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

July 15, 2018

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 II O/S in July 2017, I have excelled in all three aspects of my academic career: research, teaching, and service. My accomplishments in these activities since my hiring at UCLA are summarized in this self-statement for departmental consideration towards the merit promotion to Assistant Professor Step III O/S effective July 1, 2019.

My recruitment has brought a new research focus to the department. Specifically, I have begun a research program in systems engineering of cancer and innate immune cell behavior. This research has the potential to significantly improve our ability to design more effective cancer and immune therapies. In addition, I have developed and taught a new course on machine learning methods in bioengineering and have contributed with service to the Department and School of Engineering.

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

I have begun a successful research program in systems engineering of cancer and innate immune cell behavior that incorporates both theory and experiment. My research group currently includes 2 postdoctoral associates (one who I supervise remotely at MIT), a technical associate, and 6 undergraduate researchers. This past spring, I successfully recruited 2 new graduate students to start this coming fall quarter. To help develop collaborations and establish my research program, I visited 4 departments and institutes over the last year, giving invited seminars about my lab's work. Members of my group also attended 2 national conferences giving presentations of their own. A major focus of our research is to apply systems-level models of cell behavior in the design of better cancer and immune therapies. Accordingly, my projects have profound implications for real-world medical problems.

During the period of this review, I have published 4 original papers and have filed 1 invention report. I successfully moved both my NIH Early Independence Award and Terri Brodeur Breast Cancer Fellowship to UCLA. Additionally, in September 2017 my lab received a major new U01 grant from the National Cancer Institute to become part of the Cancer Systems Biology Consortium. Across all awards, this amounts to nearly one million dollars in total costs.

1.1. Mapping TAM Receptor Regulation, Effects, and Therapeutic Strategies

The Tyro3, AXL, MerTK (TAM) receptor tyrosine kinases are widely implicated in both resistance to targeted therapies and in the cancer immune response. Regulation of the TAM receptor family by phosphatidylserine, as opposed to mutation, amplification, or autocrine ligand, make identifying the tumors that will respond to TAM-targeted therapies especially challenging. At the

same time, the cellular consequences of TAM receptor activation, including dedifferentiation programs and suppressed innate immunity, are distinct among receptor tyrosine kinase (RTK) families with important therapeutic consequences.

My lab has aimed to apply engineering analysis methods to improve our understanding of (1) when the TAM receptors are activated, and (2) how that activation is linked to cell phenotypic response. In Zweemer *et al* (*Molecular Cancer Research*), we built upon recent work from my lab elucidating how TAM receptors respond to phosphatidylserine to study how this mechanism leads to cell death-mediated tumor cell migration. Our recent NIH funding relates to our second focus and seeks to map the signaling responses of TAM activation in lung cancer, to identify which among many TAM-driven signal transduction events drives resistance to epidermal growth factor receptor inhibitors. We plan to apply this information and develop predictive measurements of which lung cancer patients will respond to TAM inhibitors.

This past year Dr. [redacted], the postdoctoral fellow I supervise remotely, received an American Cancer Society fellowship to support his work in this area. Also, Dr. [redacted], who was a joint postdoctoral fellow between my and Doug Lauffenburger's lab, accepted a faculty position at [redacted].

Lastly, linked to our efforts here, we have been involved in a collaboration to study the systems-level response of innate immune cells of the brain during Zika virus infection. In Muffat *et al* (*Proc. Natl. Acad. Sci. U.S.A.*), we provided expertise regarding the role of TAM receptors in Zika virus entry, and led experiments using healthy donor-derived peripheral immune cells to compare the innate immune response between Zika and Dengue virus.

1.2. Systems Engineering in Innate Immunity

Antibodies are crucial and central regulators of the cancer 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 through multiple processes (e.g. antigen presentation, cytokine response, phagocytosis, etc). These are particularly versatile agents for cancer treatment on account of their immunotherapeutic effects as well as those of direct antigen binding. Indeed, IgG molecules comprise a broad range of approved cancer immunotherapies and targeted therapies, many of which are known to rely in part on effector cell response. At the same time, the multiplicity throughout—of constant region composition, Fcγ receptors, cell populations, and antigen binding in combination—make precisely understanding, measuring, and manipulating effector function a yet-elusive goal.

In Robinett *et al* (*Cell Systems*), we employed a model of multivalent immune complex (IC) binding to FcγRs and showed that it can capture and predict experimentally measured binding and effector response at differing valencies. Applying this model, we could quantitatively predict anti-tumor effector response to a single IgG of a defined constant region *in vivo*. Additionally, we could pinpoint the critical cell population driving response. We now plan to build upon this work by (1) collaborating with other groups to design Fc regions of enhanced effector response and (2) using our binding model to identify antibody interactions. IgG interactions will potentially enable, for example, combinations that only elicit effector response when they both bind to a cell, or inhibitory IgGs to protect against cancer-targeted IgG side effects.

1.3. 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. Data-driven modeling

efforts have become an accepted tool in understanding how cells respond to their environment and in drug discovery efforts. Despite success using these methods, application of systems pharmacology methods has almost universally occurred outside a physiologically-relevant extracellular environment and ignored cell heterogeneity in signaling and response. My lab is actively collaborating with labs developing more physiologically-representative environments to both demonstrate the need to perform systems pharmacology studies within physiological environments and make these studies more widely feasible. In Schwartz *et al* (*Integrative Biology*), Prof. Shelly Peyton's lab and mine collaborated to investigate the signaling response of breast cancer cells within a panel of 2D and 3D extracellular matrix environments. Through this study, we demonstrated that measuring cell response in a 3D environment was necessary to identify a successful drug combination to apply *in vivo*. In this work, my lab led all the computational analysis and interpretation of the modeling results. We also supervised and advised the cell signaling measurements. This work will lead to *in vitro* drug development efforts with greater success upon translation to *in vivo* models.

2. TEACHING

In winter 2018, I taught a new course on machine learning for 19 undergraduate and 2 graduate bioengineering students. Familiarity with data analysis techniques is an essential component of modern engineering and a recognized area of improvement for the department's undergraduate curriculum. Machine learning is a rapidly changing and broad field. Therefore, the most valuable skill our students can take away from my course is intuition about how to evaluate success when applying a modeling method and how to apply the techniques they learn to challenges in bioengineering. Resources for such a course at this intersection currently do not exist. Therefore, I created all elements of the course from scratch, including the lectures, live coding sessions, and examples of the techniques we were learning from recent literature. Each homework in the class was an implementation of the techniques using real data obtained from recent studies. The class then culminated in students identifying a question they would like to ask using existing data and implementing a project using everything learned in the class.

Students' responses to the project-based learning were remarkable and demonstrated the extent to which they were immediately empowered to apply their knowledge. The overall rating for the course was 8.42 out of 9.00, compared to the department average of 7.77 for that quarter. I also received very positive comments from the students. For example, one student mentioned, "*By far the best material I've learned at UCLA. I wish Meyer taught a series of classes… I would take them in a heartbeat… Will be a class I'll remember for an extremely long, possibly indefinite time*." Another student commented, "*We should have more of these types of classes. Professor Meyer's teaching philosophy and strategy [are] honestly one of the best I've seen in Bioengineering. The subject was also very interesting and relevant for all bioengineers... We definitely should have more of these classes*."

Moreover, one student, [redacted], used his class project as a successful proposal to the Internet Research Initiative at UCLA to continue his project during his senior year. Another student, Francis Lin, reproduced analysis within an important study on the signaling of interferons. He discovered serious errors in the paper that we plan to resolve with the authors.

In addition to teaching the abovementioned course, I mentored a capstone team in fall 2017 and winter 2018. This team executed a project to develop a competitive screening assay for identifying inhibitors of TAM receptor ligand-phosphatidylserine binding. This team made impressive progress over the course and was selected to give an oral presentation of their findings at the capstone symposium, receiving an honorable mention for their presentation. One student, [redacted]

[redacted], has continued the project and I expect will be an author on a manuscript describing this work.

While during fall 2017 and spring 2018 I was on teaching relief and a course buyout, respectively, I have been using this time for course preparation. In fall 2018 and spring 2019, I will take over instruction for the bioengineering lab course 167L. To ensure this occurs smoothly I have actively been discussing the course and potential future improvements with Prof. [redacted].

3. UNIVERSITY AND PROFESSIONAL SERVICE

I have been actively involved across campus in a number of activities. Within the department, I serve on the publicity committee and recently was appointed the chair of the seminar and alumni committees for the next year. At the conclusion of the capstone course, during the symposium, I served as a poster judge. I serve on two thesis committees—those of [redacted] and [redacted]. I volunteered to attend and present at the Bruin Engineers Reunion in May, where I presented my work to alumni of the school. In spring 2018 I served on the Engineering Awards Committee to select school-wide awards. Finally, as an alumnus and member, I serve as an adviser and am actively involved in the activities of Tau Beta Pi.

I am currently co-chair of the Association for Early Career Cancer Systems Biologists. Part of my responsibilities as co-chair has been to lead planning for the organization's biennial meeting, November 7–10 of this year. For this, I have been raising funds from corporate sponsors and through a partnership with the National Cancer Institute. I am also an ad hoc reviewer for multiple scientific journals and fellowship programs.

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

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