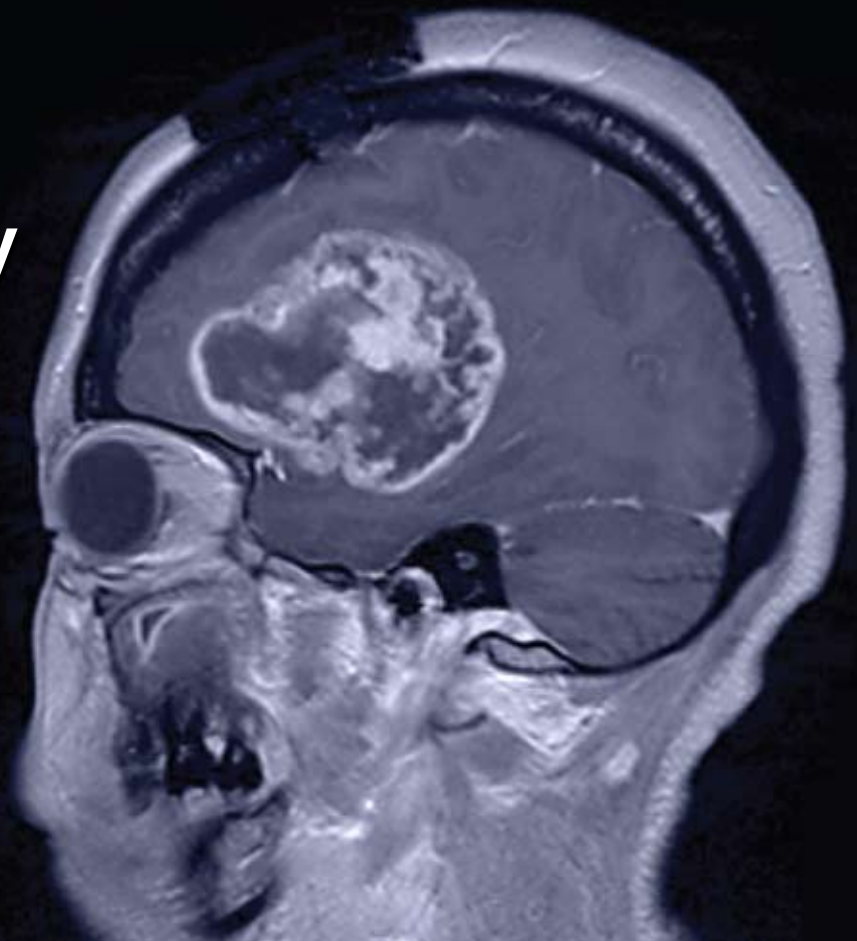


# UH Innovations In Cancer

University Hospitals Ireland Cancer Center

**Rethinking  
Chemotherapy  
for GBM** page 4



Cancer

**3** Studying a drug that blocks the sonic hedgehog pathway

**6** What does the future hold for clinical trials research?

**7** Vaccines for some of the most difficult cancers

# A Focus on Clinical Trials



Welcome to the second issue of *Innovations in Cancer*, highlighting examples of our cutting-edge clinical trials, which are fully integrated into our cancer care teams at the Ireland Cancer Center, University Hospitals Case Medical Center.

Our Cancer Center is committed to addressing the recent Institute of Medicine Report of a national shortfall in accrual to cancer clinical trials. We do this by folding clinical trials and other innovative treatments into our initial and ongoing evaluation of all patients at our weekly multidisciplinary cancer team meetings.

Innovation is our approach to improving cancer care for all patients. In fact, we designed our new cancer hospital to incorporate a multidisciplinary approach to patient care with inclusion of new diagnostic, surgical and therapeutic treatment strategies for each patient. And, patients are seen in multidisciplinary clinics.

In this issue, we highlight several of our ongoing clinical trials. **Andrew Sloan, MD**, is principal investigator for a trial of a modified MGMT gene that will be introduced into blood and bone marrow stem cells of patients with glioblastoma multiforme to enable them to receive higher and potentially more therapeutic doses of chemotherapy. **Charles Nock, MD**, leads another trial in glioblastoma, to study a drug that blocks the sonic hedgehog pathway that is critical to the growth of many glioma cells.

We also hear from **Neal J. Meropol, MD**, who discusses his vision about the future of clinical trials. Finally, we highlight other clinical trials under way at our center that involve novel cancer vaccines. **Jeffrey Hardacre, MD**, is a principal investigator for a nationwide study of a vaccine for pancreatic cancer. **Julian Kim, MD**, leads a trial of a vaccine for melanoma, and Dr. Sloan is investigating a vaccine to target glioblastoma. **Joseph Baar, MD, PhD**, is examining the efficacy of a MUC1 vaccine in highly aggressive "triple negative" breast cancer.

I thank you for taking the time to read this issue of *Innovations in Cancer*. If you would like to contact me directly, please call 216-844-8562.

Stanton L. Gerson, MD  
Director, University Hospitals Ireland Cancer Center and  
Case Comprehensive Cancer Center

## Contact Us

We have many trials including early stage trials linked to our innovative approach to care. We would be glad to discuss interest or questions about these trials. You can contact any of the physicians listed in this issue. A more complete listing of our current trials can be found at [www.UHhospitals.org/irelandcancer](http://www.UHhospitals.org/irelandcancer). This Website also features a video that introduces patients to clinical trials.

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Contributors: Stanton L. Gerson, MD; Nathan Levitan, MD; Julian Kim, MD, FACS; Neal J. Meropol, MD; Charles Nock, MD; Andrew Sloan, MD, FACS

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Among the nation's leading academic medical centers, University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a nationally recognized leader in medical research and education.

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The commitment to exceptional patient care begins with revolutionary discovery. Faculty at the Case Western Reserve University School of Medicine, who also are physicians at UH Case Medical Center, are at the forefront of medical research and innovation. The School of Medicine is the largest medical research institution in Ohio and among the nation's top medical schools for research funding from the National Institutes of Health.

# Clinical Trial for Advanced GBM

A collaboration of basic research and clinical expertise

■ BY CHARLES NOCK, MD



Charles Nock, MD, Assistant Professor of Medical and Neuro-Oncology, Case Western Reserve University School of Medicine

Very recent scientific advances have revealed the existence of both tumor cells and a small number of cancer stem cells in glioblastoma multiforme (GBM). These stem cells are resistant to both chemotherapy and radiation and are likely a principal cause of GBM progression and recurrence in patients who have received standard therapies, including tumor resection and chemoradiation.

At Ireland Cancer Center, University Hospitals Case Medical Center, we are leading a national, multicenter study of a first-in-class agent that targets a crucial signaling pathway present in GBM stem cells. This Phase II clinical trial of recurrent glioma is coordinated through the Adult Brain Tumor Consortium and funded through the National Institutes of Health's 2009 American Recovery and Reinvestment Act stimulus package.

## SONIC HEDGEHOG PATHWAY IN GBM

The co-principal investigator, **Andrew Sloan, MD, FACS**, Director, Brain Tumor and Neuro-Oncology Center at UH, and Associate Professor, Peter D. Cristal Chair in Neurosurgery, Case Western Reserve University School of Medicine, has been actively investigating the sonic hedgehog pathway (SHH) with his research team. SHH is an embryonic signaling cascade that activates gene transcription and affects cellular proliferation, differentiation and survival of cancer stem cells.

In healthy cells, the SHH pathway is actively repressed. We now know, however, that abnormal activation of this signaling pathway is implicated in a variety of cancers, including the differentiation of the cancer stem cells present in aggressive GBM.

SHH is a complicated signaling system with many components that work in concert to modulate pathway activation and inhibition. In a key step that is critical to this trial design, a transmembrane protein receptor called smoothed homologue (SMO) activates the rest of the SHH signaling pathway.

## GDC-0449 TARGETS SMO ACTIVITY

The clinical trial will evaluate the safety and effectiveness of GDC-0449, an orally bioavailable drug developed by Genentech Inc., a member of the Roche group. This agent specifically binds to and blocks the activity of



SMO, rendering it unable to activate the rest of the SHH cascade. GDC-0449 is the first systemic SMO-inhibitor entering clinical trials.

GDC-0449 may provide a greater degree of selectivity with fewer adverse effects than conventional chemoradiation for treating patients with surgically resected, progressive or recurrent GBM.

## CLINICAL TRIAL DESIGN

The trial will enroll 40 patients nationwide. Eligible subjects must have confirmed GBM that is progressive or recurrent following radiotherapy (with or without chemotherapy).

The patients are sequentially assigned to receive therapeutic conventional surgery (control arm) or GDC-0449 once daily for seven days prior to surgical resection of the tumor. All study subjects receive GDC-0449 after surgical resection. The primary outcome measure is six-month progression-free survival, but we are also monitoring toxicity and measuring tumor biopsy changes in SHH pathway members and markers of proliferation.

## Recent Success with GDC-0449

In a recently published Phase I study, GDC-0449 produced positive results in 33 patients with metastatic or locally advanced basal cell carcinoma. Eighteen patients had an objective response, including two with complete remission. GDC-0449 is now in a Phase II trial for advanced basal cell carcinoma and is being evaluated in other trials for ovarian and colorectal cancers and medulloblastoma.

# A Promising Approach

Improving tolerance and effectiveness of chemotherapy for malignant brain tumors

■ BY ANDREW SLOAN, MD, FACS



Andrew Sloan, MD, FACS, Director, Brain Tumor and Neuro-Oncology Center, University Hospitals Case Medical Center; Associate Professor, Peter D. Cristal Chair in Neurosurgery, Case Western Reserve University School of Medicine

At the Ireland Cancer Center, University Hospitals Case Medical Center, we are investigating a new approach to improve efficacy of chemotherapy for glioblastoma multiforme (GBM) while circumventing the dose-limiting bone marrow toxicity that often accompanies such therapy. While concurrent radiation and temozolomide (TMZ) chemotherapy markedly improves prognosis in large studies, the benefit of combination radio-chemotherapy appears to benefit primarily patients with MGMT promoter methylation, while those with unmethylated MGMT promoters gain little benefit despite the added toxicity. Various regimens of “dose dense” TMZ as well as combinations of TMZ and O6-benzylguanine (BG) appear to benefit some patients with the resistant phenotype, but toxicity remains problematic.

We are initiating a Phase I trial to evaluate the insertion of gene-modified hematopoietic stem cells (HSC) to facilitate selective bone marrow chemo-resistance by enabling the bone marrow to repair DNA alkylation produced by TMZ/BG, allowing patients to tolerate higher doses of chemotherapy. This approach has proven efficacious in preclinical models, and we have just received approval for a Phase I trial of this strategy in up to 16 patients.

## LIMITATIONS OF CURRENT TREATMENT

GBM is among the most deadly tumors known to man, with a median survival of less than one year from diagnosis in most large studies, even with aggressive treatment. The current standard of care includes maximum surgical resection, external beam radiation therapy, and chemotherapy with alkylating agents such as TMZ, but patients undergoing all three steps achieve only a modest benefit in overall survival. The probability of surviving two years is only about 25 percent.

TMZ exerts its antitumor effect through DNA methylation, but cellular resistance can develop in tumors. This resistance is largely attributed to the activity of the MGMT gene, which codes for O6-methylguanine methyltransferase, an alkyltransferase that repairs TMZ methylation. This enzyme is, however, rapidly and irreversibly inactivated by exposure to BG, and some investigators have added BG to the TMZ chemotherapy regimen in an attempt to maximize TMZ efficacy.

While the TMZ/BG combination may improve survival in patients with GBM, it also markedly suppresses bone

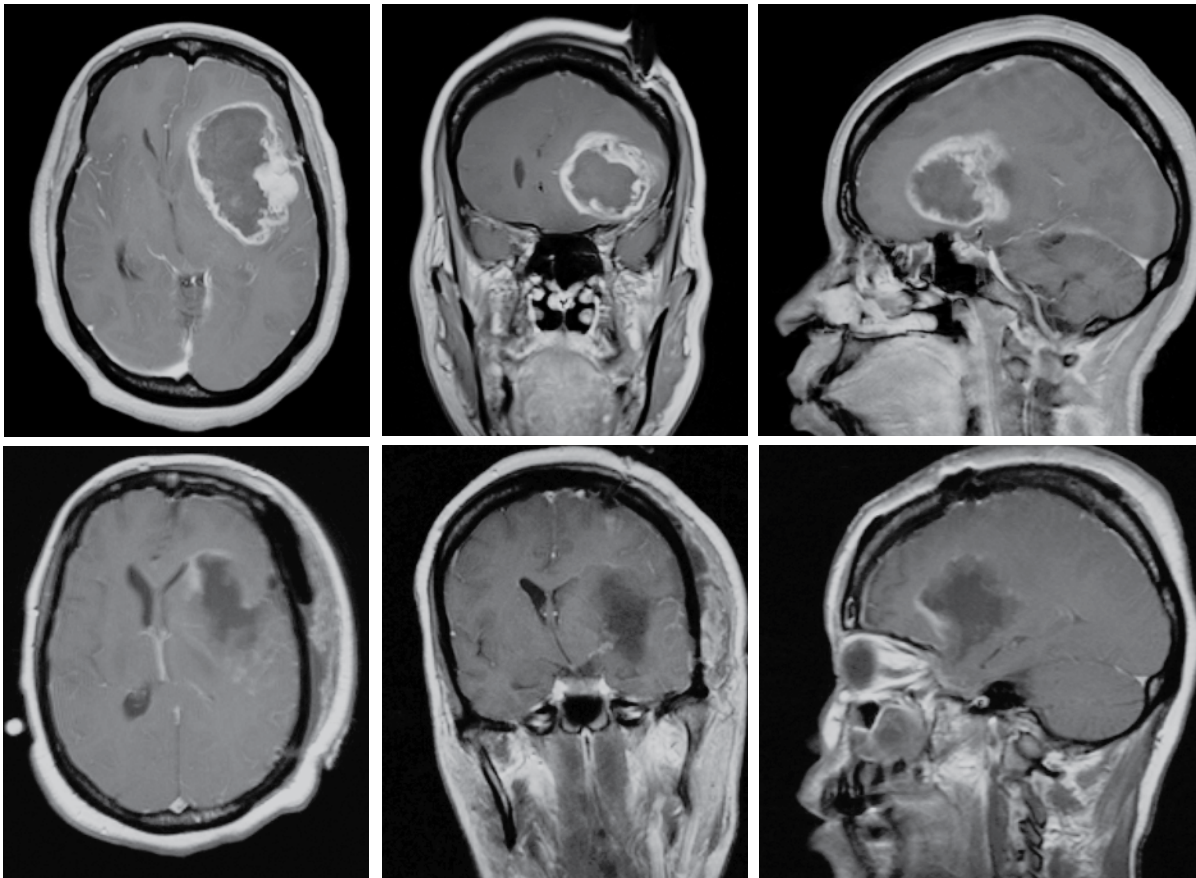


marrow function. The major dose-limiting toxicities include Grade III-IV thrombocytopenia and neutropenia, which are often so severe that many patients do not tolerate therapy. Even at the current dosing, which is known to be suboptimal for treating GBM, patients often develop bleeding problems and infections that limit their ability to complete the standard treatment regimen.

## A NEW APPROACH

Over the past two decades, **Stanton Gerson, MD**, Director, University Hospitals Ireland Cancer Center and Case Comprehensive Cancer Center, identified and pioneered studies of mutations of the MGMT that code for variant alkyltransferases that do not bind BG, and, therefore retain the ability to confer resistance to TMZ/BG. These MGMT mutations include P140K or G156A, which have an amino acid substitution at position 140 and 156, respectively, in the alkyltransferase.

The availability of these MGMT mutations suggested a novel approach to protect the bone marrow from TMZ/BG-associated toxicity, and investigators have, in fact, shown that introducing these mutations can protect



viral-transduced cell lines and primary hematopoietic progenitors from TMZ/BG-associated toxicity.

#### GOALS OF THE CLINICAL TRIAL

UH Ireland Cancer Center will enroll up to 16 patients to test if there is a possibility to protect their bone marrow and blood with autologous transplants of HSC transfected with MGMT-P140K. The approach employs a unique lentiviral vector to transfect the cells. This is believed to be safer and more effective than previous designs based on herpes simplex virus (HSV) vectors.

Preclinical data have been promising, and our group has established the safety of this approach in a previous Phase I clinical trial of seven patients treated with an earlier mutation using an HSV vector.

While the primary objective is to evaluate the feasibility and safety of introducing and expressing the modified MGMT gene in autologous HSC, there are also several secondary objectives. The UHICC researchers want to determine whether these patients tolerate BG plus dose-escalated TMZ, which should provide a more effective treatment of GBM while minimizing myelosuppression. In addition, we will evaluate tumor response, progression-free survival and overall survival. This is a Phase I trial, however, and therefore efficacy is not the primary goal.

We welcome inquiries from oncologists and their patients about potential participation in this trial.

## Details of the TMZ/BG Modified MGMT Trial

Patients with histologically confirmed, newly diagnosed, supratentorial GBM who have undergone gross total or near gross total resection (resection of >90 percent of enhancing tumor demonstrated by MRI) are eligible for enrollment in this trial within four weeks of surgery. Patients must be ages 18 to 70, with ECOG performance status 0, 1 or 2. They cannot have received myelosuppressive chemotherapy prior to the diagnosis of GBM.

Patients will be excluded if they have a medical condition associated with immunosuppression, active infection or medical illness that may jeopardize patient safety, including HIV seropositivity. Other reasons for exclusion include prior chemotherapy (including Gliadel® Wafer therapy) or hematopoietic cell transplantation.

The trial tests two approaches: gene transfer either prior to or after concurrent chemoradiotherapy. A third group of patients will participate in a dose-escalation protocol after we determine whether prior or concurrent gene transfer is the preferred approach. The gene transfer step will use a proprietary lentiviral vector designed to enhance safety and efficacy.

### Trial Details

For information about enrollment in this trial, please contact Jennifer Jochum at **216-844-7168**.

- Case Protocol 6307: O6-BG and temozolomide with infusion of autologous MGMT-P140K+ hematopoietic progenitors to protect hematopoiesis
- Andrew Sloan MD, FACS, principal investigator

# The Future of Clinical Trials Research

Evolving trial designs require skilled investigator workforce

■ BY NEAL J. MEROPOL, MD



Neal J. Meropol, MD, Chief, Division of Hematology and Oncology, Ireland Cancer Center, University Hospitals Case Medical Center and Case Western Reserve University School of Medicine; Associate Director for Clinical Programs, UH Ireland Cancer Center; Associate Director for Clinical Research, Case Comprehensive Cancer Center. Dr. Meropol is Chair, Eastern Cooperative Oncology Group Developmental Therapeutics Committee; Chair, NCI Colon Cancer Task Force; and Chair, ASCO Cancer Research Committee.

Clinical trials, which are essential to improving cancer care, represent the highest quality care that we have to offer. We live in an era with an unprecedented number of new agents and technologies undergoing clinical testing, and we must take great care in designing and conducting clinical trials to make certain we are offering the patients who participate the most innovative treatments and the best possibility for success. I have the privilege of serving on a variety of national committees that provide a global perspective on the clinical trials process. I'd like to discuss two key issues that will have significant impact on the progress we make over the next decade.

## MOLECULAR CHARACTERIZATION OF TUMORS

We are now dividing "common" cancers into ever smaller subsets based on their molecular characteristics, and these characteristics bear on treatment selection. For example, breast cancers were once divided simply by whether they expressed hormone receptors. Now we consider HER2 expression in treatment selection, and we are exploring whether expression profiling can be used to determine which patients need adjuvant therapy and which therapy they should receive. The design of clinical trials must evolve to meet this progress in understanding cancer pathogenesis.

The Eastern Cooperative Oncology Group is addressing this challenge through a new scientific committee focused on drugs and how they work. In the Developmental Therapeutics Committee we are seeking to understand the features of patients and their tumors associated with toxicity and response, independent of tumor histology.

The National Cancer Institute (NCI) also has established disease-specific "task forces" with representation from the cooperative groups, translational researchers, patient advocates and NCI. These task forces vet new Phase III clinical trial concepts and build consensus among investigators to optimize the chances for a successful study. As chair of the Colon Cancer Task Force, I am witnessing and increasing the number of study concepts tailored to smaller and smaller patient subsets.

## THE CLINICAL INVESTIGATOR WORKFORCE

In order to translate new scientific insights to the clinic, we need clinical investigators with knowledge of study design and study conduct, including regulatory compliance, data collection and management, and ethical considerations for study subjects. The clinical investigator workforce is needed at community sites and academic medical centers. Unfortunately, many centers that train medical oncologists and employ young clinical investigators are finding it increasingly difficult to support these activities. Funding for investigator-initiated clinical research is often inadequate, reimbursement for patient enrollment in NCI-sponsored trials does not cover costs, and finding support for "protected time" for clinical investigators is difficult.

Some academic institutions also find it more difficult to define the value of clinical as compared with laboratory-based research, and thus career advancement of clinical investigators is often challenging. Efforts are under way nationally to ensure a robust "pipeline" of new investigators. NCI Colon Cancer Task Force now invites junior investigators to participate for six-month terms to gain national experience with clinical trial development. The NCI has initiated an award process to recognize clinical investigators. In addition, on the Cancer Research Committee of the American Society of Clinical Oncology we have begun discussions about how to ensure the future clinical investigator workforce.

Our expanding understanding of cancer biology and the identification of new therapeutic targets present exciting new opportunities for clinical investigation. Creative approaches to clinical trials and recognition of the importance of a skilled, committed investigator workforce will help us to meet this challenge on behalf of our patients.

## Ask Our Expert

To contact Neal Meropol, MD, call **216-983-4752** or e-mail [Neal.Meropol@UHhospitals.org](mailto:Neal.Meropol@UHhospitals.org).

# A Search for Answers

Developing vaccines to treat difficult cancers

■ BY JULIAN KIM, MD, FACS

Several clinical trials are under way at the Ireland Cancer Center, University Hospitals Case Medical Center to evaluate new vaccines that may prove useful in treating a variety of difficult cancers, including metastatic melanoma, triple-negative breast cancer, pancreatic cancer and glioblastoma.

## MELANOMA

We currently are evaluating the safety and effectiveness of vaccination with Allovectin-7, a plasmid/lipid complex containing the DNA sequences that encode HLA-B7 and B2 microglobulin, in patients with metastatic melanoma. In preliminary studies, injections of Allovectin-7 directly into melanoma raised a local immune response, which then extended to uninjected distant metastases. In the ongoing Phase III trial, patients with recurrent stage 3 or 4 melanoma are randomly assigned to receive either Allovectin-7 alone or standard chemotherapy (either dacarbazine or temozolomide). Co-investigators for these trials are **Henry Koon, MD**, Disease Team Leader, Melanoma, UH Case Medical Center and Assistant Professor, Case Western Reserve University School of Medicine, and **Charles Nock, MD**, Assistant Professor, Case Western Reserve University School of Medicine.

## TRIPLE-NEGATIVE BREAST CANCER

**Joseph Baar, MD, PhD**, Director, Clinical Breast Cancer Research, UH Ireland Cancer Center, is lead investigator for a pilot trial of a vaccine containing mucus 1 (MUC1) peptide plus the adjuvant poly-ICLC. This vaccine is being evaluated in patients with stage I-III infiltrating adenocarcinoma of the breast who have completed standard therapy (surgery, radiation, biologic therapy, chemotherapy) for triple-negative (ER/PR/HER2/neu negative) breast cancer. This is a preliminary study to determine whether an immune response can be raised with this vaccine, and researchers will focus on evaluating vaccine safety and toxicity. If at least four of the first 17 patients develop an immune response to the vaccine, then the trial will be extended to an additional 20 patients for a total of 37 participants.

## PANCREATIC CANCER

**Jeffrey Hardacre, MD**, Section Head Pancreatic Surgery, UH Ireland Cancer Center; Assistant Professor

of Surgery, Case Western Reserve University School of Medicine, is principal investigator for clinical trials of a candidate vaccine for pancreatic cancer. The concept for this vaccine arose from the recognition that all mammals except humans and certain primates produce alpha-1,3-galactosyl (alpha-gal) carbohydrate residues on glycoproteins and glycolipids on cell outer membranes. Because alpha-gal is present on intestinal flora, humans routinely produce anti-alpha-gal antibodies, and these may constitute up to 1 percent of circulating IgG. The vaccine is composed of allogeneic pancreatic cells transfected with a murine gene that enables them to produce alpha-gal residues on surface membranes. In preliminary studies in patients with pancreatic cancer, vaccination induced antibody-dependent cell-mediated cytotoxicity (ADCC) in the pancreatic cancer cell allograft, which also extended to the patients' endogenous pancreatic cancer cells. The vaccine is being tested in conjunction with chemotherapy and chemoradiotherapy in patients with pancreatic cancer who have undergone tumor resection and is currently entering Phase III testing in anticipation of application to FDA for approval.

## GLIOBLASTOMA

Autologous heat-shock protein-based vaccines are being evaluated in patients with recurrent high-grade glioblastoma, under the direction of **Andrew Sloan, MD**, Neurosurgical Oncologist, UH Ireland Cancer Center, Peter D. Cristal Chair in Neurosurgery and Associate Professor of Neurological Surgery, Case Western Reserve University School of Medicine. The vaccine incorporates heat shock protein-peptide complex (HSPPC) derived from the individual patient's tumor, creating a personalized antitumor vaccination. This approach has shown promise in several Phase I and II clinical trials of other malignancies, including pancreatic cancer, colorectal cancer, chronic myelogenous leukemia (CML) and non-Hodgkin's lymphoma (NHL), as well as in Phase III trials in kidney cancer and metastatic melanoma.



Julian Kim, MD, FACS, Chief, Oncologic Surgery, UH Ireland Cancer Center, Charles A. Hubay Professor of Surgery, Case Western Reserve University School of Medicine

## Ask Our Expert

To contact Julian Kim, MD, call **216-844-8247** or e-mail **Julian.Kim@UHhospitals.org**.



## INNOVATIVE TREATMENT

# One-Stop Care

A new UH Ireland Cancer Center hospital is set to open in 2011

■ BY JULIAN KIM, MD, FACS, AND  
NEAL J. MEROPOL, MD

The University Hospitals Ireland Cancer Center, located on the University Hospitals Case Medical Center Campus, is bringing a broad continuum of cancer care under one roof in a new tertiary-care cancer hospital for northern Ohio, one of only a small number of free-standing cancer hospitals in the United States. Its design reflects our priorities for multidisciplinary care, innovative therapy, patient- and family-centered care, and access to clinical trials.

A complete menu of oncology services will be offered, including surgical oncology, general medical oncology, radiation therapy and bone marrow transplantation. The 375,000-square-foot facility will have 120 beds and the ability to expand to 150 beds. The anticipated move-in date is May 2011.

### CARE AND DESIGN

Our model of patient care emphasizes a multidisciplinary team approach for each disease and each patient. The outpatient services area includes 45 exam rooms and 42 chemotherapy infusion chairs, with a flexible design and natural light-filled settings. Disease-focused multidisciplinary physician teams will see patients together in a series of clinical pods. The teams will focus on several types of cancer, including gynecological oncology; breast cancer; gastrointestinal cancers; skin cancer; lymphoma, myeloma and leukemia; lung cancer; prostate, bladder and kidney cancers; and other hematologic disorders.

The facility will contain state-of-the-art multimodality radiation therapy, including image-guided radiation therapy and conventional treatment. An adjacent breast center with state-of-the-art digital mammography and complementary services reflects our commitment to breast cancer screening and to other imaging technology for early cancer detection.

Each patient will benefit from a comprehensive, innovative plan of care in a facility that will dedicate space to both current and future diagnostic and treatment advancements. The operating rooms for cancer patients will include options for minimally invasive surgery, video-assisted surgery and robotics. Intra-operative MRI also will be available.

### VALUED INPUT

In accordance with our value of patient- and family-centered care, the building was designed with much input from patients and their families. For example, individuals who are receiving outpatient chemotherapy infusions will be able to choose on any given treatment day between a private infusion room or a more communal infusion space that overlooks a terrace garden and a healing garden. Each inpatient room will provide a place for a loved one to sleep on a fold-out sofa.

We will continue to emphasize a tradition of conducting basic and clinical research to discover new curative therapies and medical technology to continually improve patient care. In addition, because of our commitment to offering our patients access to clinical trials, we have built a special unit for clinical trials using both inpatient and outpatient beds.

The UH Ireland Cancer Center has a commitment to patient and community education, and the new facility will allow us to expand our patient offerings and the community outreach programs. The facility will contain a resource center for patients and families, and facilities to accommodate a new Survivorship program.

We hope that the 2011 opening of the UH cancer hospital will ensure an extraordinary experience of care for patients and families, from the unique healing garden to the abundance of natural light to the art collection to the coordinated team care and extensive subspecialty expertise.

## Your Feedback is Important

As a medical professional, your input is invaluable in helping us shape future issues of *UH Innovations in Cancer*.

We want to know what's important to you. Do you want to read about cutting-edge research, learn about the latest technology, or hear firsthand case studies of how others in your specialty are improving and saving lives? Tell us what you want to read about and your name will be entered to **win one of two Apple iPads!** Simply visit [UHhospitals.org/innovations](http://UHhospitals.org/innovations).



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