Clinical Development of Adoptive Cell Therapy

Robert Hawkins
Medical Oncology, University of Manchester and The Christie Hospital
Adoptive Cell Therapy

- Two basic approaches
  - Natural T cells
    - Isolated from blood
    - Isolated from tumour
  - Genetically Engineered T cells
    - Engineered from blood lymphocytes
      - TCR based receptors
      - Antibody based chimeric receptor

Isolation/ Engineering and expansion of tumour specific T cells
Collect T-cells from Patient
T-cells returned to Patient
Considerations for Clinical Delivery of ACT

- Complex/Personalised so the efficacy bar will be high
- Need to comply with EU GMP regulations
- Main attractions
  - Short-term treatment
  - Long-term benefit
- Main Drawbacks
  - Complex/Costly
  - Toxicity of supportive therapy
    - Pre-conditioning chemotherapy
    - Supporting Cytokines
- Practical Challenges
  - How to role out to multiple centers
Overview

• Overview of Adoptive Cell Therapy
• Setting up a GMP unit for ACT
• Developing TIL therapy for Melanoma in UK
  – Planned Trials
• Engineered T-cell Trials in Manchester
  – CEA
  – CD19
• EU FP7 ATTACK – Trials targeting NY-ESO-1
Pre-clinical Evidence for TIL Therapy

1. Surgery to remove tumour sample

2. Cut Excised Tumour into 2-3 mm pieces

3. Culture bulk tumour in plates + IL-2

4. T cells Expand 2-3 weeks

5. Rapid Expansion Protocol – 2 weeks

6. “Pre-conditioning Therapy” with Cyclophosphamide and Fludarabine

7. Safety and Numbers analysed in vitro Cells Concentrated

8. Return cells to patient + supportive therapy with IL2

Patient with Melanoma

TIL Product

TIL Treatment
Setting This Up in Manchester
Cellular Therapeutics Unit (CTU)

- Move away from classical clean rooms
- Provides a controlled sterile environment
- Protects patients cells from infection or contamination
- Allows rapid decontamination with vaporised hydrogen peroxide
- Allows multi product processing
- Closed Systems outside isolators
- REP entirely in WAVE bioreactors
Where are we going with TIL ?
Trials with TIL

• Randomized Phase II trial
  – Salvage Therapy in Melanoma
  – High-Dose IL2 vs LD IL2
  – Single Centre UK Study

• Phase III Trial (PI John Haanen)
  – Randomized Trial vs Ipilimumab
  – Three Centre European Study
    (Amsterdam, Copenhagen, Manchester)
What is Special About Melanoma Biology?

Many tumour types have correlation of outcome with T-cell infiltration

Non-Synonomous Coding Mutations in Exome Sequences
Extending Cell Therapy to Other Diseases?
Engineered T cells
Receptor Development

Natural TCR

TCR-ζ

CAR scFv-ζ

CoStAR scFv-CD28

Second Generation CAR

Lamers 2009
Eshhar 1989
Hawkins1996
Finney1998
Why do use first generation CAR?

- TIL can be very effective
- Optimized 1\textsuperscript{st} generation CAR
- No benefit in animal models of 2\textsuperscript{nd} generation CAR in CD19 models
- Toxicity seen with second generation CAR in CD19 models
- Potentially important to ensure target safe before moving to enhanced receptors
Does CAR Interact with TCR? and is it important for function?

Natural TCR  scFv-ζ

α β

ε δ γ ε

ζ ζ

VH VL

ε δ γ ε

ζ ζ

VH VL
CARs with CD3ζ-transmembrane domain can integrate into the endogenous TCR complex

**EC50 values**

Symptomatic Lympho-proliferation

Fully Autologous Mouse Model of CD19-CAR Therapy

- Lympho-proliferation is largely CD4+ transduced cells

Clinical Trial Design: Based on other trials - TIL

1. Patient with advanced Cancer: *Assess presence of relevant target*

2. Collect T-cells from Patient and activate

3. Gene delivery to T cells with viral vector

4. Expansion of cell numbers

5. Cells Frozen: Safety and Efficacy Analysed in vitro

6. Return cells to patient -PLUS IL2

7. Trials designed to assess: Clinical Response, Modified Cell Survival, Safety

Tumour targeting Nucleic acid for
- T Cell Receptor
- Chimeric Receptor
Phase I : 1\textsuperscript{st} Generation CEA CAR T-cell Trial

- 14 patients treated
- Indication of biological and possible clinical activity
- T cell survival limited but some tumour localisation
- Only occurred with full pre-conditioning and high dose cells
- Coincided with maximum cytokine release
- Reversible Lung toxicity – ? Cross reacting antigen / low level CEA in lung
- No major responses (although one patient alive > 5 years)
- Trial halted
Overview of CD19 CAR Trial

CD19 Trials
HD37 – 1st Generation CAR

Low Dose Cyclophosphamide
Low Dose IL2

Dose Escalation Cells
## Summary of Patient characteristics

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Malignancy</th>
<th>Number of previous therapies</th>
<th>Number of T-cells infused (% transduced)</th>
</tr>
</thead>
<tbody>
<tr>
<td>002</td>
<td>54</td>
<td>DLBCL</td>
<td>3</td>
<td>$1 \times 10^9$ (25.7)</td>
</tr>
<tr>
<td>005</td>
<td>58</td>
<td>MCL</td>
<td>7</td>
<td>$1 \times 10^9$ (31.5)</td>
</tr>
<tr>
<td>006</td>
<td>57</td>
<td>MCL</td>
<td>4</td>
<td>$1 \times 10^9$ (54.6)</td>
</tr>
<tr>
<td>012</td>
<td>74</td>
<td>DLBCL from CLL</td>
<td>3</td>
<td>$1 \times 10^9$ (22.0)</td>
</tr>
<tr>
<td>013</td>
<td>62</td>
<td>DLBCL</td>
<td>2</td>
<td>$1 \times 10^{10}$ (20.5)</td>
</tr>
<tr>
<td>015</td>
<td>61</td>
<td>MZL</td>
<td>3</td>
<td>$1 \times 10^{10}$ (21.7)</td>
</tr>
<tr>
<td>016</td>
<td>52</td>
<td>DLBCL from FL</td>
<td>3</td>
<td>$6 \times 10^9$ (20.9)</td>
</tr>
</tbody>
</table>

Dose Escalation $10^9$ to $10^{10}$ cells
Rapid Response to Higher Dose CAR T-cells
CD19-013 - Course

- Developed Lymphomatous Meningitis
  - 50 Lymphoma : 1 CAR-T-cell in CSF

- Post Mortem Minimal Disease outside CNS

qPCR for transduced cells in post-mortem tissues
CD19-015 clinical results

Marginal zone lymphoma

Pre-treatment

Week 12 post infusion
CD3+/CD34+ cells over time
T-cell Survival / Biology

- T-cell survival better than CEA trial
- Evidence of Positive Selection in some patients
- ? Persistence better in DLBCL
  - Known to have strongest B7 Expression
Engineered T-cells Targeting CD19

- First Generation Receptor
- Low dose chemotherapy
- Low dose IL2
- Dose Escalation of Cells
  - Cohort 1: 2/4 PR
  - Cohort 2: 3/3 PR*
  - Good Persistence of CD19 T-cells - ? selection
- Generally Low Toxicity
  - transient neurotoxicity - ? mechanism
- Potential to combine earlier in treatment
Two key objectives

- Test Efficacy of ACT targeting NY-ESO-1 in Oesophagogastric cancer
- Test improved methods of cell transduction/expansion
  - Selecting CD62L + cells, expanding in IL7&IL15

Background

- Several CAR / TCR shown on target toxicity
- 1G4 TCR Targets HLA-A2 SLLMWITQC
  - Found in NY-ESO-1 and LAGE-1
  - Study at NCI found high response rate *
    - 4/6 in synovial sarcoma
    - 5/11 in melanoma
    - No On-target Toxicity
- Adaptimmune Developed Lentiviral Vector based on optimised TCR
  - Active in Sarcoma, Myeloma

* Robbins et al. J Clin Oncol, 2011: 29; 917-924
ATTACK: Trials

• OG Phase II
  – Up to 28 patients
  – Designed to establish RR in common solid Tumour
  – Opened November 2014

• Melanoma Phase II
  – Up to 34 patients
  – Designed to compare optimised production with Central Memory Type T-cells with Standard production

• Both Centralised Production
  • Manchester & Amsterdam

Key Strategic Objective:
To establish feasibility of multi-centre international trials with centralized production
Conclusions

• Cell Therapy has potential for wide range of cancers
  – Can be extremely effective and produce *durable* benefits
  – *May* be so effective because they target mutated antigens (truly tumour specific)
    • Targeting multiple targets may also be important
  – It is relatively complex but processes becoming standardised

• Engineered Cell Therapy – key challenges
  – Potentially very effective
  – Risk of “on-target” toxicity
  – *Appropriate Clinical Targets need to be defined*

• Challenges with Deliverability remain
  – Centralised vs Automated “Bedside” Production

• Engineering T-cells further to enhance efficacy and improved deliverability may facilitate improved clinical processes
Acknowledgements

Cellular Therapeutics Unit
Ryan Guest
Natalia Kirilova - CTL
Julie Duckworth - CTL
Martine Thomas - CTL
Fiona Baluwa

GMP assays & GCLP Clinical Monitoring Group
Dominic Rothwell
Debbie Burt

Experimental Cellular Therapy Group
David Gilham
Eleanor Cheadle
Vicky Sheard
John Bridgeman - CTL

CTU Design & Implementation
Ryan Guest
Nikki Price

Clinical Cell Therapy
Fiona Thistlethwaite
Was Mansoor
Manon Evans
Shien Chow
Lisa Bowden
Helen Ferns

Melanoma Group
Paul Lorigan
Jackie Hodgetts

Christie Hospital
Andrea Spencer-Shaw
Angela Cramer

Sponsor/Christie Clinical Trials Unit
Ian Emerson
Phil Barley
Angela Ball

GMP TIL Harmonisation Team
Bianca Heemskerk - NKI-AVL
Joost vd Berg - NKI-AVL
Marco Donia - CCIT/Herlev Hospital
Ryan Guest - University of Manchester

Research Management
Nicola Price - CTL
Helena Kondryn

TIL Advisors
Mark Dudley
Michal Besser

Surgeons
Aali Sheen
Piotr Krysiak
Gary Ross
Vijay Ramani

Adaptimmune
Daniel Williams
Helen Tayton-Martin
Dominic Smethurst

The Christie NHS Foundation Trust

Adaptimmune
transforming T cell therapy

Kay Kendall Leukemia Fund

Adaptimmune
Advanced Teaching and TRaining for Adoptive Cell Therapy