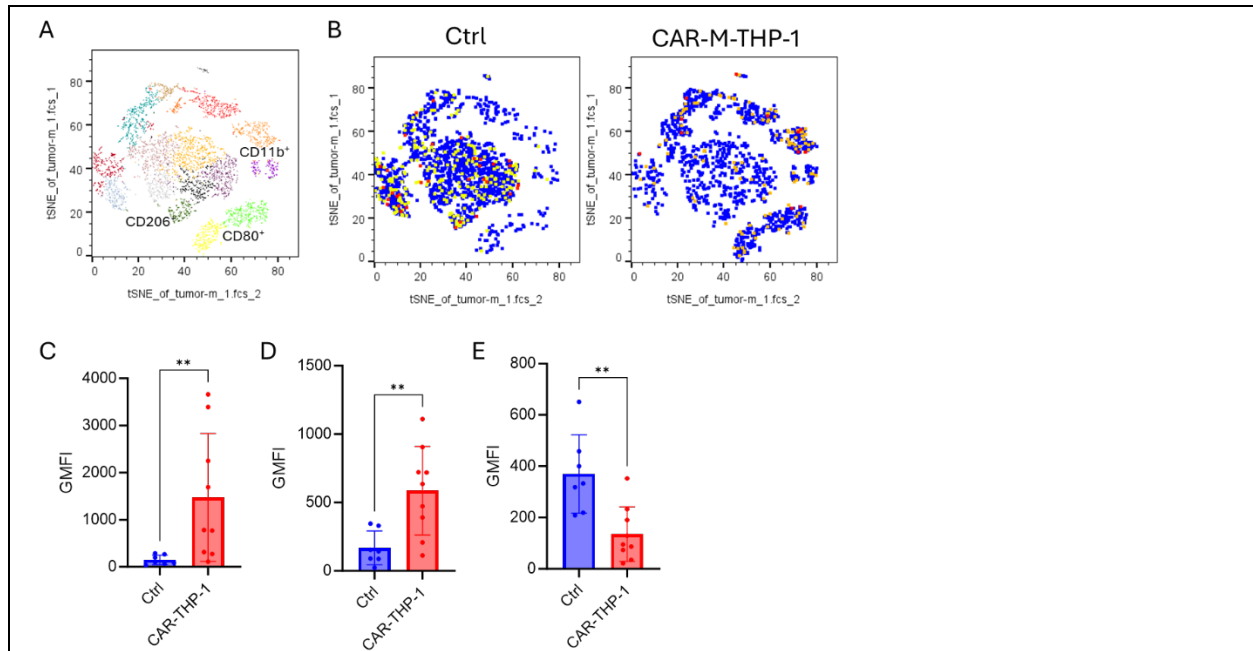


Figure 4. CAR-THP-1 Induces M1 Polarization of Macrophages Within the Tumour Microenvironment. Tumour-infiltrating lymphocytes (TILs) were isolated from tumours retrieved from humanized mice engrafted with A549 cells, either untreated or treated with CAR-THP-1 cells for one month. The extracted TILs were analysed by flow cytometry for the expression of species markers (huCD45, mouse CD45.1), macrophage markers (CD14, CD16, CD68), an M0 marker (CD11b), an M1 marker (CD80), and an M2 marker (CD206). (A) t-SNE analysis of these markers, followed by FlowSOM clustering, highlighting clusters with high contributions from CD11b, CD80, and CD206. (B) t-SNE plots displaying events from untreated or CAR-THP-1 treated groups. (C-E) Bar plots showing the geometric mean fluorescent intensity (GMFI) of CD11b (C), CD80 (D), and CD206 (E) for individual mice from the indicated groups. For t-SNE plot, each dot represents a single cell. For bar plots, mean $\pm$ SD is shown, with each dot representing an individual mouse **: $p < 0.01$. Thus, the results of Figure. 4 demonstrate that CAR-M therapy could polarize tumor infiltrating macrophages towards a pro-inflammatory M1 phenotype.

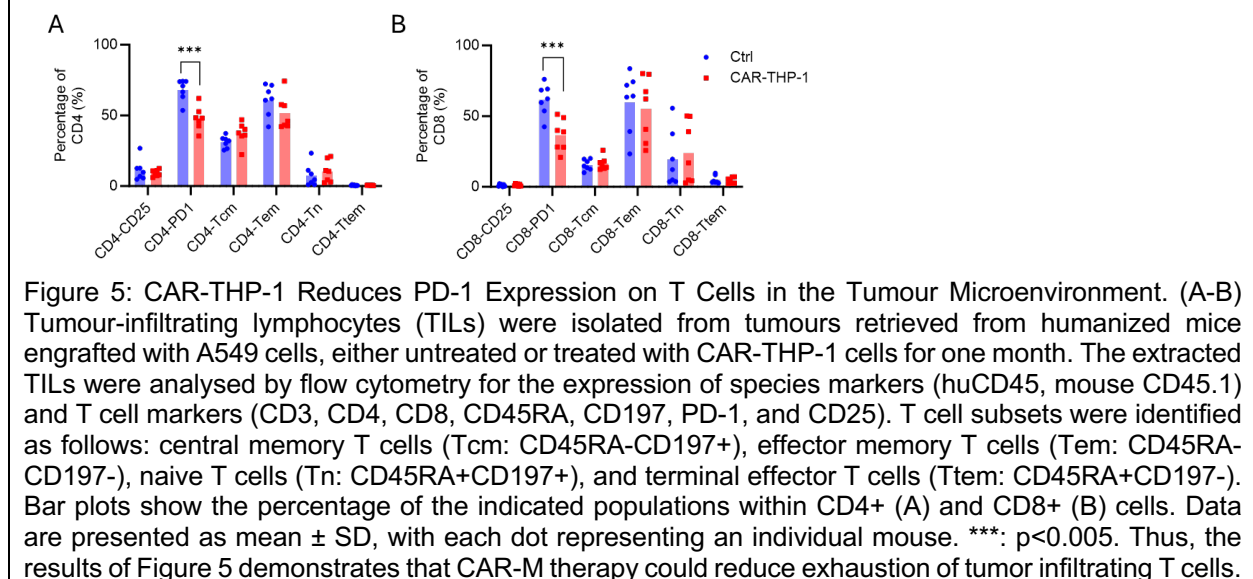


Figure 5: CAR-THP-1 Reduces PD-1 Expression on T Cells in the Tumour Microenvironment. (A-B) Tumour-infiltrating lymphocytes (TILs) were isolated from tumours retrieved from humanized mice engrafted with A549 cells, either untreated or treated with CAR-THP-1 cells for one month. The extracted TILs were analysed by flow cytometry for the expression of species markers (huCD45, mouse CD45.1) and T cell markers (CD3, CD4, CD8, CD45RA, CD197, PD-1, and CD25). T cell subsets were identified as follows: central memory T cells (Tcm: CD45RA-CD197+), effector memory T cells (Tem: CD45RA-CD197-), naive T cells (Tn: CD45RA+CD197+), and terminal effector T cells (Ttem: CD45RA+CD197-). Bar plots show the percentage of the indicated populations within CD4+ (A) and CD8+ (B) cells. Data are presented as mean $\pm$ SD, with each dot representing an individual mouse. ***: $p < 0.005$. Thus, the results of Figure 5 demonstrates that CAR-M therapy could reduce exhaustion of tumor infiltrating T cells.

Claims

Claim 1. A Chimeric Antigen Receptor (CAR) construct comprising an antigen binding domain, a hinge region, a transmembrane domain, and an intracellular domain connected in sequence;

wherein the intracellular domain comprises at least one costimulatory signaling domain, comprising a TLR4 TIR signaling domain and a 4-1BB signaling domain connected in sequence;

wherein the TLR4 TIR signaling domain is constructed to be positioned adjacent to the transmembrane domain.

Claim 2. The CAR construct according to Claim 1, wherein the antigen binding domain comprises an scFV targeting an antigen.

Claim 3. The CAR construct according to Claim 2, wherein the antigen is a tumour-specific antigen or a tumour-associated antigen.

Claim 4. The CAR construct according to Claim 2 or 3, wherein the antigen is selected from a group consisting of PD-L1, B7-H3, B7-H4, B7-H5, B7-H6, B7-H7, PD1, CD19, CD123, CD70, Her2, mesothelin, claudin 6, BCMA, and EGFR.

Claim 5. The CAR construct according to any one of Claim 1 – 4, wherein the hinge region comprises a CD8a, CD28, or C6 hinge region.

Claim 6. The CAR construct according to any one of Claims 1 – 5, wherein the transmembrane domain comprises a CD8a, CD28, or TLR4 transmembrane domain.

Claim 7. The CAR construct according to Claim 1, wherein the intracellular domain comprises an amino acid sequence of SEQ ID NO: 1 or an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1.

Claim 8. The CAR construct according to Claim 1, wherein the intracellular domain comprises an amino acid sequence encoded by a nucleic acid sequence of SEQ ID NO: 3 or a nucleic acid sequence at least 95% identical to the nucleic acid sequence of SEQ ID NO: 3.

Claim 9. The CAR construct according to Claim 1, wherein the CAR construct comprises an amino acid sequence of SEQ ID NO: 2 or an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 2.

Claim 10. The CAR construct according to Claim 1, wherein the CAR construct comprises a nucleic acid sequence of SEQ ID NO: 4 or a nucleic acid sequence at least 95% identical to the nucleic acid sequence of SEQ ID NO: 4.

Claim 11. A mononuclear phagocyte cell expressing the CAR construct according any one of Claims 1 – 10, wherein the mononuclear phagocyte cell is a monocyte or a macrophage.

Claim 12. The mononuclear phagocyte cell according to Claim 11, wherein the mononuclear phagocyte cell is (i) primary mononuclear phagocyte cell directly isolated from a biological source, or (ii) iPSC-derived mononuclear phagocyte cell differentiated from an induced pluripotent stem cell.

Claim 13. The mononuclear phagocyte cell according to Claim 11 or 12, wherein the monocyte is THP-1 cell.

Claim 14. Use of the mononuclear phagocyte cell according to any one of Claim 11 – 13 in the manufacture of a medicament for treatment of a target tumour.

Claim 15. The use according to Claim 14, wherein the target tumour is a solid tumour.

Claim 16. The use according to Claim 15, wherein the solid tumour is selected from a group consisting of lung, colon, breast, testicular, ovary, bladder, uterine, cervical, pancreatic, esophageal and stomach tumour.

Claim 17. The use according to any one of Claims 14 – 16, wherein the treatment comprises reducing a burden of the target tumour.

Claim 18. The use according to Claim 17, wherein the burden of the target tumour comprises a volume of the solid tumour.

Claim 19. A mononuclear phagocyte cell for use in the treatment of target tumour, wherein the mononuclear phagocyte cell is according to any one of Claims 11 – 13.

Claim 20. The mononuclear phagocyte cell for use in the treatment of tumour according to Claim 19, wherein the target tumour is a solid tumour.

Claim 21. The mononuclear phagocyte cell for use in the treatment of tumour according to Claim 20, wherein the solid tumour is selected from a group consisting of lung, colon, breast, testicular, ovary, bladder, uterine, cervical, pancreatic, esophageal and stomach tumour.

Claim 22. A method of treatment comprising administering the mononuclear phagocyte cell according to any one of Claims 11 – 13 to a subject with a tumour.

Claim 23. The method of treatment according to Claim 22, wherein the tumour is a solid tumour.

Claim 24. The method of treatment according to Claim 23, wherein the solid tumour is selected from a group consisting of lung, colon, breast, testicular, ovary, bladder, uterine, cervical, pancreatic, esophageal and stomach tumour.

Claim 25. The method of treatment according to any one of Claims 22 – 24, wherein the treatment comprises reducing a load of the target tumour.

Claim 26. The method of treatment according to Claim 25, wherein the load of the target tumour is a volume of the solid tumour.

Claim 27. Use of the CAR construct according to any one of Claims 1 – 10 for inducing a mononuclear phagocyte cell towards an M1 phenotype, wherein the mononuclear phagocyte cell is engineered to express the CAR construct, wherein the mononuclear phagocyte cell is a monocyte or a macrophage.

Claim 28. The use according to Claim 27, wherein the mononuclear phagocyte cell is (i) primary mononuclear phagocyte cell directly isolated from a biological source, or (ii) iPSC-derived mononuclear phagocyte cell differentiated from an induced pluripotent stem cell.

Claim 29. The method of inducing a monocyte or a macrophage towards an M1 phenotype, wherein the a monocyte or a macrophage is engineered to express the CAR construct according to any one of Claims 1 – 10, wherein the mononuclear phagocyte cell is a monocyte or a macrophage.

Claim 30. The method according to Claim 29, wherein the mononuclear phagocyte cell is (i) primary mononuclear phagocyte cell directly isolated from a biological source, or (ii) iPSC-derived mononuclear phagocyte cell differentiated from an induced pluripotent stem cell.

Claim 31. Use of the mononuclear phagocyte cell according to any one of Claims 11 – 13 in the manufacture of a medicament for mediating activities of T cells.

Claim 32. Use of the mononuclear phagocyte cell according to Claim 30, wherein the T cells are tumour-infiltrating T cells.

Claim 33. The use of the mononuclear phagocyte cell according to Claim 30, wherein the T cells include CD4+ T cells, CD8+ T cells, or both.

Claim 34. The use of the mononuclear phagocyte cell according to Claim 30, wherein the mononuclear phagocyte cell reduces exhaustion of the T cells.

Claim 35. Use of the mononuclear phagocyte cell according to any one of Claims 11 – 13 in the manufacture of a medicament for modulating a microenvironment of a solid tumour.

Claim 36. The use of the mononuclear phagocyte cell according to Claim 35, wherein the solid tumour is selected from a group consisting of lung, colon, breast, testicular, ovary, bladder, uterine, cervical, pancreatic, esophageal and stomach tumour.

Claim 37. An intracellular domain of a Chimeric Antigen Receptor (CAR) construct,
wherein the intracellular domain comprises at least one costimulatory signaling domain, comprising a TLR4 TIR signaling domain and a 4-1BB signaling domain connected in sequence;

wherein the TLR4 TIR signaling domain is constructed to be positioned adjacent to a transmembrane domain to be connected to the intracellular domain.

Claim 38. The intracellular domain according to Claim 37, wherein the intracellular domain comprises an amino acid sequence of SEQ ID NO: 1 or an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1.

Claim 39. The intracellular domain according to Claim 37, wherein the intracellular domain comprises an amino acid sequence encoded by a nucleic acid sequence of SEQ ID NO: 3 or a nucleic acid sequence at least 95% identical to the nucleic acid sequence of SEQ ID NO: 3.