# Watching the engine of life, in real time, to understand how things go wrong

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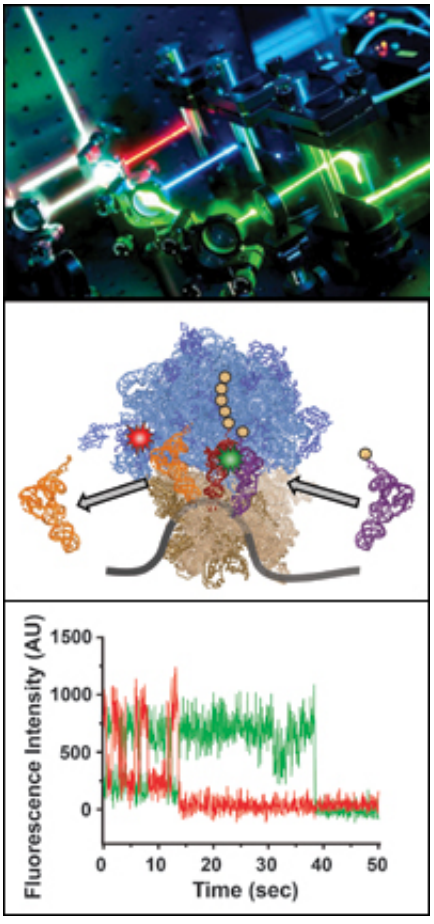


Top: lasers used to illuminate samples. Middle: depiction of ribosome (light blue and tan) walking along messenger RNA template (gray curvy line) and transfer RNA building blocks (orange, red, purple). Green and red stars represent fluorescent dyes that emit signals when illuminated. Bottom: Light signals recorded by the CCD camera reveal information about movement of ribosomal engine.

(PhysOrg.com) -- Ruben Gonzalez views ribosomes—the minute particles in cells that make proteins—as the “machines” of life. Naturally, the associate professor of chemistry is interested in watching these little protein-producing factories in real time, especially when they malfunction and cause disease.

Back when he was a postdoctoral fellow at Stanford, he combined a powerful, laboratory-built light microscope with a charge-coupled device (CCD) camera. The combination operates like a highspeed, high-megapixel video camera, letting him watch ribosomes on a computer screen in real time as they synthesize proteins.

“It’s a technology people used to dream about, but it just didn’t exist,” Gonzalez says. “Now we’re doing experiments that just weren’t possible 10 or 15 years ago.”

Ribosome molecules are about 25 nanometers in diameter—nearly 50,000 times smaller than the diameter of a strand of hair—that “walk” along messenger RNA copies of the genes encoded by a cell’s DNA and use the genetic instructions to construct proteins using amino acids attached to a different kind of RNA called transfer RNA.

Recently, Gonzalez and colleagues published a paper in *Nature Structural & Molecular Biology* that shed light on the mechanism through which the ribosome walks along its messenger RNA template.

How the ribosomal engine rapidly and precisely propels itself along the template while synthesizing a protein remains unknown. Nevertheless, Gonzalez’s team was able to show that, surprisingly, the transfer RNAs are part of the action, serving to control the speed and precision of the ribosomal movement.

The findings are significant because they suggest that transfer RNAs can

manipulate the ribosome's movements, potentially controlling how rapidly and precisely a protein can be synthesized; this provides a new understanding of various diseases caused by the failure of ribosomes to properly synthesize proteins and perhaps a new avenue for treating such diseases.

Gonzalez is one of many scientists struggling to understand aberrations in the synthesis of proteins. These can be traced to mutations in human DNA, which yield abnormal messenger RNAs.

The aberrant messenger RNAs, in turn, cause ribosomes to produce defective proteins or to prematurely terminate the synthesis of proteins, in some cases depriving the human cell of fundamental proteins it needs to stay healthy.

"This kind of mistake can be a very dangerous situation," Gonzalez says. "Our technology allows us to visualize in real time the events leading up to the aberration and then use that information to discover drugs that would prevent the ribosome from making the mistake," he says.

In his laboratory in Havemeyer Hall, Gonzalez is planning experiments building on the research published last summer.

"Understanding ribosomes and how one might regulate, control, block and/or enhance them has the potential to impact a broad array of human genetic diseases," he says.

In cancer, for example, ribosomes in a cell are supercharged, rapidly and uncontrollably generating proteins that allow tumor cells to proliferate. The messenger RNAs originating from viruses such as HIV and hepatitis C hijack ribosomes from healthy human cells, allowing the cells to become miniature factories for mass producing the proteins required to assemble new copies of the viruses.

“There are many anomalies in normal and disease-related human biology where the ribosome will need to do some sort of acrobatic trick in order to produce a protein, involving things like having the ribosome slip forward or backward on its messenger RNA template,” says Gonzalez. “We call these frame-shifting events and, interestingly, their occurrence is controlled, rather than random.”

Gonzalez credits Terri Moore, his chemistry teacher at Miami Senior High School, for sparking his passion for chemistry. He went on to study at Florida International University and completed his doctoral research at the University of California Berkeley. Following postdoctoral work, he arrived at Columbia in 2006, joining a growing group of scientists who are developing sophisticated imaging techniques to better understand the human body and disease.

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