Roadmap published for dynamic mapping of estrogen signaling in breast cancer

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The first roadmap to mathematical modeling of a powerful basic "decision circuit" in breast cancer has been developed and published in *Nature Reviews Cancer*.

The preliminary mathematical model is the first result of a $7.5 million federal grant, awarded to scientists at the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center (GUMC) and collaborators at Virginia Tech and Fox Chase Cancer Center, to develop a systems approach to understanding and treating one of the most common forms of breast cancer.

"A cell is an information processing system and cancer cells make decisions that promote their growth, so we are striving to understand how these cells make mathematically-based choices based on inputs, processing, and outputs," says lead investigator Robert Clarke, PhD, DSc, a professor of oncology at Lombardi and GUMC's newly appointed Dean for Research.

The model, which is being built in modules, is designed to understand estrogen signaling in breast cancer cells, and by extension, why some cancer cells are susceptible to endocrine therapy while others are not. The estrogen hormone drives over half of the 180,000 cases of invasive breast cancer diagnosed each year, yet endocrine therapies designed to shut down this growth pathway are not as successful as simpler, human-derived models would have predicted, Clarke says.

"We need an engineering approach to a biological problem, and this is a very novel, and promising, start," says Clarke. "No one has built a model of breast cancer cell fate decision- making like this before."

His colleagues in this endeavor are Louis M. Weiner, MD, director of the Lombardi Comprehensive Cancer Center; John J. Tyson, PhD, first author of this study, as well as a computational cell biologist and professor at Virginia Tech; and William T Baumann, PhD, an electrical and computer engineer and associate professor at Virginia Tech. Tyson and Baumann have assembled a team of graduate students and postdoctoral researchers to assist in the modeling project.

"We are providing a roadmap of how a modeler might capture, in mathematical form, the molecular events controlling cell growth, proliferation, damage responses, and programmed cell death," says Tyson. "The value of this enterprise will be measured ultimately by new insights provided by the model into the logic and functionality of estrogen-receptor signaling and by the effectiveness of the model as a tool for experimental prediction and design."

Although scientists have amassed a large body of information about the genes and proteins involved in pathways that govern cancer development and growth, and based on that, have developed some "good ideas about how they go awry in certain cancers, most of our understanding relies on intuitive reasoning about highly complex networks of biochemical interactions," the researchers say in their study. "Wouldn't it be better if we could frame a reaction network in precise mathematical terms and use computer simulation to work out the implications of how the network functions in normal cells and malfunctions in cancer cells?"

"The hallmark of cancer cells is that they are making decisions that are right for them, not for the survival of the human organism, so we need to understand those choices," Clarke says.

The roadmap detailed in *Nature Reviews Cancer* is built on the idea that a cell is an information processing system, receiving signals from its environment and its own internal state, interpreting those signals, and making appropriate cell-fate decisions, such as growth and division, movement, differentiation, self-replication, or cell death.

To that end, the investigators have already begun to model separate modules that computers can track in terms of the dynamic consequences of multiple and often conflicting interactions. These include "decision modules" (cell cycle and apoptosis), "stress modules" (autophagy and unfolded protein response), and the "signal processing modules" (estrogen receptor and growth factor signaling transduction networks).

Clarke says that a lot of "wet lab work" data from Lombardi laboratories, measuring how changes in gene and protein expression affects response to endocrine therapy, is being transferred into the model, along with published information from other institutions.

Not only does the model have the potential to explain why certain subtypes of breast cancer respond or become resistant to endocrine therapy, it could be used to help test potential new therapies, he says.

"If we tweak some gene in the model and all the breast cancer cells die, we can go back to the lab and test if that actually occurs," Clarke says. "That means that once we understand the decisions that these cancer cells are making, we have an efficient way of developing drugs or combination of drugs."

"The hard work is yet to be done, but it is just a matter a time before an effective, integrated model of regulatory networks in breast cancer cells is informing the next wave of experiments and therapies," says Tyson.