

Faculty Successes

“NExT” Opportunities for CCR Investigators in Drug Discovery and Development

The development of new therapeutics to prevent and treat cancer is one of the most important goals of CCR. The Molecular Targets Faculty (MTF) was established 10 years ago to provide the infrastructure to accomplish this goal.

“In the late 1990s, we realized that to take promising molecules out of the lab and into the clinic, we needed a more comprehensive development process—we needed to screen more thoroughly, understand pharmacokinetics more deeply, and be able to preclinically test molecules more clearly,” said Patricia Steeg, Ph.D., one of the main initiators of the MTF and currently co-chair of CCR’s Molecular Targets Faculty Steering Committee (MTFSC) along with James Doroshow, M.D., NCI Deputy Director for Clinical and Translational Research.

One of the first steps was to bring James McMahon, Ph.D., into the process with the establishment of the Molecular Targets Laboratory (MTL). McMahon’s group provides intramural investigators with an essential first step—the development of screening assays to identify inhibitors and biologic agents that interact with their molecular targets of interest.

“We create high-throughput screening assays for use with both NCI’s Natural Products Repository, the most chemically diverse repository in the world, and NCI’s Chemotherapeutic Agents Repository, housing more than 200,000 pure chemical compounds,” said McMahon. The end result of the screen, which is often a three- to six-month process, is a list of “hits” or likely molecular

candidates, which are ultimately sent to the collaborating principal investigator’s laboratory for further testing and validation.

The ultimate goal is to bring promising molecules to the NCI Experimental Therapeutics (NExT) Program, a partnership between the Division of Cancer Treatment and Diagnosis (DCTD) and CCR. The mandate of NExT is to advance clinical practice and bring improved therapies to patients with cancer by supporting the most promising new drug discovery and development projects.

One recent success of the MTF is that of Yves Pommier, M.D., Chief of the Laboratory of Molecular Pharmacology, and his efforts to bring a new class of cancer therapeutics called indenoisoquinolines from the bench to the bedside. Pommier and Mark Cushman, Ph.D., of Purdue University, initiated a high-throughput screen to discover compounds that inhibited the function of the DNA processing enzyme, topoisomerase I, and spent years revising the resulting compounds to create better derivatives. Now, several years later, after productive collaborations with several additional researchers, with the MTF, and with NExT, two derivatives are currently in clinical trials at the NIH.

As Pommier noted, “It’s all about commitment, and within the MTF, there are a lot of individuals



(Image: J. Kelly)

The Molecular Targets Faculty works to identify and validate important molecular targets in cancer and AIDS.

who are committed to making drug development work.” And work it does, with at least seven other molecules in the immediate pipeline, all hopefully headed to the clinic in the very near future.

To learn more about MTF, please visit <https://ccrod.cancer.gov/confluence/display/CCRMTF/Home>.

To learn more about A Phase I Study of Indenoisoquinolines LMP400 and LMP776 in Adults With Relapsed Solid Tumors and Lymphomas, please visit <http://clinicaltrials.gov/ct2/show/NCT01245192>.