BIOMED VOL 16.EXP 9/27/2001 11:45 PM Page 1

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Biomedical FRONTIERS

Advances in Science, Technology, and Medicine at Columbia University Health Sciences

Bow Tie for Mitral Valve

Olfactory Clues

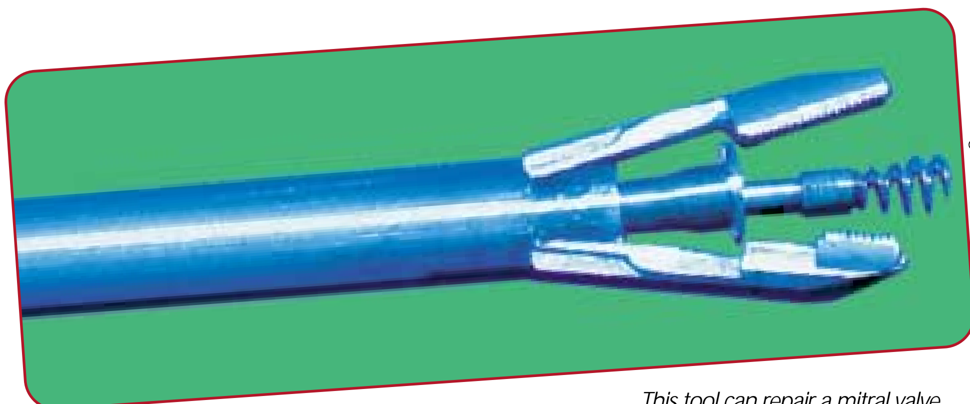
Columbia Research Goes to Market

Special Section: Columbia Genome Center

Focus on Disease, p.6
Guided by Evolution, p.8
Warp Speed Analysis, p. 9

Photos: Carlos Rene Perez / Special Effects: Howard R. Roberts

Tiny Tool Ties Bow Tie to Repair Mitral Valve



David Morales/Mehmet Oz

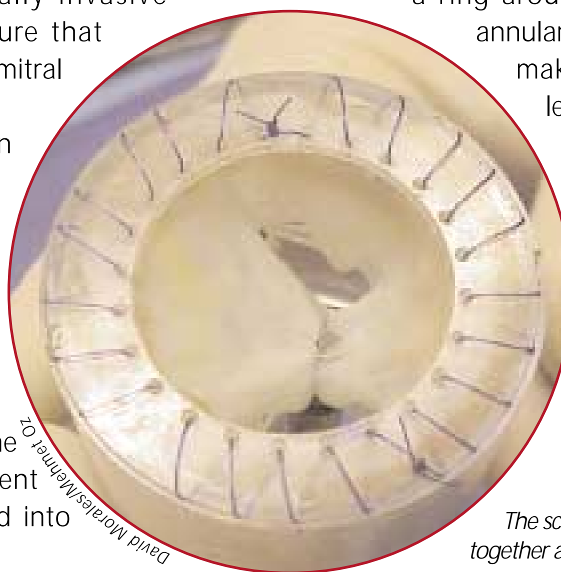
This tool can repair a mitral valve without having to open a patient's chest.

When the leaflets of the heart's mitral valve fail to meet squarely and form a seal, the heart's ability to pump blood through the body is compromised. This condition, known as mitral valve regurgitation, can be life-threatening. Assistant professor of surgery Dr. Mehmet Oz has developed a tool that allows physicians to use minimally invasive surgical techniques to repair a defective mitral valve without opening the chest or stopping the patient's heart. Dr. Oz has applied for a patent on the tool and licensed it for development.

"This tool offers a minimally invasive approach to an elegant procedure that directly addresses the problem of mitral valve prolapse," says Dr. Oz.

The mitral valve lies between the left atrium and the left ventricle. Oxygenated blood returning to the heart from the lungs collects in the left atrium. It then flows through the mitral valve into the left ventricle. When the left ventricle contracts to pump blood out the aorta to the body, the mitral valve clamps shut to prevent any blood from flowing backward into the left atrium. But if the valve doesn't close properly, some blood flows back into the atrium, robbing the ventricle of its full pumping power. While many people can live long, healthy lives with minor mitral valve prolapse, some people need it repaired to prevent ailments including arrhythmia, stroke, and heart failure.

Mitral valves are most commonly repaired by placing a ring around the outside of the valve. This annular ring squeezes the valvular opening, making it more likely that the valve's leaflets will join well enough to form a tight seal. Mitral valve repair is a major procedure, requiring open-heart surgery and use of a cardiopulmonary bypass machine to pump blood through the patient's body. And since it only indirectly addresses the problem caused by the failure of the leaflets to meet squarely, it can fail to solve the problem.



David Morales/Mehmet Oz

The screw holding the mitral valve leaflets together assures that the valve closes properly.

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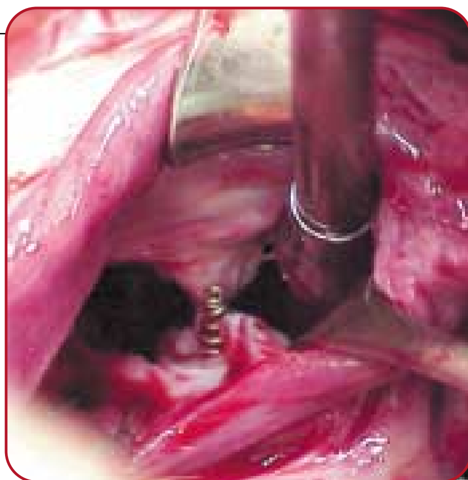
BIOMED VOL 16.EXP 9/27/2001 11:45 PM Page 3


David Morales/Mehmet Oz

Canine experiments of the grasper tool and mitral valve screw have been successful. Dr. Mehmet Oz hopes to use the tool on humans within two years.

David Morales/Mehmet Oz

In the fall of 1996, Dr. Oz learned about a new technique from Ottavio Alfieri, the Italian surgeon who developed it. In the procedure a surgeon joins the two leaflets with a single stitch. The valve can still open on both sides of the stitch, allowing adequate blood flow through the valve. But the stitch assures that the two leaflets come together properly when they need to. The procedure is called a bow tie because the open valve, stitched together in the middle, has a bow-tie shape.

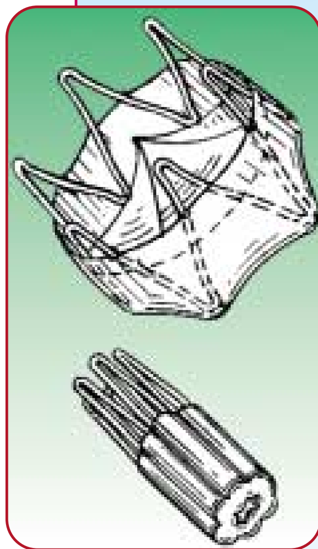
Dr. Oz tried the procedure with good results on several patients in whom an annular ring did not repair the valve prolapse. It was such a simple procedure that Dr. Oz thought he might be able to create a "more elegant" minimally invasive approach.

He developed a tiny grasping tool that could be threaded through a catheter into the heart, where it could grab the two mitral valve leaflets and bring them together. Each side of the grasping arm can move to adjust the valves so that they line up correctly. Behind the grasper is a tiny coiled wire screw, which can then be threaded into the joined flaps to hold them together.

Dr. Oz tested the tool and screw on several mitral valves removed from cadavers, then on nine dogs. Both the tool and the procedure worked properly. The tool was threaded into the dogs' hearts via a small incision in the chest. The dogs had their chests opened and were put on cardiopulmonary bypass machines for about half an hour so that surgeons could directly observe that they were placing the screw properly. In future studies, Dr. Oz plans to use echocardiography to observe the placement of the valve leaflets and the screw, thus avoiding open-heart surgery and the use of the bypass machine. Dr. Oz, postdoc residency fellow David Morales, and their colleagues reported their work in the *Heart Surgery Forum* in June 1999. The article won the journal's residents writing award, and Dr. Morales received a $10,000 grant as the prize.

The Foundry, a small company dedicated to minimally invasive surgery, licensed rights to the tool. The company is refining its design and manufacturing techniques. Dr. Oz is testing the tool on more animals and expects to use it on humans within two years. ❐

Collapsible Heart Valve May Prevent Need for Open-Heart Surgery



Sometimes a heart valve becomes so damaged that it must be replaced. In the United States approximately 100,000 defective heart valves are replaced each year. Replacement requires open-heart surgery, which is traumatic to patients and costs between $30,000 and $50,000.

Assistant professor of surgery Dr. Marc Bessler has developed a collapsible heart valve that may one day be implanted with a catheter instead of open-heart surgery. In January 1999, Dr. Bessler received a patent for the device.

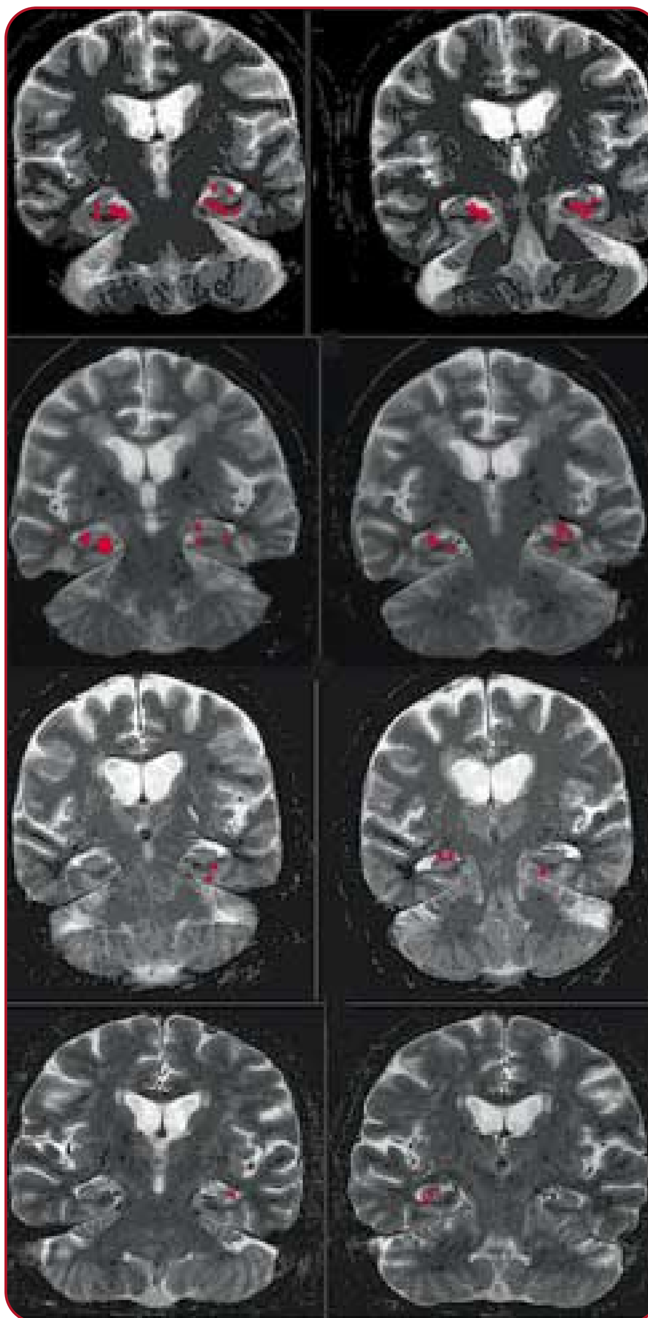
The valve is composed of a stainless steel wire frame wrapped in fibrous tissue. It can be collapsed into a shape small enough to fit in a catheter that could be threaded through a person's veins into the heart. The valve has several barbs extending from its outside surface, which anchor it to the heart muscle.

"Having these barbs allows the valve to seat itself, without any need for stitches," says Dr. Bessler.

Dr. Bessler developed the valve with Dr. Timothy Chuter, who has since moved to the University of California at San Francisco. Dr. Bessler successfully tested prototypes briefly in three pigs as replacements for aortic valves.

In addition to the valve, Drs. Bessler and Chuter's patent includes a description of how a diseased valve might be removed and the artificial valve implanted through a minimally invasive catheter. ❐

Brain Scans Could Provide Early Diagnosis of Alzheimer's Disease



Scott Small et. al

Functional magnetic resonance imaging has revealed two distinct patterns of memory loss in elderly patients. Normal memory decline is associated with continued activation of the entorhinal cortex of the hippocampus, as shown in the top four scans in the image above. Memory loss preceding the development of Alzheimer's disease is associated with decreased activation of the entorhinal complex, as shown in the bottom four scans.

Associate professor of neurology Dr. Scott A. Small has used functional magnetic resonance imaging (fMRI) to detect two distinct patterns of memory loss—one associated with normal aging and the other associated with Alzheimer's disease. The findings, published in the April 1999 issue of *Annals of Neurology*, provide hope that a test could one day be developed to diagnose Alzheimer's disease.

"A test that could do so would be extremely helpful in identifying individuals in the early stages, when the main focus of treatment is halting progression—the earlier, the better," says Dr. Small.

Memory decline with age is common, with some reports suggesting that more than 40 percent of people over age 60 have some memory impairment. But not all age-related memory decline leads to the development of Alzheimer's disease. Both Alzheimer's disease and other age-dependent physiologic changes probably contribute to memory decline in the elderly. A key question for researchers is, "how do we distinguish between these processes?"

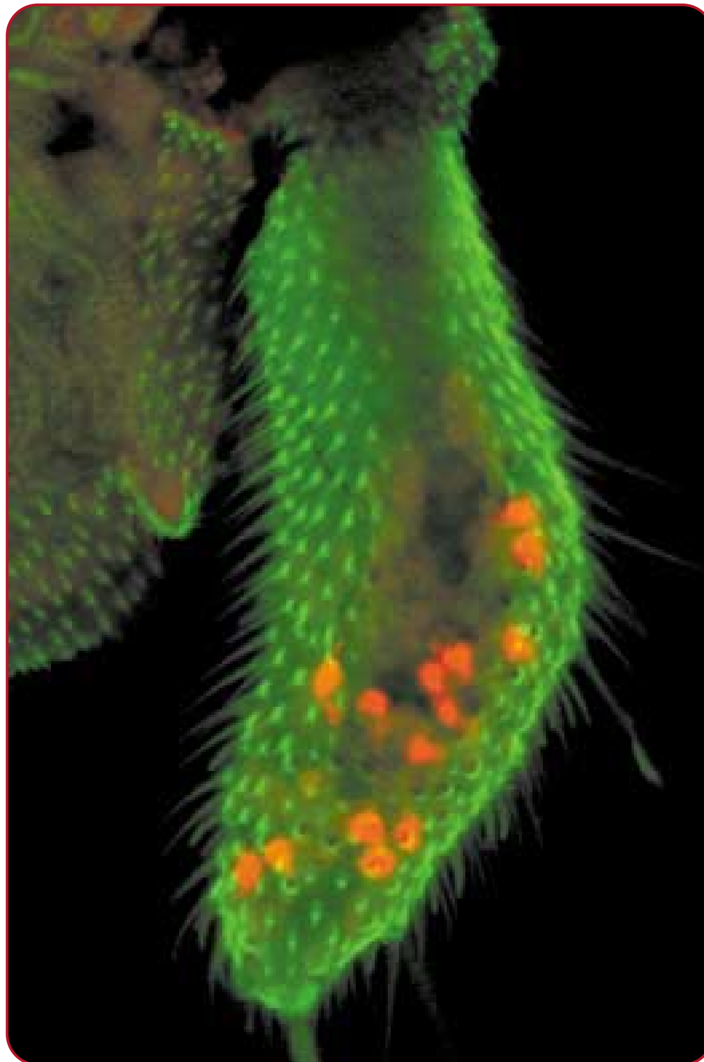
Dr. Small and his colleagues used fMRI, a non-invasive modification of traditional MRI, to analyze changes in the hippocampus region of the brain during memory tests. It's been known for decades that the hippocampus is integral to the brain's memory function. Other imaging techniques, such as PET, do not have as good a resolution as fMRI and could not show how specific areas alter as memory declines. The study led by Dr. Small is the first to document functional changes in various areas within the hippocampus.

The study first evaluated memory function in three groups of individuals over age 64: four patients with normal memory, 13 with isolated memory decline, and four with mild Alzheimer's disease. All of the study participants viewed photographic portraits for four minutes while undergoing a brain MRI. Study participants were followed for at least three years. The researchers then conducted fMRI and memory testing on the 13 individuals with isolated memory decline.

"We were able to show two distinct patterns of age-related memory decline in the healthy, non-demented elderly. We believe that those individuals with dysfunction in the entorhinal region of the hippocampus have early Alzheimer's disease, while those with dysfunction in other regions of the hippocampus do not," says Dr. Small. ❒

BIOMED VOL 16.EXP 9/27/2001 11:45 PM Page 5

Researchers Extend Olfactory Discoveries to Fruit Fly



Leslie Vosshall / Richard Axel

The discovery of odor receptors in the fruit fly may lead to better understanding of olfaction in mammals and may help scientists find valuable weapons to control insect pests. At left, the red fluorescence represents odor receptors in a fly's maxillary palp.

Researchers in Dr. Richard Axel's laboratory have discovered several genes that code for odor receptors in the fruit fly, *Drosophila melanogaster*. Similar genes in humans were discovered in Dr. Axel's lab almost a decade ago. The discovery of odor receptor genes in the fruit fly provides new tools for extensive laboratory experimentation that could help neurobiologists better understand olfaction in mammals. It may also help scientists find valuable weapons to control insects that transmit human diseases and damage crops.

It took postdoc Dr. Leslie Vosshall five years to find the genes, but she finally succeeded where more than a dozen other laboratories had failed. In 1994, Dr. Vosshall and Dr. Hubert Amrein, then also a postdoc in Axel's lab, identified 250 genes expressed only in the fruit fly antennae, that animal's olfaction organ. After technicians sequenced those genes, Drs. Vosshall and Amrein found one gene that resembled odor receptors found in other animals. But they needed to find several more similar genes before they could claim to have found the members of the odor-receptor family.

That second phase proved "enormously frustrating," according to Dr. Vosshall, as several different molecular techniques failed to uncover any more odor receptor genes. But by 1998, scientists around the world had sequenced about 10 percent of the fruit fly genome. Dr. Vosshall felt confident that somewhere in that portion of the publicly available fruit fly genome would be additional members of the odor-receptor family of genes.

"We needed to find a genome person with a great computer to crunch through the genome database," says Dr. Vosshall. She turned to postdoc Dr. Pavel Morozov and assistant professor of medical informatics Dr. Andrey Rzhetsky at the Columbia Genome Center who generated a list of 2,500 potential odor-receptor genes. Dr. Vosshall painstakingly whittled that list down to six genes similar to the one Drs. Vosshall and Amrein had found. Dr. Vosshall and her colleagues published their results in the March 5, 1999, issue of *Cell*.

Results so far indicate that the each olfactory neuron carries one kind of receptor, as do mammals. A single odorant molecule can probably bind to several receptors, and fruit flies sense a specific odor by detecting which odor receptors have been activated.

Dr. Vosshall estimates that the fruit fly has about 100 to 200 odor-receptor genes. She expects that all of the odor-receptor genes will be discovered soon after the entire fruit fly genome is sequenced, within the next year or so. Having a complete set of those genes for such a popular laboratory animal will enable researchers to forge ahead in understanding how flies, humans, and other species smell.

Indeed, according to an article in the journal *Science*, researchers are already using the newly found receptors to look for similar ones in insects that damage agricultural crops in hopes of finding chemicals that can interfere with their ability to detect odors, on which they rely to find mates and food. ❒

BIOMED VOL 16.EXP 9/27/2001 11:45 PM Page 6

Genome Center Shifts from General Mapping to Search for Disease Genes

As the federal Human Genome Project closes in on its goal of identifying all 3 billion bases of human DNA, the Columbia Genome Center is looking ahead to the next phase of genomics—understanding the information encoded in the genome's four-letter alphabet. Relying on expertise developed in the early years of the genome initiative, the genome center is now focusing on the search for specific genes, especially ones that cause disease. The center is also consolidating its laboratories in the Russ Berrie Medical Science Pavilion and preparing for a change in leadership.

Jonathan Smith

Dr. Conrad Gilliam will lead the genome center as it searches for genes associated with disease, especially behavioral diseases and cancer.

"We've shifted the goals," says Dr. Isidore Edelman, founder and co-director of the center. "We're anticipating the next phase of genomics."

Columbia researchers began work on the Human Genome Project in 1990 and developed a fine annotated map of chromosome 13. But sequencing technology has advanced dramatically during the 1990s, and the project now relies primarily on brute force sequencing performed at relatively few centers. When completed, the Human Genome Project will produce an invaluable consensus catalog of all the bases.

The real value of the Human Genome Project will be realized only when scientists decipher those sequences and find the genes encoded within them. That will require a variety of technical skills that scientists at Columbia honed during their early work on chromosome 13. The center has added expertise through recent recruits and collaborations with other departments at the university.

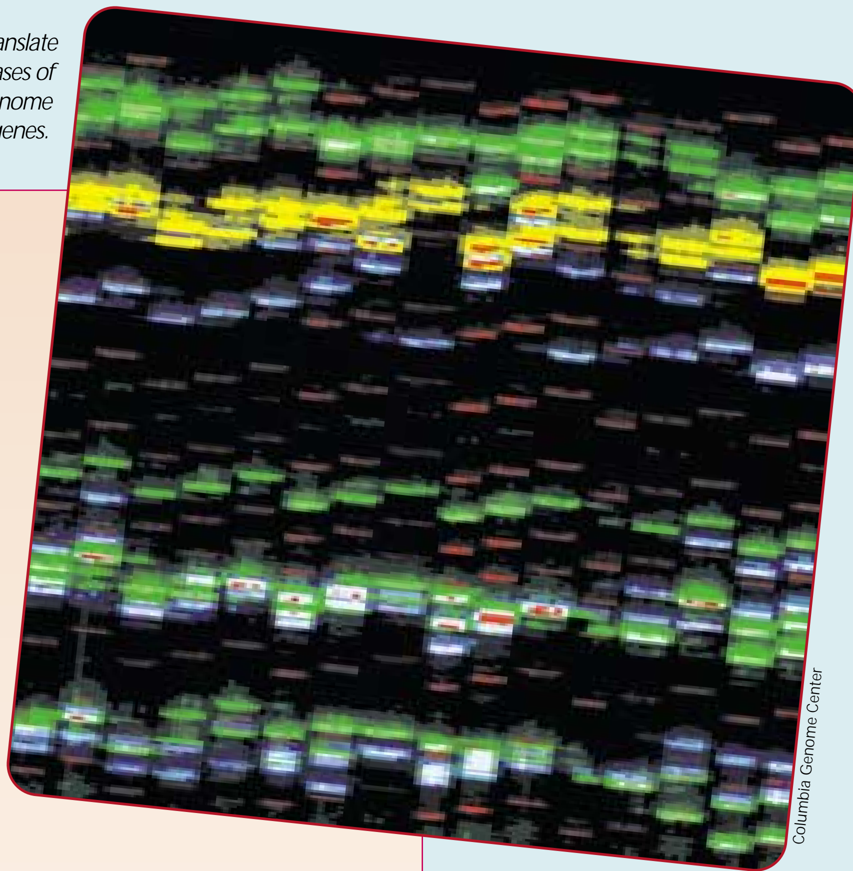
"The advantage we have is the integrity of this center," says Dr. Jianjun Liu, director of genotyping at the center. "We have separate groups all accomplished at different areas of gene discovery."

One of the most noteworthy recent recruits is Dr. Jingyue Ju, who has a joint appointment as associate professor of chemical engineering and director of DNA sequencing and chemical biology at the genome center. Dr. Ju has focused his career on the development of new technologies and reagents for DNA sequencing and genomic analyses.

Jonathan Smith

Dr. Jianjun Liu directs the Columbia Genome Center's genotyping section.

Gene sequencing machines that translate these colorful bands into the DNA bases of individual genes are crucial to the genome center's search for genes.



Columbia Genome Center

He recently developed new technologies that will vastly increase the speed of gene sequencing at the center.

"This changes the landscape of what we can do," says Dr. Conrad Gilliam, co-director of the genome center. The faster sequencing and an increasingly powerful bioinformatics program will help the center as it begins to focus increasingly on multifactorial diseases in which several genes play a role.

Dr. Riccardo Dalla-Favera leads a group that focuses on various genes involved in cancer. Dr. Gilliam leads the center's efforts to find genes associated with several behavioral diseases, such as autism, bipolar disorder, panic disorder, and schizophrenia. Recent gene discoveries have included genes associated with retinitis pigmentosa, progressive epilepsy with mental retardation, and multiple myeloma.

The center continues to consolidate physically as it takes over additional lab space in the Russ Berrie Medical Science Pavilion, part of the Audubon Biomedical Science and Technology Park. The cancer genetics, DNA sequencing, and functional genomics sections are joining the molecular genetics, physical mapping, and genomic informatics sections in the building on St. Nicholas Avenue.

In July 2000, Dr. Gilliam will take over as sole director of the center after sharing the leadership with the center's founder Dr. Edelman. ❐

RECENT GENE DISCOVERIES

Within the past year Columbia Genome Center researchers have discovered several genes associated with disease. They are:

Retinitis pigmentosa. Genome center co-director Dr. Conrad Gilliam and his colleagues found a genetic mutation carried in two extended families in the Dominican Republic, which slowly damages the retina, eventually causing blindness. In addition to identifying a mutation that causes the disease, the discovery also identifies a new gene and related protein that play a role in the physiology of the retina. "It will surely be important in the reactions involved in retinal health," says co-director Dr. Isidore Edelman.

Progressive epilepsy with mental retardation. Found in rural northern Finland, this form of epilepsy begins with seizures in childhood and the development of mental retardation two to five years after the first seizures. Dr. Gilliam and his colleagues identified the genetic mutation responsible.

Cancer. Cancer geneticist Dr. Riccardo Dalla-Favera and his colleagues discovered genes associated with B cell lymphoma and multiple myeloma.

ICF syndrome. Dr. James Russo and Xiaoyan Qu collaborated with an international team that identified the gene responsible for the syndrome Immunodeficiency, Centromere instability, and Facial anomalies (ICF). It is the first human genetic syndrome caused by defective DNA methylation, which produces unstable chromosomes that break apart and rearrange abnormally. The findings show that methylation plays an essential role in the organization and stability of at least one compartment of the human genome. They also suggest that classical satellite DNA, an abundant and repetitive class of DNA of previously unknown function, silences selected genes when methylated by forming small gene "prisons" within the nucleus. ❐

BIOMED VOL 16.EXP 9/27/2001 11:45 PM Page 8

Evolution Provides Clues to Search for Genes

Dr. Andrey Rzhetsky applies training in both mathematics and biology to the search for genes.

Scientists furiously sequencing the DNA of humans and other organisms are producing vast amounts of raw data—millions of Ts, Cs., Gs, and As. Extracting useful information from those strings of letters, which represent the individual bases of DNA, will be one of the great challenges to biologists in the coming years. Dr. Andrey Rzhetsky, assistant professor of medical informatics, is drawing on his background in both mathematics and biology to develop algorithms that find genes embedded within that data. He and his colleagues in the comparative genomics section of the Columbia Genome Center are using an evolutionary approach to search genetic databases for biologically important genes.

A scientist may know one gene that contributes to a particular disease, say cancer or epilepsy. But it is known that other genes also contribute to the disease or the risk of developing it. Genome center scientists believe that many of these genes can be found in the same metabolic or signaling pathway, either upstream or downstream of a known gene. Alternatively, the known gene may be one member of a family of genes that produce similar proteins, with similar roles. Other genes within the family may also contribute to the disease.

Many of the important biological pathways and gene families have been conserved through evolution. The same genes found in lower organisms, such as the nematode worm *C. elegans*, fruit fly, and mouse, have been passed down, with minor changes, to humans. In most cases, the genomes of those lower organisms have been sequenced more extensively and are better understood than the human genome.

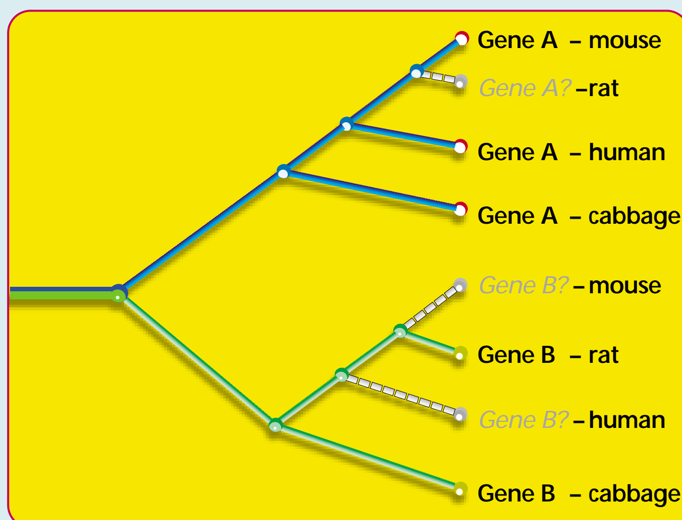
Dr. Rzhetsky searches through massive genome databases of lower organisms for clues to human genes that might be associated with disease. In addition to searching publicly available databases, he also searches through proprietary databases developed by genome center scientists and corporate partners. His mathematical training helps him create search techniques. His background in biology helps him develop a smarter search that is more likely to focus on biologically important sequences.

"These databases are a gold mine," says Dr. Conrad Gilliam, co-director of the Columbia Genome Center. "And we are going to mine them."

Sometimes a scientist finds a gene in another organism, say a mouse, that is similar to the human gene associated with a particular disease. If the mouse gene is well characterized, he can find other mouse genes in the same pathway or gene family. Those pathways and gene families often contain genes whose human counterparts have not yet been discovered. Dr. Rzhetsky then looks through human DNA sequences for the undiscovered counterpart, using the mouse gene as a guide.

Dr. Rzhetsky and his colleagues recently studied two gene families in a pathway that includes the protooncogene *c-Myc.* When they compared the known mouse and human genes, they saw that mice had a gene for which there was no known human counterpart. They figured there must be one; it just hadn't been discovered yet. Using the mouse gene as a guide, they found two human gene fragments with similar sequences. When the two fragments were joined, they coded for the missing human gene. The newly discovered human gene may play an important role in the prevention of cancer.

"Evolutionary biology has turned out to be a practical tool for gene discovery," says Dr. Rzhetsky. ❐



Evolutionary relationships between organisms and the sequences of their known genes can guide the search for new genes

BIOMED VOL 16.EXP 9/27/2001 11:45 PM Page 9

Warp Speed Genetic Analysis

Jonathan Smith

The recently purchased DNA microarray analysis machine is helping genome center scientists analyze broad patterns of gene expression.

Scientists at the Columbia Genome Center are now able to perform more complex and rapid genetic analyses thanks to the purchase of a DNA microarray analysis machine. The Genetic MicroSystems machine, purchased jointly with the Naomi Berrie Diabetes Center, allows scientists to observe broad patterns of gene expression and do rapid mutation analysis. The machine will help speed the discovery of genes that cause disease.

Genes rarely function in solitude. The expression of one gene often influences many other genes. When a person becomes ill, the expression of many genes changes, both up and down. To understand an illness or complex biological effect requires an understanding of this whole pattern of gene expression. But until recently scientists have been able to analyze the expression of one gene, or at most a handful of genes, at the same time. With the DNA microarray, researchers can look at the expression of thousands of genes at once.

"We are looking at the genes that are expressed," says Dr. Jianjun Liu, head of the genome center's genotyping section. "We can look at 20,000 genes at once."

DNA microarrays come in two basic forms. One is a gene chip, which uses premanufactured silicon chips with short stretches of DNA already attached. The other allows researchers to create their own DNA arrays on various substrates, such as glass or nylon. The genome center has purchased the second type of machine.

To analyze gene expression, researchers first take a sample of known DNA sequences, often a commercially available collection of genes. They attach a tiny sample of each DNA sequence to a substrate, creating an array of tiny DNA dots. Each dot contains a partial sequence of a different gene. Then they take messenger RNA (mRNA) from a biological sample they are analyzing. The mRNA represents the intermediate step between the gene and the protein and indicates that a gene is being expressed. A fluorescent molecule is attached to the mRNA molecules.

The full collection of mRNA molecules in the biological sample is placed on each DNA dot. Fluorescently tagged

continued on page 12

BIOMED VOL 16.EXP 9/27/2001 11:45 PM Page 10

Columbia Research Goes to Market

Earns more income from intellectual property than any other university

research conducted by scientists at Columbia University has produced numerous medications, medical devices, and experimental techniques. Many of these inventions have been licensed to private companies. In fact, in fiscal 1999 Columbia University earned more licensing income from the inventions of its faculty than did any other university in the nation.

In the fiscal year that ended on June 30, 1999, the university's technology transfer office, Columbia Innovation Enterprise, reported that intellectual property developed by Columbia University researchers generated $95.8 million in licensing revenues and attracted $16.2 million in privately sponsored research. A total of 74 new industrial licenses and 69 new research agreements were completed during the year. More than 175 new technologies were reported, and 78 new patents were issued to the university.

Below is a list of some of the more noteworthy products that have been developed from Columbia University intellectual property.

Co-transformation

P&S professors Richard Axel, Michael Wigler and Saul Silverstein patented this process for introducing genes into eukaryotic cells and producing specific proteins. While many commercially important proteins can be produced by bacteria that contain inserted genes, some cannot. They must be produced by the more complex eukaryotic cells. More than 30 companies have licensed co-transformation to produce pharmaceuticals. Among the important pharmaceuticals produced with the help of co-transformation are:

Activase (tissue plasminogen activator) is a clot-busting drug that is a widely used treatment for both heart attacks and strokes.

Epogen/Procrit (erythropoeitin) is the synthetic version of human erythropoietin, which stimulates bone marrow to produce red blood cells. It is used to treat anemia associated with chronic renal failure, cancer chemotherapy, and HIV patients treated with AZT.

Avonex (Interferon beta-1a) helps slow the progression of disability in relapsing forms of multiple sclerosis.

Benefix (recombinant Coagulation Factor IX) is used by hemophilia B patients to prevent bleeding. Since it is produced without blood or plasma products, there is no risk of transmission of blood-borne viruses, such as hepatitis or HIV.

Cerezyme (imiglucerase for injection) is an analogue of the human enzyme, ß-glucocerebrosidase, used in enzyme replacement therapy for patients with Type 1 Gaucher disease.

Pulmozyme (recombinant dornase alpha) significantly reduces the risk of serious respiratory tract infections, thus improving lung function and quality of life for cystic fibrosis patients.

Granocyte (lenograstim) promotes the generation of white blood cells, which is especially helpful for patients undergoing chemotherapy.

Genentech

Activase is one of many life-saving medications produced with the help of the co-transformation process.

Chimeric antibodies

Dr. Sherie L. Morrison, who has since left Columbia, collaborated with Stanford University researchers Leonard A. Herzenberg and Vernon T. Oi to develop a method for creating antibodies made from two different species. Among other uses, this allows scientists to use mouse genes to create antibodies with very specific binding properties, and human genes to prevent the antibody from inducing an immune response that would destroy it.

Centocor Co. has used the process to make ReoPro (abciximab) an antibody that prevents blood clotting in high-risk angioplasties. The company has also manufac-

BIOMED VOL 16.EXP 9/27/2001 11:46 PM Page 11

Dr. Jonathan Aviv uses the Air Pulse Sensory Stimulator that he and Dr. John Martin invented to detect a potentially dangerous loss of sensation in the throat of a stroke victim.

tured Remicade (infliximab) an antibody treatment for Crohn's disease, an inflammatory disease of the bowel. CIE officials expect several more pharmaceuticals to be made with this process, which was patented in 1998.

Pulsed-field gel electrophoresis

Drs. Charles Cantor and David Schwartz developed this process, which is a mainstay of genetic engineering and molecular biology. It made possible the analysis of larger macromolecules, especially DNA.

Glaucoma treatment

Dr. Laszlo Bito developed a sterile ophthalmic solution Xalatan (latanoprost), which contains a prostaglandin derivative that helps reduce pressure within the eye. It has fewer systemic side effects than previously used medications and quickly became the world's top-selling glaucoma medication.

Nutrition for preemies

Drs. Ralph Dell, Robert Winters and William Heird designed an amino acid solution, sold under the trade name of TrophAmine, to promote growth in premature infants. Widely used throughout the country, it has helped reduce mortality in this group.

Cutting and cauterizing in one step

Dr. Michael Treat developed a technology that allows surgeons to cut tissue and cauterize it to stop bleeding in one step, thus speeding surgery. The technology, called Pureheat, has been licensed by the Starion Instruments Corp. and recently gained approval for use from the U.S. Food and Drug Administration.

Air Pulse Sensory Stimulator

Drs. Jonathan Aviv and John Martin developed this diagnostic tool for detecting a loss of sensation in the throats of stroke victims, which can lead to the inhalation of food particles and aspiration pneumonia, the leading cause of death among stroke patients. Once these patients are identified, physicians can recommend dietary and behavioral adjustments that reduce the risk of developing aspiration pneumonia.

Neurological diagnostic test

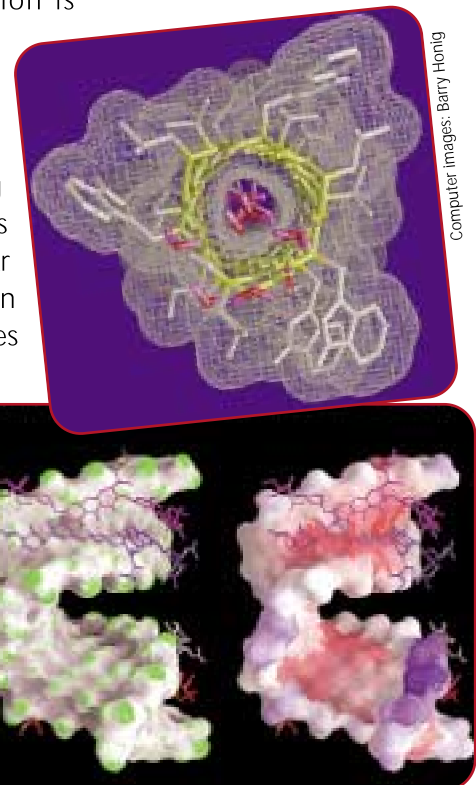
This assay for antibodies associated with motor neuron disease was developed by Dr. Norman Latov.

Delphi software

Dr. Barry Honig and several colleagues developed this computer software that simulates the electrostatic properties of macromolecules. An unsupported academic version is licensed directly by the Department of Biochemistry, and a commercial version is sold by Molecular Simulations.

GRASP software

Dr. Barry Honig and Anthony Nicholls developed this popular molecular visualization program that focuses on mapping various properties on the molecular surface. It is distributed through the biochemistry department. ❐



Computer images: Barry Honig

Dr. Barry Honig and his colleagues have developed computer programs that help visualize molecules and their properties.

BIOMED VOL 16.EXP 9/27/2001 11:46 PM Page 12

continued from page 9

mRNA binds to its corresponding DNA. The plate is then washed, removing any mRNA that does not bind. Left behind is a pattern of fluorescent dots that corresponds to the genes being expressed in the biological sample. A scanner can automatically detect the fluorescent spots and determine which genes are being expressed.

Researchers can use this system to compare the expression of genes in two different tissues. For example, by comparing gene expression in healthy and cancerous cells, they can learn which genes are turned on and off when a cell becomes cancerous. That could provide many candidates for both treatment and diagnosis.

One of the first analyses genome center researchers are conducting is part of a project to understand Wilson's disease, in which toxic levels of copper accumulate in the body. In 1994, Dr. Gilliam discovered the genetic mutation that causes the disease. Now, genome center researchers have inactivated a transcription factor that they believe turns on genes involved in the metabolism of copper. By comparing the gene expression in cells containing the inactivated transcription factor with gene expression in healthy cells, they expect to learn about the molecular-level consequences of the defective copper metabolism that occurs in Wilson's disease.

As researchers identify more genetic mutations associated with different conditions, they can place genes with those mutations on the microarrays to learn which ones a person carries. This will be especially helpful as researchers try to understand diseases that involve mutations in several different genes at once. ❐

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