Molecular Targeting Offers Specific Drugs for Specific Cancers

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BETHESDA, Maryland—The understanding of carcinogenesis that has emerged from molecular and genetic studies has provided a new vision of treatment, commonly called molecular targeting. In it, debilitating cytotoxic drugs will give way to agents that target specific proteins that mark specific cancer cells.

Every 3 years, the National Cancer Institute (NCI) asks researchers, advisory panels, and advocacy groups to recommend "extraordinary opportunities for investment," which it defines as "broad-based, overarching areas of scientific pursuit that hold tremendous promise for significantly expanding our understanding of cancer." This is the fourth in a series of interviews exploring the progress and promise of NCI’s six current extraordinary opportunities: Genes and the environment (January 2002); cancer imaging (February 2002); defining the signature of cancer cells (May 2002); molecular targets of prevention and treatment (below); research on tobacco and tobacco-related cancers; and cancer communications.

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In recent years, the National Cancer Institute has focused its drug development efforts on defining targets and agents to attack these targets. Some targeted drugs would cause tumors to shrink and disappear. Others would block tumor growth and stabilize tumor size.

The previous article in this series described NCI’s cancer signature program. In this interview, Edward A. Sausville, MD, PhD, of the Division of Cancer Treatment and Diagnosis, discusses the Institute’s related program in molecular target research with Patrick Young, ONI’s Washington bureau chief.

ONI: How do molecular targets of prevention and treatment differ from the signatures of cancer cells?

Dr. Sausville: There could be some overlap. A signature defines molecules that are differently expressed in different tumors and in comparison to normal tissues. These molecules may then actually be targets in their own right and, thus, the basis for starting a drug discovery campaign. It is also possible that some signatures might be suitable in a diagnostic sense but not really have a role in treatment or prevention. The key point is that we are going to get information from the signatures program, which then becomes useful for drug discovery.

ONI: What are the advantages of selectively attacking molecular targets?

Dr. Sausville: The hoped-for outcomes are therapeutic agents that seek out specific targets, are fairly well tolerated, and have a wide range between their efficacious concentrations and their toxic concentrations. Unfortunately, the agents that we have at the moment in the therapeutic armamentarium for cancer have a fairly close relationship between active and toxic concentrations.

ONI: Are there any downsides to this approach?

Dr. Sausville: The downsides could emerge if it turns out that individual tumors are sufficiently different from other individual tumors. Then the signature becomes, shall we say, an individual letter rather than a journal of limited subscription. There is concern that ultimately you would split the commonly defined diseases into progressively smaller subsets and, ultimately, to a single patient. One has to be concerned that the pharmaceutical industry is enthusiastic about cancer drug discovery and development relevant to its usual way of doing business, which is to look for drugs that are broadly applicable. If the set of patients that will benefit from a particular discovery effort is small, one has to be concerned that corporate enthusiasm will be tempered.

ONI: Will this targeted approach defeat resistance, or will resistance remain a major problem for patients and oncologists?
**Dr. Sausville:** The truth is probably going to be somewhere in the middle. Certainly, the targeted approach of bringing active drugs to targets that are uniquely susceptible to them should circumvent resistance, which, up to this point, has marked the common tumors. However, one must remember that all cancers have a degree of genetic instability. The inability of therapeutic agents to select the targets of their receiving cells, when the cells have changed in response to the selection pressure of the drug, will always exist. In fact, we have already seen that with Gleevec [imatinib mesylate]. So I think resistance is going to occur, and it will reflect the plasticity of the genome inherent in tumors.

**ONI:** What research issues need to be resolved before targeted therapies become fairly common in clinical practice?

**Dr. Sausville:** We need a better understanding of which particular subsets of targets are expressed in the common tumors. There is a good deal of research activity on this front in terms of defining newer ways of categorizing the different types of cancer. A little less in hand is an understanding of how combinations of potential targets can be usefully addressed. It is unusual for a drug’s action to be aimed at a single target. Gleevec was a remarkable exception in that regard. I think that we are going to find that common tumors have overlapping sets of molecular targets that will need to be addressed either by combinations of single agents or with molecules designed to affect more than one class of target. We have not yet defined how to make drugs with the ability to affect collections of different targets.

**ONI:** How is NCI promoting this effort in molecular targeting?

**Dr. Sausville:** In 1999-2000, we undertook an innovative molecular drug discovery program, which initially focused on forming cooperative agreements between NCI and academics or between academics and small business concerns. The goal was to provide funding to people knowledgeable about potential targets so they could flesh out whether their target had properties that one would want ultimately for therapeutic development. We have had nine successful competitors in the first round, and a number of grant initiatives that were of smaller size in terms of dollars. There is another initiative for interdisciplinary research in which academic groups work on targets that are already in early clinical trials to assess whether these candidate drugs are actually affecting their targets.

**ONI:** How many of these targeted drugs are actually in phase I, II, or III testing?

**Dr. Sausville:** There are several dozen molecules in phase I and II trials, including many of the kinase antagonists which have generated a lot of enthusiasm other types of agents directed at signal transduction, and antiangiogenesis drugs. There are a smaller number at the phase III level. That, in part, reflects the need for data to mature as well as the fact that not all drugs that are initially evaluated have the pharmaceutical properties in humans that you want for a phase III endeavor.

**ONI:** Do targeted molecules pose problems for getting the clinical trial data that the FDA needs to approve these drugs?

**Dr. Sausville:** The FDA is not capricious in this regard. It needs data pertaining to safety and efficacy, and the issue is what you are going to regard as effective. Traditionally, effective drugs have been viewed as those that have some impact on the survival of patients. That is the gold standard that has served well over the years. With this new type of drug, evidence on survival may be somewhat long in coming. How can we determine whether surrogates for this good outcome could be defined at an early stage? The tools to do that are being developed, and I think there will be a renewed interest in exploring that question with both clinical investigators and the FDA.

**ONI:** FDA is trying to figure out exactly what endpoints it needs. When do you envision these therapies having a significant impact on cancer prevention and treatment?

**Dr. Sausville:** One would like to hope that it will be in the near term, 2 to 5 years. At one level, we believe we are already having an impact on the treatment of chronic myelogenous leukemia with Gleevec. We look forward with great anticipation to the antagonist molecules, which look potentially very promising. I am referring to such agents as OSI-774 [Tarceva], an inhibitor of epidermal growth factor receptors. Phase I evaluations look interesting. The proteasome antagonist PS341 [now known as MLN341] has caused some noteworthy responses in myeloma, which does not respond well to conventional therapies beyond a certain point. The sense is that a lot of very interesting things are going on that deserve exploitation. There is certainly hope that in the time frame that I mentioned, we will be looking at really making people’s
lives better as the result of this general effort.

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