BIOGRAPHICAL SKETCH

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NAME: Palmer, Adam Christopher

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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. Add/delete rows as necessary.)*

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 [1, 3-7]. **My models have been prospectively validated by 9 FDA approvals**, where Progression Free Survival distributions in phase 3 trials were statistically indistinguishable from my model's predictions, across head and neck cancer, gastric cancer, renal cell carcinoma, triple-negative breast cancer, non-small cell lung cancer, and small cell lung cancer [5]. My methods are applied in the pharmaceutical industry to design combination therapy trials. My laboratory studies the mechanistic basis for the clinical efficacy of combinations of cancer therapies, and applies the principles learned in collaboration with clinicians and companies to develop new combination therapies and clinical trials. My articles have >2000 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. My undergraduate research discovered regulatory functions arising from colliding protein traffic on DNA and was published in seven articles. My Ph.D. in Systems Biology investigated how combination therapy affects the evolution of antibiotic resistance, and was published in seven articles. My finding of predictable relationships between drug mechanisms and clinical drug resistance inspired my transition to cancer biology, where the design of combination therapies is a problem of compelling need. My postdoctoral research 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 [5]. 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

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
2021	Investigator Grants Peer Review Committee, National Health & Medical Research Council
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. **How inter-patient and intra-tumor heterogeneity affect combination therapy.** The historical rationale for combination cancer therapy was to address tumor heterogeneity. In recent decades, synergistic drug interactions have become a dominant motivation to combine drugs; this is a different mechanism. By analyzing drug responses in thousands of patients, and thousands of patient-derived tumor xenografts, I discovered that **inter-patient heterogeneity** in single drug response is a major contributor to the clinical efficacy of combination therapies [1]. I experimentally studied drug interactions and cross-resistance in a curative regimen for Diffuse Large B-Cell Lymphoma, RCHOP, and discovered that it is highly effective at overcoming **intra-tumor heterogeneity** via diverse, non-interacting mechanisms of drug action [2]. My lab has built models that unify inter-patient and intra-tumor heterogeneity and showed that their joint effect explains the curability of pediatric Acute Lymphocytic Leukemia by drug combinations throughout decades of trials [3]. Our finding that inter-patient variation has a dominant impact on the efficacy of drug combinations is relevant to precision oncology and trial design in 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***, 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

(3) Pomeroy AE, Schmidt EV, Sorger PK, **Palmer AC** (2022)
Drug independence and the curability of cancer by combination chemotherapy.
Trends in Cancer 8:p915 PMCID: PMC9588605

(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. **Predictive models of the clinical efficacy of drug combinations.** We have implemented principles of tumor heterogeneity as predictive models, which use measured single-drug response distributions to predict multi-drug response distributions (Kaplan-Meier PFS curves). Our initial model (1) has been prospectively validated by accurately predicting the clinical efficacy of nearly all FDA-approved combination therapies with immune checkpoint inhibitors up to 2020 [5]. We have retrospectively analyzed the past 25 years of FDA approved drug combinations and found that 95% are additive (or less); in cases where monotherapy data was available, 100% of approved combinations were expected to succeed according to our model, and a majority of negative trials (>75%) were expected to fail [6]. These methods are now used in the pharmaceutical industry to design clinical trials of drug combinations [7]. A new arm of a phase 2 trial in high-risk subtypes of Peripheral T-Cell Lymphoma, of CHEP-brentuximab-vedotin and consolidative stem cell transplant, is soon opening, and was designed in collaboration with City of Hope Medical Center with the assistance of our simulations (NCT03113500).

(5) **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

(6) Hwangbo H, Patterson SC, Dai A, Plana D, **Palmer AC** (2022)
Additivity predicts the efficacy of most approved combination therapies for advanced cancer. medRxiv 22281013 **[Preprint]**. October 22, 2022.
Available from doi.org/10.1101/2022.10.21.22281013

(7) Schmidt EV, Sun LZ, **Palmer AC**, Chen C (2023)
Rationales for Combining Therapies to Treat Cancer.
Annual Review of Cancer Biology (posted online January 17, 2023 ahead of publication in April)
Available from doi.org/10.1146/annurev-cancerbio-061421-020411

III. **Synergistic drug combinations for biomarker-defined subsets of cancers**. My studies of approved drug combinations suggest that in unselected populations, too few tumors are responsive to both drugs for synergy to be clinically detectable [1]. However, synergy may occur in biomarker-defined subsets. I have collaborated with oncologists and industry to discover biomarkers of drug response, and analysis of synergy, to develop drug combinations for biomarker-identified subsets of ovarian cancers [8], breast cancers [9], and non-Hodgkin lymphomas [10, 11]. My analyses identified synergistic interaction between CDK4/6 inhibition and HER2 inhibition in HER2+ breast cancer [9], which was tested in a phase 2 trial (NCT02675231, monarcHER trial, 237 patients). This trial demonstrated that a triplet of targeted therapies (abemaciclib, trastuzumab, fulvestrant) elicits superior Progression Free Survival and Overall Survival compared with chemotherapy. If these results are confirmed in phase 3, they could establish a superior, chemotherapy-free treatment for hormone receptor+, HER2+ advanced breast cancer.

(8) **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

(9) 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

(10) 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

(11) 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

IV. **Graduate – Gene-drug interactions in the evolution of antibiotic resistance**. My graduate research studied how drug combinations affect the evolution of antibiotic resistance. I discovered that natural degradation of a drug into various bioactive compounds can select against drug resistance [12]. I discovered that overexpression of drug targets can both increase, decrease, or have no effect on drug resistance, and relates these differences to molecular mechanisms of action [13]. This is relevant to drug discovery because many methods for target identification are based on screening for resistance in cells that overexpress putative drug targets. I developed a technology for rapid genome-wide screening for resistance-conferring expression changes and identified hundreds of pathways to resistance across dozens of antibiotics. My study of multistep evolution of drug resistance showed that genetic interactions both exclude some adaptive mutations but also create new possibilities [14]. I described how laboratory evolution can anticipate modes of drug resistance and design resistance-delaying strategies [15].

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

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

(14) **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

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

V. **Undergraduate - Transcriptional Interference by protein traffic on DNA**. As an undergraduate I wrote the first computer simulation of protein traffic on DNA, where interactions among RNA polymerases, DNA-binding proteins, and promoters cause transcriptional interference [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 continued to contribute to research on viral and microbial gene regulation [16].

(16) 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

(17) **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

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

(19) 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

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/43899785/?sort=date&direction=descending