When lung cancer and breast cancer relapse, they often metastasize in the brain. The tumors that arise in the brain develop novel characteristics, differences that often enable resistance to existing drugs and create opportunities for new detection and treatment approaches for Yale Cancer Center researchers.

“We often think of metastasis as this orderly progression of events,” said Don Nguyen, PhD, Associate Professor of Pathology and Medicine (Medical Oncology), “whereby malignant cells first spread from a primary tumor to eventually colonize a distant organ. But it’s actually quite dynamic and context-dependent. It’s driven both by molecular underpinnings of the tumor and by how the tumor cells interact with their overall environment.”

Dr. Nguyen focuses his research efforts on the progression and metastasis of lung cancer. “The incidence of brain metastasis in patients who have other types of cancer is on the rise,” he explained. “One of the central questions we have is how can we leverage different molecular profiling to understand how the tumor cells are able to engage in similar interactions for them to survive in this unique environment.”

And if we were to disrupt that signaling, would we be able to reduce tumors that are already in the brain? These epigenetic changes, when removed from the TME, they stopped acting like immune tumors. “These immune checkpoint regulators on T cells,” Dr. Nguyen explained. “That tells us these changes are epigenetic in nature, occurring in response to input from the tumor microenvironment. That makes them a promising target.”

Dr. Nguyen’s team was also surprised to find two anti-inflammatory biomarkers, IL-1 and TGF-β, were significantly upregulated in the TME compared to healthy brain tissue. “These proteins are typically found in immune checkpoint regulators of T cells,” Dr. Nguyen explained. “We found they were expressed in resident microglia, an immune cell that’s very specific for the central nervous system. These proteins hadn’t been considered a therapeutic target in brain metastases before, but now they offer potential opportunities for treatments.”

This research provided preliminary data for a five-year, nearly $4 million grant that the National Cancer Institute (NCI) awarded to Dr. Nguyen and Katerina Politi, PhD, Associate Professor of Pathology, to generate and evaluate patient-derived models to study resistance to targeted therapies in D57IG H5 rat lung cancer. “Tyrosine kinase inhibitors are targeted therapies that are used as the first line of treatment for this disease. Resistance to these inhibitors inevitably emerges, limiting their curative potential,” Dr. Politi explained. “Through this research, we are focused on understanding how resistance is linked to metastasis, and whether resistance is different at different metastatic sites in the body. By studying patient-derived models, we can learn from the complexity of human tumors’ diversity to understand how they change through treatment, which is very exciting.”

The grant is part of the NCI’s Patient-Perturbed Model Consortium. At Yale Cancer Center, the grant is increasing cross-disciplinary collaborations, not just among Drs. Nguyen and Politi’s names, but also with experts from the lung and melanoma programs as well as the Genomics, Genomics, and Epigenetics Program.

For example, Dr. Nguyen partnered on a 2020 study with Qin Yan, PhD, Associate Professor of Pathology, to identify distinct and subclinical epigenetic changes in breast cancer cells that metastasize to the lung and brain. Furthermore, they could distinguish the phenotypic—refract to transcription factors