Breast cancer spreads when tumor cells grow protrusions called invadopodia. These structures jab and chew holes in the basement membrane surrounding the tumor, allowing cancer cells to escape. But how are invadopodia created within the cell? If that process could be discovered and disrupted, breast cancer might lose the ability to spread.

Anthony J. Koleske, PhD, Professor of Molecular Biophysics and Biochemistry and Neurobiology, is well on the way to understanding and perhaps disabling invadopodia. “The secret is that all the building materials for invadopodia are in the cell, ready to go,” said Dr. Koleske, “but there needs to be a chemical cue or signal to assemble these materials into one of these structures. One of the cues is a growth factor called epidermal growth factor (EGF). We’ve elucidated a series of steps that involves passing signals from one protein to the next, which eventually triggers the assembling of these building blocks into a protrusion.”

Dr. Koleske and his lab traced the path of all these signals to their ultimate destination: a protein called cortactin. “You can think of cortactin as the joists that help assemble the scaffolding for the structure,” said Dr. Koleske. “From our earlier work showing that cortactin could promote cellular protrusions, we started getting really interested in cancer because cortactin has been associated with many other aspects of cancer invasion. That’s what we started working on,” said John Gendrot.

Graduate Student of Koleske and Structural Biologist at Albert Einstein College of Medicine of Yeshiva University, specializing in the biogenesis of protrusions. “One expert is in biochemistry and another expert trigger the formation of these structures called invadopodia,” said Dr. Koleske. “Join us in our effort to unravel how this happens in cells in real time. The combination of approaches makes for a very powerful attack.”

The biggest breakthrough, published in a paper in 2011 was Koleske’s discovery that cortactin can’t send the signals that trigger other proteins to assemble into invadopodia until it has been phosphorylated by a tyrosine kinase called Arg. Koleske’s team is currently testing whether disrupting communication between Arg and cortactin could prevent invadopodia from forming or functioning, thereby preventing the tumor cells from escaping the tumor. To test this idea, they knocked down Arg in invasive human breast cancer cells, then transplanted them into the mammary fat pads of mice to see if the cells could invade and metastasize to the lung—which is where this particular type of breast cancer metastasizes—by about 80 percent. “That’s very promising and means we’re on the right track.”

Dr. Koleske has received pilot funding from Yale Cancer Center to begin looking for compounds that stop Arg and cortactin from interacting. “We’re already making significant progress here,” said Dr. Koleske. The strategy would be a drug that targets these interactions and its success begins to look feasible, in collaboration with Finn Bergan, Head of the Molecular Imaging group at Yale.

“The idea is that this would be used in a regime of the therapy for people who had early-stage breast cancer and had a tumor,” said Dr. Koleske. “It would be used to reduce the long-tail risk of recurrence or of progression by invasive cells that had been missed.” Koleske added that this is a perfect illustration of the “translational science” that the Cancer Center encourages—translating basic science into practical applications that solve problems in cancer medicine.