after the disease becomes resistant to standard treatments. In September, the Food and Drug Administration approved pralatrexate (Folotyn®), a drug developed at Memorial Sloan Kettering by molecular pharmacologist and Memorial Sloan Kettering Member Emeritus Francis M. Sirotnak, as a treatment for peripheral T cell lymphoma (PTCL).

Francis M. Sirotnak

Pralatrexate is the ninth drug that incorporates Memorial Sloan Kettering research to be approved by the FDA for marketing. A study led by Boston University ranks Memorial Sloan Kettering in the top three among public sector (academic) research institutes in the discovery of new therapeutic products, behind the National Institutes of Health intramural program and the ten-campus University of California system.

“Until now, patients with PTCL, a subtype of non-Hodgkin lymphoma, had no options after their first-line treatments failed,” Dr. Sirotnak said. “With pralatrexate, these patients now can be treated and look forward to a significant response, even qualifying for additional therapies that may be potentially curative, such as bone marrow transplants.”

Pralatrexate is a redesign of a chemotherapy drug called methotrexate, a compound similar to folic acid, which has been used to treat cancer for more than 50 years. Methotrexate interferes with the metabolism of folic acid — which cells use to synthesize DNA and reproduce — and targets rapidly dividing cells such as cancer cells. However, in addition to killing cancer cells, methotrexate inhibits DNA synthesis in some normal cells, resulting in side effects. Researchers were also puzzled over why methotrexate was very active against some cancer types but ineffective against others.

In the early 1980s, Dr. Sirotnak and colleagues conducted studies in mouse models to identify the factors determining a cancer cell’s response or resistance to methotrexate. They discovered that tumor cells take in natural folate — and methotrexate — via a protein identified as a plasma membrane transporter, now designated RFC-1. They also learned that noncancerous cells do not use the transporter for this purpose. Further research with these cancer models revealed that tumors responding to methotrexate had high levels of RFC-1. “When normal cells transform into cancer cells, they often overexpress the RFC-1 gene to ensure they get enough folate,” Dr. Sirotnak said.

Dr. Sirotnak collaborated with chemists at the Stanford Research Institute and the Southern Research Institute to develop a compound that would exploit the tumor cells’ dependence on RFC-1 for folate intake. “It was a targeted therapy, but our strategy was focused on interaction with the transporter rather than the ultimate effect once inside the cell,” he said. “The drug had to be tailored for RFC-1 — in other words more efficiently use the same route of entry that tumor cells use to bring in methotrexate — without losing any ability to inhibit folic acid metabolism.”

Based on promising animal data, the researchers identified pralatrexate as a viable clinical candidate in the mid-1990s. The drug was first taken into clinical trials in lung cancer patients by Mark G. Kris, Chief of Memorial Sloan Kettering’s Thoracic Oncology Service, and his colleagues. Early positive results led Memorial Sloan Kettering medical oncologist Owen A. O’Connor (now at NYU Langone Medical Center) to propose a study testing

pralatrexate in patients with different types of non-Hodgkin lymphoma, including PTCL.

Funding from Memorial Sloan Kettering's Experimental Therapeutics Center (ETC) supported the manufacturing of pralatrexate and these early trials, as well as a trial in patients with mesothelioma. After additional encouraging human trial results, Memorial Sloan Kettering's Office of Industrial Affairs licensed the drug to Allos Therapeutics, Inc., for the further testing needed for FDA approval.

"The ETC was established for this purpose — to streamline the development of new therapeutics from the laboratory through early-stage clinical trials," said David A. Scheinberg, Chair of the Molecular Pharmacology and Chemistry Program in the Sloan Kettering Institute and leader of the ETC. "It is often difficult to find government support for drug development, and private companies are frequently risk averse at the early stages. This is a terrific example of how the ETC can help bridge that gap to allow a new drug to become available worldwide for patients."