Novel cellular therapies to achieve cures in clear cell renal cell carcinoma

Wayne A. Marasco, M.D., Ph.D.
Department of Cancer Immunology & Virology
Dana-Farber Cancer Institute
Harvard Medical School
Strategic Approach of DFIR CAR T cell therapy

- **Dual-Targeting (Improving Efficacy)**
  - Tumor Cell Heterogeneity
    - Capture both populations of single+ cells only
    - Prevent neutralization escape

- **Fine-Tuned (Improving Safety)**
  - Safety issue – sharing of tumor associated antigens with normal tissues
  - Fine tune targeting moiety affinity to target only high density antigen expressed on tumor cells but not low density antigen on healthy tissues

- **Immune Restoring (Reversal of local immunosuppression to achieve “Cures”)**
  - Change the tumor microenvironment by locally secreting checkpoint blockade inhibitors to restore anti-tumor immunity
  - Bispecific antibodies – Ab-cytokine fusions – T cell engagers either conditional or constitutive
Efficacy - Overcoming tumor cell heterogeneity (immune editing)

CAIX and CD70 are overexpressed on ccRCC

ccRCC patients (Stage I-IV)

Stage I
- 477477
- 477501
- 477469
- 477496

Stage II
- 477498
- 477504
- 477475
- 477481

Stage III
- 477476
- 477487
- 477488
- 477497

Stage IV
- 477499
- 477500
- 477494
- 477503

IR Payloads mAb CBIs (TME public signatures)

Dual-Targeted CAR T-cells

SD SA 5'LTR eFlα L scFv1 V- linker L scFv2 H TM Co-stim 4-1BB CD3ζ IRES 3'LTR

Patient 477503
Patient 477486

20X, CAIX, CD70

KCRS22 Kidney Cancer Research Summit kcrs.kidneycan.org #KCRS22
Safety - Overcoming on-target, off-tumor (healthy cell) toxicity

Expand therapeutic window to address on-target off-tumor side effects

Low level CAIX expression on normal tissues

Healthy kidney

ccRCC

Bile duct

No fratricide of anti-CD70 (B7) CAR T cells

Anti-CAIX G9-41BB CAR-T cells mitigate on-target off-tumor side effects

Cytotoxicity [%] = \frac{\text{Cell Count (Negative−Sumpa)}}{\text{Cell Count (Negative−Positive)}} \times 100\%

CD8 CAR T cells E:T ratio = 2:1

PLOS One (2010) 3:e9625

Skin of CAIX+ (2010)
Immune Restoring - Reversal of CAR T cell Exhaustion

Suarez, Oncotarget 7:23 (2016)
G36-41BB IR CAR-T secreting anti-PD-L1 mAb showed promising efficacy on humanized ccRCC orthotopic mouse model.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment (CD4:CD8=2:1)</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>G36-41BB-anti-PDL142sIgG4</td>
<td>1.00E+06</td>
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<tr>
<td>2</td>
<td>G36-41BB-anti-SARS11AsIgG4</td>
<td>1.00E+06</td>
</tr>
<tr>
<td>3</td>
<td>A716-41BB-anti-PDL142sIgG4</td>
<td>1.00E+06</td>
</tr>
</tbody>
</table>

A716-41BB-aPDL1 1536-41BB-aSARS G36-41BB-aPDL1

2 weeks after treatment
Humanized orthotopic ccRCC NSG-SGM3 mouse model recapitulates ccRCC TME
• Combination cellular immunotherapy (kidney cancer market – $6.3B (2022))
• Payloads determined by advanced humanized mouse models
• Cost of a single-dose therapeutic agent aimed at restoring host anti-tumor immunity; Augmenting T cell signals 1, 2 & 3
• Manufacturing - no costs of mAb formulation or in vitro stability
• Friendly to payers
Acknowledgements

Yufei Wang  
Marion Grimaud  
Alicia Buck  
Cecile Razimbaud  
Atef Fayed  
Audrey Apollon  
Gabriella Kastruntes  
Quan Zhu  
Matthew Chang  
Taylor Keyt  
Kimberley Tran  
Sreekumar Kodangattil  
Gordon Freeman

David Barbie  
Cloud Paweletz  
Brandon Piel  
Elena Ivanova  
Luann Zerefa  
Sabina Signoretti  
Rebecca Jennings  
Maura Aliezah Sticco-Ivins  
Miriam Ficial  
Aedin Culhane

Catherine Wu  
Toni Choueiri  
David Braun  
Jon Wee  
Ying Huang  
Madison L. O'Donnell  
Martin Hemberg  
Jae-Kwon Cho  
Kevin Wei  
Zhu Zhu  
Leo Chan

Quang-De Nguyen  
Dennis Bonal  
Kristen Jones

Funding Supports
Wong Family Award
DoD KCRP FY18
DoD KCRP FY21

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