An engineering approach from Virginia Tech helps breast cancer researchers at Georgetown

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Biologists working with engineers and physicists have found a molecule they say helps determine if breast cancer cells that are resistant to antiestrogen therapy will live or die.

Their study, published online earlier this month in *Cancer Research*, represents a major finding from a unique collaboration between Georgetown Lombardi Comprehensive Cancer Center and Virginia Tech that was designed to study the living cell as an information processing system.

"We needed an engineering approach to a biological problem—no one had built a model like this before," said the project's principal investigator, Robert Clarke, PhD, DSc., Dean for Research at Georgetown University Medical Center.

His team consists of oncology and genetic researchers from Georgetown Lombardi and electrical and computer engineers, and bioinformatics specialists from Virginia Tech.

The scientists created a mathematical model that uses all of the biological data known to date about estrogen-positive breast cancer to understand the decisions that tumor cells make to ensure their survival, based on signals from their environment and their own internal state. It is supported by a $7.5 million federal grant.

"A cell is vastly harder to model than engineered systems, such as the nation's electrical grid or a complex integrated circuit, because of the incredible number of interactions among its components," explains Virginia Tech electrical engineer William T. Baumann, PhD, associate professor in the Bradley Department of Electrical and Computer Engineering, and co-author of the paper. "We are just at the beginning of being able to model an entire cell."

This approach may be key to understanding why many of the approximately 125,000 patients diagnosed with estrogen-positive breast cancer (meaning their cancer growth is fueled by the hormone) become resistant to antiestrogen therapy—such as tamoxifen, fulvestrant and aromatase inhibitors.

The problem has not been solved in the 30 years since some of these treatments have been used, Clarke says. "The result is that many estrogen-positive tumors recur as incurable, endocrine-resistant cancer cells," he adds.

Using their model, the team found a key molecular component that determines whether a breast cancer cell will turn on autophagy—a process wherein a cell chews up and eliminates toxic proteins to stay alive—or switch on apoptosis, which pushes the cell to die. This molecule, interferon regulatory factor-1 (IRF1), is engaged when a cell is under stress, such as by antiestrogen treatment.

Loss of IRF1 promoted resistance to antiestrogens, whereas silencing of IRF1 restored sensitivity to the agents, Clarke says.

Clarke says modeling "helps you find things that may be quite important that you would not have discovered using intuition alone. The molecular logic of these circuits is difficult to comprehend by intuitive reasoning, and I know had we not had the model, we would have stopped our

experiments before we discovered the importance of the IRF1 signal."

Provided by Georgetown University Medical Center