PERSONAL STATEMENT

Knowing that my strengths lie in my ability and passion for science, my chosen goal has been to explore the unknown, make it possible for others like me to do the same, and share what we discover with the outside world. My scientific objective today arose from an experiment that I thought at the time had failed. The aim of this experiment had been to generate a mouse in which a mutant p53 allele could be turned off and on using the lac operator-repressor system we had just developed. We used a p53 mutation that had been reported to be lethal during embryogenesis, and we expected that mice born carrying this mutation would develop tumors when the mutation was induced. Instead of mice with inducible tumors, the mice we generated had a tumor incidence even below that of wildtype mice. Instead of a mutation that immortalized cells by interfering with growth control by p53, cells from this mouse proliferated more slowly and senesced in culture more rapidly than cells from wild-type mice.

Changes in the ability of mutant cells to proliferate, in fact, result in the two clearest traits associated with the mutant phenotype of the animals we generated—small size and accelerated aging. This accidental aging model is now the focus of most of the work going on in my lab and all of the work planned for the future. With it, we now have a way to study mammalian aging in the context of an organism closely related to humans and on a manageable time scale (months rather than years). As an indication of how important this model is to the study of mammalian aging, the NIH recently issued a program announcement to study stem cell therapy in mouse models of accelerated aging, and our mouse (the p44 mouse) was one of few models for which this PA was intended.

The model is as complex as the process itself and has allowed us to explore widely different mechanisms that might contribute to aging in humans. For example, the mice develop type 1 diabetes, show impaired IGF signaling, lose the ability to replace central neurons, exhibit endocrine disturbances at all three levels of the HPG axis, and undergo behavioral changes that result in increased anxiety. Stem cell populations are significantly impaired. My research objective now and in the foreseeable future is to determine which of these and other mechanisms might be what drives aging in mouse and man.

This is obviously a very large objective and one I cannot hope to reach without a strong research group. My goals for this next phase of my career, therefore, are oriented much less personally and much more towards the development of the individuals in my research group. want to do this for several reasons, and I think that I can, now that I have acquired the necessary skills. understand the workings of the NIH and how to get a grant; I know what works and what doesn't in presentations to large and small groups; I am much better at finding the appropriate journal for publishing diverse kinds of papers; I have acquired some manner of diplomacy and can get things accomplished despite the rules and regulations (formal and informal) that govern academic life. I have developed something of a thick skin and I know, at least in principle, how not to take criticism personally. help others in my group to acquire these skills and, in the process, set and meet higher goals for them individually and for the group as a whole.

Currently, my group consists of two junior faculty members (research track), one senior postdoc, three graduate students (one has an MD), two technicians, and a bevy of undergraduates. Until recently, I kept track of each individual project by working with each person one-onone in a mentoring/directing relationship that involved immediate attention to benchwork, including interpretation of results and troubleshooting. As my group got larger and we were joined by senior scientists perfectly capable of doing their own troubleshooting, a hierarchical structure evolved in which each senior member gathered more junior members together to work on a project. Now, rather than having to keep up with ten projects, I have only three. have time to write and my project leaders have been allowed to develop their own leadership abilities. I would like to encourage this independence even further and I am doing this by asking them to take on increasingly more responsibility for the financial support of their work. is amazing how having to pay for, or plan to pay for, their own experiments has inspired these people to do more-and how much more enthusiastic they become as they get control over the direction their work takes.

My plan is to get each of these three senior people funded independently. At the present time, only one of them (Dr. Bernhard Maier) has secured external funding, in

this case two small grants from the Institute on Aging (UVA) and a joint program with Virginia Tech. However, Dr. Maier has applied for an R21 from NIH, which is being reviewed in about a month. Dr. Maier is currently appointed as Assistant Professor of Research in the neuroscience department. Dr. Silvia Medrano also has a faculty appointment at the rank of Instructor. She was a finalist in the Dana competition for brain imaging projects last year. She is currently writing an R21 in response to a program announcement on stem cells in aging that fits her research very closely. She will submit this by the February 1 deadline. The newest senior person is Dr. Melissa Burns-Cusato, who is currently a postdoc. Dr. Burns-Cusato held a faculty appointment before coming to Virginia, and is currently a part-time faculty member at Sweetbriar College. Her KO1 application, which will be mentored by me, will be reviewed within the next month as well. She plans to resubmit this as an R21 application as soon as possible.

This step where each senior member obtains external funding is the first step in building a center for the study of aging that is my final goal. I have been encouraged by NIA to submit a program project application to study mammalian aging within the context of our mouse model of accelerated aging, which we have been developing in my lab over the past three years. In thinking about this, I realized that all of the really interesting work I could propose is already being done or planned by these three people. Of course, a program project application with three very junior investigators heading three of the four individual projects would most likely not be competitive. Therefore, we propose to take the development of this aging center in stages. The first stage is to get individual project funding, as described above. During this time, we have been meeting as a group to decide the scope of each individual project, what cores to include, and the overarching theme of the project as a whole.

Having decided that our goal will be to explore the role of the tumor suppressor p53 as a longevity gene, the next stage after the individual funding stage, will be to obtain support for our cores. I have already asked Dr. Ariel Gomez for the opportunity to present our ideas to the Development Office. We would ask for support for the cores. This, along with publications and presentations arising from work in progress, will be used to get

preliminary evidence to support a program project application. In two to five years NIH funding is predicted to be back to more normal levels, and it is just about that time that we will be ready to submit our program project idea to the NIH.

In terms of scientific success, of being able to think and work hard, and of being willing to work together towards a common scientific goal, these people have what I want. It is my goal to help them achieve what is possible for them to achieve, and in this way to build a stronger research group that will allow me achieve my own scientific objectives in the process.

The intense interest stirred up by our 2004 paper on the role of p53 in mammalian life-span control gave me almost instant access to leaders in the field of aging research. As a consequence of the opportunities this provided for me to talk about our work worldwide, I have a very good idea where our research fits into the field as a whole and what value our unique contribution might take on. With a broader base of support here at UVA, I could easily envision the establishment of a center for the study of aging that might run parallel to the current Institute on Aging (IoA) directed by Dr. Timothy Salthouse. The IoA is committed to general problems of the elderly that pertain to quality of life. Tim has enlisted the participation of architecture, engineering, law, and the College (and others) to address social, legal, clinical, and psychological issues that arise as a consequence of old age. I would propose a parallel track, which would be devoted entirely to the scholarly endeavor of basic medical research, an institute to study the aging body, rather than the aging mind. This center for the study of the aging body would consist of a few senior principal investigators, each with their own lab group. The total number of researchers would be no more than 50 and would be housed in a single building. We would continue to focus on the idea that cell proliferation and its control are fundamentally important to the long mammalian life-span, and we would use primarily animal-based systems to study this idea.

I can also see how my interaction with UVA medical and graduate students should make it possible to awaken interest in the field of aging research and its clinical applications in people at the beginning of their professional lives. I have met all of the entering medical

students for the last ten years in the laboratory and lecture hall of medical neuroscience, which is a required course in their first year. I had even more interaction as director of laboratories for the course, and last year was course director for the first time. By integrating agingrelevant topics into the material the students must master to do well on the Boards (which has been a consistent source of pride in our department for many years), one or a few of them should be inspired to return to the aging field following their training. Instead of coming into the field late in the game (as almost all present-day researchers in the field have done), these will be people with broad knowledge and an experience base that should enable them to participate at the highest level. Furthermore, as a member of the admissions committee for the medical scientist training program, I am already helping to shape the incoming classes of students committed to careers as clinician-researchers. Wouldn't it be thrilling to see someone return to UVA to participate in research they first heard about as a first year med student? This is definitely possible.

Finally, a word about graduate mentoring. When I was a postdoc, I couldn't wait to get my own lab for two reasons. First, I wanted to organize a lab so that anyone could find anything easily. In my lab, you wouldn't need to know the person who might know (if you could find them) where that much needed reagent or piece of equipment was located. Second, I wanted to hire some postdocs of my own so that I could get more of my experiments done than I could working at the bench alone. If I were to judge, then, how things are in my lab by what my goals were for my lab, I would have to admit that this is another failure, just like my inducible tumor mouse that gets fewer tumors than wild-type mice. In fact, the parallel is quite similar in outcome: what I have is much more than what I sought. It has become a source of intense satisfaction to mentor students and postdocs. I never anticipated it, either what it meant to mentor someone or what joy it brings. My students have done well. Carolyn Cronin, my first PhD student, won the Peach award for outstanding neuroscience graduate in She is currently a neurology resident at Johns Hopkins. Amy Ryan, my second, wrote a paper that got her an invitation to speak at a conference in England. She has also spoken at local events and at the Society for Neuroscience meeting in 2003. Tsutumo Sasaki and Erica Ungewitter, my newest students, will do equally well. Mentoring junior scientists has turned out to be the most natural thing in the world for me.

I was a professional musician until I was 30 years old. I have had the experience of doing something for which I had only a modest talent and was not well suited. Science is different. I have always known that. Now that I have discovered that I can also be an educator, I am fully prepared to assume an even larger leadership role—wherever that takes me—in the future.