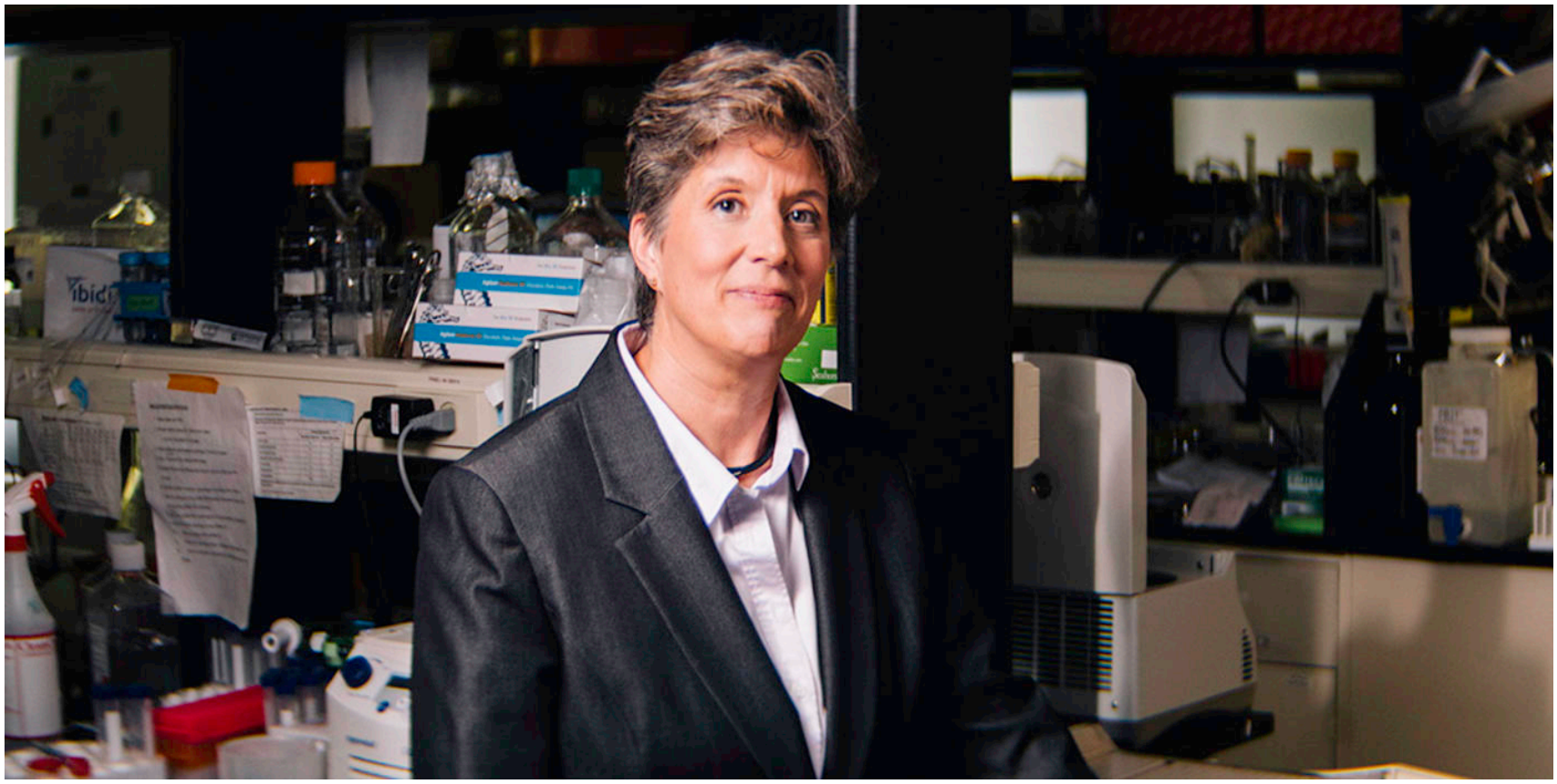

Variant of the p53 Gene Increased Tumor Cell Metabolism

PHILADELPHIA — (Feb. 22, 2018) — Scientists at The Wistar Institute have found a novel mechanism through which mutant p53 enhances metastasis by controlling tumor metabolism. The research, published online in *Genes & Development*, also revealed how this process is influenced by a naturally occurring p53 gene variant.

TP53 is the most frequently mutated gene in human cancer. Besides inactivating the tumor suppressive function of p53, mutations in this protein also confer pro-tumorigenic function to p53. In addition to these changes, multiple minor, naturally occurring genetic variants, also known as polymorphisms, have been described in the p53 gene. These variants can significantly alter p53 function, but their impact on the function of mutant p53 has not been fully elucidated.

Maureen Murphy, Ph.D., professor and program leader of the Molecular and Cellular Oncogenesis Program at Wistar and senior author of the study, evaluated the impact of one of these variants, called Pro72Arg, on the ability of p53 mutations to promote metastasis.

"Our study tied this p53 variant to mitochondrial metabolism," said Murphy. "We established an association of this variant with increased metastatic ability of p53 mutant cancers, which corresponds to a worse prognosis for breast cancer patients carrying p53 mutations, providing important information for the prognosis and treatment of these patients."

The Murphy Lab generated genetically modified cells that express several cancer-associated p53 mutations along with the Pro72Arg variant and established that this variant confers faster migration and higher ability to invade and metastasize both *in vitro* and *in vivo* in models of lung and bone metastasis.

The researchers applied a genome-wide approach to study the mechanism of increased metastasis in the absence or presence of the Pro72Arg variant and found that mutant p53 binds to the PGC-1a protein, which is a master regulator of metabolism in the mitochondria, the organelles within the cells where energy production occurs. Furthermore, cells expressing the Pro72Arg variant showed decreased association between p53 and PGC-1a, resulting in enhanced PGC-1a function and consequently increased mitochondrial function.

"Our results are in line with several studies that have recently pointed to the importance of mitochondria as drivers of metastasis in different tumor types," said Subhasree Basu, Ph.D., a postdoctoral researcher in the Murphy Lab and first author of the study.

Through gene expression studies in tissue samples from breast cancer patients, the team confirmed a higher activity of PGC-1a associated with the presence of the Pro72Arg variant. Importantly, they also observed worse survival in patients carrying p53 mutations in conjunction with this variant.

"We have assessed for the first time the impact of the Pro72Arg variant on cancer progression and metastasis," added Murphy. "Our observation that this polymorphism influences cancer metabolism suggests that inhibiting mitochondrial metabolism as a therapeutic strategy may be more effective in patients that carry the Pro72Arg variant. Our next step is to investigate this hypothesis to use this information for personalized medicine approaches."

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Other co-authors from The Wistar Institute include Keerthana Gnanapradeepan, Thibaut Barnoud, Che-Pei Kung, Michele Tavecchio, Jeremy Scott, Andrea Watters, Qing Chen, and Andrew V. Kossenkov.

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The Wistar Institute is an international leader in biomedical research with special expertise in cancer research and vaccine development. Founded in 1892 as the first independent nonprofit biomedical research institute in the United States, Wistar has held the prestigious Cancer Center designation from the National Cancer Institute since 1972. The Institute works actively to ensure that research advances move from the laboratory to the clinic as quickly as possible. wistar.org.

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