

Shibani Mukerji will be involved in an ongoing, relatively new research avenue in my laboratory focused on activin and CNS neuroprotection. My laboratory has been best known for our discovery that activin is crucial for the differentiation of pain sensing neurons and in the modulation of sensory neuron plasticity after wounding or inflammation. This major area of work is currently funded by the NIH through 2008. More recently, we have focused on the functions of related molecules in CNS development and differentiation, and these projects built our interest in CNS neuroprotection. Pilot studies performed with Dr. Warren Selman and others in Neurological Surgery at UHHS produced exciting information about activin in neuroprotection after ischemic injury in the rodent experimental stroke model, and Shibani has driven much of the continuing work in this area. As detailed below, she has acquired the mouse experimental stroke expertise and has quantitative RT-PCR observations that activin mRNA is increased rapidly after focal ischemia. Indeed, since the original submission of this proposal, she has submitted a first author manuscript on this subject. Further, Ms. Ekaterina Katsman in my lab has developed a cortical neuron culture system that allows us to examine cellular mechanisms directly. Steven Fulop, M.D. a neurological surgery resident has just joined the lab and will focus on in vivo perturbation of activin in stroke. This is a fine opportunity for Shibani take advantage of well-characterized reagents and considerable molecular expertise in the lab and apply it to a relatively independent project.

I am delighted that Shibani has decided to pursue her PhD work in my laboratory and I will insure that she receives strong guidance toward research independence. While Shibani has already made remarkable progress, she also has a number of research and professional skills still to learn, including the mature development of her own research, oral and written presentation skills, grantwriting, exposure to research in neurological fields and most importantly, scientific judgment. She will spend the next two years testing her hypotheses, refining technical approaches and preparing her work for publication and presentation. The sequence of skill development will proceed from basic technical capabilities and critical scientific analysis to more sophisticated generative proposals and manuscripts, and ultimately to more sophisticated research projects conceived and analyzed by Shibani herself. These capabilities will be developed in formal and informal interactions as described below.

Shibani has completed her required coursework and passed her PhD qualifier exam so she may focus on research. She is responsible for her own experiments, from planning the study to insuring materials are available, to processing materials to their completion. She performs all her own animal surgeries, harvests and analyzes tissues. She and I discuss the experimental plan of her work, and as she matures in her scientific thinking, she will become more confident in structuring each study. Shibani has already completed required training in responsible conduct in research at Case. Thus, Shibani already has considerable personal responsibility for the conduct of her research.

Shibani will participate in lab meetings as well as department and interest group meetings to refine her presentation and critical skills. Shibani will continue to communicate the goals and results of her work in our weekly lab meetings, and she and I meet to review her progress and discuss experimental options several times a week. I want to allay any concerns raised in the summary statement that she might not have enough individual time with me. Because my office comes off of the lab, we have frequent informal interactions (“want to look at my blot?”) perhaps daily, as well as more organized meetings one on one (“shall we use this virus?”) about once a week. We also have joint lab meetings with Drs. Dody Robinson (neonatal ischemia), and Robert Miller (CNS repair in the spinal cord). She is required to attend the Neuroscience weekly journal clubs and seminars and to present in the journal club at least once a year. Further, we participate in the Translational Neuroscience Interest Group that consists of clinical and basic science investigators (including Drs. Sophy Sundararajan and Joseph LaManna who work on stroke) and meets monthly.

Shibani has begun to master the presentation of her work nationally, both at meetings and in timely publications. She presented a poster at the 2005 Society for Neurosciences meeting as an emerging

junior colleague. We have recently submitted a manuscript on which she is first author on the subject of this proposal, and have explicit discussions about style, content, audience, etc. I expect that she will present her work at national meetings annually, and that the research will ultimately result in at least two first author publications. In the next year, I will begin to work with Shibani in reviewing manuscripts I receive from journals, so that she learns to convey constructive criticism effectively.

The most important and most difficult research skills for any young investigator to develop are those that concern which avenues to pursue. She has just formed her thesis committee, including Drs. Warren Selman MD (Chairman of Neurosurgery, UHHS and expert in stroke); Nanduri Prabhakar, PhD, Professor of Physiology and expert in hypoxia; Jerry Silver, PhD, Professor of Neuroscience and an expert in neural regeneration and Gary Landreth, PhD, Professor of Neuroscience and an expert in neurotrophin signaling. She meets with this expert committee every six months to review her progress and discuss her research goals. Further, I encourage her to prepare grant proposals to allow her to learn grantwriting skills. The ideas and writing in her proposal are her own, although I have reviewed them for clarity.

Together, we have already begun to add to Shibani's methodological "toolbox," utilizing expertise at the University and elsewhere. Dr. Selman's research team trained Shibani in the experimental stroke model in rat. I then arranged for Shibani to visit Dr. Pak Chan's laboratory at Stanford, where she worked closely with Dr. Carolina Maier, PhD a postdoc in the lab, to perfect the MCAO model in mouse. Based on her interest in HIF1alpha, Shibani contacted Dr. Gregg Semenza MD, PhD at Johns Hopkins, and recently visited his laboratory discussing common areas of interest. He has been generous with his time and also offers his adenovirus based HIF reagents for her use in her proposed studies. Dr. Semenza is also an example of an academic M.D., Ph.D. and thus also offers a strong role model for Shibani. He will have an ongoing collaborative research relationship with the lab, and Shibani will communicate with him as the studies require. This will presumably result in at least one visit between the labs each year as well as regular communication.

Shibani needs to master some new technical methods to become more confident about new approaches. My laboratory offers extensive cell culture, in vivo analyses and immunochemical and RNA based assays. She also proposes work with adenovirus, an approach that is used by my close collaborator Dr. Andrew Russo PhD at the University of Iowa as well as local experts including Dr. Yu Chung Yang in the Case Pharmacology Department (please see letter). With the successful collaborative and resourceful relationships we have already developed, I am confident that Shibani can complete the proposed study.

The proposed research plan has been designed to match Shibani's career plans that currently center on academic medicine in neurology or neonatology. As an MSTP student, Shibani seeks clinically relevant research and we have assembled both basic and clinical research experts to train and expose Shibani to academic medicine career options. The MSTP requires Clinical Tutorials during the PhD years to help students learn more about clinical specialties and to become familiar with various physician scientist lifestyles. I encouraged Shibani to work one-half day a week with Dr. Cynthia Bearer, MD/PhD, a neonatologist with neuroscience interests at UHHS beginning in Spring 2006. This clinical tutorial involves interactions with Dr. Bearer as well as other members of the NICU team, and Shibani is particularly interested in working with Dr. Mark Scher, a pediatric neurologist who consults with the service. This clinical tutorial will continue for the next 12-18 months. While we have worked to make the clinical tutorials related to her research interests, they are actually intended to assist her not in research per se, but in selecting the field she will ultimately pursue. To further address the particular area of her research, we have arranged with Dr. Selman that Shibani will become exposed to clinical stroke treatment. During the next year, he will arrange that she wears a pager and is called to Brain Attack calls, and attends the weekly 7:30 am stroke rounds to discuss management and

outcome of all cases that week. These are significant, ongoing efforts to help her become familiar with clinical aspects of her research projects.