[redacted]

February [redacted]
Gilead Research Scholars Program
Solid Tumors

Dear Members of the Review Committee:

It is a pleasure to write this letter supporting Dr. [redacted] application for a Gilead Research Scholars Award in Solid Tumors. I am a Member in the Immunotherapy Integrated Research Center and [redacted] at the [redacted], Professor of Medicine at the [redacted] and American Cancer Society Research Professor.

*Track record of productivity and funding*: My research program, which focuses on understanding interactions between the immune system and human malignancy and on the design of specific T cell immunotherapies, has been funded continuously by the NIH for thirty years. Work from my lab has resulted in more than 275 publications, including original papers in Cell, Cancer Cell, Nature, Nature Medicine, Science, Science Translational Medicine, Science Signaling, and New England Journal of Medicine, and provided the foundational preclinical and clinical data for the Liso-cel (Breyanzi) CD19 CAR T cell product commercialized by Juno Therapeutics for diffuse large B cell lymphoma. More recently the lab has focused on research in solid tumors and this work is now supported by R01 and SPORE grants from the NIH, by the Department of Defense, and by sponsored research from industry.

*Success with prior trainees:* I have mentored 30 postdoctoral fellows and 6 predoctoral students. Seven prior postdoctoral fellows received K08, K23, or K99 awards from the NIH and 3 received Damon Runyon Clinical Investigator Awards. Sixteen postdoctoral students who have completed their training went on to faculty positions, including five at [redacted] and several who obtained faculty appointments at other major institutions in the US, Europe and Japan. Notable prior trainees include: [redacted]).

*Detailed description of the training plan:* The [redacted] and [redacted] are leaders in the field of adoptive T cell therapy and have achieved this status in part by identifying promising young investigators such as Dr. [redacted] and supporting their career development. Dr. [redacted] was recently appointed as an Assistant Professor in the Division of Medical Oncology at the [redacted] and in the Clinical Research Division at the [redacted] As a postdoctoral fellow in my laboratory Dr. [redacted] was highly productive and was awarded a Lung Cancer Research Foundation Young Investigator Award in [redacted], an NIH K12 Career Development Award in 2017, and a K08 award in

2020. [redacted] acquired skills in whole exome sequencing (WES) and RNA seq and initiated an in-depth analysis of T cells from blood and tumors from patients that recognized candidate neoantigens identified by WES and RNA sequencing of tumor and normal tissue. His work has focused on melanoma and non-small cell lung cancer (NSCLC). Because T cells specific for tumor antigens are often rare and/or exhausted, [redacted] had to optimize the culture conditions to identify $CD8^+$ and $CD4^+$ T cell responses to neoantigens. He chose not to bias the conditions to isolate class I MHC restricted $CD8^+$ T cells and as a result, uncovered numerous neoantigen reactive $CD4^+$ T cell responses in both melanoma and lung cancer, including responses to epitopes encoded by oncogenic driver mutations in BRAF, K-RAS, Her2, and EGFR. He validated specificity for the mutant versus wild type epitopes, mapped the class II restricting alleles, and cloned T cell receptors (TCRs) reactive to mutant BRAF and K-RAS. Thus, [redacted] has acquired impressive skills in analysis of WES and RNA seq datasets, calling mutations, and isolating and characterizing tumor reactive T cells. His work was presented at SITC and ASCO and published in first authored papers in J*ournal of Clinical Investigation*, *Cancer Immunology Research,* and *Journal of Immunotherapy of Cancer*.

[redacted] then focused on understanding the contributions of $CD4^+$ T cells in antitumor immunity. In work recently accepted in *Cancer Cell* that provides the preliminary data supporting his research proposal, [redacted] used targeted single cell RNA sequencing and matching of T cell receptor sequences to identify signatures and correlates of tumor-specific $CD4^+$ T cells infiltrating human melanoma. He showed that $CD4^+$ T cells that are specific for tumor antigens are distinct from bystander and regulatory T cells, express CXCL13, and can be subdivided into clusters expressing memory and T follicular helper markers, and those expressing cytolytic markers, exhaustion markers and IFN-$\gamma$. The frequency of $CXCL13^+$ $CD4^+$ T cells in the tumor correlated with the transcriptional states of $CD8^+$ T cells and macrophages, maturation of B cells, and patient survival. These results identify distinct phenotypes and functional correlates of tumor-specific $CD4^+$ T cells in melanoma and suggest the possibility of using the unique phenotype to enrich this subset of T cells from tumor infiltrates and expand them for therapy to modify the tumor microenvironment, which is the subject of his proposal. As he pursues his research and transitions to running his independent lab, [redacted] will benefit from additional mentoring that will include advising him and supporting his research and teaching activities and assisting him in developing laboratory management skills.

*Research activities:* His project will leverage recent discoveries about the [redacted] to manufacture a more potent clinical product that preserves stem like qualities. Aim 1 will utilize [redacted] he has expertise in. As he progresses on this aim, I will provide [redacted] with training and advice on [redacted], including use of clinical grade sorting in manufacturing [redacted]. The [redacted] has a dedicated Therapeutic Products Program (TPP) with process development and clinical manufacturing facilities that [redacted] will have access to as his work evolves. [redacted] will attend the monthly Immunotherapy Integrated Research Center Clinical Trials meeting chaired by [redacted] where data on safety, efficacy and research studies from early stage clinical trials of adoptive T cell therapy are presented and reviewed. These activities will position [redacted] to translate the findings from his research studies into the clinic. Aim 2 of his proposal will evaluate small molecule inhibitors for minimizing differentiation of tumor-reactive $CD4^+$ T cells during their in vitro expansion. My lab has experience in studying $CD8^+$ T cell differentiation states, including analysis of transcriptional and metabolic signatures that correlate with less differentiated T cells that have improved efficacy in preclinical models. [redacted] will work adjacent to experts in Computational Biology that will assist and provide training for his analysis of data obtained from single cell transcriptomics and ATAC-seq.

*Teaching activities:* [redacted] is an attending physician in the skin oncology group at the [redacted] and is an active participant in their clinical research group. He is involved in the teaching of oncology fellows through his work on the inpatient oncology consult and leukemia services, and the teaching of [redacted] residents on the inpatient oncology service. He is actively involved in the skin cancer leadership meeting which manages how the melanoma and [redacted] are organized and planned. He will give formal talks on his work and on tumor immunology to the Skin Oncology group, the Immunotherapy Integrated Research Center, and the Lung Cancer SPORE group.

*Lab management:* Dr. [redacted] will transition from my laboratory to his independent space at [redacted] During this transition, I will assist [redacted] in reviewing resumes for lab manager and research technician positions, provide advice on budget management, and advise him in hiring postdoctoral fellows and accepting rotation students.

*Resources allocated to the proposed research project:* Funding for the laboratory component of his work that exceeds that provided by the Gilead Scholars award is available through my grants and Dr. [redacted] start-up package. My lab occupies is a fully equipped ~1500 sf molecular and cellular biology lab in the newly renovated "Steam Plant" building at [redacted]. In addition, the [redacted] has state of the art shared resources including a Flow Cytometry Core, which houses BD Fortessa, LSRII, FACsAria, Sony, and Cytof instruments and a Genomics Core, which performs RNA seq library construction and initial analysis, whole exome sequencing and provides a bioinformatic pipeline for data analysis. A Biostatistics Core will provide [redacted] with assistance in experimental design and analysis. The Therapeutic Products Program can advise [redacted] on workflow and process development necessary for the transition to cGMP production of cellular products. In addition to these laboratory resources, Josh will have access to patient samples from the [redacted] that have been previously obtained for research studies.

*Provision of protected time and available laboratory facilities:* Dr. [redacted] faculty appointment provides for 75% protected time for research and this rule is strictly followed at our institution. He will occupy independent space adjacent to my lab for the remainder of [redacted] and will have access to the equipment in my lab as needed. He will be assigned new fully equipped lab space by the end of [redacted], either in the [redacted] building.

Dr. [redacted] has demonstrated he has the dedication and skills to excel as a physician/scientist. He has been able to garner NIH, industry and foundation support for his work in a difficult funding climate. He is a tireless worker, a superb clinician, a dedicated and creative scientist, and I believe would be a superb candidate for a Gilead Scholars Award. He has my enthusiastic support and commitment to continue to mentor him during the award period.

[redacted]