From a cancer cell’s point of view, metastasis is a risky, complicated migration. First the cell must escape the primary tumor and launch itself into the bloodstream. Then it must find a way to exit this flow and establish itself on the shores of a distant organ. Finally it must develop the means to multiply and colonize a hostile foreign environment. Every stage is fraught with physiological hazards and requires a knack for adapting to new conditions. Scientists have long been curious about how cancer cells survive their metastatic journey. The cells don’t change their essential genetic nature, which is why breast cancer cells, for example, are recognizable wherever they land after metastasis. Rather, the cells rely on reversible modifications in gene expression through epigenetic changes, using enzymes that help them stay alive while moving from one environment to the next. But which enzymes? And how do those enzymes function in metastasis? Identifying those regulators of gene expression is the necessary first step to stop the migration of cancer cells.

A team at Yale Cancer Center led by Qin Yan, PhD, Associate Professor of Pathology, has discovered a regulating enzyme called RBP2 that breast cancer cells need in order to metastasize to the lung. “We found that not only is this enzyme implicated in metastasis,” explained Dr. Yan, “but also that if you suppress it, metastasis is suppressed. That suggests that RBP2 is a good target for a surgical cancer therapy against metastasis.”

This is an exciting breakthrough, since breast cancer strikes more women than any other cancer and is particularly adept at aggressive metastasis, usually to the lungs, bones, or brain. Once the cancer metastasizes, options for treatment dwindle, along with survival rates. Tracking down RBP2 (also known as JARID1A or KDM5A) and deciphering its function took Dr. Yan and his colleagues three years. First they used gene expression datasets of breast cancer patients to identify RBP2 as a recognized regulator of metastasis. Then they did global genome-wide profiling to determine which genes were regulated by RBP2 and to confirm its importance. Next they completed cell-based assays, which confirmed that RBP2 expression is critical in breast cancer tumorigenesis and metastasis. Lastly they tested these findings in two mouse models, one of which required them to use a genetically engineered mouse model that Dr. Yan created. Experiments in the mouse models validated their findings derived from the clinical datasets.

Dr. Yan and his colleagues also began screening small molecules to look for inhibitors of RBP2. They identified some first-in-class compounds that modulate or suppress the enzyme’s activity. “We are further developing these compounds so that we can use them in the clinic,” said Dr. Yan.

Some of that work is being done through the National Cancer Institute’s Experimental Therapeutics Program, called NExT, which aims to advance breakthrough discoveries in the laboratory into new therapies for cancer patients. Dr. Yan’s team is taking a three-pronged approach. The first prong is using traditional medicinal chemistry, to search for derivatives of the inhibitory compounds that are more potent and specific. The second is an expansion of the initial molecular screening from 10,000 molecules to 100,000, again with the goal of finding stronger, more specific compounds. The third approach involves computational-based drug design for inhibitors of RBP2.

“We have already identified some better compounds,” said Dr. Yan, “but in a year or so we hope to have much more potent ones.” He and his colleagues will test the new compounds in breast cancer xenografts, then in mice. If all goes well, the next stage would be a clinical trial. Dr. Yan expects to see that in about three years. Our hope is to take what we know from the clinic and run it through the experimental system, and after we know the mechanism and the inhibitors, to bring a block into the clinic, so we are learning in both directions.”

Blocking Metastasis In Breast Cancer