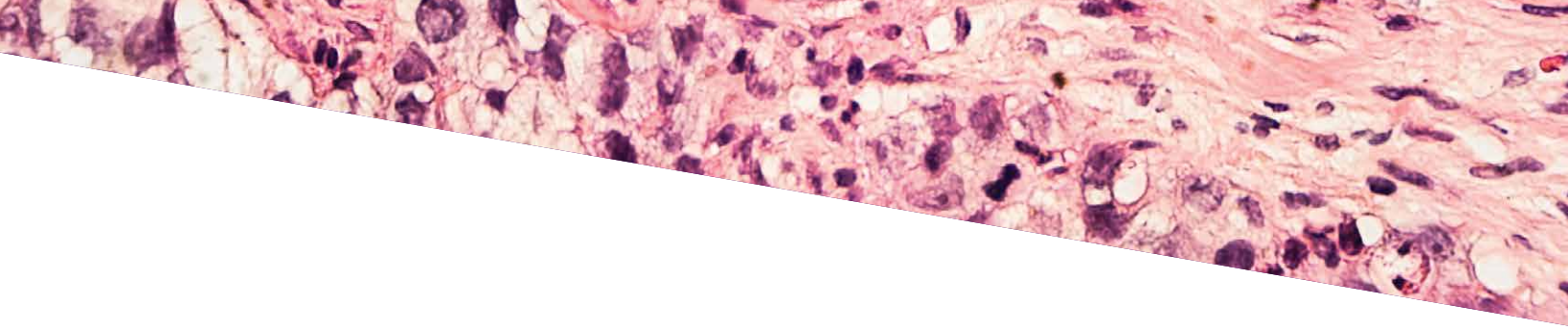


Estrogen Receptors

Yang investigates signaling mechanisms' role in cancer

A critical first step oncologists must take after finding a patient has breast cancer is to look for overexpressed hormone receptors in the cancer cells.

This determines the type of therapy that will be used to most effectively combat the disease. While it is well known that point mutations of hormone receptors are associated with several types of cancer, still elusive is a mechanistic understanding of how these receptors function at the molecular level. Sichun Yang, Ph.D., assistant professor at Case Western Reserve University, is working to understand the signaling mechanisms of two critical domains in estrogen receptors, using computer modeling resources at OSC.

"We're going to come out with a structural model regarding how these molecular domains work together," Yang said.

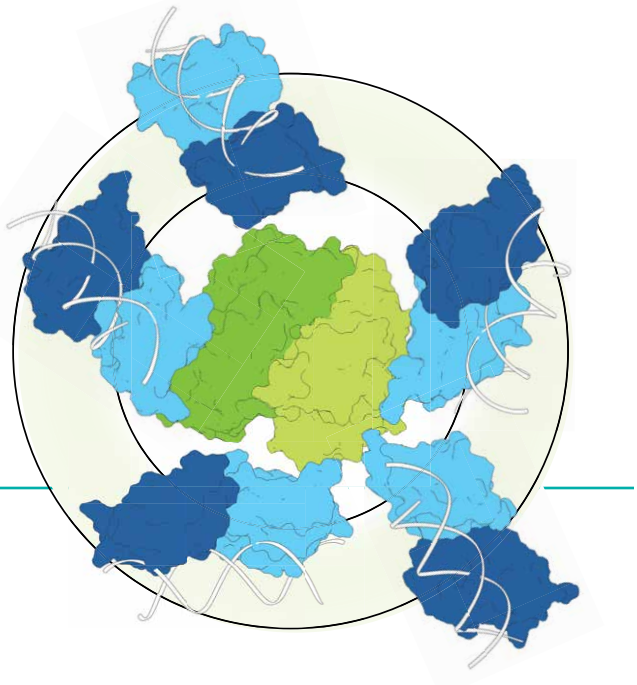
Estrogen receptors are proteins found on the surface of cells that receive signals from the hormone to direct activity within the cell. While they are critically important for healthy cells in regulating female reproductive functions, their presence in breast cancer cells work against the body. Nearly 75 percent of all breast cancers are estrogen-receptor positive, which means the presence of estrogen triggers tumor growth. To treat ER-positive breast cancer, doctors use hormone therapy to block estrogen from binding to receptors in the cancer cells, reducing their chance of survival and proliferation.

Yang's group focuses on two domains in ER that are essential for cell communication: one binds to DNA while the other binds molecules called ligands. The latter of the two is where a cancer drug would bind to the cell. Discovering how these two domains talk to each other could accelerate drug discovery for improved breast cancer therapy.

Yang's lab uses a hybrid approach in which computer simulations of the domains garnered from high-resolution structures (recently published at the Journal of Structural Biology; doi: 10.1016/j.jsb.2016.08.001) on OSC's Oakley and Ruby clusters are used to inform structural models in the lab. Driven by experimental discovery on ER, Yang's next step could mean the most to breast cancer patients.

"We're kind of excited in that we now have some ideas of how these molecules work, we're moving toward the next stage of drug discovery," Yang said.

The next step of a drug discovery project is to identify environmental substances that may have an effect in humans similar to an effect produced by a naturally occurring estrogen. This could predict highly promising substances for the design of improved breast cancer therapy. •



▶ Right: Sichun Yang's lab focuses on basic and translational studies of estrogen receptor (ER), a key molecule in breast cancer biology.

Project Lead: Sichun Yang, Ph.D., Case Western Reserve University
Research Title: Multifaceted modeling of estrogen receptor
Funding Source: National Institutes of Health
Website: theyanglab.org