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Weill Cornell Welcomes Dr. Scott C. Blanchard; His Work in Fluorescence Microscopy Is Revolutionizing Our Understanding of the Cell

For the First Time, Observing Protein Synthesis and Other Single-Molecule Processes

NEW YORK (Nov. 2, 2004) – All life relies on the actions and reactions of single molecules within cells. However, these molecules are so tiny that they have long eluded direct, real-time investigation using conventional light microscopes.

A breakthrough technology being developed by Dr. Scott C. Blanchard – recently recruited to Weill Medical College of Cornell University under the College's *Strategic Research Plan* – is finally allowing researchers an unprecedented view into the workings of individual molecules.

"What people in science have done, up until now, is look at billions of molecules all together," Dr. Blanchard explained. "Because we haven't yet been able to view single molecules at work, we've had to look at patterns of behavior in the ensemble. It's like trying to figure out how a car works by looking from a satellite at traffic on a freeway."

The new methods employed in Dr. Blanchard's research utilize state-of-the-art digital cameras to observe fluorescent biomolecules.

"Using these technologies you can collect photons of light coming from a single molecule. This information reports on a biomolecule's location, its interaction with other molecules, and tiny motions within the molecule itself," explained Dr. Blanchard, who's joined Weill Cornell as an Assistant Professor in the

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Department of Physiology and Biophysics.

"With these tools, we can now look at an enzymatic reaction from the very intuitive perspective of movements. Enzymes are molecular machines with moving parts – but these motions are on the order of a few billionths of an inch," he said.

Prior to his appointment at Weill Cornell, Dr. Blanchard worked in the Department of Applied Physics at Stanford University.

In two recent papers – one published in *Nature Structural & Molecular Biology*, the other in *Proceedings of the National Academy of Sciences* – Dr. Blanchard describes research conducted while at Stanford, based on single-molecule observations of the ribosome.

The ribosome is an assembly of about 60 different molecules working together to read the instructions for making new proteins, coded in DNA. These instructions are presented to the ribosome in the form of messenger RNA (mRNA). The process of translating mRNA instructions into protein involves the selection by the ribosome of adaptor RNA molecules, called transfer RNA (tRNA).

It's the selection of specific tRNA molecules that determines the relationship between the gene sequence and the sequence of the resulting protein.

As Dr. Blanchard explained, "The reaction between tRNA and the ribosome is the basis of what is called the universal genetic code. We are looking at single ribosomes reading mRNA, watching this decision-making process, and trying to understand how the ribosome selects one tRNA over another."

"Ultimately," he said, "we want to understand how the ribosome is mechanically designed to make the correct protein."

Using this new type of microscope, researchers can now watch as the relationship between tRNA and the ribosome plays out.

"We see tRNA approach the ribosome from far away, interacting with it transiently, and then binding

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to it through a series of step-wise motions to create a peptide bond," Dr. Blanchard said. "Our digital movies show one ribosome after another going through the decision-making process of accepting or rejecting tRNA. We have a direct view into this process as it's happening, hundreds of single molecules at a time. This virtually real-time, naked-eye view of individual enzymes at work in the cell was unthinkable before the advent of single-molecule techniques."

And just how important is the ribosome to cell function and human health? According to Dr. Blanchard, because protein synthesis is crucial to the life cycle of all bacteria, roughly 50 percent of antibiotics used today target ribosomal function. Ribosomal function is also key to the success – or failure – of deadly viral infections such as hepatitis C and HIV.

Cancer cells, too, rely on protein synthesis to survive and multiply, so drugs that block ribosomal function in a cancer-specific manner might prove safe and effective chemotherapy, Dr. Blanchard said.

Finally, genetic aberrations in the DNA-ribosome relationship can cause the enzyme to produce faulty proteins that trigger cystic fibrosis and other inherited illnesses.

"Understanding the mechanism of the ribosome may be a fundamental first step for developing antibiotics, cancer therapies, and antiviral drugs," he said. "The ribosome may one day even be a target for gene therapy."

Drug development is a key motivator driving Dr. Blanchard's work. In another experiment, he watched one drug, the antibiotic tetracycline, interact with the ribosome "at the real-time, single-molecule level."

"An advance like that marks the advent of a *major* new drug-discovery tool," he said. "Not only can you look at a drug binding to an enzyme, but also gain a better understanding of how it affects that enzyme."

But Dr. Blanchard stressed that the ribosome is only the beginning.

"Fluorescence techniques like those we are developing should work equally well for other cellular processes hitherto inaccessible to microscopic investigation," he said. "Structures like receptors lying on the

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surface of cells, or ion channels, for example."

He believes the unique resources available at Weill Cornell will speed and enhance his research.

"Even though I work primarily in basic science, what I'm ultimately interested in are discoveries that have practical applications for improving human health," he said. "So the fact that Weill Cornell is a medical school was important to me."

Cornell's cutting-edge technology was another draw.

"For example, the Cornell upstate campus in Ithaca has the nanofabrication facility, which allows me to shrink the scale of our reactions by at least another order of magnitude," Dr. Blanchard said. "That's a real stepping stone to automation of procedures to screen molecules for their potential use as drugs, using conventional high-throughput methods."

Dr. Blanchard's appointment comes as part of Weill Cornell's *Strategic Research Plan*, Phase One of the Medical College's ongoing, multi-million dollar Capital Campaign.

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