

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

Helen Heslop



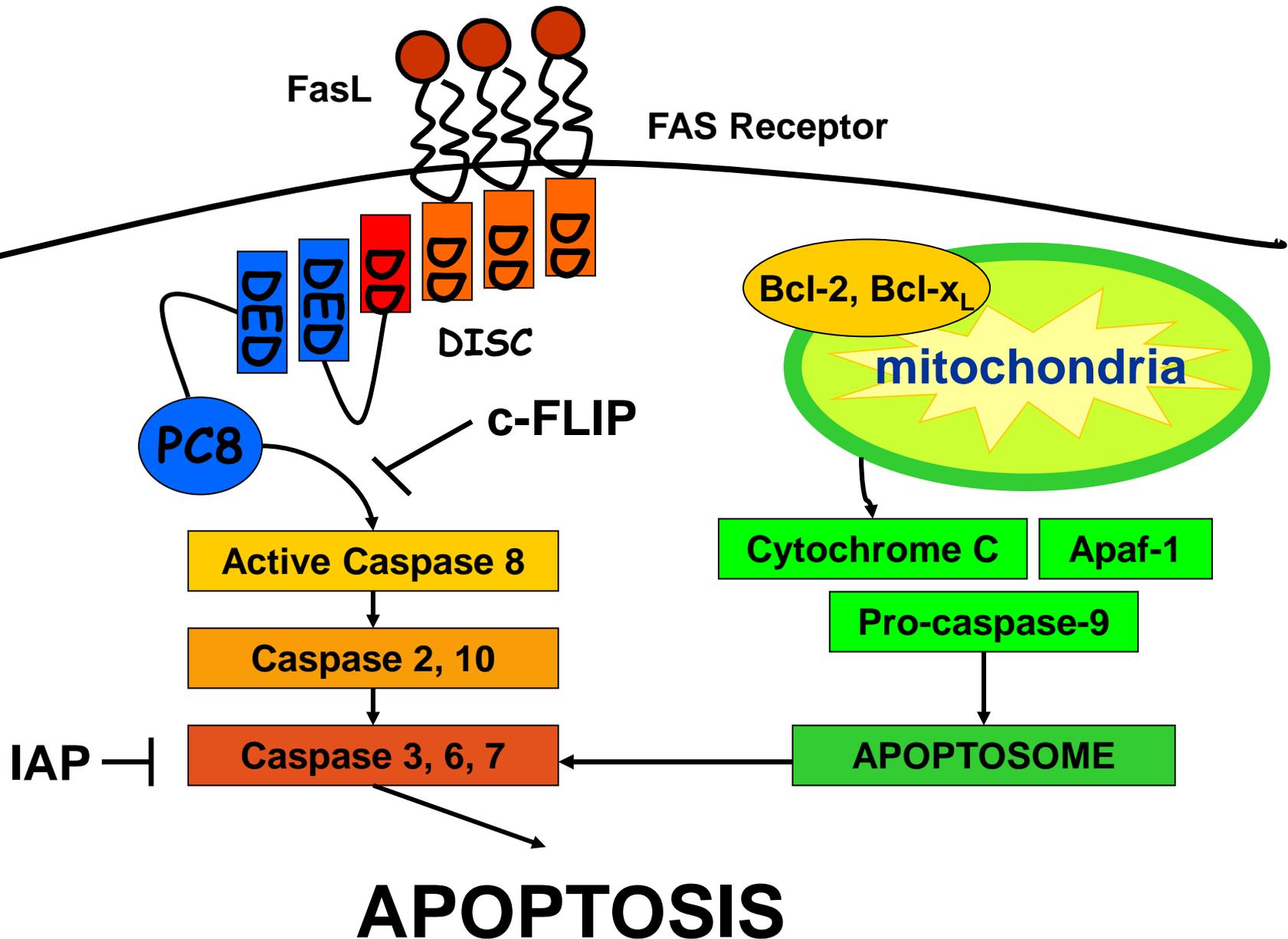
Need for An Effective “*Suicide*” for T Cell Therapies

- 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

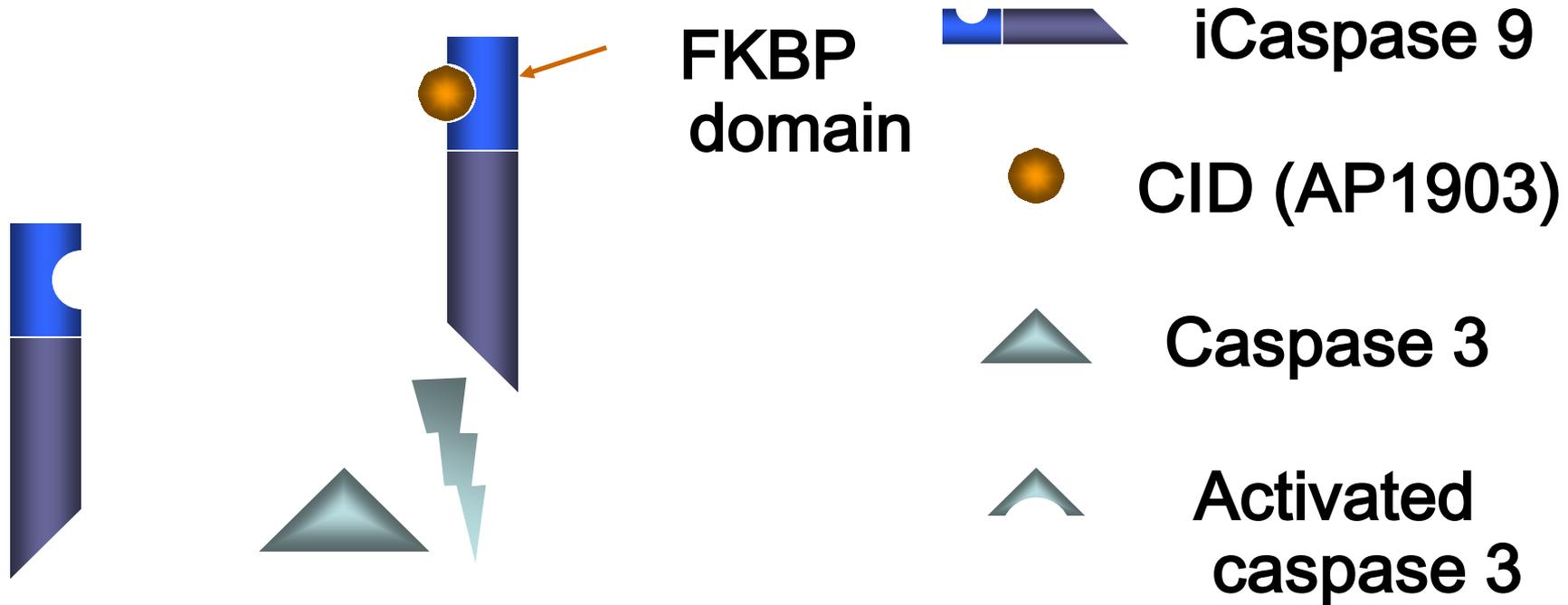
Suicide Genes in the Clinic in CAR Studies

	HSVtk	iCasp 9	Truncated (EGFR)
Source	Foreign → Immunogenic	Human derived → less immunogenic	Human derived → less immunogenic
Activating Drug	Ganciclovir	AP1903	Cetuximab
Mechanism	Dividing cells (DNA synthesis)	All cells by apoptotic killing	ADCC

Apoptotic Pathways in Lymphocytes

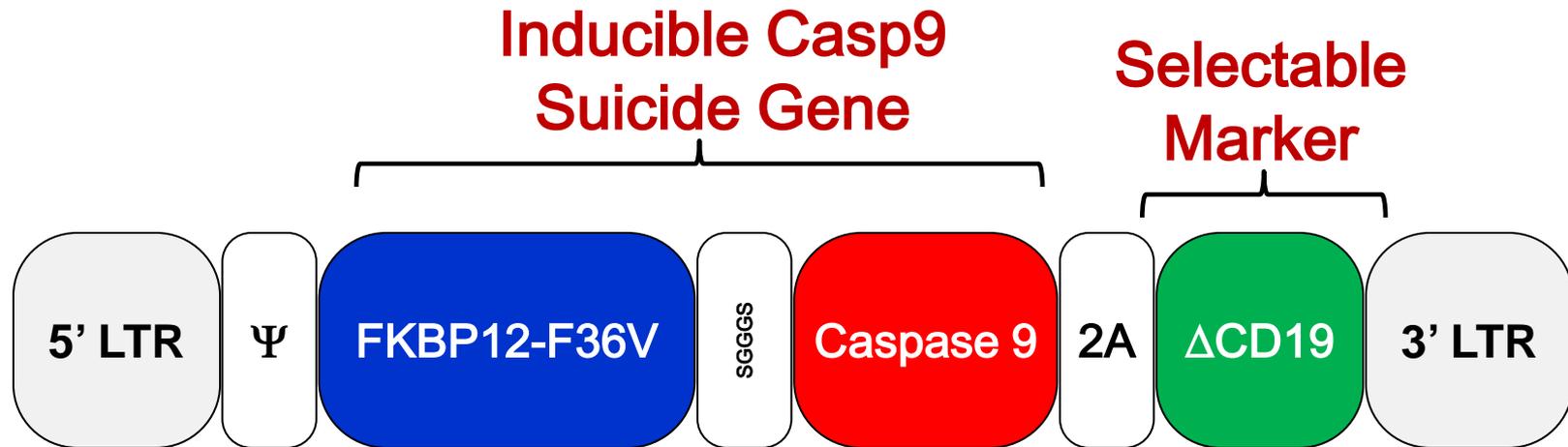


Inducible Caspase 9



David Spencer

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

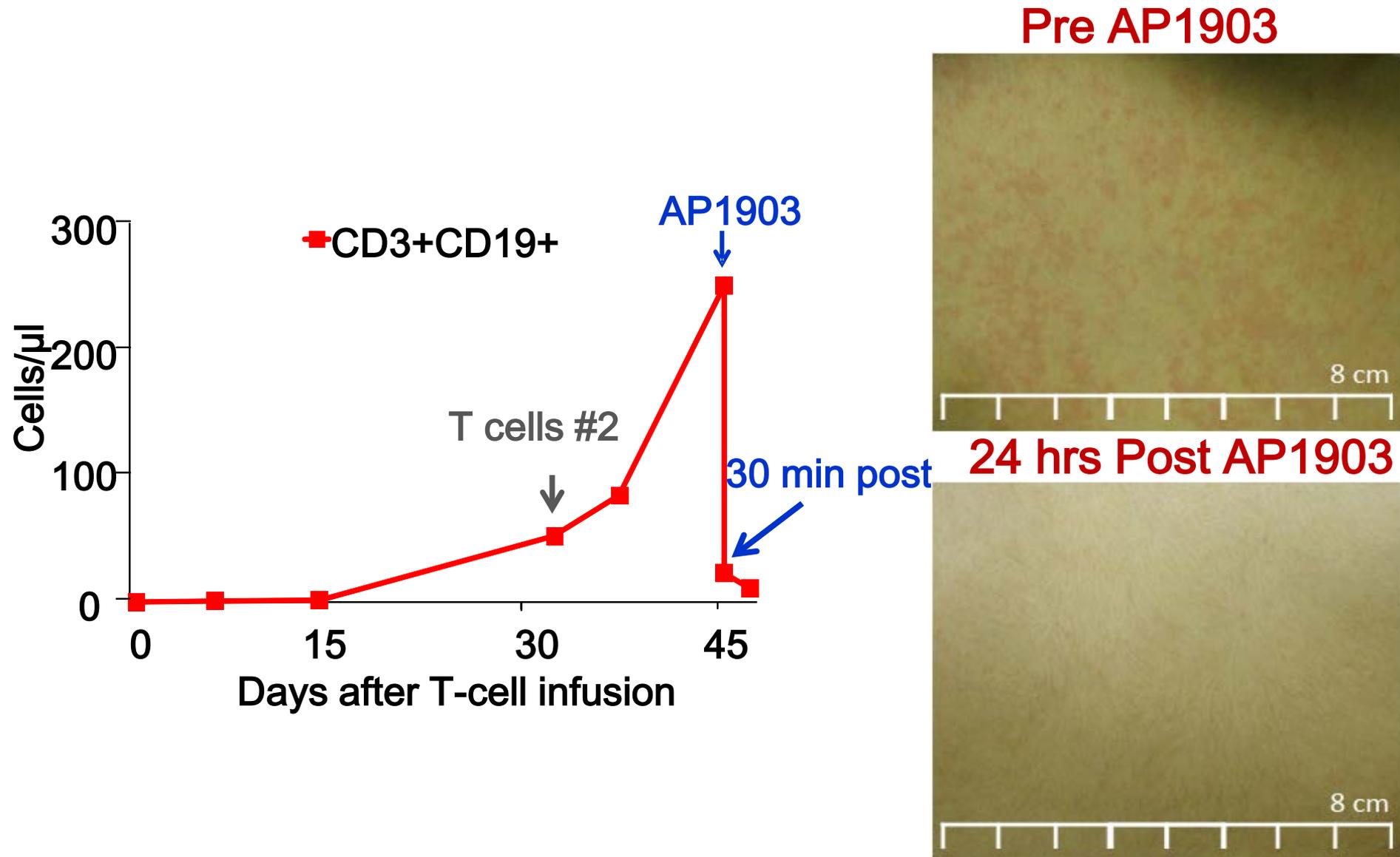


Patients on Studies

- 10 patients received allodepleted 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

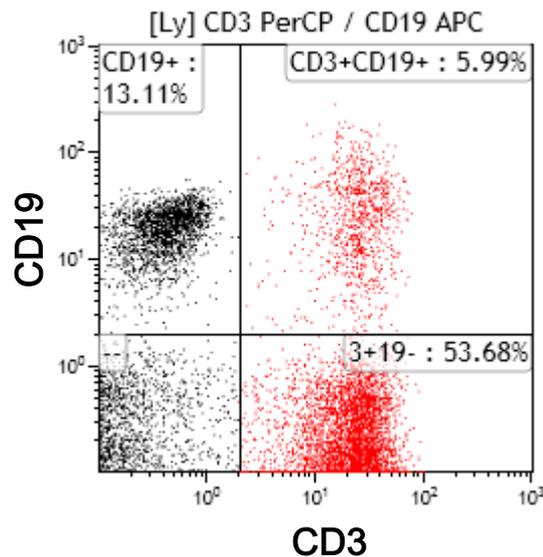
Prompt Resolution Of Skin GVHD After A Single Dose Of AP1903 (Patient 2)



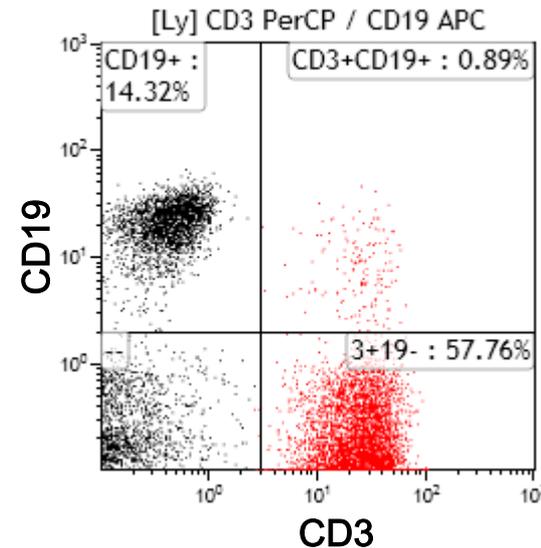
Treatment of GI GVHD

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

Pre



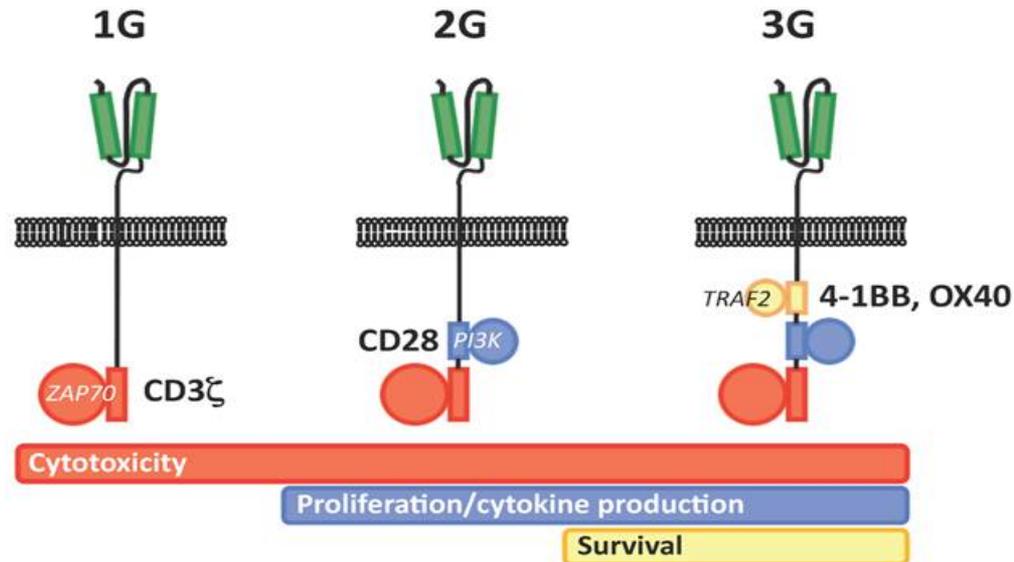
30 Minutes post AP 1903



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

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?