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Bio-Nanotechnology Breakthrough: Building "Nanomotor and "Nanostructures" with RNA

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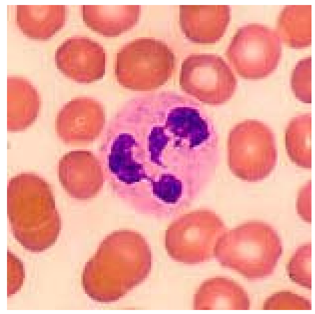
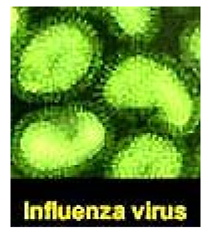




Left: Human red blood cells = 20 micrometers (microns). **Right:** Influenza viruses = about .25
1 micrometer (micron) = 1 / millionth of a meter (39.37 inches)
1 nanometer = 1 / billionth of a meter

August 21, 2004 West LaFayette, Indiana - When you enter the world of bio nanotechnology, you are so small that if one nanometer were the size of a singl regular meter of 39.37 inches would be the size of the Earth! In that nano world are usually *less than one-quarter* the size of one nanometer.

A team of scientists at Purdue University, led by Peixuan Guo, Ph.D. - a molecu virologist in Purdue's Cancer Research Center - have been studying what viruse invade and re-program cells in disease.

One particular virus that invades bacteria gets the bacteria to synthesize an unus powerful phi29 encoded RNA to build little motors so the virus can drive *its* DN protective protein shells that are then inserted into the bacteria and take over the cells' programming.

What's incredible is how the virus builds an organic motor to get its own DNA i protein shell and into the bacteria. The virus gets six bacteria RNA molecules to together in a ring. The scientists use the metaphor of six children linking hands. is able to tell one RNA molecule to clasp its right hand to the left hand of anoth molecule and to clasp its left hand to the right hand of another RNA molecule.

The little ring nano motor then surrounds the virus's DNA, apparently turning li which drives the virus's DNA into the protein shell that is inserted by the virus i host bacteria.

Dr. Guo and his colleague, Dieter Moll, Ph.D., at Purdue's Cancer Research Ce been able to copy the virus's creation of the tiny RNA motors and have been ab the nanomotors in their laboratory to do what *they* want the RNA molecules to Recently, the research team has gone even further in breakthrough work that wa published in *NANO Letters,* a journal dedicated to nanoscience and nanotechno Peixuan Guo's lab is supported by NIH (National Institutes of Health), NSF (Na Science Foundation), DOD (Department of Defense) grants, and Dieter Moll is an Erwin Schrödinger fellow of the Austrian Science Fund FWF.

Monthly journal, ***NANO Letters*** © 2004 by The American Chemical Society.

Dr. Guo and Dr. Moll have been able to make RNA molecules build structures scale that are several micrometers in size. That means the scientists have been a modify what the virus does to make the nanomotors and go beyond to build wit thousands of RNA molecules.

Before this RNA breakthrough, other scientists had been able to manipulate pro DNA, but not to make motors and delivery systems at this minute nano scale. A means that humans working in the totally invisible microscopic world of viruse and copying what the microbes do, might be able to deliver medicines directly i diseased patients or to build molecular electronics that would be the first marria organic and inorganic, a marriage of the living with the non-living.

This week I talked with molecular biologist Dieter Moll, Ph.D., whose backgro protein bio-nanotechnology at the University of Agricultural Sciences in Vienn before joining Dr. Guo's lab about two years ago.

Interview:

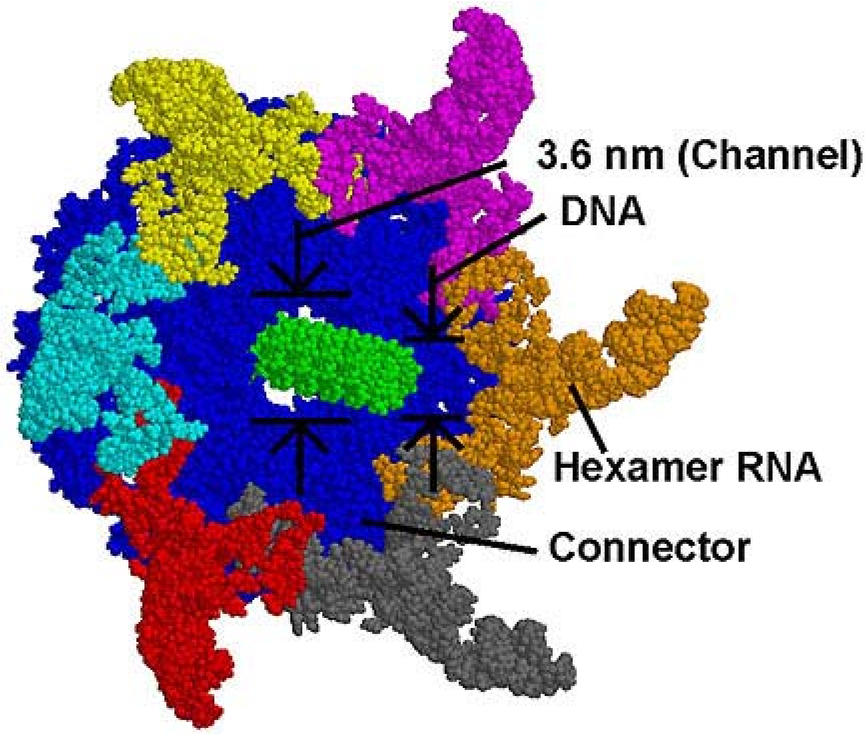
Dieter Moll, Ph. D., Post Doctorate Research Associate since February 200 Laboratory of Prof. Peixuan Guo (PAI-shun gwoe), Ph.D., who is Professo Molecular Virology, Purdue Cancer Research Center, Purdue University, Lafayette, Indiana: "Only recently, we've found out that if the virus can get su use out of this molecule, then maybe we could get some good use out of it, too.

WHEN THE VIRUS PROVOKES THE RNA TO MAKE THIS MOTOR RIN DOES THE VIRUS USE THIS 'MOTOR?'

This virus, when it infects a bacterial cell, it gets the cell to produce viral comp next generation of viruses. These viral components have to come together and f

complete virus particle. Part of that involves an empty protein shell the virus ha
involves the DNA, a long molecule carrying the genetic information. this DNA
needs to go inside the protein head so it's protected there. This DNA molecule c
really want to go in there (empty protein shell). So, the virus needs a motor to b
stuff the DNA molecule into the protein shell. This RNA molecule is an essenti
component of the molecular motor that does that job for the virus.

And what we think may be happening is that 6 RNA molecules will turn the co
the connector will act like a hex nut driving the bolt, which is the DNA, into the
shell.



"Nanomotor" that is naturally produced by a virus that infects bacteria. The virus wants to ins
(green tube at center) into a protective protein shell the virus makes to invade a bacterium. Th
"arms"
(yellow, magenta, orange, grey, red and turquoise) are six RNA molecules the virus manipul
"Hexamer RNA."
(The perspective is at a slight angle so the turquoise arm is curved up, not outward.) Each of t
molecules
has a "right and left hand" which can link up with the other RNA molecules to forma ring, th
RNA. The dark
blue area around the green DNA is a protein plate called a "Connector"that connects the six RN
leaving a 3.6 nanometer (nm) "donut hole" called a "Channel."After the virus lines up its DN
3.6nm hole, the Hexamer RNA is rotated around the DNA"like a hex nut would drive a
The "grains" throughout the 3-d computer model represent protein.
Graphic © 2004 by Peixuan Guo, Ph.D. and Dieter Moll, Ph.D.

WHERE THE 6 MOLECULES ARE RINGED TOGETHER, THE ASSUMPT
THAT IT IS TURNING. AND THAT WOULD BE THE 'MOTOR' DESIGNA
THAT WOULD BE MOVING THAT PROTRUDING DNA AT THE CENTE
THE VIRUS'S PROTEIN SHELL?

That's right. Another reason why this whole structure qualifies as a motor is bec uses energy. It takes ATP, which is molecular fuel of the cell the gasoline of th hydrolyzes ATP and converts the energy of ATP into mechanical motion. That's call it a motor.

Modifying Nature's RNA Motor Design for Human Bio-Nanotechnology

HOW DO YOU AND DR. PEIXUN GUO THINK THAT THESE NATURAL MOTORS CAN BE USED IN HUMAN BIO-NANOTECHNOLOGY?

What we did was to modify these RNA molecules. On the virus, they form this structure by holding hands. We modified the hands of these RNA molecules. Sc particular RNA molecule cannot just hold hands with any other partner, but it ca hold hands with a particular partner. so, we can basically tell one RNA molecul take this other RNA molecule to your right and this other one to your left.' That can tell each RNA molecule exactly where to go.

WHEN YOU CAN DO THAT, HOW DOES THAT HELP HUMANS AT THI NANOTECHNOLOGY LEVEL?

One of the big challenges in nanotechnology is to make defined architectures, d structures that are at the nanometer scale. We can tell RNA molecules exactly w and in which position to arrange themselves and that is a way for us to make str have nanometer dimensions and properties.

GIVE ME AN EXAMPLE OF WHAT YOU THINK YOU COULD BUILD IF COULD CONTROL THESE RNA NANOMOTORS?

First, let me explain what we have built already. We modified the hands of thes molecules so we can tell each RNA molecules which neighbor to choose. For th hand interaction, the body and legs of the RNA molecules are not really require can change them. It doesn't matter what they look like. So, what we did was to r RNA molecule and give it a very long leg and tell it, 'You go to the right of ano molecule that has got its legs chopped off. And go to the left of another RNA m that has its legs fused together. So, that way we can create a variety of shapes ar molecules, molecular assemblies, at the nanometer scale.

Beyond Building RNA Nanomotors to Building RNA Nanostructures

So far, it's not really useful because it's only long or short legs or something. Bu step we are working on right now is to make one RNA molecule that holds, for nano particle and another that holds a nano wire. Then if you can make RNA as that will line up, for instance, a nano particle with a nano tube and a nano wire, gets very interesting and elegantly surreal nanotechnology.

I SEE, AND WHEN YOU USE THE WORD 'WIRE,' YOU'RE NOT TALKIN
ORGANIC PROTEIN CHEMISTRY. YOU'RE TALKING ABOUT SOMETH
A VERY FINE COPPER WIRE THAT THE RNA NANO MOTOR COULD E
TO ASSEMBLE A COPPER WIRE WITH SOMETHING ELSE?

It wouldn't be a copper wire. Let me stress here that nanotechnology is always a
disciplinary approach. We need the input from nanotechnology from other field
material science that can make nano wires out of semi-conductors or who can h
tubes. Then we can link these components that other nanotechnologies make to
and use our RNAs as a scaffold to assemble these nano components in a definec

SO, HUMANS ARE COPYING THE VIRUS WORLD THAT USES RNA TC
ASSEMBLE THINGS FOR VIRUSES.

Exactly. And the reason that molecules of life just work on a nanometer scale ar
very well on a nanometer scale is because they have learned to do that over billi
years. For that reason, we are turning to the biological world for inspiration for
nanotechnology. But also to take the actual building blocks. We are recruiting tl
blocks that this particular virus has already developed and we are taking those b
blocks and all we have to do is modify it. And get it to do what we want it to do
than what the virus wants it to do.

Organic Computers?

IS THE IMPLICATION THAT WE COULD END UP WITH COMPUTERS M
OUT OF ORGANIC MATERIAL?

I think there are several different applications here. One is to use these nanostru
molecular electronics, basically to try to make electronic devices now by differe
on a much smaller and more powerful scale.

Another issue is that these nanostructures are the same size of the molecules of
is the reason they are also very good at interacting with living cells. So, another
application is in the biomedical fields where we can use these nanostructures fo
as bio-sensors or eventually to connect our microscopic world and computerize
world with the living world, with cells and establish a communication between
our microscopic world. It can be a two-way communication. We might be able
information out of the cells and the cells will be able to tell us how they are. It r
work the other direction. We could get information into the cells and tell them v
in a new sort of way.

RNA Delivery Structures Can Target Specific

Cells for Medical Treatment

CAN YOU GIVE ME AN EXAMPLE OF SOMETHING YOU HAVE DONE ALREADY THAT WOULD SHOW PROMISE OF USING THIS KIND OF TECHNOLOGY TO TREAT SOMEBODY? OR HEAL SOMEBODY?

Yes, we targeted a gene that played a role in cancer and by knocking out this pa gene, we were able to kill cancer cells in the lab. But it's not working in a patier

BUT THAT WAS STILL WORKING WITH RNA AND MAKING THE RNA MOLECULES DO WHAT YOU WANTED THEM TO DO?

Yes, exactly. That is based on assembling RNA superstructures in a defined wa can control by defining this hand-in-hand interaction we have been talking abou targeting these RNA nano complexes to cells and letting them to do a particular cells.

YOU'RE SEEING THAT NANOTECHNOLOGY RNA MOTORS COULD B TO DELIVER MEDICINE OR PERHAPS EVEN TO CORRECT A DNA PRO ON A LOCALIZED LEVEL THAT WOULD BE STILL TREATMENT, AS C TO A UNIVERSAL STEM CELL CORRECTION OF ALL DNA IN ALL CE

Yeah, that is right. There is a new technology that is under hot debate. It works in the lab. It is based on RNA molecules that can regulate gene expression and l particular gene. This works very well in the lab and now people are trying to us therapeutic applications and in therapy, the big issue is how are we going to get molecules that are going to do the healing job into the cells? How are we going cells? And how are we going to deliver the functioning RNA sequence? We bel our RNA nanostructures, we have a targeting and delivery vehicle because we c a functional unit that can target a particular cell for instance, a cancer cell and this targeting RNA molecule with other RNA molecules that can hold the cure a problem that the cell has.

YOU COULD TARGET AN ENTIRE TUMOR IN THE BRAIN OR LIVER C PANCREAS THAT ARE VERY DIFFICULT AND USE THIS TARGETING MECHANISM WITH THESE NANOMOTORS TO DESTROY JUST THE C. CELLS?

We are hoping in the future that may be possible. In the moment, we are just wo cell structures in the lab on a small scale. We are making the initial steps to see can do with this with these nano complexes. But the first results are very promi:

Large RNA Nanostructures for Molecular Electronics Mixing Living with Non-Living

WHAT WOULD YOU PERSONALLY LIKE TO SEE BE ONE OF THE RES

ALL OF YOUR WORK?

I would like to see that eventually that we can use our RNA nanostructures as s
make functioning nano devices. That could be nano devices that work in molec
electronics. Or they could be nano devices that work to help cure diseases.

IF YOU ARE WORKING IN ELECTRONICS, DOES THAT MEAN THAT I
FUTURE THERE WOULD BE A MARRIAGE BETWEEN THE ORGANIC
WORLD AND THE INORGANIC MINERAL WORLD?

That is what we are aiming at, yes. We have already got preliminary results wh
managed to link inorganic nano particles to RNA so that is the first step in linki
living world with the non-living world. In the long run, we are hoping to establi
communication between the living and the non-living world.

ONCE YOU DO THAT, HOW WOULD YOU SUSTAIN THE ORGANIC R
STRUCTURES MEANING THAT'S LIFE THAT HAS TO HAVE SOME KI
FOOD AND ENERGY WITH THE INORGANIC WHICH DOES NOT?

There are two different scenarios. One is that they would use these structures ju
micro-electronic applications. In that case, the job of the RNA would be to act a
scaffold to arrange nano components and after that, the job of the RNA is done
be replaced with something that is much more durable and sturdy.

The other scenario is that we use the nanostructures in cells, in cellular backgro
then the cells would be doing the job of maintaining the organic molecules.

IT'S REALLY INCREDIBLE ISN'T IT?

Yeah, it's a hot area and a lot of things can be done. The most recent progress w
got these RNA nanostructures to assemble on a large scale to form structures th
several micrometers in size. That is important because it matches the size range
can achieve in conventional micro structuring technology. The way we did that
individual RNA building blocks together so that we form a twin that has two se
So, with that architecture we are not limited to building a finite ring of RNA m
But we can get the RNA molecules to assemble infinitely and form very large s
And we got structures that are composed of several thousands of molecules and
several micrometers in size.

THE RNA WAS ABLE TO ASSEMBLE EXACTLY THE WAY YOU WAN
ASSEMBLE?

That's right. By designing the RNA molecules in a particular way, we were abl
RNA molecules how to assemble and form the structures that we wanted to for
cannot completely bend the arm of Nature. We just have to redesign the biologi
building blocks so that they assemble in the way we want. There are not unlimi
possibilities. We have to take into account what Nature wanted these molecules

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http://pubs.acs.org/journals/nalefd/