Unraveling the inner structure of a nucleus

The cells of plants and animals are superb packers. Each cell must jam large quantities of DNA, parceled into thread-like structures called chromosomes, into a microscopic sac known as the nucleus. The 46 chromosomes in the nucleus of a human cell would extend several feet if stretched out.

One of the continuing mysteries of cell biology is how a cell folds, wraps, and organizes these chromosomes inside its nuclear sac. For a long time, biologists thought that chromosomes floated at random around the fluid interior of the nucleus, without any specific organization. That view is slowly changing.

"There's remarkable organization within the nucleus," argues John W. Sedat of the University of California, San Francisco (UCSF). "People have started to appreciate that the nucleus is a gold mine and vastly understudied."

At the American Association for the Advancement of Science meeting in Seattle this week, Sedat described some of the prized nuggets his research group has recently extracted from that mine.

In one series of experiments, Sedat, UCSF colleague David A. Agard, and their coworkers studied the nuclei of fruit fly cells. They used fluorescent tags, probes made of DNA that bind to specific DNA sequences on one of the fly chromosomes.

The researchers found that about 18 percent of the DNA probes they tested consistently lit up parts of the nucleus' outer membrane, or envelope. "We can find specific chromosome regions clearly stuck to the nuclear envelope," concludes Sedat.

Moreover, certain DNA sequences tagged by some of the other DNA probes are consistently found at particular sites in the interior of the nucleus. From this evidence, Sedat draws a picture in which a chromosome regularly threads its way toward and away from the nuclear envelope.

Sedat's coworkers and their collaborators have also begun to study the movement of chromosomes within the nuclei of living cells from yeast and fruit flies. They have used proteins that both bind to specific DNA sequences and carry a fluorescent marker.

These probes show that some regions of chromosomes meander slowly around the nucleus, apparently in a random manner similar to the Brownian motion of smoke particles in the air. Yet the movement of any particular region seems to be confined to a small portion of the nucleus, says Sedat.

"These are the first measurements of how fast and how far a DNA sequence . . . roams around the relatively crowded nuclear volume," says Barbara Trask of the University of Washington in Seattle.

Sedat's group has further used its probes to study how chromosome pairs come together. In a nucleus, there are usually two copies of each chromosome, one inherited from the mother and one from the father.

During the cell cycle, these pairs split apart, then rejoin. Sedat's group has found that some chromosome regions align with their partner sequences long before the other regions follow suit. The union of maternal and paternal copies is apparently not a seamless process; rather, it leaves temporary gaps. "It's not a zippering. It's more like a buttoning," says Sedat.

By comparing their data to computer simulations of how chromosome pairs might join, he and his colleagues find support for a model in which each chromosome copy moves at random and eventually bumps into its counterpart. Another theory had held that the nucleus has some specific mechanism to bring the chromosome pairs together.

This examination of nuclear architecture remains in its early stages, Sedat notes. In the future, his team plans to study whether the organization of chromosomes varies among an organism's cell types. Trask also wonders whether it differs from one organism to the next.

Once scientists have a handle on that structure, says Sedat, they can try to explain how it aids a cell in its myriad functions. For example, nuclear organization may help determine which genes on a chromosome are turned on or off in a cell. *— J. Travis*

New drugs zap cancer cells with radiation

Radiation and chemotherapy have long been the most potent anticancer weapons. Now, researchers are testing drugs that combine the two techniques and may one day act as smart bullets for treating certain kinds of cancer.

At the American Association for the Advancement of Science meeting in Seattle this week, scientists discussed these drugs—radioactive atoms chemically attached to antibodies. The antibodies seek out and bind to specific proteins on the surface of cancer cells.

Unlike total body irradiation, the drugs bring radiation to bear directly on cancerous areas, reducing healthy tissue's exposure. The drugs might effectively treat cancers like leukemia, in which diseased cells are dispersed throughout the bloodstream, with fewer side effects than traditional remedies.

Janet F. Eary of the University of Washington Medical Center in Seattle described her team's studies of a treatment for leukemia and lymphoma that uses an antibody carrying iodine-131. These atoms emit highly penetrating gamma rays, which destroy tumor cells but also damage healthy tissue.

Taking a newer approach, a team at the Memorial Sloan-Kettering Cancer Center in New York focuses on the isotope bismuth-213, which gives off alpha particles when it decays. The researchers attach single atoms of Bi-213 to antibodies that target CD33, a protein on the surface of myeloid leukemia cells.

Alpha particles are helium nuclei, which are much heavier than other forms of radiation and don't travel very far. "One of the appealing features is that the radiation is confined to one or two cell diameters," says David A. Scheinberg, chief of the leukemia service at Sloan-Kettering. Because many antibodies can attach to a single cancer cell, the new drug delivers an estimated 50,000 times more radiation to the leukemia cells than to noncancerous tissues.

The short range of effectiveness, however, may limit the types of cancer that can be treated with the method. The alpha particles probably won't penetrate large, solid tumors. The technique could work on cancers that have spread throughout the body or those characterized by many small clusters of cells, such as ovarian cancer.

In choosing a particular radioactive atom to use, says Joel M. Tingey, a chemist at the Pacific Northwest National Laboratory in Richland, Wash., "you have to look at several different effects: its half-life, what type of radiation [it emits], how long it stays in the body, and where it goes. You have to look at what it's going to decay into and the effect of those things on the body."

Half of the Bi-213 decays in just 47 minutes; most of it is gone in a few hours.

Part of the challenge in developing these drugs is chemically binding the radioactive atoms to the antibodies. Bi-213 is "attached through a [linker molecule] known as DTPA, which is like a little cage that holds it in place," Scheinberg says. The Bi-213 can be linked to the antibody in as little as 6 minutes and can be done where patients are being treated—essential factors when using an isotope with such a short half-life. Waiting too long to inject the drug into a patient would render most of it ineffective.

A clinical trial for the Bi-213 antibody has just begun, so the researchers don't yet know how effective the method is or whether patients will suffer significant side effects. So far, the study has shown that the drug is not acutely toxic and that it reaches the cancer cells in a few minutes. *— C. Wu*