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: Adam Christopher Palmer

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

POSITION TITLE: Assistant Professor of Pharmacology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
The University of Adelaide, Australia	B.Sc.	12/2004	Biochemistry; Chemistry; Physics
The University of Adelaide, Australia	B.Sc. (Honours)	12/2005	Biochemistry
Harvard University, Cambridge MA	Ph.D.	11/2012	Systems Biology
Harvard Medical School	Postdoctoral fellowship	09/2019	Systems Pharmacology

A. Personal Statement

Most systemic treatments for cancer involve the use of drug combinations, because clinical trials have found combination therapy more effective than monotherapy at improving patient survival. The goal of our research is to understanding in quantitative detail the mechanistic reasons for the clinically observed efficacy of approved combination therapies, and to apply the principles learned to the rational design of new combination therapies. The problem of how multiple drugs affect survival in populations of patients with heterogeneous diseases is a complex one. My training in the interdisciplinary field of systems biology, with particular focus on pharmacology and evolution, allows me to lead a research a group that approaches this problem with a mix of experimental cancer pharmacology, mathematical models of drug action and tumor evolution, and computational analysis of clinical trial data. Throughout my undergraduate, graduate, and postdoctoral research I have published interdisciplinary research that blends experiments with computation and theory to understand the dynamics of complex processes in biochemistry and evolution. My undergraduate research investigated how collisions between protein traffic on DNA is used for regulatory functions, and led to seven articles. My Ph.D. in Systems Biology at Harvard University was advised by Roy Kishony, an expert in how drug combinations affect the evolution of antibiotic resistance. I discovered counter-intuitive but mathematically understandable connections between mechanisms of drug action, drug interactions, and mechanisms of drug resistance, published in seven articles. Finding predictable relationships between drug mechanisms and clinical aspects of drug resistance inspired my transition to postdoctoral research on combination cancer therapy, where I believe the challenge of designing effective combination therapies is greatest. The ongoing development of many new cancer therapies, and the clear precedent that cancer medicines will be most effective when used in combinations, makes this a problem of compelling need and opportunity to improve healthcare. My postdoctoral research at Harvard Medical School was advised by Peter Sorger and produced a detailed mechanistic understanding of combined drug action by several clinically successful combination therapies. I found that a defining feature of many successful combinations was their capacity to overcome within-tumor and between-tumor heterogeneity. My approach expanded from laboratory experiments to include substantive analysis of data from human clinical trials and patient-derived tumor xenograft drug trials, and I developed a computational method that based on principles of heterogeneity could accurately predict the clinical efficacy of a majority of combination therapies for advanced cancers based only on the clinical efficacy of monotherapies.

At UNC Chapel Hill as a PI in the Department of Pharmacology, the Lineberger Comprehensive Cancer Center, and the Computational Medicine Program, my lab consists of experimental and computational

biologists and together we are experimentally measuring drug-drug interactions in regimens known to cure patients, applying these measured relationships in models and computer simulations of tumor drug response to existing regimens and potential novel regimens, and calibrating and interpreting these models using rich clinical trial data sets that, while they have defined the practice of clinical oncology, are largely untapped by biologists interested in understanding the mechanisms of effective cancer treatments.

B. Positions and Honors

Positions and Employment

2012-2019 Postdoctoral Fellow, Laboratory of Systems Pharmacology, Harvard Medical School, Boston
2019- Assistant Professor, Department of Pharmacology / Computational Medicine Program / Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill

Other Experience and Professional Memberships

2013- Member, American Association for Cancer Research
2003- Board of Advisors, Senior Services of Eastern Missouri
2003-05 NIH Peer Review Committee: Psychobiology of Aging, ad hoc reviewer
2007-11 NIH Risk, Adult Addictions Study Section, members

Honors

2001-2004 Adelaide Undergraduate Scholarship
2005 Adelaide Priority Honours Scholarship
2005 University Medal
2005 Honours Alumni University Medal
2007-2010 George Murray Scholarship
2008 Harvard University Certificate of Distinction in Teaching
2013-2015 James S. McDonnell Foundation Postdoctoral Fellowship in Studying Complex Systems
2015-2017 Early Career Fellowship (Overseas Biomedical), National Health and Medical Research Council

C. Contributions to Science

1. Quantitative laws that describe how combination therapy overcomes tumor heterogeneity. The efficacy of combination cancer therapy was historically understood as arising from overcoming tumor heterogeneity by reducing the probability of drug resistance (as with multidrug therapy for tuberculosis). In recent decades, a profoundly different rationale of synergistic drug interactions has dominated the development of drug combinations. Classical definitions of drug independence or synergy were inapplicable to clinical trials because of the complexity of large patient-to-patient variation in drug response, which is nearly always true of cancer therapies. I developed a computer simulation that adapted pharmacological principles to clinical distributions of drug responses, producing the first method to test whether Kaplan-Meier plots of patient survival are consistent with drug independence or synergy. I discovered that a majority of FDA-approved combination therapies for advanced cancers are neither synergistic nor even additive, but instead the observed survival benefits were fully explained only by increasing each patients' chance that at least one drug works well itself (equivalently, decreasing the probability that all drugs fail). This research overturned a dogma that drug synergy is needed for clinical efficacy, validated the historical rationale for combination therapy and instantiated it as a model that can use monotherapy data to predict the clinical efficacy of most combination therapies (#a). Subsequently, I analyzed nearly all FDA-approved combination therapies with an immune checkpoint inhibitor, which have become standard first-line treatment for many common cancers, and found that every such combination has clinical activity precisely consistent with prediction (Pearson $r=0.98$, $P<10^{-8}$, $n=4173$ patients in 14 trials) (#b). Curative outcomes cannot be explained by monotherapy activity, and so I experimentally studied the treatment of diffuse large B-cell lymphoma (DLBCL) by the curative combination R-CHOP (rituximab, cytoxan, doxorubicin, vincristine, prednisone). I discovered that this combination also is not synergistic, but has additive efficacy, and high-complexity

clone-tracing and genome-wide CRISPR screens found it to be highly effective at overcoming within-tumor heterogeneity (decreasing the probability that any clone within a patient will resist all drugs) (#c). Together, my analysis of human clinical trials and my experiments on a clinically-proven combination identified the management of between-tumor and within-tumor heterogeneity as key features of effective drug combinations, identified the quantitative laws describing those effects, and produced analytical and experimental methods for the identification of novel combinations with these advantageous traits.

a) **Palmer AC**, Sorger PK. 2017. Combination cancer therapy can confer benefit via patient-to-patient variability without drug additivity or synergy. Cell 171:p1678

b) **Palmer AC**, Izar B, Sorger PK. Combinatorial benefit without synergy in recent clinical trials of immune checkpoint inhibitors. MedRxiv 2020.01.31.20019604v2 [**Preprint**]. July 10, 2020. Available from doi.org/10.1101/2020.01.31.20019604

c) **Palmer AC**, Chidley C, Sorger PK. A curative combination cancer therapy achieves high fractional cell killing through low cross-resistance and drug additivity. eLife 8:e50036

2. Graduate research – Gene-drug interactions in the evolution of antibiotic resistance. I conducted my graduate research with Prof. Roy Kishony, an expert in how drug combinations affect the evolution of antibiotic resistance. Building on my biochemistry training in a group with expertise in evolution, I studied how gene-gene, gene-drug, and drug-drug interactions control the evolutionary paths and mechanisms of antibiotic resistance. I discovered that the natural degradation of a drug into a mixture of bioactive compounds can impose selection against resistance (#a). I discovered that overexpression of a drug target can both increase, decrease, or have no effect on drug resistance, and derived a model that relates these surprising results to distinct molecular mechanisms (#c); this has major relevance to drug discovery because many methods for drug target identification are based on screening for drug resistance (or susceptibility) in cells that overexpress (or underexpress) candidate target genes. I developed a technology for rapid genome-wide screening for resistance-conferring expression changes and thereby identified hundreds of pathways to resistance across dozens of antibiotics (in revision). My study of multistep evolution of drug resistance (#d) overturned the previously held view that genetic interactions between mutations constrain evolution; I showed that genetic interactions shape the course of evolution equally by excluding some adaptive mutations and also by creating new opportunities for evolution. I described tools to study resistance evolution in the laboratory that may anticipate modes of resistance and thereby enable the design of resistance-delaying therapeutic strategies (#b).
   a) **Palmer AC**, Angelino E, Kishony R. 2010. Chemical decay of an antibiotic inverts selection for resistance. Nature Chemical Biology 6:105-7

   b) **Palmer AC** and Kishony R. 2013. Understanding, predicting and manipulating the genotypic evolution of antibiotic resistance. Nature Reviews Genetics 14:243

   c) **Palmer AC** and Kishony R. 2014. Opposing effects of target overexpression reveal drug mechanisms. Nature Communications 5:4296

   d) **Palmer AC***, Toprak E*, Baym MH, Kim S, Veres A, Bershtein S, Kishony R. 2015. Delayed commitment to evolutionary fate in antibiotic resistance fitness landscapes. Nature Commmunications 6:7385 (* contributed equally).

3. Undergraduate research – Transcriptional Interference by protein traffic on DNA. I built the first stochastic simulation of protein traffic on DNA, a process where interactions among RNA polymerases, DNA-binding proteins, and promoters cause transcriptional interference (#a). My undergraduate thesis combined *in vivo* measurements of transcriptional interference with simulations, and led to the discovery that RNA polymerase pausing can generate strong transcriptional interference by occluding regulatory elements (#b). My review of the phenomenon (#c) has been cited equally in studies of microbial and mammalian gene regulation, following discoveries by others that long intergenic non-coding RNAs (lincRNAs) can operate via mechanisms similar to those that I described in bacteria. My DNA traffic simulations contribute to ongoing research in this area (#d).

a. Sneppen K, Dodd IB, Shearwin KE, **Palmer AC**, Schubert RA, Callen BP, Egan JB. 2005. A mathematical model for transcriptional interference by RNA polymerase traffic in Escherichia coli. Journal of Molecular Biology 18:399-409

b. **Palmer AC**, Ahlgren-Berg A, Egan JB, Dodd IB, Shearwin KE. 2009. Potent transcriptional interference by pausing of RNA polymerases over a downstream promoter. Molecular Cell 34:545-555

c. **Palmer AC**, Egan JB, Shearwin KE. 2011. Transcriptional interference by RNA polymerase pausing and dislodgement of transcription factors. Transcription 2:9-14

d. Hao N, **Palmer AC**, Ahlgren-Berg A, Shearwin KE, Dodd IB. 2016. The role of repressor kinetics in relief of transcriptional interference between convergent promoters. Nucleic Acids Research 44:6625