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**Abstract/Bio:**

Triple-negative breast cancer (TNBC) is one of the most aggressive forms of breast cancer that lacks the three common targets for therapy (estrogen receptor, progesterone receptor, and HER2). TNBCs are also frequently non-responsive to new approved therapies that work in other breast cancers, such as drugs that target the PI3K pathway, a key growth signal in breast cancer. Because of this, standard treatments are limited, relapses are common, and survival is poorer than in other breast cancer types. Therefore, it is critical to find new, effective, and durable treatments for patients with TNBC. To make matters worse, relapsed TNBC tumors switch into a "hard-to-kill" state: these cells look and behave more like aggressive, migrating stem-like cells. These stem-like characteristics are called "mesenchymal cell states". Mesenchymal cell states are kept activated by powerful DNA switches called super-enhancers—stretches of DNA that act like a powerful faucet that keeps cancer-promoting genes flowing on high.

We have found that two enzymes, CDK12 and CDK13, sit at these super-enhancers and act as the hands that turn the "faucet" on. I have tested a new drug that blocks CDK12/13 from working, and this drug lowers the activity of genes that drive the mesenchymal, stem-like state. Even more promising, when we combine newly invented CDK12/13 blockers with drugs that target the PI3K pathway, the two treatments work far better together than either alone. Our goal is to disarm TNBC by pushing tumors out of the resistant, stem-like state and into a more stable, treatable state, then striking with targeted therapy. We will also test whether this approach reduces metastasis by weakening circulating tumor cells. We will also test if our combination treatment enhances the effects of immunotherapy – as immunotherapy is approved for a subset of TNBC patients, this could greatly expand the percent of TNBC patients that are eligible for immunotherapy. If successful, our work will lay the foundation for a clinical trial with this combination therapy for TNBC with the potential to reduce relapse, limit metastasis, and improve survival for patients who currently have too few options.

Dr. Indeglia received her undergraduate degree from University of Virginia and her Ph.D. in Biochemistry and Molecular Biophysics from the University of Pennsylvania in 2024. She is currently a postdoctoral fellow at Brigham and Women's Institute working in the Genetics Department. Her research focuses on identifying novel strategies for targeting heterogeneity and plasticity in triple negative breast cancer.