BIOGRAPHICAL SKETCH

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NAME: Kyle Gabriel Daniels

eRA COMMONS USER NAME (credential, e.g., agency login): kgdan18

POSITION TITLE: Assistant Professor of Genetics

EDUCATION/TRAINING *(Most applicants will begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training and residency training if applicable. High school students should list their current institution and associated information. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	START DATE MM/YYYY	END DATE *(or expected end date)* MM/YYYY	FIELD OF STUDY
University of Maryland-College Park	BS	09/2006	05/2010	Biochemistry
Duke University	PhD	08/2010	08/2015	Biochemistry/Structural Biology and Biophysics
University of California San Francisco	Postdoctoral	09/2015	12/2021	Synthetic Biology/Immunology

A. Personal Statement

My laboratory is interested in understanding how information is encoded by the biophysical and structural characteristics of receptors, signaling adapters, and gene regulatory elements of immune cell signaling systems. The goals of our work are to decode natural signaling systems to understand their functions, and to encode specific instructions in synthetic signaling systems to engineer therapeutic cells. We use synthetic biology, high-throughput library screening, and machine learning to explore how various signaling modules control cell function (Daniels KG, Wang S, et al. *Science*. 2022). We are particularly interested in understanding how modular domains can be recombined in new combinations and arrangements to give rise to diverse cellular behaviors. 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 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 also using innovative library-on-library screening approaches to optimize multiple proteins or cell-types at once to develop next-generation therapies. This potentially transformative vision for cell therapy is discussed in our recent review article (Capponi S & Daniels KG, *Immunol. Rev. 2023*). Through our interdisciplinary research in biophysics, immune engineering, and machine learning, we hope to train a new generation of scientists capable of combining emerging technologies to solve problems in human health.

B. **Positions, Scientific Appointments, and Honors**

Positions and Scientific Appointments

2023– Present	Assistant Professor, Department of Genetics, Stanford University, Palo Alto, CA
2015-2023	Postdoctoral Fellow, Department of Cellular and Molecular Pharmacology, UCSF, San Francisco, CA

Honors and Awards

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

C. Contributions to Science

1. Postdoctoral 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. It both improves our understanding of how signaling shapes T cell function and provides a roadmap for accelerating design of receptors that give immune cells enhanced anti-cancer phenotypes.
    a. **Daniels KG**,Wang S, Simic MS, Bhargava HK, Capponi S, Tonai Y, Yu W, Bianco S, Lim WA. (2022) "Decoding CAR T Cell Phenotypes Using Combinatorial Signaling Motif Libraries and Machine Learning". Science. 378(6625), 1194-1200. Available from: 10.1126/science.abq0225, PMCID: PMC10025651
    b. O'Donoghue G, Bugaj L, Anderson W, **Daniels KG**, Rawlings D, Lim WA. (2021) "T Cells Selectively Filter Oscillatory Signals on the Minutes Timescale". PNAS. 118(9), e2019285118. Available from: 10.1073/pnas.2019285118. PMCID: PMC7936380

2. 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.
    a. **Daniels KG**, Suo Y, Oas TG. (2015) "Conformational kinetics reveals affinities of protein conformational states". PNAS 112(30):9352-9357. PMCID: PMC4522757
    b. Mosley PA, **Daniels KG** , Oas TG. (2015) "Electrostatic Energetics of Bacillus subtilis Ribonuclease P Protein Determined by NMR-based Histidine pKa_a Measurements". Biochemistry. 54(35), 5379-5388. PMCID: PMC4696772

c. **Daniels KG**, Tonthat NK, McClure DR, Chang Y, Liu X, Schumacher MA, Fierke CA, Schmidler SC, Oas TG. (2014) “Ligand concentration regulates the pathways of coupled protein folding and binding,” J. Am. Chem.
d. DeArmond PD, Xu Y, Strickland EC, **Daniels KG**, Fitzgerald MC (2011) “Thermodynamic Analysis of Protein-Ligand Interactions in Complex Biological Mixtures using a Shotgun Proteomics Approach,” J. Proteome Res.10(11), 4948-4958. PMCID: PMC3208786

3. 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.

    a. **Daniels KG** and Beckett, D. (2010) "Biochemical Properties and Biological Function of a Monofunctional Microbial Biotin Protein Ligase," Biochemistry. 49, 5358–5365. PMCID: PMC3126109

    A full list of publications can be found in My Bibliography at http://www.ncbi.nlm.nih.gov/sites/myncbi/12YM8PjVl49QV/bibliography/48326004/public/?sort=date&direction=ascending