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February◆1998

Transgenic Mice Possessing Human T-Cell Receptors Created

HIV-Infectable Mice May Benefit AIDS Vaccine Research

by Dan Coulter, *ASN&R* Staff Writer

Ever since AIDS research began in the early 80's, the only animal models available for study were those dealing with primates. Using monkeys to understand the pathogenesis of AIDS however, is not ideal for many reasons. First, non-human primates are susceptible to a different virus called SIV (simian immunodeficiency virus) which behaves differently from HIV and expresses antigens that are different from HIV. In addition, the use of monkeys can become extremely expensive, limiting the number of subjects one can use in a trial and making the data difficult to interpret. Although mice would be easier and cheaper to use, scientists have always been faced with a grave problem here: mice could not be infected with HIV — until now.

A team of researchers at Einstein have recently reported a way to create transgenic mice that are susceptible to HIV infection. Although the team. headed by Dr. Harris Goldstein. has not yet been able to accomplish full-blown infection of mouse cells, Dr. Goldstein and his colleagues believe "we have taken the necessary step that will allow us to move forward towards creation of a mouse model that will help us learn how HIV progresses, how to treat it more effectively. and perhaps how to come up with a vaccine against AIDS." The team's findings were reported in the December. 1997 issue of *Proceedings of the National Academy of Sciences.*

THE "HOLY GRAIL" OF AIDS RESEARCH FOUND — CHEMOKINE RECEPTORS

After it was discovered that the HIV virus was the causative agent for AIDS in 1981, it was not until 1984 that researchers first identified the membrane-bound receptor CD4 as the primary receptor that mediated HIV entry into cells. "Naturally, people wanted to develop an animal model," observes Dr. Goldstein, "to see if mice expressing human CD4 molecules could become infected by HIV. As it turns out, HIV would stick to the outside of the mouse cells expressing human CD4 but couldn't get into the cell. Based on that evidence, people postulated that HIV required another receptor — in addition to CD4 — to gain entry into cells. That unknown receptor had to be present on all human cells and not present on mouse cells — or at least had a different structure in mouse cells that did not allow HIV to

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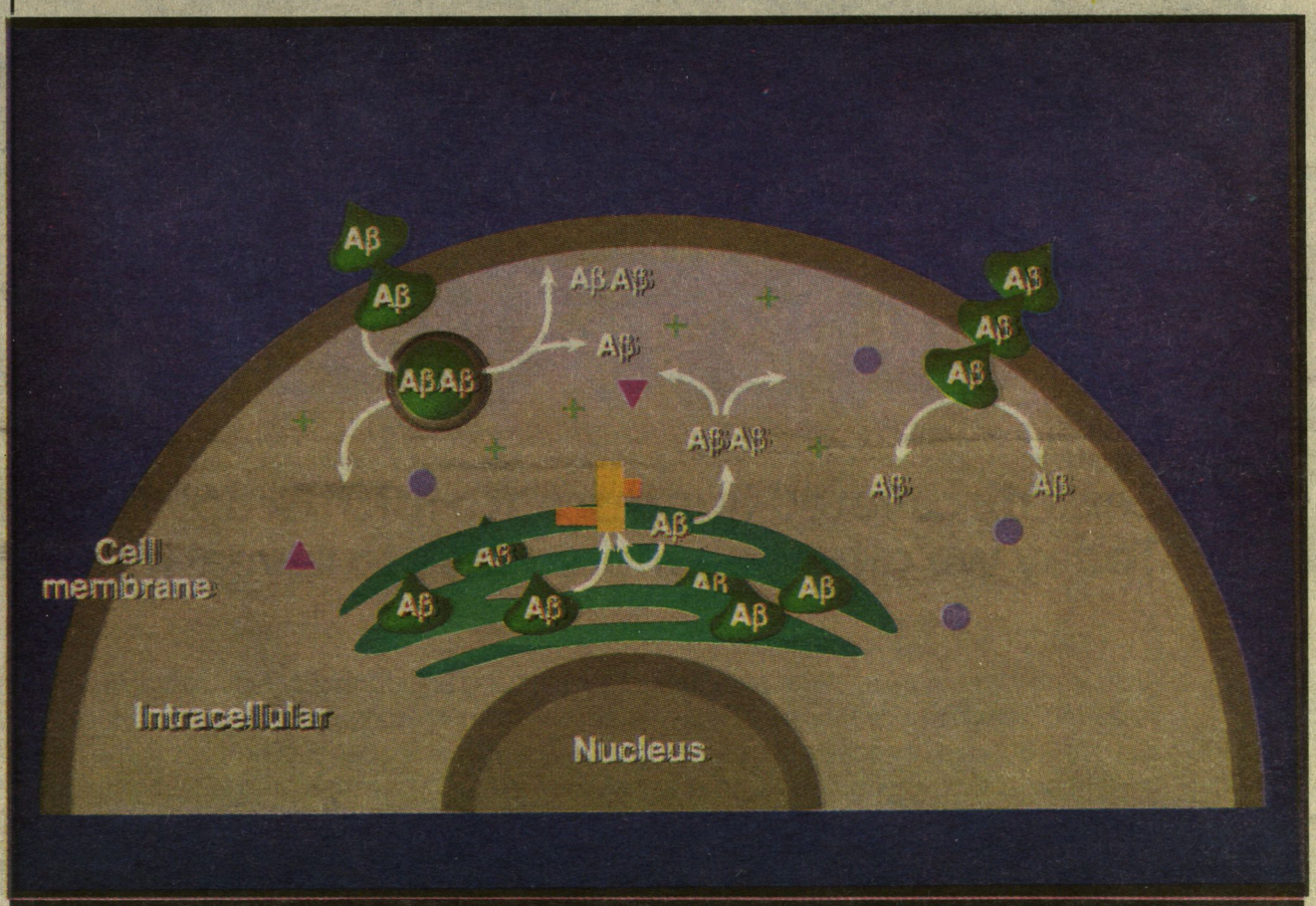
Finding Clues to Early Neuron Damage in Alzheimer's Disease

ERAB: A Novel, Implicated Intracellular Protein

by Alan Packer, Ph.D.

Arguably one of the most pressing public health problem in the developed world, the economic cost of Alzheimer's disease currently runs in the tens of billions of dollars every year, and estimates suggest that it will claim up to twelve million victims in the United States alone by the year 2020. The devastating human cost of this neurodegenerative disease also lends great urgency to the biomedical and epidemiological efforts to understand the risk factors associated with it, as well as to the search for molecules that could be targets for drug therapy during its onset and progression. While the multifactorial nature of Alzheimer's disease complicates the genetic approaches that have been so successful in identifying the molecular bases of single gene disorders such as cystic fibrosis and Huntington's disease, recent work by investigators at Columbia University's College of Physicians and Surgeons and elsewhere has begun to shed light on the mechanisms through which neurons die in affected patients.



Schematic Depiction of Aβ (Amyloid-Beta) Interaction With Intracellular Targets

A recent report in *Nature* (October 16th) by Dr. Shi Du Yan, assistant professor in the Department of Pathology at Physicians and Surgeons, Dr. David Stern, professor in the Departments of Physiology and Cellular Biophysics and Surgery, together with colleagues at Columbia and NYU Medical Center, and additional collaborators in Arizona, Saudi Arabia, and Japan, identifies a novel intracellular protein that appears to be involved in neurodegeneration in Alzheimer's disease. This protein, termed ERAB, is implicated in the pathogenesis of Alzheimer's due to its binding to amyloid-beta peptide, a well known culprit long suspected to be mediating the neurotoxic effects of the plaques found in the brains of Alzheimer's patients.

This new and important finding actually has its origin in a long line of investigations on the role of amyloid-beta in the etiology of Alzheimer's. It has been known for some time that amyloid-beta — cleaved from a larger precursor protein — is found

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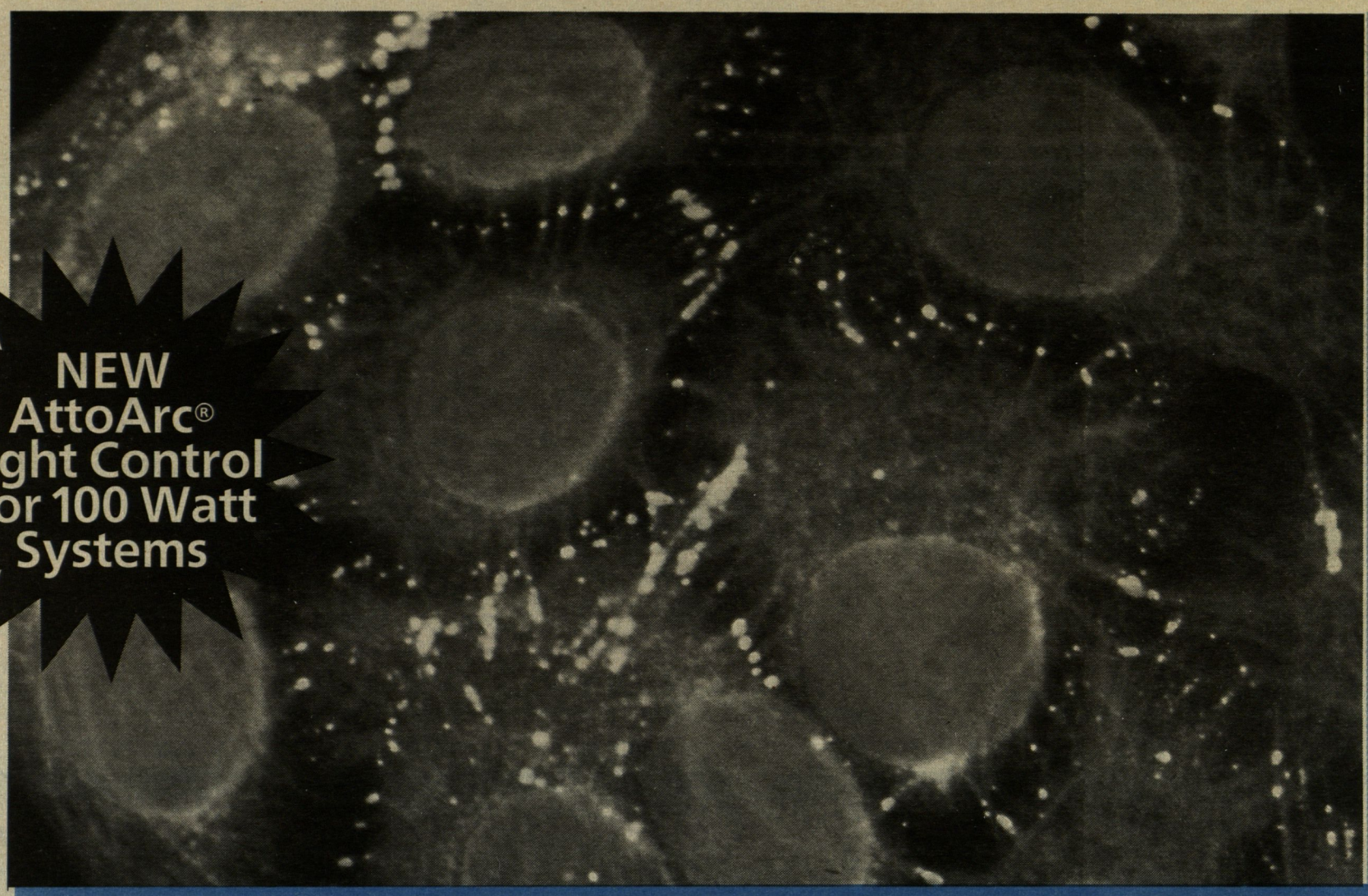

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SEE WHAT YOU'RE MISSING

Genes and Genomics, People and Plants

The *Arabidopsis* Sequencing Project

by David Shechner

It has been nearly a century and a half since Gregor Mendel performed his first fledgling studies of the heredity of pea plants, studies which would eventually lead to the birth of genetics. Today, the study of individual genes and traits has been extended to the study of organisms' complete set of hereditary information, the entire collection of its genes, otherwise called its genome. This is the science of genomics, the study of all of the genes responsible for the physical body, the chemical nature, and growth of the organism. In genomics, scientists seek to discover genetic "blueprints" of humans, bacteria, worms and now even plants — hardly the sort of thing the humble Austrian monk Mendel would ever have conceived of (or perhaps exactly what he imagined?).

(Back row, l-r) Joe Simorowski, Mark Settles, Mark Curtis; (Front row) Rob Martienssen, Mary Byrne, Catherine Kidner. (Photo: Margot Bennett, CSHL)

The Human Genome Project of the National Institutes of Health (NIH) and the U.S. Department of Energy (DOE) is the best-known project of this nature. Recently scientists at Cold Spring Harbor Laboratory embarked on a similar and very ambitious project. Together with collaborators in six sites world-wide, they hope to determine the complete genomic sequence of a plant called Arabidopsis thaliana. In addition, researchers plan to locate, identify, classify and study all 20,000 genes which compose the Arabidopsis genome.

Arabidopsis, a small plant in the mustard family, has one of the smallest genomes and the highest gene density so far identified in a flowering plant. The little plant contains a complete set of the genes necessary for all functions in the life cycle of the typical plant, from seed to flower and fruit. The project will result in the first complete gene sequence of a higher plant.

Genes and "Junk DNA"

In all DNA there are segments in which a series of base pairs (A-T, C-G) comprise a gene and there are regions of DNA, the so-called "junk DNA," which are not genes but which may serve some role in information storage. The ratio of genes to junk DNA in Arabidopsis is much higher than in most other organisms.

The entire genome of Arabidopsis is about 100,000,000 base pairs (100Mb) in length, with genes occupying approximately 50-60% of this DNA in contrast to humans, in whom genes comprise only 5% of the DNA. Humble Arabidopsis, with its minimal number of genes to perform all necessary functions, and the highest ratio of genes to non-coding DNA, is one efficient little organism.

There are approximately 2,000 so-called "essential genes," which are vital to cellular function. Rob Martienssen of Cold Spring Harbor Laboratory has found that these essential genes in Arabidopsis bear uncanny similarities to the analogous essential genes in yeast. Using a technique called 'gene traps' which Martienssen and colleague Venkatesan Sundaresan developed, Martienssen and postdoctoral fellow Patricia Springer demonstrated, with the sequencing help of W. Richard McCombie, that Prolifera, an Arabidopsis gene, was closely related to a yeast gene of known function. In yeast, Prolifera encodes a DNA replication licensing factor that is involved in cell proliferation.

The essential genes are complemented by vital "survival" genes. Important among these are genes which control growth and development in response to the plant's environment, an aspect which is crucial to the organism's survival. Since plants cannot remove themselves from an immediate environmental change by running away, many have adapted to endure dry seasons (the cactus, for example), extremes of temperature (grasses in the Alaskan tundra or the Gobi dessert), and salinity, acidity, fire, flooding, wind and nearly any other environmental alteration, depending upon where the plant has evolved.

While Arabidopsis may not have all of the genes which allow for such developmental and environmental responses, it does have representatives of each of the gene classes found in other plants. In fact, in the tiny, compressed genome of Arabidopsis, one can find genes and gene classes homologous to nearly all of the genes found in other flowering plants, sort of a basic tool box of plant genes.

Sequencing... and Function

Genome sequencing and mapping involve the determination of the sequence of base pairs in the DNA, from which the position of many genes can be determined, thus providing a map of the genome. But what about the genes' functions? Most sequencing projects are concerned only with sequencing (determining the sequence of bases that make up a gene, i.e., AACCTGTCATG) and mapping (finding the location of the gene). The Arabidopsis Sequencing Project is unique in that it seeks to determine the role of each gene, as well as its physical location.

Rob Martienssen came to Cold Spring Harbor Laboratory in 1989 to study transposable elements in maize. Also known as 'jumping genes' or transposons, these were discovered at Cold Spring Harbor by Barbara McClintock in the early 1950s. Transposable elements are genes that jump around

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FEATURES

February 1998

– O P I N I O N –

Physicians in Training Still Face Long Hours Without a Net

Can Professional Tradition, Public Apathy, and Civil Penalties Add Up to Change?

By Douglas Adler, M.D.

Would you willingly be a passenger on a plane if you knew that the pilot was being forced to fly for upwards of thirty hours straight, without sleep, and possibly without meals? Would you let your child ride in a schoolbus if you knew that the bus driver had only slept six hours in the last two days and wouldn't be allowed to sleep for another two days? Would you want your mother to be taken care of in an intensive care unit by a doctor, still in training, who was as sleep deprived as the aforementioned pilot and bus driver, and was also working without the supervision of senior doctors?

While any sane person would simply answer all of the above questions with a firm, "No!" the fact of the matter is that, while the first two cases above are unlawful, the third happens every day in hospitals all across the United States. In most states it's not even illegal. It's a tradition.

"When I first started my medical residency," said one pulmonologist, speaking under the condition of anonymity, "I had no idea what I was doing. My first rotation was in the Medical Intensive Care Unit and I was all alone with the sickest patients in the hospital from 5 p.m. until 7 a.m. the following morning. I was terrified. My goal wasn't to heal the sick, it was not to kill anybody!"

From the dawn of medical education in this country, it has been a time-honored rite of passage to train junior doctors by giving them a maximum amount of responsibility as early in their careers as possible. For modern junior doctors, known as house officers (because in days of old they actually lived in the hospital, which, in essence, became their home), this usually translates into overnight shifts in the hospital every second to fourth night, with a full day's shift beginning the following morning. This sort of schedule can routinely add up to a workweek of 80 to 100 hours. Only in New York State do formal rules and regulations exist purporting to guarantee house officers a maximum number of hours at work before they must be allowed to leave the hospital. Only in New York State do those same rules attempt to guarantee house officers enough time to go home and sleep before returning to work.

If it sounds like New York State has a thoughtful, progressive policy towards the training hours of house officers, think again.

If it sounds like New York State has a thoughtful, progressive policy towards the training hours of house officers, think again. Those rules and regulations are rarely followed. To make matters worse, they are essentially unenforceable as there is no regulatory agency in place to monitor training programs and cite violations to these rules, commonly referred to as the "Bell Laws."

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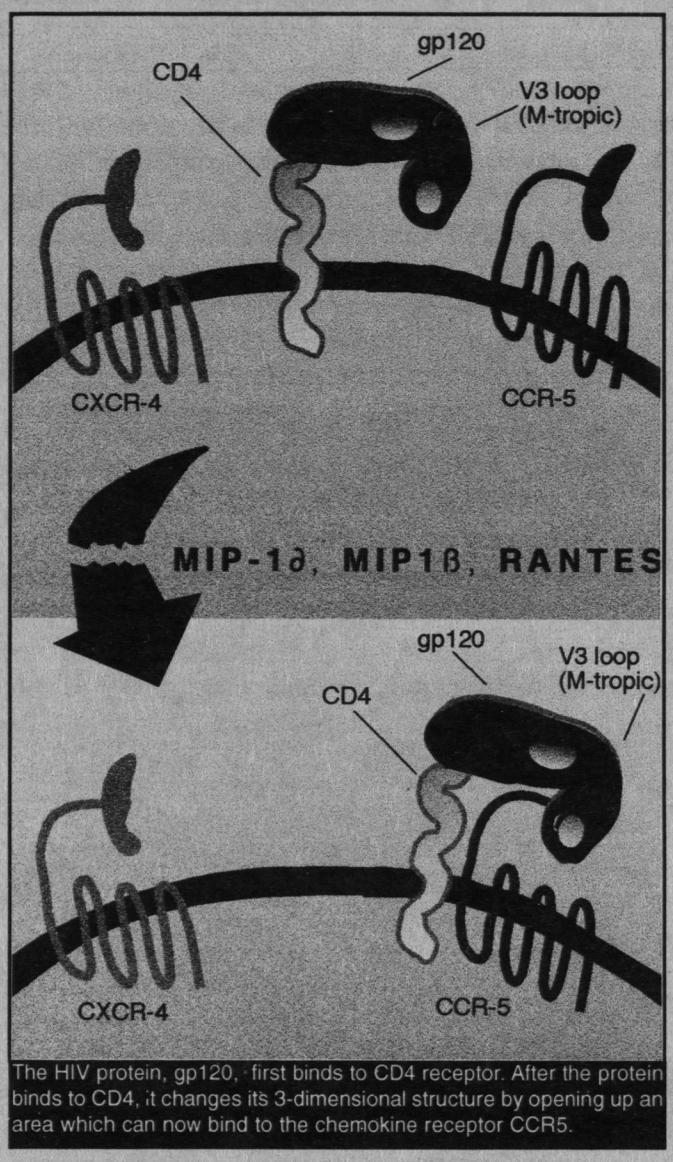
Transgenic...Continued from Page 1

use that receptor."

Subsequent studies performed between 1984 through 1986 confirmed that the expression of CD4 alone was insufficient to mediate HIV entry into a cell. "So there's this concept of HIV requiring a co-receptor to enter cells — but its identity was unknown for over ten years and many scientists have been looking for this co-receptor — it was kind of like a holy grail of HIV research" said Dr. Goldstein

The breakthrough came in 1996 when Edward Berger of NIH discovered the chemokine receptor CXCR4 (formerly known as fusin) as a co-receptor for HIV. Goldstein recalls: "Berger demonstrated that the CXCR4 receptor they called fusin could function as a co-receptor for HIV. If they expressed CXCR4 on the surface of mouse cells also expressing human CD4, it was observed that HIV could get into those cells. Chemokines are low molecular weight molecules that are secreted by a variety of immune cells as a way of stimulating the migration of inflammatory cells, such as white blood cells, to an infected area."

Since Berger's discovery, the fields of immunology and virology have seemingly fused to create a new field: the study of chemokines and their receptors as critical components of HIV infection. After it was determined that the HIV protein, gp120, must first bind to CD4 and then to a second receptor such as the chemokine receptor CXCR4 to initiate membrane fusion and viral penetration, researchers began to look at whether other members of the chemokine receptor family could also function as co-receptors for HIV. Over the last two years, many studies have shown that several other chemokine receptors and chemokine receptor-like molecules can also function as co-receptors for HIV infection.



The HIV protein, gp120, first binds to CD4 receptor. After the protein binds to CD4, it changes its 3-dimensional structure by opening up an area which can now bind to the chemokine receptor CCR5.

HIV COMES IN TWO FLAVORS (M-TROPIC & T-TROPIC)

Studies of the infectious behavior of HIV soon revealed that the virus appeared to display differing affinities for specific cell populations at different stages of the disease. This observation led to the classification of two major categories of HIV isolates (virus types) based on their preferred cellular target. One group of HIV-1 isolates, was labeled M-tropic for its ability to target and infect monocytes and macrophages. (M-tropic isolates can also infect peripheral T cells isolated from individuals but not T-cell lines propagated in tissue culture). The second group of isolates are classified as T-tropic based on their ability to target and infect T cell lines and peripheral T cells but not monocytes or macrophages.

"There are the M-tropic isolates and T-tropic isolates" explains Dr. Goldstein. "The M-tropic isolates are defined by their ability to infect monocytes — hence the letter M — as well as normal peripheral human T cells. The T-tropic isolates are defined by their ability to infect T cell lines that are growing continuously in culture. It was soon discovered that M- tropic isolates could not infect mouse cells that expressed the CD4 and CXCR4 receptors — yet the T-tropic isolates could. Several groups then began to investigate the possibility of other chemokine receptors that function for M-tropic isolates as the second co-receptor required for HIV infection." M-tropic viruses are more prevalent than T-tropic viruses and are the predominant isolate during the onset and early course of HIV infection. T-tropic isolates typically emerge later in infection in con-

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Arabidopsis... Continued from Page 3

the DNA — sometimes even from one chromosome to another. By 1992, Martienssen and Sundaresan developed a new technique called "gene traps" using transposable elements to study the function of Arabidopsis genes. In this technique a transposon can be inserted at random points within the Arabidopsis genome. This can disrupt and inactivate the gene at the insertion point, but can result in activation of the special "indicator" gene which has been inserted within the transposon. Now, at every point in which the original gene would have been expressed, the newly inserted indicator gene is exhibited instead, yielding a protein which stains cells blue. By observing the patterns of blue patches, scientists can determine in what tissues the gene is expressed, and at what time during development. Since the original gene may be inactivated, information about its function can also be deduced. With this procedure, the gene's location, expression, timing and function can all be indicated.

It takes two...

The Arabidopsis Sequencing Project brought together two types of researchers — plant geneticists like Rob Martienssen and experienced sequencers including W. Richard McCombie, also of Cold Spring Harbor Laboratory.

In 1993, McCombie was approached by Martienssen and Sundaresan , who proposed to sequence their transposon insertion sites. "The combined use of sequencing and transposons gives you the ability to functionally analyze any gene in the genome," noted McCombie. The sequencing of the Arabidopsis genome became the ultimate goal of the new collaboration.

Cold Spring Harbor Laboratory now heads one group within the Arabidobsis research consortium. Other members include the Genome Sequencing Center at Washington University in St. Louis, led by Drs. Robert Waterston and Richard K. Wilson; and the ACGT Group at Applied Biosystems, Inc., in Foster City, California, headed by Dr. Ellson Chen; The Institute for Genomic Research (TIGR) in Maryland; a group at Stanford University; and groups in Japan and Europe.

Formation of the consortium in 1996 culminated years of speculation and a handful of previous attempts at such a large scale organization of resources. "In 1992 the European Union had begun funding a multi-lab effort to sequence the genome of Arabidopsis," Martienssen recalls. "The project was led by Mike Bevan of the John Innes Center and Caroline Dean (et. al.) who had constructed the first Arabidopsis chromosome map." The present coalition is in many ways the first of its kind, not only in its focus on plant genetics, but in its scope, its well-organized broad international base, and its use of the internet as a research tool.

Technology

The McCombie laboratory is developing new technology for the sequencing effort. In particular, the use of computers has greatly exceeded simple data storage; the influence of the computer can be seen in almost all aspects of the sequencing process.

Sequencing is a complex process. The first stage is the production of a library, with the entire genome broken down into small, manageable pieces which can be examined individually. Generally these are incorporated into vectors — living carriers or "host DNA," usually containing about 100,000 base pairs of genomic DNA. These are mapped in the genome, then entered into the sequencing process. In the McCombie laboratory, as in most other large-scale sequencing laboratories, this is carried out by what is termed the shotgun sequencing strategy.

Shotgun sequencing starts with subcloning, the mechanical sheering of the DNA segments into still smaller fragments, and their insertion into a vector, optimized to produce DNA sequencing templates. Next, the DNA is isolated from a large number of these random subclones and a sequencing reaction is carried out from each. Typically, for a 100,000 base pair clone, 1800-2000 subclones are sequenced. Each of these subclone sequences, or reads, provides about 400-500 bases of sequence data.

The sequences of the individual fragments are then entered into a computer program reconstruct the original sequence of the 100,000 base pair clone from the combined set of shorter reads. The results of this assembly invariably point to problems with the reconstruction — places where there are no sequence data, called gaps; places where there are not enough data to ensure high accuracy; and places where the individual reads conflict with one another. All these problems must be solved in a process called "finishing" before the sequence is complete.

(Back row, l-r) Lidia Gnoj, Christina Haberman, Tina Gotttesman; (Middle row) Nadim Shohdy, Kendall Jensen, Kristen Schutz, Muhammad Lodhi, Melissa De La Bastide, Aliyah Hameed, Emily Huang, Dick McCombie; (Front row) Nancy Kaplan, Neilay Dedhia, Larry Parnell. (Photo: Marlena Emmons, CSHL)

In some cases conflict resolution is simple; the problem can be fixed by simply examining the raw sequence data already available. In other cases it is necessary to resequence an area to resolve the problem. Likewise, some gaps are easier to fill than others. Sometimes, resequencing using special long gels will extend a read enough to fill the gap. In more difficult cases, regions must be regenerated and reanalyzed. Finishing is by far the most time consuming part of the overall process. The sequencing of the individual fragments of a 100,000 base pair clone can take as little as 2-3 weeks while finishing that clone typically takes 1-9 months depending on the severity of the problems encountered.

The process of genome sequencing may seem laborious and daunting, but advances in data flow and processing, as well as in the chemistry involved, have allowed for a much more fluid sequencing process. Perhaps the most noticeable of these changes are the new software applications utilized by McCombie. Some of these were developed in other laboratories around the world and some specifically by the McCombie laboratory for their projects.

The process of determining base pairs from the raw data generated by the automated sequencer is carried out by 'PHRED' (developed by Philip Green of the University of Washington). This program does much of the "mess work" involved in sequencing — removing sections of vector DNA which had been added by the scientists, and which were not originally part of the Arabidopsis genome. PHRED also assigns "confidence values" to each of the base pairs, noting which sequences had been unquestionably identified, and which require further studies to ensure accuracy.

Next there is 'PHRAP', also developed by Philip Green. The PHRAP program compiles the data retrieved from PHRED and assembles them into larger fragments called contigs. This assembly is then run through a program developed by the Washington University group which converts the information into a different format so as to allow analysis on editing programs. Prior to human finishing, the first pass assembly is run through FINISH (also from the Washington University group), which searches the data for gaps and areas of low coverage, and suggests anywhere from 20 to 100 possible sequencing reactions to rectify the problems. This does not solve inconsistencies between individual sequence reads and typically only solves the simple gaps. The more complex problems are solved manually.

So far in the sequencing process we have a very long sequence of base pairs, but no indication of which base pairs comprise genes and which are junk DNA. The completed sequence, then, is analyzed by a number of methods including database searches and programs called 'GRAIL' (developed at Oak Ridge National Lab) and 'MZEF' (developed at CSHL) which locate probable areas within the sequence that may be genes. Frequently — up to 40% of the time — scientists can find a sequence similar to the one they are looking at via database searches of known genes. Then they garner insight into the type of gene it is and its function by comparison — these analogous genes may have been identified elsewhere in Arabidopsis or in other organisms including human, yeast, and C. elegans.

In addition, scientists must also discriminate between the introns and exons in the genes. Exons are the segments within a gene that carry genetic instructions for the synthesis of a protein, introns are the portions of a gene that are spliced out while the gene is making its product.

Progress on the Arabidopsis project has been excellent. So far the CSHL Consortium has sequenced and completed analysis about 1.5 million base pairs, and has approximately one megabase (1,000,000 base pairs) close to completion. McCombie predicts that the section of the project assigned to Cold Spring Harbor may reach completion considerably sooner that the original projection date of 2004.

Getting the data out

In order to track the myriad experimental steps, Neilay Dedhia of McCombie's laboratory developed KALEIDASEQ, an integrated internet software application designed to manage the flow of data. KALEIDASEQ is essentially a user interface that allows the consistent execution of a number of different programs. KALEIDASEQ can display the results of previous experiments, the progress of all current experiments, individual lab members' progress reports and efficiencies, as well as the laboratory's efficiency as a whole. Information is updated daily. The program even monitors daily sequencing activity, and will email an alert signal to

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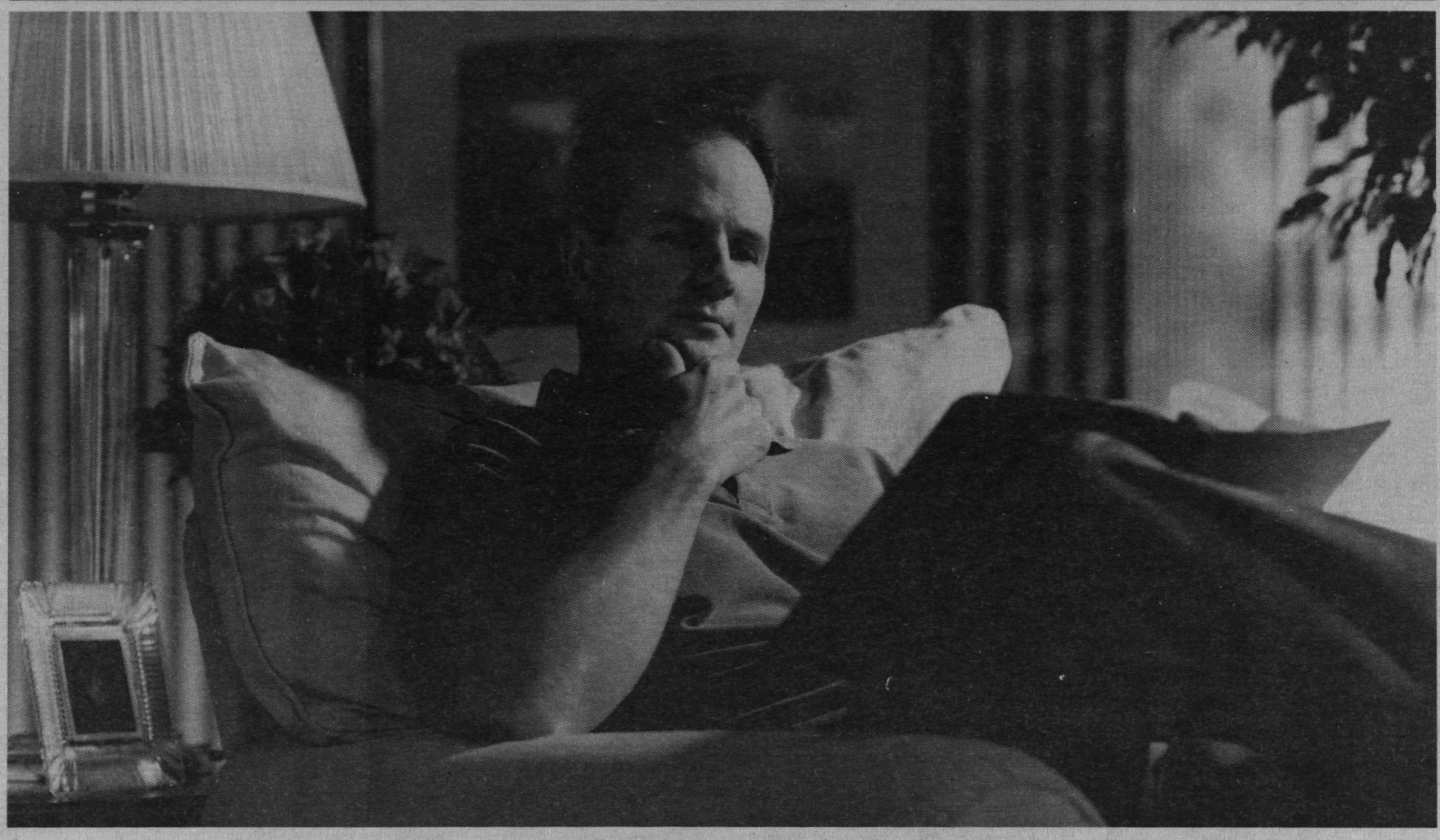

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St. John's Wort Studied By Local Researchers

Find Mechanism By Which Active Agent Gains Anti-Viral, Anti-Cancer Properties

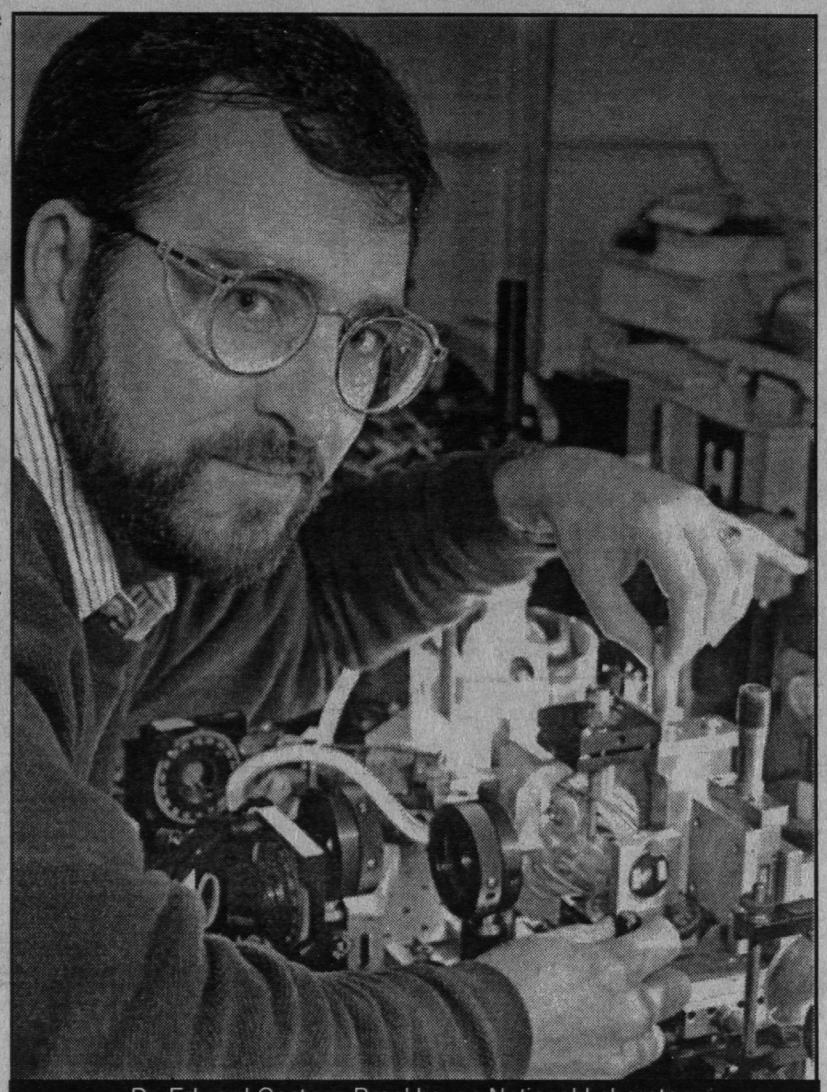
by Kathryn Gavin

The ancient herbal remedy known as St. John's wort got an ultra-modern examination recently at Brookhaven National Laboratory when chemists from BNL and Iowa State University used ultra-short laser pulses to probe the herb's active compound, called hypericin.

The experiment's results, published in December in the *Journal of the American Chemical Society,* verify an Iowa hypothesis about the light-activated chemical reaction that may give the herb its recently discovered anti-viral and anti-tumor properties.

The Iowa-BNL work demonstrated that when light strikes the hypericin molecule, it triggers a chemical reaction called a double proton transfer. The discovery could explain why hypericin is able to kill viruses and cancer cells in laboratory trials. It also raises the possibility that hypericin — and similar molecules that are also activated by light — could be used successfully in therapies to treat AIDS, hepatitis, brain tumors, and other diseases.

"The Iowa State team has long been investigating how hypericin and related chemicals kill viruses when exposed to light," said BNL chemist Edward Castner. "Through our collaboration with them, we have now verified their hypothesis about the mechanism for that effect. Knowing this may be an important step toward harnessing hypericin's power for more effective disease treatment."



Dr. Edward Castner, Brookhaven National Laboratory

Meanwhile, a SUNY Stony Brook team led by Carol Carter in the Department of Molecular Genetics and Microbiology is investigating hypericin's effect on the outer shell, or capsid, of HIV, the virus that causes AIDS.

An Herb with a History

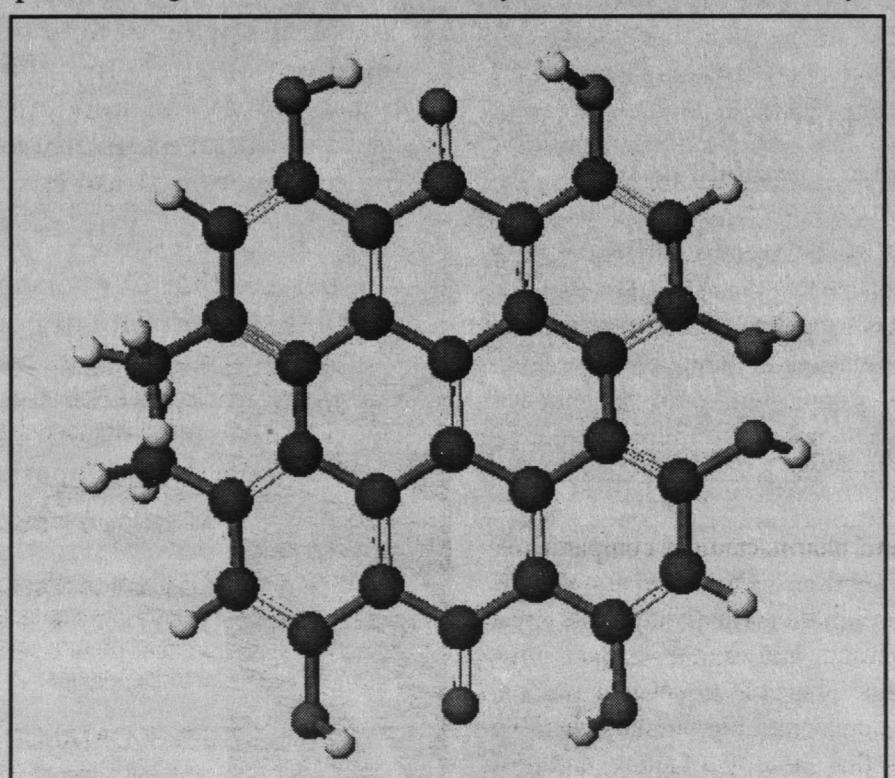
St. John's wort's history as an herbal remedy for depression, wounds and bruises stretches back nearly two thousand years. Legend has it that the plant was named for St. John the Baptist, because the red fluid produced when the plant's leaves are crushed was reminiscent of the martyred saint's blood.

The plant, whose Latin name is *Hypericum perforatum,* is found throughout Europe, western Asia and North Africa, as well as the Pacific Northwest and central U.S. A low-growing plant with a yellow flower, it is regarded as a weed in many areas.

Not so in Germany, where it is the most widely used anti-depressant, accounting for nearly half the market. It is also used throughout Europe for the same purpose.

St. John's wort is now becoming more popular in the U.S., as word of its purported anti-depressant properties with fewer side effects than conventional medications lend it the nickname "natural Prozac." Health food stores carry rows of different St. John's wort products, of varying composition but all claiming remarkable powers.

Theories abound regarding the mechanism by which it might affect brain chemistry to produce the reported effect — it has been implicated as an inhibitor of monoamine oxidase, an important regulator of brain chemistry. Research on this area is now being pursued at several institutions.



Hypericin: Under Study

Meanwhile, despite the commotion, hypericin's disease-fighting properties are not yet clinically proven. But clinical trials evaluating the effect of hypericin or St. John's wort on everything from brain tumors to clinical depression are now underway or planned. The National Institutes of Health announced recently that it will fund a three-year, $4.3 million multi-center study of the plant's effect on clinical depression.

From Cow Pasture to Chemistry Lab

The BNL-Iowa study of a light-activated mechanism for hypericin's action traces its roots back to the mystery of cows that became sick after grazing on the yellow-flowered plant on sunny days, but recovered when moved to a dark barn. The animals were suffering from hypericism, or extreme sensitivity to light, caused by the hypericin in the St. John's wort they had eaten.

Indications that hypericin could kill viruses as well as sicken cows led to independent 1991 discoveries by a team of New York University and SUNY Stony Brook scientists and Iowa State researchers, both demonstrating that hypericin must be exposed to light in order to kill viruses. Their experiments showed that hypericin was effective in killing many kinds of lentiviruses, especially the equine infectious anemia virus (EIAV), a retrovirus genetically related to the human AIDS virus, HIV. This and other studies led to early clinical trials of hypericin as an anti-AIDS drug, including one at NYU on pure hypericin delivered intravenously, though the trial ended in disappointment when patients because ultrasensitive to light.

Even as more clinical trials began, Iowa State chemists tried to find out how hypericin works. Early results showed that light exposure caused hypericin to transfer energy to nearby oxygen molecules, producing a damaging product called singlet oxygen that is highly toxic to viruses and bacteria. Later experiments showed that hypericin was still toxic even when no nearby oxygen was available, though Iowa's team is currently struggling to reproduce this effect.

Continued work suggested that another light-driven chemical process, called a proton transfer reaction, might be responsible for the toxic effect. In hypericin, proton transfer reactions occur when a proton, or positively charged hydrogen atom, moves a short distance of less than 2 Angstroms (8 billionths of an inch) between neighboring oxygen atoms on the molecule.

Using very short bursts of light from a laser, the Iowa group led by Jacob Petrich developed a theory that light causes hypericin to undergo two of the proton transfer reactions at the same time, one on either side of the molecule.

Continued on Page 18

Mismatch... Continued from Page 1

in the aforementioned extracellular plaques, and that these amyloid-rich plaques can disrupt cell membranes and promote the production of oxygen radicals which might lead to neuronal cell death. Despite an abundance of circumstantial evidence that amyloid-beta is associated with disease progression, until very recently there was little understanding of the specific interactions that might occur between amyloid-beta and various cellular components that could explain its impact on neurons.

In 1996, however, Dr. Yan and her colleagues identified such a neuronal cell-surface receptor for amyloid-beta (receptor for advanced glycation end-product, or RAGE) that is expressed at high levels in cells associated with typical plaques. Moreover, they demonstrated that cells expressing RAGE appeared to be more susceptible to amyloid-beta-induced cell death than were nonexpressing cells.

Despite the obvious importance of this finding, it was clear that a RAGE-amyloid-beta interaction alone could not entirely explain the pathogenesis of Alzheimer's disease; *in vitro* experiments using antibodies directed against RAGE did not protect all of the cells from the cytotoxic effects of amyloid-beta, implying the existence of other cellular factors mediating these effects.

Because of this, Yan and her coworkers set out to identify other proteins that could interact with amyloid-beta, screening a human brain cDNA library using the yeast two-hybrid system. The protein they identified — endoplasmic reticulum associated amyloid-beta binding protein, or ERAB — is expressed at a low level in normal tissues, but at an elevated level in neurons affected in Alzheimer's disease. When asked about this pattern of expression, Dr. Yan commented: "This issue is really important. We are currently trying to understand why there is high expression of ERAB proteins in Alzheimer's disease neurons." It is not yet clear whether the elevated levels of ERAB observed in Alzheimer's disease is due to a mutation in ERAB that might affect its level of expression, but this possibility has not been ruled out. "We need to look at familial cases of Alzheimer's to screen for a mutation (in ERAB)," adds Dr. Yan.

As is the case with RAGE, the neurotoxic effects of amyloid-beta are blocked by antibodies directed against ERAB, suggesting that it too might act to mediate such effects. Another interesting aspect of the current study arises from the sequence and potential function of ERAB, which appears to encode an enzyme involved in fatty acid metabolism and biosynthesis, called type II 3-hydroxyacyl-CoA dehydrogenase.

Since it is now well established that people carrying one or two copies of the apoE4 allele of the apolipoprotein E gene (involved in cholesterol metabolism) are at higher risk for Alzheimer's, ERAB may help to explain the still puzzling link between apoE genotype, cholesterol, and susceptibility to Alzheimer's disease. "We are trying to look at the enzyme's (ERAB's) activity,"explains Dr. Yan, "and we are also interested in making transgenic mice which overexpress the ERAB protein. We can then cross these mice either with apoE4 knockout mice or overexpressing mice to see what happens."

Perhaps the most intriguing aspect of these findings is the fact that ERAB is an intracellular protein — indeed the first intracellular protein demonstrated to bind to amyloid-beta. As suggested by its name, ERAB is normally found in the endoplasmic reticulum (ER) — that convoluted cytoplasmic compartment of the cell where nascent polypeptide chains are assembled and folded. Dr. Yan and her colleagues have observed that the addition of amyloid-beta to cells causes the translocation of ERAB from the ER to the plasma membrane. She comments, "We've started to do some cell biology and some confocal microscopy to examine the translocation. Possibly, ERAB has a normal function in the ER and is then translocated to the plasma membrane by amyloid-beta — which accumulates intracellularly in people with early Alzheimer's disease — where it can no longer function. This might be followed later by extracellular accumulation of amyloid-beta which keeps ERAB at the cell surface."

The challenge facing basic researchers and pharmaceutical companies is that of finding the appropriate target for intervention. That is, which molecule or molecules should your drug be designed to inhibit (or activate)? The great promise of the work by the Columbia group and others investigating Alzheimer's disease is that they might provide plausible targets for rational drug design. Dr. Yan has said that she will be concentrating on understanding the function of ERAB and RAGE: "We think that these two factors, and possibly others, are progression factors that induce cell stress and neuronal death. If we can find something that can block these factors, maybe we can block or slow down Alzheimer's disease." The "others" include the presenilins — intracellular proteins associated with familial cases of Alzheimer's. Since, as Dr. Yan emphasizes, "Alzheimer's disease is heterogeneous,"the list of such factors will likely grow longer as all of the coconspirators in the progression of this insidious disease are identified.■

SIGNALING THROUGH SCAFFOLD, ANCHORING, AND ADAPTOR PROTEINS [Review]

Pawson T. Scott JD.

Science. 278(5346):2075-2080, 1997 Dec 19.

The process by which extracellular signals are relayed from the plasma membrane to specific intracellular sites is an essential facet of cellular regulation. Many signaling pathways do so by altering the phosphorylation state of tyrosine, serine, or threonine residues of target proteins. Recently, it has become apparent that regulatory mechanisms exist to influence where and when protein kinases and phosphatases are activated in the cell. The role of scaffold, anchoring, and adaptor proteins that contribute to the specificity of signal transduction events by recruiting active enzymes into signaling networks or by placing enzymes close to their substrates is discussed.

REACTION OF S-2 WITH ZNO AND CU/ZNO SURFACES - PHOTOEMISSION AND MOLECULAR ORBITAL STUDIES

Chaturvedi S. Rodriguez JA. Hrbek J.

Journal of Physical Chemistry B. 101(50):10860-10869, 1997 Dec 11.

The adsorption of S-2 on ZnO and Cu/ZnO has been investigated using synchrotron-based high-resolution photoemission spectroscopy. On dosing a clean ZnO surface with S-2 at 300 K, the molecule dissociates, The S is associated first with Zn and at medium coverages with Zn-O sites. When the sulfur coverage is increased to theta( )= 0.5 ML, evidence is found for sulfur bound purely to the O sites of ZnO. The sulfur species associated with O and the Zn-O sires are unstable at temperatures above 500 K. Possible reaction pathways for the dissociation of S-2 on ZnO(0001)-Zn and Zn(1010) surfaces were studied using ab initio SCF calculations. At low sulfur coverages, an adsorption complex in which S-2 is bridge bonded to two adjacent Zn atoms (Zn-S-S-Zn) is probably the precursor state for the dissociation for the molecule, It is possible to gel much higher coverages of sulfur on ZnO (0.7 ML) than on Al2O3 (0.1 ML) at similar S-2 exposures. This, in conjunction with results previously reported for H2S adsorption on Cr2O3 and Cr3O4, indicates that the reactivity of metal oxides toward sulfur is inversely proportional to the size of their band gap. Oxides with a large band gap (e.g., Al2O3, similar to 9.0 eV) are less susceptible to sulfur adsorption than oxides with a small band gap (e.g., ZnO, similar to 3.4 eV), The presence of Cu atoms on both metal oxides enhances their respective reactivities reward S-2. Upon dosing Cu/ZnO with S-2 at 300 K, sulfur prefers to attack supported Cu followed by reaction with the Zn sites of the oxide, and at large sulfur coverages the adsorbate bonds simultaneously to metal and oxygen sites on the surface. The sulfur bonded to both the metal and oxygen sites on the surface is relatively weakly bound and desorbs by 500 K. The Cu <-> S interactions are strong and lead to the formation of copper sulfides that exhibit a distinctive band structure and decompose at temperatures above 700 K.

ALIGNMENT OF CONDUITS FOR THE NASCENT POLYPEPTIDE CHAIN IN THE RIBOSOME-SEC61 COMPLEX

Beckmann R. Bubeck D. Grassucci R. Penczek P. Verschoor A. Blobel G. Frank J.

Science. 278(5346):2123-2126, 1997 Dec 19

An oligomer of the Sec61 trimeric complex is thought to form the protein-conducting channel for protein transport across the endoplasmic reticulum. A purified yeast Sec61 complex bound to monomeric yeast ribosomes as an oligomer in a saturable fashion. Cryo-electron microscopy of the ribosome-Sec61 complex and a three-dimensional reconstruction showed that the Sec61 oligomer is attached to the large ribosomal subunit by a single connection. Moreover, a funnel-shaped pore in the Sec61 oligomer aligned with the exit of a tunnel traversing the large ribosomal subunit, strongly suggesting that both structures function together in the translocation of proteins across the endoplasmic reticulum membrane.

THE IMPACT OF SEDIMENT-LADEN SNOW AND SEA ICE IN THE ARCTIC ON CLIMATE

Ledley TS. Pfirman S.

Climatic Change. 37(4):641-664, 1997 Dec.

Sea ice formed over shallow Arctic shelves often entrains sediments resuspended from the sea floor. Some of this sediment-laden ice advects offshore into the Transpolar Drift Stream and the Beaufort Gyre of the Arctic Basin. Through the processes of seasonal melting at the top surface, and the freezing of clean ice on the bottom surface, these sediments tend, over time, to concentrate at the top of the ice where they can affect the surface albedo, and thus the absorbed solar radiation, when the ice is snow free. Similarly, wind-blown dust can reduce the albedo of snow. The question that is posed by this study is what is the impact of these sediments on the seasonal variation of sea ice, and how does it then affect climate? Experiments were conducted with a coupled energy balance climate-thermodynamic sea ice model to examine the impact of including sediments in the sea ice alone and in the sea ice and overlying snow. The focus of these experiments was the impact of the radiative and not the thermal properties of the sediments. The results suggest that if sea ice contains a significant amount of sediments which are covered by clean snow, there is only a small impact on the climate system. However, if the snow also contains significant sediments the impact on sea ice thickness and surface air temperature is much more significant.

CHILDREN WITH IN UTERO COCAINE EXPOSURE DO NOT DIFFER FROM CONTROL SUBJECTS ON INTELLIGENCE TESTING

Hurt H. Malmud E. Betancourt L. Braitman LE. Brodsky NL. Giannetta J.

Archives of Pediatrics & Adolescent Medicine. 151(12):1237-1241, 1997 Dec.

Objective: To determine if in utero cocaine exposure affects IQ scores in children at age 4 years. Design: A prospective, longitudinal evaluation by blinded examiners of the IQ scores of cocaine-exposed and control children of low socioeconomic status who have been observed since birth. Setting: A study center in an inner-city hospital. Participants: One hundred one children with in utero cocaine exposure and 118 control children, all of whom were 34 weeks' gestational age or older and nonasphyxiated at birth. Main Outcome Measure: Intelligence quotient scores on a standardized intelligence test, the Wechsler Preschool and Primary Scale of Intelligence-Revised. Results: Seventy-one cocaine-exposed and 78 control children were administered the Wechsler Preschool and Primary Scale of Intelligence-Revised. Maternal, natal, and 30-month characteristics of the children tested did not differ from those not tested. Groups did not differ on mean Performance (83.2 vs 87.0), Verbal (79.0 vs 80.8), or Full Scale (79.0 vs 81.9) IQ scores (all P greater than or equal to.10 [values for cocaine-exposed children given first]). None of these 3 scores was associated with cocaine exposure in multivariate linear regressions. Although cocaine-exposed and control groups did not differ in outcome, 93% of cocaine-exposed and 96% of control children had Full Scale IQ scores below 100, the mean IQ score for the test. Conclusions: In an inner-city cohort, IQ scores did not differ between cocaine-exposed and control children. However, both groups performed poorly.

MODEL QUAKES IN THE TWO-DIMENSIONAL WAVE EQUATION

Shaw BE.

Journal of Geophysical Research-Solid Earth. 102(B12):27367-27377, 1997 Dec 10.

This paper presents a new two-dimensional wave equation model of an earthquake fault. The model generates a complex sequence of slip events on a fault with uniform properties when there is a frictional weakening instability. Previous models of long faults in one and two dimensions had the driving in the bulk, giving the Klein-Gordon equation in the bulk. Here, I place the driving on the boundary, giving the wave equation in the bulk. The different models are, however, shown to behave similarly. I examine a whole range of frictions, with slip weakening as one end-member case and velocity weakening as the other end-member case, and show that they display a generic type of slip: complexity: there is an exponential distribution of the largest events and, for sufficient weakening, a power law distribution of small events. With the addition of a viscous-type friction term on the fault, I show that the results are independent of grid resolution, indicating that continuum limit complexity is achieved.

T CELL RECEPTOR SIGNALS ENHANCE SUSCEPTIBILITY TO FAS-MEDIATED APOPTOSIS

Wong B. Arron J. Choi YW.

Journal of Experimental Medicine. 186(11):1939-1944, 1997 Dec 1.

Fas(CD95) and its Ligand (Fast) interaction plays a pivotal role in T cell receptor (TCR)-mediated apoptosis. However, the susceptibility of T cells to Fas-mediated apoptosis is tightly regulated during immune responses, a regulation which is thought to maintain the antigen-specificity of T cell apoptosis. Here we show that TCR stimulation enhances the induction of Fas-mediated apoptosis. In addition, using a mutant T cell hybridoma with impaired Fast expression, we show that the synergy provided by TCR stimulation can be mimicked by activators of PKC but not calcium influx. This effect cannot be inhibited by actinomycin D, suggesting that TCR stimulation leads to the alteration in preexisting signaling molecules to enhance Fas-mediated apoptosis. Our results therefore provide a mechanism of how Fas-FasL interactions lead to T cell death in an antigen-specific manner via repetitive antigen stimulation.

MOLECULAR CHARACTERISTICS OF COCAINE-INDUCED CARDIOMYOPATHY IN RATS

Besse S. Assayag P. Latour C. Janmot C. Robert V. Delcayre C. Nahas G. Swynghedauw B.

European Journal of Pharmacology. 338(2):123-

129, 1997 Nov 5.

Cocaine abuse induces severe cardiomyopathy. To investigate the molecular effects of acute and prolonged administration of cocaine, mRNAs encoding markers of either mechanical overload, as atrial natriuretic factor (ANF) and alpha- and beta-myosin heavy chains, or fibrosis as type I and III procollagens, were quantitated in the left ventricle of rats 4 h after one injection of cocaine (40 mg/kg, n = 7), or 14 (n = 15) and 28 days (n = 10) after chronic infusion of cocaine (40 mg/kg per day). Plasma cocaine and benzylecgonine concentrations were both significantly augmented during the infusion while plasma levels of triiodothyronine and thyroxin-were lowered. Acute injection of cocaine induced ANF gene expression. Cocaine treatment during 28 days resulted in left ventricular hypertrophy (+ 20% after 24 days, P < 0.05) with normal blood pressure, associated with an accumulation of mRNAs encoding ANF and type I and III collagens (+66% and +55%, P < 0.05). Such a chronic treatment also induced a shift from the cu-to the P-myosin heavy chain gene expression (-40% and +50%, P < 0.05). In conclusion, cocaine activates markers of both hemodynamic overload and fibrosis. Such an activation may result from direct and/or indirect effects of the drug such as myocardial ischemia, mechanical overload and/or hypothyroidism.

POLYNOMIAL-TIME HIGHEST-GAIN AUGMENTING PATH ALGORITHMS FOR THE GENERALIZED CIRCULATION PROBLEM

Goldfarb D. Jin ZY. Orlin JB.

Mathematics of Operations Research. 22(4):793-802, 1997 Nov.

This paper presents two new combinatorial algorithms for the generalized circulation problem. After an initial step in which all flow-generating cycles are canceled and excesses are created, both algorithms bring these excesses to the sink via highest-gain augmenting paths. Scaling is applied to the fixed amount of flow that the algorithms attempt to send to the sink, and both node and are excesses are used. The algorithms have worst-case complexities of O(m(2)(m + n log n) log B), where n is the number of nodes, m is the number of arcs, and B is the largest integer used to represent the gain factors and capacities in the network. This bound is better than the previous best bound for a combinatorial algorithm for the generalized circulation problem, and if m = O(n(4/3-t)), it is better than the previous best bound for any algorithm for this problem.

INTERACTION OF 1-HYDROXYETHYL RADICAL WITH GLUTATHIONE, ASCORBIC ACID AND ALPHA-TOCOPHEROL

Stoyanovsky DA. Wu DF. Cederbaum AI.

Free Radical Biology & Medicine. 24(1):132-138, 1998 Jan 1.

Ethanol has been shown to be oxidized to a free radical metabolite, the I-hydroxyethyl radical(HER). Interaction of HER with cellular antioxidants may contribute to the known ability of ethanol administration to lower levels of GSH and ol-tocopherol. Experiments were carried out to establish a model system for the generation of HER and to study its interaction with GSH, ascorbic acid and alpha-tocopherol. A standard reaction for formation of azo-compounds using acetaldehyde and hydroxylamine-O-sulfonic acid was applied for the synthesis of 1,1'-dihydroxyazoethane (CH3CH(OH)-N=N-CH(OH) CH3). Although stable at -70 degrees C, thermal decomposition of this compound at room temperature was shown to produce HER, detected by EPR spectrometry as the PBN/HER or DMPO/HER spin adducts, and validated by computer simulation. GSH, present at the beginning of the experiment, inhibited formation of the PBN/HER signal. However, GSH did not cause any decay of pre-formed PBN/HER spin adduct. GSH was consumed in the presence of the HER-generating system in a reaction largely reversed by addition of NADPH plus glutathione reductase. Ascorbate also inhibited formation of the PBN/HER spin adduct and rapidly reduced the pre-formed adduct. HER amplified the oxidation of ascorbate, which was associated with the formation of the semidehydroascorbyl radical. alpha-Tocopherol was also consumed in the presence of HER. Production of HER in intact HepG2 cells by the redox cycling of 2,3-dimethoxy-1,4-naphthoquinone was associated with consumption of GSH. These data demonstrate the use of a simple chemical system for the controlled, continuous formation of HER and indicate that cellular antioxidants such as GSH, ascorbate, and alpha-tocopherol, interact with HER. The ability of agents such as ascorbate to reduce the PBN/HER spin adduct to EPR silent product(s) may mask the quantitative detection of HER in biological systems.

LONG-TIME TAIL EFFECT OF THE VELOCITY CORRELATION ON DIFFUSION-CONTROLLED REACTIONS

Dong W.

Journal of Chemical Physics. 107(23):9890-9893, 1997 Dec 15.

The existence of the long-time tail in the velocity correlation function of a Brownian particle is first discovered from molecular-dynamics simulations and is now well established theoretically and experimentally. In this work, we ask the following question: does this long-time tail have any effect on the kinetics of diffusion-controlled reactions, and if there is any, how the reaction rate is affected, especially in the asymptotic region, t --> infinity? We will show that this long-time tail can be taken into account by the theory developed recently by Dong and Andre. The exact asymptotic solutions to the order of t(-1/2) are found analytically with Smoluchowski and Collins-Kimball boundary conditions. This allows us to reveal chat the long-time tail of the velocity correlation function contributes to the reaction rate an additional term of O(t(-1/2)) to the long-time limit of the classic Smoluchowski and Collins-Kimball theories.

DEVELOPMENT OF A SUICIDE GENE AS A NOVEL APPROACH TO KILLING MYCOBACTERIUM TUBERCULOSIS

Rom WN. Yie TA. Tchouwong KM.

American Journal of Respiratory & Critical Care Medicine. 156(6):1993-1998, 1997 Dec.

The increase in multidrug-resistant tuberculosis and high mortality among those co-infected with HIV-1 necessitates new therapeutic approaches directed at Mycobacterium tuberculosis. We hypothesized that a dominant-negative mutation in the DNA-dependent RNA polymerase gene would inhibit transcription of all genes by blocking access of the wild-type enzyme to promoters. An evolutionarily invariant lysine was substituted with arginine by site-directed mutagenesis in the rpoB gene, The dominant-negative rpoB gene product inhibited a transposon-derived kanamycin-resistance gene in both M. smegmatis and M. tuberculosis H37Rv, leading to growth inhibition of the mycobacteria on solid media containing kanamycin. The dominant-negative mutant rpoB gene is a potential suicide gene especially for the treatment of multidrug-resistant tuberculosis once a delivery strategy is also developed.

HUMAN T-LYMPHOCYTE TRANSFORMATION WITH HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 2

Tarsis SL. Yu MT. Parks ES. Persaud D. Munoz JL. Parks WP.

Journal of Virology. 72(1):841-846, 1998 Jan.

Human T-cell lymphotrophic virus type 2 (HTLV-2), a common infection of intravenous drug users and subpopulations of Native Americans, is uncommon in the general population. In contrast,vith the closely related HTLV-1, which is associated with both leukemia and neurologic disorders, HTLV-2 lacks a strong etiologic association with disease. HTLV-2 does shares many properties with HTLV-1, including in vitro lymphocyte transformation capability. To better assess the ability of HTLV-2 to transform lymphocytes, a limiting dilution assay was used to generate clonal, transformed lymphocyte lines. As with HTLV-1, the transformation efficiency of HTLV-2 producer cells was proportionately related to the number of lethally irradiated input cells and was comparable to HTLV-1-mediated transformation efficiency. HTLV-2-infected cells were reproducibly isolated and had markedly increased growth potential compared to uninfected cells; HTLV-2 transformants required the continued presence of exogenous interleukin 2 for growth for several months and were maintained for over 2 years in culture. All HTLV-2-transformed populations were CD2 and/or CD3 positive and B1 negative and were either CD4(+) or CD8(+) populations or a mixture of CD4(+) and CD8(+) lymphocytes. Clonality of the HTLV-2 transformants was confirmed by Southern blot analysis of T-cell receptor beta chain rearrangement. Southern blot analysis revealed a range of integrated full-length genomes from one to multiple. In situ hybridization analysis of HTLV-2 integration revealed no obvious chromosomal integration pattern.

EFFECTS OF SURFACE IMPERFECTIONS ON THE BINDING OF CH3OH AND H2O ON FES2(100) - USING ADSORBED XE AS A PROBE OF MINERAL SURFACE STRUCTURE

Guevremont JM. Strongin DR. Schoonen MAA.

Surface Science. 391(1-3):109-124, 1997 Nov 26.

Studies are presented that investigate the adsorption and binding of CH3OH and H2O on the atomically clean (100) crystallographic plane of pyrite, FeS2. Temperature programmed desorption suggests that both reactants adsorb molecularly at 90 K and desorb thermally between 170 and 400 K depending on the surface coverage. Photoemission of adsorbed xenon (PAX) suggests that the surface of pyrite is heterogeneous and contains a significant fraction of defect sites that are believed to be, at least in part, anion vacancy or sulfur-deficient sites. An upper limit of 0.2 is proposed for the fraction of surface sites that are defects on FeS2(100). PAX indicates that these defect sites at low adsorbate coverage serve as the exclusive binding sites for H2O and CH3OH adsorbate, We speculate, on the basis of our ability to interpret PAX data for pyrite, that PAX may be of use for understanding the effect of short range order on adsorbate binding on other complex mineral surfaces. On the basis of high resolution electron energy loss spectroscopy, it is found that some dissociation of the adsorbate occurs on the pyrite. Vibrational data obtained with this technique sug-

REGIONAL CALENDAR OF SEMINARS

JAN 29-FEB 3

Jan 29: "Control of actin polymerization dynamics during cell motility," Matthew Welch, UCSF, Dept. of Biochemistry & Molecular Biophyisics, 4:00, Rm 301, HHSC Building, Columbia Univ., College of P&S

29: "Density Functional Theory and the Electronic Properties of Matter," Kieron Burke, Rutgers Univ., 4:00, 122 Meyer (4 Washington Pl.), Mathematics, NYU

29: "Stratocladistics" Theory, Practice and Simulation," David Fox, Museum of Paleontology, U. of Michigan, 12:00, Anatomy, Rm. 025, Lvl. 8, Health Sciences Center, SUNYStony Brook

30: "Chromosome Segregation, Asymmetric Division and Cell Fate in a Bacterium," Richard Losick, Dept. of Biology, Harvard Univ., 3:45, Caspary Auditorium, Rockefeller University

30: "Structure of Replicative T7 DNA Polymerase Complex: An Open and Shut Case for High Fideilty," Dr. Stanley Tabor, Harvard Medical, 3:00, Chemistry, Rm 1003, Main Building, NYU

30: "CFTR: lon Channel and Conductance Regulator," Dr.William Guggino, Univ. of Chicago, 12:00-1:15, Dept. of Pharmacological & Physiological Sciences, 21st Floor, Rm 92, Annenberg Building, Mt. Sinai School of Medicine

Feb 2: "Signal Transduction by Stress-activated Map Kinases," Dr. Roger J. Davis, Howard Hughes Medical Inst., U. of Mass., 12:00-1:00, Rm. VC 14-240, Humphreys Auditorium, Patholgy, Columbia Univ.

2: "Pathogensis of Alzheimer's Disease," Thomas Wisniewski, NYU School of Medicine, 12:00, Ctr. for Neural Science, Rm. 809, 4 Washington Pl., NYU

2: "Status of KTev Experiment at Fermilab," Dr. Julie Whitmore, Physics Dept., 4:00, Rm. 705, Pupin Hall, Columbia Univ.

3: "SKN-1 and PIE-1 Unusual Transcriptional Regulators that Establish Early Embryonic Fates in C. Elegans," Dr. Keith Blackwell, Ctr. for Blood Research, Harvard Medical School, 12:00, Cell Biology Dept., Rm. MSB 657, Cell Biology Library, NYU Medical Ctr./School of Medicine

FEB 3-9

3: "Functional Expression of a Mammalian odor Receptor," Dr. Stuart J. Firestein, Columbia Univ., 12:00, Physiology & Cellualr Biophysics, Rover Physiology Conference Room, P&S 11-505, Columbia Univ.

4: "Going in Without Endocytosis and Out Without Signal Sequence: Engrailed Can Do It!" Alain Prochiantz, Professor, Ecole Normale Superieure, Paris, Jacob Bleibtreu Seminar Room, Skirball Fourth Floor, NYU Medical Center

4: "DNA-Hydrolyzing Autoantibodies," Alexander Gabibov, Professor, Engelhardt Institute of Molecular Biology, Moscow, Jacob Bleibtreu Seminar Room, Skirball Fourth Floor, NYU Medical Center

5: "Image-Based Face Recognition," Nikolaus Troje, 4:00, Dept. of Psychology, Rm 878, 6 Washington Pl., NYU

5: "Glycosylation and Potassium Channel Function," Dr. William B. Thornhill, Mt. Sinai, 4:00, Dept. of Biochemistry & Cell Biology, Rm. 038, Life Sciences Building, SUNY Stony Brook

5: "LIM Homebox Genes and Neural circuits in C. Elegans," Olivar Hobert, Harvard Univ., Dept. of Biochemistry & Molecular Biophysics, 4:00, Rm. 301, HHSC Building, Columbia Univ., College of P&S

6: "Molecular analysis of G Protein alpha sub-unit," Dr. Catherine Beriot, Johns Hopkins School of Medicine, 12:00-1:15, Dept. of Cellular & Molecular Physiology, 21st Floor, Rm 92, Annenburg Building, Mt. Sinai School of Medicine

6: "TBA", Dr. Lawerance Sowers, City of Hope National Medical Ctr., 3:00,Dept. of Chemistry, Rm 1003, Main Building, NYU

9: "Saturated Chain Gangs: Organization of Proteins and Lipids in Novel Detergent-Resistant Membrane Domain," Dr. Deborah Brown, Dept. of Biochemistry, 4:00, Rm. Rm. 412, Graduate Chemistry Building, SUNY Stony Brook

9: "Cell Cycle Control of DNA Replication in Xenopus Laevis," Dr. Philip Carpenter, Howard Hughes Medical Inst., Calif. Inst. of Technology, 12:00, MSB 657, Cell Biology Library, Cell Biology Dept., NYU Medical Ctr./School of Medicine

FEB 9-12

9: "Integrating Behavioral nad Neurobiological Theories of Associative Learning: A Neurocomputational Approach," Mark Gluck, Rutgers U., 12:00, Ctr. for Neural Science, Rm. 809, 4 Washington Pl, NYU

10: "Novel Vascular Endothelial Growth Factor (VEGF) Receptors Associated with Endothelial and Tumor Cells," Dr. Michael Klagsbrun, Dept. of Surgery, Harvard Medical School, 12:00, MSB 657, Cell Biology Library, NYU Medical Ctr. School of Medicine

10: "Genetic Control of Mouse Brain and Limb Patterning," Dr. Alexandra L. Joyner, Skirball, NYU Medical College, 12:00, Dept. of Developmental & Molecular Biology, 3rd Floor Lecture Hall, Forchheimer Building, Albert Einstein College of Medicine

10: "New Mechanisms that Regulate the Activility of the Epithelial Sodium Channel, " Cecilia Canessa, Yale Univ., 12:00. Dept. Physiology & Celluar Biophysics, P&S 11-501, 630 West 168th St., Columbia Univ.

11: "Remote sensing of Cirrus clouds using MASHIS Data," Dr. Igor Geogdzyaev, NASA/GISS, 11:30, Ctr. for Terrestrial & Planetary Atmosphere, Rm. 120, Endeavor Hall, SUNY Stony Brook

11: "Roles of Microglial Scavenger Receceptors in Alzheimer's Disease And Atherosclerosis," Dr. Samuel Silverstein, Columbia Univ., 4:00, Patholgy, Rm. PH 15, Pathology Fenolio Library, Columbia Univ.

12: "Making Developmental Boundaries: Fringe Modulates Notch-ligand Interractions," Dr. Kenneth Irvine, Rutgers Univ., 4:00, Dept. of Biochemistry & Cell Biology, Rm. 038, Life Science Building, SUNY Stony Brook

12: "The Structure of the Nuclesome Core of Chromatin," Dr. Timothy Richmond, ETH, Zurich, Dept. of Biochemistyr & Molecular Biophysics, 4:00, Rm. 301, HHSC Building, Columbia Univ., College of P&S

further molecular adsorption is accommodated on the less reactive surface that we postulate is largely disulfide, the characteristic structural group of pyrite.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 POPULATIONS IN BLOOD AND SEMEN

Delwart EL. Mullins JI. Gupta P. Learn GH. Holodniy M. Katzenstein D. Walker BD. Singh MK.

Journal of Virology. 72(1):617-623, 1998 Jan.

Transmission of human immunodeficiency virus type 1 (HIV-1) usually results in outgrowth of viruses with macrophage-tropic phenotype and consensus non-syncytium-inducing (NSI) V3 loop sequences, despite the presence of virus with broader host range and the syncytium-inducing (SI) phenotype in the blood of many donors. We examined proviruses in contemporaneous peripheral blood mononuclear cells (PBMC) and nonspermatozoal semen mononuclear cells (NSMC) of five HIV-1-infected individuals to determine if this preferential outgrowth could be due to compartmentalization and thus preferential transmission of viruses of the NSI phenotype from the male genital tract. Phylogenetic reconstructions of similar to 700-bp sequences covering the second constant region through the fifth variable region (C2 to V5) of the viral envelope gene revealed distinct variant populations in the blood versus the semen in two patients,vith AIDS and in one asymptomatic individual (patient 613), whereas similar variant populations were found in both compartments in two other asymptomatic individuals. Variants with amino acids in the V3 loop that predict the SI phenotype were found in both AIDS patients and in patient 613; however, the distribution of these variants between the two compartments was not consistent. SI variants were found only in the PBMC of one AIDS patient but only in the NSMC of the other, while they were found in both compartments in patient 613. It is therefore unlikely that restriction of SI variants from the male genital tract accounts for the observed NSI transmission bias. Furthermore, no evidence for a semen-specific signature amino acid sequence was detected.

THE PROTON-PROTON REACTION, SOLAR NEUTRINOS, AND A RELATIVISTIC FIELD THEORETIC MODEL OF THE DEUTERON

Bahcall JN. Kamionkowski M.

Nuclear Physics A. 625(4):893-895, 1997 Nov 10.

In a series of recent papers, Ivanov et al. and Oberhummer et al. have calculated the rate for the p + p --> d + e(+) + v(e) reaction with a zero-range four-fermion effective interaction and find a result 2.9 times higher than the standard value calculated from non-relativistic potential theory. Their procedure is shown to give a wrong answer because their assumed interaction disagrees with low-energy pp scattering data.

BETA SUBUNITS INFLUENCE THE BIOPHYSICAL AND PHARMACOLOGICAL DIFFERENCES BETWEEN P- AND Q-TYPE CALCIUM CURRENTS EXPRESSED IN A MAMMALIAN CELL LINE

Moreno H. Rudy B. Llinas R.

Proceedings of the National Academy of Sciences of the United States of America. 94(25):14042-14047, 1997 Dec 9.

Human epithelial kidney cells (HEK) were prepared to coexpress alpha 1A, alpha 2 delta with different beta calcium channel subunits and green fluorescence protein, To compare the calcium currents observed in these cells with the native neuronal currents, electrophysiological and pharmacological fools were used

SEMINARS CONTINUED

FEB 13-24

13: "The Aquaporin family of water channels," Dr. Peter Agre, Johns Hopkins Univ., Markley Grad Program, 12:00-1:15, Dept. of Cellular & Molecular Physiology, 21st Floor, Rm 92, Annenburg Building, Mt. Sinai School of Medicine

13: Organic Chemistry of the Atmosphere and the Surface of Titan," Dr. Jonathan Lunine, Univ. of Arizona at Tucson, 3:00, Chemistry, Rm 1003, Main Building, NYU

19: "The Lipophospsphoglycan of Leishmania Parasites: A Multifunctional Virulence Molecule," Dr. Salatore J. Turco, Univ. of Kentucky Med. School, 4:00, Dept. of Biochemistry& Cell Biology, Rm. 038, Life Sciences Building, SUNY Stony Brook

19: "Cyrstal structures of general and gene-specific eukaryotic transcription factor complexes," Dr. Song Tan, ETH, Zurich, Dept. of Biochemistry & Molecular Biophysics, 4:00, Rm. 301, HHSC, Building, Columbia Univ., College of P&S

19: "If Reading 'Glasses' Primes 'Vision' , What Will Reading a Pair of 'Glasses' Do?", Jim Neely, SUNY Albany, 4:00, Psychology, Rm. 878, 6 Washington Pl., NYU

20: "Imaging Dendritic Function in Neocortex in vivo," Dr. Karel Svoboda, Cold Spring Harbor Lab., 12:00-1:15, Dept. of Cellular & Molecular Physiology, 21St Floor, Rm 92, Annenburg, Mt. Sinai School of Medicine

23: "Function and Organization of the Brain's Clock," Rae Silver, Columbia Univ., 12:00, Ctr. For Neural Science, Rm. 809, 4 Washington Pl., NYU

24: "Tumor Supressors and Regulation of Organ Sizes," Dr. Tian Xu, Dr. of Genetics, Howard Hughes Medical Inst., Yale U. of Medicine, 12:00, MSB 657, Cell Biology Library, NYU Medical Ctr. School of Medicine

24: "Biology of RNA Splicing," Dr. Philip A Sharp, Mass. Inst. of Technology, 12:00, Dept. of Development & Molecular Biology, 3rd Floor Lecture Hall, Forchheimer Building, Albert Einstein College of Medicine

FEB 25-27

25: "TBA", David Heeger, Stanford Univ., 4:00, Psychology, Rm. 878, 6 Washington Pl., NYU

25: " Measured and Calculated Clear Sky Solar Irradiance during Success: A Sensitory Study, Dr. Franisco Valero, U. OF Cali. San Diego,12:00, Marine Science Research Ctr., Rm.120, Endeavor Hall, SUNY Stony Brook

26: "The Role of the Axin Gene in Emryonic Axis Formation and Wnt Signal Transduction," Dr. Frank Costantini, Columbia Univ., 4:00, Dept. of Biochemistry & Cell Biology, SUNY Stony Brook

26: " NMR Structure of the Bacteriophage Lambda N-peptide/Box B Complex: Recognition of a GNRA fold by an Arginine-Rich Motif," Pascale Legault, Univ. of Toronto, Dept. of Biochemistry & Molecular Biophysics, 4:00, Rm. 301, HHSC Building, Columbia Univ., College of P&S

26: "In vivo Mechanisms of MHC Class II Presentation and Their Role in CD4 T Cell Development," Alexander Rudensky, Assistant Professor, University of Washington, 12:00, Jacob Bleibtreu Seminar Room, Skirball Third Floor, NYU Medical Center

27: "Combining Force Splitting with Langecin Dynamics for Faster Biomolecular Simulations, " Prof. Tamar Schlick, NYU, 3:00, Chemistry, Rm 1003, Main Building, NYU

27: "TBA," Tom Jessell, HHMI-Columbia Univ. Med. School, 12:00, Jacob Bleibtreu Seminar Room, Third Floor of the Skirball Institute, 540 First Avenue, NYU Medical Center

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Please send your seminars by email to editor@pdpub.com, by mail to 2780 Middle Country Rd., Ste. 213, Lake Grove, NY 11755, or by FAX to 516-737-3414.

ing currents in 80 mM Ba2+ that were relatively insensitive to calcium blockers. Coexpression of alpha 1A beta Ib, and alpha 2 delta produced a robust inactivating current detected in 10 mM Ba2+, reversibly blockable with low concentration of omega-agatoxin IVA (omega-Aga IVA) or synthetic funnel-web spider toxin (sFTX), Barium currents were also supported by alpha 1A, beta 2a, alpha 2 delta subunits, which demonstrated the slowest inactivation and mere relatively insensitive to omega-Aga IVA and sFTX. Coexpression of beta 3 with the same combination as above produced inactivating currents also insensitive to low concentration of omega-Aga NA and sFTX. These data indicate that the combination alpha 1A, beta Ib, alpha 2 delta best resembles P-type channels given the rate of inactivation and the high sensitivity to omega-Aga IVA and sFTX. More importantly, the specificity of the channel blocker is highly influenced by the beta subunit associated with the alpha 1A subunit.

CONFIRMATION OF EXCITED-STATE PROTON TRANSFER AND GROUND-STATE HETEROGENEITY IN HYPERICIN BY FLUORESCENCE UPCONVERSION

English DS. Das K. Ashby KD. Park J. Petrich JW. Castner EW.

Journal of the American Chemical Society. 119(48):11585-11590, 1997 Dec 3.

Fluorescence upconversion measurements of hypericin and its methylated analog, O-hexamethoxyhypericin, which possesses no labile protons, confirm excited-state proton (or hydrogen atom) transfer as the primary photophysical event in hypericin. The presence of a rising component in the time-resolved fluorescence of hypericin and the absence of such a component for the hexamethoxy analog are consistent with our assignment of excited-state proton or atom transfer as the primary photophysical process in the light-activated antiviral compound, hypericin. The results using the fluorescence upconversion technique, which detects only emission from the excited state, are in good agreement with our previous transient absorbance measurements. The results are also consistent with a heterogeneous ground state of hypericin.

CHRONIC STRESS ALTERS SYNAPTIC TERMINAL STRUCTURE IN HIPPOCAMPUS

Magarinos AM. Verdugo JMG. Mcewen BS.

Proceedings of the National Academy of Sciences of the United States of America. 94(25):14002-14008, 1997 Dec 9.

Repeated psychosocial or restraint stress causes atrophy of apical dendrites in CA3 pyramidal neurons of the hippocampus, accompanied by specific cognitive deficits in spatial learning and memory, Excitatory amino acids mediate this atrophy together with adrenal steroids and the neurotransmitter serotonin, Because the mossy fibers from dentate granule neurons provide a major excitatory input to the CA3 proximal apical dendrites, we measured ultrastructural parameters associated with the messy fiber-CA3 synapses in control and 21-day restraint-stressed rats in an effort to find additional morphological consequences of stress that could help elucidate the. underlying anatomical as well as cellular and molecular mechanisms. Although messy fiber terminals of control rats were packed with small, clear synaptic vesicles, terminals from stressed animals showed a marked rearrangement of vesicles, with more densely packed clusters localized in the vicinity of active zones. Moreover, compared with controls, restraint stress increased the area of the messy fiber terminal occupied by mitochrondrial profiles and consequently, a larger, localized energy-generating capacity, A single stress session did not product these changes either immediately after or the next day following the restraint session. These findings provide a morphological marker of the effects of chronic stress on the hippocampus that paints to possible underlying neuroanatomical as well as cellular and molecular mechanisms for the ability of repealed stress to cause structural changes within the hippocampus.

THE WEAKNESS OF C IV ABSORBER CLUSTERING IN KECK HIRES SPECTRA OF ADJACENT QUASAR SIGHT LINES

Crotts APS. Burles S. Tytler D.

Astrophysical Journal. 489(1 Part 2):L 7-L 11, 1997 Nov 1.

We observe with Keek/HIRES the z approximate to 2.5 QSO triplet 1623+27 in order to explore on the scale of 1 Mpc the spatial clustering of C Iv absorbers between adjacent sight lines. We find this signal to be significantly weaker than the clustering in velocity on corresponding scales along single sight lines, assuming that the relative velocity of absorbers in dominated hv the Hubble flow Thin indicates that small-scale clustering (200 km s(-1) < Delta v < 600 km s(-1)) of the C Iv absorbers cannot be interpreted in terms of the positions of the absorbers in space but must be considered as internal motions within individual absorbers or within clusters of absorbers whose internal velocities dominate over Hubble expansion across the cluster scale. If the single sight line signal is due to spatial clustering, it is caused by absorber clusters smaller than would be implied by their velocities if a Hubble flow is assumed. The spatial clustering of C Iv absorbers at z approximate to 2 is consistent with data on Ly alpha forest clustering measured in the same way at the same redshifts. However, present-day galaxy clustering, evolved back to z approximate to 2, is consistent with C Iv spatial clustering but perhaps not with that of the Ly alpha forest. Even so, one cannot as yet distinguish the two absorber populations on the basis of spatial clustering on these small scales.

FREE ENERGY OF THE HYDROPHOBIC INTERACTION FROM MOLECULAR DYNAMICS SIMULATIONS - THE EFFECTS OF SOLUTE AND SOLVENT POLARIZABILITY

Rick SW. Berne BJ.

Journal of Physical Chemistry B. 101(49):10488-10493, 1997 Dec 4.

Molecular dynamics simulations are used to calculate the free energy of methane association in water, using the polarizable fluctuating charge model that treats the charges on atomic sites as dynamical variables. Compared with previous studies using nonpolarizable potentials, the inclusion of polarizability leads only ro small differences in the methane pair potential of mean force. This is in contradistinction to two previous studies using other polarizable models, which do not agree with the nonpolarizable results or with each other. The potential of mean force is calculated at three different temperatures (283, 298, and 313 K) from which the temperature dependence and also the entropic part of the free energy is examined. It is found that the tendency for methane molecules to aggregate increases with increasing temperature and that aggregation is stabilized by entropy.

COMPARISON OF CHROMOSOMAL DNA COMPOSING TIMELESS IN DROSOPHILA MELANOGASTER AND D-VIRILIS SUGGESTS A NEW CONSERVED STRUCTURE FOR THE TIMELESS PROTEIN

Myers MP. Rothenfluh A. Chang M. Young MW.

Nucleic Acids Research. 25(23):4710-4714, 1997 Dec 1

Two proteins, TIM and PER, physically interact to control circadian cycles of tim and per transcription in Drosophila melanogaster. In the present study the structure of TIM protein expressed by D.virilis was determined by isolation and sequence analysis of genomic DNA (gDNA) corresponding to the D.virilis tim locus (vtim). Comparison of vtim and mtim gDNA revealed high conservation of the TIM protein. This contrasts with poor sequence conservation previously observed for the TIM partner protein PER in these species. Inspection of the vtim sequence suggests an alternative structure for most TIM proteins. Sequences forming an intron in a previously characterized D.melanogaster tim cDNA appear to be most often translated to produce a longer TIM protein in both species. The N-terminal sequence of vTIM and sequence analysis of genomic DNA from several strains of D.melanogaster suggest that only one of two possible translation initiation sites found in tim mRNA is sufficient to generate circadian rhythms in D.melanogaster. TIM translation may be affected by multiple AUG codons that appear to have been conserved in sequences composing the 5'-untranslated tim mRNA leader.

ANTI-SYNAPSIN MONOCLONAL ANTIBODIES - EPITOPE MAPPING AND INHIBITORY EFFECTS ON PHOSPHORYLATION AND GRB2 BINDING

Vaccaro P. Dente L. Onofri F. Zucconi A. Martinelli S. Valtorta F. Greengard P. Cesareni G. Benfenati F.

Molecular Brain Research. 52(1):1-16, 1997 Dec 1.

The synapsins are a family of major neuron-specific synaptic vesicle-associated phosphoproteins which play important roles in synaptic function. In an effort to identify molecular tools which can be used to perturb the activity of the synapsins in in vitro as well as in vivo experiments, we have localized the epitopes of a panel of monoclonal antibodies (mAbs) raised against synapsins I and II and have characterized their ability to interfere with the interactions of the synapsins with protein kinases, actin and Src homology-3 (SH3) domains. The epitopes of the six mAbs were found to be concentrated in the N-terminal region within domains A and B for the synapsin II-reactive mAbs 19.4, 19.11, 19.51 and 19.21, and in two C-terminal clusters in the proline-rich domains D for synapsin I(mAbs 10.22, 19.51, 19.11 and 19.8) and G for synapsin II (mAb 19.8). The synapsin II-specific mAbs 19.4 and 19.21, whose overlapping epitopes are adjacent to phosphorylation site I, specifically inhibited synapsin II phosphorylation by endogenous or exogenous cAMP-dependent protein kinase. While all the anti-synapsin I mAbs were unable to affect the interactions of synapsin I both with Ca2+/calmodulin-dependent protein kinase II and with actin monomers and filaments, mAbs 19.8 and 19.51 were found to inhibit the binding of Grb2 SH3 domains to the proline-rich C-terminal region of synapsin I.

Selected Funding Updates

Compiled by Peter M. Saal
Office of the Vice President for Research —SUNY Stony Brook

Dept. of Agriculture: Biotechnology Risk Assessment Research Grants Program

The purpose of the Program is to assist Federal regulatory agencies in making science-based decisions about the safety of introducing into the environment genetically modified organisms, including plants, microorganisms, fungi, bacteria, viruses, arthropods, fish, birds, mammals and other animals. The Program accomplishes this purpose by providing scientific information derived from the risk assessment research that it funds. Research proposals submitted to the Program must be applicable to the purpose of the Program to be considered.

The Program's research emphasis is on risk assessment and not risk management. The Program defines risk assessment research as the science-based evaluation and interpretation of factual information in which a given hazard, if any, is identified, and the consequences associated with the hazard are explored. The Program defines risk management as (1) research aimed primarily at reducing risks of biotechnology-derived agents and (2) a policy and decision-making process that uses risk assessment data in deciding how to avoid or mitigate the consequences identified in a risk assessment.

For further information, contact: Dr. Edward K. Kaleikau, USDA/CSREES, 202-401-1901, Dr. Daniel D. Jones, USDA/CSREES, 202-401-6854, or Dr. Robert M. Faust, USDA/ARS, 301-504-6918. Copies of this solicitation, the administrative provisions for the Program and the Application Kit, which contains required forms, certifications, and instructions for preparing and submitting applications for funding, may be obtained by contacting: Proposal Services Unit, Telephone Number: 202-401-5048. Application materials may also be requested via Internet by sending a message with your name, mailing address (not e-mail) and telephone number to psb@reeusda.gov which states that you wish to receive a copy of the application materials for the FY 1998 Biotechnology Risk Assessment Research Grants Program. The materials will then be mailed to you (not e-mailed) as quickly as possible. Proposals are due March 24, 1998.

DOE: Epidemiology and Other Health Studies (Notice 98-01)

The Office of Health Studies within the Office of Environment, Safety and Health of the Department of Energy announces its continuing interest in receiving applications or preapplications for grants and cooperative agreements for occupational and environmental health studies of DOE employees and DOE contractors, as well as related DOE international health programs, concerning nuclear weapons research, development, production, use, storage, and dismantling.

Applicants may obtain additional information from Dr. Paul Seligman, Deputy Assistant Secretary, Office of Health Studies (EH-6), U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290; facsimile: 301-903-3445; telephone: 301-903-5926.

NASA: NRA-98-HEDS-01 - Advanced Human Support Technology

The National Aeronautics and Space Administration Life Sciences Division solicits proposals for research investigations in support of Research Opportunities in Space Life Sciences. This announcement is specific to the Advanced Human Support Technology Program within the Life Sciences Division. A separate solicitation for the Gravitational Biology and Biomedical Research and Countermeasures Programs will be available mid-1998.

Proposals requested by this announcement may be for ground-based research investigations, and limited types of space- flight experiments designed for the Shuttle middeck or for the earliest phase of utilization of the International Space Station. This solicitation will be open for the period through April 15, 1998; proposals may be submitted at any time throughout the period. This solicitation will be available electronically via the Internet at http://peer1.idi.usra.edu/

The technical point of contact for this effort is: Dr. Guy Fogleman, Life Sciences Division, Code UL, NASA Headquarters, Washington, DC 20546.

NSF/ENG: Long Term Durability of Materials and Structures - Modeling and Accelerated Techniques

The Engineering Directorate of the National Science Foundation announces a collaborative research initiative on the long-term durability of materials, machines and structures. The focus is on innovative accelerated tests and modeling of deterioration behavior, which will enable reliable prediction of long-term performance from short-term tests. A goal of the initiative is to provide close links between basic research and engineering applications in the field of deterioration science by coordinating research efforts and combining resources from a number of agencies including the Federal Highway Administration and several State Departments of Transportation as well as other agencies on a case by case basis in terms of co-funding and utilization of testing facilities. Researchers are encouraged to visit the ENG web-site (www.eng.nsf.gov/programs/nsf98-42.htm) for any update on this initiative.

The initiative aims to support fundamental research by individual investigators and small groups on new concepts and methods for accurately assessing the durability of materials, machines and structures, with an emphasis on high-risk/high-payoff research. There are many forms of deterioration to consider, such as fatigue, overload, ultraviolet damage, corrosion, and wear. Materials of interest include the full spectrum of construction materials, metals, ceramics, polymers, composites, and coatings. Application areas include, but are not limited to, units of the constructed infrastructure such as machines, structures (above and below ground), transportation systems and units, and manufacturing machinery. Proposals must be received at NSF by March 25, 1998. (Ref: NSF 98-42)

DOE: Program Notice 98-09 - Energy Biosciences

The Office of Basic Energy Sciences of the Office of Energy Research invites preapplications from potential applicants for research funding in the Energy Biosciences program area. The intent in asking for a preapplication is to save the time and effort of applicants in preparing and submitting a formal project application that may be inappropriate for the program. The preapplication should consist of a two-to three-page concept paper on the research contemplated for an application to the Energy Biosciences program. The concept paper should focus on the scientific objectives and significance of the planned research, and include an outline of the approaches planned, and any other information relating to the planned research. No budget information or biographical data need be included; nor is an institutional endorsement necessary. The preapplication gives DOE the opportunity to advise potential applicants on the suitability of their research ideas to the mission of the Energy Biosciences program. A response indicating the appropriateness of submitting a formal application will be sent from the Division of Energy Biosciences office in time to allow for an adequate preparation period for a formal application.

The Energy Biosciences program has the mission of generating fundamental biological information about plants and non-medical related microorganisms that can provide support for future energy related biotechnologies. The objective is to pursue basic biochemical, genetic and physiological investigations that may contribute towards providing alternate fuels, petroleum replacement products, energy conservation measures as well as other technologies such as phytoremediation related to DOE programs. Areas of interest include bioenergetic systems, including photosynthesis; control of plant growth and development, including metabolic, genetic, and hormonal and ambient factor regulation, metabolic diversity, ion uptake, transport and accumulation, stress physiology and adaptation; genetic transmission and expression; plant-microbial interactions, plant cell wall structure and function; lignocellulose degradative mechanisms; mechanisms of fermentations, genetics of neglected microorganisms, energetics and membrane phenomena; thermophily (molecular basis of high temperature tolerance); microbial interactions; and one-carbon metabolism, which is the basis of biotransformations such as methanogenesis. The objective is to discern and understand basic mechanisms and principles.

For timely consideration, all preapplications should be received by February 27, 1998. However, earlier submissions will be gladly accepted. A response to timely preapplications will be communicated by April 17, 1998. The deadline for receipt of formal applications is June 17, 1998. Preapplications referencing Program Notice 98-09 should be forwarded to: U.S. Department of Energy, Office of Basic Energy Sciences,
ER-17, Division of Energy Biosciences, 19901 Germantown Road, Germantown, MD 20874-1290, Attn: Program Notice 98-09. Fax submissions are acceptable at 301-903-1003. For further information, contact: Ms. Pat Snyder, Division of Energy Biosciences, Office of Basic Energy Sciences, ER-17, 19901 Germantown Road, Germantown, MD 20874-1290, telephone (301) 903-2873; E-mail: pat.snyder@oer.doe.gov.

Funds are expected to be available for new grant awards in FY 1999. The magnitude of these funds available and the number of awards which can be made will depend on the budget process. The awards made during FY 1997 averaged close to $100,000 per year, mostly for a three-year duration. The principal purpose in using preapplications at this time is to reduce the expenditure of time and effort of all parties. Information about development and submission of applications, eligibility, limitations, evaluations and selection processes, and other policies and procedures may be found in the Application Guide for the Office of Energy Research Financial Assistance Program. Electronic access to ER's Financial Assistance Guide is possible via the Internet using the following Web Site address: http://www.er.doe.gov/production/grants/grants.html

NSF/CISE: Special Projects in Networking and Communications

Special Projects in Networking and Communications provides increased opportunities in support of research in the areas of networking and communications, emphasizing their importance in the emerging convergence of communications and computing. Special Projects meets this goal by funding (1) larger and/or multidisciplinary networking and communications theoretical and experimental research projects than typically supported through the Networking and Communications Research programs, (2) specialized infrastructure for networking and communications systems research, and (3) mechanisms for developing research agendas and enhancing community development.

Research projects theoretical or experimental in nature must focus on networking and/or communications research and may also include relevant research from other areas of computer science and engineering such as distributed systems, operating systems, databases, software, signal processing, control theory, and devices.

• Theoretical Research: Special Projects supports theoretical research that focuses on future generations of networks and communications systems and requires small teams of approximately three to four researchers.

• Experimental Research: Special Projects includes a wide range of experimental projects to demonstrate proofs of concept for novel networking and communications systems ideas. Projects may range in scope from laboratory experimentation to national collaborations.

Special Projects may also fund networking and communications research that is able to leverage resources from currently established projects. The established projects typically focus on problems from other disciplines, but may require innovative network and communications functionality, thus providing networking and communications researchers with real-world environments. Such projects may provide facilities, hardware, and/or real network traffic important for network and communications experimental research.

• Projects with Social Science Research: Special Projects may support partnerships between social scientists and networking and communications researchers in developing networking and communications systems and assessing the systems' social impacts. Example topics include: economics of the Internet; advanced telecollaboration, telescience or distance learning using experimental networks; and network security and its social impacts. Proposals should include networking and/or communications researchers and social scientists. Proposals will be co-reviewed with suitable programs as appropriate.

• Special Areas of Opportunity: Special Projects may from time to time announce on the NCRI website specific research areas for targeted consideration. The areas are expected to be identified through research community input such as workshops or panels.

Specialized Infrastructure Projects: Special Projects may fund specialized equipment or infrastructure needed by experimental researchers in networking and communications to accomplish their work. Some examples are: (a) Development of specialized testbed infrastructure for testing of subsystem proofs of concept; (b) Development and distribution of experimental software and hardware toolkits for networking and communications research

In order to enable collaborations and multidisciplinary approaches to networking and communications systems, Special Projects supports activities to formulate research agendas and enhance community development. These activities include, but are not limited to, workshops and planning grants. Support for workshops in new areas focusing on networking and communications is expected to be $10,000 to $30,000 per workshop.

Proposals must be received at NSF by August 15 and January 15 each year. Deadlines for Special Areas of Opportunity will be announced on the following Website:

Continued on Page 20

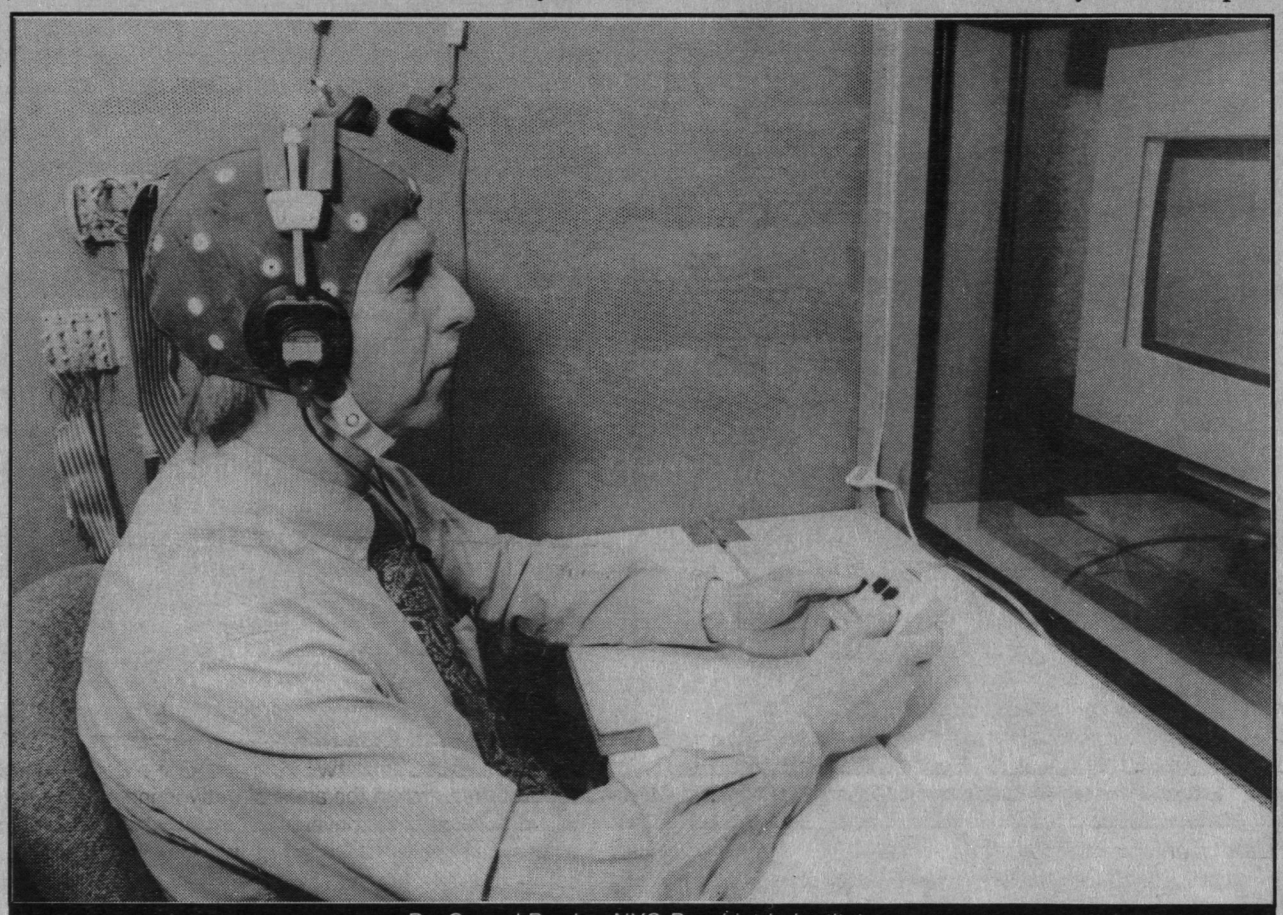
Brain Potentials Explore Cognitive Problems in Schizophrenia

Event-Related Potentials Allow High Temporal Resolution to Examine Brain's Processing of Information

by Donna Carty, Ph.D.

Research by Dr. Gerard Bruder of the Department of Psychiatry at Columbia's College of Physicians and Surgeons shows promise of shedding light on the physiological basis for auditory hallucinations in schizophrenia. It also may suggest ways in which cognitive deficits might be measured empirically, and treatments evaluated for their effects on specific symptoms.

Dr. Bruder and his team use quantitative electroencephalograms (EEGs) and event-related brain potentials (ERPs) to provide information about physiological correlates of mental function. ERPs are measures of the brain's electrical activity that are obtained by averaging EEGs recorded during the repeated presentation of a stimulus. Averaging allows 'random' fluctuations in the brainwaves to drop out, revealing a small signal buried in the noise of billions of firing neurons. This buried signal represents the brain's processing of information related to the particular stimulus or event. ERPs provide a relatively continuous record of ongoing brain activity with a temporal resolution in the millisecond range, exceeding that provided by positive emission tomography (PET) or magnetic resonance imaging (MRI). Dr. Bruder points out further that EEG-based techniques are risk-free, non-invasive, and inexpensive.



Dr. Gerard Bruder, NYS Psychiatric Institute

Dr. Bruder compared EEG recordings from schizophrenia patients with those of other individuals during the performance of a dichotic listening task. In such a task, a subject hears different sounds in each ear, and is told to respond to sounds from only one specified ear. Bruder was able to identify three instances in which the brain potentials of schizophrenics indicated a comparative functional deficit. The first was related to attention and was unlocalized. Two others, however, were localized to the left temporal lobe of the brain, a region known to be involved in language functions.

Two such dichotic listening tasks were used for these experiments. One used language syllables as the stimuli, and the other used tones. In the first, two speech syllables were presented simultaneously to the subjects' right and left ears. Most people have a right ear advantage here. Since the brain receives sensory input contralaterally, its left side receives signals from the right side of the body. Because the right ear is more directly connected to the language-processing left temporal lobe of the brain, normal people most often report hearing the syllable presented to the right ear. In schizophrenics, however, this right ear advantage was less apparent.

In the second experiment, two tones were presented simultaneously to the right and left ears. Two seconds later, another tone was presented, and the subjects were asked to determine if it matched one of the immediately preceding tones.

About 100 milliseconds after the stimulus is delivered, it evokes a negative brain potential that is not localized to either hemisphere, indicating simple reception of the stimulus. This potential, known as N1, was reduced in schizophrenics for both tones and syllables.

After about 200 milliseconds, language syllables evoke a second negative brain potential, N2, localized to the left temporal lobe's superior temporal gyrus. This potential is believed to be related to the identification of a sound as speech or non-speech. This potential was also reduced in schizophrenic patients, suggesting that they may have difficulty differentiating between speech and non-speech sounds.

After approximately 300 milliseconds, attended signals evoke a late, positive brain potential, P3, believed to be related to cognitive processing of the stimulus, and evaluation of its match with a stored template. The third tone, which must be evaluated for a match with one of the previous tones, evokes a P3 potential in normal subjects, but this too is reduced in schizophrenics.

Dr. Bruder studied both male and female schizophrenic patients. Some were receiving medication; some were not. Subjects were not chosen for clinical state, though a certain level of function and motivation was required in order to perform the experiments.

Although women's brains are known to be less strictly lateralized than men's, (that is, a single function is less likely to be carried out exclusively in one hemisphere of the brain) no sex difference was evident in the results of these experiments.

Schizophrenia is a particularly devastating and debilitating mental illness. It is also surprisingly common, occurring in one to one and a half percent of the population worldwide over the course of their lives. It is characterized by both "negative symptoms" (a lack of emotional expression, apathy, and social withdrawal) and "positive symptoms" (the grossly abnormal behavior most likely to be noticed by others, such as a diminished ability to think clearly and logically, disconnected and nonsensical language, delusions, and hallucinations). These delusions and hallucinations often take an auditory form. The patient may believe his thoughts can be heard by others. Or he or she may hear voices no one else can hear, voices describing his actions, warning of danger, or telling him what to do. There may be several voices carrying on a conversation.

Difficulty in distinguishing speech from non-speech and in matching sounds received to speech templates could lead to confusion regarding incoming information.

Physicians have debated the basis of schizophrenia for many years. The constellation of symptoms can vary widely from patient to patient. It is believed to have a biological basis, possibly associated with a breakdown in the way that different brain regions communicate with one another. This may be due to an impairment of the nervous system occurring during development or due to a dysfunction in one or more of the brain's neurotransmitters. While there is no known cure for schizophrenia, many patients respond to drug therapy which can control acute symtom outbreaks.

Though schizophrenia may not be absolutely genetically determined (for example, one of a set of identical twins may be schizophrenic and the other may not evidence the acute, full-blown disorder), there is strong evidence of genetic predisposition to the disease. The probability of schizophrenia in individuals having one parent with schizophrenia is approximately 13 percent. If both parents have the disease, the probability increases to 35 per cent. By contrast, only about one percent of the offspring of two non-schizophrenic parents develop schizophrenia.

Dr. Bruder and his colleagues hope to use the results of their experiments to distinguish cognitive differences among groups of schizophrenics and to predict which treatments might be most appropriate to a particular set of cognitive dysfunctions. For instance, a prior study indicated that patients known to have auditory hallucinations showed the strongest deficit in N2 and P3 evoked potentials. Dr. Bruder and his colleagues are presently investigating which drugs are most effective with patients evidencing these particular deficits.■

Arabidopsis... Continued from Page 6

designated persons in the event that the sequencing success rate falls below a predetermined level.

KALEIDASEQ is also part of the laboratory's effort to make all information regarding their project more directly available to scientific community and the general public. While KALEIDASEQ operates on an internal Web site, it outputs predetermined data to the McCombie laboratory's external Web pages nightly. All assembled pieces larger than 1,500 base pairs are automatically posted for public access, and data for that project are automatically updated on the public sites each evening. This results in the majority of data being made publicly available well before the project is finished — an entirely new approach to the dissemination of scientific data.

Thus, the publication process which many sequencing laboratories have undertaken strays significantly from scientific publication as usual. Publishing raw data on the internet or WWW for both the scientific community and the general population as well, has become common practice among sequencers. It is the opinion of those involved in these projects that the benefit of sharing all information outweighs the risk of publishing data outside of the standard peer-reviewed journals.

The 'big picture'

In assessing the implications here for agricultural applications, Martienssen offers the example of the relationship between the corn plant, Maize, and Teosinte, a grass common to Mexico and Latin America. At a glance, the two plants appear quite distinct: Teosinte is a small bladed grass, maize is a large, thickly stalked, cob bearing plant. Yet plant geneticists have determined that the genetic difference between the two species is confined to alterations of only five fundamental genes, and a number of minor modifiers. This would suggest that using a genetic map and today's genetic tools, scientists could manipulate specific genes to create desired changes, ultimately creating "designer plants" with various desirable qualities.

Despite its unassuming appearances, Arabidopsis, with its neat little tool box of genes, may therefore hold the key to countless future advances. Perhaps in only a matter of years we will be living in a world where deserts are colonized by fruit-bearing plants. It's perhaps axiomatic in genetics that it is through the apparently simple that great discoveries are made. Arabidopsis appears to be no exception.■

St. John's Wort... Continued from Page 8

To arrive at that hypothesis, Petrich and his team had to capture the fleeting light emission given off by hypericin after it absorbed a light pulse lasting less than 100 femtoseconds, or quadrillionths of a second. They were able to observe the signal caused by the proton-transfer reaction as it occurred — lasting only 7 picoseconds, or trillionths of a second.

"Sometimes the proton isn't transferred directly, but falls off and is absorbed in the water surrounding the hypericin," said Castner. "This proton ejection, which causes the surrounding area to become more acidic, may be important to hypericin's toxicity to viruses. We already know that certain parts of the HIV virus can be damaged by too much acidity."

A control experiment showed that the process didn't occur in a chemically modified form of hypericin in which all the protons that would have transferred had been replaced by methyl groups.

The BNL experiment that confirmed the Iowa theory is called fluorescence upconversion spectroscopy. It uses a laser in Brookhaven's Chemistry Department to produce the light pulses and "turn on" the chemical reaction. The apparatus allows the scientists to "watch" the molecules move by carefully recording the intensity and color of the light emitted from the hypericin over time after the light burst. The apparatus is now being duplicated at Iowa State.

Meanwhile, the Delaware-based biotechnology firm VIMRX is testing a synthetic form of hypericin in clinical trials for use against the HIV, hepatitis C, and glioblastoma, a highly malignant form of brain tumor. In October, the University of Pennsylvania began a VIMRX-sponsored trial of topically-applied hypericin for skin diseases including psoriasis, cutaneous T-cell lymphoma and warts.

Besides Castner and Petrich, the collaboration included Iowa State Ph.D. candidate Doug English, postdoctoral fellow Kaustav Das, and scientists Kyle Ashby and Jaehun Park. The research at Iowa State was supported by the National Science Foundation. Brookhaven's research was funded by DOE.■

Physicians... Continued from Page 4

The Bell Laws were drawn up by a group of physicians charged with reforming the medical education protocols for house officers after the death of a young woman in a New York City hospital was felt to be at least partially attributable to the sleep-deprived state of the house officer caring for her.

In defense of the hospitals, however, it must be said that many have enacted rules and regulations similar to those outlined by the Bell Commission of their own volition. Many hospitals have a "Night Float" system in place, wherein a freshly rested group of doctors begin in the early evening either to assist or to replace doctors who have been working since the early morning hours. While programs with the Night Float system are not the rule — they are still quite rare in the midwestern states — they are growing in number. While almost universally lauded by house officers, many senior doctors find such systems distasteful and overly pampering.

"I think they are a horrible mistake," said one cardiologist at a large Boston academic medical center, "I don't understand a system where doctors on call admit ill patients to the hospital and then simply leave them in the care of people who aren't familiar with their medical cases. It hurts continuity of care. Patients need to be cared for by people who know them and not just by somebody with an M.D. after their name."

One medical house officer disagrees. "That doesn't make any sense. Would you rather have a doctor who knows you better but is exhausted taking care of you? It's better to have a Night Float house officer come in who is well-rested and almost certainly just as competent." Indeed, nurses have worked under a similar system of shift-changes for many years with no detriment to patient care.

The same medical house officer felt that despite his appreciation for the Night Float system, occasional overnight call duty had its advantages. "It's a double-edged sword. At night, you have the least help, but you also get to call the shots without someone looking over your shoulder every two seconds. When I started out as an intern [a doctor who has just graduated from medical school] I didn't know how to handle any emergencies, but now I'm really confident. I can handle just about anything that is thrown

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http://www.cise.nsf.gov/anir/index.html. (Ref: NSF 97-108)

AR-98-005: Basic Research on Biomechanical Signaling Mechanisms in Cartilage

The National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Aging invite applications for basic research on mechanisms of biomechanical signaling in cartilage. The applications may be for individual research projects or for a group of independent research projects that use the interactive research project grant (IRPG) mechanism. The research should be specifically targeted towards understanding the signal transduction and regulatory pathways through which articular cartilage chondrocytes sense and respond to mechanical stimuli. This Request for Applications (RFA) requests basic and applied research projects, but not epidemiological or clinical treatment projects. Letter of Intent Receipt Date: March 15, 1998; Application Receipt Date: April 28, 1998.

PAR-98-017: Collaborative R01's for Clinical Studies of Mental Disorders

The National Institute of Mental Health invites applications for collaborative research efforts on Clinical Studies of Mental Disorders (CSMD) including schizophrenia, mood disorders, anxiety disorders, and other severe mental illnesses.

Collaborative CSMD grants support research on a highly related topic at two or more sites. The work may involve either identical protocols at multiple sites, or the sites may have different roles in investigating a common topic. The purpose of collaborative CSMD is to facilitate research that requires integration/interaction among organizationally distinct entities. It ensures that there will be a Principal Investigator (PI) at each site, as well as a way for the PIs to make decisions and coordinate efforts across sites. This would assure quality control, cross-site training and/or reliability monitoring, and allow pooling of data for analyses.

Although the investigators as a group must request advance permission from NIMH to submit such applications if the overall total annual funding requested will exceed $500K in any year, there is no Government involvement in the conceptualization, data collection or publication of results. This makes it different from a Cooperative Agreement (U01 or U10) application in which the Government is considered an integral part of the research team.

While the collaborative CSMD is appropriate for studies at different sites of a multi-campus institution, it is not appropriate for collaborations within a single campus institution. Such collaborations within a single campus institution should consider using the Program Project (P01) mechanism. Because of the complexity inherent in most collaborative CSMD applications, and the additional review criteria related to their administration, applicants are strongly encouraged to consult with NIMH program staff.

PAR-97-007: Jointly Sponsored NIH Predoctoral Training Program in the Neurosciences

This notice is to remind the scientific community of the ongoing Jointly Sponsored NIH Predoctoral Training Program in the Neurosciences (see PAR-97-007, available at http://www.nih.gov/grants/guide/pa-files/PAR-97-007.html). The receipt date for new and revised applications is May 10. Letters of intent are due March 1 and are strongly encouraged for both new and revised applications.

PA-98-019: Management of Symptoms at the End of Life

The National Institute of Nursing Research, National Cancer Institute, National Institute of Allergy and Infectious Diseases, National Institute of Mental Health, and Office of Alternative Medicine seek research grant applications concerning the clinical management of symptoms and syndromes that are associated with life-limiting illness, such as pain, dyspnea, delirium, cachexia, nausea, fatigue, and depression. The purpose of this initiative is to stimulate research that will lead to improved quality of life for those at the end of life and decreased distress for their caregivers.

PAR-98-018: NCRR Shared Instrumentation Program

The National Center for Research Resources is continuing its competitive Shared Instrumentation Grant (SIG) Program initiated in Fiscal Year 1982. Results of the most recent study, "The National Survey of Academic Research Instruments and Instrumentation," published in 1997 identified bioanalytical equipment of the type provided through this Program as the top most priority. The objective of the program is to make available to institutions expensive research instruments that can only be justified on a shared-use basis and for which me itorious research projects are described. The SIG Program provides a cost effective mechanism for groups of NIH-supported investigators to obtain commercially-available, technologically sophisticated equipment costing more than $100,000.

Applications are limited to instruments that cost at least $100,000 per instrument or integrated instrument system. The maximum award is $400,000. Since the nature and scope of the instruments that may be requested will vary, it is anticipated that the size of an award will vary also. Awards will be made for the direct costs only. The institution must meet those costs (not covered in the normal purchase price) required to place the instrumentation in operational order as well as the maintenance, support personnel, and service costs associated with maximum utilization of the instrument. There is no upper limit on the cost of the instrument, but the maximum award is $400,000. Cost sharing is not required. If the amount of funds requested does not cover the total cost of the instrument, the application should describe the proposed sources(s) of funding for the balance of the cost of the instrument.

An institution may submit more than one application for different instrumentation; however, if several applications are submitted for similar instrumentation from one or more eligible departments on the same campus, documentation from a high level official must be provided stating that this is not an unintended duplication, but part of a campus-wide institutional plan.

A minimum of three major users must be Principal Investigators on NIH peer reviewed research grants at the time of the application and award. The application must show a clear need for the instrumentation by projects supported by multiple NIH research awards and demonstrate that these projects will require at least 75 percent of the total usage of the instrument.

A recent NIH/NSF Memorandum of Understanding permits the joint agency review and funding of requests for a single instrument costing more than $500,000 which would normally be eligible for submission to both NIH and NSF. Such a request may be submitted to NIH for the March 20 (SIG) deadline for review by NIH with NSF participation, thus avoiding separate agency peer review. Under this arrangement, the agencies may offer joint funding in excess of their current award limits of $400,000. Application Receipt Date: March 20, 1998

DA-98-004: Neurobiological Effects of Drug Addiction Therapies

This Request for Applications (RFA) solicits research grant applications that investigate the effects of behavioral and/or pharmacological drug addiction therapies on structure and/or function of the human central nervous system. Through the use of clinical neurobiological approaches, such as neuroimaging, considerable information is now being amassed that reveals how drugs of abuse and addiction alter brain processes. However, a critical question that remains to be addressed is how drug addiction therapies (whether behavioral, pharmacological, or both) might affect altered brain structure and/or function. For example, do drug addiction therapies "reset" or "normalize" brain biology and/or chemistry altered by chronic drug exposure? Results from such studies could provide vital insights for the development and improvement of behavioral and medication treatment of patients with drug use disorders.

This research program is intended to support individual research project grants, mentored career development awards, and competitive supplements on the clinical neurobiological effects of specific treatments for drug use disorders. Research using animals (particularly primates) is not excluded, but any animal research submitted under this RFA must serve an essential, but secondary role, in a predominantly clinical study. Letter of Intent Receipt Date: February 26, 1998; Application Receipt Date: March 26, 1998.

DE-98-001: Competitive Supplements - Oral Dimensions of HIV Transmission, Therapies, and Outcomes

The National Institute of Dental Research invites competitive grant supplement applications to address critical gaps in knowledge concerning the role of the oral environment in HIV transmission, the etiology and treatment of HIV- related oral symptoms and neuropathic pain, and dental interventions which may contribute to treatment adherence or clinical outcomes. These supplements are expected to enrich scientifically or to extend the scope of relevant NIH-funded research grants supporting biological, biomedical, behavioral, or epidemiological studies. The primary (parent) grants being supplemented may be funded by any of the Institutes or Centers of the National Institutes of Health (NIH).

Through this Request for Applications (RFA) NIDR seeks to stimulate collaborative studies capitalizing on current NIH- wide investments in HIV research by building upon resources already available (e.g., tissue samples, cohorts of HIV+ or high risk subjects with well- delineated medical data, pediatric or adult clinical trials testing drugs or drug combinations). Studies are specifically encouraged on oral mucosal immunity, mechanisms underlying the development of HIV-related oral opportunistic infections, prevention of oral HIV transmission, improved therapies for oral opportunistic infections, mechanisms underlying and treatments for HIV-related neuropathic pain, and dental care-based interventions to enhance prevention, symptom management, or clinical outcomes in HIV. Letter of Intent Receipt Date: March 1, 1998; Application Receipt Date: March 26, 1998.

AA-98-001: Developing Alcohol-Related HIV Preventive Interventions

The National Institute on Alcohol Abuse and Alcoholism seeks to stimulate the design, development, and testing of alcohol-related HIV preventive interventions that have the potential for reducing the risk of transmission of HIV in alcohol using, abusing, and dependent populations. Investigators are encouraged to move beyond basic behavioral studies to measure the efficacy and effectiveness of substance use risk-reduction interventions in populations at risk for both alcohol problems and HIV infection. The emphasis of this RFA on prevention research in the alcohol/AIDS area continues the previous focus of the NIAAA Prevention Research Branch on primary prevention of HIV and alcohol abuse among male and female alcohol users. In addition, this RFA addresses secondary prevention issues among HIV infected male and female alcoholics who may be more likely than other HIV infected individuals to engage in high-risk sexual behavior, to use unclean needles, and to have problems adhering to therapeutic treatments for HIV and AIDS.

Research support may be obtained through an application for a regular research project grant (R01). Applications are also encouraged for Exploratory/Developmental Grants (R21), which are limited to 2 years for up to $70,000 per year for direct costs. Exploratory/Developmental Grants are also available for the secondary analysis of existing alcohol abuse prevention research data that examine intervention effects related to alcohol use. These grants are limited to 2 years for up to $100,000 per year for direct costs. Applicants may also submit applications for Investigator-Initiated Interactive Research Project Grants (IRPGs). Letter of Intent Receipt Date: March 20, 1998; Application Receipt Date: April 21, 1998.

PAR-98-021: NIA- Pilot Research Grant Program

The National Institute on Aging is seeking small grant (R03) applications in specific areas to: (1) stimulate and facilitate the entry of promising new investigators into aging research, or (2) encourage established investigators to enter new targeted, high priority areas in this research field. This Small Grant (R03) Program provides support for pilot research that is likely to lead to a subsequent individual research project grant (R01) and /or a significant advancement of aging research.

New or established investigators are eligible to apply for this award. (1) For a new investigator to be eligible the individual should be in the first five years of his or her independent research career. If the applicant is in the final stages of training it is permissible to apply for an R03 but no award will be made to individuals who are still in training or fellowship status at the time of award. (2) For an established investigator to be eligible, the individual must propose research that is unrelated to a currently funded research project in which the investigator participates.

Applicants may request up to $50,000 (direct costs) for one year through the small grant (R03) mechanism. These awards are not renewable. Before completion of the R03, investigators are encouraged to seek continuing support for research through a research project grant (R01). Application Receipt Dates: March 17, 1998; July 17, 1998; November 17, 1998.

HG-98-002: Research Network for Large-Scale Sequencing of the Human Genome

The purpose of this Request for Applications (RFA) is to seek applications to participate in a Research Network, the goal of which is to make a major contribution to the completion of the first human genome sequence by 2005. This Research Network will be comprised of sequence production centers, specialized sequencing projects and a quality control center.

The administrative and funding mechanism to be used to support this program will be the Cooperative Agreement (U01), an "assistance" mechanism, which is distinguished from a regular research grant in that substantial scientific and/or programmatic involvement by NHGRI staff with the awardee is anticipated. Letter of Intent Receipt Date: July 1, 1998; Application Receipt Date: October 9, 1998. ■

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at me because I've been battle hardened by all those nights alone. Besides, if I really get in over my head, I can call for help."

Calling for help, however, is itself a convoluted issue. In many progressive hospitals there exist protocols that allow junior doctors access to more senior physicians at all hours. For example, one large Boston medical center has a critical care specialist whom house officers can call during the night when taking care of patients in the intensive care units. At this hospital, it is the house officer, in the hospital with the patients, who has the final say as to whether or not the critical care specialist must come in to assist. The specialist is bound by his contract to come in if requested, even in the middle of the night. Again, while all of this sounds good, there is some degree of stigma surrounding the call for help.

"Once when I was an intern," a medical resident recalled, "I had a guy who was really crapping out on me. 'Circling the drain,' as we say. Low blood pressure, high heart rate, the works. Anyway, I knew I was in trouble, so I called the senior resident to the bedside. Now, he came right away, and really was invaluable to that patient's care. But when all was said and done and the patient was stable, he told me point-blank that he thought that I was 'weak' for calling him. I was crushed. It made me think twice about calling for help again."

Another junior doctor, this one a surgeon, had a different opinion. "I believe in calling for assistance if the situation demands it. Sure, some people will criticize you for not being able to handle things on your own, but how else am I supposed to learn? This business forces you to develop a thick skin. You get used to being treated harshly. I'd much rather get chewed out for asking for too much help than have somebody die on my watch who could have been saved."

The issue of adequate help and supervision for training doctors has another facet; it is not only the safety of the patients that is at risk, but also the safety of the doctors themselves. One recent case involved a Yale-trained doctor who took the university to court because she felt that she had been undersupervised during a procedure on a patient infected with HIV, the virus that causes AIDS. During the course of the procedure, the then junior doctor was stuck with a needle containing the patient's blood. The doctor has subsequently gone on to contract the virus and is currently under treatment for AIDS. At the time of the incident, no senior physician was present to supervise. The jury in this case awarded the physician $12.2 million.

Feelings on this case among doctors are divergent. Some feel that the university and her training program failed the resident by not supervising her adequately. Others feel that she was at least partially to blame for attempting such a procedure by herself, a feeling which the jury in this case shared in some measure, although still awarding her a record sum in damages. Although regulations such as those proposed by the Bell Commission have not led to any criminal actions to-date, one wonders if civil actions such as the Yale trial will lead to changes in house officer staffing and supervision.

While much of the old guard still finds itself at odds with a system that allows young doctors such "luxuries" as night float and I myself have written in these pages about the mix of emotions young doctors go through as they learn their craft; elation at finally putting their skills to good and productive use, frustration and resentment over the sometimes unreasonable demands placed on their all-too-limited hours. I too have acknowledged the value of handling emergencies alone at night and yet have also known the sickening feeling one gets with the realization that much-needed help is not on the way.

Clearly, opinions on all of these issues remain divided, but the nationwide trend is towards a more supportive environment for young doctors. Night Float systems at many hospitals have been in place for almost 10 years. A large number of senior physicians in practice today trained under such systems, which provide not only much-needed relief at night but also definitive and adequate backup from senior doctors. It is likely that this trend will continue — although at perhaps too slow a pace.

Public opinion on these matters is unclear. While, objectively, few would support any profession that works it's practitioners for 80 to 100 hours per week, sympathy for young doctors is in short supply. Few feel the need to rush to support the cause of those they see as training for lucrative, prominent jobs. At the same time, many have been and would be quick to find fault with that same system if they or one of their own loved ones were to fall through the all-too-common and very wide cracks. ■

Transgenic... Continued from Page 5

junction with T cell decline and the progression to AIDS.

CHEMOKINE RECEPTOR CCR5 IS CRITICAL TO HIV INFECTION

In the same year that Berger made his discovery of CXCR4, subsequent studies were published showing the importance of M-tropic HIV isolates in the initial infectious process after individuals with a 32- base pair deletion on the gene that expresses the CCR5 receptor were protected against sexually transmitted HIV-1. Despite numerous multiple exposures to HIV, these individuals were resistant to in vitro HIV infection with M-tropic HIV isolates. Although CD4 can act together with one of several members of the chemokine receptor superfamily, CCR5 began to emerge as the critical co-receptor for HIV in the initial stages of infection.

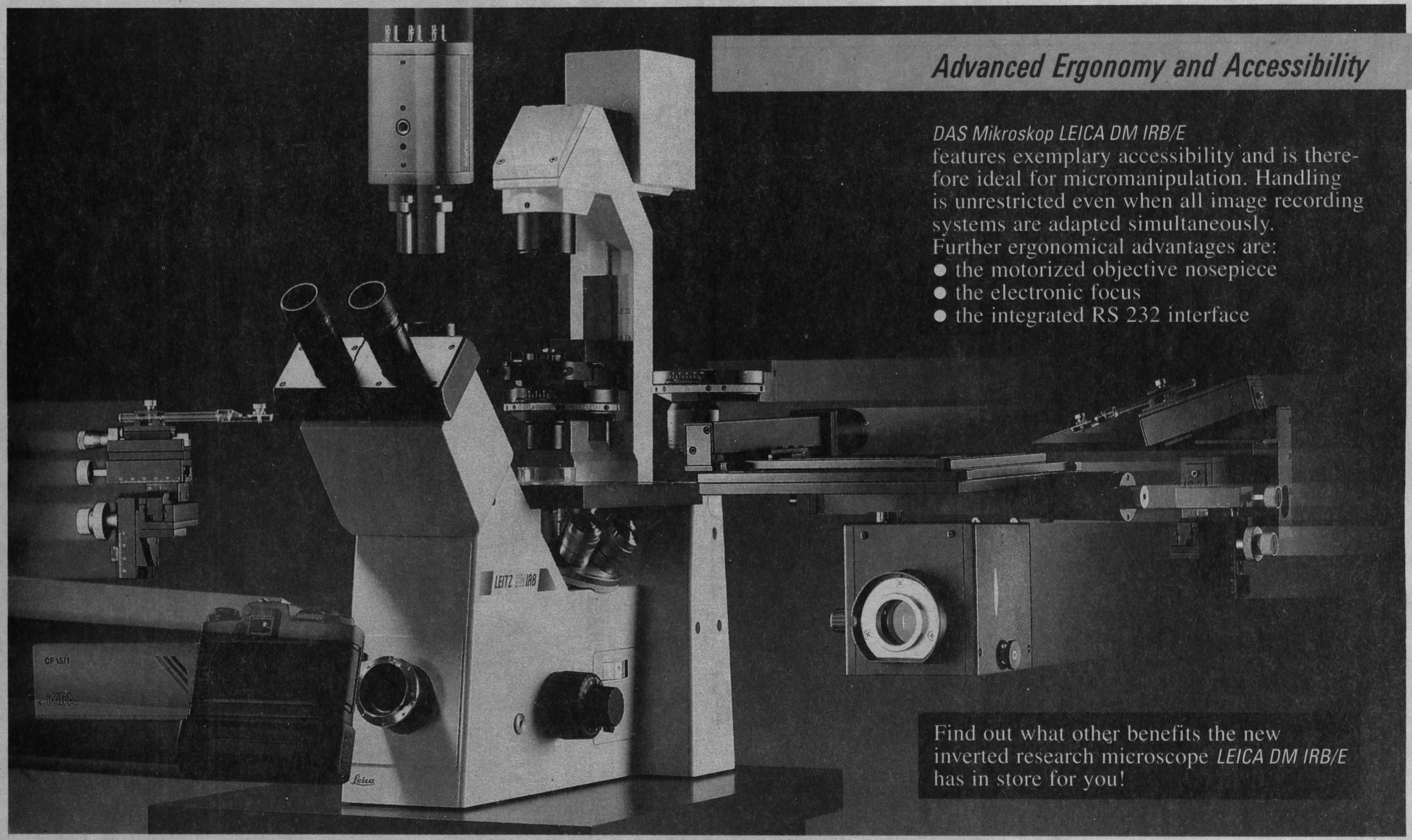
"It turned out that some of these patients had a mutation in their CCR5 chemokine receptor and did not express it on their T cell surfaces," said Dr. Goldstein. "They were homozygous for this mutation — and were relatively protected from infection. Even though several chemokine receptors can function as a receptor for HIV infection — CXCR4, CCR5, CCR3 — the fact that individuals with the CCR5 mutation were not infectible suggests that CCR5 is the key physiological receptor in the initiation of HIV infection. It was also found that approximately 1-2% of the Caucasian population have the CCR5 mutation which is not present in the Black or Asian populations."

In order for HIV to fuse successfully with a cell membrane and penetrate, the HIV protein, gp120, first binds to CD4. After this, it changes its 3-dimensional structure by opening up an area which can now bind to CCR5 (see figure). "Cells express thousands of proteins on their surface and they express high levels of CD4 and CCR5 - probably at high enough density that CD4 and CCR5 molecules are sitting next to each other on the surface," explains Dr. Goldstein. "CD4 itself is a very large molecule - it basically juts out of the surface of the cell and may then flag the gp120 protein. CCR5 is a very flat molecule very close to the surface and doesn't protrude. CCR5 alone is unable to find the gp120 protein simply because it's so close to the cell surface. CCR5 must also wait for the gp120 protein to bind to CD4 in order for its hidden binding site to open up — it's a two step process."

A POTENTIAL MODEL FOR AIDS VACCINE RESEARCH

To determine whether the expression of human CD4 and CCR5 is sufficient to render mouse cells susceptible to HIV infection, the team made transgenic mice that were able to express these two receptors' T-cells. Dr. Goldstein recalls, "although we were able to demonstrate that HIV could now penetrate and integrate into the genome of these mouse cells, we could not really get high level production of HIV from these cells. I think the problem is not so much of binding and getting into the chromosome of the mouse; the problem is that once you get into the chromosome of the mouse, the virus has to tell the cellular machinery to make large amounts of viral RNA and viral proteins. The virus will then begin barking orders that human cells understand but that mouse cells don't. As a result, HIV will not replicate very efficiently. We're currently looking to see what orders are different, and determine how to replace those factors into mouse cells. Perhaps we can change the virus so that it could now bark orders in a language that a mouse cell recognizes by using different proteins than the existing viral regulatory proteins that work in mouse cells."

When asked whether the team feels optimistic about using mice as a model to study AIDS despite their resistance to HIV, Dr. Goldstein responded: " I think that there are two issues. One is: will a mouse resemble humans and all the manifestations of the disease that humans are subject to? Probably not. The amount of tweaking and changes that we would have to do in order to make the mouse infectible with HIV and replicate efficiently will most likely alter the natural course of the disease from that occuring in infected humans. So it is reasonable to say that it is unlikely that the mouse model would closely recapitulate the progression of HIV-mediated disease in humans. The second is: will a mouse infectible with HIV be a useful research system? There is a major need for an animal model to test HIV vaccines. We want to have a situation where we can take mice — immunize them with many candidate vaccines — see if they develop the immune response directed against HIV proteins and protect the mouse from infection. With that situation, the infectious process doesn't necessarily have to mimic what happens in humans as long as the virus uses the same entry pathways and has the same antigens as the virus that infects humans. For this purpose I think that that would be an extremely valuable model." In addition, since the major steps of viral replication will be similar, these mice should also be useful as an *in vivo* model for studying new antiviral therapies."■



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