Chimeric Antigen Receptors (CARS)

- A total of 30 children and adults received CTL019. Complete remission was achieved in 27 patients (90%), including 2 patients with blinatumomab-refractory disease and 15 who had undergone stem-cell transplantation.

- All the patients had the cytokine-release syndrome. Severe cytokine-release syndrome, which developed in 27% of the patients, was associated with a higher disease burden before infusion and was effectively treated with the anti-interleukin-6 receptor antibody tocilizumab.
CANCER IMMUNOTHERAPY

- Monoclonal antibodies
  - checkpoint inhibitors
  - Redirected T cells

- Adoptive T cell transfer
  - Tumour infiltrating lymphocytes (TILs)
  - Chimeric antigen receptors (CAR) T cells

- Cancer Vaccines
  - Oncolytic viruses
  - vaccines
VACCINES

- Stimulate *de novo* CD4 and CD8 T cell responses
- CD4+ or helper T cells (Th1) can reverse the immunosuppressive tumour environment
- CD8+ or killer T cells (CTL) directly kill tumour cells

1st GENERATION VACCINES:
Rosenberg, Nature Medicine (2004) - 3% clinical response rate to vaccines
- 4% for peptide vaccines
- 0% for viral encoded vaccines
- 4% for native or modified tumour cells
- 7% for dendritic cell vaccines (Provenge)

PROBLEMS:
- They did not stimulate potent T cells that could overcome the immunosuppressive environment and kill tumours
- T cells recognising self antigens may have been deleted
SECOND GENERATION VACCINES – TVEC

- **T Vec, Talimogene laherparapvec (Amgen)**
  - Oncolytic viruses injected into the tumour
  - Risk is do not surgically remove the lesions
  - Very good response to the injected lesion but weaker response to other lesions
  - Approved for Stage IV melanoma
  - Combination studies with checkpoint inhibitors

- Overcomes immunosuppressive environment due to viral infection and tumour cell lysis

  **BUT...**

- Uses the tumour as the immunogen so immunises with the same dominant epitopes the tumour has already evolved to avoid
**Figure 1. The prevalence of somatic mutations across human cancer types**

Every dot represents a sample while the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase while the different cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We would like to thank Gad Getz and colleagues for the design of this figure\textsuperscript{26}. 

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**MUTANOME**

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IMMUNISE AGAINST NEO-EPITOPES

Synthesize long peptides containing the neoepitopes

Select neoepitopes on basis of diversity of HLA alleles, peptide characteristics, etc.

Test ability of neoepitopes to stimulate patient’s T cells

Eliminate unstable or hard-to-manufacture neoepitopes

Determine if predicted neoepitopes are presented

Refine first list through DAI and other different-from-self criteria

Predict potential 8-mers neoepitopes by NetMHC or similar tool

HLA haplotyping

PBMCs as normal tissue

Cancer tissue

Exome

Transcriptome

Compare and identify SNVs

Relevant cancer-specific SNVs ⇒ Identify SNVs restricted to the cancer transcripts

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Making CANCER VACCINES WORK

Dr Richard Goodfellow: CEO
Prof Lindy Durrant: CSO
# ImmunoBody® and Moditope®

<table>
<thead>
<tr>
<th>ImmunoBody®</th>
<th>Moditope®</th>
</tr>
</thead>
<tbody>
<tr>
<td>High avidity CD8+ T cell responses</td>
<td>Potent CD4+ T cell responses</td>
</tr>
<tr>
<td>DNA product</td>
<td>Peptide or DNA product</td>
</tr>
<tr>
<td>Eradicates small primary and metastatic tumours</td>
<td>Eradicates large bulky tumours</td>
</tr>
<tr>
<td>Checkpoint inhibitors may enhance responses</td>
<td>No requirement for checkpoint inhibitors</td>
</tr>
<tr>
<td>Potent killer cells induced</td>
<td>Reverses immunosuppressive tumour environment</td>
</tr>
<tr>
<td>Targets tumour-associated antigens</td>
<td>Targets modified self-antigens</td>
</tr>
</tbody>
</table>
**IMMUNOBody® - Dual Mechanism of Action**

- Combination of **CROSS-PRESENTATION**...
- ...with **DIRECT-PRESENTATION**
- Results in amplification of immune response to induce **HIGH FREQUENCY, HIGH AVIDITY** T cells
- Potent **ANTI-TUMOR** response

---

*Metheringham et al., Mabs 2010*
SCIB1 INDUCES HIGHER AVIDITY T CELLS THAN OTHER VACCINES

- Whole antigen DNA or peptide alone induce low frequency, low avidity responses

![Graph showing the comparison of different vaccine types in terms of cytotoxicity](image)

*Pudney et al., 2010 EJI*
ICHOR TRIGRID™ DELIVERY SYSTEM

- Uses electrical fields to increase DNA drug delivery efficiency
- Electrode array consists of four electrodes in a diamond-shaped grid around a central injection needle
- Simple hand-held device developed for use in humans
- Can deliver equivalent doses in man to mouse
- IM easier to deliver in humans than ID
SCIB1 IMMUNOBODY: DESIGN OF PHASE 1/2 TRIAL

PART 1 – Dose escalation in 17 patients with stage III/IV melanoma (with or without tumor)

- Primary Objective – safety and tolerability
- Secondary Objectives – immune responses; tumor responses

Dose escalation with safety assessment after 3 doses (0.4 mg, 2 mg, 4 mg, 8 mg)

PART 2 – Extension phase in 18 patients with fully-resected stage III/IV melanoma

- Primary Objective – safety and tolerability
- Secondary Objectives – immune responses; disease free survival

STUDY SCHEDULE

- Patients dosed at Weeks 0, 3 and 6 weeks with boosts at 3 and 6 months
- Immune samples taken pre- and post-dosing
- Optional continuation phase with dosing every 3-6 months for up to 5 years
SCIB1: EXCELLENT CLINICAL SAFETY PROFILE

- No dose-limiting toxicities observed
- No adverse events (AEs) leading to discontinuation of study treatment
- Vast majority of AEs were common toxicity criteria (CTC) grade 1 or 2
- No CTC grade 4 or 5 toxicities other than those related to disease progression and one episode of pneumonia (grade 4)
- Most common AEs were transient – injection site pain, tenderness, bruising and fatigue
- None of the serious AEs reported were related to study drug or study device
- Electroporation causes transient, but manageable, pain in some patients
- Study drug has been given on more than 220 occasions

Mild side effects of SCIB1 suggest treatment would be acceptable both in combination with checkpoint inhibitors and in early stage patients post-surgical resection (adjuvant setting)
3 of 9 patients in Part 1 receiving a 4-8 mg dose of SCIB1 have shown evidence of clinical activity:

- Patient 04-28 in Cohort 4 who received 8 mg SCIB1 showed a reduction in size in all lung lesions, resulting in a **partial response** as defined by RECIST by Week 9.

- Patient 04-16 in Cohort 3 who received 4 mg SCIB1 had a **differential response** in which multiple tumour lesions decreased in size or disappeared except for one lesion which was resected.

- Patient 04-27 in Cohort 4 who received 8 mg SCIB1 and had both lung and breast tumours at study entry, remained stable for 6 months.
SCIB1: SYNERGY IN COMBINATION WITH ANTI-PD.1

- Immunised with SCIB1, murine-specific anti-PD.1 antibody or both SCIB1 + anti-PD.1
- SCIB1 provides largely equivalent survival compared to inhibiting PD.1
- Combining anti-PD.1 therapy with SCIB1 significantly enhances survival, resulting in 85% survival of immunised mice
**Potential SCIB1 Combination Trial**

**Safety Run-In**
- 6 pts
  - Melanoma patients without evidence of response to pembrolizumab at 12 week assessment
  - SCIB1 4 mg
  - Pembrolizumab 2 mg/kg

**Stage 1**
- 12 pts
  - Pembrolizumab alone

**Stage 2**
- 4 pts
  - Pembrolizumab + SCIB1
  - ≥1 RECIST response required to progress to Stage 2
  - Considered worthy of further study if ≥3 RECIST responses

**Assumptions**
- Late response rate to pembrolizumab = 5%
- Response rate of interest for combination = 25%
- Total study size: **38 patients**

**Alternative A**
- Null response rate 10%, improved to 30%
- Total study size: 15 + 10 per arm, **56 patients**

**Alternative B**
- Randomize at start of pembrolizumab
- Null response rate 35%, improved to 55%
- Total study size: 21 + 18 per arm, **84 patients**
SCIB1 - SURVIVAL IN PATIENTS WITH RESECTED DISEASE

- 16 patients received 2-4 mg doses of SCIB1
  - All except one remain alive and only five have had disease recurrence
  - Median observation time = 45 months from study entry

- 4 patients received 8 mg doses of SCIB1 (recruited after 2-4 mg patients)
  - All remain alive and none have experienced disease recurrence
  - Median observation time = 14 months since study entry

- Overall, 20 patients with resected disease recruited – 19/20 REMAIN ALIVE

- Recurrence-free survival (RFS) and overall survival (OS) at 3 years: in first 16 patients

<table>
<thead>
<tr>
<th>Fully resected melanoma patients</th>
<th>SCIB1</th>
<th>Peptide vaccine ¹</th>
<th>Yervoy</th>
<th>Untreated ²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RFS (%)</td>
<td>OS (%)</td>
<td>RFS (%)</td>
<td>OS (%)</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>69</td>
<td>94</td>
<td>52</td>
<td>79</td>
</tr>
<tr>
<td>Stage III</td>
<td>67</td>
<td>89</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>Stage IV</td>
<td>71</td>
<td>86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results compare favorably to historical data
¹Slingluff et al 2011; ²Eggermont et al 2015; ³Sosman et al 2011; TBD = to be determined
**Potential SCIB1 or SCIB1+ Adjuvant Trial**

**Patient Population**
Melanoma patients with complete resection of:
- Stage IIB & IIC disease
- Stage IIIA-C disease
- Stage IV disease
- ECOG 0-1
- Adequate organ function
- Excluding uveal and ocular
- No prior adjuvant treatment

**Recruitment**
455 pts
SCIB1 or SCIB1+

**Follow-up for Relapse**
Primary analysis of RFS at 463 events*

**Approaches to Uncertainty Surrounding Treatment Effect Size**
Phase 2 data suggests that treatment effect may be greater than 0.73

- **Group Sequential Design** with early stop for greater efficacy
  Lan & DeMets alpha spend to control Type I error rate

- **Adaptive Design** with A vs B analysis at early interim by DMC to adjust sample size
  Control of Type I error rate may not meet regulatory standard
MODITOPE® - ADDRESSING THE LIMITATIONS

- Modified epitopes are targets for CD4+ T cells in autoimmune diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS)
- When normal cells are stressed or dying, they start to digest their own internal proteins (autophagy)
- Activated enzymes modify the digested protein fragments within autophagosomes and convert certain arginine amino acids to citrulline
- CD4+ T cells recognise these modified epitope

CAN THESE T CELLS BE HARNESSED TO KILL TUMOUR CELLS?

**ARGININE**
(+ charge)

**CITRULLINE**
(neutral)

Purified PAD activity
(peptidylarginine deiminase)

Ca^{2+}
THE MODITOPE CONCEPT

- Moditopes taken up by Antigen Presenting Cells (APC)
- Presented on APC cell surface
- Activation and expansion of CD4+ killer T cells
- Induction of IFNγ at the tumor site
- Induces expression of MHC Class II & cit-peptide
- **DIRECT KILLING**
**Vim-1, Vim-2 and Eno-1 Stimulate Potent Responses Against Established Tumors**

- B16 tumor established in transgenic HLA-DR4 mice (Day 1)
- Single immunisations of Vim-1 and Vim-2 and/or Eno1 administered on Day 4 (with CpG-MPLA adjuvant) at 25 μg doses

*Brentville et al., Cancer Research 2016*
Potential Modi-1 Combination Trial

Dose Escalation

10 pts 'vaccine' esc. design

- Modi-1 dose escalation

Stage 1

- 15 pts 'vaccine' esc. design
- 10 pts Modi-1 alone

Stage 2

- 10 pts Modi-1 alone

Patient Selection

To be considered - based on vimentin and/or enolase expression or epithelial mesenchymal transition features

- but may not be required

Assumptions

Null response rate = 10%
Response rate of interest for combination = 30%
Total study size: 85 patients

Stage 1:
- 15 pts 'vaccine' esc. design
- 10 pts Modi-1 alone

Stage 2:
- 10 pts Modi-1 alone

≥2 RECIST responses required to progress to Stage 2
Considered worthy of further study if ≥6 RECIST responses
MODITOPE® - A BROAD PLATFORM

- Many proteins can be citrullinated
  - Adenylylclase associated protein, α-enolase, aggregan, albumin, aldolase, anti-thrombin, asporin, β-actin, B23, BiP, calreticulin, capping protein α-1 subunit, cartilage intermediate layer protein, cathepsin D, co-activator complex, collagen, elongation factor 1α, F-actin, far upstream element-binding proteins 1 and 2, fibrinogen, filaggrin, glucose regulated protein, heparin binding protein, histamine receptor, histone, HSP60, HSP90, mitochondrial aldehyde dehydrogenase, nucleophosmin, phosphoglycerate kinase 1, protein disulphide-isomerase ER60 precursor, vimentin

- Any of these could be targets for incorporation into Moditope® immunotherapies

- Other post-translational modifications also occur
  - Homocitrullination
  - Oxidation of tryptophan
  - Deamination of glutamine or asparagine

- Many such modified amino acids have been found within MHC-bound peptides, indicating they may also be targets for immunotherapy
SUMMARY

- Two powerful immunotherapy platforms delivering ultra-high T cell avidity (making cancer vaccines work)

- Lead ImmunoBody® product SCIB1 delivering outstanding survival in resected stage III/IV patients with metastatic melanoma

- Second ImmunoBody®, SCIB2 for NSCLC, starting preclinical development/GMP manufacturing 2016

- SCIB1 checkpoint combination trial led by Prof Flaherty scheduled for 2017

- Moditope platform based on novel citrullination MoA

- Modi-1 phase 1/2 clinical Proof of Concept monotherapy in advanced breast and ovarian cancer and osteosarcoma starting 2H 2017
SUMMARY

Early tumours
Vaccines
Non-toxic
Potent T cell

Late tumours
Checkpoint inhibitors, CAR T cells, redirected T cells
Oncolytic vaccines
Combinations of vaccines and checkpoint inhibitors
Toxic
Overcome immune suppression
ImmunoBody® and Moditope®

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University of Nottingham
Prof Poulam Patel, Prof Durrant

University of Manchester
Dr Paul Lorigan

University of Newcastle
Prof Ruth Plummer

Leeds Teaching Hospitals NHS
Dr Clive Mulatero

University of Southampton
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Wei Xue
Lee Machado
Ian Daniels
Katherine Cook
Tracey Pitt
Mo Gijon

Nottingham

Using Immunology to Fight Cancer

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