UCLA Engineering
HENRY SAMUELI SCHOOL OF ENGINEERING AND APPLIED SCIENCE
Department of Bioengineering

July 24, 2020

To: Song Li, Professor and Chair
Department of Bioengineering

From: Aaron S. Meyer

Re: Self-Statement Summary of Activities

Since my appointment to Assistant Professor Step III O/S in July 2019, I have excelled in all three aspects of my academic career: research, teaching, and service. My accomplishments since my last promotion are summarized in this self-statement for departmental consideration towards the merit promotion to Assistant Professor Step IV O/S effective July 1, 2021.

I have continued the successful activities that I started during my first review period. Specifically, my lab's research program in systems engineering of cancer and innate immune cell behavior is fully established. Our research findings this and the coming years will demonstrate its impact on engineering cancer and immune responses. During the period of this review, I have published 5 original papers and have filed 1 invention report (to become a provisional patent this year). In addition to the continuing grants from the previous period, I received a major new U01 award from the National Institute of Allergy and Infectious Diseases ($1,594,420), administrative supplement from the National Cancer Institute, UCLA Hellman Fellowship, UCLA Faculty Career Development Award, and research agreement with Visterra, Inc. These awards signify the importance of my lab's work and provide substantial continuing financial support for my research program. I also gave 4 invited seminars at various departments and institutions, as well as presented 4 selected talks at national and international meetings. Due to my visibility in my research field, I have been able to establish strong collaborations with researchers throughout the world. In parallel, my educational contributions to the department have expanded, with the establishment of my course on machine learning methods as a required component of the curriculum. My service is also summarized in this self-statement, with my contributions to diversity indicated by italics throughout.

1. RESEARCH: Systems Engineering of Cancer and Innate Immune Cell Behavior

I have continued to successfully develop and expand our lab's research program in systems engineering of cancer and immune cell behavior using both theory and experiment. My research group currently includes 2 postdoctoral associates (one supervised remotely at MIT), 1 technical associate, 4 graduate students, and 12 undergraduate researchers. This past spring, I successfully recruited a 5th graduate student to start this fall, and 2 graduate students in my group recently completed their advancement to candidacy. In addition, 7 of my lab members gave presentations at national meetings. A major focus of our research is to apply systems-level models of cell behavior for the design of better cancer and immune therapies. Accordingly, our projects have profound implications for real-world medical problems.

1.1. Systems Engineering in Innate Immunity

Antibodies are crucial and central regulators of the immune response. Those of the immunoglobulin G (IgG) isotype interact with Fcγ receptors (FcγRs) on effector cells. IgGs transduce effector function through multiple cell types (e.g., macrophages, monocytes, etc.) and multiple processes (e.g., antigen presentation, cytokine response, phagocytosis, etc). These are particularly versatile therapies on account of their direct binding and immunotherapeutic effects. Indeed, IgG molecules comprise a broad range of approved therapies, many of which are known to rely in part on effector cell response. At the same time, the multiplicity throughout—of Fc region composition, Fcγ receptors, cell populations, and antigen binding—make precisely understanding, measuring, and manipulating effector function a yet-elusive goal.

As mentioned above, we recently received a major NIH grant to continue modeling of FcγR-IgG interactions. Working with the Nimmerjahn lab at the University of Erlangen, we will identify how different IgG Fcs interact when they are simultaneously present. This is a critical issue to antibody manufacturing because different glycosylation forms, which affect FcγR binding, are always simultaneously present. This work also has the potential to identify novel ways to combine antibodies so that their effect in combination is synergistic and greater than either would elicit alone, thereby leading to new antibody therapies.

In 2019 we also established a research agreement with Visterra, Inc., an early-stage biotechnology company, to build a model of the common gamma chain cytokines. These cytokines modulate the abundance and activity of cells throughout the immune system. As such, they have existing and future potential as both immune-enhancing and -inhibitory molecules. Our modeling helped to identify receptor affinity changes that would drive regulatory T cell selectivity in engineered IL-2 muteins. A specific mutein, identified in part through our work, has now entered clinical development for lupus treatment. We have a pre-print describing the first phase of this analysis currently under review (*Farhat et. al.*), and follow-up analysis underway.

Another important feature of antibodies is their pharmacokinetics and thus half-life within the body. An increase in therapeutic half-life can lead to a decrease in the frequency of patient injections and less toxic side effects. In Lee *et. al.*, we identified an engineered human Fc domain that has an exceptionally long half-life *in vivo*. This was surprising to our collaborators because this Fc domain did not have an exceptionally high FcRn affinity (which helps to preserve antibodies from degradation). Using a computational model, we were able to explain these results by recognizing that this new Fc improved release from FcRn after recycling, thereby preventing reinternalization and degradation. These results will enable therapies that can last for months with reduced costs.

Viral therapies are used for gene delivery, vaccination, and oncolytic cancer treatments. One of the key features of viruses is their tropism, or ability to infect specific types of cells. Working with the Morizono lab which developed a targeting system to rapidly change the tropism of a virus, we characterized a series of viral strains with tropism for receptor tyrosine kinases. Specifically, in *Situ et. al.*, we looked at the signaling effects of viruses binding to the TAM or EGFR receptors. This system can help to rapidly screen viruses with different targeting moieties for the right tropism when trying to target cancer cells for example.

1.2. Systems Pharmacology Accounting for Cell Heterogeneity and Microenvironments

Cells respond to their environment using a network of signaling mediators. The complexity of this regulation precludes our intuition when designing therapeutic interventions. Furthermore, while we often make decisions about the effectiveness of therapies based on measures of the average response, cells display a high degree of heterogeneity in their response to their environment and therapies. I reviewed some of these challenges, and systems biology solutions for tackling them, in *Meyer and Heiser*.

In *Bae et. al.*, we developed an automated pipeline to quantify both the cell growth and death effects of cancer compounds. These measurements helped us identify that drugs with similar efficacies, when quantified using standard techniques, actually have very different cell death outcomes. Because blocking proliferation can have very different immunologic effects compared to inducing cell death, and different forms of cell death can similarly cause divergent host responses, this characterization will be critical to interpreting the relationship between *in vitro* and *in vivo* responses. This potentially could lead to better predictions of how drugs will perform in the body based on results obtained in the laboratory. Further, we identified that additive compound interactions can falsely appear synergistic if not properly analyzed.

A central mechanism of feedback inhibition for cell surface receptors is their downregulation. Conversely, their inhibition can lead to cell surface accumulation and adaptive resistance. In *Claas et. al.*, we developed a quantitative experimental and computational analysis for the trafficking of cell surface receptors. Surprisingly, we found that different Mek/Erk inhibitors, which are used in melanoma treatment, had divergent effects on adaptive resistance development based upon their capacity to upregulate the receptor tyrosine kinase AXL. These results present quantitative methods to analyze cell surface trafficking and identify important differences among Mek/Erk inhibitors. Controlling this process could improve the effectiveness of these drugs in cancers such as melanoma.

Finally, research is an opportunity for mentorship. *I actively recruit students through activities such as Program for Excellence in Education and Research in the Sciences and SEAS Transfer Summer Research program, to ensure that we are recruiting a diverse student group. Our lab is a diverse group, with equal representation of women and consistently greater URM representation than the average school enrollment (table).* Former trainees of the lab have gone on to successfully apply their training. At the undergraduate level, this includes students who have entered Ph.D. or M.D./Ph.D. programs at University of Chicago (Computer Science), Stanford (Data Science), Harvard (Systems Biology), Harvard (Biological and Biomedical Sciences), Rockefeller University (Computational Biology), University of Illinois (M.D./Ph.D.), and University of Michigan (Biomedical Engineering) over the last two years. No graduate students have yet graduated, but two successfully completed their advancement to candidacy. One postdoctoral associate had started as an Assistant Professor at University of Leiden in previous years, and another moved to a new position recently for family reasons.

	Postdoc	Graduate	Undergraduate	Staff
Total	4	4	24	2
Women	3	1 (0.9)	12 (6.6)	1
URM	1	0	5 (2.7)	0

Laboratory member composition. Each category besides postdoctoral associates only includes members while at UCLA. Parentheses indicate expected composition based on the 2019 school enrollment. Gender is assessed through preferred pronoun usage. URM status is an estimate based on knowledge from mentoring relationships; students were not directly polled.

2. TEACHING

I have expanded my teaching impact based on initial successes and took on new responsibilities over the past two years. Part of my role within the department has been to empower our students to apply data science and machine learning techniques to bioengineering problems. This role is reflected in many of the course enhancements below. In fall 2019, I presented a larger plan for a course series that received positive feedback from the department. In addition, I teach the core sophomore-level Bioengineering Laboratory (BE 167L) and have made improvements and adjustments to this class as described below. During this review period, I received an average overall instructor rating of 7.97 out of 9, which is consistent with the departmental average over that same time period (7.96). I also received excellent comments. For example, a graduate student (BE C275) mentioned:

> "The format of this class should be a model for others—the idea of reading (text/papers), listening (podcasts) and seeing (implementations, lecture) is great, with culmination into a final project. Really enjoyed the freedom of the final project to implement our own ideas."

An undergraduate student (BE C175) commented:

> "Dr. Meyer is able to pack such challenging material into something that piqued my interest. I feel like this class will give me a very useful skill for my future plan. Dr. Meyer chooses the topic carefully to ensure that we understand the fundamental concept... Even though I [had] no background in statistics whatsoever, I [felt] supported in my endeavor for this class."

Another undergraduate student from BE 167L remarked:

> "Professor Meyer was very approachable with questions and I was able to learn a lot from him. It was very apparent that he wanted us to learn and do well, especially due to the fact that he would host his own review sessions before every exam."

I taught my machine learning class, "Machine learning & data-driven modeling in bioengineering", first in winter 2018, again in winter 2019 and winter 2020. Both the course and instructor ratings have been consistently very positive, with enthusiastic feedback. Based on this feedback and the critical role data science will continue to have in bioengineering, the department made this course permanent (BE C175/275) in 2018 and a required course in 2019. During this process, I have made some adjustments to prepare for larger class sizes, including streamlining the course materials, simplifying code submission, and assembling a compendium of teaching assistant resources.

In fall 2018, I took over instruction of BE 167L, and have continued teaching the course in spring 2019, fall 2019, and spring 2020. Additionally, I have made some adjustments to the course based on feedback

from colleagues and students. I initially worked to improve the data analysis component of the course. Students were using statistical tests and regression after a cursory introduction, and so I added the underlying principles of these methods to the lectures. A common piece of feedback from this course has been to question the integration of the lecture and laboratory components; to address this, I expanded the literature review we perform in lectures so that students can see the application of the methods we discuss. These papers also serve to prepare students for lecture—for example, they prepare by reading a review article about antibody-drug conjugate chemistry, we cover bioconjugation techniques in lecture, and then they conjugate fluorescein to bovine serum albumin in the lab. I have felt that such an approach reinforces key concepts, leading to retention of these principles by the students. After our most recent ABET (engineering accreditation) review, I worked with Profs. Seidlits and Schmidt to implement a new lab module in BE 167L on mechanical measurements of living tissue. In this module, students measure the mechanical properties of chicken skin, demonstrating the theory they learn about viscoelastic deformation during lectures. This resolved a weakness ABET identified in "measurements of living systems" in our courses.

Due to COVID-19, BE 167L had to be converted to online instruction in just weeks with no access to the teaching labs. I therefore very quickly and completely restructured the course. We used laboratory time for an interactive discussion of key literature, virtual lab sessions with synthetic measurements distributed so that students could still complete their lab reports, and a new final project structured as a project proposal. While students clearly prefer in-lab, hands-on instruction, this restructuring allowed us to still meet our learning objectives within the extreme constraints of the situation.

I have contributed to two classes outside our core curriculum. In academic year 2018/2019, I organized our department's seminar series (BE 299). In this role I helped to raise the department's visibility by inviting and hosting department chairs from a variety of bioengineering programs. Starting in January 2019, I took over from Prof. Kasko as a faculty mentor in the Integrated and Interdisciplinary Undergraduate Research Program (i2URP). i2URP is a two-year program that prepares juniors and seniors for graduate studies and careers in biomedical research. I am one of four faculty who lead this highly selective program, wherein students present research each week. Through these activities, students develop their communication skills and critical analysis of the scientific literature. I have led adjustments in the course to raise the standards for student's presentations and educate students about proper statistics reporting. I have also expanded recruitment to students from the engineering school, including Chemical Engineering and Bioengineering.

I have also volunteered to mentor Bioengineering senior capstone design teams each year. Like elsewhere in the curriculum, I have aimed to offer projects that develop new data analysis techniques in bioengineering. In 2018/2019 the team developed a machine learning model to classify cells based on their phenotypic response to drug and lineage relationships. This analysis has the potential to identify the specific tumor cells that cause resistance within a tumor, and design therapies that specifically target them. In 2019/2020 the team used tensor factorization to merge multi-omic data for studying the differences among tumors, which can help to determine which cancer patients should respond similarly to treatment. Both years the team was selected to give an oral presentation and compete in the Senior Capstone Design Symposium. In 2018/2019 the team also won the best poster presentation prize (there was no symposium in 2019/2020 due to COVID-19). Finally, members of the 2018/2019 team also attended the Biomedical Engineering Society Annual Meeting to present their work.

3. UNIVERSITY AND PROFESSIONAL SERVICE

I have been actively involved across campus in several activities. Within the department, I serve on the Undergraduate Curriculum Committee, the Graduate Admissions Committee, and am the Biosystem Science and Engineering Field Chair for the Graduate Program. This past winter and spring I served as the Co-Chair for a joint hiring search between the Bioengineering and Computational Medicine departments. *As an outcome of this search, we were able to recruit an outstanding female candidate, improving the diversity of our department.* Within the school, I served on the HSSEAS SEASnet Review Committee, as a *faculty volunteer at the Society of Women Engineers Recruitment Dinner*, *as a faculty representative and poster judge at the Annual Biomedical Research Conference for Minority Students*, and as a faculty adviser to Tau Beta Pi. Finally, across campus, I serve as a co-organizer for the Systems Immunology Seminar

Series, a reviewer for the Amgen Scholars Program, and a panelist for the Summer Programs for Undergraduate Research (SPUR).

I am currently co-chair of the Association for Cancer Systems Biologists. Part of my responsibilities as co-chair has been to lead planning for the organization's biennial meeting in November of this year. For this event, I have been raising funds from corporate sponsors and through a partnership with the National Cancer Institute. I also established the organization as a 501(c)(3) tax-exempt corporation. Finally, I am an ad hoc reviewer for multiple scientific journals (e.g., Cell Systems, PNAS, Cancer Research, Scientific Reports, PLOS Biology), and fellowship/funding programs (e.g., NSF Graduate Research Fellowship Program, USC Ming Hsieh Institute, Amgen Scholars Program).

4. SUMMARY

I believe all of my academic activities in research, teaching, and service have been highly productive. I look forward to continuing these activities with the high standards set by myself and the university.

5. REFERENCES

M. Farhat, A. C. Weiner, C. Posner, Z. S. Kim, S. M. Carlson, & A. S. Meyer. Modeling Cell-Specific Dynamics and Regulation of the Common Gamma Chain Cytokines. *bioRxiv*. 2020 Mar 19.

S. Y. Bae, N. Guan, R. Yan, K. Warner, S. D. Taylor, & A. S. Meyer. Measurement and models accounting for cell death capture hidden variation in compound response. *Cell Death & Disease*. 2020 Apr 20; 11(4): 255.

C.-H. Lee, 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. An engineered human Fc domain that behaves like a pH-toggle switch for ultra-long circulation persistence. *Nature Communications*. 2019 Nov 6; 11(1): 5031.

A. S. Meyer, & L. M. Heiser. Systems biology approaches to measure and model phenotypic heterogeneity in cancer. *Current Opinion in Systems Biology*. 2019 Oct; 17: 35–40.

K. Situ, B. A. Chua, S. Y. Bae, A. S. Meyer, & K. Morizono. Versatile targeting system for lentiviral vectors involving biotinylated targeting molecules. *Virology*. 2018 Dec; 525: 170–181.

M. Claas, L. Atta, S. Gordonov, A. S. Meyer, & D. A. Lauffenburger. Systems Modeling Identifies Divergent Receptor Tyrosine Kinase Reprogramming to MAPK Pathway Inhibition. *Cellular and Molecular Bioengineering*. 2018