

Ruth M. Greenblatt, MD
Professor of Clinical Medicine
and Epidemiology

405 Irving Street
Second Floor
San Francisco, CA 94122
tel: 415/502-6287
fax: 415/476-8528
email: ruthg@itsa.ucsf.edu

Campus Box 1352

Date

HIV Review Section
National Institutes of Health
Bethesda, MD

Re: *Mentee Doe*, K-23 Mentored Patient Oriented Research Career
Development Award application

Dear Committee Members,

It is my pleasure to affirm my commitment to serve as the primary mentor for *Mentee Doe*, MD, MPH during her five year K-23, Mentored Patient Oriented Research Career Development Award application. In this letter I will outline Dr. *Doe's* qualifications in the area of HIV/metabolism and sex effects research, my previous experience as a research supervisor, and the nature and extent of the supervision I will provide during the award period.

Dr. *Doe's* qualifications:

I first met *Mentee* during her fellowship training at the Center for AIDS Prevention Studies at UCSF during 1999, which is a favored venue for Infectious Diseases fellows to extend their training in HIV research methods. She was interested in the growing problem of HIV infection in women, and unanswered research questions concerning this population. She also had plans to do a research project concerning vaginitis in Vietnam (which she completed). Her initial work with me focused on the effects of the ovulatory cycle on HIV viremia and immune responses. This interest led to a fairly intensive project that enrolled 30 men and women who had not received any antiretroviral therapy. Women, all of whom reported regular menses, underwent vaginal ultrasound to accurately determine cycle phase and then had plasma and intracellular viral RNA and DNA levels, lymphocyte subset quantification and activation markers and sex steroid levels determined during the early follicular and midluteal phases. A comparison group of men were enrolled and had similar measures performed at random times. Enrollment targets were met despite the complicated eligibility requirements for the study. Analyses and publication of this work has been tardy, in large part because of delays in the virology laboratory. However *Mentee* demonstrated superb organizational and interpersonal skills during this work, and was able to manage this project despite the complexities of recruitment, enrollment and completing its intensive protocol. She was calm, goal oriented and productive in the setting

During her work with me, she was presented with two opportunities to join research collaborations that required her clinical and research skills as well as her focused and calm approach. The first was as the first project director for the 18-site FRAM study which was just being initiated. This study featured a multitude of clinical sites and a protocol that required detailed metabolic studies to be performed in a standardized and rigorous manner. Cohort studies are always a challenge to start, and this one, with so many sites, and such extensive technological specifications was no exception. *Mentee* took on this challenge, and rapidly acquired expertise in body habitus changes associated with HIV infection and in directing such a large research program.

The second opportunity was within WIHS, which was struggling to launch investigations in the effects of HIV and its treatment on metabolic perturbations, but lacked expert and savvy investigators to take a leading role. Due to her expertise and productivity in studies of the metabolic complications of HIV infection, *Mentee* was asked to take a leadership role in developing metabolic studies within WIHS. She wrote several proposals for WIHS studies and is currently leading an intensive study based at two sites.

Mentee's intellectual and personal skills were tested through the start of FRAM and her growing role in WIHS but this also coincided with her father's unexpected illness (and eventual death) and pregnancy and childbirth. She maintained her leadership in these projects throughout this time, demonstrating her ability to focus and see projects through despite tumult in her life. This ability is of obvious benefit for any academic medicine based researcher, since all of us face a long list of competing needs be they professional or personal.

So, I believe, based on her record, that *Mentee* is **very capable, in terms of intellectual and functional abilities, to conduct research**. The direction of her proposed research focus is also very promising. As technological progress and insights provided by molecular biology influence translational work, importance of the interface between infectious diseases, host response, and metabolic perturbations has become very clear. HIV is a great model of these interactions because it is a chronic infection, directly produces a myriad of inflammatory responses, and indirectly encourages other pathogens, and its treatment may also perturb metabolism. Studies of women should be a high priority since women constitute the majority of HIV cases worldwide, and yet clinical research on this population is limited. Furthermore, sex dimorphism in metabolic conditions is likely due to differences in body habitus, dimorphism in immune responses and in the occurrence of cardiovascular diseases. **Thus, the focus of the research program *Mentee* is seeking to develop is both original and addresses important issues involving the mechanisms of disease and health research.**

I am sometimes approached by early career faculty who have no research training to assist them in applying for career development awards, and I find this is a very difficult thing for them to do. Skills in clinical medicine do not translate directly into research ability, and development of a research career without any formal research training is a very difficult goal. *Mentee* has completed an MPH, a research-oriented Infectious Diseases Fellowship and a Fellowship program in research methods. So her background is definitely adequate for scientific research. Her current goal, as an early career faculty member, is to develop a research program that spans the fields of infectious

diseases, metabolism and some hepatology. None of the traditional postdoctoral programs provide this training, and since she seeks to become an independent investigator, the additional training she needs is at an advanced level. **So, while she has an already impressive background in scientific research, a K-23 award would provide her the time and support to acquire the advanced skills she will need to work in an interdisciplinary translational setting.**

Mentee has published, as first author, 3 papers in peer reviewed journals, and 6 papers as a coauthor. Since much of her research is based in large cohort studies, which have a fairly long period time from initiation to fruition in published reports, this record is good. Her paper on lipoatrophy and lipohypertrophy was the first focused on women, and also challenged conventional concepts about the definition of the metabolic syndrome associated with HIV and its treatment. Many other papers are in the process of preparation, and her productivity is so well regarded that she has been invited to join the expert OAR priority setting panel for clinical studies and epidemiology. **The high quality of her research and papers is being recognized**, and her letters of reference likely attest to this.

Previous experience as a research supervisor:

I have supervised, and mentored, early career faculty and fellows in a variety of settings. I am co-Director, with Jim Kahn of the UCSF/Gladstone CFAR mentoring program that was launched this year and has enrolled 12 mentees for intensive assistance. I have been the principal mentor for 3 infectious diseases trained physicians and 1 general internist who progressed to join the faculty. I have been a secondary mentor for a much larger number of faculty and fellows, and I have led campus initiatives on the climate for faculty, promotions and retention and have chaired several academic senate committees including Privileges and Tenure, so I am fairly well acquainted with UCSF resources, policies and procedures. As Principal Investigator of the Northern California WIHS site, I am also in an excellent position to assist *Mentee* in her interactions with this large research group, and to facilitate her projects within WIHS, though at this point in time she is a well-recognized member of the study group. I am not based at the San Francisco Veteran's Administration Hospital, but the infectious diseases division at UCSF spans all the campus sites, and I know the VA group quite well. In addition, I am a member of the CFAR senior leadership group, and work in this capacity with Paul Volberding who is chief of the Department of Medicine at the VA. It is clear that *Mentee* is highly valued by the department and that she can expect to receive full institutional support for her research efforts.

In general, for early career faculty, I believe that mentoring should focus on developing organizational and communication skills as well as scientific directions and career strategy. At this point in her experience in science, *Mentee* has acquired an extensive knowledge base, access to various settings in which new research frontiers and methods are presented, and she is familiar with the members of UCSF's large HIV research community. The challenges for anyone intending to succeed as a clinician scientist are significant, and success depends on effective use of time, the ability to focus on priority tasks, a sense of humor, good communication skills (including the diplomatic application of the word "no"). She has already made excellent progress in this, and I will continue to work with her to provide her access to my knowledge as well as campus resources.

Extent of supervision I will provide during the award period:

I will meet with *Mentee* weekly and have a private meeting with her twice monthly. I will also talk with Drs. Grunfeld, Bacchetti, Gange, Peters and Taylor at least quarterly to get their input on her progress. During my meetings with *Mentee* we will review her general progress, input from her other mentors, time management, any problems, her sense of well-being, updates to her goals and plans and publication productivity. We will discuss the course work and other work she is doing to acquire new skills and in the later years, her strategies for obtaining independent funding.

Overall, I am very enthusiastic about the direction of the research Dr. *Doe* has proposed, and I think she is an outstanding candidate for a K-23 award and for a career as a clinician scientist. This K-23 award would support her continued development as a researcher enabling her to pursue an original translational program that spans several medical disciplines to address important issues that concern how chronic infections influence metabolism. With regards to HIV, until there is a cure, the metabolic outcomes of antiretroviral therapy will become an increasing concern as the global program to provide universal treatment proceeds. It is also of great importance to encourage investigators who are interested in and able to study women, particularly in diseases like HIV, that afflict relatively disadvantaged women, because they have been somewhat neglected by medical research. *Mentee Doe* is one of the most promising young investigators I have worked with and I vigorously support her application for this K-23 award.

Sincerely Yours,

Ruth Greenblatt, MD