OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Daniels, Kyle Gabriel

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-9992-1210

Position Title: Assistant Professor of Genetics and, by courtesy, Neurosurgery

Organization and Location: Stanford University, Palo Alto, California, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of California San Francisco, San Francisco, California, United States	Postdoctoral	09/2015	04/2023	Synthetic Biology/Immunology
Duke University, Durham, North Carolina, United States	Doctor of Philosophy (PHD)	08/2010	08/2015	Biochemistry/Structural Biology and Biophysics
University of Maryland-College Park, College Park, Maryland, United States	Bachelor of Science (BS)	09/2006	05/2010	Biochemistry

Appointments and Positions

2023 - present	Assistant Professor of Genetics and, by courtesy, Neurosurgery, Stanford University, Palo Alto, California, United States
2023 - 2024	Fellow, Hypothesis Fund, Palo Alto, California, United States
2015 - 2023	Postdoctoral Fellow, Department of Cellular and Molecular Pharmacology, UCSF, San Francisco, California, United States

Products

Products Closely Related to the Proposed Project

1. Daniels KG, Wang S, Simic MS, Bhargava HK, Capponi S, Tonai Y, Yu W, Bianco S, Lim WA. Decoding CAR T cell phenotype using combinatorial signaling motif libraries and machine learning. Science. 2022 Dec 16;378(6625):1194-1200. PubMed Central PMCID: PMC10026561.
2. Capponi S, Daniels KG. Harnessing the power of artificial intelligence to advance cell therapy. Immunol Rev. 2023 Nov;320(1):147-165. PubMed PMID: 37415280.
3. Lunger JC, Sant'Anna LE, Salcido-Alcántar A, Arroyo Hornero R, Cho W, Vaughan-Jackson A, Gu M, Liu JY, Beckett AN, Parrilla-Garcia J, Ramakrishna S, Bassik MC, Daniels KG. Programmable synthetic cytokine receptors polarize macrophages to user-defined functional states. bioRxiv. 2026 May 14; PubMed Central PMCID: PMC13192837.
4. Bailey SR, Bartee E, Daniels KG, Heery CR, Kaumaya P, Lesinski GB, Lowinger TB, Nelson MH, Rubinstein MP, Wittling MC, Paulos CM, Posey AD Jr. Constructing the cure: engineering the next wave of antibody and cellular immune therapies. J Immunother Cancer. 2025 Aug 25;13(8) PubMed Central PMCID: PMC12382549.
5. O'Donoghue GP, Bugaj LJ, Anderson W, Daniels KG, Rawlings DJ, Lim WA. T cells selectively filter oscillatory signals on the minutes timescale. Proc Natl Acad Sci U S A. 2021 Mar 2;118(9) PubMed Central PMCID: PMC7936380.

Other Significant Products Highlighting Contributions to Science

1. Daniels KG, Tonthat NK, McClure DR, Chang YC, Liu X, Schumacher MA, Fierke CA, Schmidler SC, Oas TG. Ligand concentration regulates the pathways of coupled protein folding and binding. J Am Chem Soc. 2014 Jan 22;136(3):822-5. PubMed Central PMCID: PMC3977005.
2. Daniels KG, Suo Y, Oas TG. Conformational kinetics reveals affinities of protein conformational states. Proc Natl Acad Sci U S A. 2015 Jul 28;112(30):9352-7. PubMed Central PMCID: PMC4522757.
3. Chaikof EL, Chen J, Gillette MU, Boyer LA, Deans TL, Li P, Hilton IB, Daniels K, Goyal Y, Mei Y, Linghu C, Loveless TB, Truong DM, Blatchley MR, Gu M, Bashor CJ, Yang JH, Raman R, Reddy AB, Saha K, Davis J, Gupta K, Gao XJ, Galloway KE. Integrating synthetic biology to understand and engineer the heart, lung, blood, and sleep systems. Cell Syst. 2025 Dec 17;16(12):101446. PubMed Central PMCID: PMC13081558.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Daniels, Kyle Gabriel

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-9992-1210

Position Title: Assistant Professor of Genetics and, by courtesy, Neurosurgery

Organization and Location: Stanford University, Palo Alto, California, United States

Personal Statement

The goals of my lab's work are to decode natural signaling systems to understand their functions, and to encode specific instructions to engineer therapeutic cells for cancers, HIV, or blood disorders. We are also interested in understanding how information is encoded by the biophysical and structural characteristics of receptors, signaling adapters, and gene circuits. We use synthetic biology, high-throughput library screening, and machine learning to create new synthetic receptors that improve CAR T cell anti-tumor activity. Our approach to AI-enabled design of improved cell therapies is discussed in a review article. To explore cell signaling we curate a modular toolkit of domains involved in cell signaling, combine them in novel arrangements to make combinatorial libraries of hundreds to thousands of synthetic signaling molecules, and test these libraries for their effects on human immune cell (T cell, macrophage, natural killer cell) or hematopoietic stem cell (HSC, HSPC) phenotypes. Using neural networks, we build predictive models to quantitatively and systematically understand cell signaling networks, decode structure-function relationships, and design new immune cell therapeutics.

We are now able to engineer enhanced CAR T cells and CAR macrophages with programmable receptors. These synthetic cytokine receptors (SCRs) can tune CAR T cell proliferation, cytotoxicity, differentiation, and enable survival in the absence of cytokine. SCRs can also polarize macrophages to user-defined cell states, including a state that is simultaneously pro-inflammatory and highly phagocytic. Our SCR CAR T cell and SCR CAR macrophage work are described in publicly available pre-prints. In the proposed work, we will use these enhanced immune cells as effectors and delivery vehicles for the immunomodulatory peptide LL-37 in treatment of glioblastoma. LL-37 is a powerful TLR and STING agonist that can repolarize the tumor microenvironment to potentiate immunotherapy responses. Our preliminary data, experience with SCRs and LL-37, and our team (cell engineer, neurosurgeon, LL-37 expert, and others) will enable us to explore a new modality of therapy for glioblastoma. Eventually, we hope to extend this technology to pancreatic cancer.

Through our interdisciplinary research in biophysics, immune engineering, and machine learning, I hope to train a new generation of scientists and physician-scientists capable of combining emerging technologies to solve problems in human health.

Honors

2025 - 2030	NIH Director's New Innovator Award (DP2), NIH Common Fund
2025 - 2028	Trailblazer R21 Award, NIBIB
2016 - 2020	Postdoctoral Fellowship, Damon Runyon Cancer Research Foundation
2016 - 2019	Postdoctoral Enrichment Program, Burroughs Wellcome Fund
2011 - 2015	Graduate Research Fellowship, National Science Foundation
2010	Diversity Enhancement Fellowship, Duke University
2010	Merck Index Award, University of Maryland Dept. of Chemistry and Biochemistry
2010 - 2013	Dean's Fellowship, Duke University
2009	First Place in Biochemical Sciences, UMBC Undergraduate Research Symposium in Chemical and Biological Sciences
2007 - 2010	Undergraduate Research Fellowship, Howard Hughes Medical Institute
2006 - 2010	Banneker-Key Scholarship: housing, food, tuition, and fees, University of Maryland

Contributions to Science

1. Immune cell engineering/Professional Career: T cells are quickly becoming a vehicle for cell-based immunotherapy in cancer and autoimmune diseases. To effectively use T cells to treat disease will require the ability to modulate the many variable properties of T cells—proliferation, persistence, memory formation, killing, metabolism, and cytokine release—all of which are controlled by cell signaling events. I focused my postdoctoral research on understanding how immune signaling events control T cell function. To do this, I developed a platform to rapidly construct libraries of thousands of synthetic receptors (CARs) that differ in their signaling domains, with each receptor containing a different combination and arrangement of conserved signaling motifs. I screened these libraries in primary human CAR T cells to find receptors (and signaling motif combinations) that promote or inhibit activation, proliferation, cytotoxicity, and persistence. In a collaboration with scientists at IBM, we used neural networks to learn and predict how combinations of signaling motifs dictate T cell phenotype and function such as stemness and anti-tumor cytotoxicity. I developed an analysis to quantify the contribution of signaling motifs to each of these biological functions. This work is the first implementation of combined high-throughput screening and machine learning/artificial intelligence to create an improved cell therapy prototype with enhanced in vitro and in mouse efficacy. This area of work improves our understanding of how signaling shapes T cell and macrophage function and provides a roadmap for accelerating design of receptors that give immune cells enhanced therapeutic phenotypes for cancers and chronic viral infections.

   Since starting my lab at Stanford in May 2023, we have extended our engineering to macrophages and natural killer cells, as well as T cell-macrophage dual cell systems. Our initial T cell and macrophage work are described in pre-prints.

2. Protein Folding/Graduate Career: My graduate research focused on understanding the kinetic mechanisms of coupled binding and conformational changes in proteins and RNAs. In this work I performed kinetic, thermodynamic, and structural experiments and used machine learning to globally fit a complex model to the data. The results of my research provided the first experimental demonstration that molecular recognition could occur through both induced fit (binding before conformational change) and conformational selection (conformational change before binding) in the same molecule. This challenged the current view of the field, which traditionally described molecular recognition as happening either exclusively through induced fit or conformational selection, but not both. My results also demonstrated that molecular recognition for complex systems can be well described in terms of flux, and that the flux through various molecular recognition pathways depends on the concentration of ligand and protein or RNA. This work to understand coupled binding and conformational change improves our understanding of biological regulation and conformational changes relevant to drug design.

3. Biotin Ligase Biophysics/Undergraduate Career: My early career contributions as an undergraduate were in determining the biochemical characteristics that make biotin protein ligases either able to transfer biotin (monofunctional) or able to both transfer biotin and regulate biotin biosynthesis (bifunctional). I measured the ability of the monofunctional biotin protein ligase from Pyrococcus horikoshii to bind biotin and ATP and its ability to dimerize. By comparing these biochemical properties to the properties of the bifunctional biotin protein ligase from Escherichia coli, I showed that the biotin-dependent dimerization is a critical feature of bifunctional (but not monofunctional) biotin protein ligases. The quantitative approach used here to understand protein structure-function relationships still informs some of my work.

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