BIOGRAPHICAL SKETCH

NAME: Aaron Samuel Meyer

eRA COMMONS USER NAME: aameyer1

POSITION TITLE: Assistant Professor of Bioengineering

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of California, Los Angeles (UCLA)	B.S.	6/2009	Bioengineering
Massachusetts Institute of Technology (MIT)	Ph.D.	6/2014	Biological Engineering

A. Personal Statement

I have a background in biological engineering, with training in applied machine learning, cell signaling, and pharmacodynamics. My research broadly applies integrated experimental and theoretical approaches to study the complex signaling that underlies cell-to-cell communication and resistance to therapies. My lab is particularly interested in how signaling cues operate in combination to direct cancer and immune effector cell behavior and how we might optimally target their dysregulation. For example, my previous work has shown how (1) to use a pharmacodynamic model of IL-2 signaling across cell populations to engineer cell-specific cytokines, (2) IgG antibody effector function is transduced through multiple receptors and effector cells, (3) an RTK family expressed in cancer and innate immune cells is activated in response to extracellular cues in the tumor microenvironment, and (4) receptor crosstalk is a mechanism of signal diversification promoting breast tumor invasion.

I have extensive experience with projects that merge quantitative molecular biology with computational analysis such as in the work described here. This experience includes a track record of success mentoring graduate students, postdoctoral associates, and technical associates.

1. Farhat, A.M., A.C. Weiner, C. Posner, Z.S. Kim, B. Orcutt-Jahns, S.M. Carlson, **A.S. Meyer**. (2021). Modeling Cell-Specific Dynamics and Regulation of the Common Gamma Chain Cytokines. *Cell Reports.* 35(4): 109044. PMCID: 8179794.
2. Robinett, R.A., N. Guan, A. Lux, M. Biburger, F. Nimmerjahn, **A.S. Meyer**. (2018). "Dissecting FcγR Regulation Through a Multivalent Binding Model." *Cell Systems.* 6(7): 1–8. PMCID: 6062446.
3. **Meyer, A.S.**†, A.J.M. Zweemer, D.A. Lauffenburger†. (2015). The AXL Receptor Is a Sensor of Ligand Spatial Heterogeneity. *Cell Systems*, 1(1): 25–36. PMCID: 4520549.
4. **Meyer, A.S.**, M.A. Miller, F.B. Gertler, D.A. Lauffenburger. (2013). The receptor AXL diversifies EGFR signaling and limits the response to EGFR-targeted inhibitors in triple-negative breast cancer cells. *Science Signaling*, 6(287), ra66. PMCID: 3947921.

†Co-corresponding authors.

B. Positions and Honors

Positions and Employment

2006–2009 Undergraduate Researcher, Bioengineering Department, UCLA
2008 Summer Intern, Bioprocess Development Division, Schering-Plough Corporation, Watchung, NJ
2009–2014 Graduate Researcher, Department of Biological Engineering, MIT
2014–2017 Principal Investigator/Research Fellow, Koch Institute for Integrative Cancer Research, MIT
2017–Present Assistant Professor, Bioengineering Department, UCLA
2017–Present Member, Broad Stem Cell Research Center, UCLA

2017–Present Member, Jonsson Comprehensive Cancer Center, UCLA
2018–Present Member, Bioinformatics Interdepartmental Program, UCLA

Other Experience and Professional Memberships

2010–Present Member, Biomedical Engineering Society
2014–2017 Committee Member, Association of Early Career Cancer Systems Biologists
2015–Present Organizer, Systems Approaches to Cancer Biology meeting
2017–Present Chair, Association of Cancer Systems Biologists

Honors

2009 Momenta Presidential Fellowship, MIT
2009 Graduate Research Fellowship, National Science Foundation
2010 Breast Cancer Research Predoctoral Fellowship, Department of Defense
2012 Repligen Fellowship in Cancer Research, Koch Institute
2012 Travel grant to attend PTMs in Cell Signaling Conference in Copenhagen, Denmark
2013 Whitaker Fellowship, MIT
2013 Siebel Scholar, Class of 2014
2016 Ten to Watch, Amgen Scholars Foundation
2017–2019 Fellowship, Terri Brodeur Breast Cancer Foundation
2019 UCLA Hellman Fellow
2019 UCLA Faculty Career Development Award
2021 Northrop Grumman Excellence in Teaching Award

C. Contributions to Science

Understanding and targeting receptor family communication

Receptor families can have many ligands and receptors while being expressed in distinct configurations across cell populations. This multi-layered multiplicity confounds intuition about how these receptors are regulated in homeostasis, dysregulated in disease, and might be targeted with therapies. Through a combination of modeling and experiment, we have been working to develop tools enabling improved understanding of these families' regulation and how best to target them (4). For example, we recently used a pharmacodynamic model of IL-2 signaling across cell populations to engineer cell-specific cytokines (1). Within the FcγR family, which enacts effector function in response to IgG antibodies, we showed that a multivalent binding model could predict effector function *in vivo* better than previously-used metrics, which will enable more potent anti-tumor antibodies (2). Within the TAM family of receptor tyrosine kinases, we developed a kinetic model of AXL activation, mechanistically explaining the dependence of the receptor upon phosphatidylserine for activation (3). This basic understanding of γ_c, TAM and FcγR signaling enables more rationally designed therapies and understanding of which factors in the extracellular environment drive response.

1. Farhat, A.M., A.C. Weiner, C. Posner, Z.S. Kim, B. Orcutt-Jahns, S.M. Carlson, **A.S. Meyer**. (2021). Modeling Cell-Specific Dynamics and Regulation of the Common Gamma Chain Cytokines. *Cell Reports.* 35(4): 109044. PMCID: 8179794.
2. Robinett, R.A., N. Guan, A. Lux, M. Biburger, F. Nimmerjahn, **A.S. Meyer**. (2018). Dissecting FcγR Regulation Through a Multivalent Binding Model. *Cell Systems.* 6(7): 1–8. PMCID: 6062446.
3. **Meyer, A.S.**†, A.J.M. Zweemer, D.A. Lauffenburger†. (2015). The AXL Receptor Is a Sensor of Ligand Spatial Heterogeneity. *Cell Systems*, 1(1):25–36. PMCID: 4520549. †Co-corresponding authors.
4. Tan, Z.C., B. Orcutt-Jahns, **A.S. Meyer**. (2020). A quantitative view of strategies to engineer cell-selective ligand binding. *bioRXiv.* 2020.11.25.398974 [Preprint].

Problem-driven computational methods development

Studying complex signaling requires approaches tailored to the biologic system and scientific challenge at hand. We have adopted a wide range of mathematical and computational methods to provide new views of cell signaling mechanisms. For example, in (1) we demonstrated how tensor factorization can help to visualize the high-dimensional response of the common gamma chain receptor cytokine family. In (2) we uncovered that the TAM receptor family senses local clusters of ligand, and used a partial differential equation model to explore this process. Finally, we have used Bayesian inference techniques of increasing scalability to perform robust parameterization of our models of interest (1, 3, 4).

1. Farhat, A.M., A.C. Weiner, C. Posner, Z.S. Kim, B. Orcutt-Jahns, S.M. Carlson, **A.S. Meyer**. (2021). Modeling Cell-Specific Dynamics and Regulation of the Common Gamma Chain Cytokines. *Cell Reports*. 35(4): 109044. PMCID: 8179794.
2. **Meyer, A.S.**†, A.J.M. Zweemer, D.A. Lauffenburger†. (2015). The AXL Receptor Is a Sensor of Ligand Spatial Heterogeneity. *Cell Systems*, 1(1):25–36. PMCID: 4520549. †Co-corresponding authors.
3. Lee, C.H., T.H. Kang, O. Godon, M. Watanabe, G. Delidakis, C.M. Gillis, D. Sterlin, D. Hardy, M. Cogné, L.E. Macdonald, A.J. Murphy, N. Tu, J. Lee, J.R. McDaniel, E. Makowski, P.M. Tessier, **A.S. Meyer**, P. Bruhns, G. Georgiou. (2019). An engineered human Fc domain that behaves like a pH-toggle switch for ultra-long circulation persistence. *Nature Communications*, 10(1):5031.
4. Bae, S.Y., N. Guan, R. Yan, K. Warner, S.D. Taylor, **A.S. Meyer**. (2020). Measurement and models accounting for cell death capture hidden variation in compound response. *Cell Death & Disease*, 255(11), Apr 2020.

Therapeutic resistance and design

The benefits cancer patients derive from targeted therapies are limited by genetic and non-genetic mechanisms of resistance. This is in part due to an incomplete understanding of the many compensatory molecular changes that occur when one treats with a therapy. In (1) we explored a panel of resistance mechanisms to RTK inhibitors, showed that coordinate JNK/Erk/Akt measurement was essential to predict cellular response, and showed that the resistance mechanism's effects could be explained through their effects on these pathways. In (3) we showed that a complication of targeting autocrine growth factor signaling is the length-scales on which ligand release and recapture occur. Through a diffusion-reaction model, we instead predicted and showed that inhibiting ligand release through protease inhibition is much more effective. In (2), we showed that a common consequence of kinase inhibitors is reduced proteolytic shedding on the cell surface. This change switches the kinase dependence of cells, in turn driving resistance to therapy (in large part via AXL). These results highlight the complexity underlying targeted inhibitor response and demonstrate methods to understand and overcome it.

1. Manole, S., E.J. Richards, **A.S. Meyer**. JNK pathway activation modulates acquired resistance to EGFR/HER2 targeted therapies. *Cancer Research.* 2016 Sept 15; 76 (18): 5219-5228. PMCID: 5026573.
2. Miller, M.A., M.J. Oudin, R.J. Sullivan, S.J. Wang, **A.S. Meyer**, H. Im, D.T. Frederick, J. Tadros, L.G. Griffith, H. Lee, R. Weissleder, K.T. Flaherty, F.B. Gertler, D.A. Lauffenburger. (2016). Reduced Proteolytic Shedding of Receptor Tyrosine Kinases is a Post-Translational Mechanism of Kinase Inhibitor Resistance. *Cancer Discovery*, 6(4):331–333, April 2016. PMCID: 5087317.
3. M.A. Miller, M.L. Moss, G. Powell, R. Petrovich, L. Edwards, **A.S. Meyer**, Linda G. Griffith, D.A. Lauffenburger. Targeting autocrine HB-EGF signaling with specific ADAM12 inhibition using recombinant ADAM12 prodomain. *Scientific Reports*, 5:15150 EP –, October 2015. PMCID: 4609913.
4. Schwartz, A.D., L.E. Barney, L.E. Jansen, T.V. Nguyen, C.L. Hall, **A.S. Meyer**, S. Peyton. (2017). A Biomaterial Screening Approach to Reveal Microenvironmental Mechanisms of Drug Resistance. *Integrative Biology*. 2017 Dec 11; 9(12):912-924. PMCID: PMC5725273.

Migration and metastasis mechanisms

Invasion and dissemination of cells underlie many diseases including cancer. Studying these processes is hindered by the complex regulation and the multiple biophysical steps involved. In earlier work, we quantified the growth factor responsiveness of cell migration overall and individual processes involved in cell migration, then compared each condition in its 3D invasion through the extracellular matrix (1). This identified that these same individual processes still regulated migration in 3D, but that the overall rate-limiting steps and thus migration response were different. By studying the signaling (3) and protease (2) regulation of migration, we then linked these processes and invasion to identify therapeutic possibilities.

1. **Meyer, A.S.**, S.K. Hughes-Alford, J.E. Kay, A. Castillo, A. Wells, F.B. Gertler, D.A. Lauffenburger (2012). 2D protrusion but not motility predicts growth factor-induced cancer cell migration in 3D collagen. *Journal of Cell Biology*, 197(6), 721-729. PMCID: 3373410.
2. Miller, M.A.‡, **A.S. Meyer**‡, M. Beste, Z. Lasisi, S. Reddy, Jeng, K., Chen, C.-H., Han, J., Isaacson, K., Griffith, L.G., Lauffenburger, D.A. (2013). ADAM-10 and -17 regulate endometriotic cell migration via concerted ligand and receptor shedding feedback on kinase signaling. *Proc. Natl. Acad. Sci. USA*, 110(22), E2074-E2083. PMCID: 3670354. ‡Equal contribution.
3. Kim, H.D., **Meyer, A.S.**, Wagner, J.P., Alford, S.K., Wells, A., Gertler, F.B., Lauffenburger, D.A. (2011). Signaling network state predicts Twist-mediated effects on breast cell migration across diverse growth factor contexts. *Molecular & Cellular Proteomics*, 10(11), M111.008433. PMCID: 3226401.
4. Riquelme, D.N., **A.S. Meyer**, M. Barzik, A. Keating, F.B. Gertler. (2015). Selectivity in Subunit Composition of Ena/VASP Tetramers. *Bioscience Reports*, 2015. PMCID: 4721544.

Complete List: https://www.ncbi.nlm.nih.gov/myncbi/aaron.meyer.1/bibliography/public/

D. Research Support

Ongoing Research Support

NCI Administrative Supplement 9/01/2020 – 8/30/2021
Mechanistic Autoencoders for Patient-Specific Phosphoproteomic Models
This project aims to integrate the machine learning concept of an autoencoder into a mechanistic model. This will be used to fit patient-derived phosphoproteomic data, to predict individualized responses to FLT3 inhibitors in AML.
Role: Co-PI

American Cancer Society 1/1/2020 – 12/31/2023
Tissue-engineered models of glioblastoma for evaluating treatment responses
The major goal of this project is to characterize how well biomaterial-based models of GBM tumors recapitulate treatment responses across the patient population and within a single tumor composed of patient-specific, heterogeneous subpopulations.
Role: Co-I

Jayne Koskinas Ted Giovanis Foundation 9/1/2020 – 8/30/2022
Cell cycle-specific drug responses in breast cancer
We are developing lineage tree-based hidden Markov models as a way to analyze the plasticity of breast cancer cells. This is combined with live cell cycle reporters to quantify the cell cycle-specific effects of drug response.
Role: Co-PI

NIH U01-AI148119 12/18/2019 – 11/30/2024
Mapping the effector response space of antibody combinations

We are extending a binding model for IgG-effector cell interaction to predict the effects of antibody combinations. With that, we will evaluate whether complex mixtures of antibodies have distinct properties from their constituents.
Role: Co-PI

Visterra, Inc. 4/01/2019 – 5/31/2021
Modeling the IL-2 pathway to engineer cell-selective signaling
This project applies a binding and activation model of the common gamma chain receptor cytokines to identify engineered changes in ligand affinity that translate to changes in cell selectivity.
Role: PI

NIH U01-CA215709 9/01/2017 – 8/30/2022
Precision Lung Cancer Therapy Design Through Multiplexed Adapter Measurement
We propose to develop a global picture of bypass resistance mediated by receptor tyrosine kinases (RTKs) not targeted by therapy. By examining multiple RTKs variable in their resistance-promoting capacity at once, we will be able to determine features essential to the development of resistance.
Role: Co-PI

Completed Research Support

UCLA Hellman Fellows Program 7/01/2019 – 6/30/2020
Engineering anti-tumor antibody combinations for more effective and less toxic therapies
This project uses a binding model of IgG-FcγR engagement to predict combinations of anti-tumor antibodies that operate synergistically together.
Role: PI

NIH DP5-OD019815 9/22/2014 – 9/1/2019
Adapter-Layer RTK Signaling: Basic Understanding & Targeted Drug Resistance
The goal of this project was to study sets of resistance mechanisms to RTK-targeted therapies, to identify commonalities and ways to determine which mechanism may be driving individual tumors.
Role: PI

Foundation Grant 7/1/2017 – 6/30/2019
Terri Brodeur Breast Cancer Foundation
This project used a computational model to direct the design of new inhibitors for the TAM receptors. Using these well-characterized compounds, we examined the effects of inhibiting different TAM receptor complements.
Role: PI