Mining Brain Metastasis for Answers

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 confer resistance to existing drug therapies 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, are the mechanisms that drive a lung cancer to metastasize to the brain similar, or different, than in other disease types? And how can we leverage different molecular profiling techniques to compare and contrast these metastases so we can analyze what is going on in the tumors as well as in the tumor microenvironment?"

In their recent research, Dr. Nguyen and his team have made several significant discoveries on both fronts. Their experiments began in mice with a human lung cancer cell line that quickly metastasizes to the brain. They found changes in thousands of genes in the tumor cells and stromal cells, induced by the tumor microenvironment (TME). "The extent of those changes surprised us," he said.

They validated some of their findings by examining human tissue samples. They then expanded their scope by testing xenograft models of breast cancer and melanoma metastases in the brain. They found the same surprising scale of epigenetic change.

"Regardless of where the cancer originated, once it spread to the brain the tumors exhibited molecular changes that made them act more like neurons," Dr. Nguyen said. "They started to express molecules that are involved in cell communication. Neurons are known to do this because cell-to-cell interactions are essential for propagating more signals in the brain. One of the fascinating questions we're trying to answer is whether 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 cells exhibited remarkable plasticity; when removed from the TME, they stopped acting like neurons. "These traits were reversible," he added. "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, Lag-3 and Tim-3, were significantly upregulated in the TME compared to healthy brains. "These proteins are typically found as immune checkpoint regulators on T cells," Dr. Nguyen explained. "We found they were expressed on 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."

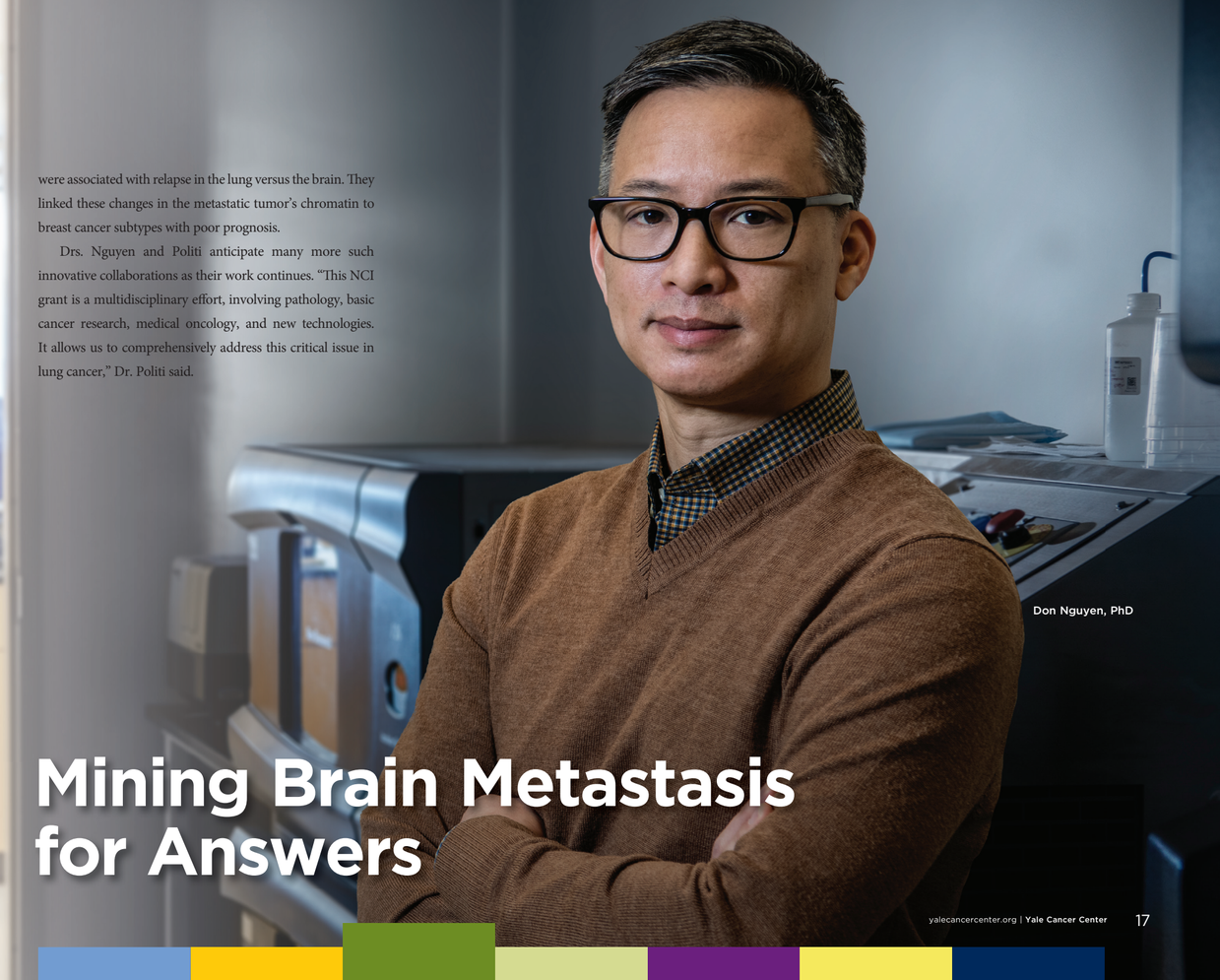
This research provided preliminary data for a five-year, nearly $4 million grant that the National Cancer Institute (NCI) awarded to Dr. Nguyen and Katerina Politi, PhD, Associate Professor of Pathology, to generate and evaluate patient-derived models to study resistance to targeted therapies in EGFR mutated lung cancer.

"Tyrosine kinase inhibitors are targeted therapies that are used as the first line of treatment for this disease. However, drug resistance 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 directly to understand how they change through treatment, which is very exciting."

The grant is part of the NCI's Patient-Derived Models Consortium. At Yale Cancer Center, the grant is increasing cross-disciplinary collaboration, not just among Drs. Nguyen and Politi's teams, but also with experts from the lung and melanoma programs as well as the Genetics, 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 substantial epigenomic changes in breast cancer cells that metastasize to the lung and brain. Furthermore, they could distinguish the pathways—which transcription factors were associated with relapse in the lung versus the brain. They linked these changes in the metastatic tumor's chromatin to breast cancer subtypes with poor prognosis.

Drs. Nguyen and Politi anticipate many more such innovative collaborations as their work continues. "This NCI grant is a multidisciplinary effort, involving pathology, basic cancer research, medical oncology, and new technologies. It allows us to comprehensively address this critical issue in lung cancer," Dr. Politi said.



Don Nguyen, PhD