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STORY AND PHOTO CAN BE FOUND AT:
http://news.uns.purdue.edu/html4ever/030204.Guo.ATP.html

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NOTE TO JOURNALISTS: A publication-quality graphic of a microscopic motor assembled by Peixuan Guo's team is available at ftp://ftp.purdue.edu/pub/uns/guo.atp.jpeg.

Purdue Researchers Connect Life's Blueprints With Its Energy Source

WEST LAFAYETTE, Ind. - The Purdue University research team that recently created a tiny motor out of synthetic biological molecules has found further evidence that RNA molecules can perform physical work, a discovery that could advance nanotechnology and possibly solve fundamental mysteries about life itself.

Purdue's Peixuan Guo has discovered how viral RNA molecules bind an energy-bearing organic molecule known as ATP. While linking these two substances might seem to create no more than a longer string of letters, the upshot is that now one of life's most mysterious and ancient storehouses of information can be moved by one of its most important fuels. The discovery could shed light on the fundamental role RNA plays in the creation of living things.

"RNA could be even more of a key player than we realize," said Guo, professor of veterinary pathobiology in Purdue's School of Veterinary Medicine. "The fact that it can be made to bind ATP in the phi29 virus could imply that these two molecules were among the first to partner in Earth's dance of life."

On a more practical level, the discovery could have immediate technical applications - such as driving a

Lilliputian motor of the sort Guo's team has recently constructed.

"I think RNA can be made to do mechanical work," he said. "ATP binding could power a motor made of six strands of RNA, and we are now exploring the myriad possible applications of such a tiny mechanism."

The research appears in the February *Journal of Biological Chemistry*.

DNA, RNA and ATP are substances long known to be central to life's processes, but knowledge about their many functions in living things is still emerging. Several years ago, scientists were stunned by the discovery that some forms of RNA - well-known as the "messenger molecule" that carries instructions between DNA strands in a cell's nucleus - could serve as a catalyst for important chemical reactions in the body. The discovery of these RNA catalysts, called ribozymes, convinced many scientists that RNA probably existed on earth before DNA or complex proteins, the two other ingredient molecules necessary to create life.

"There are thousands of kinds of RNA in your body," Guo said. "Most varieties have an unknown function. When ribozymes were discovered, it taught us that RNA was probably responsible for the creation of other complex biological molecules. RNA might be more significant to life on earth than we imagined a few years ago."

Guo's group has discovered another way that RNA might be the keystone for biological processes: they have found that it is able to bind adenosine triphosphate, or ATP, which is the crucial substance used to transfer metabolic energy in living things.

"You couldn't live for one second without ATP," Guo said. "Your muscles, for example, are able to flex because an enzyme called ATPase binds the ATP molecule, breaking one of ATP's chemical bonds and releasing the energy you use when walking or talking."

Guo theorizes that because RNA can also bind ATP, it might be not only life's original seed molecule, but also able to direct the release of the energy needed to create life from that seed.

"We are just beginning to learn about RNA's many functions," he said. "But it is possible that it plays a crucial role in metabolism, too. In that case, RNA would play a more central role in biology than we originally thought. We are seeking fundamental knowledge here."

It is uncertain whether the RNA in living things has ever directed any of ATP's actions, but for the moment, Guo's group has already found a way to make ATP move RNA around. His team has learned to assemble several strands of RNA into a hexagonally-shaped "engine" with a strand of DNA functioning as the axle. When fed a supply of ATP fuel, the RNA strands kick against the axle in succession, much like pistons in a combustion engine. Such minuscule motors could find applications in nanotechnology.

"The world's smallest machines will need equally small motors to propel them," Guo said. "Ours uses organic molecules as fuel, so no special power source would need to be developed."

The motors could also be used not only to spin the DNA strand, but also as potential gene delivery vehicles. Guo's team had already found that the motor could drive its axle into a virus' protein shell, and has recently also learned that the ATP-binding RNA derived from the phi29 virus can deliver a ribozyme that destroys Hepatitis B. A paper detailing this work is forthcoming in the journal Gene Therapy.

"Delivering healthy genes or therapeutic molecules into damaged cells is the goal of gene therapy," Guo said. "With some modifications, we hope our research will enable us to deliver therapeutic molecules to cancerous or other virus-infected cells as well."

Guo's current research is headed in this direction, but he emphasizes that more work also needs to be done on RNA's fundamental capabilities.

"We would like to find other examples of how RNA operates in the body," Guo said. "We know from our research that RNA can be made to perform physical work in a viral system and in the laboratory, so it is possible that it is also involved in the transportation of components within cells."

Such ideas remain speculative for the moment, but Guo said that naturally occurring hexagonal loops of other RNA have been found performing protein transport in drosophila fly embryos.

"The RNA loops in these developing flies are similar to the loops we assembled," he said. "It's a clue that we may be on the right track."

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cb/Guo.ATP

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Related Web sites:

Previous release on Guo's research: http://news.uns.purdue.edu/UNS/html4ever/9808.Guo.RNA.html

Peixuan Guo's Purdue Web page: http://www.vet.purdue.edu/PeixuanGuo/

Journal of Biological Chemistry Web Site version of article:
http://www.jbc.org/cgi/reprint/M209895200v1.pdf

PHOTO CAPTION:

One promising application of RNA-ATP binding is this microscopic motor, assembled by Peixuan Guo's team at Purdue University. The motor, only a few nanometers wide, is formed by six strands of RNA surrounding an "axle" made of DNA. When fed a supply of ATP as fuel, the RNA molecules kick against the DNA in succession, much like the pistons in a conventional motor. (Graphic/Guo Laboratory)

A publication-quality graphic is available at ftp://ftp.purdue.edu/pub/uns/guo.atp.jpeg.

ABSTRACT

Dan Shu and Peixuan Guo

The intriguing process of free energy conversion, ubiquitous in all living organisms, is manifested in ATP binding and hydrolysis. ATPase activity has long been recognized to be a capability limited to proteins. However, the presence of an astonishing variety of unknown RNA species in cells and the finding that RNA has catalytic activity have bred the notion that RNA might not be excluded from the group of ATPases. All DNA packaging motors of dsDNA phages involve two nonstructural components with certain characteristics typical of ATPases. In bacterial virus phi29, one of these two components is an RNA (pRNA). Here we

report that this pRNA is able to bind ATP. Comparison between the chemically selected ATP-binding RNA aptamer and the central region of pRNA reveals similarity in sequence and structure. Replacement of the central region of pRNA with the sequence from ATP-binding RNA aptamer produced chimeric aptRNA that is able both to bind ATP and to assemble infectious viruses in the presence of ATP. RNA mutation studies revealed that changing only one base essential for ATP-binding caused both ATP-binding and viral assembly to cease, suggesting that the ATP-binding motif is the vital part of the pRNA, forming a hexamer to drive the phi29 DNA packaging motor. This is the first demonstration of a natural RNA molecule that binds ATP, and the first case to report the presence of a SELEX-derived RNA aptamer in living organisms.