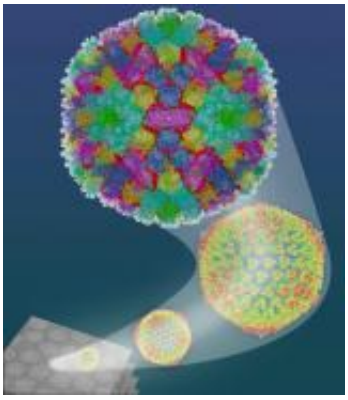
Novel nanotechnology collaboration leads to breakthrough in cancer research

September 1 2010, By Mike Rodewald



Structure of an adenovirus. By averaging thousands of noisy cryo-electron microscopy images (left bottom), researchers have determined the atomic structure of the human adenovirus (color). This structure reveals complex interactions among protein networks (center). Such interactions can be targeted to optimize an adenovirus for anti-cancer and gene therapy applications.

(PhysOrg.com) -- One of the most difficult aspects of working at the nanoscale is actually seeing the object being worked on. Biological structures like viruses, which are smaller than the wavelength of light, are invisible to standard optical microscopes and difficult to capture in their native form with other imaging techniques.

A multidisciplinary research group at UCLA has now teamed up to not only visualize a virus but to use the results to adapt the virus so that it can deliver medication instead of disease.

In a paper published last week in the journal *Science*, Hongrong Liu, a UCLA postdoctoral researcher in microbiology, immunology and molecular genetics, and colleagues reveal an atomically accurate structure of the adenovirus that shows the interactions among its protein networks. The work provides critical structural information for researchers around the world attempting to modify the adenovirus for use in vaccine and gene-therapy treatments for cancer.

To modify a virus for gene therapy, researchers remove its disease-causing DNA, replace it with medications and use the virus shell, which has been optimized by millions of years of evolution, as a delivery vehicle.

Lily Wu, a UCLA professor of molecular and medical pharmacology and co-lead author of the study, and her group have been attempting to manipulate the adenovirus for use in gene therapy, but the lack of information about receptors on the virus's surface had hampered their quest.

"We are engineering viruses to deliver gene therapy for prostate and breast cancers, but previous microscopy techniques were unable to visualize the adapted viruses," Wu said. "This was like trying to a piece together the components of a car in the dark, where the only way to see if you did it correctly was to try and turn the car on."

To better visualize the virus, Wu sought assistance from Hong Zhou, a UCLA professor of microbiology, immunology and molecular genetics and the study's other lead author. Zhou uses cryo-electron microscopy (cryoEM) to produce atomically accurate three-dimensional models of biological samples such as viruses.

Wu, who is also a researcher at the California NanoSystems Institute (CNSI) at UCLA, learned of Zhou's work after he was jointly recruited

to UCLA from the University of Texas Medical School at Houston by the UCLA Department of Microbiology, Immunology and Molecular Genetics and UCLA's CNSI.

About a year ago, once the transfer of Zhou's lab was complete, Sok Boon Koh, one of Wu's students, sought out Zhou's group for their expertise and initiated the collaboration.

"This project exemplifies my excitement about being part of an institute as innovative as CNSI," Zhou said. "Not only am I able to work with state-of-the-art equipment, but because CNSI is the hub for nanotechnology research and commercialization at UCLA, I have the opportunity to collaborate with colleagues across many disciplines."

Working in the Electron Imaging Center for Nanomachines at the CNSI, a lab run by Zhou, the researchers used cryoEM to create a 3-D reconstruction of the human adenovirus from 31,815 individual particle images.

"Because the reconstruction reveals details up to a resolution of 3.6 angstroms, we are able to build an atomic model of the entire virus, showing precisely how the viral proteins all fit together and interact," Zhou said. An angstrom is the distance between the two hydrogen atoms in a water molecule, and the entire adenovirus is about 920 angstroms in diameter.

Armed with this new understanding, Wu and her group are now moving forward with their engineered versions of adenovirus to use for gene therapy treatment of cancer.

"This breakthrough is a great leap forward, but there are still many obstacles to overcome," Wu said. "If our work is successful, this therapy could be used to treat most forms of cancer, but our initial efforts have

focused on prostate and breast cancers because those are the two most common forms of cancer in men and women, respectively."

The group is working with the adenovirus because previous research has established it as a good candidate for gene therapy due to its efficiency in delivering genetic materials inside the body. The virus shell is also a safe delivery vehicle; tests have shown that the shell does not cause cancer, a problem encountered with some other virus shells. The adenovirus is relatively non-pathogenic naturally, causing only temporary respiratory illness in 5 to 10 percent of people.

CryoEM enables such a high-resolution reconstruction of biological structures because samples, in water, are imaged directly. In contrast, with X-ray crystallography (the conventional technique for atomic resolution models of biological structures), researchers grow crystal structures replicating the sample and then use diffraction to solve the crystal structure. This technique is limited because it is difficult to grow crystals for all proteins, samples for x-ray crystallography need to be very pure and uniform, and crystals of large complexes may not diffract to high resolution. These limitations resulted in critical areas of the adenovirus surface being unresolved using x-ray crystallography.

More information: *Science* paper: www.sciencemag.org/cgi/content … ct/sci;329/5995/1038

Provided by University of California Los Angeles

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