Basic Research Plays a Key Role In New Patient Treatments

The promise that basic research holds for society can be difficult to explain, but in recent months, examples of how basic research findings can be directly translated into the development of effective, new drugs for the treatment of patients are emerging.

Topotecan

In 1958, a screening project for natural sources of steroids led the late Jonathan Hartwell, M.D., from the National Cancer Institute, and Monroe Wall, Ph.D., then at the U.S. Department of Agriculture, to discover the anti-tumor activity of an extract from a Chinese tree, *Camptotheca acuminata*. This led NCI to support Wall and Mansukh Wani, Ph.D., both at the Research Triangle Institute, Research Triangle Park, N.C., in a quest to discover the active ingredient of the extract. Camptothecin was isolated in 1966, and now 30 years later SmithKline Beecham Pharmaceutical Co., Philadelphia, which developed the derivative topotecan under a National Cooperative Drug Discovery Group grant, has received approval from the Food and Drug Administration to market topotecan (Hycamtin®).

Topotecan is a semi-synthesized derivative of camptothecin, and is intended as a second-line defense against ovarian cancer. In phase III trials examining topotecan as a treatment for recurrent ovarian cancer, response rates were 10% and 15% among patients who had not responded to prior chemotherapies, and 25% to 30% among patients who had.

The elucidation of topotecan’s and its parent compound’s mechanism as an inhibitor of the enzyme topoisomerase-I was also made possible by basic research efforts supported by NCI and other institutions.

“The approval of topotecan is significant because it is the first of a series of drugs with a new mechanism of action,” said Edward Sausville, M.D., associate director of NCI’s Developmental Therapeutics Program. “It also re-emphasizes the importance of natural products and their derivatives in the search for better cancer treatments.”

HIV Protease Inhibitors

Another example of laboratory-to-treatment research comes from crystallography, an often undervalued research tool.

The usefulness of crystallography in the development of new chemotherapeutic agents was demonstrated by the creation of HIV protease inhibitors based on three-dimensional images developed using crystallographic techniques.

In 1989, Alexander Wlodower, Ph.D., now director of the Macro-molecular Structure Laboratory, a contract-funded lab at NCI’s Frederick Cancer Research and Development Center, and his team pieced together the puzzle of the HIV protease enzyme’s structure producing a 3-D image. They were then able to solidify the enzyme with a substance docked in the active site. This second 3-D picture revealed the very different shape the enzyme assumes at work as opposed to at rest.

From these structures, various pharmaceutical companies built inhibitors. These rationally designed inhibitors, approved by the FDA in 1995, arrest the action of protease that is essential for the maturation of the AIDS virus: no protease, no virus.

Results from initial clinical trials, reported at the 3rd Conference on Retroviruses and Opportunistic Infections in Washington, D.C., earlier this year, have shown that the inhibitors dramatically reduce detectable virus and increase CD4+ T-cell counts in HIV-infected individuals.

“This major achievement emphasizes that basic research is worth the effort,” said George VandeWoude, Ph.D., special advisor to the director of NCI’s Division of Basic Sciences. “The fact that the entire process, from structural determination to FDA approval, took only 7 years, is really very exciting.”

— Catherine Law