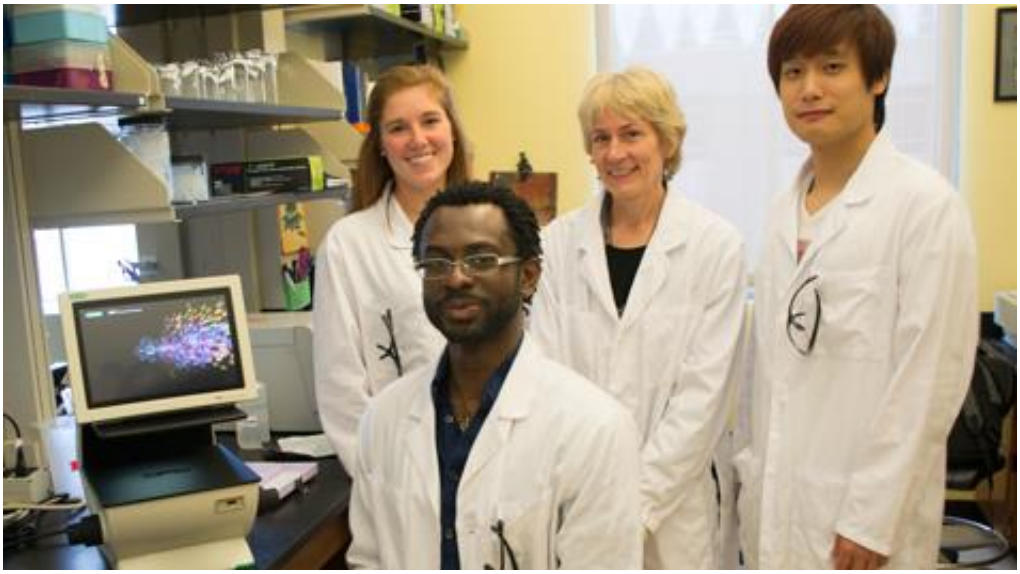
How do you get into downtown Cell City? It's kinda complicated

November 16 2015, by Joseph Mcclain



Some members of the research squad investigating proteins known as thyroid hormone receptor are (from left) Sara Schad '16, Cyril Anyetei-Anum '16, Chancellor Professor of Biology Lizabeth Allison and M.S. student Dylan Zhang. Credit: Joseph McClain

Think of a cell as a city, a metropolis both constructed of and populated by proteins.

Cell City's architects and planners all are downtown, in the nucleus. Proteins move in and out of the nucleus to transact aspects of Cell City's civic business.

But one just doesn't walk into the nucleus and announce that one has business with the genetic information inside the DNA. There is a puzzlingly complex set of biochemical passwords and handshakes that regulate the entry and exit of proteins to and from the nucleus. Lizabeth Allison refers to the phenomenon as intracellular traffic control.

"I like to make those kinds of analogies," she said. Allison is a Chancellor Professor in William & Mary's Department of Biology. Her lab studies nuclear transport—the biochemical processes that allow proteins to travel between the cell's cytoplasm and the nucleus.

Nuclear transport gone awry is at the root of the genesis of a number of cancers as well as some genetic disorders. Allison's nuclear transport work has received a total of $3,086,690 in funding since 2001 from the National Institutes of Health and the National Science Foundation.

Allison's lab focuses on a set of proteins called thyroid hormone receptors. As the name suggests, these proteins bind with thyroid hormone and deliver it to the work site. A thyroid hormone receptor, she explained, has a set of important roles in cell function.

"It functions in the nucleus," she said. "It binds DNA. It turns genes on or off in response to hormone."

Scientists use the term "gene expression" to describe the on-or-off, activation-or-repression of genes. Your DNA contains information for a number of inherited traits, but those traits only "kick in" when the relevant gene is turned on by a molecule such as a thyroid hormone receptor. Differences in gene expression constitute one of the explanations of why identical twins can look so different.

But the role of gene expression goes far beyond transmission of heritable traits and thyroid hormone receptors have some of the most important

jobs in cellular biology.

"Thyroid hormone influences just about every cell in the body, so it's very important in development—development of the brain, development of hearing and vision," Allison explained. "As adults, it's very important for our metabolism."

Bad things can happen when a thyroid hormone receptor is defective in binding the hormone, or can't get in or out of the nucleus. Allison noted that a number of hormone-related disorders and some types of cancer could result.

The transport of the thyroid hormone receptor in and out of the nucleus is far more complex than a simple biochemical version of red light/green light. Allison said that each thyroid hormone receptor has multiple signals for both import and export. Her lab's initial studies have been concentrating on these signals.

"We've really defined those signals pretty well. We know what exact amino acids in a protein are required for interacting with the machinery that takes it into or out of the nucleus," she said. "We're pretty close to understanding what interactions have to occur."

She has found evidence of links between mutations that could lead to various cancers and particular export sequences of the thyroid hormone receptor. Her lab will continue examination of possible effects of genetic mutations on receptor export.

The thyroid hormone receptor has to stay downtown long enough to take care of business, but not so long that it causes trouble. Now that Allison has a good grasp on import and export mechanisms, her lab is switching their focus to retention—the factors that keep the receptor inside the nucleus.

"Since thyroid hormone receptor has both import and export signals, what's keeping it in the nucleus, where it's supposed to function? Why doesn't it just go in and back out and not do anything?" she asks.

To try to answer such questions, Allison's lab is concentrating on the receptors' activities and binding partners inside the nucleus—beyond a receptor's primary nuclear task of binding with DNA.

The lab will drill down into thyroid hormone receptors role in other cellular transport issues as well. Allison said that in addition to mutations that could be links in a chain of cellular miscues that leads to cancer, there are a number of inherited diseases related to improper function of the thyroid hormone receptor.

"They're called resistance to thyroid hormone disorders," Allison explained. "These are ones where people have normal levels of thyroid hormone, but they have a defective receptor that doesn't interact properly."

The methodology relies on sophisticated microscopy and a technique of inserting fluorescent tags into individual proteins to make them stand out under the microscope. The technology allows the researchers to study nuclear transport with the equivalent of a highway traffic camera.

"We use confocal microscopy to do live-cell imaging," Allison explained. "We can actually track movement in time, either between the nucleus and cytoplasm, or we can track movement of a protein within the nucleus."

The lab typically includes a dozen William & Mary undergraduate students. Allison said that five of the current undergraduate lab members are doing honor theses on various aspects of the thyroid hormone receptor investigation. The current team is rounded out by two graduate

students and a lab manager.

Allison pointed out that each of the undergraduates in her lab is focusing on a different aspect relating to the bigger thyroid hormone receptor picture.

"The aim is always that they will accomplish enough to be a co-author," Allison said. "They can look at a paper in a peer-reviewed journal and say, 'This part of it, this figure—that's mine."

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