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## MAKING IT PERSONAL

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The treatment options for many kinds of cancer have improved tremendously over the years. But two particular challenges have dogged cancer researchers for as long as we have been treating patients with this disease.

Why do some patients benefit from a course of therapy while others, apparently with the same or similar cancer, don't?

How do we tailor all of our therapies – surgery, radiation, chemotherapy – to optimize their effects against cancer cells while steering clear of healthy cells and tissue?

We are becoming increasingly skilled at addressing both of these questions, and are truly excited by the opportunity to greatly improve our treatment approaches. By further connecting specific therapies to better defined groups of patients, we are sharpening our attack on cancer and developing ways of making treatments specific to an individual patient.

Tailoring therapy is important. Because the consequences can be so dire, particularly when the disease has reached advanced stages, it's easy to think of "cancer" as a monolithic disease. Cancer actually comprises more than 200-300 separate diseases, with different types affecting the same organ. For reasons we don't yet fully understand, patients with one type of cancer can actually vary substantially from one another. As a result, general approaches to treatment fail many patients.

The focus must now turn to targeted approaches, using new drugs that stifle a specific molecular aspect of one type of cancer. Two spectacular examples of this are Gleevec for treating chronic myeloid leukemia (CML) and Herceptin for treating types of breast cancers that overproduce a certain growth-related protein.

Before Gleevec, half of CML patients died within five years. Today, more than 90 percent reach that milestone. Herceptin, taken with chemotherapy, cuts the recurrence of a particularly aggressive form of breast cancer by 50 percent and reduces a patient's risk of dying of the disease by 33 percent.

However, even these two drugs don't help every patient with the relevant molecular

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target. And medications initially aimed at one type of cancer have sometimes serendipitously succeeded against other types. Gleevec is also quite effective against gastrointestinal stromal tumors.

Many other cancers don't have an obvious single target, but instead rely on multiple molecular pathways and genetic changes that create an environment where they can thrive. Ferreting out the appropriate targets takes time, but progress is being made. This is why it is so important to support research. Current research projects are aimed at finding new targets and better drugs to attack those targets.

Take colorectal cancer, my own research and clinical specialty, for example. There are at least five or six different types of this disease, and within those types individual patients can differ substantially.

The targeted therapy Erbitux blocks a growth-promoting protein common in most types of colorectal cancer. The results in some colon cancer patients have been remarkable. Unfortunately, like many new targeted drugs, Erbitux seems to help only about 10 percent of patients. Researchers have found that certain colorectal cancers with a specific genetic mutation are unaffected by Erbitux. Screening of patients for this mutation has begun – a vital step in more effectively targeting the drug to those who will benefit the most. It's important to know whether a patient is a candidate for this therapy in order to save precious time and avoid a course of treatment that may be doomed to fail.

Erbitux also has been approved for head and neck cancer, where further targeting refinement is under way. Instead of having one drug that treats all patients with a specific type of cancer, the future belongs to drugs that treat patients with common molecular targets across several types of cancer. Instead of being classified according to the affected organ, cancers may eventually be typed by their molecular characteristics.

In the meantime, it's vital to better characterize the drugs that we have now and to match them to appropriate targets present in the tumor.

For example, four oral medications are being tested in an unusual lung cancer clinical trial at my home institution, The University of Texas M. D. Anderson Cancer Center in Houston. Lung cancer patients have a biopsy conducted on a tumor sample before being randomized to receive one of the drugs. Eight weeks later, they are evaluated again, including another biopsy.

Patients with improved or stable disease stay on the first treatment. Those whose disease has progressed drop their initial treatment and receive one of the other three drugs. Over time, the researchers will build a profile of a drug's effectiveness against specific tumor types. Ineffective drugs will be dropped from the trial.

Although this winnowing of therapies to match specific patients is initially expensive, over time it will greatly improve cancer treatment and help us avoid putting patients on

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a totally ineffective course of treatment.

Recent scientific breakthroughs in genetics, proteins and the molecular mechanisms that drive biology have provided a strong foundation for cancer researchers by illuminating how healthy cells form into cancerous cells and how the disease progresses within the body. Funding for such basic science research usually comes through the National Institutes of Health, principally through the National Cancer Institute, as well as through foundations and philanthropic gifts.

Taking that next step, moving ideas out of the lab and into the clinic, is the major challenge that Stand Up To Cancer has embraced. It could not have chosen a better goal.

This process of creating a continuum from bench to bedside is known as translational research, and it enables scientists to carry discoveries made in the laboratory forward into preclinical research and on into the very earliest stages of human clinical trials. Translational research is critical for developing targeted and individualized treatments, but it is the least reliably funded phase of therapy development.

The financing for a smooth continuum has not kept pace with the research. Basic science can rely on funding from the National Institutes of Health (NIH), even with the strain of reduced levels during the last several years. Late stage clinical trials required for new drug approval are financed by pharmaceutical and large biotech companies.

Translational research, however, is much more haphazardly funded. Support comes from a patchwork of institutional funds, philanthropy, investments by small and start-up biotech companies, and limited NIH funding, mainly through the National Cancer Institute's Specialized Programs in Research Excellence (SPORE) grants.

Stand Up To Cancer is not only providing new support for this important area of research; it is also encouraging fresh approaches that more rapidly and accurately translate scientific findings into new treatments for cancer. The collaborative Dream Team model established by Stand Up To Cancer will improve patient care and provide innovative examples of new research approaches.

My colleagues in the American Association for Cancer Research, the world's oldest and largest professional organization dedicated to advancing cancer research, not only whole-heartedly welcome this groundbreaking approach, but are also supplying ideas to Stand Up To Cancer's scientific advisory committee for important translational research projects.

Stand Up To Cancer is generating an unprecedented force behind our effort to maximize what we know now about this disease, to create lines of communication and collaboration, and to advance the pursuit of optimal care for people with cancer.

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