Noted Breast Surgeon Appointed Chief of Breast Surgery at Weill Cornell

On August 20, 2018, Lisa A. Newman, MD, MPH, an internationally renowned breast surgeon and researcher, joined NewYork-Presbyterian/Weill Cornell Medical Center as Chief of Breast Surgery and Chief of the Interdisciplinary Breast Program. Dr. Newman leads a multispecialty team that offers advanced screening and imaging technologies; innovative surgical and reconstruction techniques, including nipple- and skin-sparing mastectomies; and novel radiation approaches, including intraoperative radiation therapy. Much of this clinical and surgical care will be based at the new state-of-the-art NewYork-Presbyterian David H. Koch Center. The expanded multidisciplinary breast program led by Dr. Newman will also involve services at NewYork-Presbyterian Lower Manhattan Hospital, NewYork-Presbyterian Brooklyn Methodist Hospital, and NewYork-Presbyterian Queens.

“Our goal is to provide a multidisciplinary approach to breast cancer treatment through a standardized clinic and tumor board system implemented in each hospital so that patients receive the same high quality care with optimized experiences and outcomes,” says Dr. Newman, who joined NewYork-Presbyterian from the multi-hospital Henry Ford Health System in Michigan, where she was Director of its Breast Oncology Program. “In a country renowned for the strength of its multicultural and multiracial population, metropolitan New York is truly the

A New Take on BMT and Cellular Therapies

Just six years ago, Markus Y. Mapara, MD, PhD, joined NewYork-Presbyterian/Columbia University Irving Medical Center to build a clinical and translational oriented blood and marrow transplant (BMT) and cell therapy program from the ground up. This has included the recruitment of several new faculty including, in 2015, Ran Reshef, MD, to lead the clinical research efforts as Director of Translational Research for the BMT program, and, in 2017, Pawel Muranski, MD, to focus on the in-house development of cellular therapies as Director of Cellular Immunotherapy.

“We now have four transplant faculty members – three of whom have their own laboratories in the Columbia Center for Translational Immunology (CCTI) directed by Dr. Megan Sykes. Dr. Sykes founded the CCTI in 2010 and is a pioneering researcher in hematopoietic cell transplantation and organ allograft tolerance induction,” says Dr. Mapara. “Our program is well integrated with the CCTI and we closely collaborate with each other and with Dr. Sykes.”

Today, the Adult Blood and Marrow Transplant Program has undergone a rapid expansion and offers the full array of treatment options. These range from autologous to allogeneic and haploidentical transplantation for patients with benign conditions, such as sickle cell disease, and malignant hematopoietic disorders, including multiple myeloma, leukemia, and lymphoma.

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epicenter of this beautiful diversity. Our NewYork-Presbyterian and Weill Cornell Medicine clinical and research teams are therefore uniquely poised to characterize biologic, genetic, environmental, and cultural influences on health — information that enhances our efforts to provide personalized care to our patients.”

A Researcher Focused on Scientific Disparities

Dr. Newman has long investigated how and why breast cancer risk and disease outcomes vary by race and ethnicity. She is particularly focused on the genetics of aggressive breast tumors, including triple-negative breast cancer. It is also one of the reasons she chose to specialize in breast cancer.

“I became interested in disparities in breast cancer dating back to the first phase of my professional career as a general surgeon in the SUNY Downstate system,” says Dr. Newman. “My practice was based in Brooklyn Heights, and in caring for the extremely diverse communities of Brooklyn, it was quite concerning to see stark differences in breast cancer presentation and outcome between our African American and white American patients.”

As Dr. Newman explains, her black patients with breast cancer tended to be younger at diagnosis and have a worse outcome. “Back in the early 1990s, we didn't have as many insights regarding the heterogeneity of breast cancer as a disease compared to where we are today in an era of precision medicine and understanding variations in breast tumor biology,” she says. “It was commonly assumed that outcome disparities were completely explained by socioeconomic disadvantages that are more prevalent in the African American community. Socioeconomics and healthcare access are clearly important in health outcomes, but characteristics such as the younger age distribution suggested that additional factors were also contributing to breast cancer disparities.”

Observing these differences prompted Dr. Newman to refocus her career so that she could address disparities “in a more scientific fashion,” and she went on to pursue a surgical oncology fellowship at the MD Anderson Cancer Center in Houston, followed by joining their faculty with a practice dedicated to managing breast cancer. “As the years progressed, we developed a greater understanding of the biology of breast cancer,” she says. “We have learned to identify particular patterns of tumors that tend to be more aggressive than others, including a subset known as triple-negative breast cancer.”

“Triple-negative breast cancers are inherently more challenging because they possess greater metastatic potential and because we don’t have targeted therapies for these tumors,” continues Dr. Newman. “Tumors that are positive for hormone receptors – the estrogen receptor and/or the progesterone receptor – are cases where we can rely upon a variety of hormonally active cancer-fighting treatments that are very effective in eliminating the threat of metastasis and cancer progression. For cancers that overexpress a different marker called HER2/neu, we have other special medical therapies designed to target the HER2/neu protein. But we can’t use any of those targeted therapies for the triple-negative breast cancers.”

According to Dr. Newman, in the United States and in most parts of Europe, while triple-negative breast cancers account for only about 15 percent of breast cancers overall, they account disproportionately for more deaths from breast cancer, “due to the inherent biologic aggressiveness of this subtype and our lack of targeted therapeutic approaches,” she says. “We can use chemotherapy for triple-negative breast cancers but would prefer to use targeted therapies, which tend to be more effective and less toxic.”

Young breast cancer patients are more likely to have triple-negative disease, notes Dr. Newman, as well as women that have inherited susceptibility for breast cancer because they carry a BRCA-1 mutation, and African American women. “African American women are twice as likely to have triple-negative breast cancer compared to white American women; this predisposition is seen regardless of age and stage at diagnosis,” she says.

Global Efforts to Combat Breast Cancer

A champion of global health, Dr. Newman has spent the last 15 years training physicians and working with patients in developing countries. She is the founding Medical Director for the International Center for the Study of Breast Cancer Subtypes, a collaboration among multiple hospitals in the United States, Africa, and the Caribbean. In addition to studying breast cancer incidence across the world and conducting research to identify the genetic origins of triple-negative breast cancer and determine why it disproportionately affects young women as well as women of African descent, the Center provides medical supplies and training opportunities to its partners.

“In studying the breast cancer burden of women from Africa,” says Dr. Newman, “the data support the likely role that genetics plays because we are seeing higher rates of triple-negative breast cancer in women from western Sub-Saharan Africa. Interestingly, our work in east Africa has shown low rates of triple-negative breast cancer.”

Dr. Newman refers to the colonial-era slave trade as further hypothesis-generating evidence regarding the presence of an association between African ancestry and triple-negative breast cancer risk. “We see very high frequencies of triple-negative breast cancer in countries such as Ghana, located in western sub-Saharan Africa. In contrast, we have seen low rates of triple-negative disease in the east African country of Ethiopia. African Americans tend to have more shared ancestry with Ghanaians compared to Ethiopians because the trans-Atlantic slave trade brought western sub-Saharan Africans over to the colonies. Our research suggests that this shared ancestry may also be linked to particular inflammatory patterns that can influence breast cancer risk. Characterizing these genetic patterns will be important in understanding breast cancer disparities in the United States, and it can lead to important insights regarding a type of breast cancer that is particularly dangerous to women regardless of where they live in the world.”

Dr. Newman has held leadership positions on several national committees, including the Center for Disease Control’s Advisory Committee on Breast Cancer in Young Women, the National Institutes of Health’s Clinical Trials Advisory Committee, and the National Institute on Minority Health and Disparities’ Advisory Council. Dr. Newman holds Adjunct Professorships at the MD Anderson Cancer Center, as well as the University of Michigan, where she previously served as Breast Center Director for 13 years.

“We've made wonderful advances in breast cancer, this disease continues to cause far too much pain and suffering,” adds Dr. Newman. “We are obligated to identify all of the features that account for variation in our ability to detect and control breast cancers.”

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A Steadfast Focus on Graft-versus-Host Disease

Dr. Mapara and his colleagues are also at the forefront of studying new approaches to making transplant safer and more effective and methods to induce immune tolerance.

Graft-versus-host disease (GVHD) is one of the most common and serious side effects of allogeneic bone marrow transplant. “In solid organ transplant, the major risk is that the recipient rejects the graft from the donor. In BMT, the donor cells attack the recipient’s tissue,” says Dr. Mapara. “However, the ability of donor cells to react against the foreign tissue of the recipient can also be harnessed to attack the underlying malignancy of the patient. One area of my active research is to separate GVHD from graft versus leukemia [GVL] effect. The hope is to maintain the anti-tumor response, but also try to mitigate or possibly prevent the response of the donor cells against the normal tissues. One of the fascinating aspects of bone marrow transplantation is that if things go well, true tolerance develops and patients can be taken off immunosuppressants. Eradicating graft-versus-host disease is crucial because it would allow us to also use stem cell transplantation as an adjuvant to solid organ transplant to induce long-lasting and permanent tolerance.”

To accomplish this, Dr. Mapara and his colleagues are moving from using pure mouse models to working with humanized mouse models – the next step closer to clinical studies. “We are taking a certain strain of mice that are highly immunosuppressed, which allows us to establish a human blood system in these mice,” he says. “There is clear evidence that the interferon signaling the JAK/STAT pathway plays a significant role, not only in mice, but also in humans in terms of GVHD.”

The initial mouse studies from the Mapara laboratory have been recently confirmed by early clinical trials, which demonstrated that small molecular drugs inhibiting the JAK1/2 molecule (which is upstream of STAT) are active in patients with GVHD. “Based on our own studies and with the goal of further enhancing outcomes, we are now initiating a clinical trial that will focus on targeting JAK1 together with another key pathway, the IL-6 signaling pathway, in patients with steroid refractory GVHD,” says Dr. Mapara.

“The environment at Columbia is unique as it allows us to conduct bench-to-bedside studies and then take clinical observations back to the bench to perform in-depth mechanistic studies.”

— Dr. Markus Y. Mapara

According to Dr. Mapara, the concept of using bone marrow for the induction of tolerance dates back three to four decades. “Drs. David Sachs and Megan Sykes of the CCTI were pioneers in developing this concept. In close collaboration with Dr. Sykes and Dr. David Cohen, Director of the Kidney Transplant Program at NewYork-Presbyterian/Columbia, we have a clinical protocol in which the patients receive a combined kidney and bone marrow transplant from the same donor. In addition, we are planning to add regulatory T cells – which modulate the immune system – following the combined kidney and bone marrow transplant to enhance the development of donor cell engraftment and tolerance induction,” says Dr. Mapara. “These clinical trials will soon be ready to begin in patients.”

Dr. Mapara seeks to further advance this approach through research he is pursuing in his laboratory to identify molecular switches that could turn off GVHD. “By finding potentially druggable targets, we could use a drug to suppress or prevent GVHD without blunting the anti-malignancy or GVL effect in patients with blood cancers. One signaling pathway we are particularly interested in is interferon/JAK/STAT1,” says Dr. Mapara. “A number of years ago, we found in mouse models that if you block the STAT1 pathway in donor cells, you are able to significantly reduce or even prevent GVHD. This was associated with the expansion of regulatory T cells. We are at the moment trying to understand in more detail in mouse models how to better manipulate that approach and how this will affect the anti-tumor response in the human setting.”

A Comprehensive Program in Cellular Immunotherapies

Scientific innovator and hematologist Pawel Muranski, MD, gained expertise in cell-based immunotherapy of cancer at the Surgery Branch of the National Cancer Institute and the National Institutes of Health, where he performed pioneering studies aimed at understanding the role of CD4+ T cells as mediators of curative anti-tumor immunity. Prior to joining Columbia, Dr. Muranski served in the Hematology Branch of the National Heart, Lung and Blood Institute at the NIH. There his research focused on using T cell-based therapies to prevent viral infections in patients undergoing donor-based stem cell transplantation for blood cancers and to treat other patients who developed life-threatening infections as a side effect of their anti-cancer therapies.
As head of the new Cellular Immunotherapy Laboratory in Columbia’s Good Manufacturing Practices (GMP) cell production lab, Dr. Muranski notes, “Developing a comprehensive program in cellular immunotherapies is a complex endeavor. Despite recent spectacular advances in the field of cancer immunotherapy, relatively few institutions have GMP laboratories with the capacity to grow and manipulate T cells. Our plan is to manufacture clinical grade immune cells based on the research taking place here at Columbia, as well as in the labs of our collaborators.”

“It takes a major organizational effort to manufacture clinical grade cells that the FDA would allow to be given to our patients,” continues Dr. Muranski. “There are many regulations and quality standards that we have to meet to be able to conduct investigator-initiated clinical trials here. Typically, new therapeutic agents are based on the research performed by industry and manufactured by pharmaceutical or biotech companies. In our case, we will be developing our own equivalent of the industrial product, but we’ll be making it here on site.”

The initial goal of Dr. Muranski and his team is to manufacture a relatively simple cell product that will allow them to gain logistical expertise. “Once we have all of the elements in place and are certain that all of those elements function, we’ll move to more complex cell products aimed at more difficult targets and with a higher degree of manipulation,” he says.

The first protocol in development will mirror the work that Dr. Muranski had begun at the NIH. “There is a huge clinical need for developing treatments for refractory viral infections. So, we’re going to manufacture the T cells that recognize the common viruses that affect immunocompromised patients following bone marrow transplant and solid organ transplant,” says Dr. Muranski. “This protocol will aim at rebuilding the patient’s immune system immediately after the bone marrow transplant when the patient is most vulnerable with the type of cells that will prevent the occurrence of infection rather than waiting for the infection to happen.”

The researchers will also develop treatments for common refractory infections that will be applicable for all critically ill immunocompromised patients regardless of the underlying cause. “Next steps will involve the development of more ambitious projects that will target cancer antigens with novel treatments for common cancers using our in-house-developed methodologies,” says Dr. Muranski. “That will include gene engineering and other sophisticated manipulations.”

“Cellular immunotherapy has revolutionized how cancer patients are being treated,” adds Dr. Muranski. “This is a completely different approach to treatments. It can be labor intensive, as every type of personalized medicine is, but it is lifesaving and offers the potential for a cure.”

As Director of Translational Research for the BMT program, Dr. Ran Reshef oversees the clinical research efforts of Columbia’s blood and marrow transplant and cell therapy program. “While the major success stories involving CD19 targeting CAR-T cells in B-cell malignancies, for example, non-Hodgkin lymphoma and acute lymphoblastic leukemia, are turning some incurable diseases into curable ones,” says Dr. Reshef, “this represents only a small proportion of all cancers. We still have a very large field of different types of tumors and targets that are a major focus of clinical research in oncology.”

At Columbia, Dr. Reshef and his colleagues are applying the latest CAR-T cell therapies in patients with aggressive lymphomas. “We are now opening a number of clinical trials looking at these therapies for other types of cancers, including indolent lymphomas and myeloma,” notes Dr. Reshef. “The expectation is that this field, at least on the clinical research side, will expand dramatically over the next decade. At the same time, the number of companies and academic institutions that are developing these cell approaches is also expanding. We are in an era where there are a lot of exciting developments in cancer therapy in general and in bone marrow transplants specifically. Every day we wake up to new publications, new clinical trials, and new medications getting approved for the treatment of cancer. And every day, we can offer better treatments than we could the day before.”

Reference Articles

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Weill Cornell Medicine Faculty Win NCI Outstanding Investigator Awards

Weill Cornell Medicine investigators David C. Lyden, MD, PhD, the Stavros S. Niarchos Professor in Pediatric Cardiology and a Professor of Pediatrics, and Ari M. Melnick, MD, the Gebroe Family Professor of Hematology/Oncology and a Professor of Medicine, have been awarded Outstanding Investigator Awards from the National Cancer Institute.

The NCI’s Outstanding Investigator Awards were created to support leaders in cancer research who are developing applications that may lead to major breakthroughs. Each award recipient is given $600,000 per year for seven years to fund their research. Drs. Lyden and Melnick are two of 20 researchers around the country who received Outstanding Investigator Awards this year.

In his research, Dr. Melnick focuses on deciphering at a basic level how B-cells – which should in theory protect the body from cancer by producing antibodies – can transform into cancer itself. It’s known that with lymphoma, it’s the proteins that interact with the genome that are mutated. These proteins are analogous to the software of the cell because they are responsible for writing instructions on DNA – the hard drive – that control how genes are expressed.

“Our preliminary results suggest a major perturbation in the software that involves changing the instructions that control how B-cells in the immune system can cross-talk with other immune cells,” says Dr. Melnick, who is also a member of the Meyer Cancer Center at Weill Cornell Medicine. “But we don’t know how that leads to cells behaving like cancer cells, and we don’t know the impact on the rest of the immune system. So that’s what we’re interested in studying.”

As a next step, Dr. Melnick and his team plan on using cutting-edge genomic technologies to explore the changes affecting the readout of genetic instructions. He is also interested in developing drugs that can restore the correct instructions in immune cells to regain control and fight against the transformed cancer cells.

“It’s an honor to be considered worthy of getting an award from the National Cancer Institute,” Dr. Melnick says. “It’s very competitive so it is gratifying that they appreciate the kind of work coming out of our group.”

Dr. Lyden’s research is aimed at understanding metastasis. His first major discovery was a microenvironment – pre-metastatic niche, or PMN – that tumors induce in distant organs that is favorable to the survival of tumor cells before their arrival at the site. “This emphasizes that cancer metastasis is not a late event as previously thought,” says Dr. Lyden, who is a member of the Sandra and Edward Meyer Cancer Center and the Gale and Ira Drukier Institute for Children’s Health at Weill Cornell Medicine.

Dr. Lyden and his team have illuminated the role of exosomes, which are comprised of tumor-derived nanoparticles, in metastatic disease progression and their contribution to creating biological conditions that are favorable to metastasis at distant organs. They found exosomes have specific molecules packaged within, including double-stranded DNA that represents the entire genome of the tumor cell of origin. “This is helpful in monitoring response to therapy and predicting the progression of cancer in patients,” says Dr. Lyden, who is also a pediatric oncologist at NewYork-Presbyterian/Weill Cornell Medical Center.

Most recently, Dr. Lyden’s group adapted a new technology, asymmetric-flow field-flow fractionation, to isolate exosome subpopulations and discovered novel, but even more prominent exomeres, which are secreted by tumor cells.

“This award can be a real game-changer. It allows us to explore new directions and further investigate the metastatic evolution of cancer,” says Dr. Lyden. “We also hope to conduct patient-related studies on a larger scale and develop new technologies to help identify molecular changes that occur in the pre-metastatic environment.”

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