ARTICLE
RESEARCH & DEVELOPMENT

How Mount Sinai Health System Fosters Collaboration to Fight Cancer

by Joel Dudley, PhD and Samir Parekh, MD
Precision cancer medicine — sequencing a patient’s DNA in order to customize cancer treatments — shows promise, but is very much in its infancy. It’s still not nearly precise enough to launch a winning battle against many forms of cancer. To dramatically advance in this field, clinicians, medical researchers, and computer scientists must substantially deepen their collaboration.
This is a challenge for most academic medical centers, which are typically hierarchical, segmented organizations. The hospital stands apart from the medical school, and for employees of each to join forces, the chains of command must approve. Granting researchers access to extraordinary computational brainpower, essential for some of today’s medical research, often requires even more authorization.

The Mount Sinai Health System is organized differently from most, as one integrated institution. Doctors from the seven Mount Sinai hospitals work side by side with researchers from the Icahn School of Medicine at Mount Sinai. Indeed, many clinicians also have Sinai research labs. If a clinician and a researcher devise a viable idea to solve a medical problem, they are free to join forces and pursue the project. This makes it possible to rapidly bring a finding from the lab bench to the patient bedside.

By taking advantage of Mount Sinai’s collaborative freedom, we are using advanced computer analytics to effectively treat some of the most challenging cancers, those that affect the blood and bone marrow. Cells from these cancers are highly heterogeneous, arising from different genetic drivers, each of which may or may not respond to a particular medicine. While solid tumors, like lung cancers, often respond well to treatments selected based on an analysis of the tumor’s DNA, such analysis cannot provide the information needed to effectively target blood cancers such as multiple myeloma. These kinds of liquid cancers are so complex and difficult to treat — virtually all patients relapse — that DNA analysis has yet to make a dent in treatment.

To unmask the genetic anomalies that are specific to multiple myeloma and that could guide treatment, our teams at the Icahn School of Medicine at Mount Sinai collaborated to map both DNA and RNA signatures of multiple myeloma tumors. RNA is the ultimate messenger of the genetic instructions a cell needs to manufacture proteins. Only information transcribed from DNA into RNA will ultimately impact the structure of proteins, including the mutations that lie behind cancers. So it is critical to understand the RNA of a complex cancer.

As we planned to crack and classify the RNA profile of multiple myeloma, it quickly became clear that the task would require a large amount of dedicated computing power. Our Institute for Next Generation Healthcare created a dedicated server for the multiple myeloma research, named CRUSHER, at an off-campus Mount Sinai computer lab, and a customized software program, named DAPHNE, to get the job done. With this high-power computing capability we were able not only to decipher the RNA of multiple myeloma cancer cells but also to link mutations affecting protein structure to disease patterns, and identify novel associations between clinical traits and genomic markers. Together, our myeloma specialists, genomics scientists, and drug repurposing experts used the DAPHNE software to integrate DNA and RNA sequencing, as well as clinical data, to identify non-myeloma drugs that might be repurposed to help patients whose disease had relapsed after receiving standard therapy approved for multiple myeloma.
Preliminary trials are highly encouraging. In one patient, the RNA analysis revealed abnormal activation of a molecular pathway that enables the transmission of a signal from a receptor on the surface of a cell to the DNA in the cell’s nucleus. After he was treated with a drug approved for other cancers that inhibits this pathway, his myeloma went into remission. In another case, RNA and DNA analysis identified oral drugs approved for breast cancer and chronic leukemia that should be effective against myeloma. A 70-year-old painter whose myeloma had relapsed after standard therapy went into remission following treatment with the new combination and has returned to painting.

RNA analysis turned out to be far more helpful than DNA sequencing in determining the most effective drugs for each patient. Of the 21 evaluable patients in our study, 11 received a personalized drug based upon RNA profiling, two received a drug based on both RNA and DNA, and eight received a drug based on DNA. This is remarkable because the vast majority of diagnostic companies and oncologists using genetic analysis are studying only patient DNA, not RNA.

The merging of high technology with medical research is still in its early stages while we strive to build our understanding of disease. As we embrace a new paradigm — treating cancers based on multiple genetic drivers rather than histology (cell structure) — academic medical centers should loosen their hierarchies and clear the way for computer scientists to deepen their collaborative efforts with oncologists, pathologists, and geneticists to look beyond DNA sequencing. This is how we will generate the knowledge that will achieve major progress in the war against the most difficult cancers.

Joel Dudley, PhD, is Associate Professor of Genetics and Genomic Sciences and Director of the Institute for Next Generation Healthcare at the Icahn School of Medicine at Mount Sinai.

Samir Parekh, MD, is Associate Professor of Hematology and Medical Oncology at The Tisch Cancer Institute of the Icahn School of Medicine at Mount Sinai.