Adoptive Cell Therapy For Melanoma: 
A perspective on Tumour Infiltrating Lymphocyte Therapy

Robert Hawkins
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
What is TIL therapy?

- Type of Adoptive Cell Therapy – TILs, CAR-T, TCR
- Tumour Infiltrating Lymphocytes – white blood cells (T cells, B cells, NK cells)
- Natural anti-tumour mechanism – to identify, infiltrate and attack solid tumours
- Highly potent & highly selective for cancerous tissue
- However, tumour microenvironment often ‘switches off’ natural tumour-killing function of TILs
- TIL therapy involves isolation and massive ex-vivo expansion of T cells from TILs before re-infusion into same patient
- Large influx of TIL derived T cells, plus pre- and post-conditioning therapy to dampen immunosuppressive environment and further expansion of TILs in-vivo results in significant and durable responses in melanoma patients:
  - ~ 50% overall responses of which many remain as durable responses
  - 10-25% probably “cured”

**Blood – Cancer Specific**

_T-cells are very rare_

**Tumour - Cancer Specific**

_T-cells are enriched_

**Tumour - stained to show high levels of T-cells (in brown)**
Correlate of Immune Cells with Outcome

- Is it cause and effect?
- What are they recognising?

In Vitro Activity of TIL

Overall 90% success rate in growing melanoma TIL
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

Evolving Treatment
◆ RR 1990 20%
◆ RR 2010 50-75%
• CR 20-25%
## Historical TIL Studies

<table>
<thead>
<tr>
<th>Indication</th>
<th>Publication</th>
<th>Year</th>
<th>Responses</th>
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<tr>
<td>Melanoma</td>
<td>Dillman et al</td>
<td>1991</td>
<td>OR = 29%&lt;br&gt;CR = 5%</td>
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<tr>
<td>Melanoma</td>
<td>Rosenberg et al</td>
<td>1994</td>
<td>OR = 34%&lt;br&gt;CR = 6%</td>
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<td>Renal</td>
<td>Goedegebuure et al</td>
<td>1995</td>
<td>OR = 50%&lt;br&gt;CR = 0%</td>
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<tr>
<td>Gastric</td>
<td>Xu et al</td>
<td>1995</td>
<td>OR = 35%&lt;br&gt;CR = 13%</td>
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<tr>
<td>Renal</td>
<td>Figlin et al</td>
<td>1997</td>
<td>OR = 26%&lt;br&gt;CR = 9%</td>
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<tr>
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<td>Rosenberg et al</td>
<td>2011</td>
<td>OR = 56%&lt;br&gt;CR = 22%</td>
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<td>Cervical</td>
<td>Stevanovic et al</td>
<td>2015</td>
<td>OR = 33%&lt;br&gt;CR = 22%</td>
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Considerations for Clinical Delivery of ACT

• Complex/Personalised so the efficacy bar will be high
• Need to comply with EU GMP regulations

Main attractions
  – Manipulate cells outside body – free from immunological controls
  – Short-term treatment
  – Long-term benefit

Main Drawbacks
  – Complex/Costly
  – Toxicity of supportive therapy
    • Pre-conditioning chemotherapy
    • Supporting Cytokines
  – Potential on-target toxicity

Practical Challenges
Developing GMP Cell Therapy Manufacturing

- 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
Why Pre-Conditioning Chemotherapy?

- Effects on Tumour Microenvironment
  - Elimination of immune-suppressive cells
  - *For example* Treg, MDSC
- Enhances T-cell Engraftment
  - Increases homeostatic cytokines (IL7/IL15)
Schematic Representation of ACT process

Normal whole blood
- Monocytes (M)
- Lymphocytes (L)
- Neutrophils (N)
- Red blood cells (R)

After pre-conditioning chemotherapy
- M
- L
- N

Depletes White blood cells
- Fludarabine has a specific long term effect upon lymphocytes

Patients own Therapeutic TIL

Post TIL Therapy
- M
- L
- N
- R

TIL engraftment
- Manufactured TIL expand and make up a major compartment of the lymphocytes
Lymphocyte Recovery

**Average Lymphocyte**

- Days From Cells: -8 to 9
- Peripheral Blood Cell Count [Per mm³]: 0 to 2.5

**Lymphocyte**

- Days From Cells: -9 to 17
- Peripheral Blood Cell Count (per mm³): 0 to 7

Graphs showing the recovery of average lymphocytes and lymphocytes over time.
Practicalities of Therapy

- Admission
  - Median 16 days
  - Range 14 – 25
- On average 8 doses IL2 given
A straight forward case

Pre- Treatment  Post-Treatment
Patients on B-Raf Inhibitors
TIL with B-Raf Inhibitor

Female, 60 yr

Received 3.67x10^{10}

Previously failed B-raf inhibitors, anti-PD1 and Ipilimumab

December 2014

September 2015
Long-term benefits in CTL TIL Therapy: *relapse/refractory melanoma*

- Globally > 500 patients treated
  - RR 40-70%
  - CR 10-25% - almost all durable ? cures

Responses

- OR 58%
- PR* 42%
- CR 16%

* Some may become CR
Key Outcome – Durable Responses
Is more intensive therapy better?

Goff et al., J Clin Oncol. 2016 Jul 10;34(20):2389-97

Overall Survival

Progression-Free Survival

Response rate 45% vs 62%
Complete Response Rate 24% vs 24%
What is happening in TIL Therapy?

• NCI – trials of combinations
  – Pembrolizumab
  – B-Raf inhibitors

• Lion Biotech
  – Testing NCI approach in multi-centre trials

• Netherlands/Denmark/(UK)
  – Randomized trial Ipilimumab vs TIL
What about other types of Melanoma?

Non-Synonomous Coding Mutations in Exome Sequences
NCI Data in Uveal Melanoma

7/21 patients responded
1 complete remission > 21 months
2 other PRs on-going

SS Chandran et al., Lancet Oncol 2017;18:792-802.
How do we plan to improve TIL?

- Rapid Isolation
- Refined Specificity
- Improved Expansion Process
- Cryopreservation / Improved Transport
- Enhanced Activity
- Improved Persistence
- Improved Safety

Second Generation TIL/ACT
Development of Next-Generation Products

- Focus is development of next-generation product
- Greater Efficacy
  - Focus on long-term benefits
- Improved Tolerability
  - Reduced need for toxic conditioning
Conclusions

- TIL therapy can be extremely effective and produce **durable** benefits
  - *May* be so effective because they target multiple antigens
    - A Key *may* be mutated / tumour **specific** antigens

- In principle active in range of solid tumours but process more complex
  - Processes can be standardised / automated

- Hopefully can become a standard therapy
  - *In principle* TIL harvest should be considered when patients are having surgery for metastatic disease

- **Future potential to engineer in novel activity to enhance activity**
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**Contact Information**

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Advanced Teaching and TRaining for Adoptive Cell Therapy

**ATTACK**
Adoptively Engineered T-cell Targeting to Activate Cancer Killing