THE NEW FRONTIER

NewYork-Presbyterian Pursues Innovative Research and Precision Therapeutics to Redefine Cancer Care

— PART 1 —

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At NewYork-Presbyterian Hospital and its affiliated medical schools, Columbia University College of Physicians and Surgeons and Weill Cornell Medical College, innovators in science and medicine are pursuing cancer research with the potential to redefine the field. There is an urgency in their work that is palpable as each day spent in research or with patients brings them closer to treatments for malignancies once considered insurmountable. As you will read in the Winter and Spring 2016 special editions of *Forum*, novel approaches to better understanding and ultimately treating the complexities of cancer are underway, moving at an accelerated pace spurred on by enlightened programs in precision medicine and collaborations that cross over into computational and systems biology.

Looking for the Personal Best in Cancer

The Caryl and Israel Englander Institute for Precision Medicine at Weill Cornell Medicine and NewYork-Presbyterian directed by **Mark A. Rubin, MD**, and the Precision Medicine Initiative at Columbia University College of Physicians and Surgeons and NewYork-Presbyterian directed by **Thomas P. Maniatis, PhD**, are at the center of a new frontier in cancer care, moving from a one-size-fits-all approach to therapies derived from the genetic makeup of an individual's tumor. The approach

Dr. Mark A. Rubin

> Dr. Mark A. Rubin and Dr. Thomas P. Maniatis were among a select group of scientists and physicians to be invited to the White House to participate in last year's announcement by President Barack Obama of a $215 million precision medicine initiative.

originated from medical necessity – no two cancers are exactly alike, and each individual's cancer has its own genetic characteristics – and took hold with the advent of genomic sequencing. Within these programs, physician-scientists are using advanced gene-sequencing technologies to identify the genetic alterations that give rise to and drive these very

personal tumors and that may be targetable with drugs already on the shelf or those entering the market.

"Advances in sequencing have dramatically increased the likelihood of discovering mutations that drive tumor growth in certain people and in certain tumors – even in specific cells within tumors," writes Dr. Rubin in his commentary highlighting the need to connect genomic and clinical data published in the April 15, 2015 issue of *Nature*. Dr. Rubin detailed the need for searchable databases that compile information from a wide range of medical centers to allow researchers and clinicians to look for patterns and trends in cancer across a large patient population. "With this vast clinical data, if we have a patient sitting in front

On the Cover: Systems biology has made it possible to investigate the multitude of mutations found in the cells of malignant tumors. Courtesy of the Elemento Lab.

Dr. Thomas P. Maniatis

of us who has a mutation that we've never seen before, we can ask the question – has anyone ever seen it before? With the development of big databases of clinical information, researchers will be able to say with certainty that there are, for instance, 12 people in the country who have this mutation and we think that they would benefit from a certain treatment."

"With all the pieces in place, we can explore the universe of gene functions and this will, in turn, lead to an understanding of how genetic mutations cause cancer and other diseases," says Dr. Maniatis, one of the pioneers of modern molecular biology and a cofounder of the New York Genome Center. "We have developed the computer hardware and algorithms necessary to interrogate genetic information extremely rapidly, and there are increasing examples in which the relationship between specific genetic mutations and the cause of disease is understood. This information allows the identification of new drug targets, which are required for rational drug design, and it identifies the patients who would be likely to respond to the new drug. Thus, both the cost of clinical trials, and ultimately, treatment of diseases will dramatically decrease by treating only those patients likely to respond."

"Having the advantage of all this detailed data that science and computer analysis gives us about each disease – that's the precision side," says **Stephen G. Emerson, MD, PhD**, Director, Herbert Irving Comprehensive Cancer Center, NewYork-Presbyterian and Columbia University College of Physicians and Surgeons. "The personalized side is taking that information and putting it in the context of each individual and their family, their life. The advent of this analytic power is going to flow over not just into treatment, but also into screening and prevention. If we do our job right, a generation from now you won't need a cancer center because we will have fixed it. That's our goal."

"Even if you define the cancer very narrowly, it's still not a single disease," says **Lewis C. Cantley, PhD**, Meyer Director, Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine/Ronald P. Stanton Clinical Cancer Program at NewYork-Presbyterian. "So we are learning to divide and conquer. There has already been a lot of progress in breast cancer by dividing it into subgroups and treating each subgroup differently. In today's world of cancer research we need clinicians, basic scientists, bioinformaticists, sequencers, and frontline translational experts who work together in a seamless manner. That's the basis of our cancer centers – to facilitate collaborations among experts in systems biology and computational analysis with clinicians and basic scientists in light of what we now know and need to know about cancer."

Finding the Logic in Cancer Cells

Andrea Califano, PhD, is the Founding Chair of Systems Biology and serves as Director of the JP Sulzberger Columbia Genome Center and Associate Director for Bioinformatics in the Herbert Irving Comprehensive Cancer Center. He also serves on the Board of Scientific Advisors of the National Cancer Institute.

"Systems biology is paving the way toward new, more rational approaches in basic and translational research," says Dr. Califano, whose lab published the first genome-wide regulatory networks for normal and tumor-related human cells, including neoplastic malignancies such as lymphoma, glioma, and breast and prostate cancer. "Everyone is enthralled by the idea that you can study the genome of an individual, in cancer for instance, and from that identify actionable mutations that can then be targeted for pharmacological attack."
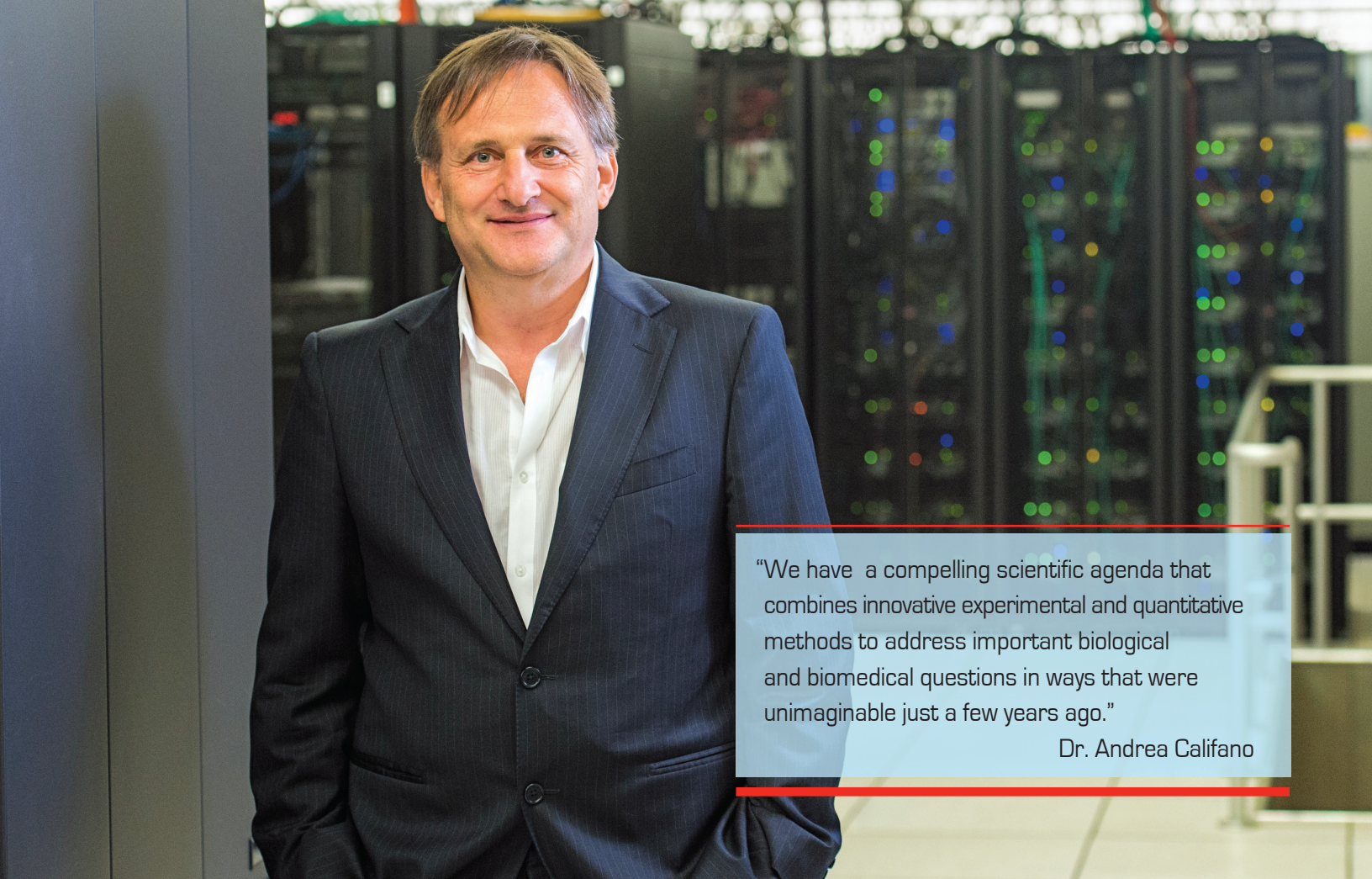

Dr. Stephen G. Emerson

Dr. Lewis C. Cantley

According to Dr. Califano, in order to make a suitable link between a gene mutation and a potential therapy, you have to build a genome-wide model of how the cell works, understand how certain mutations change how the cell works and then, based on that changed model, consider what drug will work. "We can now take a single patient's tumor and map it to a set of vulnerabilities – proteins that will kill the tumor when targeted pharmacologically," says Dr. Califano. "Then we can prioritize the drugs and drug combinations – either already FDA approved or experimental compounds in clinical trials – that are most likely to target these vulnerabilities and kill the tumor – all in a space of two weeks for cancers where the required drug database has already been assembled. Databases are currently available for triple negative breast cancer, neuroendocrine tumors, GIST sarcoma, meningioma, and soon glioblastoma and neuroblastoma. If the database needs to be generated, turnaround for analysis can take two to four months. But it only has to be done once for a specific cancer type. We are not doing novel drug discovery. We're basically asking the question: Which one of the very large repertoire of existing drugs – either in isolation or in combination – is most likely to destroy this particular tumor?"

More than a decade ago, Dr. Califano began developing an algorithm that could be used to reconstruct the logic of the cells using a combination of computational and experimental methodologies. "It's reverse engineering, if you will – like taking apart a watch to figure out its mechanism," he says. The Califano Lab has shown that analysis of this logic can identify master regulator proteins responsible for human disease, including cancer and neurodegenerative syndromes. By developing methods to model cancer cell regulatory networks, he and his team have been able to systematically and efficiently identify the regulatory modules – or tumor checkpoints – that are responsible for maintaining cells in a cancerous state, as well as the individual proteins – the master regulators – that comprise these modules. Surprisingly, these are almost never mutated and cannot thus be identified by cancer genome sequence analysis. Because the activity of these modules is essential for the survival of tumor cells, they constitute a distinct type of Achilles' heel of cancer. Dr. Califano has repeatedly shown that the tumor checkpoint hypothesis offers a complementary strategy to genomics-based approaches targeting oncogenes, including for patients with no actionable mutations or following relapse.

In addition, his lab has developed methods for discovering compounds and compound combinations that can inactivate these proteins, thus providing valuable therapeutic strategies. These findings have been translated into several clinical studies, including two combination therapy clinical trials in breast cancer and a very innovative set of N-of-1 studies in which disease master regulators are identified and pharmacologically targeted on an individual patient basis.

This past November, Dr. Califano's collective body of work to date resulted in a National Cancer Institute Outstanding Investigator Award, a grant that provides the stability necessary for scientists to focus on research that has the greatest potential for improving cancer care. Dr. Califano's seven-year grant will support the development of systematic approaches to identify the molecular factors that lead to cancer progression and to the emergence of drug resistance at the single-cell level.

"Our goal is to tackle the challenge that doctors and scientists currently face when trying to predict the potential success of available cancer therapies in specific patients," says Dr. Califano. "Although targeted therapeutics can be highly effective in some patients, others presenting with virtually identical genetic profiles often fail to benefit. Moreover, even in patients who initially respond to targeted agents, the relief can be fleeting as the tumor eventually loses its susceptibility to treatment."

One explanation, he says, is that individual cancer cells are incredibly diverse at the molecular level, both across different patients and within the same tumor. Researchers believe such heterogeneity can lead to drug resistance and cancer relapse either because there will always be a few cancer cells with mutations that enable them to bypass the effects of targeted therapies, or because the nature of cancer as a complex, dynamic system allows them to adapt to treatment, even without genetic alterations.

Dr. Califano will test the hypothesis that dissecting the regulatory mechanisms that lead to the heterogeneity of individual tumors at the single-cell level could reveal more effective ways of preventing, diagnosing, and treating cancer. Rather than attempting to identify the individual genetic events that contribute to tumorigenesis, he will concentrate on the regulatory mechanisms that allow cancer cells to maintain their tumorigenic state, a process called cancer dystasis.

Dr. Califano suggests that this could dramatically simplify the problem of how to cut off the escape routes that allow tumors to become resistant to treatment. "When you think about intra-tumor heterogeneity, studying each individual resistance-inducing mutation would be close to impossible. However, if we can confirm our previous findings that entire mutational repertoires are integrated by the same tumor checkpoint modules, it will collapse an intractable level of tumor genetic heterogeneity into a small set of distinct, targetable functional dependencies that account for the entire tumor cell population."

The Proverbial Needle in a Haystack

Olivier Elemento, PhD, Associate Professor of Computational Genomics in Computational Biomedicine, and co-leader of the Meyer Cancer Center's research program in Cancer Genetics, Epigenetics and Systems Biology, Weill Cornell Medical College, describes cancer as an evolutionary process.

"Cancer is a result of the accumulation of mutations," says Dr. Elemento. "A tumor could have a hundred million cells, and each of these cells has a capacity to acquire additional mutations. If there is one fundamental principle of cancer, it is the Darwinian theory. Cancer keeps changing all the time. It evolves."

And that is the crux of the mission of the Elemento Lab: to understand the complexity of how these tumors are changing in time and how to be predictive in this complexity. "There are potentially hundreds of mutations that can occur in a given tumor cell," says Dr. Elemento. "The impact of these mutations is complicated and we have to call on powerful methods such as systems biology to tackle this complexity. Using high-throughput sequencing, also known as next-generation sequencing, we can sequence the same tumor from the same patient at different time points to determine the trajectory of the cancer. If we can predict how a tumor is going to change then we can direct treatment accordingly."

Applying the systems biology approach to B cell lymphomas, Dr. Elemento and his colleagues found that by profiling a patient's tumor when it is first detected, they could tell by looking at the heterogeneity of the tumor whether the patient was going to relapse. "If we see a lot of diversity in terms of the genome or even the epigenome, meaning that each cell is a little bit different from the other cells, relapse is more likely than if the tumor has more homogeneous cells," explains Dr. Elemento. "With systems biology we can quantify the diversity of the tumor, enabling us to some extent to predict which patients are more likely to relapse compared to patients who are going to be cured of the disease."

Dr. Elemento notes that genomic and epigenomic profiling is critical to being able to make a prognosis. "It is only by looking at all of those locations at the same time and integrating this information that you can make reliable predictions about tumor behavior."

Add to this the numerous drugs and different combination of drugs that are now available to use on most cancer cells. How do you choose the drug or combination therapy that is best for the patient given the genetic makeup of the tumor? Dr. Elemento is tackling this challenge as well. He and his team essentially build *in silico* computational models of signaling pathways to predict whether combinations of drugs can target the pathway better than single drugs. Using these computational models, they can screen hundreds of thousands of combinations in search for the best ones.

"What happens in many cancers is that a signaling pathway, which is fundamental to normal cells, is corrupted by cancer cells and their mutations," says Dr. Elemento. "The corruption of this pathway by these mutations is making this pathway active all the time. One way to destroy the cancer is to shut down this pathway. You need models that simulate the behavior of these
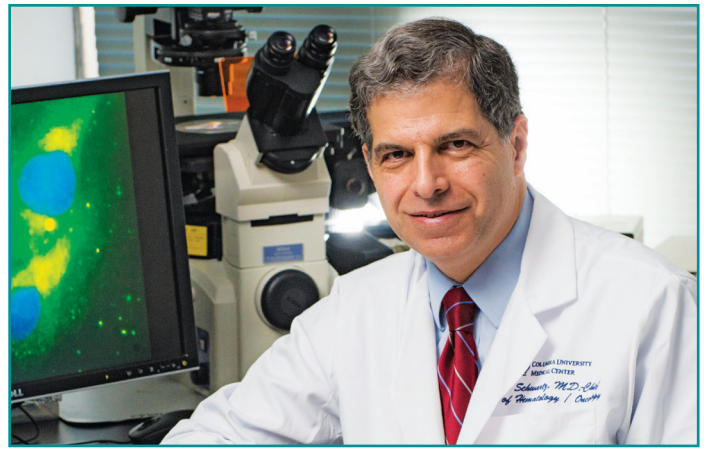
Dr. Gary K. Schwartz

networks so that you can narrow down the choices to a small subset of combinations that will be effective. Only then will we be able to achieve a predictive understanding of what happens when, for example, you inhibit a pathway. Does it lead to cells being killed? Or does it lead to cells growing faster? We need to understand that. This is really fundamental."

Finding the Perfect Match

The cancer centers of NewYork-Presbyterian have in their sights the sequencing of every patient's tumor, adding that information to the patient's medical record, and incorporating it into a searchable database where each individual's disease progress can be monitored based on what is occurring at the molecular level. This can then be used to direct patients to the right clinical trial or the correct therapy early on in their disease.

"Personalized medicine has become part of what we do every day in oncology therapy," says **Gary K. Schwartz, MD**, Chief of Hematology/Oncology and Associate Director of the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia University Medical Center. "With our ability to sequence DNA – especially tumor DNA – we're on the forefront of being able to personalize medicines specifically to a patient's tumor. That is the future of oncology."

The goal of having every cancer patient profiled has been aided by the decrease in cost and increase in speed at which sequencing can occur. "The sequencing takes about 14 days now, where it used to take several months, and the timeline continues to shrink," says Dr. Schwartz. "We are building infrastructures to store and have easy access to the data. In this way, when we have a trial for a drug targeted to a particular gene mutation, we can search all of the databases to identify patients with that mutation and advise them of the trial."

Dr. Schwartz and his team are participating in a number of ongoing clinical trials studying targeted drugs based on genomic signatures and oncogenic drivers in patients' tumors. This includes the recently launched Molecular Analysis for Therapy Choice (MATCH) trial, sponsored by

Dr. Himisha Beltran

Dr. David M. Nanus

the National Cancer Institute. Investigators plan to obtain tumor biopsy specimens from as many as 3,000 patients nationwide. Each specimen will undergo DNA sequencing to determine whether they contain genetic abnormalities for which a targeted drug exists. Patients will then be assigned to one of more than 20 treatment substudies based on the abnormality.

"This study will break down the barriers of tumor-specific diseases," says Dr. Schwartz. "Currently, patients are enrolled in clinical trials based on their type of cancer – patients with breast cancer in one clinical trial, patients with colon cancer in another, and so on. With the knowledge that there are genomic mutations shared by all cancers, the MATCH trial will be genomically driven rather than dictated by disease type." It is the largest trial of its kind to test the hypothesis of matching genomics to cancer therapeutics. It is hoped that MATCH will also address an obstacle faced by Dr. Schwartz and other clinicians in the field, i.e., making a drug available to a patient to target a mutation when that drug is only approved for a specific disease type.

Dr. Schwartz is also the key clinical investigator on the N-of-1 studies in collaboration with Dr. Califano and **Andrew L. Kung, MD, PhD**, Chief of Pediatric Hematology, Oncology, and Stem Cell Transplantation at NewYork-Presbyterian/Morgan Stanley Children's Hospital.

At Weill Cornell Medicine, a research team recently demonstrated that a more global look at the body using next-generation sequencing offers new insights and targets in patients with advanced, treatment-resistant disease. "Most institutions are using focused or panel sequencing to look at a few hot spot mutation areas in cancer," says Dr. Mark Rubin, the study's senior author. "But we believe that whole exome sequencing, which tests more than 21,000 genes in the cancer's exome, is ideal for patients with advanced cancer where we don't know where the mutations of resistance are."

Dr. Rubin, **Himisha Beltran, MD**, a medical oncologist who is lead author on the study, and their team of investigators developed a clinical trial to examine this theory. They enrolled 97 cancer patients with advanced, treatment-resistant

disease. All participants had their metastatic disease genome, as well as their normal tissue, tested with a whole exome sequencing clinical test called EXaCT-1, which was developed at Weill Cornell.

"These are patients who had exhausted every treatment option available to them," says Dr. Beltran. "But with whole exome sequencing and reviewing the cancer's exome, which is believed to harbor the vast majority of mutations that drive disease, we were able to identify new therapeutic possibilities."

The team examined 154 tumors from the 97 patients and found an average of 16 mutations per patient. Of the mutations, 16 could be immediately targeted by available drugs, 98 had targeted therapies in clinical or preclinical development, and 1,474 will require additional research to understand their clinical or biological significance. A multidisciplinary precision medicine tumor board reviewed the patients' genomic sequencing results, medical histories, and radiology reports and developed treatment recommendations for 92 percent of cases. The board's recommendations led to a positive outcome for one patient with advanced bladder cancer after a combination therapy successfully reversed the disease's spread to the lungs and liver. Another patient with an aggressive form of prostate cancer went into complete remission.

"The EXaCT-1 assay takes an unbiased, exploratory look at the genes in both healthy and malignant cells, allowing researchers to find alterations in the cancer development process in unexpected regions of the exome, where DNA is transcribed into RNA," explains **David M. Nanus, MD**, Chief, Hematology and Medical Oncology, NewYork-Presbyterian/Weill Cornell Medical Center, and Associate Director for Clinical Services, Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine/Ronald P. Stanton Clinical Cancer Program at NewYork-Presbyterian. "Whole exome sequencing can be effective in advanced-stage patients for whom other treatments have failed because it uncovers mutations that the less comprehensive tests miss."

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NewYork-Presbyterian Pursues Innovative Research and Precision Therapeutics to Redefine Cancer Care
— Part 2 —

Precision and personalized medicine approaches are already making their mark in clinical care. Several cancers that were once lethal are now treatable. Targeted therapies are enabling patients to live longer with cancer. To turn a fatal disease into a chronic disease requires a multifaceted perspective, including a broad-based genomics approach as discussed in this issue of *Forum*. In the Spring 2016 issue of *Forum,* we will explore the role of experimental therapeutics, immunotherapies, and other innovative tactics in cancer care taking place at NewYork-Presbyterian that are making a difference for patients with some of the more difficult-to-treat diagnoses, including hematological malignancies, melanoma, and lung cancer.

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