Perspective

SERIES on targets for cancer therapy

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Taking aim at novel molecular targets in cancer therapy

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During the past 2 decades our understanding of the molecular basis of cancer has grown exponentially. In contrast, this period has witnessed only modest improvements in the treatment of the most common forms of cancer. This issue of the *JCI* contains the first 2 of a series of papers devoted to translating our growing understanding into new drugs to treat cancer patients.

Cancer remains a leading cause of death in this country. Next year over 500,000 Americans will die of this disease. In addition, cancer also causes a great deal of emotional and physical suffering. Since 1971, when President Richard Nixon signed the National Cancer Act, there have been dramatic improvements in outcomes for patients with selected cancers, such as childhood leukemia and testicular cancer, and we have seen measurable, but modest, improvement in outcomes for cancer patients in general. However, the treatment of the most common forms of cancer, such as lung cancer, breast cancer, and colon cancer, remains abysmal for patients whose disease cannot be controlled by surgery. Clearly, we need to develop cost-effective strategies to diagnose patients earlier. In addition, we need drugs that will either prevent the emergence of malignant cells or eradicate existing ones.

The list of FDA-approved drugs added to the cancer physician's armamentarium during the past 2 decades is painfully short and includes drugs such as etoposide, carboplatin, paclitaxel (Taxol), topotecan, and gemcitabine, none of which was devised based on a working understanding of the genetic abnormalities that lead to cancer. Rather, these drugs, like most chemotherapeutic agents, were identified based on their ability to kill dividing cells. This limited approach at least partly accounts for the meager therapeutic index associated with most such drugs available today. Indeed, arguably the biggest advances in the medical treatment of cancer over the past 2 decades relate to the development of drugs, such as potent antiemetics and hematopoietic growth factors, that aim to treat or prevent the side effects associated with chemotherapy. Now, however, a picture of the molecular basis of cancer is emerging.

This picture remains fuzzy and incomplete, so the choice of molecular drug targets, while less empirical than in the past, will likely remain an imprecise science in the near future. It is clear, however, that cancer cells must overcome multiple obstacles to proliferate in vivo. These obstacles arise because of molecular safeguards that prevent cells from growing at the wrong time or place. Some of these safeguards are cell-intrinsic. Others involve complex interactions between cells and their microenvironment.

In an accompanying Perspective article in this issue of the *JCI*, I discuss some general considerations for choosing anticancer drug targets to take advantage of idiosyncracies of tumorigenesis in order to attain potent and tumor cell–specific cytotoxicity. Also in this issue, Eli Keshet and Shmuel A. Ben-Sasson consider a different approach to the control of tumor progression, the development of drugs that block angiogenesis in tumors. The next issue of the *JCI* features reviews on 2 fundamental and intimately related cellular processes, cell division and apoptotic cell death. Each of these processes offers an ample range of promising targets for cancer therapies. Geoffrey Shapiro and Wade Harper will provide an overview of opportunities for drug discovery related to cell-cycle control. William Sellers and David Fisher will discuss the development of drugs that affect the regulation of programmed cell death. This series will conclude in the early January 2000 issue with a pair of articles on specific molecular targets. There, Jay Gibbs will discuss drugs that affect signaling by growth factors and their receptors, and Brian Druker and Nicholas Lydon will discuss lessons learned from the development of a promising therapy for chronic myelogenous leukemia — a small-molecule inhibitor of the bcr-abl fusion protein. This series of papers is not, by necessity, all-inclusive with respect to the number of targets and strategies being explored. For example, telomerase is but 1 of several interesting targets that is not covered due to space limitations. Rather, we intend to provide a sense of the range of anticancer drugs that are likely to be tested in humans over the next decade.

One might reasonably ask why progress in the war on cancer has been so slow, especially when compared with another Presidential directive, namely, John F. Kennedy's challenge to put a man on the moon. As noted by National Cancer Institute director Richard Klausner, however, putting a man on the moon was primarily an engineering problem (personal communication, 1998). All of the relevant laws of physics were known by the time of Kennedy's inauguration. In contrast, curing cancer has been primarily a scientific problem. Our understanding of molecular biology in general, and cancer molecular biology in particular, was in its infancy at the time of Richard Nixon's challenge to cure cancer. It will be some time before the optimal strategy for eliminating cancer becomes completely transparent and unambiguous. In the meantime, our guesses regarding strategy are becoming increasingly more informed. With some measure of luck, 1 or more of the strategies outlined in this series will make a significant impact on cancer care in the next decade. Our patients are waiting anxiously.