A DNA plasmid melanoma cancer vaccine, SCIB1, combined with nivolumab + ipilimumab induces functional CD4 and CD8 T cell responses in patients with advanced unresectable melanoma

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1. Background: what is SCIB1?

- SCIB1 is an off-the-shelf DNA vaccine designed to induce tumour-specific T cell responses against melanoma antigens TRP-2 and gp100.
- CD8 and CD4 T cell epitopes from TRP-2 and gp100 are incorporated into an antibody framework which allows Fc targeting of activated dendritic cells to elicit a dual mechanism of action:
  - **Direct presentation:** uptake of plasmid and expression of engineered antibody by antigen-presenting cells.
  - **Cross presentation:** secretion of the engineered antibody which is targeted to CD64 FcγR present on dendritic cells via its Fc domain.
- SCIB1 is currently being evaluated in the phase 2 **SCOPE trial** in combination with checkpoint inhibitors for patients with advanced unresectable melanoma.
- So far in this setting, SCIB1 has shown **84% disease control** rate, **80% progression free survival** rate, **72% overall response** rate, and **20% complete response** rate.

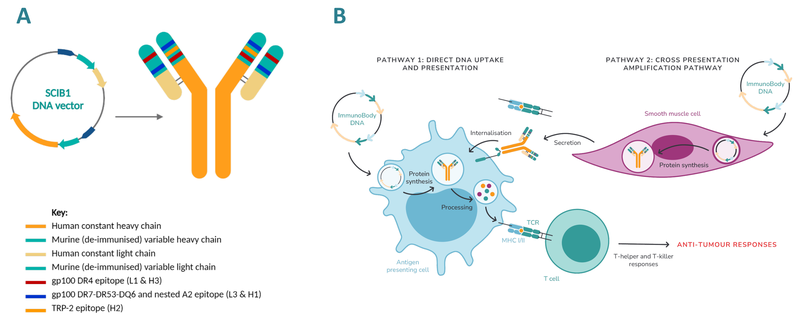


Figure 1. (A) SCIB1 is an off-the-shelf DNA vaccine which incorporates CD8 and CD4 T cell epitopes from melanoma antigens TRP-2 and gp100 into an APC targeting antibody framework. (B) SCIB1 elicits anti-tumour immune responses via dual mechanisms of direct presentation and cross presentation.

2. SCOPE trial study design

- Phase 2, multicenter, open-label study of the SCIB1 vaccine with ipilimumab plus nivolumab (cohort 1) or pembrolizumab (cohort 2).
- Eligible patients with stage IIIB/IV unresectable melanoma were treated with ipilimumab, nivolumab and SCIB1 (8mg i.m.) via the needle-free injection device Stratis® (Pharmajet).
- SCIB1-specific T cell responses were assessed via a combination of IFNγ ELISpot, single-cell RNA- & TCR-seq and TCR repertoire analysis.
- Presented here are data on functional T cell responses for 41 patients enrolled in cohort 1 (SCIB1 plus ipilimumab and nivolumab).

3. SCIB1 induces CD4 and CD8 T cell responses

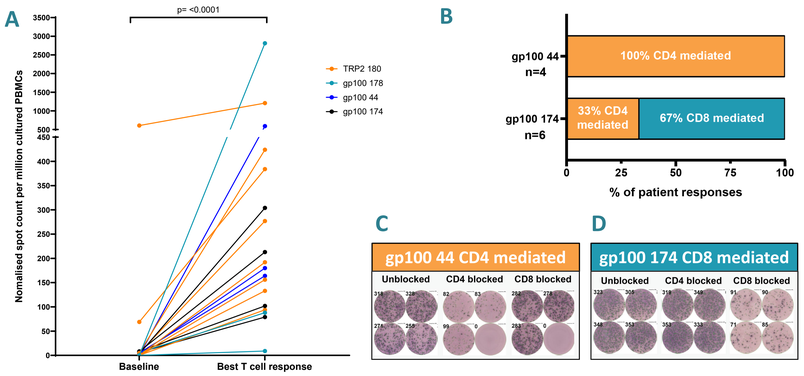


Figure 2. T cell responses to SCIB1 peptides assessed by cultured ELISpot. (A) Best ELISpot response to a SCIB1 peptide for patients who received ≥3 doses of SCIB1 (n=18). (B) Summary of CD4 and CD8 mediated responses for some patients with strong responses to gp100 peptides. (C-D) representative examples of (C) a CD4 mediated response to gp100 44 and (D) a CD8 mediated response to gp100 174.

4. Isolation of SCIB1 specific TCRs

- Single cell RNA- and TCR-sequencing was performed on IFNγ+ CD8 T cells sorted from 3 patients with strong responses to SCIB peptide(s).
- 2 patients with TRP-2 responses (data for patient 02-004 shown below) and 1 patient with a gp100 174 response.

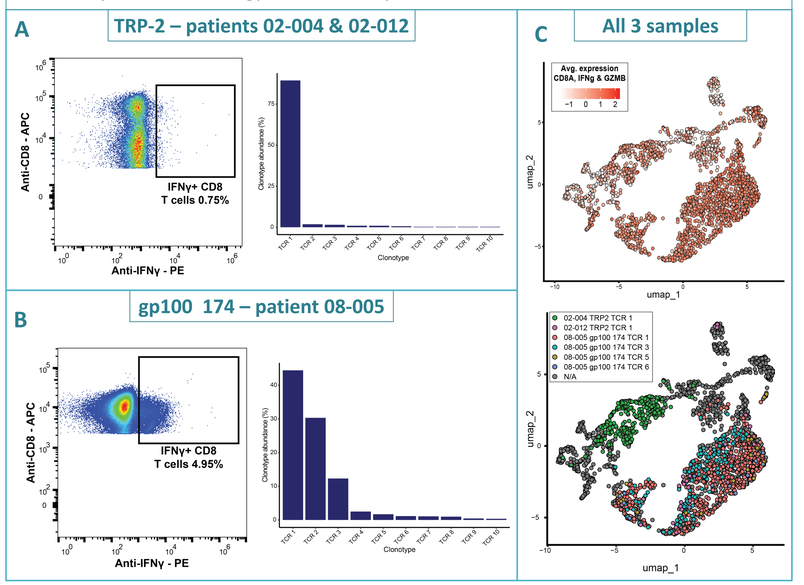
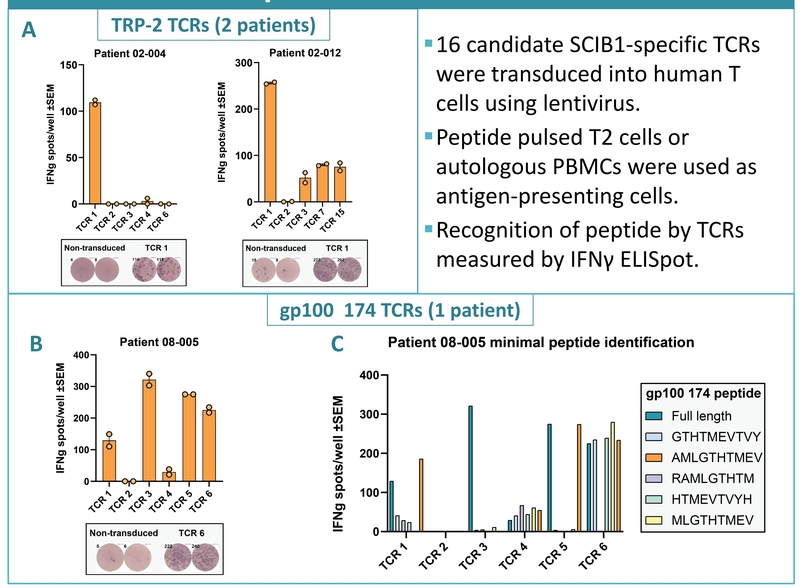


Figure 3. RNA- and TCR-sequencing was performed on sorted IFNγ+ CD8 T cells following stimulation with a SCIB peptide. (A-B) Sorting of IFNγ + CD8+ T cells and TCR clonotype abundances of the sorted cells for (A) patient 02-004 (TRP-2 stimulation) and (B) patient 08-005 (gp100 174 stimulation). (C) (Top) RNA sequencing data showing the average CD8A, IFNγ and granzyme B expression for sorted T cells for each patient. (Bottom) Cells expressing any of the 6 SCIB1-reactive TCRs are highlighted.

5. Six SCIB1-specific TCRs were characterized



- 16 candidate SCIB1-specific TCRs were transduced into human T cells using lentivirus.
- Peptide pulsed T2 cells or autologous PBMCs were used as antigen-presenting cells.
- Recognition of peptide by TCRs measured by IFNγ ELISpot.

Figure 4. Recognition of peptide pulsed (10 µg/mL) target cells by TCR transduced T cells. (A) From 2 patients, 10 candidate TRP-2 TCRs were tested. (B) From 1 patient, 6 candidate gp100 174 TCRs were tested. (C) Recognition of overlapping 9-mer and 10-mer peptides for candidate gp100 174 TCRs.

6. SCIB1 induced vaccine-specific TCR expansion

- Bulk TCR α and β sequencing performed on *ex vivo* CD8+ T cells sorted from pre-vaccination and on-treatment PBMC samples.

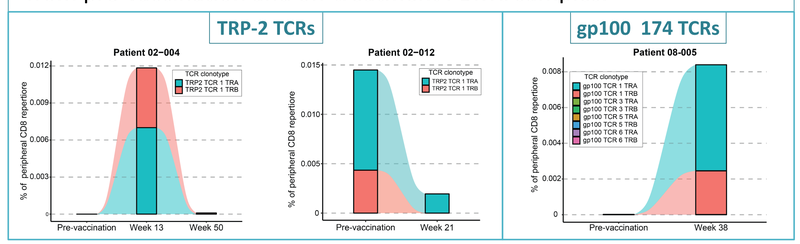


Figure 5. Abundance of each TCR α (TRA) and TCR β (TRB) chain for each validated SCIB-reactive TCR clonotype in the *ex vivo* peripheral CD8+ T cell repertoire of the corresponding patient.

7. Conclusions

- SCIB1 combined with nivolumab and ipilimumab consistently induced functional CD4 and CD8 T cell responses to melanoma antigens.
- 6 SCIB1-specific TCRs identified and functionally validated.
- 2 out of 3 patients showed demonstratable vaccine induced expansion of SCIB1-specific TCR clonotypes following SCIB1 vaccination.
- The longer gp100 174 peptide induced an oligoclonal repertoire of vaccine-specific TCRs, whereas the shorter TRP-2 180 peptide induced largely monoclonal TCR repertoires.

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