Suicide Genes - Potential Role in Avoiding Short Term and Long Term Toxicities

Helen Heslop
Need for An Effective “Suicide” for T Cell Therapies

• Adverse events may be prolonged and worsen as the cells expand
  – SIRS / cytokine release
  – GvHD
  – Malignant transformation

• Need rapid and effective means to eliminate infused cells in case of adverse events
## Suicide Genes in the Clinic in CAR Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>HSVtk</th>
<th>iCasp 9</th>
<th>Truncated (EGFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Foreign</td>
<td>Human derived → less</td>
<td>Human derived → less</td>
</tr>
<tr>
<td></td>
<td>→ Immunogenic</td>
<td>immunogenic</td>
<td>immunogenic</td>
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<tr>
<td>Activating Drug</td>
<td>Ganciclovir</td>
<td>AP1903</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Dividing cells (DNA synthesis)</td>
<td>All cells by apoptotic killing</td>
<td>ADCC</td>
</tr>
</tbody>
</table>
Apopotic Pathways in Lymphocytes

- FasL
- FAS Receptor
- DISC
- Bcl-2, Bcl-xL
- c-FLIP
- PC8
- IAP
- Apoptotic Pathways in Lymphocytes
- Active Caspase 8
- Caspase 2, 10
- Caspase 3, 6, 7
- Cytochrome C
- Apaf-1
- APOPTOSOME
- APOPTOSIS
Inducible Caspase 9

FKBP domain

iCaspase 9
CID (AP1903)

Caspase 3
Activated caspase 3

David Spencer
Inducible Caspase 9 (iCasp9).2A.dCD19 Transgene Construct

Patients on Studies

• 10 patients received allosedepleted T cells
  – 4 developed Grade 1 GVHD and received the dimerizer
    Di Stasi et al NEJM 2011

• 8 patients received CD3 activated T cells
  – 1 developed GI GVHD and received the dimerizer
Prompt Resolution Of Skin GVHD After A Single Dose Of AP1903 (Patient 2)

![Graph showing CD3+CD19+ cells over time after T-cell infusion.](image)

- **Pre AP1903**
- **24 hrs Post AP1903**

- **Graph Details**:
  - X-axis: Days after T-cell infusion
  - Y-axis: Cells/µl
  - Red square markers indicate CD3+CD19+ cells
  - T cells #2
  - AP1903 at 30 min post
  - 0, 15, 30, 45 days markings
Treatment of GI GVHD

- 55 year old post haploidentical transplant received $5 \times 10^5$ CD3 cells/kg
- 8 weeks post infusion skin rash then diarrhea

Pre

30 Minutes post AP 1903
T cells With Suicide Gene

- iCasp9 expressing T cells can persist and expand in vivo

- Treatment with single dose AP1903 rapidly ablated (>90%) alloreactive iCasp9 T cells with resolution of aGVHD in all 5 patients treated
3rd Generation CAR in Current Neuroblastoma Study

OX40 and 4-1BB endodomains
  • Belong to the TNF receptor superfamily

CD28-OX40
  • Improved regulation and proliferation of CD4⁺ cells versus effects of 41BB on CD8 T cells

Pule at al Mol Ther 2005
3rd Generation CAR with OX40 and iCasp9

- Inclusion iCasp9 in construct
  - Collaboration with “CaspaCIDe” developer and AP1903 supplier, Bellicum Pharmaceuticals

- If Grade 3 or greater toxicity attributed to T cell infusion
  - 0.4 mg/kg IV over 2 hrs
Implementing Suicide Genes

- Activating drug needs to be available
- AP1903 not FDA approved
  - Cells + AP1903 regulated as combination product
  - Only available from investigational pharmacy at study sites
- Out of town patients need to stay in town 4 weeks post infusion
  - Patient accommodation
  - Grants from Alex’s Lemonade Stand to families who travel for Phase I studies
Questions re Suicide Genes

• Would ablating infused cells abrogate all adverse reactions?
• Possibility of redosing
• Timing of suicide activation
  • Acute toxicity
  • What long term effects justify activation suicide gene?