Tumors, by their very nature, are acidic, and the most acidic cancers are also the most aggressive. A team of scientists at Yale Cancer Center has developed a way to use tumor’s acidity to guide drug therapy straight into the cell.

In a healthy cell, every tumor across all tumors, this new delivery system would deliver the payload of a chemotherapy drug through nanotechnology.

A breakthrough demonstrates the multiplier effect of combining insights from several disciplines to create something revolutionary. Nearly 20 years ago Dr. Engelman’s lab discovered that a small piece of soluble protein called a pHLIP peptide would spontaneously insert itself across a membrane in an acidic environment. “But what I didn’t know until mid-2005 or 2006,” said Dr. Engelman, “was that tumors are acidic.” This information came from colleagues Dr. Oleg Andreev and Dr. Yana Reshetnyak, now at the University of Rhode Island, who wondered if pHLIP would enter tumors. Dr. Engelman began exploring the idea.

Meanwhile two other Cancer Center researchers—W. Mark Saltzman, PhD, Goizueta Foundation Professor and Chair of Biomedical Engineering, and Frank J. Slack, PhD, formerly of the Yale Cancer Genetics and Genomics Program and now at Harvard—were collaborating on a project. Dr. Slack’s lab had developed a genetically engineered mouse model for lymphoma, and Dr. Saltzman’s lab had designed technology capable of delivering drugs via nanotechnology.

Which leads to another key collaborator: Peter M. Glazer, MD, PhD, Robert E. Hunter Professor and Chair of Therapeutic Radiology. Dr. Glazer’s lab is expert at designing and synthesizing analog treatment compounds. Dr. Glazer provided peptide nucleic acids (PNAs) that Dr. Saltzman loaded onto nanoparticles that targeted lymphoma in Dr. Slack’s mice. Early experiments indicated that the PNAs slowed down the growth of lymphomas by interfering with the tumor’s microRNAs (miRs). These are small but influential signaling RNAs that shut down tumor suppressors and thus are critical to the spread of cancer. The principal miR implicated in lymphoma is miR-155. This is when Dr. Engelman joined the collaboration. He offered a new method of delivery—pHLIP, the peptide whose attraction to acidity allows it to penetrate cancer cells. “The beauty of pHLIP,” said Dr. Engelman, “is that it essentially uses the acidity of the tumor as a homing device.”

The team loaded pHLIP with anti-miR PNAs aimed at switching off signals from miR-155. “It’s like a guided missile delivering a warhead,” explained Dr. Engelman. “The missile is guided by acidity, the propulsion system is the pHLIP, which penetrate the protective system of the cancer cell, and the PNA is the warhead.”

When they tested this weapon on Dr. Slack’s mice, the tumors died and metastasis was suppressed. Because the weapon attacked only cancer cells, side effects on surrounding cells were minimal. The team took a video of a cancerous mouse, unable to move and clearly almost dead. Three days after being treated, this same mouse looked transformed, ambling around its cage.

“So it was a constellation of research by four labs,” said Dr. Engelman. “Each of us contributed expert knowledge that made the whole enterprise work, and it was all made possible by the Cancer Center, which funded it and brought us together.”

Dr. Engelman is excited by the delivery system’s possibilities. Many hundreds of microRNAs have been identified in human cells, and if science can identify their functions, he says, “then we could throw switches for all kinds of purposes, not just for treating cancer.”

Turning Cancer’s Metabolism Against Itself

Yale Cancer Center