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: Palmer, Adam Christopher

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. 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 computational analysis of clinical data, pharmacological simulations, and experimental pharmacology. I am a member of the Department of Pharmacology, Computational Medicine Program, and UNC Lineberger Comprehensive Cancer Center. I have developed simulations of clinical trials that use the clinical efficacy of single drugs to predict the clinical efficacy of drug combinations [2, 6-9]. **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 [8]. My methods are applied in the pharmaceutical industry to design combination therapy trials. My analyses of drug combination trials have **changed clinical practice by introducing precision medicine to first-line of treatment of the most common blood cancer** [5]. My laboratory studies the mechanistic basis for the clinical efficacy of combinations of cancer therapies, and applies the principles learned in collaboration with biologists, clinicians and companies to develop new combination therapies and clinical trials. My articles have been cited >4000 times, including 32 publications in the Nature, Cell, and American Association for Cancer Research (AACR) families of 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 computational analysis of clinical trial data, experimental pharmacology, and mathematical models of drug action and tumor evolution. 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. As a postdoctoral fellow I transitioned to cancer biology where the design of combination therapies is a problem of compelling need. My postdoctoral research created a foundation for predictively accurate models of combined drug action in oncology [6,7]. As a PI I have developed quantitatively accurate models of the clinical efficacy of decades of FDA-approved drug combinations [9] including immune checkpoint inhibitors [8], chemoimmunotherapy regimens for Diffuse Large B-Cell Lymphoma (DLBCL) [2], and the effect of combining bridging therapies with CAR T-cell therapies [4].

Ongoing projects I would like to highlight include:

R01CA279968, NIH/NCI
Palmer (PI)
01/26/24 – 01/25/29
Modeling and analysis of curative combination therapy for Diffuse Large B-Cell Lymphoma

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2025	Blood Cancer grant review committee, New Jersey Commission on Cancer Research
2024	*Ad hoc* reviewer, MCTA and NCI P01 study sections; invited for quantitative pharmacology
2023 – Present	OncoCollective Biomarkers Working Group
2021 – 2022	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. **Pharmacologic models that explain the clinical efficacy of curative regimens for blood cancers.** To understand mechanistic principles of curative regimens for Diffuse Large B-Cell Lymphoma (DLBCL) I experimentally studied drug interactions and cross-resistance in the curative-intent RCHOP combination and discovered it overcomes intra-tumor heterogeneity via diverse, non-interacting (not synergistic) mechanisms of drug action [1]. We built quantitative models of these pharmacologic principles in human populations to understand and predict the clinical efficacy of RCHOP+X regimens, developing a 'bottom-up' mechanistic model of curative therapy that reproduces observed Progression-Free Survival distributions [2]. We showed how principles of independent drug action, in contrast to contemporary focus on synergistic interaction, explain decades of progress in curative-intent regimens for pediatric acute lymphocytic leukemia [3]. We extended these approaches to model population-pharmacokinetics and pharmacodynamics of CAR T-cell therapies for LBCL, explaining inter-patient variance in outcomes, the prognostic effect of CAR T expansion and tumor burden, and how pre-infusion tumor debulking could improve the rate of durable (essentially curative) response to CAR T-cell therapy [4].

(1) **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

(2) Pomeroy AE, **Palmer AC** (2025)
A model of intra-tumor and inter-patient heterogeneity explains clinical trials of curative combination therapy for lymphoma
Blood Cancer Discovery 6:p254 PMCID: PMC12050944

(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) Pomeroy AE, Sworder BJ, Plana D, Cao Y, Alizadeh AA, **Palmer AC** (2025)
A pharmacologic model predicts that tumor debulking improves CAR T-cell efficacy in Large B-Cell Lymphoma
Blood Cancer Discovery 7:41 PMCID: PMC12626407

II. **Precision medicine for first-line treatment of the most common blood cancer.** For over 20 years Diffuse Large B-Cell Lymphoma (DLBCL), the most common blood cancer, was known to have two subtypes but their treatment was uniform. Our article in *The New England Journal of Medicine* [5] (a collaboration between this proposal's Co-I Palmer and PI Alizadeh) was the first to establish the clinical value of subtype-specific first-line treatment for DLBCL. We showed that the antibody-drug conjugate polatuzumab-vedotin, which is approved for the treatment of DLBCL in the pola-R-CHP regimen, had in seven independent clinical studies consistently shown greater efficacy in one subtype versus the other. We showed that in the phase 3 POLARIX trial, which had led to approval of pola-R-CHP, the reason the trial observed no *net* change in overall survival (Hazard Ratio 1.0) was because polatuzumab-vedotin improved overall survival in one subtype (Hazard Ratio for death 0.27) but worsened survival in the other (Hazard Ratio 1.64) [5]. This discovery justifies subtype-specific use of polatuzumab-vedotin, which will reduce deaths from DLBCL and **save the US healthcare system approximately $1 Billion per year** (cost of ≈$100,000 per patient × ≈10,000 patients per year with the subtype that should not be treated with polatuzumab-vedotin at their first-line of care).

(5) **Palmer AC**, Kurtz DM, Alizadeh AA (2023)
Cell-of-Origin Subtypes and Therapeutic Benefit from Polatuzumab Vedotin
The New England Journal of Medicine 389:p764-766

III. **Predictive models of the clinical efficacy of drug combinations.** 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. My work has shown that variation in single-drug response, both between patients and among tumor subclones, explains most of the clinical efficacy of combination therapy. By analyzing drug responses in thousands of patients and patient-derived tumor xenografts, I discovered that inter-patient variation in drug response is a major contributor to the efficacy of combination therapies [6], which has implications for precision oncology and biomarker-based endpoints in clinical trials [7]. Our theory has been prospectively validated by accurately predicting the clinical efficacy of nearly all FDA-approved combination therapies with immune checkpoint inhibitors up to 2020 [8]. Across 25 years of FDA approved drug combinations with available monotherapy data, 100% of approved combinations were expected to succeed according to our model, and a majority of negative trials (>75%) were expected to fail [9]. Our models are now used in the pharmaceutical industry to design clinical trials.

(6) **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

(7) 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

(8) **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

(9) Hwangbo H, Patterson SC, Dai A, Plana D, **Palmer AC** (2022)
Additivity predicts the efficacy of most approved combination therapies for advanced cancer.
Nature Cancer 4:1693 PMID: 37974028

IV. **Precision therapy strategies for T-cell lymphomas.** Peripheral T-cell lymphomas are aggressive, heterogeneous, and most subtypes still have low cure rates by standard chemotherapy regimens. My work has addressed the clinical dilemma that new targeted therapies have been active only in subsets of patients, by identifying which lymphoma subtypes are most likely to benefit from which specific drug mechanisms. Both in my own lab, and in collaboration with clinicians and companies, we have combined functional genomics, proteomics, drug-sensitivity profiling, and clinical trial analysis and modeling to develop biomarker-based strategies for inhibitors of anti-apoptotic BCL-2 family proteins [10, 11], anti-folates [12], and histone deacetylase inhibitors [13].

(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) 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

(12) Pantazis JC, Pomeroy AE, **Palmer AC** (2026)
Functional genomics and proteomics identify Folate Carrier SLC19A1 as a predictor of pralatrexate sensitivity in diverse T-cell lymphoma models
Molecular Cancer Therapeutics (*accepted, in press*)

(13) Pantazis JC, **Palmer AC** (2026)
Cross-resistance of belinostat and romidepsin in non-T-follicular helper Peripheral T-Cell Lymphoma models suggests subtype-specific implications for belinostat-CHOP
Molecular Cancer Therapeutics 25:672 PMID: 41403140

V. **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 [14]. 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 [15]. 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 [16]. I described how laboratory evolution can anticipate modes of drug resistance and design resistance-delaying strategies [17].

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

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

(16) **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

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

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