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The Prevention and Treatment (and Cost) of Cancer

More than 35 years after President Nixon declared a War on Cancer, this insidious disease still affects one in four U.S. families. Although deaths have been slowly declining since the 1990s, more than a half-million Americans will die from cancer this year. The hope that scientists would find a single "cure" dissolved once it was revealed that cancer is actually a set of hundreds of diseases with distinct causes, characteristics, and responses to treatment. The burden of dealing with this often intractable disease is exacerbated by the increasing cost of care, which reached a total of $78.2 billion for 2006 (*1*).

The good news is that tremendous progress has been made in preventing and treating many of the subsets of cancer. In fact, a growing number of cancers can currently be cured by surgery, chemotherapy, and radiation, especially if they are discovered early enough. More advanced screening methods are being developed constantly, and a genetic test can now warn women of a predisposition to breast cancer. New vaccines directed against cancer-causing viruses have the potential to stop cancer before it even begins.

Many of the exciting discoveries in cancer research are occurring at the interface of chemistry and biology. High-throughput screening of massive small-molecule libraries allows scientists to cast a wide net when searching for useful compounds. Once a promising compound has been found, the ability of chemists to fine-tune these "hits" with an array of modifications means that specificity can be honed to the target of interest.

One example of this strategy is the development of the tyrosine kinase inhibitor imatinib (Gleevec). It was known that a hallmark of chronic myelogenous leukemia (CML) is a fusion of the *Bcr* and *Abl* genes that results in constitutive activation of Abl's tyrosine kinase activity. Recognizing that Bcr-Abl could be a molecular target for treatment, researchers screened small-molecule libraries and identified a family of 2-phenylaminopyrimidines as lead compounds. A host of derivatives was then tested, and a molecule modified with benzamide and methyl groups displayed greatly enhanced specificity and activity (*2*). That compound, now sold as Gleevec in the U.S., is the first-line treatment for CML and can induce complete remissions in some patients.

Creative and sophisticated new methods for the identification of inhibitors continue to populate the literature. Until recently, existing screens examined the biochemical effects of compounds *in vitro* or followed the behavior of cells as a read-out. Allen et al. (*3*) reported an assay that bridges this gap by using fluorescent labels to monitor kinase activity in live cells. High-throughput screening in this system allows the target protein to be examined in its normal cellular environment and helps correlate cellular effects with specific biochemical events.

The ability of chemists to generate new and potentially useful derivatives has also seen exciting breakthroughs. Kwon et al. (*4*) recently described a novel approach for generating analogues of natural products by using polyketide synthases (PKSs) and post-PKS tailoring enzymes. Using these modifying enzymes in various combinations, they were able to create a diverse set of products. Because the reactions were performed on glass microarray slides, the spots where the reactions occurred became sites for testing these compounds against

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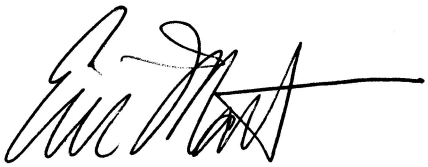
tyrosine kinases. This approach generated three novel compounds that inhibit the Src-family kinase Fyn in the low picomolar range.

As such work continues apace and the number and quality of diagnostic and treatment options for cancer grow, so too does their cost. Some treatments are priced well over $50,000 a year (*5*), leaving sizable payments even for the well-ensured. Those without insurance, more than 15% of the population, end up impoverished if they can pay for treatments at all. Genetic tests that expose a bias toward developing cancer may save lives, but they may also cause patients to be excluded from the very insurance they need to cover their treatment. Promising new therapies and technologies are becoming available, but the U.S. must make the medical coverage of its citizens a priority for these to reach the many who need them. The urgency of this issue was recently accentuated by the fact that the American Cancer Society devoted the entirety of its 2007 advertising budget to the consequences of inadequate health coverage.

The War on Cancer slogs onward, but battles are being won. Thousands of new compounds are making their way through clinical trials, and countless more are being developed. Many of these potential drugs owe their existence to talented chemists and chemical biologists, and it is exciting to see the fruits of their research come to bear in the clinic.



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