

# NEW YORK-PRESBYTERIAN Oncology

Affiliated with COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS & SURGEONS and WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY

Fall 2005

## Hospital Studies Targeted Therapy for GI Cancers

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are deep into groundbreaking clinical trials and translational studies in the fast-developing field of targeted cancer therapies that they hope will eventually move from laboratories into life-prolonging clinical practice. The investigative work in targeted gastrointestinal cancer therapies is illustrative of new pharmacologic approaches that may continue to extend patients' lives and ultimately transform "intractable" cancers into treatable chronic diseases.

"Our program in targeted therapies covers most of the major solid tumors and lymphomas and leukemias," said Scott Wadler, MD.

An example of the ongoing efforts at the Hospital is the National Cancer Institute-funded colon cancer trial involving 2 targeted therapies, bevacizumab and cetuximab, in combination with a chemotherapy regimen called FOLFOX-6, in previously untreated patients with stage IV or metastatic disease. Bevacizumab blocks cancer cell growth by homing in on the vascular endothelial growth factor (VEGF) receptor and choking off the cells' blood supply, whereas cetuximab prevents growth by inhibiting the epidermal growth factor (EGF) receptor on the surface of the cell.

According to Dr. Wadler, Columbia

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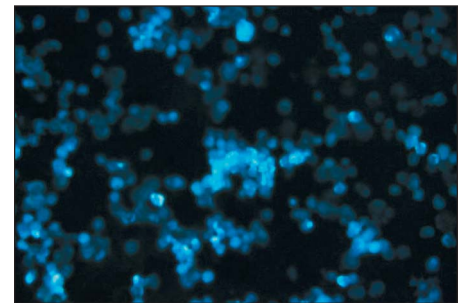
## Researchers Unravel Mystery of Multiple Myeloma Pathogenesis

The Multiple Myeloma Program at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, one of the leading myeloma programs in the United States, is forging ahead with several clinical and basic science investigations that may yield promising new treatments for patients.

The clinical trial program includes an investigation of a unique combination regimen based on lenalidomide, a new thalidomide analog that has already shown promising activity in a variety of hematologic malignancies.

The lenalidomide study is funded in part by a \$7.5 million Specialized Center of Research (SCOR) grant from the Leukemia and Lymphoma Society.

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Myeloma cells: Ongoing investigations at NewYork-Presbyterian Hospital include studies of new combination regimens for the treatment of multiple myeloma.

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## Ongoing Trials Seek Preventive Measures for At-Risk Groups

Progress in defining the molecular signals that drive tumor formation and growth has provided the basis for new therapeutic strategies. Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are looking at issues ranging from the impact of tobacco smoke exposure on cyclooxygenase-2 (COX-2) expression to cancer risk in Caribbean immigrants in New York. The data are being used to improve care and identify risk reduction strategies for often underserved populations.

COX-2 is a proinflammatory protein that has been implicated in a wide variety of tumors. Epidemiologic studies have associated the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit COX enzymes with a significantly reduced risk for cancer, particularly gastrointestinal malignancies. Most recently, Andrew J. Dannenberg, MD, evaluated the impact of tobacco smoke exposure on COX-2 expression. In work that was presented at this year's meeting of the American Association for Cancer Research, he reported that COX-2 levels were increased by as much as 4 times in the oral mucosa of active smokers versus people who never smoked. Tracing the mechanism, he and his co-investigators concluded that COX-2 levels were increased as a downstream consequence of activation of epidermal growth factor receptor (EGFR) signaling.

"In an oral cell line, tobacco smoke clearly activated the EGFR, leading to enhanced COX-2 gene expression," noted Dr. Dannenberg. Activation of EGFR occurred because tobacco smoke stimulated the production and release of amphiregulin, a ligand of

EGFR. "COX-2 expression was blocked by using either an inhibitor of EGFR activity or an antibody that prevented amphiregulin from binding to EGFR," he continued.

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**"[Our] results strengthen the rationale for targeting not only COX-2 but also EGFR as approaches for reducing the risk for tobacco-related malignancies of the mouth and throat."**

—Andrew J. Dannenberg, MD

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Tobacco smoke causes mutations in cells that are proliferating. Activation of EGFR signaling or induction of COX-2 stimulates cell proliferation, which in turn should increase the mutagenicity of tobacco smoke. The results of this study raise the possibility that inhibitors of either COX-2 or EGFR, or both, may have the potential for preventing or delaying the development of tobacco smoke-induced cancer.

"These results strengthen the rationale for targeting not only COX-2 but also EGFR as approaches for reducing the risk for tobacco-related malignancies of the mouth and throat," according to Dr. Dannenberg. Further experimental studies in advance of possible clinical studies are planned.

In work being performed by Alfred I. Neugut, MD, PhD, the Caribbean immigrant populations in New York are being evaluated in regard to their risks for different cancers, their attitudes toward cancer, and the health-care they receive for cancer, both from a socioeconomic standpoint and from a biological perspective. Eventually, studies will be conducted to compare changes in the incidence of specific cancers among immigrants versus the incidence in their native countries, an important step for isolating environmental risks. However, the data collected so far have already generated some important theories about cancer risk.

"It has long been suspected that the higher incidence of prostate cancer among African-Americans in this country was the result of some environmental factor, but we are finding that the rates among individuals with African blood are also very high in immigrants from the West Indies," said Dr. Neugut. Moreover, there appears to be some correlation between increased risk and the purity of African ancestry. For example, prostate-specific antigen levels are higher in individuals from Tobago, where the average individual is of nearly 100% African ancestry, than in Trinidad, where, on average, individuals are more



Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are seeking to improve care and identify risk-reduction strategies for underserved populations, such as Caribbean immigrants in New York.

likely to be of mixed European and African ancestry.

“It is clear that it is very important to recognize that the Caribbean immigrant population is very heterogeneous, and this provides us an opportunity to learn much more about environmental versus genetic risks for malignancy,” Dr. Neugut added.

Based on the epidemiologic information gathered so far, some initiatives have already been developed to better reach Caribbean immigrants at risk for cancer. Screening programs specifically designed for the needs of immigrants are being contemplated. Effective programs cannot be developed generically for immigrants but must address the very diverse populations of the Caribbean, which are separated by culture and language.

“We have been looking at whether immigrants from English-speaking islands, such as Jamaica and Trinidad, are more likely to be screened and effectively treated for cancer than those from non-English-speaking islands, such as Haiti and the Dominican Republic,” Dr. Neugut reported. “This information is critical for determining how to provide care for populations at risk.”

Importantly, the information generated by these studies may not only help Caribbean immigrants but also generate new insights into differences in environment versus genetics relevant to all populations. Dr. Neugut suggested that these studies are an important source of epidemiologic data that can generate advances in the understanding of the pathophysiology of cancer and steps toward prevention.

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## NewYork-Presbyterian Oncology

is a publication of the Cancer Centers of NewYork-Presbyterian Hospital. The Cancer Centers are at the forefront of cancer screening and diagnosis, basic science, and clinical research. The Cancer Centers serve over 6,500 new cancer patients each year, who receive state-of-the-art multidisciplinary care. The Cancer Centers include the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/Columbia University Medical Center and the Weill Cornell Cancer Center at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, which are respectively comprised of faculty from the Columbia University College of Physicians and Surgeons and the Weill Medical College of Cornell University.

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## CANCER Prevention

NewYork-Presbyterian Hospital's Cancer Prevention Newsletter and Web site offer information for professionals on the latest developments in the field of cancer prevention and screening. Visit [www.nypcancerprevention.org](http://www.nypcancerprevention.org).

## Interdisciplinary Collaboration Spurs Neuro-oncology Initiatives

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are driving innovations in multiple fields of neuro-oncology, including targeted pharmacologic agents, stereotactic radiosurgery, and stem cell transfer, with the goal of implementing these advances when they offer a potential advantage over the existing standard of care.

It is already standard that an interdisciplinary collaboration begins at the time of diagnosis. Treatment options are discussed, and patients are channeled to a course of therapy on which experts from several disciplines agree.

“The weekly tumor board includes a full spectrum of specialists, including oncologists, surgeons, and radiologists,” noted Steven S. Rosenfeld, MD, PhD. “We can no longer work in isolation.” One of the most significant innovators worldwide in targeted therapy as it applies to the treatment of brain tumors, Dr. Rosenfeld is optimistic about the potential of several new classes of agents, a large proportion of which are in active trials at NewYork-Presbyterian Hospital.

“We are looking at a range of agents that can be used alone or in combination, particularly agents that can block signal transduction important to tumor growth and survival,” he said, adding that ongoing work with chloride channel inhibitors derived from scorpion venom (a new class of drugs that block the enzymes within a tumor cell responsible for chromosome transport) and agents targeted at receptors unique to malignant gliomas (leaving surrounding tissue unaffected) have been the focus of recent neuro-oncology research at the Hospital.

Because of the rapid progress in identifying new pharmacologic targets for

control of brain tumors, Dr. Rosenfeld predicted that his center may have as many as 2 dozen simultaneous, ongoing clinical trials in the near future. Drug tests include those funded by grants from the National Institutes of Health as well as those funded by private industry. Much of the progress has been possible because of gains in understanding the

biochemistry that signals such processes as tumor proliferation and angiogenesis.

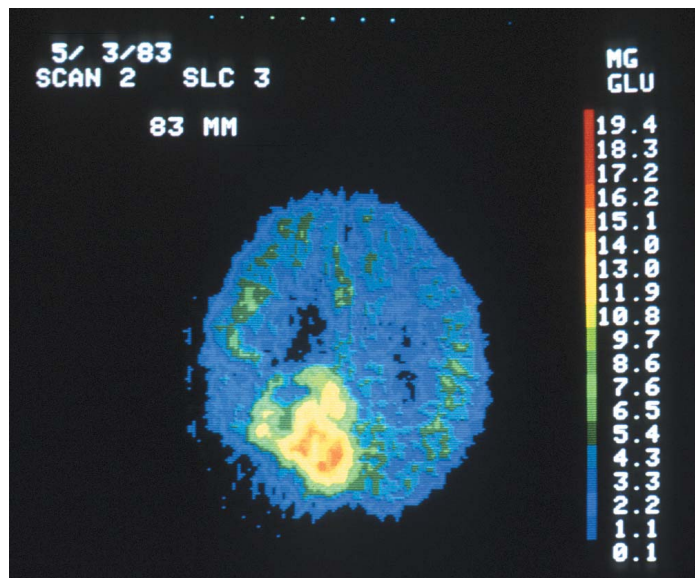
Innovation is important, but a characteristic feature of the neuro-oncology programs at NewYork-Presbyterian is the emphasis on coordinating care to employ innovations where there is a consensus about an opportunity for an improved outcome. With so many advances being pursued simultaneously, this type of consensus is essential so that patients may be directed to the optimal choice. Indeed, the success of these innovations depends on careful patient selection. As a result, physician teams at the Hospital frequently coordinate patient consultations, helping the patient meet individually with each of the physicians participating in care. The stereotactic radiosurgery program, which has been innovative in the use of a gamma knife for excising brain metastases, is one example. According to

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—Steven S. Rosenfeld, MD, PhD

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PET scan of a 62-year-old man with a brain tumor. Interdisciplinary collaboration among Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital is helping to drive multiple advances in neuro-oncology.

Susan Pannullo, MD, care can be relatively seamless as experts not only consult, but also collaborate, in day-to-day management.

“Patients are often seen by a neurosurgeon and a radiation oncologist on a single visit,” reported Dr. Pannullo, who noted that the stereotactic radiotherapy program is a joint effort of both the NewYork-Presbyterian/Columbia and NewYork-Presbyterian/Weill Cornell centers. Although the gamma knife is used in the treatment of both primary tumors and metastatic brain cancer, the treatment of metastases can often be planned as an outpatient procedure. This allows patients to receive uninterrupted treatment of the primary tumor. In appropriate patients, the efficacy of the gamma knife in excising brain metastases exceeds 95%, while at the same time the risks and complications of open brain surgery or less targeted radiotherapy are avoided.

Brain tumors are the second most common type of childhood cancer, after acute lymphocytic leukemia. Treatment of infants and young children is especially challenging because of the sensitivity of the developing brain to the side effects of radiation. James Garvin, MD, PhD, leads

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**“Patients are often seen by a neurosurgeon and a radiation oncologist on a single visit.”**

—Susan Pannullo, MD

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the pediatric brain tumor program at Morgan Stanley Children’s Hospital of New York-Presbyterian/Columbia, and in 3 successive clinical trials he has pursued a strategy of intensive chemotherapy with autologous stem cell rescue to limit the need for radiation. This approach has also been promising in children with tumors that have recurred following standard radiation and chemotherapy. Patients with refractory tumors are offered investigational agents through the Phase I Developmental Therapeutics Consortium of the Children’s Oncology Group. Future plans include an expanded drug discovery program for pediatric brain tumors and a multidisciplinary late effects clinic devoted to optimizing quality of life

in these young patients.

“Neuro-oncology is highly collaborative at our center,” said Dr. Rosenfeld. As a result of the diversity and depth of expertise at NewYork-Presbyterian Hospital, the latest advance is never more important than the best outcome.

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## GI Cancer

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and Weill Cornell researchers are “very hopeful” about the trial, which was developed by the New York Phase 2 Consortium of medical centers. Allyson J. Ocean, MD, noted that FOLFOX in combination with bevacizumab had already shown a survival advantage in stage IV colon cancer.

“Our study is taking what is a standard and adding another monoclonal antibody”—cetuximab—to see if it prolongs survival, she said.

Another study will look at FOLFOX plus bevacizumab in stage II and III colon cancer patients whose tumors have been resected. “We really wanted to address a pivotal question: whether the benefits associated with bevacizumab as first-line therapy for metastatic colorectal cancer can be translated to the adjuvant setting,” said Abby Siegel, MD,

adding that the median survival of patients with colon cancer used to be 6 months when 5-fluorouracil (5-FU) was the only available treatment. “Now the median survival is 22 months,” she continued, “and many people live longer.”

Additional studies are examining the use of targeted therapies in cancers of the liver and pancreas. One trial will focus on gemcitabine plus bevacizumab and either cetuximab or erlotinib in previously untreated pancreatic cancer patients. Erlotinib is a new oral EGF receptor inhibitor approved by the FDA for treating non-small-cell lung cancer.

Another trial is looking at bevacizumab as a single agent in liver cancer patients. The trial is at an early stage, said Dr. Siegel, but “we’ve actually seen very good responses.” One issue is that patients with a history of bleeding problems are excluded from the study because, she said, “liver cancers are very vascular and

[bevacizumab] has a tendency to make you both bleed and clot.”

Also under way is a large multicenter trial investigating sorafenib in the treatment of liver cancer. Sorafenib is a new agent that targets the pathways that lead to cancer cell proliferation. Robert Fine, MD, is involved in studies that seek to translate laboratory research to clinical practice. One potential treatment combines arsenic, ascorbic acid, and disulfiram. Arsenic and ascorbic acid are already used in treating leukemia patients, according to Dr. Fine. They raise the levels of free radicals in cells that are driven by mutations in the *ras* gene. In all, 95% of pancreatic cancers fall into this category.

“Addition of disulfiram, at clinically achievable concentrations, causes the free radicals generated by arsenic and ascorbic acid to deplete ATP energy levels preferentially in pancreatic cancer cells with mutant *ras*,” noted Dr. Fine.

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## Researcher Hopes To Build Bridge From Science to Patient Care

**R**iccardo Dalla-Favera, MD, one of the world's leading cancer geneticists and lymphoma researchers, is hoping to take a leading role in translating basic science insights into revolutionary new cancer therapies in his new role as Director of the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/Columbia University Medical Center.

Dr. Dalla-Favera has been at NewYork-Presbyterian/Columbia for more than 15 years and was a founding member of the Institute for Cancer Genetics. He has made pioneering contributions to cancer research, authoring more than 250 publications.

"It has become very clear that 'cancer' is not a single disease," Dr. Dalla-Favera said. "For each cancer type, we have to know the distinct mechanisms of tumor development, the different genes that are altered, and the complex relationship of each tumor type with the other tissues in the host. Only then will we be able to develop new therapies that will attack the tumor cells specifically where they are different from normal cells."

Recently, NewYork-Presbyterian/Columbia reinvigorated its commitment to cancer research and care with the opening of the Herbert Irving Cancer Research Center, an 11,000-square-foot, 11-story facility dedicated to laboratory cancer research. The Avon Foundation Breast Imaging Center is on the first floor.

"These initiatives will facilitate a new era of clinical and basic cancer research," Dr. Dalla-Favera said of the new facility. "We will have an unprecedented opportunity to take basic research from the laboratory and translate that into the clinic."

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**"It has become very clear that 'cancer' is not a single disease. For each cancer type, we have to know the distinct mechanisms of tumor development, the different genes that are altered, and the complex relationship of each tumor type with the other tissues in the host. Only then will we be able to develop new therapies."**

—Riccardo Dalla-Favera, MD

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Dr. Dalla-Favera has dedicated more than 20 years of his career to investigating lymphomas, identifying many novel oncogenes involved in their pathogenesis. A major priority for Dr. Dalla-Favera and colleagues has been the study of the function of *bcl-6*, a proto-oncogene that codes for a B-cell-expressed transcription factor; in many human lymphomas, the regulatory region of this gene is altered. The researcher's insights into *bcl-6* have been translated into new, experimental therapies that are currently undergoing clinical evaluation in multiple institutions.

Dr. Dalla-Favera and colleagues have also studied the involvement of key oncogenes in chromosomal translocations and deletions associated with lymphomas. They have discovered that lymphomas have a unique mechanism for altering genes, called *aberrant somatic hypermutation*.

"This mechanism is generating genome-wide genetic damage while the lymphoma develops," Dr. Dalla-Favera noted. "We are trying to understand what combinations of genes are altered in different cases—bringing up, again, the theme that different tumors will have different characteristics. Our hope is that our findings will lead to very personalized therapeutic approaches based on the genetic makeup of particular tumors."

Dr. Dalla-Favera has received national recognition for his efforts from the Leukemia and Lymphoma Society of America, which presented him with the Stohlman Scholar Award for Leukemia and Lymphoma Research. He has also received 2 MERIT Awards from the National Institutes of Health. As principal investigator in a study funded by a prestigious 5-year, \$5 million grant from the Leukemia and Lymphoma Society, Dr. Dalla-Favera will examine mechanisms of cancer development and evaluate experimental lymphoma therapies.

In addition, he is the principal investigator in study supported by a \$15.5 million National Cancer Institute grant that researchers hope will yield new insights into molecular mechanisms in the pathogenesis of breast cancer. "We will have to build a full axis from basic research to therapeutic development, and 1 important area of emphasis will



be breast cancer, thanks also to the support of the Avon Foundation,” he said.

An important strength of the Herbert Irving Comprehensive Cancer Center, according to Dr. Dalla-Favera, is its integration with Columbia University College of Physicians and Surgeons, an institution known for the depth of its research resources, not only in traditional medical and biological sciences but also

in chemistry, physics, and bioinformatics—all of which have a tremendous impact on modern cancer research and drug development. In addition, research is conducted at the Hospital. “Patients have access not only to promising experimental treatments that could dramatically change their life expectancy,” he noted, “but also to the best multidisciplinary medical care to improve their quality of life.”

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## Myeloma

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Through the SCOR initiative, the Program takes an aggressive and multidisciplinary approach to multiple myeloma, offering patients transplants, vaccines, and drugs, along with participation in clinical trials of all stages of the disease. Leading the SCOR initiative is Selina Chen-Kiang, PhD.

“Multiple myeloma is a disease that has been treated, but not cured, for 150 years, which suggests we must forge ahead with a new approach,” said Dr. Chen-Kiang. “Toward that end, we have coupled a very strong basic research program with a comprehensive clinical trial program.”

Recently, the Myeloma Program has generated a considerable amount of excitement by launching a multiple myeloma treatment study evaluating a combination regimen, known as BiRD, that includes the antibiotic clarithromycin, lenalidomide, and dexamethasone.

The BiRD regimen represents an important next step in the development of new therapeutic regimens for multiple myeloma. While the standard of care, dexamethasone alone, achieves a response rate of only approximately 50%, a combination called BTLN (clarithromycin, thalidomide, dexamethasone) has yielded a response rate of 93% and complete remission rate of 13% in recent clinical studies.

Unfortunately, thalidomide is associated with debilitating side effects, while lenalidomide—1,000 times more potent than the parent drug—avoids many of those side effects. Ruben Niesvizky, MD, and colleagues hope that the BiRD combination, by replacing thalidomide with lenalidomide, will

improve patient safety while maintaining the favorable patient outcomes seen with BTLN.

“We fully anticipate that [lenalidomide] will achieve an impressive complete remission rate, therefore allowing patients to achieve long-term survival,” said Dr. Niesvizky, adding that the BiRD investigation is just 1 of several ongoing clinical trials in which Myeloma Program investigators are playing a major role.

In particular, investigators look forward to initiating a trial of second-line treatment for multiple myeloma with dexamethasone plus the proteasome inhibitor bortezomib along with autologous stem cell transplant. The investigators are also evaluating a new class of drugs, called *histone deacetylase inhibitors*, in 3 separate protocols. Together, these protocols cover a wide range of patients.

“Our goal is to improve treatment and ultimately to find a cure,” Dr. Niesvizky explained. “Toward that end, we want to investigate treatments for patients in every stage of the disease.”

Dr. Niesvizky’s focus on treatment and drug trials is just 1 of 3 complementary aspects of the Myeloma Program. Those clinical investigations are enhanced by the work of Dr. Chen-Kiang, who leads the research team. Dr. Chen-Kiang is a molecular immunologist who is currently focused on elucidating the mechanism of cell cycle control of myeloma pathogenesis. Likewise, the work of Scott Ely, MD, an expert in hematopathology, plays another distinct role in this synergy. Notably, Dr. Ely has spearheaded efforts to use histology to identify cell cycle molecules. Complementing Dr. Chen-Kiang’s molecular approach, Dr. Ely is using immunohistochemical analysis to identify key cell cycle

regulators in myeloma pathogenesis.

“We have found that when patients are stable, there is very little proliferation of myeloma cells, but when they relapse or develop aggressive disease, there is a loss of cell cycle control,” he explained. “We have worked for 5 years to elucidate which molecules are most important in cell cycle control in myeloma. The next step is to develop drugs that will target those specific molecules.”

Drs. Chen-Kiang, Ely, and Niesvizky collaborate with a full team of expert scientists and physicians who meet regularly to share new ideas and communicate findings in multiple myeloma.

“This is a group of people with a common goal—trying to understand the disease better to achieve a cure,” Dr. Niesvizky said. “In order to do that, we must translate research from the bench to the bedside, and likewise, from the bedside to the bench.”

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“This induces a form of cell death only in the tumor cells.”

Dr. Fine’s current translational studies, as well as his earlier work with a regimen called GTX (the combination of gemcitabine, docetaxel, and capecitabine) in pancreatic cancer patients, help to illustrate the fact, he said, that “if you use good science [and] translate your findings from the laboratory to the clinic, you can significantly improve the current state of the art. GTX, developed in our lab, has high response rates and prolonged survival rates [relative] to the standard of care.” One “caveat,” he added, is that “we have to learn how to use chemotherapy better and then figure out how to add targeted therapy so that there is no antagonism, because we have found that some targeted therapies are actually antagonistic to chemotherapy in the lab.” The reason is that “targeted

## Studies are examining the use of targeted therapies in cancers of the liver and pancreas.

therapy in general blocks cell growth or causes cell stasis while most chemotherapy works only in growing cells,” he said.

Everyone agrees that it is an exciting time for new cancer treatments. “This is the first time we’ve been able to see patients living with cancer rather than dying of the disease. We’ve been able to extend their lives,” said Dr. Ocean. “The other amazing thing is that the side effects” of these new therapies are “manageable for the most part, and people are able to live their lives with these regimens.”

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