Melanoma
Researchers Study Immune Response

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are actively looking for new ways to treat melanoma through the induction of an antitumor immune response and are closely monitoring the development of skin cancer in patients to ensure that they are quickly referred to the appropriate protocols.

“We are interested in developing vaccines because melanoma is very sensitive to [an] attack by the immune system,” said Howard Kaufman, MD. Studies worldwide have demonstrated the ability of immunization to trigger the development of antibodies and T-cell responses to melanoma, he said. However, vaccines are not always an effective treatment for the disease.

Melanoma may be clever at tricking the immune system or may secrete immunosuppressive molecules, said Richard Granstein, MD. Without question, the development of nonmelanoma skin cancer is highly linked to the immune system, he noted. For example, immunosuppressed organ transplant recipients have a 30- to 40-fold higher risk for squamous cell cancer and a 3-fold higher risk for basal cell carcinoma. However, the risk for melanoma in these patients is not increased as much as their risk for nonmelanoma skin cancer, Dr. Granstein said. “This is a little

Lung Cancer: Advances In Detection and Treatment

At NewYork-Presbyterian Hospital, simultaneous initiatives from several directions are poised to extend survival or the quality of survival in patients with lung cancer. These include novel methods to diagnose lung cancer early, new molecular targets to improve therapy, creation of care coordinators to derive the most from various treatment modalities, and development of minimally invasive surgical techniques that reduce trauma and facilitate recovery. Columbia and Weill Cornell investigators and clinicians at NewYork-Presbyterian Hospital are not only pioneering methods to define current standards of care for lung cancer but also setting the pace to change its prognosis.

One exciting initiative is the effort to diagnose lung cancer at its earliest stages. Led by Claudia Henschke, MD, PhD, a team of Weill Cornell investigators at NewYork–Presbyterian Hospital has published several papers demonstrating that the smaller the lung cancer, the more likely there is to be a durable disease-free status after treatment. This has provided a basis for a nationwide initiative to evaluate lung cancer screening strategies.

“We have expanded our original study of CT [computed tomography] screening...
Researchers Study Treatments For Gastric Carcinoid Tumors

Surgery is an effective treatment for type 1 gastric carcinoid tumors, according to new research published in the Journal of Surgical Oncology by Columbia and Weill Cornell investigators at NewYork-Presbyterian Hospital (Dakin GF et al. J Surg Oncol 2006;93:368-372).

“This study indicates that surgery in itself causes regression of disease in patients who fail medical therapy,” said lead study author William Inabnet, MD. “Clearly, if lesions are greater than 1 cm in size, we recommend surgery,” he said.

Type 1 gastric carcinoid tumors are rarely malignant, explained Dr. Inabnet. However, depending on the extent of multifocal disease, patients may experience pain, diarrhea, and other abdominal complaints.

Overall, gastric carcinoid tumors are rare, said study co-author Gregory Dakin, MD. Type 1 tumors account for 8% to 20% of all carcinoid gastrointestinal tumors. The incidence of type 1 tumors may be increasing because endoscopy is becoming more common, said Dr. Dakin.

These tumors arise in the setting of pernicious anemia, which causes high levels of the hormone gastrin in the gastrointestinal tract, explained Dr. Dakin. Type 1 carcinoid tumors are composed of enterochromaffin-like cells that are highly gastrin-responsive. “Researchers don’t really know at what point these cells turn into tumors,” he said.

Patients who have pernicious anemia are monitored for the development of type 1 gastric carcinoid tumors, whose symptoms may mimic those of gastric ulcers, bleeding gastric polyps, or gastric carcinoma. While the most commonly reported presenting symptoms include abdominal pain, vomiting, bleeding, and diarrhea, up to 33% of patients are asymptomatic, and the tumor is discovered as an incidental finding on endoscopy.

Although type 1 gastric carcinoid tumors are rare, an experienced gastroenterologist should be able to recognize their gross appearance, which is characterized by growths carpeting the lining of the stomach, said Dr. Inabnet.

Treatment options vary. Surgery may provide a long-term durable cure, said Dr. Dakin, and a minimally invasive approach with laparoscopic gastric resection is now available. “The patient only spends a day or 2 in the hospital,” he explained. Surgery is efficacious because it removes the cells that produce gastrin, said Dr. Inabnet.

Surveillance is necessary after tumor removal, said Dr. Dakin. Generally, patients should undergo screening endoscopy a year after surgery. If total regression is observed, screening may not need to be done as often.

Medical treatment is also available and can suppress the disease, “but it isn’t curative,” said Dr. Dakin, adding that patients may not easily tolerate this type of therapy.

The most common medical treatments are to acidify the stomach with hydrochloric acid or acidified lemonade or to administer octreotide, which suppresses the disease mechanism at the cellular level, said Dr. Inabnet.

“However, treatment has to be individualized to the patient and depends on whether they have multifocal or relatively limited disease,” said Dr. Dakin. If patients have a solitary tumor, endoscopic polypectomy may be the appropriate option, while patients with multiple or recurrent tumors probably require surgery instead of continued medical therapy.

Because several treatment options are available for type 1 gastric carcinoids, Drs. Inabnet and Dakin, and colleagues, conducted a study to further clarify the presentation, treatment, and outcome of patients at their hospitals. The Columbia and Weill Cornell researchers performed a retrospective review of 1,600 carcinoid patients to identify those who had these growths.

Upper gastrointestinal endoscopy showed 18 patients to have biopsy-confirmed type 1 gastric carcinoid tumors varying in size and number, for an incidence of 1.1%. Reasons for endoscopy included abdominal pain, gastrointestinal bleeding, and surveillance for pernicious anemia.

To help determine how successful surgery and medical treatment would be, researchers measured the mean pre-treatment levels of serum gastrin and
chromogranin A, other indicators of disease. They were 1,436 ng/mL (±771 ng/mL) and 91.6 ng/mL (±68.6 ng/mL), respectively.

Imaging revealed evidence of gastric carcinoid in 4 of 10 patients undergoing computed tomography and in 3 of 10 patients undergoing octreotide scintigraphy. Of the 18 patients, 8 were treated medically with acidification or octreotide, both of which were generally well tolerated. Comorbidities, patient age, and refusal of surgery were factors favoring medical therapy in these individuals. The other 10 were treated with either laparoscopic antrectomy or partial gastrectomy. Reasons why patients opted for surgical therapy included multiple or recurrent carcinoid tumors, failure of medical therapy, the inability to comply with medical treatment, or patient preference.

At a median follow-up of 6 months, mean gastrin levels had decreased by 37.2% in the medically treated group, versus 94.0% in the surgically treated patients at a median follow-up of 5 months. Mean chromogranin A levels had decreased by 56.2% in the patients undergoing surgery.

Based on these findings, the researchers concluded that gastric antrectomy is an efficacious treatment for type 1 gastric carcinoid, leading to a significant reduction in serum gastrin levels and regression of carcinoid tumors. However, the viability of surgery as an option depends on many factors, including the severity of disease, the size and number of carcinoid tumors, the presence of comorbidities, and patient age and preference.

While surgery is an alternative in these patients, “ideally we need to find a noninvasive method to influence the pathway of [enterochromaffin-like] regression on the cellular level,” said Dr. Inabnet. Blocking that pathway completely should allow physicians to treat patients with type 1 gastric carcinoid without surgery, he concluded.

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Researchers Advance Treatment Of Chronic Myeloid Leukemia

At NewYork-Presbyterian Hospital, a team of Weill Cornell researchers from the Division of Hematology and Medical Oncology and Department of Pathology and Laboratory Medicine played a significant role in a 5-year study examining imatinib, a drug that increases the survival rate among patients with chronic phase chronic myeloid leukemia (CML) and, as a result, has changed the way the disease is treated.

NewYork-Presbyterian/Weill Cornell was among the 5 leading contributors of patients to the trial, enrolling more than 300 patients, said Dr. Silver. The trial, which began in 2000, consisted of 1,106 previously untreated patients with chronic phase CML. Patients received a 400-mg daily dose of either imatinib or interferon-alpha/cytosine arabinoside. Of the 553 patients initially treated with imatinib, 382 (69%) continued taking the drug at an average daily dose of 382 mg. Of the remaining patients, 5.8% withdrew from treatment because of side effects or death unassociated with CML, and 11% withdrew because of lack of efficacy or disease progression. At 5 years, the overall rate of survival in the imatinib group reached 89.4%. With death unrelated to CML excluded, the overall rate of survival was 95.4%

Recent study results indicate that the rate of disease progression diminished with imatinib use, with fourth-year rates lower than those in each preceding year. More important, among the patients in the initial imatinib group, 93% have survived without progression to accelerated phase or blast crisis CML. “We are getting fantastic clinical results on a disease that, heretofore, was fatal except for those patients successfully transplanted,” said Richard Silver, MD. “It’s a rational drug that was designed for taking advantage of the molecular and cytogenetic abnormality characterizing the disease. It has provided the model for other drugs that have since come down the line, not only in leukemia but in other forms of cancers.”

In addition to the impact imatinib has had on patients, the drug has affected how chronic phase CML is treated. Imatinib has become the treatment of choice, diminishing the need for transplantation, which carried such risks as mortality, graft-versus-host disease, and delayed consequences including infertility, cataracts, or second malignancies. “It’s now very difficult to justify transplantation initially except in unusual circumstances such as a very young patient or those few patients who fail to respond to imatinib,” said Dr. Silver.

There remains a small percentage of patients who are unresponsive to imatinib. For such patients, 2 drugs—dasatinib and AMN107—offer alternative treatment options. Although dasatinib, AMN107, and imatinib differ, they share a similar trait in that they target the BCR-ABL protein, whose abnormal activity is linked to CML. NewYork-Presbyterian/Weill Cornell participated in studies relating to the efficacy of dasatinib, which was recently approved by the U.S. Food and Drug Administration. NewYork-Presbyterian/Weill Cornell also will take part in AMN107 drug trials, said Dr. Silver, who will serve as principal investigator.

In addition to its findings, the 5-year imatinib study serves as an example of the importance of collaboration in science among and within institutions, noted Dr. Silver. Researchers and faculty from the Weill Cornell Division of Hematology and Medical Oncology, and the Department of Pathology and Laboratory Medicine were among the researchers involved.

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New Pediatric Leukemia Initiative Fociuses on Patients and Research

Columbia Physicians at Morgan Stanley Children’s Hospital of NewYork-Presbyterian’s Herbert Irving Child & Adolescent Oncology Center are making strides in enhancing patient care and developing new clinical research initiatives for children with leukemia.

NewYork-Presbyterian Hospital recently organized the pediatric oncology service into disease-oriented areas including leukemia and lymphoma, as well as neurology and solid tumors, said Kara Kelly, MD. “The reorganization helps us to better ensure that we enroll patients on trials and that they are being cared for by oncologists with expertise in their specific cancer type,” she said.

NewYork-Presbyterian Hospital is applying to be part of a new experimental therapeutics consortium focusing on childhood leukemia. Collaboration with the Dana-Farber Cancer Institute’s Acute Lymphoblastic Leukemia Consortium is another important trial initiative, in which both pediatric and adult patients can enroll. “We are forging more collaborative relationships with colleagues who treat adults,” said Dr. Kelly. “Adults treated on pediatric regimens are having better outcomes.”

The pediatric oncology program is also working on a new leukemia cell banking protocol, which will enable practitioners to more uniformly collect samples for the laboratory. “We’ll have more samples available for translational research,” said Dr. Kelly.

Translational research is key to developing new drugs that target pediatric leukemia. NewYork-Presbyterian/ Columbia researchers are evaluating the role of NOTCH-1 mutations in T-cell lymphoblastic leukemia. “This cancer accounts for approximately 15% of lymphoblastic disease in our pediatric patients,” said Adolfo Ferrando, MD, PhD. This form of leukemia is very aggressive, he said, adding that it will sometimes respond to more intensive therapy but at the expense of a much higher toxicity to the patient.

Dr. Ferrando and colleagues are trying to understand the molecular basis of T-cell lymphoblastic leukemia and studying potential targets for therapy, including NOTCH-1, that will lead to more effective and less toxic treatment. In the laboratory, researchers are trying to activate and inhibit NOTCH-1 pathways in T cells grown in vitro.

“NOTCH-1 is mutated and activated in about 55% of patients with T-cell lymphoblastic leukemia,” said Dr. Ferrando. “It signals development, proliferation, and survival of the disease.”

New technologies derived from the completion of the human genome are becoming increasingly important in studying T-cell lymphoblastic leukemia. “We’re using genomic tools to analyze thousands of genes at a time,” said Dr. Ferrando. Microarrays allow researchers to determine which genes are expressed and which ones are not when NOTCH-1 is activated. “We look at 54,000 genes at a time, which generate a lot of data, but it gives us the power to explore this cancer in depth,” he added.

The NOTCH-1 gene itself is a good candidate for targeted therapy because it is a receptor on the cell membrane. “Only some genes or pathways are good candidates for targeted therapy,” said Dr. Ferrando. Receptors are good candidates because scientists can design strategies for blocking them. Gamma-secretase inhibitors, which were originally designed to treat Alzheimer’s disease, appear to block NOTCH-1 signaling, he said.

More clinical studies are needed to help researchers understand the function of such drugs as gamma-secretase inhibitors. Scientists are trying to determine when to give patients these agents and other drug combinations, and what the side effects will be.

“I’m optimistic about the progress we’ve made in this line of research,” said Dr. Ferrando. Researchers have found 500 to 1,000 genes directly regulated by NOTCH-1. There are many different pathways regulated by this gene, and researchers are starting to understand how these pathways interact with oncogenes that contribute to cancer growth.

In addition to new therapeutic targets, NewYork-Presbyterian/Columbia scientists are interested in the effects of nutrition on leukemia treatment side effects and outcomes, said Dr. Kelly, adding that antioxidant status may be influential. The Hospital is collecting prospective nutritional data on more than 500 children with acute lymphoblastic leukemia, she said.

Researchers have also been looking at polymorphisms in detoxification genes and how they correlate with therapy side effects and outcomes, said Dr. Kelly. “We’re starting to look at an individual’s genetic profile to predict outcome and discern toxicity to help tailor agents to each patient,” she said, adding that much more research is needed.

While the Hospital is involved in myriad research projects and clinical trial initiatives, it is also opening a cancer survivor center for pediatric and young adult patients that will provide comprehensive medical assessment for long-term survivors of at least 5 years, said Dr. Kelly. The center will provide a comprehensive medical and psychosocial evaluation, building upon an integrative therapies program, that provides patients with nutritional, exercise, acupuncture, massage, energy healing, and an overall focus on wellness, said Dr. Kelly.

“We’re not just treating leukemia,” she explained, “but supporting the patient as a whole and helping with survival.”

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bit of a surprise because melanoma shows regression in some patients. It is believed that this regression occurs when the immune system acts against the cancer. There are even very rare cases of advanced melanoma going into spontaneous remission, indicative of an immune response,” said Dr. Granstein.

To better understand immune response in patients with melanoma, Dr. Kaufman and his colleagues decided to investigate what was occurring at the tumor site. “We found what’s been discovered for a lot of cancers,” said Dr. Kaufman. “Within growing melanoma—what we call the tumor microenvironment—are substances that shut the immune system off.”

A vaccine may be able to create an immune response, but it is being shut down at the tumor site. “This is one way the tumor is able to outwit the immune system,” explained Dr. Kaufman.

Instead of immunizing patients systematically, researchers are now trying to vaccinate at the tumor site by using a poxvirus with costimulatory molecules to change the local environment and cause an effective immune response. The vaccination spurs cytokine development, giving the immune system an advantage over tumor cells, he said.

In 2 of 3 Phase I clinical trials conducted at NewYork-Presbyterian Hospital/Columbia University Medical Center, patients who underwent this therapy showed a dramatic response. Two of them had a complete response. Not only did the tumors at the injection site disappear, but so did other tumors throughout the body. “Somehow, we’re getting a much stronger immune response that seems to overcome tumors’ defenses against the immune system. We may be getting stronger T cells,” he said. The Hospital is moving this work forward to larger clinical trials.

Dr. Kaufman and his colleagues also published data on patients with melanoma who received interleukin-2, which is currently 1 of 2 FDA-approved treatments for the disease (Cesana GC et al. J Clin Oncol 2006;24:1169–1177).

The drug induces a complete response in about 10% of patients, he said. NewYork-Presbyterian/Columbia is the only academic center in the New York City area using high doses of interleukin-2, so researchers are better able to study this patient population.

In individuals with melanoma, the number of regulatory T cells, which shut the immune system off, was nearly 4 times higher than the number in the general population.

The level of regulatory T cells may be an indicator of who will respond to interleukin-2. “This finding could be a big advance in how we select patients for treatment,” said Dr. Kaufman.

NewYork-Presbyterian/Columbia researchers are also looking at genetic markers and differences between responders and nonresponders to interleukin treatment, and are trying to validate this finding in a larger number of patients. One promising marker may be CCR5, a gene expressed on T cells, guiding them on where to go and what to do, said Dr. Kaufman.

A number of new studies are being started at the Hospital this year, he added, including one that uses herpesvirus to deliver a vaccine, rather than poxvirus. While researchers continue to evaluate potential treatments for melanoma, physicians emphasize the importance of closely monitoring patients at risk for the development of the disease. At NewYork-Presbyterian Hospital/Weill Cornell Medical Center, Dr. Granstein recently added professional photographers to take high-quality photos of atypical-appearing moles. “This way, we can better follow people longitudinally,” he said.

The risk for melanoma is greater in people with atypical nevi than in the general population. These patients are seen at regular intervals and are encouraged to evaluate their own skin at home. A photo record helps physicians and patients determine if a lesion has changed or is new, said Dr. Granstein. If a cancer develops, patients are then referred to the appropriate treatment, or to experimental protocols involving immunomodulators or vaccines.

Melanoma is one of the fastest-growing cancers in the country right now, and researchers do not entirely understand why, said Dr. Kaufman. “Care has to be individualized,” he added. “And we have the resources to do that.”

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for lung cancer of 1,000 people to more than 33,000 worldwide. We are serving as the coordinating center for this CT screening program that is being conducted at 40 institutions,” Dr. Henschke said. The data being collected in the screening study are used to determine the efficacy of early treatment following early diagnosis by CT as well as when to screen, whom to screen, and how often to screen. Findings are being discussed at semiannual conferences of the participants in the screening consortium with the intention of developing applicable strategies.

“The concept would be very much like mammography. The earlier the detection, the greater the likelihood of cure,” Dr. Henschke explained. However, she acknowledged that early detection creates new dilemmas about treatment. As more lung cancers are detected at early stages, studies will be needed to consider such issues as reducing the size of the removed segment of lung from a lobectomy to smaller sections such as wedge or segmentectomy. This challenge is already being undertaken by a separate team of Weill Cornell researchers, led by Nasser Altorki, MD, at NewYork-Presbyterian Hospital. He is working with the National Cancer Institute to design and launch a nationwide study comparing lobectomy with lesser lung resections in early lung cancer.

“Minimally invasive lung surgery is an important focus on the Weill Cornell campus, where thoracic surgeons already have considerable experience performing thoracoscopic tumor resections of the lung through small incisions. This approach facilitates a faster and easier recovery after the operation,” Dr. Altorki said.

The early detection of cancers and attempts to identify treatments that provide optimal outcome are related efforts at NewYork-Presbyterian/Weill Cornell. Dr. Altorki said that he is enthusiastic about the diagnostic studies of Dr. Henschke, with whom he has co-authored several peer-reviewed papers. Dr. Altorki and his group have been active in pioneering studies of lung cancer vaccines to prevent or reduce cancer recurrence as well as using new types of agents that are highly specific to tumor cells, leaving normal cells unaffected. He has also been involved in the study of biologic therapies that target mechanisms of tumor survival, such as the angiogenesis critical to maintaining a blood supply.

Columbia researchers at NewYork-Presbyterian Hospital are testing an increasing number of treatments directed at very specific molecular mechanisms of tumor growth in clinical trials that promise both more effective and safer treatments. In work being led by Haralambos Raftopoulos, MD, efforts to inhibit angiogenesis in order to starve tumors of their blood supply are maturing, while new targets are being pursued. One clinical study about to enroll lung cancer patients will employ antibodies to kill cells expressing the Lewis Y antigen, a very specific focus that may spare normal cells in an effort to reduce toxicity. Dr. Raftopoulos has been active in studying both targeted biologic therapies and conventional chemotherapies.

“One of the recent approaches has been to combine the biological therapies focused on inhibiting angiogenesis with traditional chemotherapies. We already have some evidence that there may be some synergies with these approaches,” Dr. Raftopoulos said. He noted that many of these studies are being performed in patients with advanced lung cancer, but there are also numerous studies combining oncologic agents with other modalities, including radiation and surgery, in patients with earlier stages of tumor in which the goal is to achieve complete remissions.

“We have created a highly collaborative approach that I think is really making a difference to patient care. Specialists can each make a contribution towards a consensus about a specific treatment plan for individual patients. There are an increasing number of options for managing patients, and we agree as a team about which makes the most sense,” Dr. Raftopoulos said.

To facilitate the multidisciplinary approach, the clinical team at NewYork-Presbyterian/Columbia recently funded a dedicated nurse coordinator to monitor the treatment protocol. The nurse coordinator ensures that patients stay current with a treatment protocol that may include multiple modalities. This includes documenting and recording not only care administered at the Hospital but also the care at other clinical centers, a circumstance that is common when patients from distant towns return home for portions of their therapy.

“The coordinator is totally dedicated to our thoracic oncology patients, and they are a resource not just for the patient but for physicians seeking a status report as a patient progresses through multimodality care,” said Joshua R. Sonett, MD. Dr. Sonett reiterated the importance of the team approach at NewYork-Presbyterian Hospital, which includes a dialogue between surgeons, oncologists, and radiologists to identify an optimal strategy. As a surgeon, he emphasized the increasing number of lung cancer patients who are candidates for minimally invasive lung resection, an approach that reduces hospital stay from 5 days to 2 days and recovery time from 6 weeks to 2 weeks when compared to open procedures.

“Often minimally invasive surgery can be performed that is essentially no different from an open procedure in regard to the tumor resection and lymph node removal, except that it puts dramatically less stress on the patient,” said Dr. Sonett, who noted that recent data suggest that less stressful procedures may have an influence on outcomes. One of the most recent examples of the pioneering work in minimally invasive, lung-preserving surgery that is being conducted at NewYork-Presbyterian/Columbia involves treatment of malignant mesothelioma. Under a treatment protocol developed by Robert Taub, MD, an oncologist with a great interest and expertise in treating abdominal and pulmonary malignant mesothelioma, Dr. Sonett and his team are utilizing a unique approach to a lung disease that has had
limited treatment options. With lung-preserving therapy, curative intent treatment with chemotherapy and radiotherapy is delivered directly to the tumor lining the pleural cavity. The treatment shows great promise in improving the quality of survival and is attracting patients from as far away as Europe.

“This has been an exciting example of where we can go with minimally invasive surgery to not only improve postoperative recovery but possibly improve outcome and treatment paradigms,” Dr. Sonett said.

The work at NewYork-Presbyterian/Columbia and NewYork-Presbyterian/Weill Cornell has made an important contribution to making lung cancer a treatable disease with an increasing likelihood of survival. Dr. Altorki suggested that recent progress is just the beginning.

“For the first time in decades, the disease is attacked on 2 fronts simultaneously: both that of early detection and that of novel, safer, and hopefully more effective treatments,” Dr. Altorki observed. “If we continue to make progress, we are likely to see some significant changes in overall survival.”

Other tertiary care centers are pursuing some of the same initiatives in the management of lung cancer as those at NewYork-Presbyterian Hospital, but few can claim to have the range of initiatives and the depth of talent to rapidly incorporate approaches with proven benefit into patient care. The multidisciplinary teams that work to agree on a course of action ensure that patients receive treatment endorsed by several experts.

“I think it is appreciated that patients receive better care when specialists work together,” Dr. Altorki said. “This is something we emphasize at NewYork-Presbyterian Hospital.”

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