KOCH INSTITUTE
for Integrative Cancer Research at MIT

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Mr. Jean-Marc Joerin
Misrock Foundation
c/o JOERIN Advokatur & Mediation
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Dear Mr. Joerin,

We are honored and delighted by the Misrock Foundation's continued support for cancer research at the Koch Institute at MIT. I am pleased to write to you now to announce the three new fellows selected for 2014. However, I first want to share final reports from the 2013 Misrock Fellows, Tal Danino (Bhatia Laboratory) and Rama Suntharalingam (Lippard Laboratory). Enclosed you will find confidential formal reports from each, along with publications, but I want to add a few comments of my own about their accomplishments.

Tal's work has been particularly interesting to follow over the last two years, as he is exploring the potential of new categories of nanotechnologies for cancer diagnostics and therapy. Currently, most nanoparticles are composed of polymers or lipids, but Tal is working with bacteria- and probiotics-based vehicles. He has been at the forefront of developing these emergent approaches, and also of envisioning how their particular properties can be adapted for both static and independently responsive diagnostic and therapeutic uses.

Tal hoped that the minicells he created in his initial project would be able to detect and treat cancer cells, however they did not function independently enough to do so. So, he temporarily narrowed his focus, applying lessons learned to create another synthetic gene-circuit approach, this time a static diagnostic. Tal's orally-administered probiotic diagnostics have done very well in detecting tiny, early-stage colorectal cancer metastases in the liver, and in revealing them clearly via simple urinalysis. However, he is not yet clear on the effect that an individual patient's gut bacteria or immune system may have on the efficacy of the probiotics, which will require further study.

Tal anticipates that gene circuit-based approaches can still be adapted for therapeutic use, specifically for self-triggered delivery of therapeutic cargo to tumors, and in recent months has continued working on the minicells as both static agents and the responsive ones he originally envisioned. In addition to investigations with colleagues at MIT, his research now includes collaborations at the Broad Institute of MIT and Harvard and at the Rockefeller University in New York City. These collaborations will help to expand our understanding of how we might most effectively engineer bacteria for use in fighting cancer. For example, Tal's work with Broad investigators has focused on studying human tumor samples and the bacteria normally found in them. Not only are these samples quite different to his previous mouse models, but he can also study how the bacteria get into the tumors so that he can engineer his minicells to do the same.

Tal currently has a manuscript on his programmable probiotics in submission to a major journal, and also published a first author piece in the *Journal of Visualized Experiments*, a peer-reviewed scientific video journal, during his second formal fellowship term. You may recall from my previous correspondence that Tal is an accomplished filmmaker and actively uses the medium to engage young people and general audiences in scientific inquiry. It is therefore especially fitting that his novel research approaches appear in this unique journal. A print version of Tal's paper is enclosed with his report, but the original video can be viewed online at the URL listed below the citation.

Rama, in turn, has achieved the goals of his Misrock Fellowship project, designing new and vastly improved nanoparticle carriers for phenanthriplatin, the new platinum-based compound identified by members of the Lippard laboratory, including inaugural Misrock Fellow Ga Young Park. The latest version of Rama's nanoparticles show marked improvement over the laboratory's first-generation ones; they are smaller and more easily taken up by cells, load higher concentrations of cargo, and evoke the same cellular response as free phenanthriplatin, meaning that they do not alter how cells react to the compound. While the nanoparticles are effective at killing lung cancer cells, their selectivity for cancer cells over normal cells is not yet as high as Rama would like, so he will look at supplementary targeting components as a next step.

In addition to advancing the development of phenanthriplatin nanoparticles during his tenure as a Misrock Fellow, Rama has identified and characterized a new therapeutic osmium compound, and devised a first-generation nanoparticle carrier for that drug as well. Genetically targeted cancer therapies have received a great deal of attention in recent years and are powerful tools, yet they often work exclusively for smaller patient populations. Thus, we must also continue to develop and refine more traditional, broadly applicable drugs like the ones that Rama is focused on, using nanotechnology and other advancements to maximize their effectiveness while minimizing their systemic toxicity and serious side effects.

As you will likely remember from my update to you in December, this year we are able to name three Misrock Fellows: Drs. Yi Wen Kong, Partha Gosh, and Mark Tibbits.

A member of the laboratory of Koch Institute Professor Michael Yaffe, Yi Wen has designed a promising research project titled, "Exploiting synthetic lethality and nanotechnology to sensitize non-small cell lung cancer to chemotherapy in vivo." The Yaffe Laboratory is particularly focused on cell signaling, how it is disrupted or co-opted by cancer, and how we can interrupt these processes for therapeutic benefit. Yi Wen's investigation builds on two key Yaffe Laboratory discoveries, the first being that the staggered, precisely-timed administration of drug combinations can significantly increase their effectiveness. More recently, the group has found that certain drugs that do not show benefit against cancer on their own can, in concert, make cancer cells with a mutation of the p53 gene much more vulnerable to chemotherapy by blocking another gene called MK2. (Roughly half of all cancer patients have p53 mutations.) Both findings were profiled by MIT news media, and I have enclosed those summaries here.

Yi Wen plans to identify an optimally time-staggered regimen for a new combination of a therapeutic siRNA, to knock out MK2, and cisplatin, a standard chemotherapy drug. He then aims to develop nanoparticles capable of delivering both the siRNA and cisplatin at the appropriate interval. Yi Wen earned his undergraduate and doctoral degrees in biochemistry, at the University of Leicester and the University of Nottingham respectively.

Partha Gosh, the second new Misrock Fellow, is a postdoctoral researcher in the laboratory of Koch Institute Clinical Investigator Peter Ghoroghchian. Our clinical investigators are physician-scientists, who conduct cutting-edge cancer research while continuing to spend 10-50 percent of their time treating patients at the Boston-area oncology treatment centers with which they are affiliated. This dual role ensures that investigators remain involved in active practice, which benefits the KI community by providing front-line views of clinical challenges in cancer treatment.

Although Partha's project title, "High-throughput screening for small molecule inhibitors of protein-protein interactions based on surface enhanced resonance raman spectroscopy of gold nanoparticles," is exceptionally long, his goal is actually to shorten the process of finding new therapies to target the genetic underpinnings of cancer. Partha is developing drug discovery assays that use gold nanoparticles to enable high-throughput screening of small molecule, or conventional, drugs to determine their potency and selectivity against epigenetic readers. Epigenetic readers are proteins that each regulate the transcription of a specific gene, and may be inhibited to silence that target gene. Currently, the process of identifying small molecule inhibitors for epigenetic readers is not amenable to high-throughput screening, but must be done via much slower and more intensive traditional assays.

Ultimately, this technology is likely to be useful for screening for inhibitors of other targets as well, including nuclear receptors, transcription factors or their coregulators, and may well help accelerate development of novel therapies against numerous newly discovered gene mutations in a range of cancer types. Partha is a graduate of the Indian Institute of Technology and earned his doctorate in chemistry from the University of Massachusetts at Amherst.

Finally, I want to tell you about Mark Tibbits, a member of the laboratory of Koch Institute Professor Robert Langer. In his project, "Injectable nano-network for cancer diagnostics and therapy," Mark aims to engineer an easy-to-use, injectable nano-network to noninvasively diagnose, stage, and treat metastatic breast cancer. A technology that detects migrating tumor cells prior to the onset of significant lesions and relays a signal outside of the body during the earliest phases of metastasis would be extremely beneficial to diagnosis and treatment, allowing oncologists to tailor strategies for each patient.

Mark proposes just such a technology. His tiny nano-network, like a spider's web catching flies, attracts remote, metastatic tumor cells to the site of injection and sequesters them, relaying a signal to the clinician when tumor cells are present. Additionally, the network includes localized doses of chemotherapeutics to kill invading metastatic cells and limit additional metastases elsewhere. This approach shifts the cancer diagnosis and treatment paradigm, from seeking out rare populations of cells throughout the body to concentrating metastatic cells within a specific location in the body for early detection and therapy.

A graduate of Northwestern University, and of the University of Colorado at Boulder's doctoral program in chemical engineering, Mark is also a co-founder of Nanoly Bioscience, Inc. Nanoly is developing a nano-shield that eliminates the need for vaccine refrigeration, for which it received a Best of Category in Social Innovation Award in 2012.

Like the previous Misrock Fellows, this newest cohort of young talent is thinking big about tackling cancer, and using nanoscale, 'tiny technologies' to realize their visions. The Foundation's support has enabled Fellows at MIT's Koch Institute to complete essential foundational research on innovative and diverse approaches to fighting cancer. I am sure that we will see similarly promising work from this group, and I look forward to keeping you up to date in the months ahead.

Sincerely,

Tyler Jacks

Enclosures (4)

CC: Kathy Misrock