“Advancing Immunotherapy Platforms for the Treatment of Prostate Cancers”

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Disclosures

• I am on the SAB of Mustang Therapeutics and Imugene Ltd

• I am a consultant for Mustang Therapeutics, Apterna, Imugene Ltd, Bayer

• I have equity in Imugene Ltd

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Adoptive Therapy using CAR-Engineered T Cells


COH CAR TRIALS: 200+ PATIENTS

Anticipated Total Patients

Treated Patients

Number of Patients

CONFIDENTIAL
CD19-CAR T Cells for Relapsed B-Cell Lymphoma and Leukemia

**Case Report:**
61 yr; male
Relapsed high-grade B cell lymphoma
**Lymphodepletion:** Flu/Cy
CD19-28z CAR T cells (200M; Tn/mem)
Grade 2 CRS (1x toci); no neurotoxicity

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Disease</th>
<th>Cell Population</th>
<th>Cell Dose (CAR+)</th>
<th>Treated Patients</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT 02051257</td>
<td>NHL w/ auto-transplant (MRD: low/neg antigen)</td>
<td>Tn/mem</td>
<td>200M</td>
<td>6</td>
<td>Pending</td>
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<tr>
<td>NCT 02153580</td>
<td>CD19+ B cell Neoplasms (Active disease)</td>
<td>Tn/mem</td>
<td>200M</td>
<td>5</td>
<td>1 of 1 CR (4 Pending)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>600M</td>
<td>2</td>
<td>Pending</td>
</tr>
<tr>
<td>NCT 02146924</td>
<td>B-ALL (Active disease)</td>
<td>Tcm</td>
<td>200 M</td>
<td>3</td>
<td>30% CR (1 of 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tn/mem</td>
<td>200 M</td>
<td>13</td>
<td>100% CR (13 of 13)</td>
</tr>
</tbody>
</table>
Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S.,
Lihong Weng, M.D., Jamie R. Wagner, B.A., Araceli Naranjo, B.A.,
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and Behnam Badie, M.D.
CAR T Cell Therapies for Solid Tumors: *Resistance Mechanisms*

- **Tumor antigen heterogeneity**
  - Multitargeted CAR T cell strategies: tandem CARs, universal, syn-notch
  - Sparking endogenous anti-tumor immunity?

- **Immunosuppressive tumor microenvironment (TME)**
  - Combination strategies: radiation therapy, chemotherapy, oncolytic viruses
  - Intrinsic strategies: gene editing checkpoints, secreting ICB, targeting TGFβ
  - Preconditioning, routes of T cell administration, repeat infusions
T Cell Therapy at COH

- Brain
  - Glioma
  - Brain Metastasis

- Solid Tumors
  - Prostate
  - Breast
  - Pancreatic
  - Ovarian
  - Liver

- Hematological
  - Leukemia – AML, ALL
  - Lymphoma
  - Multiple Myeloma
PSCA Expression in Prostate Cancer

- Prostate Stem Cell Antigen (PSCA) was identified by Reiter et al. at UCLA in 1998

- Over-expressed in <60% of primary prostate tumors and 80-100% of metastatic tumors

- Limited expression pattern in normal tissue, making it an ideal target for CAR T cell therapy
PSCA-41BBζ CAR T Cells Show Increased Control of Disseminated Disease

-4-1BB co-stimulation demonstrates durable anti-tumor activity in patient-derived PSCA+ PCa bone metastasis xenograft model, compared with CD28 co-stimulation.

Priceman, et al. *OncoImmunology* 2018
Phase I Clinical Trials to Evaluate PSCA-BBζ CAR T Cells in Solid Tumors

- PSCA+ metastatic castration resistant prostate cancer
  (Clinical PI: Tanya Dorff, MD, Research PI: Saul Priceman, PhD) – Enrolling
- PSCA+ metastatic pancreatic cancer – TBD
Immunologically “Hot” vs. “Cold” Tumors

“Hot”
- CD8 T cells
- Th1
- NK cells
- DCs

IFNg
TNFa
IL-2
IL-12
CXCL9/10

“Cold”
- TAMs
- G/M-MDSCs
- Tregs
- STAT3
- TGFb
- PD-1/PD-L1
- CTLA-4
- VEGF
- IDO

Prostate Cancer / Pancreatic Cancer

Melanoma

Tumor mutational burden:
- ↑

Stromal/Fibrosis contribution:
- ↓

T cell accumulation:
- ↑

High suppressive myeloid/T cells:
- ↓
Syngeneic Immunocompetent Cancer Mouse Model
“Safety and Efficacy”

- Generation of fully-murine CAR construct in retrovirus

- Effective transduction and ex vivo expansion of murine splenic T cells

Murad et al. Mol Ther 2021
Requirement of Lymphodepleting Preconditioning for Solid Tumor CAR T Cell Efficacy

- Safe and effective CPA-preconditioning and PSCA-CAR T cell-mediated anti-tumor responses

Murad et al. Mol Ther 2021
- Tumor infiltration of T cells and PSCA-CAR T cell antitumor activity requires CPA pre-conditioning
- CPA converts to immunologically “warm” tumors with increased CD11c+ DCs and reduced CD206+ M2 macrophages
Lymphodepleting Preconditioning Promotes Endogenous and CAR T Cell Infiltration to Solid Tumors

**WITHOUT Pre-conditioning**
- Endogenous and CAR T cell infiltration
- CD8/Treg ratio
- M1/M2 ratio
- Pro-inflammatory signature

**WITH Pre-conditioning**
- Endogenous and CAR T cell infiltration
- CD8/Treg ratio
- M1/M2 ratio
- Pro-inflammatory signature

Tumor cell
- M1 Macrophage
- M2 Macrophage
- CAR T cell
- CD8 T cell
- Treg
- Fibroblast
- Vessel
What are the most rational immunotherapy combinations for CAR T cells?
Despite the benefits of CPA pre-conditioning, PSCA-mCAR T cells only achieve ~50% CR

In PSCA-mCAR T cell + CPA treatment groups, IPA analysis of enriched canonical pathway reveals increased XXX signaling:

Could combination of PSCA-CAR T cell + targeted XXX inhibition improve outcomes?

XXX Pathway Upregulation Following CAR T Cell Therapy

[Image of table showing upregulated pathways with p-values]
XXX Blockade Promotes CAR T Cell Efficacy

-Xi inhibition promotes anti-tumor efficacy of PSCA-CAR T cells
What are the most rational immunotherapy combinations for CAR T cells?

Oncolytic Viruses?
Oncolytic Viruses (OV)

- **Selectively** infect and replicate in tumors, causing direct killing or promoting immunogenic cell death (ICD)

- ICD can induce tumor-associated antigen release, recruitment of APCs, and elicit adaptive antitumor immunity

- Engineer-able to express genes of interest for tumor delivery

- T-VEC – FDA approved HSV-I expressing GM-CSF for metastatic melanoma

- Challenges with using OV as a single therapeutic reagent
Oncolytic Viruses Deliver CAR Targets and ‘Warm Up’ Solid Tumors
Oncolytic Viruses Deliver CAR Targets to “Targetless” Solid Tumors

[Diagram]

- Vaccinia Oncolytic Virus CF33-(SE)hCD19t
- J2R
- hCD19t

Legend:
- Green: Vaccinia Virus
- Pink: CD19
- Blue: DAPI

Park et al. Science Translational Medicine 2020
CD19-CAR T Cells Kill OV19t-Infected Tumors

-OV19t + CD19-CAR T cells show potent anti-tumor activity in vitro
OV19t Drive CD19-CAR T cell Anti-Tumor Responses in Solid Tumors

Combination of OV carrying CD19t and CD19-CAR T cells promotes tumor regression in xenograft model of TNBC

Park et al. Science Translational Medicine 2020
OV19t Promotes Endogenous and CAR T Cell Tumor Infiltration

Combination of OV carrying CD19t and CD19-CAR T cells promotes endogenous cytotoxic T cells and CAR T cells, and memory T cell responses.

Park et al. Science Translational Medicine 2020
CD19-CAR T Cells Drive Intratumoral OV Spread

- CD19-CAR T cells amplify viral spread in solid tumors
- CD19-CAR T cells do not amplify virus spread in normal tissues

Park et al. Science Translational Medicine 2020
Where do we go from here?

• **Lessons from phase 1 trials: reverse translation**
  – Prostate, brain metastasis, ovarian cancer, pancreatic cancer

• **Overcoming tumor antigen escape / immunosuppression**
  – Do immunologically “warm” tumors following better engage endogenous immunity (ICB, CAR, etc)?
  – What is the right combination approach?
  – What is the optimal timing and duration of combination strategies for durable anti-tumor activity?
  – What constitutes a responsive/non-responsive tumor to immunotherapy?
  – Contribution of microbiome? Contribution of neuro-signaling?
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Cari Young (GSR)
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Cody Cullen, BS
Catalina Martinez, BS (Proj Mgr)

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Jamie Wagner, BS (Reg Mgr)
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