



September 18, 2009

The Markoff Family
Rachel Molly Markoff Foundation

Dear Eliane, Gary, and Audrey,

I would like to thank you again for your generous support of our research, which came during a critical time for my laboratory. As you may know, government funds for academic scientists have been scarce for the past several years, and foundations such as yours have been essential for advancing America's biomedical research. Our Brain Tumor Society/Rachel Molly Markoff Foundation grant enabled my students and postdoctoral fellows to discover four new inhibitors of the Hedgehog pathway, which has been linked to the onset and progression of several cancers such as medulloblastoma and glioma.

During the past few years, there has been considerable excitement about the possibility of using Hedgehog pathway antagonists as anti-cancer therapies, and the first clinical data confirming this hypothesis was published just last month. Scientists at Genentech were able to develop a chemical inhibitor of Smoothed, a transmembrane protein within the Hedgehog pathway, and this compound exhibited very promising activity against metastatic basal carcinoma. This compound even caused rapid regression of metastatic medulloblastoma in one patient and a reduction of his symptoms. Unfortunately the patient's cancer eventually became resistant to the drug, but the fact that he responded at all to the treatment means that we are on the right track. What is needed now are new ways to pharmacologically inhibit the Hedgehog pathway, and our research is focused precisely on that goal. In fact, our studies have shown that our four inhibitors act downstream of Smoothed in the Hedgehog pathway, suggesting that mechanistically similar compounds might someday avoid or counteract the drug resistance mechanisms observed during the clinical trial. Two of our compounds were able to block the growth of cultured medulloblastoma progenitor cells, and we are now collaborating with Dr. David Rowitch at UCSF and Dr. Matthew Scott at Stanford to investigate the efficacy of these inhibitors in mouse models of medulloblastoma. In addition, one biotech company is evaluating the potential of our compounds as developmental leads for new anti-cancer agents.

Our findings were published in the *Proceedings of the National Academy of Sciences* last month, and we were recently awarded a National Institutes of Health grant to continue our research on these molecules. None of these accomplishments would have been possible without the support of the Rachel Molly Markoff Foundation, and my students and I sincerely thank you and the contributors to your foundation. Your continued commitment will help other young scientists pursue cutting edge research and achieve new milestones in our fight against cancer. I truly believe that the biomedical advances made in the next ten years could be transformative for future cancer treatments.

Thank you again for your generous support of our research. If your travels ever bring you to the Bay Area, please let me know. I would be happy to show you around Stanford and introduce you to my laboratory.

Warmest regards,

James K. Chen, Ph.D.
Assistant Professor of Chemical and Systems Biology