KOCH INSTITUTE
for Integrative Cancer Research at MIT

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April 14, 2017

Mr. Jean-Marc Joerin
c/o JOERIN Advokatur & Mediation
Schneidergasse 1
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Dear Mr. Joerin,

I am pleased to write to you to share the enclosed confidential summary reports from the 2016 Misrock Fellows, Li Gu and Neelkanth Manoj Bardhan.

Li successfully achieved the aims of his project, which was to develop and test a nanoparticle to engage a molecular target overexpressed in ovarian cancer. The target, a cell surface receptor, plays a strong role in mediating signaling that supports tumor growth and chemotherapeutic resistance; this receptor has previously been targeted in clinical trials without success. Li developed a nanoparticle platform that carries a payload of standard chemotherapy, but incorporates certain design characteristics into its outer 'packaging material' that allow the material to interact with the receptors in a way that improves targeting, improves cancer cell uptake of the chemotherapy, and shuts down receptor-mediated signaling. The nanoparticles, which Li tested in cell culture models, appear to create a powerful therapeutic synergy invovlving the chemotherapy and the carrier components.

At the conclusion of his fellowship term, Li accepted a research position at a biopharmaceuticals company, although he remains in contact with his mentor, Koch Institute faculty member Paula Hammond, and her laboratory. He transitioned his project to another member of the Hammond group, who will test the nanoparticles in a robust mouse model of ovarian cancer and keep this work moving toward clinical application.

The second fellow, Neel, has made significant progress in moving a powerful new cancer-fighting tool toward first-in-human clinical trials and commercial development. Neel, you may recall, has led the development of a nanotechnology-based imaging and detections system that is highly sensitive, capable of revealing tumors smaller than a millimeter in size, even in deep tissue. The system is also safer and less expensive than existing imaging methods, and holds great promise for cancers like ovarian disease, which often go undetected until advanced stages. The system has been tested most extensively as a real-time guided imagery surgical tool in advanced ovarian cancer models, in collaboration with clinical partners at the Massachusetts General Hospital, and has shown impressive results.

During his fellowship, Neel has completed critical research and legal preparations for a first-in-human trial of the system, which he plans to conduct with his MGH partners.

I also want to tell you about the 2017 Misrock Fellows, Yulia Rybakova and Pedro Pires Goulart Guimaraes. Interestingly, both fellows are using the same tactic—developing nanoparticle-based vehicles for RNAi delivery—to advance different therapeutic strategies. Yulia is trying to combine siRNA with chemotherapy to make liver cancer more sensitive to therapy, while Pedro is trying to use siRNA to shut down a signaling molecule that helps drive multiple myeloma.

Yulia is a member of the laboratory of Koch Institute faculty member Daniel Anderson and, in her fellowship project, is working to develop and test a combinatorial nanotherapeutic approach for a form of liver cancer. Hepatocellular carcinoma (HCC) is one of the most common liver cancers, comprising more than two-thirds of all cases, and has a median survival time for patients of just 6 to 20 months from diagnosis. This poor prognosis is attributed in part to the speed and frequency with which patients develop resistance to standard chemotherapy regimens. Yulia proposes to target HCC with a novel strategy that combines conventional therapy with nanoparticle-formulated siRNAs, ones that knock down genes crucial to the tumor's ability to resist the chemotherapy. Successful development of this and other new approaches will ultimately help to circumvent cancer drug resistance, to advantage existing HCC treatment options, and to improve overall patient survival.

Yulia holds a graduate degree in cell biology and histology from Lomonosov Moscow State University, and a doctoral degree in biochemistry from the Russian Academy of Sciences, both in Moscow; she also received an award from the Fulbright Foreign Students Program to support a year as a visiting researcher in the University of Iowa's Free Radical and Radiation Biology Program. In her free time she enjoys dancing tango, and serves as a board member of the MIT Tango Club.

A member of the laboratory of Koch Institute faculty member Robert Langer, Pedro is developing a nanoparticle platform to deliver RNAi therapeutics to a novel target in multiple myeloma, which is an incurable hematologic cancer characterized by accumulation of plasma cells in the bone marrow. Whereas tumor progression has been traditionally viewed as a process intrinsic to tumor cells, recent research has shown that bone marrow microenvironment components, specifically a signaling molecule secreted by some bone marrow endothelial cells, actually provides the conditions that encourage multiple myeloma cells to home to, colonize and proliferate in the bone marrow.

No conventional, or small molecule, drugs are known to inhibit this molecule, so Pedro is working to create and test a nanoparticle platform that can deliver siRNA to shut it down. It is worth noting here that, in published research targeting RNA to lung endothelial cells, the Langer laboratory has achieved some of the most potent RNAi gene-silencing to date in non-liver tissues, and Pedro will be adapting that technology for this project. He is also partnering with a clinician at the Dana Farber Cancer Institute in Boston, and expects that

positive results from his project will be translated into clinical trials to be carried out by his collaborator.

Pedro earned his doctoral degree in chemistry from the Universidade Federal de Minas Gerais in Brazil; he holds degrees in pharmacy and biopharmaceutical innovation from the same institution. In addition to his work as a researcher, he has worked in intellectual property development for the biotechnology sector.

I understand that Yulia and Pedro will be the final Misrock Fellows at MIT. Over the past several years, the Misrock Fellowships have provided a springboard for exceptional researchers like them, and exceptional new ideas and technologies. I fully expect to see former Fellows emerge as leaders of the next generation in cancer research and, before too long, to see the advances they have devised in the hands of patients and physicians. I want to reiterate my deep appreciation to the Foundation for supporting this program, and for its investments in young talents and technologies, which will continue to bear fruit long after the formal conclusion of the fellowships.

Sincerely,

Tyler Jacks

CC: Victoria Misrock-Stein
Kathy Misrock