Eric Holland, Franziska Michor, and Desert Horse-Grant

Summary

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People don't usually think of math when considering weapons in the anticancer arsenal. But a new grant from the National Cancer Institute (NCI) allows Memorial Sloan Kettering Cancer Center scientists to use mathematical modeling to clarify how cells accumulate mutations, give rise to tumors, and respond to therapies.

In October 2009, a team of eight researchers, six of whom are at Memorial Sloan Kettering, received an $11 million, five-year grant from the NCI to form one of 12 Physical Sciences-Oncology Centers (PS-OCs) in the United States. The PS-OCs bring together experts from physics, mathematics, chemistry, engineering, and oncology to better understand the physical and biological principles of the emergence and behavior of cancer.

The PS-OC at Memorial Sloan Kettering, focused on mathematics and computational biology, is led by evolutionary biologist Franziska Michor in the Computational Biology Program. Dr. Michor, who arrived at the Sloan Kettering Institute in 2007, uses the tools of applied mathematics and evolutionary biology to study cancer initiation, progression, and resistance to treatment.

“Cancer develops as the result of an evolutionary process in tissues, and the laws of evolution can best be formulated as mathematical equations,” she explained. “The PS-OC initiative is a great platform for combining math with clinically important questions to test models for cancer and explore new theories.”

In addition to Dr. Michor, other physical science investigators in the PS-OC are Computational Biology Program Chair Chris Sander, computational biologist Grégoire Altan-Bonnet, and biomedical engineer Maribel Vazquez at the City College of New York. The cancer biology, oncology, and surgery investigators on the team are Eric C. Holland, Director of the Brain Tumor Center and senior co-investigator of the PS-OC; Ross L. Levine, a medical oncologist on the Leukemia Service and a member of the Human Oncology and Pathogenesis Program (HOPP); medical oncologist Ingo K. Mellinghoff, a member of HOPP and the Department of Neurology; and medical oncologist William Pao, who recently moved from Memorial Sloan Kettering to Vanderbilt University. The team is supported by Memorial Sloan Kettering biostatistician Mithat Gonen and PS-OC administrator Desert Horse-Grant.

“The PS-OC, superbly led by Franziska and Eric, will strengthen the interdisciplinary orientation and reach of Memorial Sloan Kettering’s Computational Biology Program,” Dr. Sander enthused. “We will build on the institution’s existing expertise in mathematics, theoretical and experimental physics, computer science, software engineering, medicine, and chemical engineering, as applied to problems of cancer biology in this creative collaborative effort.”

The new center is organized around three projects at the interface of physical sciences and cancer biology. One project seeks to predict the order in which cells accumulate genetic mutations during the development of blood cancers and brain malignancies. Another attempts to identify the most likely cell of origin for such cancers — stem cells or progenitor cells, which are cells that have differentiated from stem cells but can still produce multiple cell types. The third project investigates how and why lung and brain tumors become resistant to therapy, with the goal of crafting optimal dosing strategies.

For each project, Dr. Michor, in collaboration with Drs. Sander and Altan-Bonnet, uses what is known about the diseases — for example the types of mutations driving tumors — and constructs mathematical models describing the steps leading to an observed biological outcome. This could include the initiation of a tumor, recurrence of disease after remission, or resistance to therapy. Then the researchers attempt to validate the model in cell lines or mice. The mouse-modeling experiments might involve introducing mutations at specific times and locations in the animal, or following a new dosing schedule for a treatment.

“You hope the animal test fits the prediction of the model,” Dr. Michor said. “If not, you use any new information from the animal experiment to refine the model so it conforms to what is happening in biology. It’s an ongoing process of testing and reformulating.”

Pinning Down the Cell of Origin

The potential of mathematical modeling is demonstrated by Dr. Michor’s collaboration with Dr. Levine, who focuses on blood cancers known as myeloproliferative neoplasms (MPNs). Dr. Levine and colleagues had already discovered that most MPN patients have a mutation in a gene called *JAK2*. They also knew that the cancer cells in MPN patients with this mutation must at some point have acquired the ability to repeatedly self-renew — the hallmark of all malignancies.

Ross Levine

What remained unclear was the order in which this occurred, and in which of the two undifferentiated cell types that give rise to blood cells — stem cells or progenitor cells. Working together, Drs. Levine and Michor produced a mathematical model based on rate of turnover, differentiation, and apoptosis (programmed cell death) in these different cell types. They reported their finding in the September 29, 2009, issue of the *Proceedings of the National Academy of Sciences*. [PubMed Abstract]

“The conventional wisdom in these diseases has been that they originate in a blood stem cell, but Franziska’s model — which is a bit heretical — suggests it’s more likely that these diseases arise in a progenitor cell,” Dr. Levine said. “A mutation confers the ability to self-renew, the ’stemness,’ onto the progenitor cell, which later acquires the *JAK2* mutation that initiates the cancer.”

The researchers will try to determine whether the model can be validated in mice. Although occurrence of disease would not conclusively establish the

cell of origin, it would prove that MPNs could plausibly develop in this way. “The models offer probability rather than certainty,” Dr. Michor explained. “They are not meant to replace animal or human cell experiments, but they are an important tool in guiding the research.”

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The Path to Brain Cancer

Dr. Michor is collaborating with Drs. Holland and Mellinghoff to shed light on gliomas, cancers that arise in the brain, by identifying the probable cell of origin for these tumors and the most likely order in which mutations arise to make the cell cancerous. Dr. Holland’s laboratory is able to test Dr. Michor’s models with great precision, turning genes on and off at precise times.

“The system we designed lets us target a particular cell type and region of the brain at a specific stage of development of the mouse,” Dr. Holland said. “It allows us to ask, ’Do cells of this type in this location form tumors at this particular age?’ The mouse modeling tells you whether a given cell is capable of forming a tumor; the math tells you what is probable. You marry those two things and end up with a good idea of what is likely happening.”

Drs. Levine and Holland both emphasized that the importance of their collaborations with Dr. Michor has more to do with improving an understanding of the origin and progression of the disease rather than producing short-term clinical benefits. “Anytime you understand the biology better, you gain an advantage in how to approach the specific cancer,” Dr. Holland said.

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Preventing Resistance to Therapy

Dr. Michor also is working with Dr. Holland as well as Dr. Pao at Vanderbilt University on the third PS-OC project — investigating how cancer cells develop resistance to therapy. “When a drug targets specific pathways, evolutionary pressure will select for cells that become resistant,” she said. “If the drug binds to a specific receptor in the target cells, some cells will change in ways that alter the receptor, and the drug won’t bind anymore.”

Other cells may have a mechanism to evade the drug from the start. Shortly before coming to SKI, Dr. Michor had used mathematical modeling in a collaboration with HOPP Chair Charles L. Sawyers (then at the University of California, Los Angeles) to understand why the drug imatinib (Gleevec ®) was only temporarily effective against a blood cancer known as chronic myeloid leukemia, or CML. The model suggested that imatinib did not deplete the population of leukemic stem cells that drive the disease and therefore could not cure this type of leukemia.

Mathematical models can help predict which treatment schedule should work best to address the tendency of cells with stem-cell-like characteristics to repopulate a tumor shrunk by drugs or radiation. “A lot of the treatment schedules used in the clinic are based on limited information,” Dr. Holland explained. “A mathematician can calculate what would work best, which you can test in mice to see whether it’s better than the standard of care.”

Dr. Michor is also investigating the development of resistance in lung cancer in a collaboration begun with Dr. Pao before he left Memorial Sloan Kettering. “In parallel with designing new drugs that address resistance arising due to mutations, we can look for better ways to use existing drugs so resistance doesn’t emerge so quickly,” Dr. Michor said. “Instead of low doses of chemotherapy over long periods, it might be better to try high doses at specific intervals with breaks in between.”

Dr. Michor said Memorial Sloan Kettering provides an ideal environment for making the best use of the opportunities provided by the PS-OC grant. “Combining math with clinical research is definitely a new way of thinking about oncology,” she said. “Ultimately, I hope that this type of research will have an impact on patients. Who knows whether it will work or not, but it certainly deserves a shot. And researchers I’m working with here are incredibly interested in listening to unconventional ideas and providing input. I’ve never seen that in any other institution.”

Dr. Michor has been named a 2009-2010 Leon Levy Foundation Young Investigator at Memorial Sloan Kettering. The award recognizes highly innovative work in the area of neuroscience research and was established by a grant of $1 million to MSK from the Leon Levy Foundation.

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