BIOGRAPHICAL SKETCH

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NAME: Labanieh, Louai

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

POSITION TITLE: Postdoctoral Research 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 California, Irvine (Irvine, CA)	BS	05/2016	Biomedical Engineering
Stanford University (Stanford, CA)	PHD	06/2022	Bioengineering
Stanford University (Stanford, CA)	Postdoctoral	Present	Bioengineering and Immunotherapy

A. Personal Statement

I am a Parker Institute for Cancer Immunotherapy Scholar at Stanford University with an overarching goal to leverage synthetic biology and immune engineering to develop curative therapies for cancer that can reach patients around the world. I have had the privilege to be trained and develop expertise in multidisciplinary fields spanning chimeric antigen receptor (CAR) T cell therapy, synthetic biology, immunology, protein engineering, nucleic acid technologies, and translational research.

CAR-T cell therapy has revolutionized the care of patients with relapsed and refractory in B cell cancers, but has not demonstrated consistent durable responses in solid tumors, where efficacy and safety barriers are a major challenge. As a PhD student, my primary focus was to improve CAR-T therapy by innovating novel genetically engineered systems for regulating the immune functions of T cells. I developed a high performance, drug-regulated CAR platform called SNIP that displayed dramatically enhanced efficacy and safety compared to conventional CARs. I performed extensive in vivo studies using clinically relevant mouse tumor models and immunological phenotyping that credentialed this system as best-in-class. Engineering next-generation cell therapies with enhanced capabilities requires introduction of additional genetic modules that often do not fit within the cargo capacity of a single lentiviral vector, requiring the use of multiple lentiviral vectors. I developed STASH Select, a simple platform technology for enriching cells that have been engineered with multiple lentiviral vectors using a single selection marker, which will help to propel sophisticated cell therapies containing multiple enhancements into the clinic.

I have demonstrated expertise in the CAR-T space by writing highly cited reviews in top journals, where I synthesized the current conceptual understanding of CAR-T immunobiology, the major engineering and clinical challenges, platforms for increasing the access of cell therapies, and future prospects of the field. I have enjoyed a collaborative environment at Stanford, where I have established collaborations with multiple labs to advance next-generation CAR-T platforms, identify targets and optimize CAR-T therapy for pediatric solid tumors, and develop tools for monitoring and manipulating adoptively transferred cells. My work thus far has resulted in 25-peer reviewed publications (H-index=22, >3000 citations) in high-impact journals with multiple other publications under revision and in preparation.

I am committed to developing innovative technologies that can be translated to the clinic where they can benefit patients. I am an inventor of 12 patents, eight of which are already licensed to biotechnology companies. I helped

to secure a $500,000 grant from the Alliance of Cancer Gene Therapy to kick start a clinical trial of the SNIP CAR platform I developed at Stanford. This technology was also licensed to a clinical-stage company. While I have a record for translation and recognize the importance of bringing new therapies into the commercial realm, my dream and passion is to establish an academic lab that tackles the most pressing clinical challenges with bold thinking and multidisciplinary approaches.

I have overcome significant adversity as an immigrant growing up in a low-income household and a first-generation college student. My personal journey motivates me to lead outreach efforts focused on increasing diversity in STEM. I have served as the outreach chair for the Biomedical Association for the Interest of Minority Students (BioAIMS), where I led efforts to bring high school and undergraduate students to visit Stanford and learn about paths to graduate school. During the pandemic, I organized the Science-in-Action speaker series, in collaboration with the Math, Engineering & Science Achievement (MESA) programs at local community colleges. Through this virtual seminar series, community college students got to learn about the journeys of PhD and MD students that had diverse careers and trajectories. As a former community college student myself, I was able to connect with this often-underserved community. I also co-organized a paid summer internship program with the Stanford Office of Diversity in Medical Education (ODME) to host two undergraduate students within our lab. I have also served as a mentor in the Undergraduate Stanford Summer Research Program, Bay Area Graduate Pathways to STEM conference, and the Biosciences NSF fellowship mentorship programs at Stanford.

Citations:

1. **Labanieh L,** Majzner RG, Klysz D, Sotillo E, …, Mackall CL. “Enhanced safety and efficacy of protease-regulated CAR-T cell receptors.” ***Cell* 2022.** PMID: 35483375
2. **Labanieh L**, Mackall CL. “CAR Immune Cells: Design Principles, Resistance and the Next Generation.” ***Nature* 2023.** PMID: 36813894
3. Tousley, AM, Rotiroti, MC, **Labanieh L,** Rysavy, LW,… Majzner RG. “Co-opting signalling molecules enables logic-gated control of CAR T cells." ***Nature* 2023**. PMID: 36890224
4. Grosskopf AK#., **Labanieh L#,** Klysz D, Gillie AR,…Mackall CL.*, Appel EA.* “Delivery of CAR-T cells in a transient injectable stimulatory hydrogel niche improves treatment of solid tumors.” ***Science Advances 2022***. PMID: 35394838

   # denotes equal contribution

B. Positions, Scientific Appointments, and Honors

2023–present	Reviewer, Science Advances
2023–present	Reviewer, ACS Biomaterials Science & Engineering
2023–present	Reviewer, Acta Biomaterialia
2022–present	Postdoctoral Research Fellow, Stanford University
2016–2022	PhD Student, Stanford University
2019–2020	Outreach Chair, Biomedical Association for the Interest of Minority Students
2015–2016	Editor, UCI Undergraduate Research Journal

Honors

2022	Society for the immunotherapy of cancer (SITC) 2022 Young Investigator Award
2022	Parker Institute for Cancer Immunotherapy-Parker Scholar Award
2021	Siebel Scholar Award
2020	Excellence in Education TA Award
2017	Fellow, NIH Biotechnology Grant
2016 - 2021	Fellow, Stanford Graduate Fellowship
2016 - 2021	Fellow, NSF Graduate Research Fellowship

2016 Fellow, Stanford EDGE Diversity Fellowship
2016 Chancellor's Award for Excellence in Undergraduate Research
2016 2nd place Paul Merage Business Plan Competition (campus-wide)
2016 3rd place Beall Student Design Competition (School of Engineering)
2015 Research Award, Chemical and Biological Microsystems Society
2014 Undergraduate Research Fellowship (UROP)
2014 1st place Science Honor Society Poster Competition
2013 Irvine Valley College Foundation Scholarship

C. Contributions to Science

1. **Developing next-generation CAR platforms with improved efficacy and safety**. Risks of toxicity and limited efficacy are major barriers facing CAR-T therapy for solid tumors. Platforms designed to enhance potency often diminish safety and those that are created for safety can diminish potency. To overcome these previous shortcomings, I developed an extensively engineered drug-regulatable CAR platform, termed SNIP that dually serves to enhance the efficacy and safety of CAR-T cells. I demonstrated that SNIP CAR-T cells are tightly controlled using an FDA-approved small molecule, do not display leaky activity, and are less exhausted and markedly more efficacious than standard CARs in six different mouse tumor models. We uncovered that providing CAR-T cells with periods of "rest" using pharmacological control of CAR signaling reduces their propensity for exhaustion and promotes long term functionality. Using an on-target off-tumor toxicity model in mice, I showed that SNIP CAR-T cells can be "tuned" to fall within a therapeutic window, whereby activity can be directed towards tumor cells expressing high levels of antigen, while sparing healthy tissues that express lower levels of antigen.

   CAR-T therapy for solid tumors has had limited clinical success, due in part to antigen heterogeneity, T cell exhaustion, and a hostile tumor microenvironment. Next-generation CAR-T therapies will need to be programmed with additional genetic modules to be sophisticated enough to overcome these various axes of resistance, which will likely require genetic engineering with multiple lentiviral vectors. I developed STASH-Select, a conditionally active selection marker system to enrich cells that have been engineered with multiple lentiviral vectors by encoding an inactive selection marker component on each lentiviral vector. Once all the STASH Select components are assembled into the same cell, the selection marker becomes activated and can be used to purify the multi-engineered cell population.

   a. **Labanieh L**, Mackall CL. "CAR Immune Cells: Design Principles, Resistance and the Next Generation." ***Nature* 2023.** PMID: 36813894
   b. **Labanieh L,** Majzner RG, Klysz D, Sotillo E, …, Mackall CL. "Enhanced safety and efficacy of protease-regulated CAR-T cell receptors." ***Cell* 2022.** PMID: 35483375
   c. Weber EW, Parker KR, Sotillo E, Lynn RC, Anbunathan H, Lattin J, Good Z, Belk JA, Daniel B, Klysz D, Malipatlolla M, Xu P, Bashti M, Heitzeneder S, **Labanieh L**… Mackall CL. "Transient Rest Restores Functionality in Exhausted CAR-T Cells through Epigenetic Remodeling." ***Science* 2021.** PMID: 33795428
   d. **Labanieh L,** et al**. "**STASH select, a simple and robust method of purifying cells engineered with multiple vectors using a single selection marker." ***Journal for Immunotherapy of Cancer* 2022.**

2. **Monitoring the expansion and trafficking of adoptively transferred CAR-T cells.** Technologies that allow for imaging transferred cells serve as valuable tools for studying the dynamics of T cell responses and trafficking in vivo as well as monitoring therapeutic responses in people. In collaboration with Dr. Sanjiv Gambhir's lab at Stanford, we engineered T cells with an improved thymidine kinase (TK)-based PET reporter. We demonstrated sensitive detection of B7H3-specific CAR-T cells by PET and followed their homing to orthotopically implanted osteosarcoma cells. As a proof of principle, we showed that TK can double as a suicide switch when the prodrug ganciclovir is administered, where it is converted into a cytotoxic agent only in TK-expressing cells. I also collaborated with Dr. Michael Lin's lab at Stanford to

develop new substrates for Antares, a bright luciferase which is orthogonal to standard firefly luciferases. We demonstrated that the new substrate yields dramatically improved sensitivity in tracking cells. We applied this technique for simultaneous dual imaging of B7H3 CAR-T and Ewing's sarcoma cancer cells. In a collaboration with Dr. Eric Appel's group, we devised a strategy to deliver CAR-T cells in an injectable hydrogel loaded with immunostimulatory cytokines directly at the tumor site. CAR-T cells and stimulatory cytokines delivered in this manner displayed distinct T cell phenotypes and enhanced tumor efficacy compared to control treatments delivered intravenously. We also observed T cell trafficking and enhanced antitumor activity even if the CAR-T cells were implanted distant from the tumor site.

a. **Labanieh L**, Majzner RG, Mackall CL. "Programming CAR-T cells to kill cancer." ***Nature Biomedical Engineering*** **2018**. PMID: 31011197
b. Murty S[#], **Labanieh L[#],** Murty T, Gowrishankar G,… Gambhir SS. "PET reporter gene imaging and ganciclovir-mediated ablation of chimeric antigen receptor T-cells in solid tumors." ***Cancer Research*** **2020**. PMID: 32958548
c. Su Y, Walker JR, Park Y, Smith TP, Liu LX, Hall MP, **Labanieh L**, … Lin MZ "Novel NanoLuc substrates enable bright two-population bioluminescence imaging in animals." ***Nature Methods*** **2020**. PMID: 32661427
d. Grosskopf AK#, **Labanieh L#,** Klysz D, Gillie AR,…Mackall CL*, Appel EA.* "Delivery of CAR-T cells in a transient injectable stimulatory hydrogel niche improves treatment of solid tumors." ***Science Advances 2022***. PMID: 35394838

# denotes equal contribution

3. **Identifying tumor targets and optimizing CAR-T therapy for solid tumors.** New therapies for certain pediatric solid tumors, such as relapsed sarcomas and brain tumors, are desperately needed as these diseases have mortality rates exceeding 90%. Current immunotherapy-based approaches suffer from a paucity of known differentially expressed antigens to target. To address this clinical need, we identified B7H3 as a pan cancer antigen and constructed a B7H3-targeting CAR with strong activity in mouse models of osteosarcoma, Ewing's sarcoma, and medulloblastoma. In a follow-up preclinical study, we showed that this CAR can clear atypical teratoid/rhabdoid CNS tumors, which are nearly universally fatal diseases. We demonstrate that locoregional administration of B7H3 CAR-T cells directly into the CNS results in more rapid and potent clearing of these tumors while inducing less systemic cytokine activity than intravenously administered CAR-T cells. Finally, in a collaboration with Dr. Michelle Monje at Stanford, we identified uniformly high expression of the ganglioside GD2 on diffuse midline gliomas (DMG), another class of universally fatal pediatric CNS tumors. Using a GD2-targeting CAR we demonstrated potent activity against patient-derived DMG tumors orthotopically implanted in mice. These preclinical studies paved the way for a clinical trial at Stanford that demonstrated remarkable and unprecedented clinical responses in this universally fatal disease (GD2 CAR in DMG, NCT04196413). A clinical trial is also underway for the B7H3 CAR we developed for recurrent glioblastoma multiforme (B7H3 CAR in GBM, NCT05474378). We are hopeful that the targets and therapy optimizations we have identified will lead to potentially curable treatment options for patients suffering from these devastating diseases. Working with the Majzner lab, I helped to develop the first true AND gated CAR platform which could expand the realm of targetable antigens by combinatorial antigen sensing.

a. Tousley, AM, Rotiroti, MC, **Labanieh L,** Rysavy, LW,… Majzner RG. "Co-opting signalling molecules enables logic-gated control of CAR T cells." ***Nature*** **2023**. PMID: 36890224
b. Mount CW, Majzner RG, Sundaresh S, Arnold EP, Kadapakkam M, Haile S, **Labanieh L**, … Mackall CL. "Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M+ diffuse midline gliomas." ***Nature medicine*** **2018**. PMID: 29662203
c. Theruvath J, Sotillo E, Mount CW, Graef CM, Delaidelli A, Heitzeneder S, **Labanieh L**, …Mackall CL. "Locoregionally administered B7-H3-targeted CAR T cells for treatment of atypical teratoid/rhabdoid tumors." ***Nature Medicine*** **2020**. PMID: 32341579
d. Majzner RG, Theruvath JL, Nellan A, Heitzeneder S, Cui Y, Mount CW, Rietberg SP, Linde MH, Xu P, Rota C, Sotillo E, **Labanieh L**, … Mackall CL. "CAR T cells targeting B7-H3, a pan-cancer

antigen, demonstrate potent preclinical activity against pediatric solid tumors and brain tumors." ***Clinical Cancer Research*** **2019**. PMID: 30655315

4. **Nucleic acid-based biosensors and droplet microfluidic devices for high-throughput screening and disease diagnostics**. As an undergraduate student at UC Irvine, I was interested in technologies that allow for interrogating large populations of cells for high-throughput screening, but noticed that few exist for tracking cells over time at the single-cell level. To overcome this challenge, I developed a droplet-based microfluidic device, termed Floating Droplet Array, capable of encapsulating hundreds of thousands of cells in micron-scale droplets. The droplets are then trapped in a large static microwell array for longitudinal tracking by microscopy to monitor cell phenotypes. I went on to develop a laser-based technique for extracting single droplets of interest from the device for further analysis (e.g., single-cell RNA sequencing). In addition, I collaborated with fellow researchers on droplet microfluidic technologies for early detection of cancer and infectious diseases. We developed nucleic acid based biosensors such as structure-switching aptamers, novel RNA probes, and DNAzymes that allowed for sensitive detection of analytes.

    a. **Labanieh L**, Nguyen TN, Zhao W, Kang DK. "Floating Droplet Array: An Ultrahigh-Throughput Device for Droplet Trapping, Real-time Analysis and Recovery." ***Micromachines*** **2015**. PMID: 27134760
    b. Li Y, Cherukury H, **Labanieh L**, Zhao W, Kang DK. "Rapid Detection of β-Lactamase-Producing Bacteria Using the Integrated Comprehensive Droplet Digital Detection (IC 3D) System." ***Sensors*** **2020**. PMID: 32824984
    c. Zhang K, Kang DK, Ali MM, Liu L, **Labanieh L,**… Zhao W. "Digital quantification of miRNA directly in plasma using integrated comprehensive droplet digital detection." ***Lab on a Chip*** **2015**. PMID: 26387763
    d. Ma H, Liu J, Ali MM, Mahmood MA, **Labanieh L**.,…Wan Y. "Nucleic Acid Aptamers in Cancer Research, Diagnosis and Therapy." ***Chemical Society Reviews*** **2015**. PMID: 25561050

5. **Engineering designer proteins for cancer immunotherapy by directed evolution and yeast surface display.** During my PhD, I was co-mentored by Dr. Jennifer Cochran, who is a pioneer in protein engineering and protein-based therapies. I worked with members of the Cochran lab to develop affinity engineered antibodies, ligand traps, and cell surface receptors that modulate interactions with immune checkpoint molecules, cancer associated cytokines, and macrophage "don't eat me" signals.

    a. Longwell CK., **Labanieh L**, Cochran JR. "High-Throughput Screening Technologies for Enzyme Engineering." ***Current Opinion in Biotechnology*** **2017*.*** PMID: 28624724
    b. Mehta N., Maddineni S, Kelly RL, Lee RB, Hunter SA, Silberstein JL, Parra Sperberg RA, Miller CL, Rabe A, **Labanieh L**, Cochran JR. "An Engineered Antibody Binds a Distinct Epitope and Is a Potent Inhibitor of Murine and Human VISTA." ***Scientific Reports*** **2020**. PMID: 32938950
    c. Hunter, S A, McIntosh, B J, Shi, Y, Sperberg, R A P, Funatogawa, C, **Labanieh, L**.,…Cochran JR. "An Engineered Ligand Trap Inhibits Leukemia Inhibitory Factor as Pancreatic Cancer Treatment Strategy." ***Communications Biology*** **2021**. PMID: 33846527
    d. Yamada-Hunter SA, Theruvath J, McIntosh BJ, Freitas KA, Radosevich MT, Leruste A, Dhingra S, Martinez-Velez N, Xu P, Delaidelli A, Desai MH., Good Z, Labanieh L,…Mackall CL. "Engineered CD47 protects T cells for enhanced antitumor immunity." [Preprint] ***bioRxiv*** **2023.** Available from: https://doi.org/10.1101/2023.06.20.545790

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/1L_pdv-SBx25W/bibliography/public/