BIOGRAPHICAL SKETCH

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NAME: Richman, Sarah

eRA COMMONS USER NAME (credential, e.g., agency login): richmans

POSITION TITLE: Assistant Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Princeton University, Princeton, NJ	AB	06/2001	Molecular Biology
University of Illinois at Urbana-Champaign, Urbana, IL	PHD	05/2007	Biochemistry
University of Illinois at Urbana-Champaign, Urbana, IL	MD	05/2010	
Columbia University Medical Center, New York, NY	Resident	06/2013	Pediatrics Residency
Children's Hospital of Philadelphia, Philadelphia, PA	Fellow	07/2016	Pediatric Hematology-Oncology fellowship

A. Personal Statement

My career goal is to be a physician-scientist and continue to work on tumor immunotherapy with a focus on engineered T cell therapy in the basic/translational research arena. To begin to pursue this longstanding interest, I joined the lab of Dr. David Kranz for my PhD work to engineer the alpha/beta T cell receptor (TCR) targeting tumor antigens. In Dr. Kranz's lab, I studied the protein folding of antigen-binding domains of the TCR and developed a novel method for affinity-engineer TCRs against tumor antigen. To continue this pursuit, I joined the lab of Dr. Michael Milone at the University of Pennsylvania as a clinical fellow in Hematology-Oncology to study chimeric antigen receptor (CAR) T cells targeting solid tumors. My work in Dr. Milone's lab targeting solid tumors has focused on two main areas: strategies for preventing/reducing CAR T cell off-tumor toxicity using CAR regulation (including Boolean-gated systems) and mechanisms to enhance CAR T cell anti-tumor activity in targeting solid tumors. Using the GD2 glycolipid tumor antigen in a neuroblastoma model, I evaluated how an increase in CAR antigen binding affinity influences tumor control and off-tumor toxicity. I found that a higher affinity variant of the anti-GD2 CAR T cell exhibited more potent anti-tumor effect but concomitantly induced a fatal neurotoxicity with CAR T cell infiltration into the normal CNS. These results are described in a publication in Cancer Immunology Research on which I am first author. They highlighted the important role of antigen binding affinity on anti-tumor effect in vivo, which is the basis of the studies proposed here, and showed just how linked off-tumor toxicity can be to CAR T cell potency. The research and training plan that I have developed with my mentors, updated to reflect my change of institution, will allow me to more deeply investigate the role of CAR T cell affinity on T cell function. Building on my skills in antigen receptor engineering I developed in the Kranz lab as well as in T cell functional assays and in vivo studies in the Milone lab, I plan to gain additional training, including in advanced microscopy techniques to investigate the CAR T cell immune synapse, as well as in career development. These selected endeavors will help me to accomplish my goal of becoming an independent physician-scientist.

1. Richman SA, Wang LC, Moon EK, Khire UR, Albelda SM, Milone MC. Ligand-Induced Degradation of a CAR Permits Reversible Remote Control of CAR T Cell Activity In Vitro and In Vivo. Mol Ther. 2020 Jul 8;28(7):1600-1613. PubMed PMID: 32559430; PubMed Central PMCID: PMC7335755.
2. Sellmyer MA, Richman SA, Lohith K, Hou C, Weng CC, Mach RH, O'Connor RS, Milone MC, Farwell MD. Imaging CAR T Cell Trafficking with eDHFR as a PET Reporter Gene. Mol Ther. 2020 Jan 8;28(1):42-51. PubMed PMID: 31668558; PubMed Central PMCID: PMC6953896.

3. Richman SA, Milone MC. Neurotoxicity Associated with a High-Affinity GD2 CAR-Response. Cancer Immunol Res. 2018 Apr;6(4):496-497. PubMed PMID: 29610424.
4. Richman SA, Nunez-Cruz S, Moghimi B, Li LZ, Gershenson ZT, Mourelatos Z, Barrett DM, Grupp SA, Milone MC. High-Affinity GD2-Specific CAR T Cells Induce Fatal Encephalitis in a Preclinical Neuroblastoma Model. Cancer Immunol Res. 2018 Jan;6(1):36-46. PubMed PMID: 29180536; PubMed Central PMCID: PMC6004321.

B. Positions and Honors

Positions and Employment

2016 - 2020	Instructor, Children's Hospital of Philadelphia, Division of Oncology, Philadelphia, PA
2020 -	Assistant Professor of Pediatrics, Children's Hospital Los Angeles/University of Southern California, Los Angeles, CA

Other Experience and Professional Memberships

2001 -	Member, Society of Sigma Xi
2010 -	Member, Alpha Omega Alpha Society

Honors

2001 - 2003	Herbert Carter Graduate Fellowship in Biochemistry, University of Illinois at Urbana-Champaign
2004 - 2009	F30 Ruth L. Kirschstein National Research Service Award , NIEHS
2007	School of Molecular and Cellular Biology "Teacher ranked as excellent,", University of Illinois at Urbana-Champaign
2010	William E. Sorlie Award for Outstanding Clinical Core Clerkships Performance , University of Illinois College of Medicine at Urbana-Champaign
2010	American Medical Women's Association Glasgow-Rubin Citation for Academic Achievement,, University of Illinois College of Medicine at Urbana-Champaign

C. Contribution to Science

1. ENGINEERING THE T CELL RECEPTOR FOR THERAPEUTIC APPLICATIONS. As a graduate student in the laboratory of Dr. David Kranz at the University of Illinois, my research area was in molecular immunology. In particular, I focused on engineering the T cell receptor (TCR) for potential therapeutic applications, and my work was supported in part by an F30 Ruth L. Kirschstein National Research Service Award (NIEHS). In one study, I developed a novel method for selecting high affinity variants of antigen specific T cell receptors, which could be more effective in targeting tumor antigens and would also allow further study of how TCRs interact with peptide:major histocompatibility complex antigen. In my other paper, I focused on understanding which regions of the TCR are critical for domain stability. A better understanding of domain stability and folding can improve efforts to use TCRs in cancer immune diagnostics or immunotherapy.

    a. Richman SA, Aggen DH, Dossett ML, Donermeyer DL, Allen PM, Greenberg PD, Kranz DM. Structural features of T cell receptor variable regions that enhance domain stability and enable expression as single-chain ValphaVbeta fragments. Mol Immunol. 2009 Feb;46(5):902-16. PubMed PMID: 18962897; PubMed Central PMCID: PMC2666936.
    b. Richman SA, Kranz DM, Stone JD. Biosensor detection systems: engineering stable, high-affinity bioreceptors by yeast surface display. Methods Mol Biol. 2009;504:323-50. PubMed PMID: 19159105; PubMed Central PMCID: PMC3096842.
    c. Richman SA, Kranz DM. Display, engineering, and applications of antigen-specific T cell receptors. Biomol Eng. 2007 Oct;24(4):361-73. PubMed PMID: 17409021.
    d. Richman SA, Healan SJ, Weber KS, Donermeyer DL, Dossett ML, Greenberg PD, Allen PM, Kranz DM. Development of a novel strategy for engineering high-affinity proteins by yeast display. Protein Eng Des Sel. 2006 Jun;19(6):255-64. PubMed PMID: 16549400.

2. T CELL RECEPTOR ENGINEERING, FURTHER CONTRIBUTIONS. As I completed my PhD studies, my work on developing more stable single-chain versions of T cells receptors was expanded and helped serve as a foundation for the further engineering of higher affinity TCRs, and this work was described in two publications.

    a. Schmitt TM, Aggen DH, Stromnes IM, Dossett ML, Richman SA, Kranz DM, Greenberg PD. Enhanced-affinity murine T-cell receptors for tumor/self-antigens can be safe in gene therapy despite surpassing the threshold for thymic selection. Blood. 2013 Jul 18;122(3):348-56. PubMed PMID: 23673862; PubMed Central PMCID: PMC3716200.
    b. Aggen DH, Chervin AS, Schmitt TM, Engels B, Stone JD, Richman SA, Piepenbrink KH, Baker BM, Greenberg PD, Schreiber H, Kranz DM. Single-chain VαVβ T-cell receptors function without mispairing with endogenous TCR chains. Gene Ther. 2012 Apr;19(4):365-74. PubMed PMID: 21753797; PubMed Central PMCID: PMC3321103.

3. SOLID ORGAN TRANSPLANT IMMUNOLOGY. During my residency training, I participated in a research project in the lab of Dr. Megan Sykes, studying the interplay between host and donor immune cells and its effect on graft tolerance in liver and visceral organ transplant patient.

    a. Zuber J, Rosen S, Shonts B, Sprangers B, Savage TM, Richman S, Yang S, Lau SP, DeWolf S, Farber D, Vlad G, Zorn E, Wong W, Emond J, Levin B, Martinez M, Kato T, Sykes M. Macrochimerism in Intestinal Transplantation: Association With Lower Rejection Rates and Multivisceral Transplants, Without GVHD. Am J Transplant. 2015 Oct;15(10):2691-703. PubMed PMID: 25988811; PubMed Central PMCID: PMC4575629.

4. CAR T CELLS TARGETING SOLID TUMORS. My work in Dr. Milone's lab targeting solid tumors has focused on two main areas: strategies for preventing/reducing CAR T cell toxicity using CAR regulation (including Boolean-gated systems) and mechanisms to enhance CAR T cell potency in targeting solid tumors. Using the GD2 glycolipid tumor antigen in a neuroblastoma model, I evaluated how an increase in CAR antigen binding affinity influences tumor control and off-tumor toxicity. By evaluating anti-GD2 CAR T cells in vitro and in vivo, I found that a higher affinity variant of the anti-GD2 CAR T cell exhibited more potent anti-tumor effect but concomitantly induced a fatal neurotoxicity with CAR T cell infiltration into the normal CNS. These results are described in a publication in Cancer Immunology Research on which I am first author. They highlighted the important role of antigen binding affinity on anti-tumor effect in vivo, which is the basis of the studies proposed here, and showed just how linked off-tumor toxicity can be to CAR T cell potency. Recognizing the importance of non-invasive tracking of CAR T cells, we helped develop and test a preclinical system of imaging CAR T cells by PET in collaboration with Drs. Farwell and Sellmyer's nuclear medicine group. This work is described in a publication in Molecular Therapy on which I am co-first author. Additionally, we have developed a system of CAR T cell regulation that allows remote control of these cells in vivo and in vitro.

    a. Richman SA, Wang LC, Moon EK, Khire UR, Albelda SM, Milone MC. Ligand-Induced Degradation of a CAR Permits Reversible Remote Control of CAR T Cell Activity In Vitro and In Vivo. Mol Ther. 2020 Jul 8;28(7):1600-1613. PubMed PMID: 32559430; PubMed Central PMCID: PMC7335755.
    b. Sellmyer MA, Richman SA, Lohith K, Hou C, Weng CC, Mach RH, O'Connor RS, Milone MC, Farwell MD. Imaging CAR T Cell Trafficking with eDHFR as a PET Reporter Gene. Mol Ther. 2020 Jan 8;28(1):42-51. PubMed PMID: 31668558; PubMed Central PMCID: PMC6953896.
    c. Richman SA, Milone MC. Neurotoxicity Associated with a High-Affinity GD2 CAR-Response. Cancer Immunol Res. 2018 Apr;6(4):496-497. PubMed PMID: 29610424.
    d. Richman SA, Nunez-Cruz S, Moghimi B, Li LZ, Gershenson ZT, Mourelatos Z, Barrett DM, Grupp SA, Milone MC. High-Affinity GD2-Specific CAR T Cells Induce Fatal Encephalitis in a Preclinical Neuroblastoma Model. Cancer Immunol Res. 2018 Jan;6(1):36-46. PubMed PMID: 29180536; PubMed Central PMCID: PMC6004321.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

K08CA237868, National Cancer Institute
Sarah Richman (PI)
07/05/19-06/30/24
The role of antigen binding strength in CAR T cell activity
Role: PI

Completed Research Support

Scholar (Career Development Award), St. Baldrick's Foundation
Richman, Sarah (PI)
07/01/17-07/05/19
Addressing toxicity in CAR T cell therapy for solid tumors
The goal of this career development award is to evaluate strategies to maintain tumor specificity in CAR T cells as the potency is increased in order to create safe and effective CAR T cells.
Role: PI

5 K12 CA 76931-18, NIH
Schuchter (PI)
07/01/16-06/30/17
Cellular and Molecular Biologics in Clinical Cancer Research K12 at the Childrenâ□□s Hospital of Philadelphia Cancer Center
The goal of this training grant is to prepare the next generation of translational cancer researchers, with a particular focus on the development and evaluation of cellular and molecular biologics.
Role: TA

Fellowship, St. Baldrick's Foundation
Richman, Sarah (PI)
07/01/15-06/30/17
Regulating CAR T cell activity for targeting solid tumors
The goal of this fellowship award is to develop CAR regulation platforms in order to reduce CAR T cell toxicity
Role: PI

5T32CA009615-25, NIH T32
Maris (PI)
07/01/14-06/30/15
Cancer Center Research Training Program
The goal of this training program is to prepare post-doctoral fellows for careers as translational cancer researchers by providing protected time in an environment dedicated to the enhancement of research skills and concepts.
Role: TA

F30 ES013571-01, National Institute of Environmental Health Sciences (NIEHS)
RICHMAN, SARAH ANN (PI)
08/01/04-07/31/09
Engineering T Cells to Chemically-Induced Carcinomas
Role: PI