Session III: Dilemmas and Challenges: Approaches and Assessments

Session III
Current Status of Cancer Immunotherapy: Trials, Results, and Challenges

University of Pennsylvania

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Affinity enhanced HLA A1 restricted TCR for MAGE A3/A6 for melanoma (#1007-1056) and myeloma (#1007-1056)

Product: affinity enhanced TCR originally isolated from a patient with melanoma. Resulting TCR had Kd of 6.5 uM; parental TCR was ~300 uM

Events: onset of severe cardiogenic shock on day 4 (pt #1, melanoma) and day 5 (pt #1, myeloma) after T cell infusion
Pre-Clinical Evaluation of MAGE A3/A6 TCR Failed to Reveal Off Target Toxicity

- ELISPOT analysis against tumor cell lines and primary cells for specificity and activity
  - Primary cells: Epidermal melanocytes, hepatocytes, dermal microvascular endothelial cells, ciliary epithelial cells, PBMC and platelets
  - Readouts: IFN-γ, GrB
- Luminex to measure cell function in presence of HLA-A1 + Mage-A3 tumor cells & PBMC
  - IFN-α, IFN-γ, MIP-1α, MIP-1β, IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, GM-CSF, TNF-α, RANTES, MCP-1, IP-10, Eotaxin, MIG.

- Cytotoxicity assays
  - LDH assays (normal and tumor cells)
  - Degranulation assays (tumor cells)

- In Vivo Efficacy
  - Demonstration of anti-tumor activity in vivo using clinical candidates in a NSG mouse model
MAGE A3 T Cells in Autopsy Tissues: qPCR
MAGE A3 T Cells: Cytokine Profile in Blood

Case 1 – Melanoma
- IL-5 and IFN-γ

Case 2 – Myeloma
- IL-6, G-CSF, IP-10, MIG, IL-8
Off Target Reactivity of the TCR for Titin

• Summary of clinical course

• Summary of laboratory investigation
Lessons Learned: Engineered TCRs

- First example of off-target effects with TCR-engineered T cells
  - Affinity enhanced TCR engineered T cell therapy at risk for cross-reactivity
  - Biologically relevant preclinical screening of new TCRs is critical
- Dose reduction may not ameliorate risk and may only delay onset of toxicity (due to in vivo T cell expansion)

- Toxicity management: corticosteroids did not ablate toxicity in case #2. Would suicide systems or other forms abort toxicity?

- NY-ESO-1 TCRs are safe with encouraging results to date
Lessons Learned: Engineered TCRs II

- Preclinical screening of all available HLA A1 cell lines did not identify the reactivity
- Current in vitro studies are not predictive of in vivo outcomes with TCRs. CARs have a more predictable to pre-clinical evaluation
- Off target effects are established only in Phase I trials
- Mouse models currently available do not predict reactivity
- iPSCs have promise for preclinical screens