

# Cut to the Cure

*As a staff clinician in the Surgery Branch of CCR, Marybeth Hughes, M.D., is involved in a number of different collaborative projects aimed at improving the care of cancer patients. In some cases, she is looking for ways to apply an innovative surgical technique to treat a particular form of cancer. In others, a well-established procedure is a means to both excise and study a tumor for molecular and genetic clues to its origin and, hopefully, its cure. When she is not in the operating theater, Hughes may be found conferring with her bedside colleagues over symptoms of an unidentified endocrine tumor, working with her benchside colleagues to develop effective immunotherapies, leading a multicenter clinical trial for the treatment of liver metastases, or teaching medical students at the Uniformed Services University of the Health Sciences. The common thread running through the diversity of her professional activities is a desire to push the limits of understanding and treatment of cancer in its many guises. Hughes attributes her decision to specialize in surgical oncology to a combination of personal experience with unusual forms of cancer in her family and positive mentoring at critical junctures in her education.*

## Tracking Endocrine Tumors

Although we may imagine a molecular-medicine future in which oncologists administer a smart pill to deliver a targeted treatment exactly and only to cancerous cells, right now, surgery is still the only option to cure cancers in many settings. In part, that is because many cancers are so rare that we know surprisingly little about them.

Endocrine tumors are a lesson in just how complex our physiology really is. Abnormal cells producing a variety of hormonal or neural signals—ranging

from insulin to serotonin—can be lodged virtually anywhere in the body, and the resulting symptoms such as flushing, diarrhea, or abnormal blood sugar levels can be misdiagnosed for years. Even when biochemical analyses correctly reveal the presence of a tumor, finding it can still be a challenge (see “Where Is the Tumor?” page 32). Intellectually, the diagnosis of these tumors can be fascinating and ultimately satisfying because surgical removal has a high success rate in many cases, particularly when the tumors are caught early.



(Photo: R. Baer)

Marybeth Hughes, M.D.

Because we have some of the world's foremost endocrinologists here at the NIH, we see some very unusual cases, and I often provide surgical consults for their treatment. Karel Pacak, M.D., of the National Institute of Child Health and Human Development, world expert on pheochromocytoma, consults with me about surgical removal of this rare, tumor of the adrenal gland. Constantine Stratakis, M.D., D.Sc., Head of the Program in Developmental Endocrinology and Genetics, studies a rare, inherited form of adrenal disorder known as primary pigmented nodular adrenocortical disease (PPNAD), which causes affected children to go through cycles of high cortisol levels that produce dramatic changes in weight. The only treatment for both of these disorders is surgical removal of the adrenal glands.

As has proven the case for many other types of cancers, we believe that familial patterns of endocrine tumors might teach us not just about these rare cases but about the more prevalent, sporadic forms of endocrine cancers as well. I am also currently working with Steve Wank, M.D., Chief of the Digestive Diseases Branch at the National



(Photo: R. Beer)

Marybeth Hughes, M.D. (*left*) and colleagues in CCR's Surgery Branch work continuously to redefine the scope of technologies used in surgical oncology.

Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), to study and treat familial carcinoids, slow-growing tumors that secrete serotonin to cause flushing and digestive complaints but usually only after the disease has advanced to liver metastases. Some patients are fortunate—they may have had a carcinoid in the small bowel that bled, prompting a capsule endoscopy (essentially, a camera in pill form) study that locates the tumor. Many are not properly diagnosed until their disease has metastasized to the liver, and the prognosis is poor. We recently saw a patient whose mother, uncle, and brother had all died of the disease. A capsule endoscopy revealed small tumors in her intestines, which we have removed surgically.

We hope that, when surgically removed early, these carcinoids will not have an opportunity to metastasize to the liver. However, because it is often diagnosed so late, it is difficult to

understand the natural history of the disease or how effective treatments may be when administered early. We do not know, for instance, whether the carcinoid is part of a “field defect” involving a whole segment of the bowel or whether it is isolated to the ostensibly abnormal cells. Thus, in addition to simply excising the tumors, we are also analyzing single nucleotide polymorphisms (SNPs) and gene expression patterns in the tumors themselves and the adjacent tissue. Without an identified genetic defect, we are still trying to determine the best way to screen for the disease.

In general, endocrine surgeries require a great deal of patience because the tumors are often embedded in neovasculature that must be painstakingly worked through. The dissection can be tedious. As in every other medical speciality, surgeons must also keep abreast of new technologies that may improve outcomes for our patients. For some types of endocrine

tumors, advances in minimally invasive surgical techniques can not only be of cosmetic benefit in reducing scarring, but they can also provide real treatment benefits through better visualization and easier postoperative recovery. We have a robotically assisted platform for minimally invasive surgery that the surgeon operates from a separate console interface that mimics the conditions of open surgery (and yes, akin to a video game environment). The robotic arms have much greater dexterity than conventional laparoscopic instruments, greatly increasing their utility. There is currently discussion of using this technique in the United States as a means to do thyroid surgery from a “transaxillary approach” beginning under the arm rather than through an incision in the neck. Surgical technologies, like other therapeutic approaches, are evaluated for their efficacy in clinical trials.

### Surgically Targeting Liver Disease

The pinnacle of clinical research must be the Phase III multicenter randomized control trial (RCT). Such a trial is the culmination of years, sometimes decades, of research and development, and it is the moment when you can finally prove whether all of the hypotheses, animal data, and encouraging results of earlier human trials have really succeeded in producing a better treatment.

Our branch has been studying ocular melanoma and its metastasis to the liver for some time. Our patients have been diagnosed from their twenties to their seventies, and their prognoses are not good. Fortunately, the disease is rare—ocular melanoma affects 2,000 cases per year with only a fraction developing liver metastases. Unfortunately for the affected few, ocular melanoma is another example of an orphan disease cancer with the associated difficulties in conducting research directed towards cures. The current best effective treatment for these liver metastases leads to survival rates of only 4–6 months.

As a result, some seemingly extreme measures have been used to treat this disease. In the past, we have used a

technique known as open isolated hepatic perfusion to surgically isolate all of the blood vessels in the liver so that we could deliver very high doses of the chemotherapeutic agent melphalan for 60 minutes on the operating table without damaging other more sensitive organs in the process.

I am currently coordinating a Phase III RCT to treat these patients with peripheral hepatic perfusion in a dozen centers across the country. The goal is to once again deliver melphalan directly to the liver but to do so in a much less invasive manner. Instead of opening up the abdomen to get to the liver, catheters are threaded through the hepatic artery from small incisions in the groin to deliver the drug. Catheters above and below are also inserted to suck out the melphalan-laden blood, which is then filtered before being returned to the

body. Each treatment takes from 1–4 hours, and patients can have up to six treatments, depending on how they are responding, particularly to the toxic side effects of the drug.

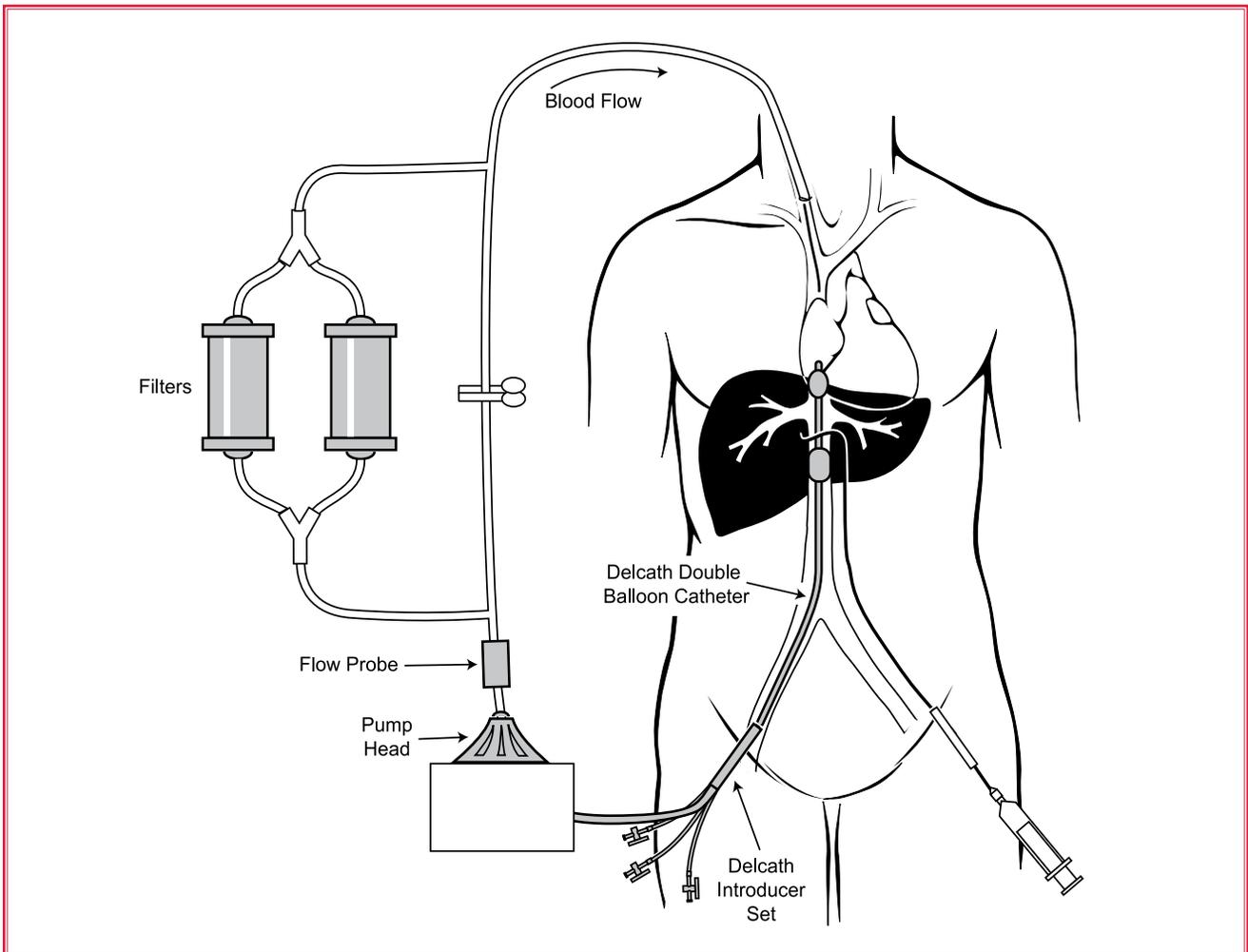
Advancing surgical technology has refined this macroscopic approach to targeted drug delivery from its much cruder earlier form. We have initiated the use of these techniques to treat other types of tumors, and we hope to use them, in time, to deliver more specific therapeutic agents.

### Developing Immunotherapies

When I first joined CCR as a Surgical Oncology Fellow, I was very lucky to have the optimal experience of combining clinical work and research. I joined a project to develop immunotherapies for cancer, which put me exactly in the right place at the right time to participate in

translational research at its finest. It was almost a fairy tale of clinical research—to make a novel scientific discovery that goes to the clinic over the course of just a few years. Although I am no longer involved in the laboratory work to develop these therapies, I am still actively involved in testing them in patients and working with my colleagues in the laboratory to further develop them.

The broad concept of immunotherapy is to help the immune system to do its job, namely, to clear out cells that are “bad,” whether as a result of infection or disease. Normally, this purging is done by a special class of white blood cells, T lymphocytes, which express receptors (T cell receptors or TCRs) that recognize aberrant proteins on defective cells and then activate the immune cascade that ultimately destroys them. In the case of cancer, the problem for the immune system is to identify the cancerous cells



(Image: M. Hughes, CCR)

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that, in turn, are continuously evolving to evade detection. Certain cancers do display characteristic proteins (antigens) on their cell surface that T lymphocytes are able to recognize, and we can find these T lymphocytes in tumors. However, they are not always present or available in sufficient numbers to mount an effective defense.

In the project I worked on as a Fellow, we asked whether we could introduce a gene that coded for a TCR recognizing a tumor-specific antigen associated with melanoma, MART-1, into a patients' circulating T-lymphocytes to boost the natural immune response. To do this, we isolated lymphocytes from two patient's blood and grew the cells in a dish where we could introduce the TCR gene. Once we were sure that the T-lymphocytes were expressing the TCR, we put them back in the patients and monitored the results. We found that the genetically altered T-lymphocytes remained in circulation for over a year after they were introduced and that the tumors had regressed. The results were published in the journal *Science* in 2006, and we are still working on improving the conditions for this type of adoptive immunotransfer, both for melanoma and for other forms of cancer for which tumor-associated antigens are identified.

There are several other methods for boosting the immune response to cancers that we are actively studying. Adoptive immunotransfer has, thus far, had greater success when we are able to find T-lymphocytes that have infiltrated

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the tumor already (tumor-infiltrating lymphocytes or TILs). We surgically remove the tumors and grow the cells that have made their way into the tumor in large numbers. Then we give a chemotherapeutic agent to reduce the background immune response and introduce the army of TIL-derived cells into the patient. In melanoma patients, we have had approximately a 50 percent success rate with this approach, and we are currently working to optimize this process through the use of immune modulators like cytokines.

We know that introducing cytokines like IL-2 in high doses or inhibitors such as anti-CTLA4 that take the brakes off the immune system can be effective in fighting tumors. However, many of these interventions have resulting toxicities in which the immune system becomes too active and causes problems with autoimmunity. Increasingly, we are realizing that the immune system must achieve a perfect balance in deciding what to attack and that our efforts to circumvent this balance for therapeutic purposes may look promising in the laboratory but have unforeseen consequences in the clinic. For instance, we do not really understand the tumor microenvironment well enough to know how it is responding to our manipulations—it seems clear that there are mechanisms that can turn off all of the switches that we are trying to turn on. Patient-to-patient variability, both in terms of the cancer and the immune system, also makes it hard to tease out the responses we would like to see. To move this kind of research forward really requires continual interaction between lab and clinic to understand what is working and why.

### Looking Ahead

Perhaps because it is where I began my work at the NIH, I believe that cancer immunology holds a very special promise for the future of cancer therapies. If you think about the kind of damage that our cells sustain over the course of a normal lifetime, the surprising thing is that only one in four of us is diagnosed with cancer. The role of the immune system in resisting cancer normally must be substantial, and we must be able to tap those normal mechanisms when they fail.

Even in the molecular age, however, there is still a strong role for surgical innovation in the treatment of cancer. We are, of course, learning an enormous amount on the molecular and genetic levels about different types of cancers, and I look forward to the day when we can translate that information into diagnostics and treatments for rare cancers. Like many other medical specialties, surgical oncology is continuously redefining its scope as well as its technology. My work brings me into diagnosis in the form of biopsies, treatment in the form of surgical intervention, and research in the form of developing new biologic-based therapies and new techniques to deliver them.

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To learn more about Dr. Hughes's research, please visit her CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?profileid=6156>.

To learn more about the Surgery Branch at CCR, please visit <http://ccr.cancer.gov/labs/lab.asp?labid=93>.

# Where Is the Tumor?



(Photo: Courtesy of B. Hogerty)

Marybeth Hughes, M.D., treated Brandon Hogerty's insulinoma—a rare type of endocrine tumor—at the CCR Surgery Branch. He now looks forward to returning to the university.

*To say that Brandon Hogerty owes his life to a social networking site would be a definite exaggeration, but there is nonetheless a grain of truth to it. A few months into his first semester at James Madison University, his friends noticed that he had not emerged from his room in a couple of days, but they thought maybe he was just upset about something. Then a friend from home tried to reach him, and when she could not, she chatted about her concern to mutual friends at the university on Facebook.*

*They found Brandon in bed, unable to move, and phoned for an ambulance.*

Brandon's blood level sugars had dropped to zero, and he had suffered a hypoglycemia-induced seizure. "They couldn't get a glucose reading," he was later told.

As many incoming freshmen do, Brandon had come down with a common virus a few days earlier and had not felt like eating anything. Fasting naturally lowers glucose levels, but the fact that his had gone to zero meant that something was seriously wrong. The local hospital was able to stabilize him but could not diagnose the underlying metabolic problem. Doctors back home in Richmond, Va., concluded that Brandon must have an insulinoma—a rare type of endocrine tumor that secretes insulin. Insulin is normally released in response to rising blood sugar levels, but when it is secreted continuously from a tumor, it can easily mop up all of the available blood sugar. There was only one problem—they could not find it.

That is when Brandon was referred to NCI where he underwent a series of

diagnostic tests. Marybeth Hughes, M.D., and her colleagues were also unable to find the tumor through conventional imaging methods. However, they were eventually able to localize the tumor to the head of the pancreas by doing intra-arterial calcium stimulation tests—infusing calcium into the arteries feeding the pancreas to induce insulin release and track its source.

Eight months elapsed from the episode of hypoglycemia in college to removal of the tumor. But Brandon and his family had suspected something was amiss even earlier. "For like a year before, I'd start getting the symptoms of hypoglycemia—I didn't know what it was—I just knew I had to eat right away." And his parents noticed that sometimes he would just tune out and "act like a zombie." Because he did not know how long the illness would last, Brandon withdrew from James Madison in late January and, this July, enrolled in community college. He plans to get an associate degree in Business before reapplying to the university.

The doctors say that cases like these are very rare in people as young as Brandon, and so they do not know for sure what the long-term consequences could be. But like any teenager with goals ahead of him, Brandon is happy to be healthy. "I was worried there would be huge scars," he said. "But they appear to be healing nicely."