BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Raghuveer Ranganathan

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

POSITION TITLE: Hematology/Oncology Fellow

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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Michigan	BS	05/2004	Molecular and Cell Biology
Temple University	MD	06/2008	Doctor of Medicine
Drexel University		06/2011	Internal Medicine Residency
University of Pennsylvania		02/2015	Adoptive Cellular Immunotherapy research
University of North Carolina at Chapel Hill		06/2018	Hematology/Oncology Fellowship
University of North Carolina at Chapel Hill		09/2020	Clinical Instructorship for Hematology/Oncology
University of Southern California		Present	Assistant Professorship in Hematology/Oncology

A. Personal Statement

I have long possessed a focus in forming a career which fuses my interest in cellular immunology with my clinical interest in oncology together. My past medical training and laboratory experience have provided me with an excellent clinical background and scientific foundation in cancer therapy and have also given me perspective to the shortcomings of current standards of care in the field. My current research goals are driven by the prospective therapeutic capacity of innovative immunotherapies to advance the clinical outcomes of cancer patients.

During my residency training, research into cellular immunotherapy was gaining momentum within clinical trials in cancer patients, and I wanted more exposure to this prospective treatment. After completion of my Internal Medicine residency, I joined a research laboratory at University of

Pennsylvania under the tutelage of Dr. Steven Albelda. I was initially given a contributory role on an ongoing project investigating the immunosuppressive effects of the tumor microenvironment on chimeric antigen receptor T cells (CAR-T). I helped to study how tumor-induced inhibition occurred with cytotoxic CAR-T targeting tumor-associated antigens, and helped demonstrate the potential reversibility of CAR-T cell hypofunction with the use of immune checkpoint inhibitors in this setting. My contributory role served as my introduction to the basics of benchwork, giving me a platform to continue acquiring a deeper understanding of adoptive cellular immunotherapy.

I then was granted a larger participatory role in generating a model for tumor-infiltratinglymphocyte (TIL) hypofunction, but using human T cells expressing a specific unique T cell receptor (TCR) targeting NY-ESO-1, a tumor antigen expressed in various cancers including ovarian carcinoma and mesothelioma, instead of a CAR. I helped to demonstrate that the transgenic TCR cells displayed tumor cytotoxicity in the presence of mesothelioma tumor in a murine model, but also displayed eventual hypofunctionality, similar to my first project with CART. I then assisted to show that immune checkpoint inhibition with PD-1 blockade resulted in significant dampening of hypofunction of the TCR-expressing TILs while also boosting their antitumor efficacy. In addition, this experience further expanded my benchwork skills in both the in vitro and in vivo areas of research training.

My third endeavor while working at the University of Pennsylvania involved helping to develop an innovative CAR-T cell that integrated a switch receptor targeting PD-L1. One of the intrinsic inhibitory receptors on CAR-T and TCR TILs which was found to continually be overexpressed in our previous research was PD-1. I helped conceptualize co-transducing mesothelin-targeting CAR-T cells (mesoCAR) with a previously established chimeric switch-receptor containing the extracellular domain of PD1 fused to the transmembrane and cytoplasmic domain of the costimulatory molecule CD28. While the research built on previous PD1CD28 studies by extending them to CAR-T efficacy in solid tumors, the project was personally important as it led to a co-first author publication, solidifying my foundation in immunological cellular studies in cancer.

My clinical fellowship in Hematology/Oncology at the University of North Carolina-Chapel Hill (UNC) has given me avenues to further refine and advance my understanding and interest in oncology. As a clinical fellow, I developed a keen interest in specifically studying and treating hematological malignancies, with a specific focus in lymphomas. Since my second year of fellowship, I have had the honor of working under the mentorship of Dr. Gianpietro Dotti, a wellrecognized leader within the field of cellular immunotherapy. My primary project involves the preclinical evaluation of CAR-T directed at the clonally restricted light chain portion of surface immunoglobulin in mature B-cell non-Hodgkin lymphomas. Additionally, I am investigating a method to develop a CAR-T that harnesses a dual-targeting mechanistic approach for eradicating lymphoid malignancies. Also, I am collaborating on a project to blunt the overstimulation of CART by secreted immunoglobulin in the peripheral blood prior to their encountering of lymphoid malignant cells.

Starting my third year of fellowship, I started to become more engaged with the clinical aspects of ongoing CAR-T cell patient trials targeting lymphomas at UNC in the inpatient and outpatient settings. This involvement led to developing significant collaborative relationships with my current mentors and clinical patients. These influences have steered me into transitioning my career focus from benchwork to more clinical-translational research. To this end, I have become involved with

two clinical trials with CAR-T as a site co-investigator at UNC: a phase I study looking at CAR-T targeting CD30 in CD30-positive Hodgkin's and Anaplastic Large Cell lymphomas, and a phase I study with relapsed/refractory B-cell lymphoma patients receiving autologous CD19-targeting CAR-T containing an inducible Caspase-9 suicide gene. I'm also working to open a Phase II trial examining the efficacy of bendamustine-rituximab in the treatment of frontline or relapsed/refractory nodular lymphocyte predominant Hodgkin lymphoma. While the benchwork research sphere will always retain some appeal for me, I have a larger and more growing interest in the translational-clinical aspect of immunotherapy. With a concentration in the CAR-T cell arena, I am continuing to shift my focus into becoming a clinical trials specialist and translational researcher.

I have since moved on from UNC Chapel-Hill and joined as faculty at University of Southern California (USC) to conitnue my clinical and preclinical research in cellular therapy, while engaging in treating lymphma patients. Selection into the USC Comprehensive Cancer Center Membership would provide critical support to further investigate the clinical potential of surface immunoglobulin-targeting CAR-T cell therapy for B cell lymphomas, with the ultimate goal of developing this therapy into a clinical trial at USC within the next year. It is my long-term intention to continue acquiring fundamental skills to mature into an independent, academic clinical-translational researcher in cellular immunotherapeutics directed at lymphoma treatment, while also refining my clinical expertise in the administration and complications in such therapies.

1. Ranganathan R, Shou P, Ahn S, Sun C, West J, Savoldo B, Dotti G. CAR T cells Targeting Human Immunoglobulin Light Chains Eradicate Mature B-cell Malignancies While Sparing a Subset of Normal B Cells. Clin Cancer Res. 2021 Nov 1;27(21):5951-5960. PMID: 33858858.

2. **Ranganathan R**, Foster MC. The Limitations and Promise of Immunotherapy with Chimeric Antigen-Modified T Cells. Oncology (Williston Park). 2016 Oct 15;30(10):889-90. PMID: 27744646.

3. *Liu X, ***Ranganathan R**, Jiang S, Fang C, Sun J, Kim S, Newick K, Lo A, June CH, Zhao Y, Moon EK. A Chimeric Switch-Receptor Targeting PD1 Augments the Efficacy of Second-Generation CAR T Cells in Advanced Solid Tumors. Cancer Research, 2016; 76(6): 1578-90. * = co-first author

4. Moon EK, **Ranganathan R**, Eruslanov E, Kim S, Newick K, O'Brien S, Lo A, Liu X, Zhao Y, Albelda SM. Blockade of Programmed Death 1 Augments the Ability of Human T Cells Engineered to Target NY-ESO-1 to Control Tumor Growth after Adoptive Transfer. Clinical Cancer Research, 2016; 22 (2); 436-47.

B. Positions and Professional Memberships

Positions and Employment

2008-2011	Internal Medicine Resident Physician, Drexel University
2011-2015	Attending Physician, Penn Presbyterian Hospital
2013-2015	Research Fellow, University of Pennsylvania
2015-2018	Hematology/Oncology Fellowship, University of North Carolina-Chapel Hill
2018-2020	Clinical Instructorship in Hematology/Oncology

2020-Present Assistant Professorship, University of Southern California

Other Experience and Professional Memberships

2004-2008	Member, American Medical Student Association
2008-present	Member, American Medical Association
2012-present	Board Certification in Internal Medicine
2015-present	Member, American Society of Clinical Oncology
2015-present	Member, American Society of Hematology

C. Contributions to Science

1. **Early Career:** My first career contributions focused primarily on investigating tumor induced inhibition upon cytotoxic T cells expressing chimeric antigen receptors (CAR) targeting tumor-associated antigens. My particular role in the project was to genetically modify cytotoxic T cells so that they express CAR targeting mesothelin. Our group then processed and analyzed the tumors and tumor infiltrating T cells to derive the results. The outcomes showed the CAR T cells targeted and trafficked into the tumor well, but eventually became exhausted and hypofunctional. Our team showed this hypofunction and exhaustion was associated with upregulation of intrinsic T-cell inhibitory enzymes, as well as in the expression of surface inhibitory receptors such as PD1, TIM3, and LAG3. The research provided new details to possible mechanisms of overcoming CAR T cell hypofunction involving targeting the surface inhibitory receptors.

    a. Moon EK, Wang LC, Dolfi DV, Wilson CB, **Ranganathan R**, Sun J, Kapoor V, Scholler J, Puré E, Milone MC, June CH, Riley JL, Wherry EJ, Albelda SM. Multifactorial T-cell hypofunction that is reversible can limit the efficacy of chimeric antigen receptortransduced human T cells in solid tumors. Clinical Cancer Research, 2014; 20 (16); 4262-73.

2. **Hypofunction in Novel T cell Receptor (TCR) research:** I received more autonomy after my early career contributions with this project involving a unique TCR targeting NY-ESO1, a tumor antigen expressed on many tumors such as mesothelioma, ovarian carcinoma, and melanoma. The goal was to generate a model of human tumor-induced TIL hypofunction to study mechanisms and to test anti-human therapeutics. More specifically, I genetically modified T cells to express an optimized TCR directed against NY-ESO-1, then used these cells to target a human lung cancer line expressing NY-ESO-1 growing in immunodeficient mice. The ability of anti-PD1 antibody to augment efficacy was tested. I injected the mice in their flanks with the lung tumor line expressing NY-ESO-1, letting it grow for 4 weeks, then intravenously injecting the aforementioned optimized TCR-bearing T cells into these mice. In addition, I was in charge of injecting the anti-PD1 antibody into the tumor-bearing mice, sacrificing the mice and processing the tumors and tumor infiltrating T cells to derive the results. The research definitively showed that injections of an anti-PD1 antibody in combination with T cells led to decreased TIL hypofunction and augmented the efficacy of the adoptively transferred T cells. It provided a platform for preclinical testing of adjuvant immunotherapeutics targeted to human T cells prior to transition to the bedside.

a. Moon EK, **Ranganathan R**, Eruslanov E, Kim S, Newick K, O'Brien S, Lo A, Liu X, Zhao Y, Albelda SM. Blockade of Programmed Death 1 Augments the Ability of Human T Cells Engineered to Target NY-ESO-1 to Control Tumor Growth after Adoptive Transfer. Clinical Cancer Research, 2016; 22 (2); 436-47.

3. **Targeting PD-L1 with Chimeric Antigen Receptor (CAR) T cells:** Building on the TCR research, I received more independence with this project which involved using a CAR switch receptor which would overcome potential hypofunction by targeting an inhibitory molecule, PDL1, expressed by tumor cells. I was primarily in charge of cloning the CAR molecule, using it to genetically modify T cells to express the CAR, prove the model worked against established cell lines in vitro, and use the CAR T cells to target a human lung cancer line growing in immunodeficient mice. I was also in charge of maintaining and eventually sacrificing the mice, tumor and T cell processing and cell characterization. I was involved with the development of the methodology, analysis and interpretation of the data, and writing the manuscript for the publication, for which I was co-first author. The research helped elucidate new mechanistic pathways to overcome T cell hypofunction using CAR T cells.

    a. Liu X*, **Ranganathan R***, Jiang S, Fang C, Sun J, Kim S, Newick K, Lo A, June CH, Zhao Y, Moon EK. A Chimeric Switch-Receptor Targeting PD1 Augments the Efficacy of Second-Generation CAR T Cells in Advanced Solid Tumors. Cancer Research, 2016; 76(6): 1578-90.
    * denotes co-first author

4. **CAR-T cells targeting Light Chains on Surface Immunoglobulin on B cell Lymphomas:** I am currently leading a pre-clinical study investigating the use of CAR-T cells targeting the lambda (λ) light chain on surface immunoglobulin of mature B cell lymphomas. The preliminary results from the pre-clinical studies illustrating the efficacy of the λ-light chain targeting CAR-T cells in eradicating B cell lymphomas were presented at the ASH Conference in 2018.
    a. **Ranganathan R**, Shou P, Ahn S, West J, Sun C, Savoldo B, Dotti G. Chimeric Antigen Receptor T cells Redirected Against the Lambda Light Chain of Human Surface Immunoglobulins Efficiently Eliminates B-Cell Lymphoma Tumor. Clin Cancer Res. 2021 Nov 1;27(21):5951-5960. PMID: 33858858.

D. Additional Information: Research Support and/or Scholastic Performance Ongoing
<u>Research Support</u>

Lymphoma Research Foundation Clinical Investigator Development Grant 610516
Raghuveer Ranganathan (PI) 03/30/20-Present
Study of Kappa Chimeric Antigen Receptor (CAR) T Lymphocytes Co-Expressing the Kappa and CD28 CARs for Relapsed/Refractory Kappa+ Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- The major goals of this project are to determine whether receiving the Kappa light chain targeting CAR-T cells is safe and tolerable and learn more about the side effects and how effective these cells are in fighting lymphoma.

Completed Research Support

T32 CA211058 JS. Serody and N. Chao (co-PIs) 08/15/18-07/01/19
Duke-UNC Immunotherapy Training Program

- The goals of this grant are to train MD, MD PhD and PhD postdoctoral fellows in translational cancer immunotherapy and allogeneic transplantation immunology - Provides salary support from 8/15/18-7/01/19

R01 CA193140 G. Dotti (PI) 07/15/16-Current
Pre-Clinical Evaluation of Chimeric Antigen Receptor T cells Targeting the Lambda Light Chain on Surface Immunoglobulin in B-Cell Lymphomas

- Support for buying laboratory supplies, reagents, antibodies, animals, and equipment - No salary support provided by R01 grant

RO1 2R01CA120409 Y. Zhao and C. June (PIs) 02/15/13-03/1/15
K08 CA163941-04 E. Moon (PI) 02/15/13-03/1/15
A Chimeric Switch-Receptor Targeting PD1 Augments the Efficacy of Second-Generation CAR T Cells in Advanced Solid Tumors.