BIOGRAPHICAL SKETCH

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NAME: Palmer, Adam Christopher

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POSITION TITLE: Assistant Professor of Pharmacology

EDUCATION/TRAINING

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, Boston MA	Postdoctoral	09/2019	Systems Pharmacology

A. Personal Statement

I am a **systems biologist and pharmacologist studying combination cancer therapy**, especially in the context of **clinical trial data**, through a synthesis of experiments, computational analysis, and modeling. I am a member of the Department of Pharmacology, Computational Medicine Program, and UNC Lineberger Comprehensive Cancer Center. I have developed computer simulations of clinical trials that use the clinical efficacy of single drugs to predict the clinical efficacy of drug combinations, including chemotherapies, targeted therapies, and immunotherapies [1]. **My models have been prospectively validated by 9 FDA approvals** of combination therapies that improve survival for >100,000 patients per year in the United States [2]. Specifically, Progression Free Survival distributions in practice-changing trials were statistically indistinguishable from model predictions, in advanced/metastatic head and neck cancer, gastric cancer, renal cell carcinoma, PD-L1+ triple-negative breast cancer, non-small cell lung cancer, and small cell lung cancer [2]. My methods are applied in the pharmaceutical industry to design combination therapy trials in oncology. My laboratory studies the mechanistic basis for the clinical efficacy of approved combinations of cancer therapies, and applies the principles learned toward predictive, model-guided design of new combination therapies. My research has ~1900 citations and I have 15 publications in Nature and Cell series journals.

My interdisciplinary training as a systems biologist, with a focus on pharmacology and evolution, allows me to lead a group that studies combination cancer therapy using a mix of experimental pharmacology, mathematical models of drug action and tumor evolution, and computational analysis of clinical trial data. At all stages of my career I have published research that combines experiments with computation and theory to understand the dynamics of complex processes in biochemistry and evolution. My undergraduate research discovered regulatory functions arising from collisions between protein traffic on DNA and was published in seven articles. My Ph.D. in Systems Biology at Harvard University was advised by Roy Kishony and studied how combination therapy affects the evolution of antibiotic resistance, and was published in seven articles. Our findings of predictable relationships between drug mechanisms and clinical drug resistance inspired my transition to cancer biology, where I believe the design of combination therapies is a problem of compelling need and opportunity to improve healthcare. My postdoctoral research with Peter Sorger at Harvard Medical School produced a predictively accurate understanding of combined drug action by many effective combination therapies [1], including the majority of FDA-approved combinations with immune checkpoint inhibitors [2]. My approach expanded from my background in experimental and theoretical molecular biology, to include substantive modeling and analysis of human clinical trials, which now has equal importance in my group, closely integrated with our experimental research on the systems pharmacology of drug combinations.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021 – Present Investigator Grants Peer Review Committee, National Health & Medical Research Council
2019 – Present Assistant Professor, Department of Pharmacology and Computational Medicine Program, University of North Carolina at Chapel Hill
2019 – Present Member, UNC Lineberger Comprehensive Cancer Center
2012 – 2019 Postdoctoral Fellow, Laboratory of Systems Pharmacology, Harvard Medical School, Boston
2013 – Present Member, American Association for Cancer Research
2006 – 2007 Research Fellow, The University of Adelaide, Australia

Honors

2021 V Scholar Award, V Foundation for Cancer Research
2019 Investigator Grant, National Health and Medical Research Council, Australia (declined)
2015-2017 Early Career Fellowship (Overseas), National Health and Medical Research Council, Australia
2013-2015 James S. McDonnell Foundation Postdoctoral Fellowship in Studying Complex Systems
2008 Harvard University Certificate of Distinction in Teaching
2007-2010 George Murray Scholarship
2005 Honours Alumni University Medal
2005 University Medal
2005 Adelaide Priority Honours Scholarship
2001-2004 Adelaide Undergraduate Scholarship

C. Contributions to Science

I. Quantitative laws that describe how combination therapy overcomes tumor heterogeneity. The historical rationale for combination cancer therapy was to address tumor heterogeneity with different mechanisms of drug action. In recent decades, synergistic drug-drug interaction has been the dominant motivation to combine drugs; this is a different mechanism. I developed the first quantitative method to test for drug independence or synergy in Progression-Free Survival results from drug combination trials, and applied it to data from thousands of patients and thousands of patient-derived tumor xenografts. I discovered that a majority of FDA-approved combination therapies for advanced cancers show no evidence of 'more-than-additive' interaction, and most trial results are as expected from overcoming **inter-patient heterogeneity** with independently active drugs [1]. This overturned a dogma that drug interaction is needed for effective combination therapy, confirmed the neglected historical rationale, and implemented the historical idea as a predictive model. After its initial publication, the model's accuracy was validated by accurately predicting the efficacy of nearly all FDA-approved combination therapies with immune checkpoint inhibitors: predicted PFS distributions were near perfectly correlated with clinical results (Pearson r=0.96, $P<10^{-8}$, n=4173 patients in 14 trials) [2].

Curative outcomes cannot be explained merely by responses to the most active monotherapy in a regimen, 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) [3]. Together, my analysis of many human clinical trials and experimental studies of a clinically-proven regimen identified the control 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. These models are now used in the pharmaceutical industry to design clinical trials. Our finding that inter-patient variation has such a strong impact on the efficacy of drug combinations is widely relevant to precision oncology and improving treatment strategies for many types of cancer [4].

(1) **Palmer AC**, Sorger PK (2017)
Combination cancer therapy can confer benefit via patient-to-patient variability without drug additivity or synergy.
Cell 171:p1678 PMCID: PMC5741091

(2) **Palmer AC**, Izar B, Hwangbo H, Sorger PK (2022)
Predictable Clinical Benefits without Evidence of Synergy in Trials of Combination Therapies with Immune-Checkpoint Inhibitors.
Clinical Cancer Research 28:p368 PMCID: PMC9068233

(3) **Palmer AC***, Chidley C*, Sorger PK (2019) (* contributed equally)
A curative combination cancer therapy achieves high fractional cell killing through low cross-resistance and drug additivity.
eLife 8:e50036 PMCID: PMC6897534

(4) Plana D*, **Palmer AC*‡**, Sorger PK‡ (2022) (*contributed equally, ‡ co-corresponding)
Independent Drug Action in Combination Therapy: Implications for Precision Oncology.
Cancer Discovery 12:p606 PMCID: PMC8904281

II. Synergistic combination therapies for biomarker-defined subsets of cancers. My research on patient-to-patient variability in drug response [1] suggested that in unselected populations, too few patients have tumors responsive to each drug in a combination for potential synergistic drug interactions to be clinically detectable. However, synergy may occur in biomarker-defined subsets of patients. I have collaborated with oncologists and industry to contribute to the discovery of biomarkers of drug response, and analysis of synergy, to develop combination therapies for biomarker-identified subsets of ovarian cancers [5], breast cancers [6], and non-Hodgkin lymphomas [7, 8]. I contributed computational analyses that identified synergistic interaction between CDK4/6 inhibition and HER2 inhibition in HER2-positive breast cancer [6], which was tested in a phase 2 randomized clinical trial (NCT02675231, monarcHER trial, 237 patients). This trial demonstrated that a triplet of targeted therapies (abemaciclib, trastuzumab, fulvestrant) elicits more durable Progression Free Survival than chemotherapy. If these results are confirmed in a phase 3 trial they could establish a superior, chemotherapy-free combination regimen for patients with hormone receptor-positive, HER2-positive advanced breast cancer.

(5) **Palmer AC***, Plana D*, Gao H*, Korn JM, Yang G, Green J, Zhang X, Velazquez R, McLaughlin ME, Ruddy DA, Kowal C, Goldovitz J, Bullock C, Rivera S, Rakiec DP, Elliott G, Fordjour P, Meyer R, Loo A, Kurth E, Engelman JA, Bitter H, Sellers WR, Williams JA, Sorger PK (2020) (* contributed equally)
A proof of concept for biomarker-guided targeted therapy against ovarian cancer based on patient-derived tumor xenografts.
Cancer Research 80:4278 PMCID: PMC7541581

(6) Goel S, Wang Q, Watt AC, Tolaney SM, Dillon DA, Li W, Ramm S, **Palmer AC**, Yuzugullu H, Varadan V, Tuck D, Harris LN, Wong KK, Liu XS, Sicinski P, Winer EP, Krop IE, Zhao JJ (2016)
Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers With CDK4/6 Inhibitors.
Cancer Cell 29:p255 PMCID: PMC4794996

(7) Koch R, Christie AL, Crombie JL, **Palmer AC**, Plana D, Shigemori K, Morrow SN, Van Scoyk A, Wu W, Brem EA, Secrist JP, Drew L, Schuller A, Cidado J, Letai A, Weinstock DM (2019)
Biomarker-driven strategy for MCL1 inhibition in T-cell lymphomas.
Blood 133:p566 PMCID: PMC6367646

(8) He Y, Koch R, Budamagunta V, Zhang P, Zhang X, Khan S, Thummuri D, Ortiz YT, Zhang X, Lv D, Wiegand JS, Li W, **Palmer AC**, Zheng G, Weinstock DM, Zhou D (2020)
DT2216—a Bcl-xL-specific degrader is highly active against Bcl-xL-dependent T cell lymphomas.
Journal of Hematology & Oncology 13:95 PMCID: PMC7364785

III. Graduate research – Gene-drug interactions in the evolution of antibiotic resistance. I conducted graduate research with Prof. Roy Kishony on how drug combinations affect the evolution of antibiotic resistance. I discovered that the natural degradation of a drug into a mixture of bioactive compounds can impose selection against resistance [9]. 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 counter-intuitive results to differences in molecular mechanism of action [10]. This is relevant to drug discovery

because many methods for drug target identification are based on screening for resistance (or susceptibility) in cells that overexpress (or underexpress) possible drug targets. 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. My study of multistep evolution of drug resistance [11] overturned the prior view that genetic interactions among mutations constrain evolution; I showed that genetic interactions shape evolution equally by excluding some adaptive mutations and also by creating new opportunities. 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 [12].

(9) **Palmer AC**, Angelino E, Kishony R (2010)
Chemical decay of an antibiotic inverts selection for resistance.
Nature Chemical Biology 6:105-7 PMCID: PMC2811317

(10) **Palmer AC** and Kishony R (2014)
Opposing effects of target overexpression reveal drug mechanisms.
Nature Communications 5:4296 PMCID: PMC4408919

(11) **Palmer AC***, Toprak E*, Baym M, Kim S, Veres A, Bershtein S, Kishony R (2015) (*contributed equally)
Delayed commitment to evolutionary fate in antibiotic resistance fitness landscapes.
Nature Commmunications 6:7385. PMCID: PMC4548896

(12) **Palmer AC** and Kishony R (2013)
Understanding, predicting and manipulating the genotypic evolution of antibiotic resistance.
Nature Reviews Genetics 14:243 PMCID: PMC3705945

IV. Undergraduate research – Transcriptional Interference by protein traffic on DNA. As an undergraduate I wrote the first computer simulation of protein traffic on DNA, a process where interactions among RNA polymerases, DNA-binding proteins, and promoters cause transcriptional interference (the lead authors made analytical and mean-field models, I made the stochastic simulation [13]). My undergraduate thesis combined *in vivo* measurements of transcriptional interference with simulations, and discovered that RNA polymerase pausing generates transcriptional interference by occluding regulatory elements [14]. My review of the phenomenon [15] has been cited 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 I discovered in bacteria. My DNA traffic simulations are continuing to contribute to research on viral and microbial gene regulation [16].

(13) 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 PMID: 15670592

(14) **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 PMCID: PMC2697128

(15) **Palmer AC**, Egan JB, Shearwin KE (2011)
Transcriptional interference by RNA polymerase pausing and dislodgement of transcription factors.
Transcription 2:9-14 PMCID: PMC3023640

(16) 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 PMCID: PMC5001618

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