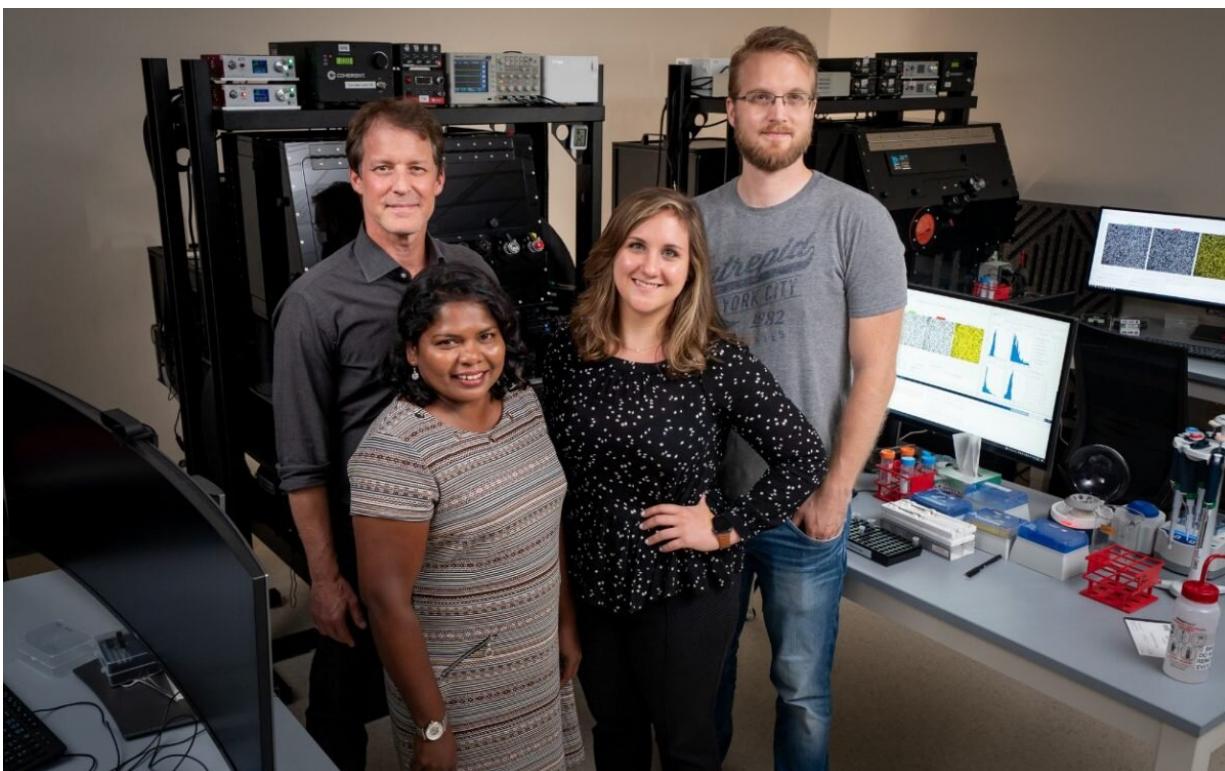


Researchers capture six new structures of the ribosome in action

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From left to right: Co-authors Scott Blanchard, PhD, Structural Biology; Kundhavai Natchiar; Emily Rundlet; and Mikael Holm, PhD, researched how six new structures of the ribosome and how it moves. Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital scientists have used single-molecule fluorescence resonance energy transfer (smFRET) and

cryogenic electron microscopy (cryo-EM) to capture six new structures of the ribosome and its precise, directional movement. A paper on this work was published today in *Nature*.

The ribosome is the cellular organelle responsible for decoding messenger RNA to make proteins. Many antibiotics target the ribosome; therefore, a better understanding of how it works has important implications for [drug development](#).

"A fundamental question in science is how molecules harness thermal and chemical energy to perform their diverse functions," said corresponding author Scott Blanchard, Ph.D., St. Jude Structural Biology. "One of the real mysteries of life is figuring out how molecules navigate between various conformations, in an ordered way, to generate directional motion and work."

Synergistic technologies power research

Expression of the information encoded in DNA makes life possible. DNA is first transcribed into RNA; RNA is then translated into protein. The ribosome is the [molecular machine](#) responsible for this second step. It decodes messenger RNA and makes proteins. Importantly, the ribosome is responsible for the synthesis of cellular proteins in all forms of life.

As the ribosome goes to work, it moves, undergoing what are called conformational changes. The researchers wanted to visualize and thus better understand how that precise movement along the messenger RNA occurs so that it can make a protein.

The researchers used both smFRET and cryo-EM. The work underscores the usefulness and precision of single-molecule technology, as well as how the [imaging techniques](#) together can paint a fuller picture of the

molecules and their associated movement. Cryo-EM has a long history as a powerful structural biology tool, with resolution capabilities that have improved dramatically in recent years. smFRET is a newer technology that provides dynamic structural information that enables researchers to visualize how individual molecules move while they function in real time.

"Our work integrates single-molecule data where we obtain molecular movement information in real time, with cryo-EM, which is a static structural method," Blanchard said. "smFRET is extraordinarily powerful in its ability to reveal an ordered sequence of events with molecular interpretations."

Using these techniques, the researchers captured six high-resolution structures of the bacterial ribosomal complex, including messenger RNA, transfer RNA and elongation factor EF-G, an enzyme involved in reading RNA. The work reveals for the first time how EF-G engages with the ribosome complex.

"One thing that smFRET makes evident is that you need to add the dimensions of time and change to structural biology to really understand molecular functions and [drug](#) actions," said first author Emily Rundlet, Ph.D., St. Jude Structural Biology.

Understanding antibiotics to aid drug development

Antibiotics used to treat bacterial infections target the ribosome. This makes understanding how the [ribosome](#) works, and importantly how it interacts with drug compounds, essential for improving the design and development of new therapies.

"These findings provide a background for studying how antibiotics work, at a molecular scale, how they actually inhibit the functions of this

ribosomal machine in a precise way, in a way that mediates clinical treatment of infectious disease," said author Mikael Holm, Ph.D., St. Jude Structural Biology.

"One of the take-home lessons from our work is that context is everything," Rundlet said. "Molecules are dynamic; you need to look at the actual transition state that the drug actually prevents or that the drug stabilizes to understand the full architecture of the drug-binding site, which can inform medicinal chemistry efforts to make the drugs more potent."

More information: Emily J. Rundlet et al, Structural basis of early translocation events on the ribosome, *Nature* (2021). [DOI: 10.1038/s41586-021-03713-x](https://doi.org/10.1038/s41586-021-03713-x)

Provided by St. Jude Children's Research Hospital

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