Upcoming Battles in the War on Cancer

Three of the challenges in implementing personalized medicine in the next decade

The vision has been clear for more than a decade: Some day, a cancer patient will have her germline DNA decoded and compared with the genetic material in her tumor cells. Treatment will be based on the molecular make-up of the tumor, not its organ of origin.

To that end, researchers around the world have made extraordinary discoveries and scientific advances. They have unmasked oncogenes and tumor-suppressor genes for targeted therapy, improved preclinical models of disease, developed monoclonal antibodies to harness the body's immune system in attacking tumors, and turned to nanoparticles to deliver a toxic payload to cancer cells. Survival rates have improved, but cancer's heterogeneity and the inability of most therapies to produce a durable response have stymied the adoption of personalized medicine.

As the University of Chicago's Michael Maitland, MD, PhD, and Richard Schilsky, MD, wrote in a November article (CA Cancer J Clin 2011;61:365–81), “Although we savor the promise of a new era of personalized oncology, we are more transitioning to that era than truly there.”

Aside from a steady infusion of cash for research and innovative treatments, what will it take for personalized medicine to become the standard in cancer care in the next 10 years? Experts offer numerous answers to that question, but many of their responses hit three broad themes: rethinking and rebuilding clinical trials, raising the bar on data sharing and standardization, and assembling multidisciplinary teams to make sense of the data.

Genetically Informed Clinical Trials

Traditional Trial

1 box = 10 random patients

Phase II 60 patients

Phase III 3,000 patients

Personalized Trial

1 box = 10 genetically screened patients paired to potential drug

Phase II 60 patients/drug

Partial confirmation

Phase III 300 patients/drug

Crizotinib (Xalkori; Pfizer), a drug for patients with non-small cell lung cancer whose tumors carry the EML4–ALK gene fusion, gained approval from the U.S. Food and Drug Administration following a genetically informed clinical trial, similar to the hypothetical example above. Using a companion diagnostic test, which was also approved, researchers only enrolled patients carrying that particular mutation in a clinical trial. The required number of patients was smaller than in a traditional drug trial because the study focused on patients who were most likely to respond based on their tumor's make-up.
RETHINKING AND REBUILDING CLINICAL TRIALS

“There are a lot of great ideas out there and a lot of targets, but clinical trials take too long and cost too much money for us to pursue all of them,” says Safi R. Bahcall, PhD, founder and president of Synta Pharmaceuticals. According to widely cited estimates, the cost of bringing a new drug to market runs $1.8 billion, though some experts say the true cost is at least twice as much (Nat Rev Drug Discov 2009;8:959–68). Add in an uncertain regulatory environment and the slim chance of moving a drug from preclinical studies through phase III trials to approval—about 1%—and “the system becomes unsustainable,” Bahcall says.

Obtaining molecular profiles of patients’ tumors prior to study enrollment may save time and money in the end. That’s because a drug can be tested in the subset of patients most likely to respond to it, meaning that fewer patients need to be enrolled in the trial to yield a statistically significant result, explains Levi Garraway, MD, PhD, coleader of the genetics research program at the Dana-Farber/Harvard Cancer Center. This was the case with crizotinib (Xalkori; Pfizer), a drug that hit the market just 4 years after target discovery, because lung cancer patients who received the agent were tested for the EML4–ALK gene fusion, which crizotinib targets, before enrolling in a clinical trial.

Researchers may also test a panel of targeted drugs early on, see which agents elicit the strongest responses compared with placebo in given subpopulations and then proceed with a phase III trial in just one or two of them.

Finding biomarkers to help monitor cancerous activity might quicken the pace of discovery, too. Researchers studying HIV can easily determine whether an agent is working by measuring the amount of the virus in a blood sample. But for most cancers, such a biomarker doesn’t exist.

“Even though we have lots of drugs, we don’t always know whether they are really working,” says Garraway. Examining biopsy samples or circulating tumor cells not only at diagnosis but also throughout treatment might yield that valuable information but also throughout treatment might yield that valuable information.

Cancers Caused by Infectious Agents

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Cancer</th>
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<tbody>
<tr>
<td>Epstein–Barr virus</td>
<td>Stomach cancers, Hodgkin and non-Hodgkin lymphomas, and nasopharyngeal cancers</td>
</tr>
<tr>
<td>Hepatitis B virus, hepatitis C virus</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Helicobacter pylori infection</td>
<td>Stomach cancers</td>
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<tr>
<td>Human immunodeficiency</td>
<td>Kaposi sarcoma and non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Cervical, anogenital, head and neck, and oral cancers</td>
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Globally, more than 18% of all new cancer cases can be attributed to infectious agents (not counting HIV-associated cancers). Immunization or elimination of the underlying infections, when done early, may prevent a significant number of cancers.

Thanks to an increasingly sharp focus on prevention, medicine has recorded numerous victories in the War on Cancer, including the following:

- the development of vaccines against hepatitis B virus (HBV) and human papillomavirus (HPV)
- the creation of smoking-cessation programs and nicotine replacement therapies
- the use of colonoscopy to detect and remove polyps and precancerous lesions before they become malignant.

“But we’re still not where we want to be,” says Barnett Kramer, MD, MPH, editor-in-chief of the National Cancer Institute’s PDQ Screening and Prevention Editorial Board. He notes, for example, that HPV vaccines don’t protect against every cancer-causing strain of the virus. Also, findings from observational studies hinting that certain vitamins and nutrients might protect against cancers haven’t been borne out in large, randomized controlled trials.

“A lot of our clinical-trial efforts have been based on epidemiology, and we’ve learned from those,” says Scott M. Lippman, MD, chair of the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center. “But our approach going forward must increasingly incorporate molecular biology.” He says that allocating additional resources to study premalignant tissue samples with next-generation technologies (Can Prev Res 2011;4:803–17), might help researchers find and target the proverbial needle in the haystack—the molecular switches that can turn on an aggressive, life-threatening cancer.

Lippman’s colleague, Waun Ki Hong, MD, head of the Division of Cancer Medicine at MD Anderson, advances the concept of reverse migration (Cancer Prev Res 2011;4:962–72), in which targeted drugs developed for patients with advanced/metastatic disease are tested in earlier disease and as adjuvant therapy in patients with the same cancer subtype. If they are shown effective at these stages, they can then be tested in patients with precancerous lesions and in patients at high risk for the same disease, based on genetic and molecular profiles. Tamoxifen (Nolvadex; AstraZeneca), initially used as therapy for metastatic breast cancer, followed just such a path.

The reverse migration concept dovetails with a concept propounded by Elizabeth Blackburn, PhD, called cancer interception—actively combating cancer and carcinogenesis at earlier and earlier stages with advanced technologies and targeted drugs (Can Prev Res 2011;4:787–92).

“I am hopeful that these strategies will allow us to prevent even more cancers,” says Hong.
THE ACT THAT SET THE STAGE

In his 1971 State of the Union address, President Richard Nixon declared war on cancer: “The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease.”

On December 23, 1971, Nixon signed the National Cancer Act, which significantly expanded the authority and responsibility of the National Cancer Institute (NCI). The legislation mandated that:

- the President appoint the NCI director, who would develop a focused cancer research program with input from a presidentially appointed 18-member committee (the National Cancer Advisory Board) composed of scientists and physicians as well as members of the public
- a 3-member panel review the program annually and submit a progress report to the President
- the NCI’s annual budget be submitted directly to the President
- the NCI director be given the authority to create 15 cancer centers; appoint advisory committees; expand research facilities; award research grants and contracts; collaborate with federal, state, and local agencies and private industry; conduct cancer control activities; and establish an international cancer research data bank to collect, catalog, disseminate, and store cancer research findings.

Although subsequent laws have been passed to promote prevention efforts and research on specific cancers, the broad outlines of the Act remain intact today.

ASSEMBLING TEAMS TO MAKE SENSE OF IT

The pace of technological advancement has been astonishing. Early gel-based sequencing techniques have given way to capillary sequencing methods. To hunt for genetic amplifications, deletions, translocations, and variations in copy number, researchers can perform whole-genome sequencing, RNA sequencing, and whole-exome sequencing. Massively parallel sequencing may soon become the norm.

Integrating proteomic, epigenetic, and other forms of data will give researchers additional insights into subsets of cancers. But rather than simply latching on to additional technologies, some cancer experts point to the need to better understand the data already generated, which will require building multidisciplinary teams. “Separating wheat from chaff—and doing it quickly enough for patients to benefit—remains one of our key analytical challenges,” says Stephen Gruber, MD, PhD, MPH, director of the USC Norris Comprehensive Cancer Center. The goal is to find actionable mutations, but most mutations are passenger mutations whose function remains unknown.

“Some would argue that we’re missing information contributed by proteomic variation,” he continues. “I say, ‘One step at a time.’ We will get there, but we need to walk before we learn how to run.” —Suzanne Rose

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