JOINING FORCES

The 25th anniversary of U-M's Comprehensive Cancer Center provides an opportunity to reflect on how collaboration among physicians and scientists has revolutionized cancer research and care.

BY SALLY POBOJEWSKI
ILLUSTRATION BY ALEX NABAUM

The University of Michigan Comprehensive Cancer Center is a research powerhouse — ranking first in the nation among medical schools in research grants awarded by the National Cancer Institute (NCI). The Cancer Center provides a beacon of hope for patients seeking the country's best physician-scientists and access to clinical trials of new cancer therapies. With nearly 150,000 patient visits per year, the center's outpatient clinics, infusion and radiology centers are a hub of activity on the U-M's medical campus.

And it all started with notes scrawled on the back of a cocktail napkin.

Max Wicha, M.D., director of the Cancer Center, remembers that night in 1985 very well. He was in Washington, D.C., attending the annual meeting of the American Society of Clinical Oncology. During dinner with U-M colleagues Allen Lichter (M.D. 1972), and Ray Ruddon (Ph.D. 1964, M.D. 1967), the three friends started talking about what would happen if cancer research could be integrated somehow with clinical care.

Academic medical centers at the time were organized by medical school departments. Urologists associated with other urologists; hematologists congregated with hematologists; surgeons hung out with surgeons. Laboratory scientists lived in a different world entirely and rarely saw clinicians at all. As a result, physicians weren't aware of the latest scientific advances outside their fields of specialty, and scientists had no efficient track for developing and refining their discoveries to help patients.

But what if physicians from different disciplines worked together in one cancer clinic, rather than in separate clinics scattered throughout the health system? What if these physicians worked side-by-side with scientists who did research on cancer?

Grabbing a napkin, Wicha sketched out a plan of how it might work. It wasn't the first time that a great idea started over drinks and dinner with friends — the difference was that the three U-M faculty members came back to Ann Arbor and found a way to make it happen.

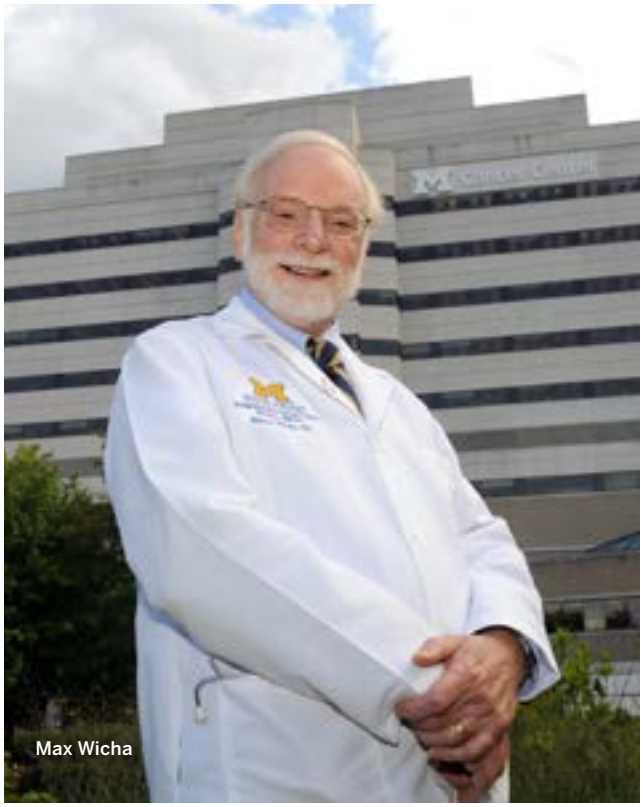
"Our idea was to create a cancer center that would link clinical care and research," says Wicha, Distinguished Professor of Oncology and professor of internal medicine who recently announced he was stepping down to focus on research.

Last September, Cancer Center administrators, physicians, researchers, nurses, staff and supporters celebrated the 25th anniversary of the first National Cancer Institute Core grant awarded to the U-M in 1988. This was the grant that designated the U-M as an official NCI Cancer Center and a pioneer in the concept of integrated care.

To understand how revolutionary integrated care was then, it helps to step back and see what it was like to be a cancer patient in the 1980s. It's never easy to hear that you have cancer, but 25 years ago, it was a devastating diagnosis. There was a fear associated with a cancer diagnosis, and public focus on the disease was limited. Doctors controlled the information patients received about their disease and its treatment. Support groups were sparse and Internet forums didn't exist.

"When I had to tell patients they had cancer back then, it was terrifying; the outcomes were often poor," recalls Kathleen Cooney, M.D. (Residency 1991), the Frances and Victor Ginsberg Professor of Hematology/Oncology, who in 1988 was a chief resident at University Hospital. "Chemotherapy had so many toxic side effects that we admitted most patients to the hospital to receive their infusions."

Patients who sought treatment from a specialist at an academic medical center faced another set of challenges. Clinical care was provided in department-specific clinics



Max Wicha

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— so a patient with breast cancer, for example, might see a surgeon in the clinic, then make another appointment to see a medical oncologist, and then a third appointment to see a radiation oncologist. This model of care often resulted in three different treatment options being recommended, leading to confusion for many patients.

"The care of the cancer patient was much more siloed then," says Diane Simeone, M.D. (Residency 1995), who in 1988 was an intern at the U-M, and who is now the Lazar J. Greenfield Professor of Surgery and professor of molecular and integrative physiology. "If a patient was referred for surgery, surgeons made all the decisions about their care. Patients who came to see an oncologist were treated with no initial input from surgeons. The decision-making process wasn't integrated."

A TRAILER AND A VISION

In 1986, Wicha and colleagues took the first step toward making that cocktail-napkin idea a reality by submitting a proposal to the U-M Board of Regents to establish the Health System's first cancer center. The Regents approved the idea that year. The center's administrative offices were housed in a trailer parked on the edge of the medical campus, and research was performed in limited laboratory space in existing research buildings.

To grow, the fledgling program needed a core grant from the National Cancer Institute. Not only would an NCI grant bring much-needed funding, it would be an official stamp of approval from national experts for the U-M's proposal to integrate cancer treatment and research. After two years of work, an intensive peer-review process, and an on-site evaluation, the U-M was awarded its designation as an NCI Cancer Center.

The Cancer Center worked with departments in the Medical School and other schools to hire the country's best young scientists — many of whom were interested in cancer biology and wanted to be part of the new approach to research taking shape at the U-M Cancer Center.

"During our first decade," says Wicha, "we jumped from being nowhere on the map to being one of the top 20 cancer centers in the country."

Following a rapid expansion of the Cancer Center's research and clinical programs, it faced a new challenge — creating adequate space to house the programs and facilitate its mission to seamlessly integrate multidisciplinary research and patient care. The goal was to enable patients to see all their physicians in the same place on the same day, so a comprehensive evaluation and treatment plan could be generated quickly with input from all specialties. Common at cancer centers today, the concept was new when Wicha, Lichter and colleagues established the Health System's first multidisciplinary clinic for breast cancer in 1985 — one of the first such programs in the nation.

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To make room for more clinics and research labs, the Cancer Center needed a new multi-purpose building. "There was no building that combined clinical care of patients with laboratory science," Wicha says. "A few people didn't understand the benefits of combining research with clinical care; they said we shouldn't mix mice with people." Many, however, saw the benefits of such an approach.

Then there was the issue of how to raise all that money — enough to build the new center and hire more physician-scientists to work in it. NCI building grants covered part of the construction cost, but Wicha had to work closely with Medical School, hospital and university leadership to develop and implement plans for the new building. To spread the expense more broadly, part of the building was designated for the new U-M Geriatrics Center. Private giving from many generous donors — including early commitments from Cis Maisel Kellman, John and Suzanne Munn, the Edward and Helen Mardigian Foundation, and Gifford Upjohn (Ph.D. 1928) — played a pivotal role.

It took two years of committee meetings, focus groups, presentations — and $88 million — but on May 5, 1997, the nine-level Cancer and Geriatrics Center opened for business. More than 800 people attended the center's formal dedication ceremony that June.

"This facility is dedicated to our patients and their families," said Wicha at the event. "Their courage and determination inspires us every day."

TARGETED THERAPIES

Researchers knew little in the 1980s about the molecular biology of cancer or the relationship between genetics and cancer. Then came the 1990s: the decade of the human genome, when scientists began the 13-year odyssey to sequence the building blocks of human DNA. Researchers finally had the data and technology they needed

to discover links between genetic mutations and cancer, and to understand how these mutations made it possible for cancer cells to spread throughout the body. The U-M Cancer Center was a pioneer in the genetic sequencing of tumors from cancer patients, and research continues today under the direction of Arul Chinnaiyan, M.D., Ph.D., the S.P. Hicks Professor of Pathology, who directs the Michigan Center for Translational Pathology.

"Comparing the tumor's genome to the patient's normal genome allows us to identify the genetic changes that drive the tumor's development," Chinnaiyan says. "Our goal is to treat patients with targeted therapies aimed at specific mutations in their tumor. We were one of the first cancer institutions to do this, but now everyone is jumping on the bandwagon and we are training other cancer centers to set up sequencing programs similar to ours."

Cancer cells are programmed to survive and often have multiple mutations. If scientists succeed in blocking the pathological effects of one mutation, cancer cells will switch to a back-up survival mechanism and continue multiplying. So most cancer researchers believe the future of cancer treatment will require multiple targeted therapies tailored to fight a particular patient's tumor. While it may not be possible to cure every patient's cancer, the goal is to keep it in remission for long periods of time.

In the future, Chinnaiyan believes every patient will have their genome and their tumor's genome sequenced as the first step in standard treatment for cancer. Physicians will select a therapy based on their individual genetic "fingerprint."

"It took more than a decade and cost more than $3 billion to sequence the first human genome," says Chinnaiyan. "Now we can do it in a matter of weeks for a fraction of that cost."

But there's a catch: genome sequencing can't help patients without the availability of new targeted therapies. That requires developing more experimental drugs, all of which must be tested in expensive human clinical trials.

"If there's no open clinical trial to refer patients to, all these clinical sequencing efforts end up being a dead end with no clinical impact on the patient," says Chinnaiyan.

Wicha says the Cancer Center's next 25 years will be characterized by intense focus on developing new targeted therapies and testing them in clinical trials with U-M patients. This will require close working relationships with pharmaceutical and biotechnology companies who develop experimental therapies, and more spin-off companies established by cancer center investigators to market their research discoveries.

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To facilitate more clinical trials at the U-M, in July 2012 the university established a Translational Oncology Program located at the North Campus Research Complex. Directed by Diane Simeone, the program provides support services and expert guidance to scientists who want to turn their laboratory discoveries into experimental treatments for cancer.

"Figuring out how to take a key research finding and translate that work into a meaningful clinical trial is really unknown territory for many basic scientists," says Simeone. "Our program is designed to accelerate the pace of that activity."

For example, Simeone notes, U-M researchers have developed a Primary Tumor Xenograft Core in which they implant human tumors into mice to study the effects of new drugs on individual patient tumors. Developing the xenografts is costly and difficult for researchers to do on their own. The Xenograft Core provides this resource for cancer researchers to use. There is also a team of researchers embedded in the Translational Oncology Program who are working to develop new cancer drugs.

"So if a scientist discovers an important target or pathway in cancer, we can develop new targeted drugs right here," she says.

And scientists can use all the help they can get, because taking an experimental drug through pre-clinical laboratory and animal studies followed by human clinical trials is complicated, risky and expensive. Every step in the process is regulated by the Food and Drug Administration. Before an experimental drug is tested in people, the FDA requires detailed documentation showing how the drug works and whether the side effects are tolerable.

Plans are underway to expand the Cancer Center's phase 1 clinical trials program, established in 2008 to test new cancer therapies for safety and efficacy in U-M patients. Positive data from phase 1 clinical trials makes it more likely that pharmaceutical and biotechnology companies will take


Arul Chinnaiyan


Kathleen Cooney


Diane Simeone

on the risk and multi-million-dollar expense of conducting the phase 3 clinical trials required by the FDA. It also gives U-M patients access to experimental cancer therapies that aren't available outside a clinical trial.

THE FUTURE IS NETWORKING

Wicha believes that a key element in accelerating the progress of cancer research is increasing collaborations — not only within the Cancer Center, but with the community, as well as with scientists and physicians nationally and globally. The development of instantaneous Internet communication has facilitated these interactions, breaking down barriers that previously existed.

Diversification of research funding sources is also necessary because the traditional revenue sources — research grants and clinical care revenue — are disappearing. Only 14 percent of NCI research proposals were funded in 2012 and even previously awarded grants are being cut or frozen. At the same time, Medicare, Medicaid and private insurance reimbursements for clinical care are decreasing, which limits the amount of internal funding available to support research.

To facilitate clinical research, Cancer Center investigators have expanded their interactions with pharmaceutical and biotech industries and have founded more than a dozen biotech startups, which are focused on moving research discoveries at the Cancer Center into applications that benefit patients.

Philanthropy will play an increasingly important role in supporting the most innovative research. Instead of relying exclusively on research grants, a diversified portfolio needs to include pharmaceutical/biotech collaborations and philanthropy. Another key collaboration involves formation of integrated networks of cancer centers and community hospitals, with the U-M as the hub for tumor sequencing and clinical trials.

Much of the responsibility for meeting this challenge falls to Kathleen Cooney, who was recently appointed the cancer center's first deputy director for clinical services. One of her tasks is to forge additional alliances between the Cancer Center and community hospitals throughout Michigan.

"We are thinking of a hub-spoke model with the U-M as the hub for complex, multi-disciplinary care of patients and for clinical trials," Cooney explains. "We want to reach out to community oncologists and offer services that aren't available in their area."

Although plans are still in the discussion stage, Cooney says these services could include online consultations with U-M experts or developing a specialty pharmacy to supply oncologists with new cancer drugs and advice on how to manage their side effects.

"The new biologics and targeted agents are wonderful, but they can be challenging for oncologists," Cooney explains. "Older drugs have quite predictable side effects and we know how to manage them, but we're still learning how to manage unexpected complications from these new therapies."

Cooney says feedback from community oncologists indicates they are eager to enroll their patients in clinical trials developed at the U-M. Expanding the statewide clinical trial network is another major priority.

"Our goal is to cast a wider net, and to position the U-M Cancer Center in a way that makes sense," says Cooney. "What makes us unique is our ability to improve the care of cancer patients through scientific discoveries. We are the leaders and best. That is our differentiating factor." [M]

LEFT: SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY
CENTER AND RIGHT: AUSTIN THOMASON, MICHIGAN PHOTOGRAPHY