Cellular Therapy for Kidney Cancer: Lessons from Immunotherapy
Exceptional Responders

Edus H. Warren
Fred Hutchinson Cancer Center
University of Washington
Seattle, WA, USA
Disclosures – Edus H. Warren, MD, PhD

No conflicts of interest.

I am a lymphoma / cellular therapy / transplant doc, but I am fortunate to work with very good kidney cancer docs.
Cellular and molecular dissection of antitumor T-cell reactions can help us design more effective immunotherapy.
αβ T-cell receptors can recognize a diversity of ligands

Genome-wide CRISPR-Cas9 screening reveals ubiquitous T cell cancer targeting via the monomorphic MHC class I-related protein MR1


Inge Marie Svane†, John D. Phillips† and Andrew K. Sewell*†‡∥

Graft-versus-RCC reactions following allogeneic HCT

The New England Journal of Medicine

REGRESSION OF METASTATIC RENAL-CELL CARCINOMA AFTER NONMYELOABLATIVE ALLOGENEIC PERIPHERAL-BLOOD STEM-CELL TRANSPLANTATION

RICHARD CHILDS, M.D., ALLEN CHERNOFF, M.D., NATHALIE CONTENTIN, M.D., ERKUT BAHCECI, M.D., DAVID SCHRUMP, M.D., SUSAN LEITMAN, M.D., ELIZABETH J. READ, M.D., JOHN TISDALE, M.D., CYNTHIA DUNBAR, M.D., W. MARSTON LINEHAN, M.D., NEAL S. YOUNG, M.D., AND A. JOHN BARRETT, M.D.
Sum of Tumor Measurements (RECIST)

$\alpha$-Interferon

% Donor Chimerism

4 months post HCT  | 9 months post HCT  | 15 months post HCT  | 2 years post HCT

Tykodi et al., Clin Can Res 2004
Tykodi et al., Clin Can Res 2008
Leveraging alloreactivity to eradicate RCC

T Cell Recipient

Tumor or Normal Cell

Donor T Cell

ARHGAP45:

...VLRDDLLEA...

C19orf48:

...CIPPDTLLFPA...

ARHGAP45:

...VLHDDLLEA...

C19orf48:

...CIPPDSLFFPA...

GVH

GVT
Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q. M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Oduensi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthi, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

TCGA/hERV: Smith et al. J Clin Invest 2018
CHECKMATE studies: Braun et al., Nature Medicine 2020
ADAPTeR/TRACERx: Au et al., Cancer Cell 2021
...and others
Complete regression of NSCLC to XRT followed by anti-PD-L1

March 2011: 68 year-old female with history of breast cancer and smoking diagnosed with stage IV \text{K-\textit{RAS}}^\text{mut} (G12F) lung adenocarcinoma; achieved CR after XRT to lungs and brain, and adjuvant chemotherapy.

November 2012: Recurrence in lung, bones, lymph nodes; chemotherapy \rightarrow progress.ion.

July 2013: developed additional metastases involving the buttocks and vaginal vault \rightarrow palliative XRT in August 2013.

September 2013: Enrolled on trial of MPDL-3280A (atezolizumab), an anti-PD-L1 monoclonal antibody, at MSKCC. Achieved a durable CR after 2 cycles, and completed one year of treatment. Developed patchy skin depigmentation \rightarrow Biopsy: no tumor \rightarrow Rx: immune suppression (prednisone and MMF).

September 2018: Enlarging RUL lesion treated with empiric SBRT.

October 2022: Remains in CR.
Targeted scRNAseq of “sentinel clone” (CD8+), 5 months post atezolizumab

Coffey et al., Front Immunol 2022
αβ T-cell receptors can recognize a diversity of ligands

MHC-independent T-cell recognition of soluble TRAIL/DR4 on RCC

Characterization of a Novel Nonclassical T Cell Clone with Broad Reactivity against Human Renal Cell Carcinomas

Qiong J. Wang, Ken-ichi Hanada, and James C. Yang

*J Immunol* 2008; 181:3769-3776; doi: 10.4049/jimmunol.181.6.3769

Molecular identification of an MHC-independent ligand recognized by a human α/β T-cell receptor

Ken-ichi Hanada, Qiong J. Wang, Takashi Inozume, and James C. Yang

*BLOOD*, 5 MAY 2011 • VOLUME 117, NUMBER 18

*from*: Hanada et al., *Blood* 2011
Functional genomic approach to identify RCC antigens targeted by T cells in the tumor microenvironment

Lentiviral library

T-cells

Barcoded lentivirus carrying sgRNA
RCC tumor cell expressing antigen of interest
RCC tumor cell infected with lentivirus
CD8+ or CD4+ T-cell
The RCC Team – and our Support

Scott Tykodi  Yuexin Xu  Chris Miller  Ram Akilesh  Andrea Towlerton  Shashidhar Ravishankar  David Coffey  Patrick Paddison  Nithya Ramnath