Tailoring Treatment in Translational Cancer Research

AN INTERVIEW WITH RAYMOND N. DuBois, MD, PhD

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Dr. DuBois

For Raymond N. DuBois, MD, PhD, a combination of new technologies, basic science discoveries, and groundbreaking clinical study design make for an exciting new landscape in translational cancer medicine. The provost and executive vice president of the University of Texas M. D. Anderson Cancer Center in Houston, Dr. DuBois oversees and participates in research that will result in better targeted treatments for cancer patients.

In the past, Dr. DuBois notes, most cancer treatment was based on a “one-size-fits-all” philosophy. For example, 20 years ago, there was only 1 drug given to all patients with colon cancer. Now, with 5 or 6 different drugs available to treat colon cancer, it is possible to examine tumors in the lab and determine which drug is most likely to reduce or eradicate them. “That really is a complete change in how we look at the disease,” Dr. DuBois says. “We have to examine each cancer individually to see what sort of collection of mutations is present, what alterations there are in signaling pathways that make that cancer more or less responsive to certain drugs.” Today, he observes, “we’re tailoring the treatment so that it can more appropriately fit what the molecular fingerprint is for each individual cancer.”

Such novel approaches are made possible because of improvements in determining the phenotype and genotype of cancerous tumors. As Dr. DuBois explains, now “it’s possible to sequence an entire cancer genome in about 7 days.” With further advances, that time frame can be shortened even more, meaning, he hopes, that patients can initially be given the treatment best suited to their situations. This approach would help avoid a delay in the delivery of the treatment regimen most likely to help them fight the disease and lessen the risk for cancer cells developing resistance to treatment later on.

The Cutting Edge of Cancer Research

At M. D. Anderson, Dr. DuBois’s responsibilities include oversight of the center’s research and training programs. The institution, founded in 1941, has contributed to the evolution of cancer treatment from almost purely surgical strategies through the advent of radiation and chemotherapy. Now M. D. Anderson is at the forefront of the effort to tailor treatments to the individual cancer because, as one of the nation’s and the world’s most prominent cancer care centers, it has the resources to perform the kinds of studies necessary to inform future clinical decisions. As Dr. DuBois points out, in addition to the expertise of the M. D. Anderson staff, “we have a very large volume of patients—we see

over 90,000 patients a year, and 30,000 of those are new cancer diagnoses—so we’re able to run a lot of these trials simultaneously to advance the translation of basic research that is done both here and all over the country into some sort of clinical treatment that could be useful for the patient.”

The M. D. Anderson Web site (www.mdanderson.org) reveals the wide range of studies performed under the aegis of the institution. One of the most ambitious projects is the BATTLE trial (Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination), a trial with a novel and flexible design focused on fast-progressing lung cancer because patients’ responses to treatment can be quickly determined. How does the BATTLE trial differ from conventional clinical trials? “We have 4 different arms in the study with different treatment regimens,” Dr. DuBois explains. “We’re taking biopsies of the primary tumor and then measuring over 20 different either genetic or protein or histopathological endpoints and then deciding based on those 25 measurements which treatment the patient should go on.” Patients whose cancers progress over the first 8 weeks of 1 regimen are switched to another regimen based on the profile of their cancer.

This is not an easy study to perform, Dr. DuBois emphasizes, for reasons both logistical and financial. Early on, critics argued that patients would choose not to participate because of the invasive biopsies, numerous restrictions, and intensive follow-up required. In fact, the 300 patients needed for the first trial were quickly recruited, and the first trial has been so successful that a second and third BATTLE trial have already been designed.

At M. D. Anderson, traditional practices are also challenged in care delivery. The institution has developed multidisciplinary care centers targeted at one form of cancer, such as sarcoma or breast cancer. A patient will see doctors and technicians focused on one cancer type and housed together, making visits more efficient for patients and enabling collaboration among staff. As Dr. DuBois observes, basic scientists “can really interface with a multidisciplinary care clinic and get clinical information, tissues to study, images from the patients, and then some information on what types of treatment are effective.”

This organizational strategy also allows for rotations that give medical fellows introductions to different cancers, Dr. DuBois notes. M. D. Anderson has a large educational component, serving annually hundreds of fellows, about 5,000 trainees, and many of the graduate students attending the Graduate School of Biomedical Sciences at the University of Texas in Houston. For individuals performing doctoral or postdoctoral work, the cancer center offers primer courses in clinical medicine and clinical research. Dr. DuBois hopes these will serve the students later in their careers when they may be able to recognize the potential to translate their basic science discoveries to the clinic.

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Colon Cancer: The Road to Cure and Prevention

Dr. DuBois's contributions to cancer research began long before he assumed the position of chief academic officer at M. D. Anderson in mid-2007. At the start of his training, however, he would not have foreseen the translational framework that now informs his investigations. A few years into a PhD program in biochemistry at the University of Texas Southwestern Medical Center in Dallas, he began to recognize his deep interest in the clinical implications of his basic research. As a result, he decided to pursue a medical degree at the University of Texas Health Science Center in San Antonio and a residency and fellowship in internal medicine and gastroenterology at Johns Hopkins University School of Medicine in Baltimore, Maryland. There, after 2 years of clinical training, Dr. DuBois joined the Hopkins-based laboratory of Daniel Nathans, MD, where, Dr. DuBois says, "I really got a primer in the latest techniques in molecular biology." He subsequently joined the faculty at Vanderbilt University in Nashville, Tennessee, and there continued research that led to the discovery that selectively inhibiting COX-2, an enzyme associated with inflammation and tumor growth, reduced the growth of cells in colon cancer.

Dr. DuBois's success and continuing research in this area have led to many honors and increased responsibilities. Before coming to M. D. Anderson, Dr. DuBois served as the director of the Vanderbilt-Ingram Cancer Center in Nashville. Among other awards, he received the

2004 Dorothy P. Landon Prize for Translational Cancer Research, issued by the American Association for Cancer Research, for which he served as president for the 2008–2009 term ending in April.

In addition to his administrative responsibilities at M. D. Anderson and his service on national advisory boards, Dr. DuBois maintains his own laboratory. With a research program funded by grants from the National Institutes of Health (NIH), he reports that now "we're investigating some very basic changes in inflammatory pathways, how inflammation causes progress of cancer, and what targets might be available" for treatment, either to prevent cancers or to treat patients appropriately once cancer has developed.

Biologically-Driven Clinical Decision Making

The research Dr. DuBois does and facilitates at the institutional level falls under what is often referred to as personalized medicine, but he is reluctant to invoke that ambiguous term. "A better way to look at it," he says, "may be the phrase 'biologically-driven clinical decision making.' We want to decide what clinical action to take based on the biology of disease." In the case of cancer, he explains, what determines the clinical action is "the biology of the particular tumor in the individual patient."

There are still obstacles to the goal of understanding an individual disease in order to treat it most effectively. The first BATTLE trial revealed the challenges involved in complex and adaptive clinical trials. The process required separate applications

to the Food and Drug Administration (FDA) for Investigational New Drugs, and also several Institutional Review Board approvals. The FDA approval process was cumbersome because the traditional clinical trial model does not easily accommodate combinations of drugs, especially those not produced by the same pharmaceutical company, or diagnostic tests that determine the treatment regimen to which clinical trial subjects will be assigned. "It's just not the way that cancer clinical trials are usually done," Dr. DuBois acknowledges. However, initial trials with this type of design will assist regulatory agencies to make the process easier in the future when, Dr. DuBois predicts, there will be more clinical trials for diseases in addition to cancer that could determine which treatments are given to patients.

Dr. DuBois considers the issues of funding and recruitment critical to the success of translational medicine. He notes that for the past several years, federal funding for the NIH has actually decreased because of rising inflation, and some members of the next generation of scientists and clinicians have been discouraged from considering biomedical research as a career. In the absence of sufficient federal funding, Dr. DuBois says that at M. D. Anderson "one of the ways we've been trying to help here is to

raise more philanthropic funding for these types of really high-priority, high-risk projects." Up until last fall, the institution was fairly successful in this endeavor. Now, he notes, the current economic climate is affecting

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all facets of health care delivery. Nevertheless, Dr. DuBois is hopeful about the future of translational medicine.

Dr. DuBois knows from experience how rewarding it is when a finding can make a real difference to a patient's health and how long valuable discoveries can take. His COX-2 inhibitor research ultimately led to FDA approval for use of a drug for patients with familial adenomatous polyposis, a genetic disease of the colon that causes polyps to develop and turn malignant. His current projects focus on other signaling pathways, and he is eager to see that research move through clinical trials into the clinic. "But," Dr. DuBois warns, "from start to finish it's anywhere from a 10- to 20-year process to get some discovery in the laboratory translated into the clinic." In his estimation, that time needs to be shortened significantly through the use of new technologies, including faster whole genome analysis and proteomics that allow the simultaneous analysis of multiple proteins within one sample. "Our challenge now is to learn how to deploy all this technology into the translational research realm," he says, thereby reducing the time a finding takes to travel from the lab to the clinic to a 5- to 10-year-period.

It is an ambitious goal, but, at M. D. Anderson and in his own lab, Dr. DuBois is doing everything he can to facilitate the research, training, and outreach needed to evolve biologically-driven clinical decision making from a novel experiment to normal practice.

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