A Clinical trial of a DNA vaccine (SCIB1) that targets dendritic cells in vivo in fully resected melanoma patients; a vaccine to prevent disease recurrence?

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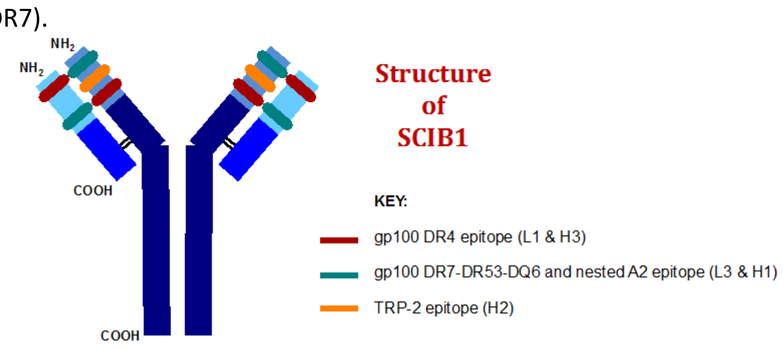
Introduction:

SCIB1 design

• SCIB1 is a DNA vaccine (ImmunoBody®) that encodes for a human IgG1 antibody.

•SCIB1 has four epitopes from two melanoma antigens (three from gp100 and one from TRP-2) engineered into its CDR region.

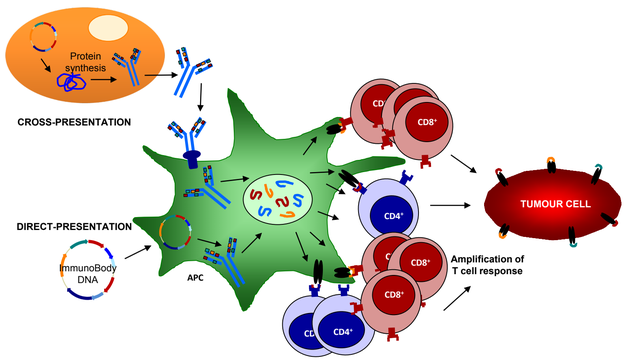
• Two epitopes stimulate CD8 responses (TRP2 and gp100-A2) and two stimulate CD4 responses (gp-100-DR4 and gp100-DR7).



SCIB1 mode of action

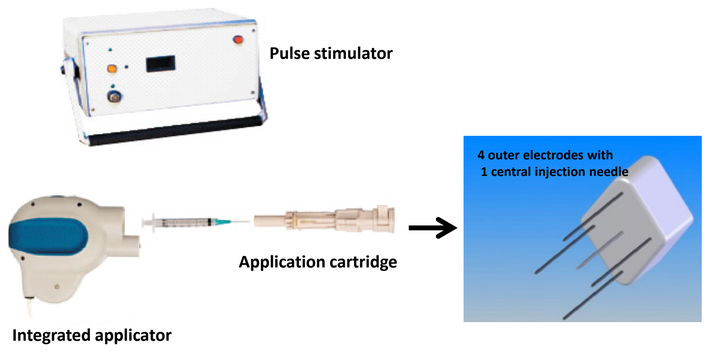
• SCIB1 targets dendritic cells *in vivo* via the high affinity Fc receptor, CD64. By a combination of CROSS PRESENTATION and DIRECT PRESENTATION it stimulates the production of T cells that have:

• HIGH FREQUENCY
• HIGH AVIDITY
• POTENT ANTI-TUMOUR CAPABILITIES



Methods:

• 16 patients with fully resected stage III (9) or stage IV (7) melanoma, were immunised with 2-4mg of SCIB1 by intramuscular electroporation at 3 weekly intervals, then subsequently at 3 and 6 months. Patients tolerating treatment were allowed to continue treatment for up to 5 years receiving further vaccinations every 3 months.



• Immune responses (PBMC) were monitored by assaying proliferation (by uptake of ^{3}H –thymidine) and the secretion of IFNγ (cultured elispot)

Results –Clinical responses:

Safety profile

• SCIB1 was safe and well tolerated.

• More than 190 doses were administered.

• No common term criteria adverse events (CTC AE) grade 4/5 toxicities that were associated with SCIB1 were reported.

• The most common adverse advents were injection site reactions e.g. pain, tenderness, bruising and swelling.

Summary of clinical responses

• Only 5/16 patients have has a recurrence of disease at 4, 14, 17, 18 and 30 months

• All other patients have been disease-free for between 27 and 46 months since study entry.

•Median survival for stage III patients (n=9) is 34 months and 31 months for Stage IV patients (n=7).

•ALL PATIENTS REMAIN ALIVE

Fig A: Swimmer plot showing disease staging, disease recurrence, treatment milestones and current trial status of fully resected patients (n=16):

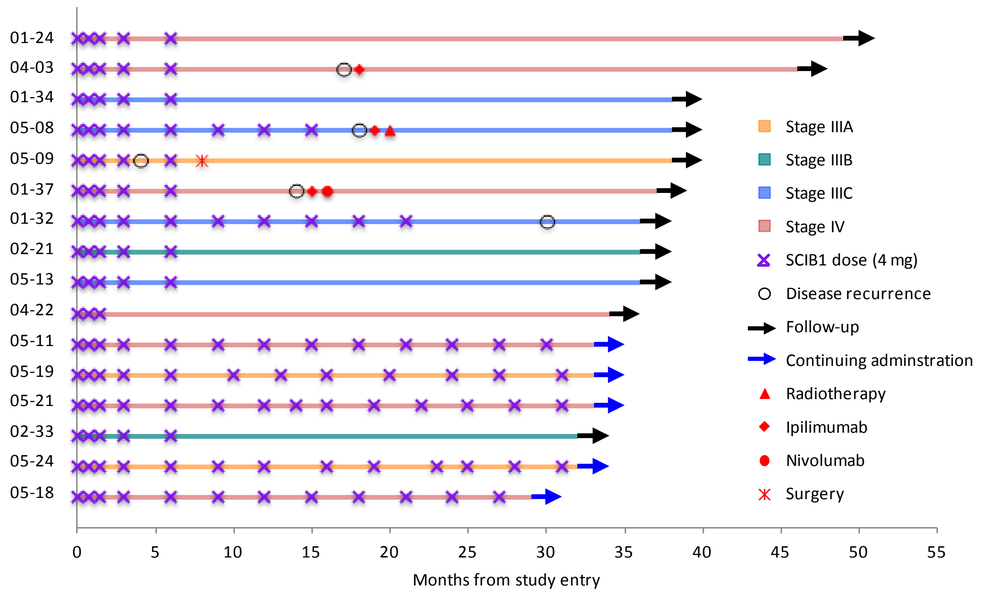


Fig B: Kaplan-Meier analysis of the recurrence-free survival of patients with fully resected tumour at study entry (n=16):

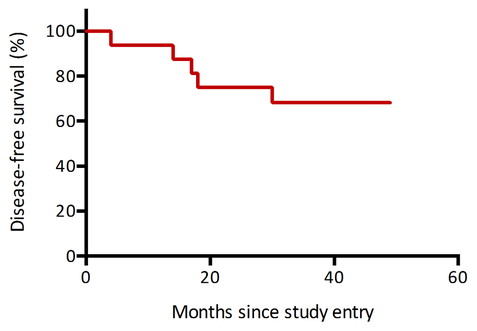


Fig C: Summary of recurrence-free survival of fully resected patients by disease stage:

Fully resected melanoma patients	No patients	Disease-free survival (%)	Died (%)
Stage III/IV	16	69	0
Stage III	9	67	0
Stage IV	7	71	0

Results - immune responses:

Summary of immune responses

• All 16 patients showed a vaccine-epitope specific proliferation response *ex vivo* and an IFNγ Elispot response *in-vitro* following T-cell expansion.

• Twelve patients responded to all 4 epitopes, two patients to 3 epitopes, one patient to 2 epitopes and one patient to 1 epitope.

• All patients who continued treatment (n=7) showed strong T-cell memory responses following 3 monthly boosts with SCIB1.

• Six of the seven patients on continuation therapy increased their repertoire of melanoma epitopes recognised during this treatment phase.

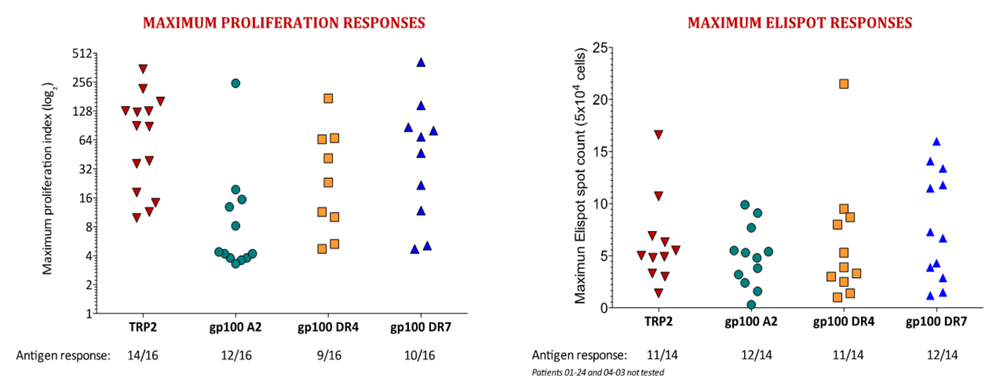
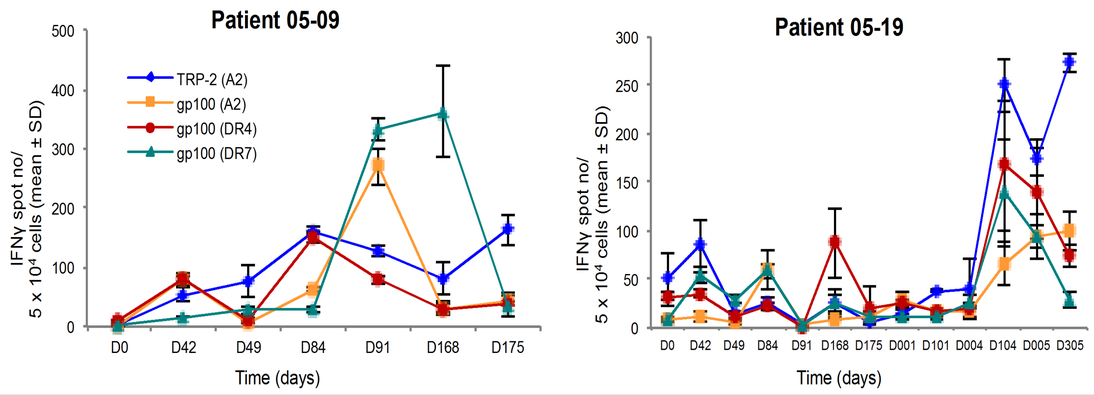


Fig D:Maximum proliferation and Elispot responses to melanoma-derived epitopes in fully resected patients (n=16).

Fig E: Typical INFγ Elispot reponses following challenge by melanoma-derived epitopes.
05-09 responded to all four epitopes during the course of the trial.
As exemplified by 05-19, all patients receiving continuation therapy showed strong memory responses following 3 monthly boosts.



Conclusion

These results suggest that a DNA vaccine encoding epitopes from melanoma antigens that targets dendritic cells can induce measurable T- cell responses, furthermore, it may confer protection from the recurrence of melanoma with little associated toxicity. SCIB1 deserves further evaluation as an adjuvant therapy.