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Trio to Receive Lasker Award

The Albert and Mary Lasker Foundation announced today that Howard Hughes Medical Institute investigators Brian J. Druker at Oregon Health & Science University and Charles L. Sawyers of Memorial Sloan-Kettering Cancer Center, will join Nicholas J. Lydon, formerly of Novartis, in receiving the 2009 Lasker-DeBakey Clinical Medical Research Award.

The three scientists are being recognized for groundbreaking work on the treatment of chronic myeloid leukemia. Their research has led to the development of drugs that have converted chronic myeloid leukemia (CML) from a fatal cancer into a manageable condition for most patients.

The first of these drugs, Gleevec (imatinib), is one of modern oncology's greatest success stories. The first cancer therapy to avoid damaging normal cells by specifically targeting a cancer-causing molecule, Gleevec virtually halts the progress of CML. Druker identified the compound that ultimately became Gleevec, and was responsible for shepherding the drug through clinical trials. Gleevec is now the treatment of choice for patients with CML, and its success has opened the door to developing targeted therapies for other cancers.

Some patients with CML, however, eventually develop resistance to Gleevec and their cancer returns. Sprycel, or dasatinib, is a second-line therapy developed by Sawyers -- who was also one of the principal investigators in the early clinical trials for Gleevec -- that overcomes Gleevec resistance and effectively stops the progression of CML in most of these patients.

Including Druker and Sawyers, 11 current HHMI investigators have won Lasker Awards. The awards, which carry an honorarium of \$250,000, will be presented at a ceremony on October 2 in New York City.

Since 1945, the Lasker Awards program has recognized the contributions of scientists, physicians, and public servants around the world who have made major advances in the understanding, diagnosis, treatment, cure, and prevention of human disease. Seventy-six Lasker laureates have gone on to receive a Nobel Prize.

Targeted Cancer Therapy: The Backstory

CML can be traced to a single genetic event—the swapping of pieces of DNA between two chromosomes. This gene rearrangement produces a faulty signaling protein – a tyrosine kinase enzyme -- that causes white blood cells to divide incessantly. Gleevec and Sprycel thwart CML—without provoking the toxic side effects associated with standard chemotherapeutic agents—by taking aim at this single rogue enzyme.

More than a decade ago, Druker identified STI571, the precursor to Gleevec, as a promising anticancer compound for its ability to kill CML cells by turning off the signal of the abnormal cancer-causing protein. He also conducted the first clinical studies of Gleevec, demonstrating that the drug could effectively return white blood cell counts to normal in CML patients, with only minor side effects.

Lydon and others at Novartis were already synthesizing various inhibitors of protein kinases using the tools that Druker had developed in his laboratory, and he obtained several to evaluate against leukemia cells. He found that one drug—Gleevec—inhibited cancerous white blood cells without affecting healthy human cells.

A phase I clinical trial began in June 1998, and within six months all of the patients' white blood cell counts had returned to normal. This result was considered nothing less than remarkable for patients with terminal cancer who had exhausted all other treatment options. Clinical trials were soon expanded to include other patients with CML, and results were similarly stunning. Today, the average five-year survival for CML patients who take Gleevec is close to 90 percent.

Over time, however, some of the patients who responded so well to Gleevec began to relapse. As an HHMI investigator at the University of California, Los Angeles, Sawyers ferreted out the molecular basis of resistance by studying patients he was treating on the early clinical trials. He found that resistance to Gleevec develops when patients acquire mutations in the aberrant protein that is targeted by Gleevec. At least 50 different mutations can have this devastating effect. In collaboration with HHMI investigator John Kuriyan, he investigated how Gleevec and its target enzyme fit together and how mutations that alter the enzyme's shape can help it evade the drug.

Based on this information, Sawyers conceived ways to halt the growth of cancer cells that no longer succumbed to Gleevec and began working with scientists at Bristol-Myers Squibb to develop a second-line drug. In clinical trials led by Sawyers and collaborators at M.D. Anderson Cancer Center, Sprycel was shown to be effective against all but one of the commonly occurring gene mutations responsible for Gleevec resistance. As a result of this work, the Food and Drug Administration approved Sprycel for the treatment of CML in patients whose cancer does not respond to Gleevec.

In developing Gleevec and Sprycel, Druker, Lydon, and Sawyers have not only revolutionized the treatment of CML, but also clearly demonstrated how detailed understanding of a tumor's survival strategies can lead to new treatment options for patients. Dozens of targeted therapies have now been approved for the treatment of many different cancers, and researchers continue to employ similar strategies in their quest to develop better drugs.