UCLA Engineering
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Department of Bioengineering

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June 7, 2022

To: Song Li, Professor and Chair
Department of Bioengineering

Re: Self-Statement Summary of Activities

I wish to review the many ways in which I have excelled in my research, teaching, and service activities since my recruitment to UCLA in July 2017. My accomplishments as an Assistant Professor, with focus on the period since my last promotion, are summarized in this self-statement for consideration towards promotion to Associate Professor Step I O/S effective July 1, 2023.

My lab has made extensive progress in each area of our research program. I have published 23 original research papers as an independent principal investigator (PI; 7 papers within the last period), and have an additional 4 under review. Because I have obtained high levels of independent funding to fully support my lab (including 3 R01-equivalent NIH awards and 9 other grants as a PI), my recent efforts have focused on contributing to collaborative proposals. I received one new foundation grant from the Jayne Koskinas Ted Giovanis Foundation and two supplements to expand the scope of our existing grants. Building on my successful teaching program and evaluations, I have continued to implement new course refinements, particularly in response to the pandemic. I was recently recognized as a recipient of the school-wide Northrop Grumman Excellence in Teaching Award for my extraordinary contributions to the department and school's teaching missions. Finally, I have expanded my service contributions with a focus toward serving underrepresented groups in Bioengineering (BE). *My contributions to diversity, equity, and inclusion (DEI) are highlighted in italics throughout.*

## 1 Research

As a brief introduction to my research program, I lead a group that applies experimental and computational strategies to measure, model, and then therapeutically manipulate cell-to-cell communication, with applications in the development of immune and cancer therapies. We focus on problems that can be solved through the fusion of new modeling and experimental approaches, and use these to derive insights spanning basic biology mechanisms to translational applications. As our projects have profound implications for real-world medical problems, we have been sought out to work collaboratively with other academic and industry research groups.

My research group currently includes 1 staff, 6 Ph.D. students, 2 M.S. students, and 10 undergraduate researchers. All four eligible Ph.D. students have successfully advanced to candidacy. The most senior three Ph.D. students are completing their fourth year; each already has multiple publications and has satisfied the program requirements to graduate. Among the four postdoctoral fellow alumni of the lab, two run their own independent academic labs, and the others remain in biomedical research. My group has maintained continual and significant (R01-level) NIH support for 8 years since 2014 when I won the NIH Director's Early Independence Award. I chose to spend three years as an independent fellow before establishing a full research program at UCLA in July 2017.

**Systems Engineering of Immunity** Antibodies (Abs) are a central part of the immune system. Although therapies using Abs have existed for over 100 years, we still have only a basic understanding of how these molecules function. Conceptually, Abs are simple—one end adapts to recognize a pathogen, while the other end (Fc domain) interacts with immune cell receptors to induce responses. These interactions operate in combinations across many receptors and cell types. Thus, at its core, understanding Ab-mediated protection is a systems engineering challenge.

We have been pioneering the use of mechanism-based binding models to study and engineer immune cell responses to Abs. I received a major NIH grant in 2019 based on our first work showing multivalent binding models can improve predictions of anti-tumor Ab therapy effectiveness [**18**]. This proposal was also selected for its clarity to serve as *the* proposal example for the entire National Institute of Allergy and Infectious Diseases[1]. Since then, we have greatly expanded the situations for which we can model Ab function. We generalized this model to account for polyclonal Ab mixtures, such as the responses one creates during a natural infection or vaccination [**25**]. The model's generality enables its application

[1] https://www.niaid.nih.gov/grants-contracts/sample-applications#U01

to nearly any cell surface interaction and, indeed, we have used it to examine cytokine receptors [**32**, **33**], growth factor signaling, and even general rules for inducing selective signaling in specific cell types [**26**].

While most of our Ab engineering takes a bottom-up approach, there has been a recent revolution in immunologists' ability to track the features of endogenous Ab responses like infection or vaccination. These "systems serology" findings are enabled by a simple array-based measurement. At the same time, analysis of these studies has been rudimentary. We found, in fact, that existing modeling approaches are not suitable for identifying the mechanisms of Ab-mediated protection [**24**]. A high degree of measurement intercorrelation exists, making standard data-driven models inconsistent in their results. We instead proposed a tensor-based dimensionality reduction and data integration method that properly recognizes the patterns in immune responses according to each antigen target or immune receptor. This allowed us to uncover several simple and fundamental mechanisms of infection response in these data (e.g., HIV progression corresponds to a shift in immune system focus from surface to internal viral antigens). Identifying these patterns reveals new ways of combatting immune dysfunction.

Similar to our approach with Ab-directed responses, we have been integrating experiments with computational methods to study responses to cytokines—soluble extracellular proteins that coordinate immune responses. We recently published a first paper in this area, looking at how IL-2 responses are signaled across cell populations. There is widespread interest in designing engineered cytokine variants that are selective for regulatory T cells ($T_{reg}$s) as an autoimmunity treatment. However, engineering or even *defining* selectivity requires analysis of both on- and off-target responses. Our model was the first to incorporate multiple cell types and receptor/ligand trafficking, the latter of which turned out to be essential for the model to accurately model signaling response [**23**]. We also showed here that our tensor-based analysis improves one's ability to identify patterns in cytokine signaling. Since this publication, we have nearly completed a study showing that cytokine fusions are mostly $T_{reg}$ selective through valency effects, which overturns thinking in the field that IL-2 receptor affinities are exclusively how these therapies work. We have used this observation to design a more $T_{reg}$-selective IL-2 than any made to date [**32**], and have a provisional patent application and additional disclosure covering this invention[2].

Several of the computational tools we have developed, such as the multivalent binding model and tensor analysis, have general utility in studying immunity. We have consequently been sought out by other groups to apply these same tools in other projects. With the binding model, we have been working with Jamie Spangler's lab (Johns Hopkins Univ.) to model both IL-2 immunocytokines and engineered variants of IL-4. We have collaborative papers on both of these engineering efforts now under review [**33**]. We have also been sought out by collaborators such as George Georgiou (Univ. of Texas) to use modeling for insights about Ab function. For instance, we used a model to explain a perplexing observation that *enhanced* release from FcRn can further extend Ab half-lives [**21**].

**Systems Pharmacology of Cell Heterogeneity and Microenvironments** A major focus of my lab over the last 8 years has been the mechanisms of AXL-mediated drug resistance in cancer. AXL is a receptor tyrosine kinase (RTK) that drives resistance to several therapies in ways that are still elusive. Additionally, AXL seems to primarily drive resistance through so-called bypass resistance, a process in which tumor cells switch their dependence to AXL signaling to overcome the effect of an anti-cancer drug. It is critical that we identify where, when, and how AXL drives cancer drug resistance so that we can identify the appropriate patients and timing for effective treatments.

I was the first to take a quantitative approach to studying AXL activation and resistance mechanisms, and my lab has made several fundamental discoveries about the mechanisms of AXL activation and signal transduction. My discoveries include the observation AXL diversifies EGFR signaling in response to EGF through transactivation [**6**]. My lab, first funded through the NIH Director's Early Independence Award, used modeling and experiments to discover that AXL is primarily activated through surface clustering, rather than just binding to its protein ligand [**8**]. We then built on this work to show AXL is activated in response to apoptotic cell debris in the tumor microenvironment, and more sensitive to small debris as a consequence of its activation mechanism [**14**].

Shortly before moving to UCLA, my lab took a quantitative approach to studying bypass resistance more generally [**12**]. Observing that bypass resistance occurs through reactivation of some conserved downstream pathways, we used quantitative proteomics and modeling to observe that RTKs differ in their bypass resistance capacity, and identify these essential downstream signals. We worked with Shelly Peyton (Univ. of Mass., Amherst) to take a similar approach studying resistance mechanisms within engineered extracellular matrix (ECM). With my lab leading the proteomics analysis and modeling, we discovered that Src inhibition was necessary to overcome resistance specifically within 3D ECM [**15**].

These findings formed the basis of a major grant from the NCI Cancer Systems Biology Consortium, wherein we have been using a similar perspective to identify the specific downstream signaling that drives AXL tumor-promoting effects. We use a novel approach, breaking AXL signaling in subtle ways through mutants of the receptor to pinpoint which, among many, AXL-driven pathways drive resistance. This project has required improved ways of analyzing phosphoproteomic

[2] U.S. provisional patent application 63/216, 718, 2021. UCLA invention disclosure 2022-969-1.

data acquired through mass spectrometry (MS). Typically, MS-based phosphoproteomics is either analyzed by looking at peptide sequence motif enrichment or clustering peptides based on the variation in their abundance. We developed an algorithm to do both at once, improving our ability to model these data, predict patients' driver mutations, and identify mechanisms of tumor progression [**28**]. While we are still finishing the last validation experiments within a large paper describing our findings of how AXL drives resistance, we have published some initial work in which we characterized the pathways downstream of AXL [**27**]. A key finding of this study was that many existing AXL inhibitors have cytotoxic effects independent of AXL inhibition.

Multivariate measurements of cell signaling and phenotypes have been critical to studying AXL because the receptor, like many RTKs, drives many pathways and phenotypes. We have developed new multiplexed methods for studying several aspects of cell biology. These include multiplexed trafficking assays [**17**] and high-throughput measurements of pharmacologic response capturing both growth inhibition and cell death [**22**].

The unique proteomics capabilities of my lab, and tools we have developed for studying AXL signaling in particular, have led others to seek out our expertise. We worked with Koki Morizono's lab (UCLA) to characterize their engineered viral targeting system, using AXL and EGFR targeting as examples [**19**]. Rudolph Jaenisch's lab (Whitehead Institute) sought out our unique reagent tools and experience with the TAM receptors (of which AXL is a member) to help study neuronal organoid responses to Zika and Dengue infection, as AXL is an entry factor for both viruses [**16**]. Finally, I have been invited several times to provide my perspective on and review opportunities for using quantitative models and experiments to learn about drug resistance and oncogenic mechanisms [**13**, **20**, **29**].

**Future Outlook** With my lab's research program established, I anticipate developing three areas to broaden and deepen the impact of our work. First, many groups have found our application of tensor-based dimensionality reduction methods for biomedical data analysis broadly useful. New collaborators, such as Peter Lee (City of Hope) have sought me out to apply these techniques in large-scale immune profiling experiments in cancer clinical trials. I have been asked to serve as the computational core director in several large center proposals in the medical school. I also intend for my lab to lead the development of tools and resources to make these techniques available to a broader range of investigators. Second, we have used our combined experimental and computational modeling to uncover new ways of designing cytokines with exceptionally selective effects. We are working to translate these findings by experimentally validating that our engineered, tetravalent cytokines are more selective in their signaling than anything currently designed. With this key validation data, I plan to pursue further commercial development of these molecules. Lastly, my unique expertise spanning immune and cancer systems biology has helped me uncover key gaps in both fields. While Ab responses are widespread in cancer, the immune cell interaction properties of these Abs have *never been examined*. I have established collaborations with several clinicians (e.g., Sanaz Memarzadeh, UCLA gynecologic oncology) to develop new technologies[3] for profiling these Abs.

## 2 Teaching

I have become an integral part of the department, school, and campus educational mission. Working at the interface of BE and computational analysis, and as an alumnus of the UCLA BE undergraduate program, I provide a unique perspective to the revolution data-driven modeling is bringing to biomedical research. I employ a combination of active learning, review techniques, and iterative improvement that students positively respond to, **reflected in instructor and course evaluation scores that are consistently greater than the department average (overall average during my time at UCLA of 8.28/9 versus 8.02/9, and 8.04/9 versus 7.75/9, respectively)**. My contributions, some of which are described here, were recently recognized through the Northrop Grumman Excellence in Teaching Award, an engineering school-wide recognition conferred to one junior faculty member who has had an extraordinary impact to the teaching mission of the school.

Since 2017, I have led the establishment of data-driven modeling and machine learning as a central part of our BE curriculum. This has been a recognized area of need, by both our industry advisory and accreditation boards, as statistics and computational expertise has become integral to BE. I developed a course that familiarizes our students with the fundamentals of data modeling and machine learning[4]. Because few resources exist for teaching these concepts to students with a BE background, I designed all the teaching resources from the ground up to be accessible to our students. The course has been a complete success, with consistently outstanding student reviews. Students *regularly* describe this course as changing the trajectory of their careers, and there are examples from every class of students subsequently choosing to pursue modeling opportunities in academia and industry because of the course. As one example, one student wrote: "Overall, I loved this course, and it encouraged me to further pursue... the field of data science. Dr. Meyer was very helpful explaining material during lectures... This was one of my favorite classes at UCLA." In 2020, we made the course a requirement for our undergraduate degree, a major change to the undergraduate curriculum. The unique offering and positive reputation of the

[3] UCLA invention disclosure 2022-291-1.

[4] A syllabus and outline can be found here: https://aarmey.github.io/ml-for-bioe/

course have attracted students across the school and university, including from Computer Science, Materials Science & Engineering, Chemical & Biomolecular Engineering, Computational & Systems Biology, and Chemistry. I have joined several students' thesis committees because the course material has become central to their studies.

I have led several improvements to this course in the last review period in response to pandemic-related challenges and to accommodate increased enrollment. First, I split the undergraduate and graduate offerings into BE 175 and 275. This has let me emphasize the final project and more deeply cover concepts at the graduate level while enabling increased enrollment from undergraduate students. Second, I pre-recorded and edited versions of all the lectures. Returning to in-person instruction, these resources have let me partly flip the classroom so that we now spend the majority of in-class time on concepts review and discussion points. It has also afforded flexibility when students have not been able to attend class. These videos allow students to stay up-to-date until they can return, rather than offer a hybrid option that, in my experience, reduces student engagement. An unintended consequence is several videos are quite popular (e.g., one on partial least squares regression has >2,000 views outside of UCLA). My intention is to eventually add to these videos with better visualizations to make them even more effective. These adjustments have maintained high student learning and evaluations even as enrollment has further increased (31 in 2021, 45 in 2022). *Finally, I have incorporated a module on the ways in which modeling can exacerbate disparities. For instance, we have covered the Boston housing dataset, where race as a variable leads to models suggesting race drives housing prices, when this relationship is in fact a consequence of historical redlining. We have also covered how pulse oximeters require training and testing using subjects with diverse skin colors.*

I also teach our introductory laboratory course, BE 167L. Students learn molecular and cellular engineering techniques common to BE laboratories. I have made several course improvements taking advantage of teaching techniques that have worked in BE 175. A consistent challenge for this course, over several instructors, has been establishing a clear link between the theory in lecture and the laboratory experiments. The pandemic led to further challenges because we could not provide students with hands-on wet lab experience. In spring 2021, I completely transformed how BE 167L is taught to adapt it to remote instruction. First, I pre-recorded all of the theory lectures. Instead of covering this material live, students divided into teams that each presented one research article during a lecture. Students also individually presented one experimental technique interlaced within the paper presentations. Despite being a laboratory class with no laboratory, students greatly appreciated the overview of experimental techniques and student reviews vastly improved relative to the first online offering. Now having returned to in-person instruction and laboratory sessions, I have adapted these lessons to the spring 2022 course offering. Lecture content is pre-recorded and in-class time is used for the research article and experimental technique presentations. I provide feedback individually and to the whole class on effective presentation techniques while guiding discussions about critical evaluation of the research and experimental methods.

Outside of the department, I am a faculty director for the Integrated and Interdisciplinary Undergraduate Research Program (i2URP). i2URP is a selective two-year program run by the Undergraduate Research Center that prepares juniors and seniors for graduate studies and careers in biomedical research. Students present research each week; in doing so, they develop their communication skills and ability to critically analyze the scientific literature. I have led adjustments in the course to raise the standards for student's presentations and educated students about proper statistics reporting. I also facilitate recruitment of engineering students, including Chemical & Biomolecular Engineering and BE.

In 2021, I was invited to become a member of the Computational & Systems Biology (CSB) major's advisory committee. I have used this role to improve CSB's integration into programs within the school. For instance, we have made my BE 175 course available to CSB majors as an elective. I have served as a member of the CSB minors committee over the past year to refresh the CSB minor degree offerings. We completely redesigned these minors to best use campus resources and serve the student groups (from life sciences to engineering) interested in these degrees.

My laboratory tightly integrates research, graduate mentorship, and undergraduate teaching. Students interact with me both at lab meeting and during weekly subgroup meetings, where both graduate and undergraduate students present their progress. I provide regular feedback on presentation, writing, and visualization techniques in addition to scientific advice. Graduate students additionally meet with me once a year to complete and discuss an Individualized Development Plan. Students have also gone on to win numerous scholarships, travel awards, and presentation prizes. Undergraduate students from the lab have gone on to prestigious graduate programs including Harvard Systems Biology, MIT Biological Engineering, and Stanford Computational & Mathematical Engineering.

Finally, I am very actively involved in several summer programs to provide research opportunities to outstanding students from UCLA and elsewhere. I participate every year as a faculty mentor in and alumnus of the Amgen Scholars program. In 2020, when the standard program had to be postponed, I worked with the national program to develop several professional development resources for students considering research careers. In 2021 and 2022, I again participated in the program's national symposium and helped in the application review and selection process. I also host students each summer through the Bruin In Genomics (BIG) summer program. *BIG summer provides research experiences in computa-*

*tional biology, especially to students from underprivileged backgrounds. I have mentored three students and design appropriate introductory projects to ensure their success.*

**3 University & Professional Service**

I contribute to the department, university, and profession in many ways and cannot exhaustively list them here. Therefore, I will only cover a selection of my service activities.

*In mid-2020, I became an active participant in the BME UNITE (Underrepresented Needs In Technology & Engineering) group. This is a national group of BE faculty who are interested in educating themselves, improving representation, and combating racism in STEM. I have several key roles in the organization:*

- *Working with Shelly Peyton (Univ. of Mass., Amherst), I organized a national virtual seminar series to showcase 28 faculty candidates of underrepresented backgrounds. These candidates also received mentoring during a private session with department chairs across the country. We are still tracking program outcomes; several presenters have successfully found faculty positions in the last year. Feedback from the series was overwhelmingly positive, both from the candidates and faculty attendees, and we are continuing the program this coming year.*
- *I lead a subgroup working to improve access to research experiences for undergraduates (REUs). While students at strong research institutions like UCLA have access to research experiences and mentorship about becoming involved in summer REUs, students from schools with smaller research programs are often unaware of these opportunities or lack information on how to prepare a competitive application. We have compiled a database of REU programs and are in the process of putting together a central resource. Successful applications will be included as a resource for writing competitive applications.*
- *I volunteered to setup an organization website to provide an online presence and help raise funds for new projects.*

After serving as a founder, meeting organizer, and then co-chair of the Association for Cancer Systems Biologists, I have now moved to the role of its financial officer. The primary activity of this organization is a biennial meeting in November providing a unique opportunity for the cancer systems biology to come together. In 2020, I established the organization as an independent, tax-exempt corporation which has allowed us to solicit ∼$20,000 in donations from academic and industry sponsors. *In addition to helping run the meeting, we intend for these funds to support outreach wherein we bring students of underrepresented backgrounds with fewer research opportunities to the meeting. They will have the chance to learn about the field and establish a mentorship relationship with one of the meeting PIs.*

I contribute to several student groups in various roles. I have continued to be a faculty advisor for Tau Beta Pi. In this role, I provide input on the club's activities and judge events such as their quiz bowl. I have also participated as a judge for the UCLA Biomedical Engineering Society's hackathon. *As the only out LGBT+ faculty in the department, I recently participated in a panel to discuss ways in which the UCLA BMES community can be more inclusive and where I have seen my LGBT+ identity intersect with BE.*

Finally, I am an ad hoc reviewer for many scientific journals (e.g., Cell Systems, Science Signaling, Cancer Immunology Research), and fellowship/funding programs (e.g., Amgen Scholars Program, National Science Foundation, Australia Medical Research Future Fund, Biomedical Engineering Society). Within the department, I serve as the Data Science Field Chair and a member of the Teaching/Shared Equipment Committee, Strategic Planning Committee, DEI Committee, and most recent Hiring Search Committee.

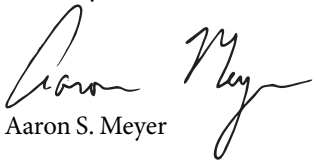
**4 Summary**

I am confident you will find my academic activities satisfy the high standards set by myself and the university. My research program has made important discoveries about how to therapeutically manipulate cell communication. My lab's unique capabilities and discoveries have led to significant funding, national recognition, and key roles in collaborative programs. Beyond positive student evaluations, my teaching has become an integral component of the department and school's educational mission. Finally, my service has improved representation in the bioengineering and computational systems biology fields.

**5 References**

See CV for information on the bolded number references.

Sincerely,



Aaron S. Meyer