PRESS RELEASE

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The Wistar Institute Recruits Brian Fuglestad, Ph.D., to Study Cell's "Dual-mode" Proteins

Biophysics & biochemistry expert joins Center for Advanced Therapeutics to study little-understood class of proteins that switch roles inside cell, could translate into future therapies

PHILADELPHIA — (WEDNESDAY, AUG. 19, 2026) — The Wistar Institute, a world leader in cancer, immunology, and infectious disease research, announces the appointment of **Brian Fuglestad, Ph.D.**, as associate professor in the Center for Advanced Therapeutics (CAT). Fuglestad uses biophysical and biochemical approaches to study proteins at the molecular and atomic level. Using advanced tools including nuclear magnetic resonance (NMR), X-ray crystallography, membrane mimetic reverse micelles, and other biophysical techniques, he studies a category of mysterious proteins that drift within the cell until a signal prompts it to latch onto—or release from—the cell membrane.

Most proteins do one of two things: dissolve in the cell's watery interior, called the cytoplasm, or embed within the greasy cell membrane. A cell's outer surface is a membrane that forms the border between inside and outside. Most everything that crosses this border, from molecules to signals, is controlled by proteins that reside in the cell membrane.

The proteins Fuglestad studies are peripheral membrane proteins, specifically reversible membrane proteins that can do either and are unique because their function depends on what is happening in the cell at a given time.

"Between five to upwards of ten percent of our proteins behave like peripheral membrane proteins. They free float in the cell's cytoplasm, staying transient until a signal locks them onto the cell membrane, where they do their work," said Fuglestad. "That's a surprisingly large share of our proteome (the entire set of proteins encoded by our DNA) and it's an untapped space for drug discovery. Because these proteins must travel to the membrane to switch on, you could

selectively target and alter that movement to block it from reaching the membrane, or in other cases shut its function down after it reaches the membrane."

To study these proteins, Fuglestad develops and uses reverse micelle technology to create tiny, lifelike nanoparticles that reproduce the chemistry of a real cell membrane. Then he uses NMR, X-ray crystallography, and other biophysical techniques to probe the structure and function of the proteins at atomic-level resolution.

"We can recreate in a reverse micelle the same chemical composition that you would see in a natural cell membrane, or we can even use lipids extracted from soybeans or other natural sources," said Fuglestad. "We can create a native-like environment that shows us how a protein actually behaves in the cell membrane. We put the reverse micelle into an NMR instrument and look at the protein atom by atom to understand: how it behaves differently when bound to a membrane, what happens when we add a potential drug, and even discover new potential drug candidates using these methods."

Fuglestad's understanding of how peripheral membrane proteins work has led him to target proteins that may point to new treatments for resistant cancers.

One such project focuses on GPX4, a protein central to ferroptosis—a form of cell death driven by iron. In ferroptosis, iron fuels a chain reaction of oxidative damage within the cell's membrane and when left unchecked, the damage can cause the cell membrane to rupture, causing the cell to die. GPX4 is the protein that repairs this damage. Many types of cancer cells are especially dependent on GPX4 to survive.

Fuglestad is working on ways to block GPX4 selectively in cancer cells—sparing healthy cells which also rely on it—as a promising strategy against treatment-resistant cancers.

Another protein he studies is $p47^{phox}$, which resides in the cell cytoplasm and activates NOX2, a member of the seven-protein NOX family implicated in many different diseases. NOX proteins are notoriously difficult to target individually—try to inhibit one but all are inhibited. Fuglestad's approach sidesteps this: rather than blocking NOX2 he targets its activator, $p47^{phox}$. He explains, "when $p47^{phox}$ is switched on it attaches to the cell membrane and activates NOX2." Fuglestad's goal is to prevent that attachment and keep $p47^{phox}$ harmlessly circulating in the cytoplasm.

Another technique in Fuglestad's drug discovery toolkit is applying fragment-based drug discovery to protein membrane interactions on which peripheral membrane proteins depend. Fuglestad puts a spin on this 30-year-old technology by "stitching together many membrane interface target fragments that alone are weak but together can make something more drug-like and stronger binding to a peripheral membrane protein, allowing us to target its function for inhibition."

"Brian brings a rare mix of biochemistry and biophysics and real translational knowhow to a class of proteins that are extremely hard to study," said Paul Lieberman, Ph.D., director of the Center for Advanced Therapeutics and Hilary Koprowski, M.D., Endowed Professor. "He has the tools to see these proteins in action at the atomic level and turn that understanding into finding potential new therapies. That combination is exactly what the Center for Advanced Therapeutics is built for."

Fuglestad received a B.S. in Biochemistry, from Oklahoma State University and a Ph.D. in Chemistry from the University of California, San Diego, in the lab of Elizabeth Komives, Ph.D. He completed a postdoctoral fellowship at University of Pennsylvania Perelman School of Medicine, Dept. of Biochemistry & Biophysics in the lab of A. Joshua Wand., Ph.D. He started his independent career at Virginia Commonwealth University's Dept. of Chemistry before moving to The Wistar Institute.