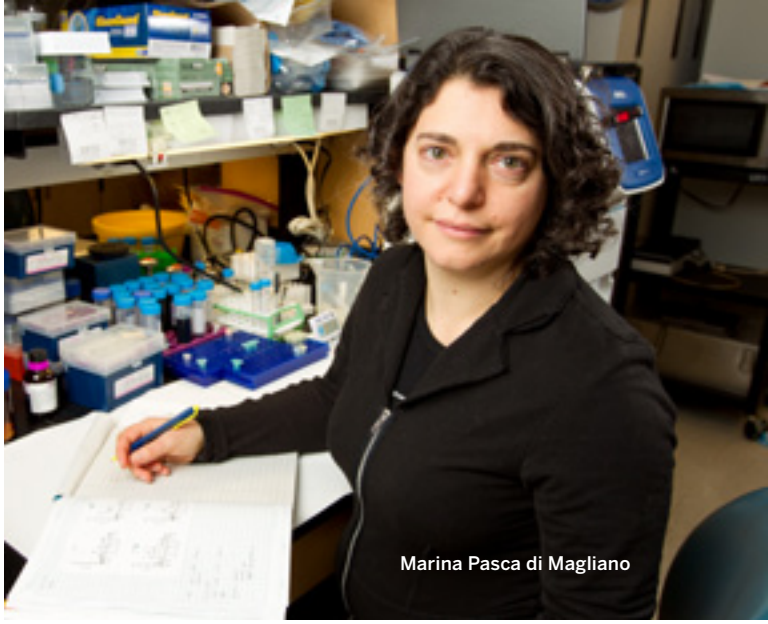
BELIEVING IN

U-M RESEARCHERS WORK TO SHED LIGHT ON THE GRIM WORLD OF PANCREATIC CANCER

BY SALLY POBOJEWSKI


Marina Pasca di Magliano

Pancreatic cancer is a cruel disease. In spite of doctors' best efforts to cut out the tumor, poison it with chemotherapy and sear it with radiation, it usually comes back and spreads malignant cells to other organs in the body. Unless the tumor is detected early and removed before it spreads outside the pancreas, patients often die within a few weeks to a few months after diagnosis.

This devastating disease makes up only 2 percent of all cancer cases, but is the fourth most common cause of deaths from cancer in the U.S. The 43,000 Americans diagnosed last year have few reasons to hope for a different outcome.

But hope often is found in unexpected places — like the animal research facility in a basement on the U-M medical campus. It is home to 1,000 genetically engineered mice that were created in the research laboratory of Marina Pasca di Magliano, Ph.D., assistant professor of surgery and of cell and developmental biology in the Medical School.

Some of these mice are dying from pancreatic cancer, but others are running around their cages, eating mouse chow and living the good life. They are the world's first genetically engineered mice to be cured of pancreatic cancer, thanks to the discovery by Pasca di Magliano and her research team, of how to turn off the activity of an oncogene, or cancer-promoting gene, called KRAS (pronounced K-ras).

In a recent series of experiments, U-M scientists turned on the mutant KRAS gene and induced inflammation in the mouse pancreas. Cells began to change and divide abnormally, until after just a few weeks, the entire mouse pancreas was filled with pre-malignant lesions. But when KRAS was turned off, the lesions regressed and pancreatic cells returned to normal within just a few days. Six months later, the mice were still cancer-free. Even in mice who developed advanced cancers, turning off KRAS resulted in the primary tumor and metastatic lesions melting away.

Other researchers have attempted to cure pancreatic cancer in a similar research mouse in which the mutant form of KRAS is always active or turned on. But in spite of many attempts by many scientists, "nobody was able to cure those mice," says Pasca di Magliano. "We figured out a genetic trick to turn KRAS on and off in the mouse. This has never been done before and it made all the difference."

In a nearby building, there's another colony of research mice belonging to Diane Simeone, M.D. (Residency 1995), the Lazar J. Greenfield Professor of Surgery and director of the Pancreatic Cancer Research Program. These mice serve as living incubators for pancreatic tumors removed from U-M patients during surgery. Small pieces of a patient's tumor are implanted and grow in the pancreas of these mice. Simeone's research team and her colleague Chandan Kumar, assistant professor of pathology, can then analyze the mutant genes expressed in each patient's tumor and test in mice experimental drugs designed to block the activity of those mutant genes.

"There is a significant amount of genetic diversity in these tumors," says Simeone. "It gets to the concept of personalized therapy — we hope to use the mouse models we've developed to help us understand which treatments to give to specific patients in a clinical trial setting to optimize success."

Using both types of research mice, Simeone and Pasca di Magliano are working together to identify the combination of mutant genes that drive the development of pancreatic cancer and figure out how to block their activity. Curing mice is one thing. Curing people will be much more difficult. But the two U-M scientists are cautiously optimistic.

"We have tumors directly from patients, and a mouse that gets a tumor in a step-wise manner just like a human patient does," says Pasca di Magliano. "In terms of a research model, this is as good as it gets."

It's a novel approach to finding more effective treatments for this deadly type of cancer. And it could mean that people with pancreatic cancer will finally have reasons to hope for a brighter future.

MUTANT KRAS PLUS ... "SOMETHING ELSE"

On a scale of one to 10, pancreatic cancer rates a 12 for aggressiveness and a one in terms of how well it responds to existing treatments. Unlike other types of cancer where early symptoms are obvious, the symptoms of pancreatic cancer — abdominal discomfort, bloating and loss of appetite — are vague and easy to ignore. Although researchers are searching for bio-

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markers to help diagnose pancreatic cancer early, there is nothing currently available.

As the tumor grows, symptoms of pain and jaundice become severe enough to send someone to the doctor. But by then, the tumor is often too advanced to be removed with surgery, because it may have grown into or around major arteries and veins or has already spread to the liver, intestines and other organs. Intense chemotherapy combined with radiation can shrink the tumor, but it often grows back.

Many types of cancer develop resistance to chemotherapeutic drugs over time, but pancreatic cancer seems to be inherently resistant and emerges unscathed from chemotherapy and radiation that can eradicate other solid tumors.

"If you look at pancreatic cancer under a microscope, it's a sea of scar tissue with nests of cancer cells," says Simeone. The dense fibrotic tissue surrounding the tumor makes it harder for drugs and radiation to reach and treat the cancer cells and explains some of pancreatic cancer's resistance to treatment.

But there's something else about pancreatic cancer that makes it so deadly — an innate aggressiveness that comes from the genetic mutations that drive its development and growth.

"I look at the tumor as a miniature natural selection process," explains Pasca di Magliano. "It accumulates mutations randomly, but if one clone of tumor can grow faster, it will take over. The tumor selects for the meanest cells — the ones that ignore all the signals saying you really shouldn't divide anymore."

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Scientists like Pasca di Magliano who study the genetics of pancreatic cancer focus on KRAS, because a mutant form of this gene is present in 90 to 95 percent of all human pancreatic tumors. The cancer-causing KRAS mutant triggers chronic inflammation in the pancreas, according to Pasca di Magliano's newest research. Instead of recruiting immune cells that promote healing, the gene recruits immune cells that inflame surrounding tissue and help the tumor to grow.

Although the KRAS mutation is extremely important, Pasca di Magliano points out that many people acquire this mutation as they age, but never develop pancreatic cancer. "You need to have the KRAS mutant and then something else has to happen," she says. The "something else" could be a mutation in a major tumor suppressor gene called p53; abnormal expression of a gene called ATDC, an oncogene discovered in Simeone's lab that is a critical trigger to promote invasiveness; or defects in a signaling pathway called the Hedgehog signaling pathway. All of these genetic abnormalities are common in pancreatic cancer.

In fact, researchers have found that malignant pancreatic tumors have an average of 63 mutations, and the specific combination of mutations varies widely from patient to patient. So drugs that target just one mutation may not be the answer.

Simeone believes an important clue to eradicating pancreatic cancer could involve targeting a subset of cells called cancer stem cells, which recently have been found to be present in several types of cancer. In 2007, Simeone and other U-M researchers discovered pancreatic cancer stem cells in human tumors by looking for three specific proteins on the cell's surface. She found that it took just 100 of these stem cells to trigger cancer in research mice, as opposed to thousands of regular tumor cells.

"All our data supports the concept that this cell population is a driver of pancreatic cancer and is particularly resistant to standard therapies," Simeone says. "If we want to cure pancreatic cancer, this cell population needs to be accounted for."

In recent research, Simeone discovered that all pancreatic cancer stem cells are not created equal. She found that cancer stem cells in some human tumors have a different surface protein called c-Met. In combination with another cancer stem cell marker called CD44, c-Met triggers a super-aggressive form of pancreatic cancer that grows and metastasizes rapidly.

Diane Simeone

Up to 30 percent of the cancer stem cells found in some patient tumors analyzed in Simeone's research were positive for CD44 and c-Met and were "incredibly aggressive," according to Simeone. "Tumors with lower populations of CD44 and c-Met were much less aggressive and don't seem to metastasize in mice." These cells may be key to defining a cancer stem cell "signature" in pancreatic cancer.

LIMITED TREATMENT OPTIONS

In 15 to 20 percent of patients diagnosed with pancreatic cancer, surgery is an option, because the tumor is still confined within the pancreas. But the procedure is complicated by the tumor's tendency to surround major blood vessels and nearby organs in the abdomen. Removing the tumor without damaging a major artery or vein requires the highest levels of experience and skill and sometimes is simply impossible.

Giving patients chemotherapy and radiation prior to surgery can help shrink the tumor and make it easier to remove surgically. And if the tumor cannot be removed with surgery, chemoradiation is the only possible treatment option.

One of the drugs most often used to treat pancreatic cancer is gemcitabine. It's called a radiation sensitizer because, in addition to directly killing tumor cells, it makes tumor cells more sensitive to radiation. Determining the most effective way to combine gemcitabine with radiation has been a major focus of clinical trials conducted by U-M oncologists. U-M clinical researchers also are testing the effectiveness of combining gemcitabine with another class of drugs called checkpoint inhibitors that interfere with cells' ability to repair damaged DNA.

While surgery and chemotherapy are widely accepted as treatments for pancreatic cancer, the effectiveness of radiation therapy is more controversial, especially for patients after surgery. A clinical trial in Europe of patients who had chemoradiation therapy after surgical resection of their tumor found no benefit. But a trial in the United States found that patients lived longer if they received post-surgical chemoradiation. A new clinical trial involving pancreatic cancer patients from many medical centers in Europe and the U.S., including the U-M Health System, will attempt to answer the question more definitively.

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Theodore Lawrence

Theodore S. Lawrence, M.D., Ph.D., the Isadore Lampe Collegiate Professor of Radiation Oncology and chair of the department, believes the results of the new trial will prove that radiation is an important part of the treatment protocol.

"In my opinion, the evidence is incontrovertible that, for patients who have a tumor that can't be removed, adding radiation to chemotherapy is better than using chemotherapy alone," says Lawrence. But he emphasizes that not just any type of radiation will do.

Lawrence says U-M researchers have perfected the use, in pancreatic cancer, of an advanced technique called intensity-modulated radiation therapy (IMRT). It allows radiation oncologists to deliver the most intense dose of radiation to the tumor, while minimizing radiation to surrounding tissue and organs — especially the duodenum of the small intestine, which surrounds the pancreas.

"With IMRT technology, we can curve the high-dose region, so it hits the tumor and just skims the duodenum," says Lawrence. "Minimizing radiation damage to the duodenum helps reduce side effects from treatment."

Even though treatment options are limited, current outcomes aren't good, and a cure remains a distant goal, those who work with and on behalf of pancreatic cancer patients are undaunted. "I'm a big believer in hope," says Simeone. "I always talk to my patients about the various therapies we have to buy them time." [M]

AUSTIN THOMASON, MICHIGAN PHOTOGRAPHY

"ANY PATIENT, ANY TIME"

Experience — and compassion — counts when treating pancreatic cancer

In addition to the fear and uncertainty that come with a diagnosis of pancreatic cancer, patients have to cope with another burden — deciding where to go for treatment. Experience is the most important factor to consider, because treating pancreatic cancer is not a job for amateurs. Diane Simeone, M.D., surgical director of the U-M Cancer Center's Multidisciplinary Pancreatic Tumor Clinic, recommends going to a comprehensive cancer center with surgeons, oncologists and gastroenterologists who specialize in caring for people with the disease.

"If you focus on one disease, you understand all aspects of it in greater detail and have a deeper understanding of the nuances," says Simeone. "If an operation is required, it will be performed by a surgeon who has done the same procedure many times before."

There is no one-size-fits-all treatment protocol for pancreatic cancer. At the Pancreatic Tumor Clinic, a multidisciplinary team of experts — including surgeons, radiation and medical oncologists, researchers and a social worker — work together to design an individualized treatment plan based on the stage of the tumor and each patient's situation.

The clinic saw 575 new patients during 2011 and there were more than 2,000 visits from patients who were either in treatment or seeking a second opinion. The clinic treats patients with pancreatitis, cystic tumors and other pancreatic diseases, in addition to cancer.

"It's very different from the old model where a surgeon would see a patient to decide if he or she could operate," says Mark Zalupski, M.D., a professor of internal medicine and medical director of the U-M's Pancreatic Tumor Clinic. "If the answer was no, the patient was just cast adrift to find another doctor.

"It's not uncommon for us to see a patient who had a CT scan elsewhere months ago, but still doesn't have a diagnosis or treatment plan," Zalupski adds. "When we see a patient, we often have a CT scan done the same day, schedule a biopsy, and then see that patient within a week to 10 days to present a treatment plan."

"Advanced pancreatic cancer is also associated with many symptoms, which makes patient care more difficult," Zalupski says. "Pain, difficulty eating and drinking, new onset diabetes and blood clots are very common. These symptoms tend to persist and progress until effective therapy is initiated. This is another reason to be treated at an institution with a team approach and experience in pancreatic cancer."

And there's one last and most important reason. Even after U-M oncologists have exhausted every option only to find that nothing is working, pancreatic cancer patients are never abandoned by their doctors.

"They are our patients," Simeone says firmly. "We do everything we can to prolong their lives with the highest quality of life possible. We will see any patient any time and follow them as long as they want to be followed." —SP

Mark Zalupski

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