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Dec/Jan◆1996-97

Rockefeller Receives Funding to Create a "New Kind of Biologist"

Interdiciplinary Training Program Brings Biology Together With Physics, Math, Chemistry, and Computer Science

by James L. Ulrich

Rockefeller University has received a $2.5 million, five-year grant from the Burroughs Wellcome Fund. The award will be used to fund partially the Interdisciplinary Training Program in Physics, Chemistry, and Biology which has recently been established by the University. Additionally, a portion of the award will be used to create a Biophysics Teaching Laboratory.

The Interdisciplinary Program is intended to bring together graduate and post-doctoral students in the mathematical, physical, chemical, and computer sciences, with the purpose of grooming those students to work on problems in biology and medicine. The Program will be co-directed by Dr. Stephen K. Burley, a biophysicist and medical scientist, and Dr. Albert Libchaber, an experimental physicist.

The award is significant in that traditional sources of research funding such as the National Institutes of Health are not widely available to interdisciplinary programs, because these programs are generally of a more theoretical nature and less likely to yield relatively immediate dividends such as new treatments for disease. "By its very nature, interdisciplinary research represents some risk of not getting a result. If you're trying to do something that's relatively new in an established area, you can present evidence which allows one to make a good case that you'll actually be able to do the research. At the NIH, if you can't present a clear road map from the starting point to the result, it's very hard to get funded for any kind of scientific project," notes Burley.

For an interdisciplinary research project, the task of soliciting NIH funding is particularly onerous. The project must be evaluated by NIH-assigned experts in each of the different fields which the project incorporates, and these experts must concur that the project is viable. "That's not an easy task," Burley observes. "As the successes come, it will be easier to persuade people. But for now, if you wrote to the NIH requesting money for a training grant of the type that we've proposed here, it would not be funded."

On the other hand, private foundations are more willing to finance research projects which carry a level of risk. As Burley notes, "they're not spending the taxpayer's money. I don't think that a review panel at a private foundation has the

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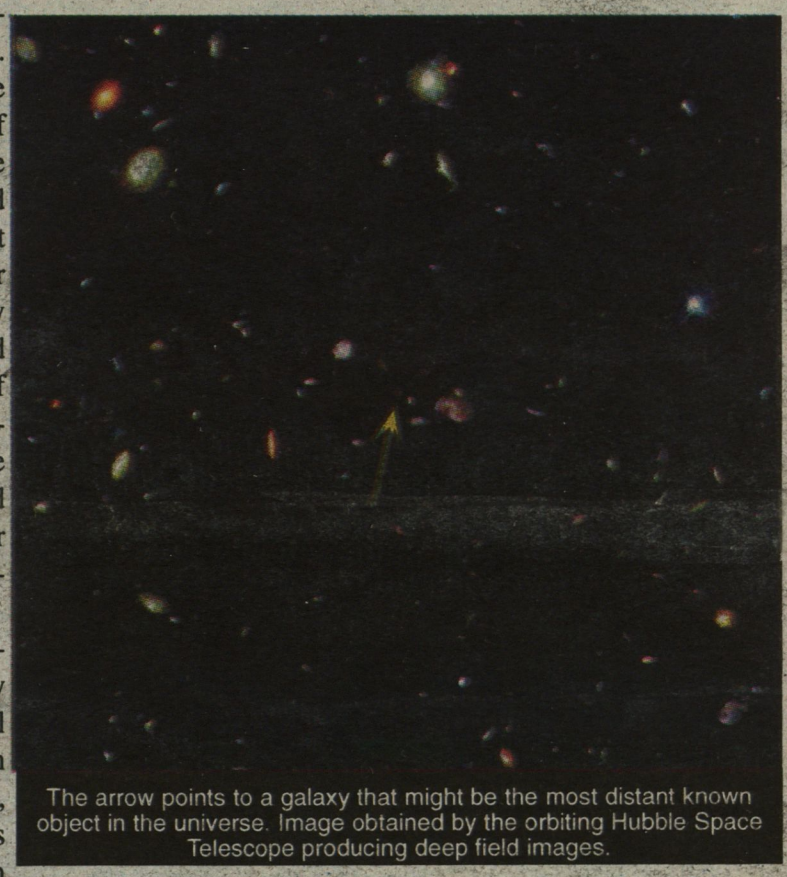
Stony Brook Astronomers Claim Discovery of Most Distant Galaxies Ever Observed

Epochs Reach Back Near the Time of the Big Bang

by Dan Coulter, *ASN&R* Staff Writer

During ten consecutive days in December of 1995, the Hubble Space Telescope was focused on a small patch of sky just above the Big Dipper that was seemingly blank to even the most powerful ground-based telescopes. Much to the amazement of astronomers, the images produced by Hubble at that time revealed over 1,500 previously undiscovered galaxies, some of which are estimated to be far more distant — and formed far earlier — than any previously seen.



The arrow points to a galaxy that might be the most distant known object in the universe. Image obtained by the orbiting Hubble Space Telescope producing deep field images.

Modern cosmology, the study of the physical nature and origin of the universe, began early this century when Albert Einstein published his theories of relativity suggesting that space and time are components of a single entity. Einstein went on to demonstrate "space-time's" relation to gravity and the distribution of matter in the universe, and the work of other scientists such as Edwin Hubble then revealed that the universe is expanding. Since then, the study of cosmology has become the joint effort of astronomers and physicists to understand the origin, evolution, and fate of the universe.

Drs. Kenneth Lanzetta and Amos Yahil of Stony Brook, together with their colleague Dr. Alberto Fernandez-Soto of the University of Cantabria in Spain, are among the many astronomers scrutinizing the Hubble images for distant galaxies. "The search for very distant galaxies has been going on for over twenty years. We want to understand how galaxies formed and evolved into the objects that we see today," said Lanzetta. According to Lanzetta, the study of distant galaxies could also provide significant clues into the shape or geometry of the universe as well.

"Because light travels at a finite speed, the galaxies are seen as they were in the distant past" said Lanzetta. Big Bang theory holds that the universe began with a singular event, much like a vast explosion, sometime between 10 and 20 billion years ago. In the first few minutes following this event, the universe began to expand and matter began to cool. At some later point, it is believed that galaxies began to form when vast clouds of gas contracted, and an epidemic of star formation was triggered. It can be assumed from the Big Bang theory that the very first galaxies that formed will appear at greater distances today, due to the expansion of the universe.

In a paper that appeared this year in the June 27th issue of *Nature*, the team published their study of the Hubble images heralding the discovery of the most distant galaxies observed to date. More specifically, Drs. Lanzetta, Yahil and Fernandez-Soto claim they have discovered six galaxies that are perhaps twice as distant as any previously known. They further suggest that these galaxies may have existed when the universe was less than 5% of its present age — only a few hundred million years after the Big Bang.

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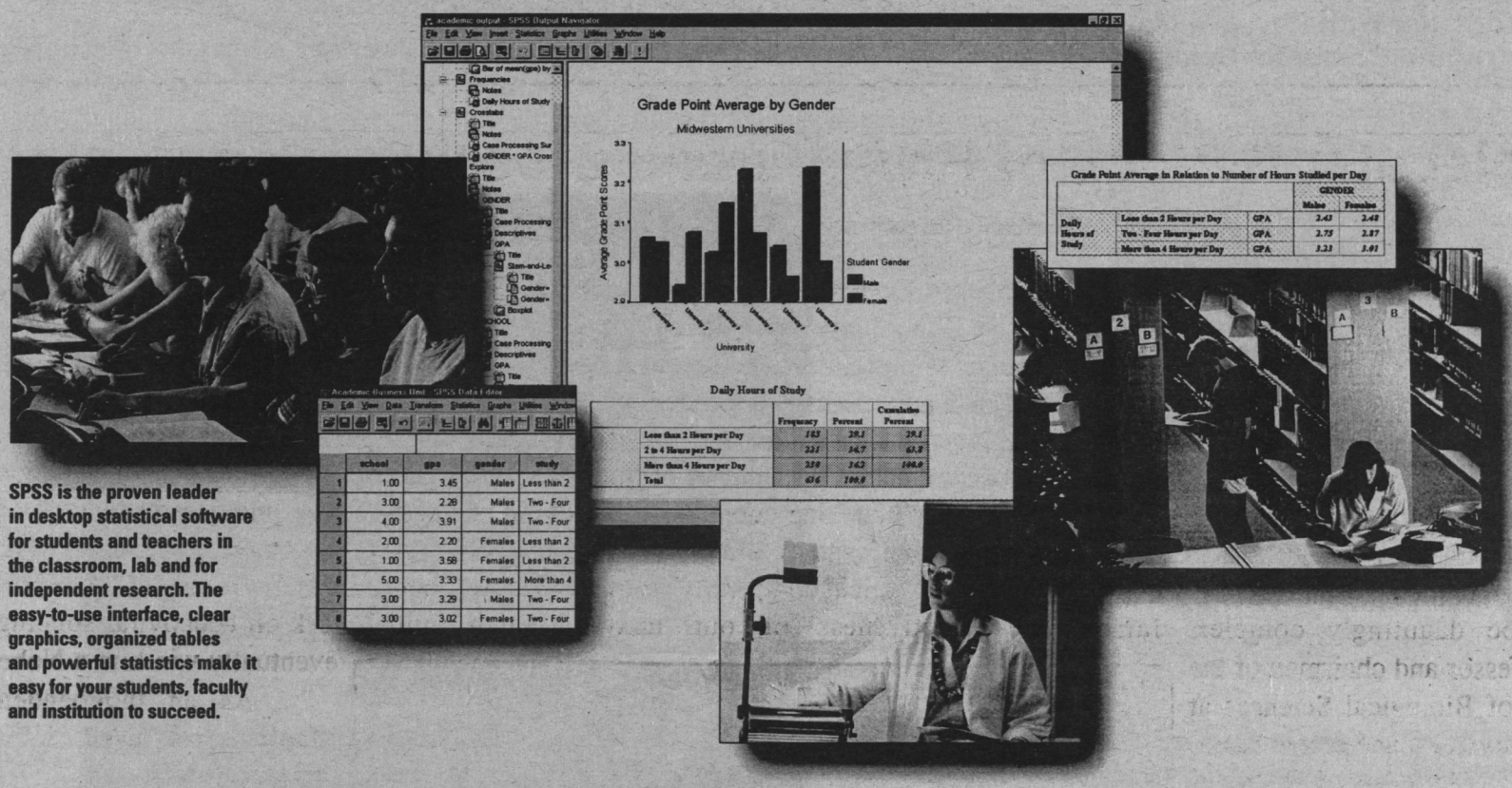

	school	gpa	gender	study
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2	3.00	2.28	Males	Two - Four
3	4.00	3.91	Males	Two - Four
4	2.00	2.20	Females	Less than 2
5	1.00	3.58	Females	Less than 2
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OVERVIEW — Dec/Jan 1996-97

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- Rockefeller University has received funding to set up a multidisciplinary training program for biologists which aims to bring biology together with physics, chemistry, math, and computer science. p 1.
- Studies on RNA splicing have proven that the translation of genetic information into physical organisms is a more complex process than previously considered by molecular biologists. p 3.
- Martin Chalfie's work probes the nature of the sense of touch by examining its most basic biology. p 7.
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- Primary care research finds that "non-difinitive" methods may provide a solution to physician-patient impasse in chronic illness. p 21.

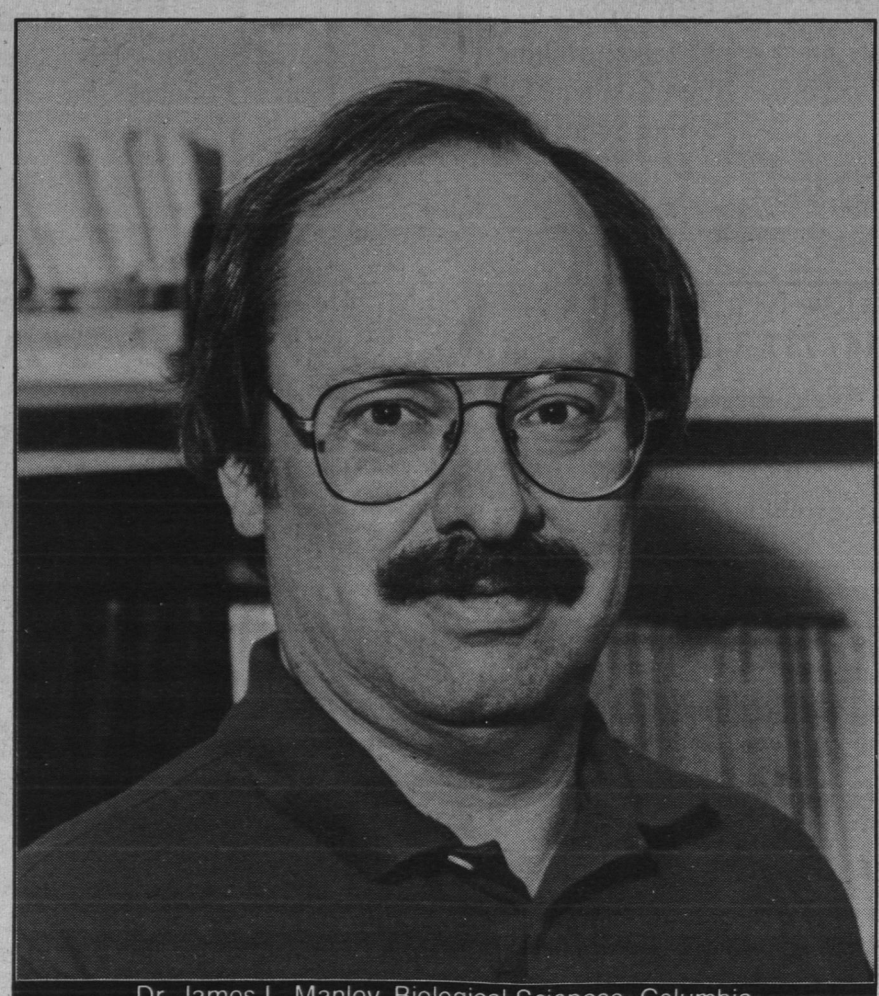
Molecular Biology of RNA, Viewed Closely, Yields Complex Secrets of the Genome

Study of RNA Splicing Factors Questions Central Dogma, Provides for Tremendous Biological Complexity

by Alan Packer

Although Francis Crick's central dogma of molecular biology (DNA makes RNA makes protein, with apologies to the retroviruses) is simple enough to be placed on even the smallest bumper sticker, the mechanisms underlying the translation of genetic information into enzymes, cells, tissues, and organisms appear to be dauntingly complex. James Manley, professor and chairman of the Department of Biological Sciences at Columbia University and recent recipient of an NIH Merit Award, is one of the leading investigators in the field of RNA splicing, a burgeoning area of research on the ways in which fragments of transcribed RNAs are cut and spliced together to generate a mature messenger RNA that will be translated into protein.

An evolving rule of thumb in the study of gene expression is that every step in the process from genotype to phenotype is tightly regulated. Examples range from the inhibition of transcription by DNA methylation to modifications like polyadenylation and phosphorylation that affect translation and protein activity, respectively. The 1977 finding by Philip Sharp, Richard Roberts, and their colleagues—that adenoviral genes had a split structure—was an equally important discovery in the field of gene expression. Work by a number of investigators determined that intervening sequences (introns) are spliced out and the expressed sequences (exons) joined together to form the mature mRNA. The subsequent finding that cellular genes in eukaryotes had a similar structure led to the realization that alternative splicing of mRNAs could produce a large number of protein products from a single transcription unit, perhaps dependent on cell type.



Dr. James L. Manley, Biological Sciences, Columbia

Thus, a limited number of genes could encode a much larger number of functions. By mixing and matching components, this kind of combinatorial system allows for the development of biological complexity, as evidenced by the effectiveness of our mix-and-match immune systems in recognizing an extraordinary array of foreign antigens.

Dr. Manley's work in the area of RNA splicing has focused primarily on an attempt to identify the factors that regulate the splicing events in both viral and cellular transcription. The NIH Merit Award, established to provide long-term support for productive researchers, is in part a recognition of the significance of his contributions to the field.

Manley's interest in splicing grew out of a general interest in mRNA production in vitro, fostered by undergraduate study at Columbia and postdoctoral work with Malcolm Gefter and Philip Sharp at MIT, shortly after Sharp's initial work on adenoviral splicing that would eventually win him a Nobel Prize.

As an independent scientist, Manley has used what he calls "pseudogenetic assays" to identify the factors that regulate splicing. Although yeast is the most suitable organism for genetic approaches to cellular biochemistry, Manley points out that there is a limited amount of regulated splicing in yeast, and some of the key players in splicing in mammalian cells do not appear to be present in yeast cells. As such, he has studied SV40 early pre-mRNA splicing as a model of the splicing events that occur in mammalian cells.

Splicing is regulated by spliceosomes—large complexes of RNAs (small nuclear RNAs, or snRNAs) and proteins (many are termed SR proteins because they are rich in serine and arginine residues). The spliceosome complex mediates the two essential steps of the splicing reaction: 1) cleavage at the 5' splice site, followed by 2) cleavage at the 3' splice site and ligation of the 5' exon to the 3' exon, with the spliced out intron released in a "lariat structure." A number of investigators, including Manley, have been attempting to define the individual components of the spliceosome that are required for each step, with the ultimate goal being the reconstitution of a complete splicing reaction in

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To Our Readers

A Year-End Report

At this time, one year ago, we were working diligently to begin production of what was then called *Campus Science Newspapers*, to serve the academic/scientific community at The State University of New York at Stony Brook. We published our first issue in March, and then another in April. We spent the summer preparing to expand our circulation to include many of the major academic research institutions in New York City. We also decided to change our name to *Academic Science News&Review*, to describe better what we are and what we do. In October, we printed two separate issues, one for Stony Brook and one for New York City, which included Columbia University, New York University, Cold Spring Harbor Laboratory, and The Rockefeller University. In November, we merged the two issues and created a regional New York Edition, adding Mt. Sinai and Albert Einstein medical schools to our circulation.

We have received many phone calls, letters, and email consistently welcoming our efforts, and a number of departments and libraries have asked that they be supplied with an increased number of copies to meet the sizeable demand. In the coming year, we plan to expand our coverage even further, to include major research universities in Boston.

We want to thank our staff for their work this past year. We could not have funded the newspaper without the hard work of Tanya Tohill, Debbie Dellasso, and Cherylann Frank. Kristin Harrison and Daniel Huber gathered all the information included in our centerspread calendar, which is the most complete and comprehensive such calendar now available. We would also like to thank the members of our editorial staff and our contributing writers, whose efforts mean so much to this newspaper.

We wish health and happiness to all in the coming year. Happy Holidays!

Matthew S. Seidner, Publisher Peter S. Bernstein, Editor-in-Chief

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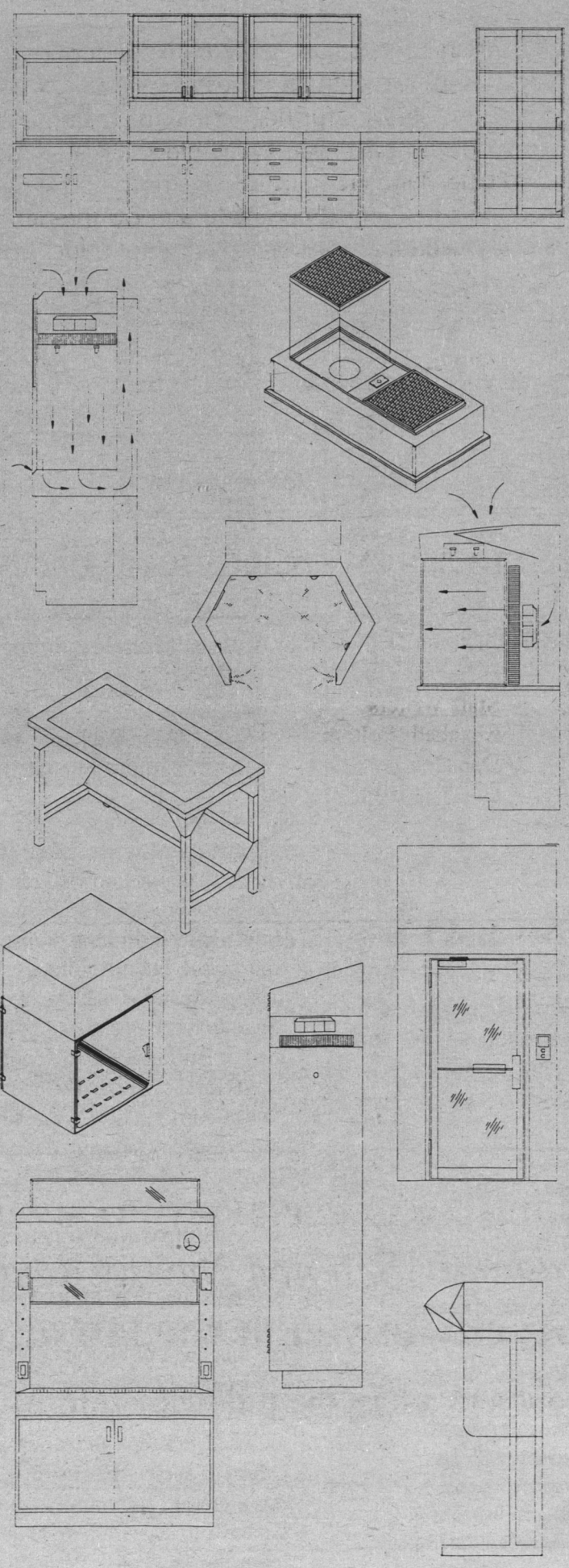

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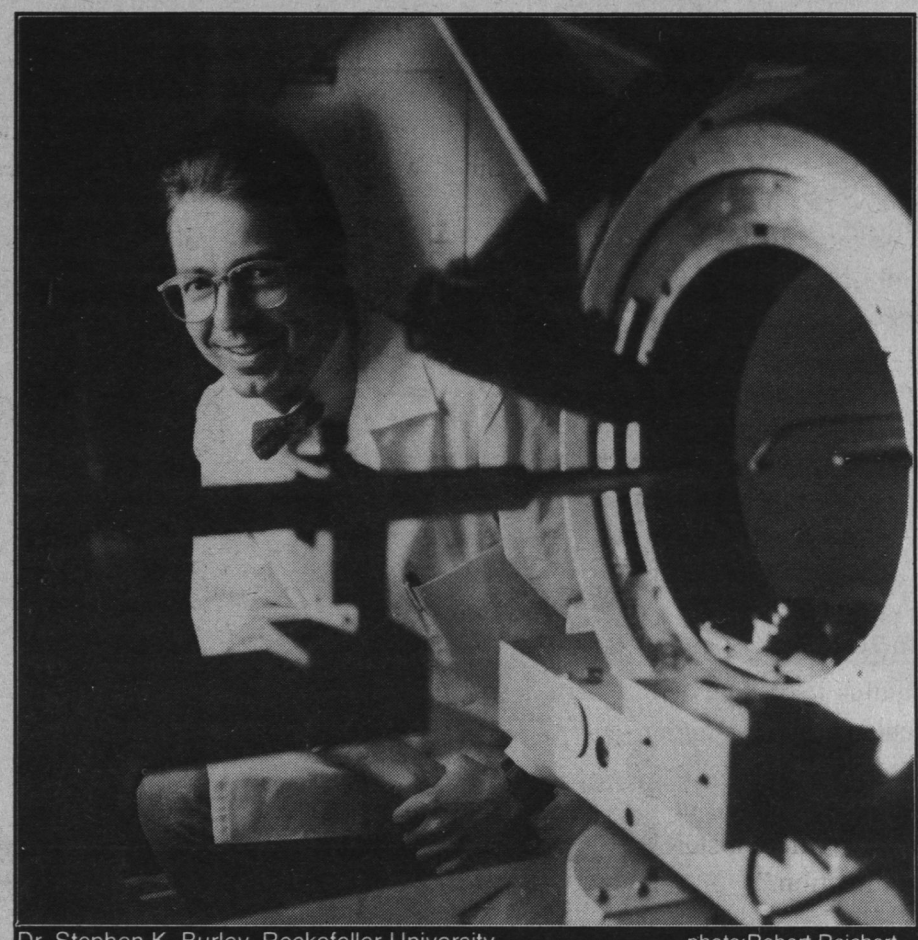
sense that they've got to be able to certify that the project is going to be successful. There are some projects for which you've just got to be able to take risks." Burley asserts that "this is particularly true in the context of interdisciplinary research, where it might take some time to apply the existing technology of one field to another."

Accordingly, Burley doubts that the Burroughs Wellcome Fund, which was created in 1955 by the Burroughs Wellcome pharmaceutical company, has any expectation of realizing immediate gains in the pharmaceutical industry as a result of the work being done within the Interdisciplinary Training Program.

Yet Burley believes interdisciplinary research will be a key to future gains in medicine, and suggests that Burroughs Wellcome shares his view. "They, like Rockefeller University, seem to believe that the future of biology is to a large part going to come from the application of the more quantitative sciences



Dr. Stephen K. Burley, Rockefeller University photo:Robert Reichert

to biological problems."

Historically, the "more quantitative sciences" have been physics and chemistry. Burley acknowledges that past efforts to merge these disciplines with biology were not always successful, in part because there weren't enough scientists interested in applying physics and chemistry to biology problems. One aim of the Interdisciplinary Training Program will be to entice graduate and post-graduate physicists, chemists, mathematicians and computer scientists to come to work in a group of biology laboratories which have been recently created at Rockefeller University.

The laboratories include the Protein/DNA Technology Center, the Electron Microscopy Facility, a mass spectrometry center, a nuclear magnetic resonance spectroscopy facility, three x-ray crystallography set-ups, and a proposed BioPhysics Training Laboratory. "We're trying to create a new kind of biologist," says Burley. "Our goal is to try to attract very good students from physics and chemistry, who are already pretty expert in those areas, and expose them to biology, and help them find avenues where they can actually apply the technologies that they've learned, either as undergraduate students or as graduate students, to biological problems. Part of the challenge for them will be to learn the language of biology."

For biology, it seems, has a rather intimidating vernacular. Notes Burley, "every specialty has its own code, its own language. Those specialized words are used to keep others out, and of course for efficient communication. Every subset of society has its own language which has the pragmatic effect of creating a private community, and biologists are no different. So one of the things we have to do with people coming from chemistry and physics is to help them learn the language. We actually developed a new course this year in which, over the space of two months, through a very intensive series of lectures, students get exposed to a very very wide range of biology, and hopefully of the sort of three letter abbreviations" which are ubiquitous in the biological sciences. Burley admits, "if you don't know the three letter abbreviations, the TLAs, you just can't function, because you don't know what people are talking about."■

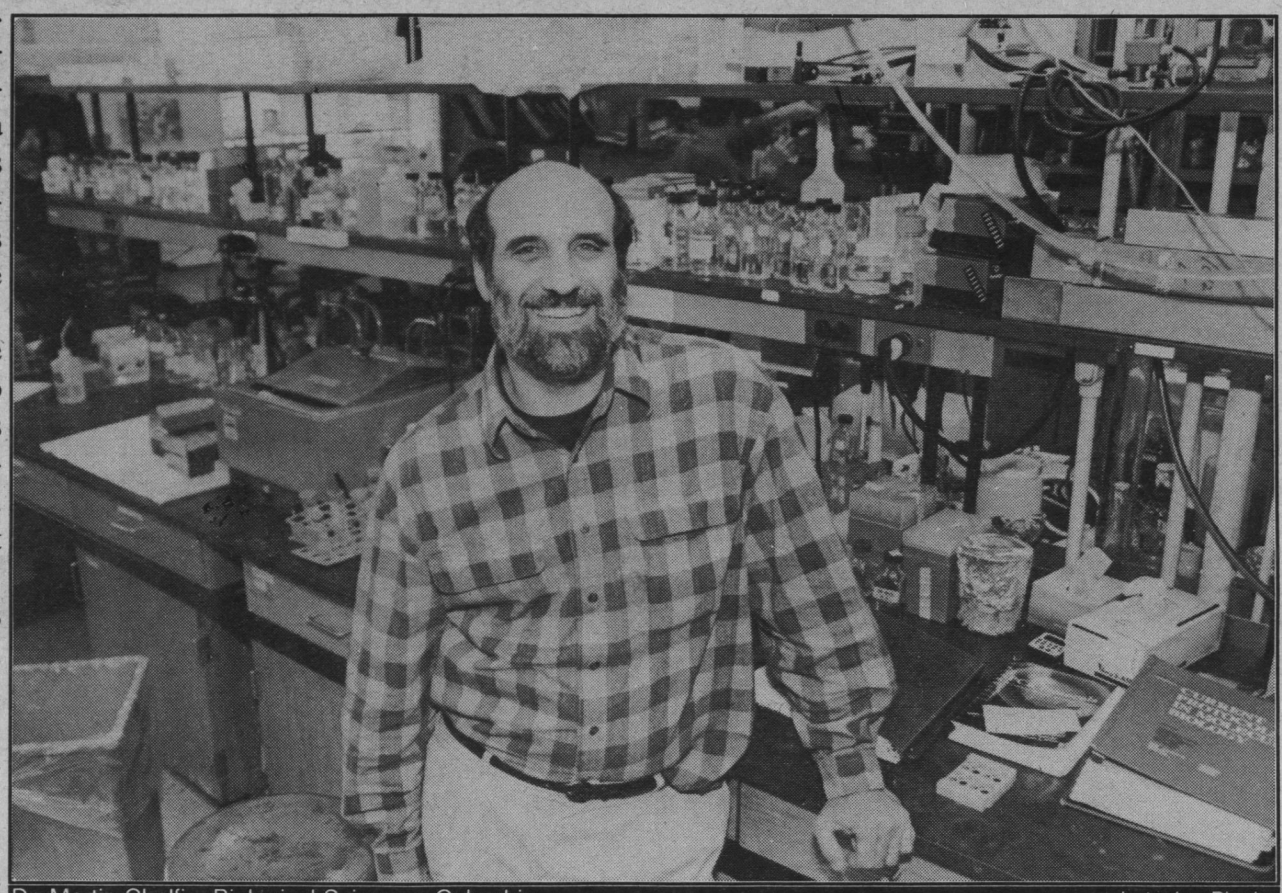
IN THE Spotlight

Martin Chalfie
Biological Sciences, Columbia

Probing the Mystery of Touch Through Molecular Genetics

by Gretel Schueller, *ASN&R* Staff Writer

When we touch something—the velvety nose of a dog, a burlap sack, a rose petal—we set in motion a complex web of touch receptors, making them fire by exposing them to a sensation, changing it, exposing them to another. The brain reads the firings and stopfirings like Morse Code and registers cold, rough, silky. But how we feel—how receptors cells in the skin receive and translate these mechanical stimulations into electrical messages that pulse to the brain is not well understood by scientists. Martin Chalfie, a professor of biological sciences at Columbia University, however, has developed the first molecular model that offers an explanation of the sense of touch.



Dr. Martin Chalfie, Biological Sciences, Columbia photo:Joe Pineiro

"This is a major type of stimulus for which no molecular receptor has been identified in animals," says Chalfie. "This work offers a start in that direction."

The sense of touch is vital not only for feeling, but also for balance, movement, and hearing. Sound waves, for example, strike the eardrum, transmitting the vibrations to the cochlea. The receptor cells in the cochlea then translate the movements to the otic nerve, which carries the information to the brain.

"As opposed to something like the visual system where you can easily take out tissue, the receptors for touch are all over the body," explains Chalfie. "To try and get them molecularly is an extremely daunting task." He and his colleagues took another approach: "We let the organism tell us—an organism defective in the sense of touch." Through experiments with the microscopic roundworm, *Caenorhabditis elegans,* they have described a model for the mechanotransduction apparatus, the way mechanical contact translates into sensation.

The roundworm, a premier organism for development studies, matures from an egg to a one millimeter adult in about three days. In addition to its rapid growth, the worm is also transparent, allowing a window for watching the animal's cells divide. "We know what every single cell looks like," says Chalfie. All 302 nerve cells and their connections have been well studied. "It's also a model system of the genome project." He believes it will probably be the first multicellular animal to have all its genes sequenced.

Normal roundworms respond to the gentle touch of an eyebrow hair glued to the end of a toothpick by moving in the opposite direction. (Eyebrow hairs, says Chalfie, are ideal because they're perfectly tapered and easy to manipulate under a microscope.) Of the 306 nerve cells, 6 were determined to play a major role in sensing touch. Both through surgery and selective breeding, Chalfie and his colleagues have reared more than 500 mutant roundworm-strains that are touch insensitive. These mutant worms either lack the receptor cells, or the cells are non-functioning. Experiments with the mutants allowed Chalfie to pinpoint a series of 12 genes that in some way control the development or function of a roundworm's six touch cells. So far, they've managed to clone eight of the genes, which are dubbed mec for mechnosensory. "The dominant enhancement and suppression exhibited by the mutations suggested that the products of several touch genes interact." The work, says Chalfie, "is really about these 12 genes. Getting the sequence of these genes has led us to propose a model of how a receptor cell works."

A cross-section of a roundworm receptor cell depicts a cell jam-packed with a network of microtubules, strands of the cytoskeleton. Larger in diameter than the microtubules of non-touch cells, these cylindrical strands are tethered to channels on the cell's surface. Chalfie believes that these channels on the surface of receptor cells are the key to the process of sensing touch. On the outside of a cell, the channels are held in place by a coating of proteins, including collagen. According to his model, when a cell is jarred, the microtubules tug on the channel, distorting it and allowing charged ions to flow into the cell. The ions depolarize the cell, setting up an electrical stimulus that is eventually passed on to the brain. Since the microtubules are linked together in a network, any disturbance to them could open several channels at once.

The products of the twelve mechanosensory genes isolated interact to build various elements of the cellular sensing apparatus: channels, extracellular proteins, microtubules, and proteins that regulate the whole process. Many mutant roundworms that were touch-insensitive lacked the larger diameter microtubules or protein coating on the cell. Some had no microtubules at all. Other mutants had touch cells that swelled and died when stimulated. Chalfie believes the lysing of the touch cells was caused by channels in the mutant cells staying open too long, bringing in a continuous influx of ions that eventually caused the cell to explode.

The exact chemistry of the process—what ions flow through the channel and how they create an electrochemical response—is still being investigated. But Chalfie has observed some interesting connections that may eventually explain how touch works in other animals and humans. For example, the middle part of the mec-2 gene sequence looks very much like that for stomatin in human blood. When stomatin is missing in the blood, the disease causes red blood cells to lyse. Chalfie suspects that stomatin may actually be connected to the channels and microtubules, responsible for regulating ion channels.

"The cloning is almost done and the animal has served us extremely well," says Chalfie. "Now we're testing [the model] electrophysically and biochemically."

Working as a post-doc with Sydney Brenner in England, Chalfie has since spent almost twenty years delving into the mysteries of touch. For the past fourteen of those productive years, he's been at Columbia, where he's most recently reported aspects of his work in the June 1996 issue of the Proceedings of the National Academy of Sciences, along with post-doc Guy Caldwell and graduate student Guoqiang Gu.■

Animal Life Appears Older than Fossil Record Suggests

Gene Sequences Reveal Divergence of Modern Animals Happened One Billion Years Ago

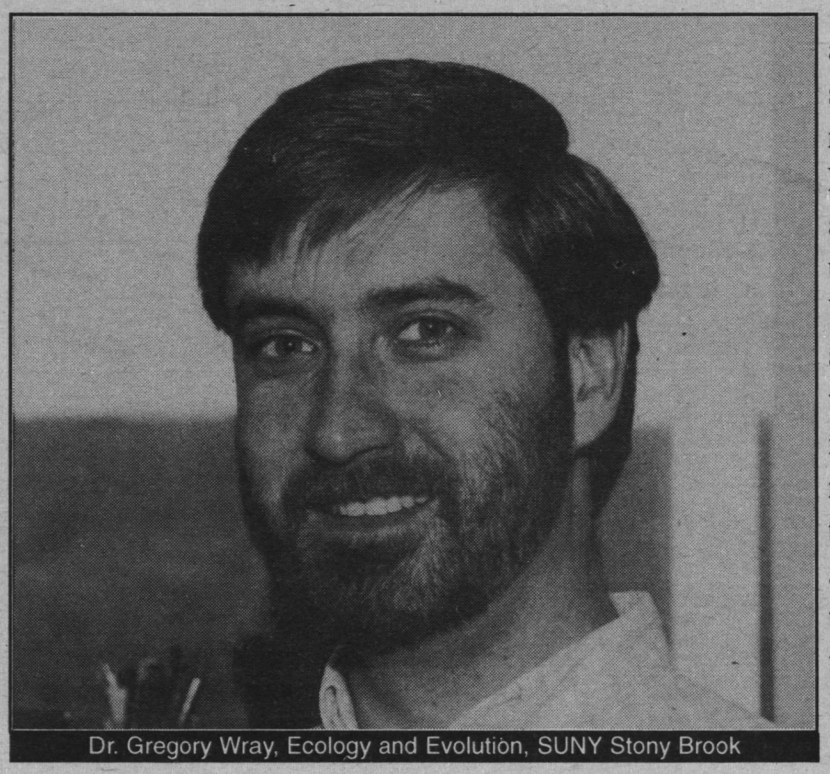
by James Polichak

A group of scientists at the State University of New York at Stony Brook have conducted research that suggests that the divergence of animal life on earth occurred at a much earlier date than previously thought. Their work, reported in the journal *Science* in October, uses gene sequences as a kind of molecular clock to determine when the major groups of animals first split in primordial oceans. The date they set for this occurance is approximately one billion years ago, twice as long ago as most believed.

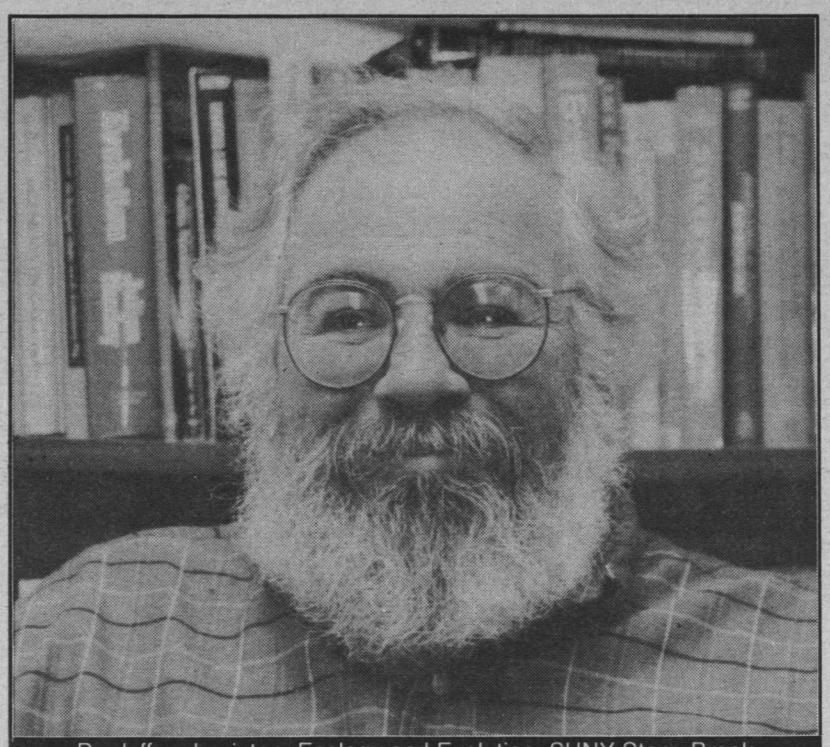
The fossil record leads evolutionary biologists to believe that animal life, which is multicellular, has a nervous system, and can move about using muscles, appeared about half a billion years ago. Fossils of nearly all major groups of animals have been found dating from around this time. This great development of animal forms is known as the Cambrian Explosion. There is, however, little evidence in the fossil record of animal life before this time, and it is difficult to base a strong theory on a lack of evidence.

Gregory A. Wray, Jeffrey S. Levinton, and Leo H. Shapiro of the Department of Ecology and Evolution at SUNY Stony Brook compared differences in gene sequences among various groups of animals living today to determine when these different groups diverged from each other. This technique, which has been used in the past to determine when the common ancestor of modern humans lived, uses differences in gene sequences for assorted proteins as a molecular clock. As time goes on, the genes encoding the information to make a protein slowly mutate and become more and more different in different populations. By determining the rate of mutation, the amount of time since the groups shared a common ancestor can be found. It is usually assumed that although the rate of mutation may change, getting faster or slower for some periods, in the long run these differences will average out and the rate will be effectively constant.

Wray, Levinton, and Shapiro examined the gene sequences of seven genes encoding common proteins, and nucleotides which had been well-studied in a wide variety of animal groups. They compared these sequences for a number of different kinds of animals, from vertebrates to molluscs. All of the evidence pointed to the same date for the divergence of the major animal groups, about a billion years ago. The scientists also used their data to examine more closely differences among some of the particular groups they studied, and offered dates for when this groups diverged from each other. This research argues strongly that animal life appeared on earth long before it was previously thought to, and that the various forms of animal life began diverging from each other long before the Cambrian Explosion.



Dr. Gregory Wray, Ecology and Evolution, SUNY Stony Brook



Dr. Jeffrey Levinton, Ecology and Evolution, SUNY Stony Brook

This work, which conflicts directly with the fossil records and the most prominent theory of animal development, has been rather well received. Levinton said that "in the past month, we have not heard many objections—far fewer than expected." Some have expressed doubts about the molecular clock technique used, while others have agreed that they expected all along that animals emerged before the Cambrian period.

If animals appeared one billion years ago, as their genes suggest, why is there so little evidence for them in the fossil record? The answer favored by Levinton and others is that these early animals were "small and very soft" and unlikely to leave fossils. Geerat J. Vermeij, of the Department of Geology at the University of California at Davis, wrote in an editorial in Science that animals alive today which are likely to resemble the early soft-bodied ancestors of all animals are not in fact found as fossils. While this makes it doubtful that fossils of the earliest animal life will be found, Levinton offers some hope.

Levinton compared the current situation with that of the sixteenth century, when great interest was first taken in the fossils which were being unearthed. "People of the time simply didn't know what they were looking at. It took time for them to realize what fossils were and that there were previously unknown forms of life which were no longer around," he said. Similarly, researchers today may not be finding fossils of early animals because they aren't sure what to look for. According to Levinton, though, some progress is being made, noting that "some of my colleagues around the country have found what they believe is fossil evidence for early animal life, including what may be animal burrows in rocks one billion years old and a possible cone-shaped animal fossil in an egg that might lead to discoveries far earlier in the fossil record." It may be expected that if the molecular clocks of the genes examined by these researchers are accurate, then more evidence will be found for animal life in pre-Cambrian times. As more gene sequences are determined, they should also support the one billion year date for the emergence of animal life, as well as pinpoint it more accurately. The times of divergence of the major animal groups should also become better known, giving a more accurate picture of our family tree.■

Nutrients, Not Grazing, Restrict Phytoplankton Population

Consumption of CO_2 Tied to Presence of Iron

by BNL News Services

Phytoplankton are the lungs — and the lifeline — of the planet. But without a balanced diet that includes iron, these tiny ocean plants cannot exhale the oxygen we humans breathe, nor inhale the carbon dioxide we, our cars, and our factories spew out.

So report scientists from the U.S. Department of Energy's Brookhaven National Laboratory (BNL) and their colleagues, in two papers in *Nature:* one in the October 10 issue, and one that appeared August 29. Both describe results collected on two 1995 research cruises — one near the Galapagos Islands, the other in the subarctic Pacific. The studies' results add to what is known about an important cornerstone of the global ecosystem.

On the Galapagos cruise, described in the Oct. 10 article, a BNL-designed instrument helped prove that underachieving phytoplankton could be revved up to consume more carbon dioxide if they got an iron supplement. The August article discussed a BNL-developed molecular detection method that showed that subarctic phytoplankton are underproductive because they're stressed for iron.

Both studies answer longstanding questions about phytoplankton. But the scientists adamantly state that fertilizing the ocean with iron would not be a "quick fix" for the potentially climate-changing effects of humankind's carbon dioxide production. "Too many factors would erase any increase in carbon dioxide absorption, not to mention the risks of such a huge environmental manipulation," said BNL oceanographer Michael Behrenfeld.

Phytoplankton are tiny single-celled plants, trillions of which have floated freely on the ocean's surface for nearly 3.5 billion years. Together, they process about 40 percent, or 43 billion tons, of the world's carbon annually, much of it atmospheric carbon dioxide.

When phytoplankton do not get all their necessary nutrients, say the scientists, they cannot absorb as much carbon dioxide as usual. The two cruises studied areas of ocean where phytoplankton productivity is "limited" by lack of iron, so that they cannot take full advantage of abundant nutrients such as nitrogen and phosphorous.

Underwater Overachievers

In the Galapagos study, scientists fertilized an underproductive patch of the South Pacific with iron three times over eight days, while taking measurements to see how phytoplankton activity in the 25-square-mile area changed.

The result was dramatic: within 32 hours of the first application, an area 6 miles wide and 81 feet deep turned green with phytoplankton. The effect lasted two weeks. "Our boat towed BNL's submersible instrument, which repeatedly dove down to 200 feet and returned to the surface, taking readings all the while. We could see immediately how the phytoplankton responded to the iron — their photosynthetic efficiency increased tremendously in the first 48 hours," said Behrenfeld. A second instrument inside the boat showed that the phytoplankton began making much larger "antennae" to capture sunlight, in order to take advantage of the iron-rich diet.

The team calls the effect "bottom up" control of phytoplankton, to contrast it with the long-held "top-down" control theory that says that tiny animals called zooplankton were eating the phytoplankton as fast as they grew. The BNL scientists show that it is nutrients, not grazing, that restricts the population. But they stop far short of saying that adding iron to underproductive patches of ocean could slow global climate change.

The experiment was led by scientists from Moss Landing Marine Laboratories in California. The researchers who designed and built Brookhaven's instruments with funding from the U.S. Department of Energy and NASA also include BNL's Zbigniew Kolber and Paul Falkowski, and scientists from Britain's Plymouth Marine Laboratory.

Lack of Iron Stresses Them Out

It may be easy to tell when humans are stressed, but what about phytoplankton? BNL biochemist Julie LaRoche and her colleagues reported in *Nature* on August 29 that they have devised a phytoplankton stress test and used it in the waters off of Vancouver, British Columbia.

The test takes advantage of the fact that phytoplankton living in iron-poor oceans "make do" by substituting an iron-free protein, flavodoxin, for their usual ferredoxin, which has to be made with iron. "So, by detecting whether the phytoplankton cell is making flavodoxin, we can tell if it's stressed for iron," LaRoche explained.

In May and September of 1995, LaRoche and her colleagues sampled populations of diatoms, a kind of phytoplankton known to be particularly sensitive to iron deficiency, at five stations in the ocean. Their 560-mile course ran from just off Vancouver to the center of the Pacific Ocean. After collecting the samples, they mixed phytoplankton cells with antibodies that bound to flavodoxin and revealed how much there was. They found that phytoplankton taken from offshore, iron-poor waters had nearly 200 times more flavodoxin than those from fertile waters close to shore. The test may help oceanographers with their experiments, since it can indicate phytoplankton iron-stress levels in water samples carried home from a research cruise, without sophisticated equipment or large-scale fertilization.

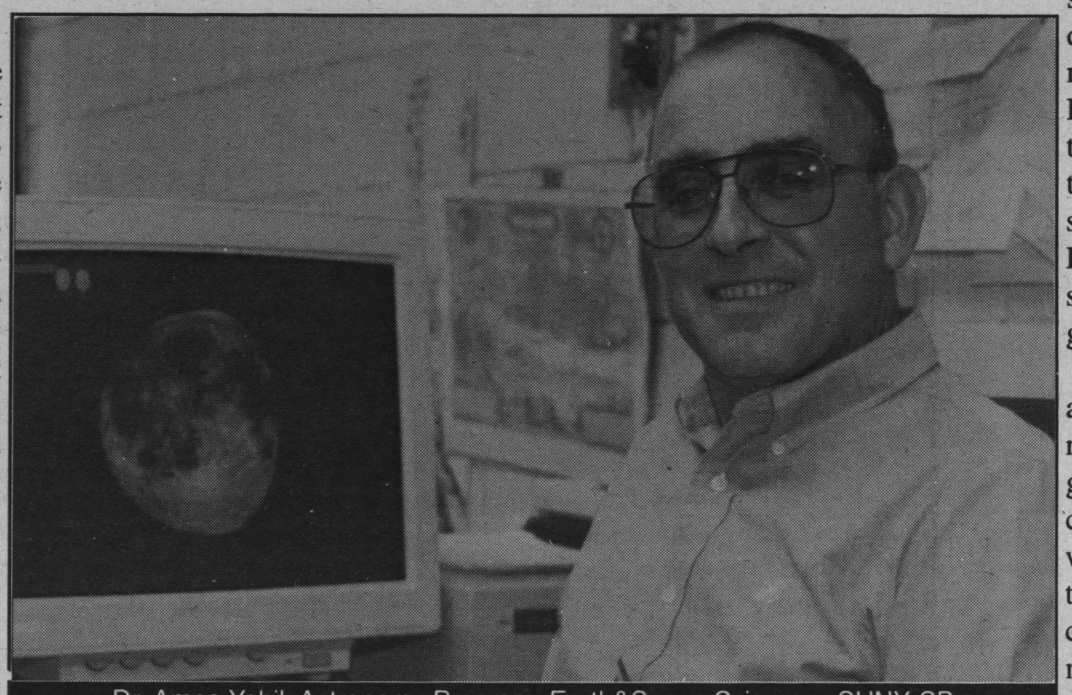
The study, which included scientists from the University of British Columbia, the University of Delaware and the Plymouth Marine Laboratory, was funded by DOE, the National Science Foundation and the Canadian Joint Global Ocean Flux Study.■

Continued from Page 1

The implications of the team's findings have a direct impact on two very important cosmological issues which dominate the field today: the evolution of galaxies, and the determination of the universe's geometry. According to Lanzetta, these two issues are intimately coupled.

THE EVOLUTION OF GALAXIES

After obtaining the Hubble deep field images, the team set out to catalogue a total of 1,683 celestial objects recorded by the telescope. Among this number, the team identified six very distant galaxies. The next step was to determine their distances by calculating the galaxies' "redshift " value. This value is based upon the relationship between speed and distance in the expanding universe. In 1929, Edwin Hubble showed that, due to the expansion of the universe, distant galaxies are receding from our viewpoint, with a velocity of recession proportional to their distance from us.



Dr. Amos Yahil, Astronomy Program, Earth&Space Sciences, SUNY SB

It has been estimated that many billions of cubic miles of new space appear between the rapidly receding galaxies every day. The resultant velocity of their motion away from us means that blue light leaving a distant galaxy arrives at the Hubble as red light due to the increased wavelengths produced by the speed at which it is traveling away from the telescope. For a nearby galaxy, the spectrum's shift from blue to red is relatively small—but for a distant galaxy the shift is dramatic, because more distant objects recede from us with greater velocity. Hence, the higher the redshift value, the more distant the object.

"The way to get an absolute, unambiguous identification of a galaxy and its distance is to obtain a spectrum of the object and to look for narrow emission or absorption lines of various elements such as hydrogen, oxygen, or iron. Once you have done that, you may determine very precisely the redshift of the galaxy," indicated Dr. Lanzetta. Since elements emit spectra consisting of light of known wavelengths, the degree of redshift can be determined by comparing the known wavelengths to the observed ones in the spectra of distant, fast-receding galaxies.

The problem facing the team, however, was that these newly discovered galaxies were too faint to allow the team to obtain spectra directly. To obtain redshift estimates indirectly, the team inferred the galaxies' distances by taking closer galaxies at known distances and artificially redshifting them on a computer by different amounts until they matched the spectra seen in Hubble Deep Field images. On the basis of these estimates, the team reported redshift values for some galaxies to be as high as six. Prior to this study, the highest redshift value assigned to a distant galaxy was three.

Not unexpectedly, other astronomers question the team's redshift estimates for these distant galaxies because definitive conclusions will be possible only with further data. Although the team agrees with this, they are confident that their redshift estimates are accurate. Up to 85% of the team's original estimates for some (relatively) brighter galaxies have been confirmed by other researchers using direct spectroscopic techniques since their paper was published last June. The remaining 15% of the estimates have not been confirmed, but Lanzetta maintains "that our technique works because it seems to hold up in a regime where it can be tested. Our

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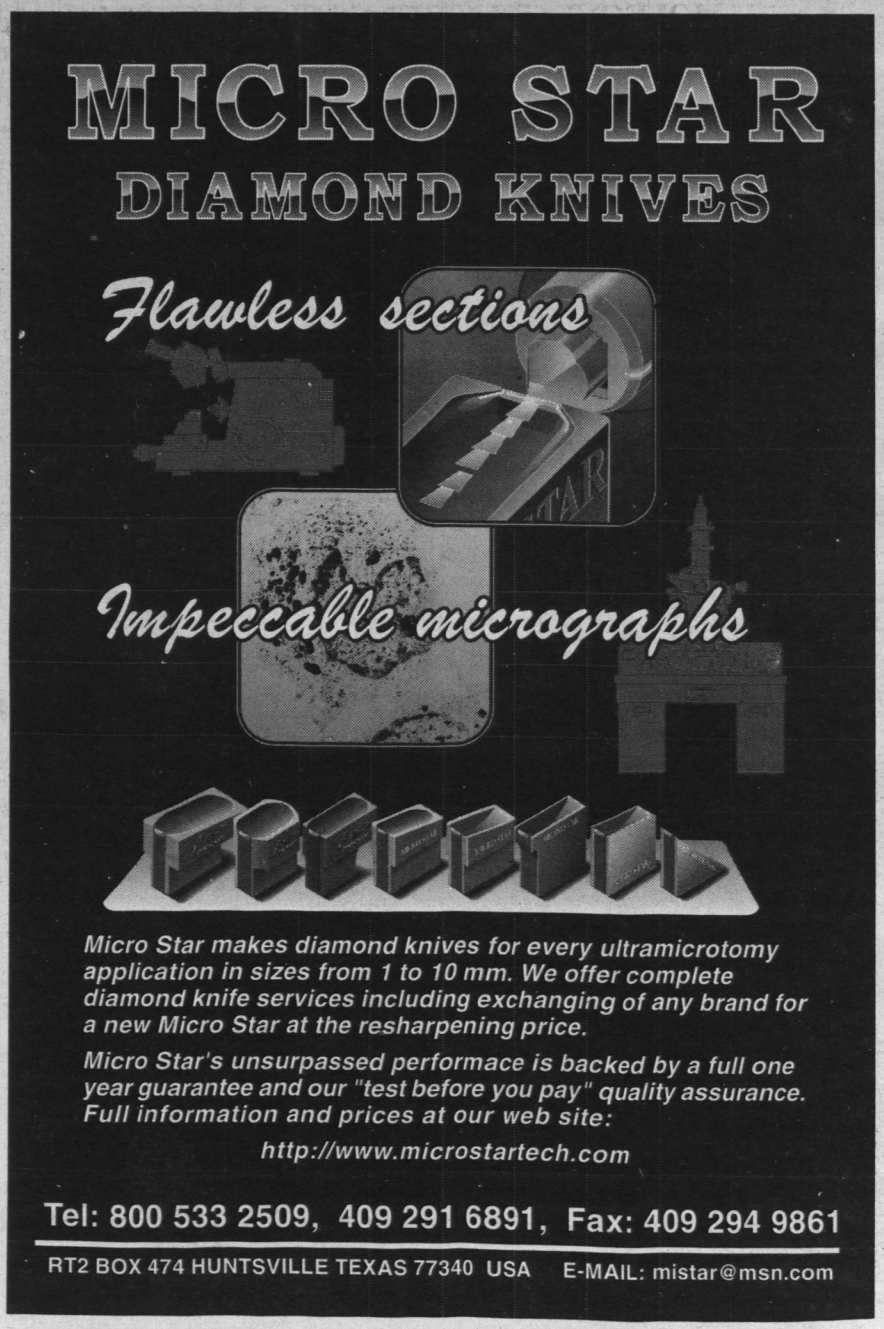

PRESERVED NEURON NUMBER IN THE HIPPOCAMPUS OF AGED RATS WITH SPATIAL LEARNING DEFICITS.

Rapp, P.R. and Gallagher, M.

Proceedings of the National Academy of Science (USA), 93, 9926-9930. (1996)

Abstract

Hippocampal neuron loss is widely viewed as a hallmark of normal aging. Moreover, neuronal degeneration is thought to contribute directly to age-related deficits in learning and memory supported by the hippocampus. By taking advantage of improved methods for quantifying neuron number, the present study reports evidence challenging these long-standing concepts. The status of hippocampal-dependent spatial learning was evaluated in young and aged Long-Evans rats using the Morris water maze, and the total number of neurons in the principal cell layers of the dentate gyrus and hippocampus was quantified according to the optical fractionator technique. For each of the hippocampal fields, neuron number was preserved in the aged subjects as a group and in aged individuals with documented learning and memory deficits indicative of hippocampal dysfunction. The findings demonstrate that hippocampal neuronal degeneration is not an inevitable consequence of normal aging and that a loss of principal neurons in the hippocampus fails to account for age-related learning and memory impairment. The observed preservation of neuron number represents an essential foundation for identifying the neurobiological effects of hippocampal aging that account for cognitive decline.

RELEASE OF MALARIA CIRCUMSPOROZOITE PROTEIN INTO THE HOST CELL CYTOPLASM AND INTERACTION WITH RIBOSOMES

Hugel FU. Pradel G. Frevert U.

Molecular & Biochemical Parasitology. 81(2):151-170, 1996 Oct 30.

Abstract

To date, the circumsporozoite (CS) protein has been implicated in guiding malaria sporozoites to the liver [Cerami et al., Cell 70, 1992, 1021-1033]. Here we show that shortly after invasion, P, berghei and P. yoelii sporozoites lie free in the invaded cell and release considerable amounts of CS protein into the cytoplasm. The intracytoplasmic deposition of CS protein begins during the attachment of the sporozoite to the host cell surface and reaches its peak during the first 4-6 h after invasion. Initially, the CS protein spreads over the entire cytoplasm of the infected cell where it interacts with cytosolic as well as endoplasmic reticulum-associated ribosomes. During the subsequent development of the parasites to exoerythrocytic forms, the CS protein binding becomes gradually restricted to ribosomes lining the outer membrane of the nuclear envelope of the host cell. The distribution pattern of the parasite-released CS protein in the host cell cytoplasm is independent of the permissiveness of the host cell for the development of the parasites to exoerythrocytic forms. It requires neither the host cell metabolism nor does it involve the endocytotic machinery. Recombinant P. falciparum CS protein interacts with RNAse-sensitive sites on endoplasmic reticulum-associated ribosomes as shown by microinjection and immunoelectron microscopy. The generalized interaction of the CS protein with host cell ribosomes suggests that the CS protein has an intracellular function during the hepatic phase in the life cycle of Plasmodium and may also explain the generation of a CD8(+) T cell response in the course of rodent malaria infections.

MOLECULAR EVIDENCE FOR DEEP PRECAMBRIAN DIVERGENCES AMONG METAZOAN PHYLA

Wray GA. Levinton JS. Shapiro LH.Sturmbauer C. Levinton JS. Christy J.

Science. 274(5287):568-573, 1996 Oct 25.

Abstract

A literal reading of the fossil record suggests that the animal phyla diverged in an "explosion" near the beginning of the Cambrian period. Calibrated rates of molecular sequence divergence were used to test this hypothesis. Seven independent data sets suggest that invertebrates diverged from chordates about a billion years ago, about twice as long ago as the Cambrian. Protostomes apparently diverged from chordates well before echinoderms, which suggests a prolonged radiation of animal phyla. These conclusions apply specifically to divergence times among phyla; the morphological features that characterize modern animal body plans, such as skeletons and coeloms, may have evolved later.

QUANTUM ACTIVATED RATES - AN EVOLUTION OPERATOR APPROACH

Schwartz SD.

Journal of Chemical Physics. 105(16):6871-6879, 1996 Oct 22.

Abstract

This article presents a derivation of the rate of reaction in the quantum activated rate problem. In this problem, one studies the rate of a chemical reaction when the reaction is placed in a dissipative bath. Our derivation defines the rate in terms of the flux autocorrelation function and proceeds via the recently developed interaction representation for nonadiabatic corrections to adiabatic evolution operators. This methodology is an infinite order resummation of nonadiabatic corrections to evolution operators. The approach produces an analytic expression which yields accurate results over a range of temperatures, viscosities and system parameters through the Kramers turnover region. (C) 1996 American Institute of Physics.

MAJOR HISTOCOMPATIBILITY CLASS I PRESENTATION OF SOLUBLE ANTIGEN FACILITATED BY MYCOBACTERIUM TUBERCULOSIS INFECTION

Mazzaccaro RJ. Gedde M. Jensen ER. Vansanten HM. Ploegh HL. Rock KL. Bloom BR.

Proceedings of the National Academy of Sciences of the United States of America. 93(21):11786-11791, 1996 Oct 15.

Abstract

Cell-mediated immune responses are essential for protection against many intraceIluIar pathogens. For Mycobacterium tuberculosis (MTB), protection requires the activity of T cells that recognize antigens presented in the context of both major histocompatibility complex (MHC) class II and I molecules. Since MHC class I presentation generally requires antigen to be localized to the cytoplasmic compartment of antigen-presenting cells, it remains unclear how pathogens that reside primarily within endocytic vesicles of infected macrophages, such as MTB, can elicit specific MHC class I-restricted T cells. A mechanism is described for virulent MTB that allows soluble antigens ordinarily unable to enter the cytoplasm, such as ovalbumin, to be presented through the MHC class I pathway to T cells. The mechanism is selective for MHC class I presentation, since MTB infection inhibited MHC class II presentation of ovalbumin. The MHC class I presentation requires the tubercle bacilli to be viable, and it is dependent upon the transporter associated with antigen processing (TAP), which translocates antigenic peptides from the cytoplasm into the endoplasmic reticulum. The process is mimicked by Listeria monocytogenes and soluble listeriolysin, a pore-forming hemolysin derived from it, suggesting that virulent MTB may have evolved a comparable mechanism that allows molecules in a vacuolar compartment to enter the cytoplasmic presentation pathway for the generation of protective MHC class I-restricted T cells.

ISEQUENCE-SPECIFIC AND LENGTH-DEPENDENT INTERACTION OF C2H2 ZINC FINGERS AND (TA)(N) MICROSATELLITES

Gogos JA. Karayiorgou M.

Human Genetics. 98(5):616-619, 1996 Nov.

Abstract
A possible function for microsatellite elements still remains elusive. Here we demonstrate that (TA)(n) microsatellites can be recognized in vivo in transient assays by a combination of naturally occurring C2H2 zinc fingers with high affinity that depends on specific protein-DNA contacts. This interaction results in an upregulation of the basal transcription level, when (TA)(n) elements are placed upstream of a minimal promoter. Upregulation depends on the length of the element. Our results suggest that specific interaction of transcription factors with microsatellite sequences may underlie effects on transcriptional regulation exerted by these sequences. Identification of such interactions would be a first step towards understanding the function and evolution of microsatellite elements.

FUNCTIONAL ANALYSIS OF YEAST-DERIVED PHYTOCHROME A AND B PHYCOCYANOBILIN ADDUCTS

Kunkel T. Neuhaus G. Batschauer A. Chua NH. Schafer E.

Plant Journal. 10(4):625-636, 1996 Oct.

Abstract
Investigations of phytochrome mutants of Arabidopsis suggested that the expression of chalcone synthase (chs) and anthocyanin accumulation is predominantly controlled by phytochrome A. To test the functionality of phytochrome A and B at the molecular level recombinant, yeast-derived phytochrome-phycocyanobilin adducts (phyA*, phyB*) and oat phytochrome A (phyA) were microinjected into etiolated aurea tomato seedlings. Subsequent to microinjection anthocyanin and chlorophyll accumulation was monitored as well as beta-glucuronidase (GUS) expression mediated by light-regulated promoters (chs, chlorophyll a/b binding protein (lhcb1] and ferredoxin NADP+ oxidoreductase (fnr)]. Microinjection of phyA* under white light conditions caused anthocyanin and chlorophyll accumulation and mediated chs-GUS, lhcb1-GUS and fnr-GUS expression. Microinjection of phyB* under identical conditions induced chlorophyll accumulation and mediated lhcb1-GUS and fnr-GUS expression but neither anthocyanin accumulation nor chs-GUS expression were observed. The characterization of Arabidopsis phytochrome mutants and the microinjection experiments suggested that phyB cannot induce the accumulation of juvenile anthocyanin. Microinjections under far-red light conditions demonstrated that phyA can act independently of other photoreceptors. By contrast, phyB* injections under red light conditions indicated that phyB* needs interactions with other photoreceptors to mediate a rapid and efficient de-etiolation signal.

EXTRATERRESTRIAL HE-3 AS A TRACER OF MARINE SEDIMENT TRANSPORT AND ACCUMULATION

Marcantonio F. Anderson RF. Stute M. Kumar N. Schlosser P. Mix A.

Nature. 383(6602):705-707, 1996 Oct 24.

Abstract
The deposition rate of deep-sea sediments, and their focused redeposition by deep-sea currents, can be evaluated from analyses of sedimentary Th-230 with a temporal resolution limited only by bioturbation(6,7,10,11). Th-230 is produced uniformly throughout the ocean by radioactive decay of dissolved U-234 and is removed sufficiently fast by sorption onto sinking particles to act as a 'constant-flux' tracer of sedimentation rates. But the half-life of Th-230 (75 kyr) limits its use for this purpose to the past 200-250 kyr. Here we explore the use of extraterrestrial He-3 from interplanetary dust particles(1-4) (IDPs) as a constant-flux proxy that is free from this limitation. A comparison of He-3 with Th-230 in two cores from the equatorial Pacific Ocean indicates that the variability in the mean flux of IDPs over the past 200 kyr is less than 75%. But in contrast to this relatively constant rate of supply of He-3 to the deep sea, the local burial rates of He-3 and Th-230 have varied by a factor of five over the past 450 and 200 kyr, respectively. We interpret this variability as reflecting sediment focusing, with a temporal pattern that suggests regular cycles of climate-driven reorganization of near-bottom currents in the deep Pacific Ocean.

MECHANISM OF TRANSLESION DNA SYNTHESIS BY DNA POLYMERASE II - COMPARISON TO DNA POLYMERASES I AND III CORE

Pazelizur T. Takeshita M. Goodman M. Odonnell M. Livneh Z.

Journal of Biological Chemistry. 271(40):24662-24669, 1996 Oct 4.

Abstract
Bypass synthesis by DNA polymerase II was studied using a synthetic 40-nucleotide-long gapped duplex DNA containing a site-specific abasic site analog, as a model system for mutagenesis associated with DNA lesions. Bypass synthesis involved a rapid polymerization step terminating opposite the nucleotide preceding the lesion, followed by a slow bypass step. Bypass was found to be dependent on polymerase and dNTP concentrations, on the DNA sequence context, and on the size of the gap. A side-by-side comparison of DNA polymerases I, II, and III core revealed the following. 1) Each of the three DNA polymerases bypassed the abasic site analog unassisted by other proteins. 2) In the presence of physiological-like salt conditions, only DNA polymerase II bypassed the lesion. 3) Bypass by each of the three DNA polymerases increased dramatically in the absence of proofreading. These results support a model (Tomer, G., Cohen-Fix, O., O'Donnell, M., Goodman, M. and Livneh, Z. (1996) Proc. Natl. Acad. Sci. U. S. A, 93, 1376-1380) by which the RecA, UmuD, and UmuC proteins are accessory factors rather than being absolutely required for the core mutagenic bypass reaction in induced mutagenesis in Escherichia coli.

STRUCTURE OF THE C-TERMINAL REGION OF P21(WAF1/CIP1) COMPLEXED WITH HUMAN PCNA

Gulbis JM. Kelman Z. Hurwitz J. Odonnell M. Kuriyan J.

Cell. 87(2):297-306, 1996 Oct 18.

Abstract
The crystal structure of the human DNA polymerase delta processivity factor PCNA (proliferating cell nuclear antigen) complexed with a 22 residue peptide derived from the C-terminus of the cell-cycle checkpoint protein p21(WAF1/CIP1) has been determined at 2.6 Angstrom resolution. p21 binds to PCNA in a 1:1 stoichiometry with an extensive array of interactions that include the formation of a beta sheet with the interdomain connector loop of PCNA. An intact trimeric ring is maintained in the structure of the p21-PCNA complex, with a central hole available for DNA interaction. The ability of p21 to inhibit the action of PCNA is therefore likely to be due to its masking of elements on PCNA that are required for the binding of other components of the polymerase assembly.

SOLUTION STRUCTURE OF AN OLIGODEOXYNUCLEOTIDE DUPLEX CONTAINING THE EXOCYCLIC LESION 3,N-4-ETHENO-2'-DEOXYCYTIDINE OPPOSITE 2'-DEOXYADENOSINE, DETERMINED BY NMR SPECTROSCOPY AND RESTRAINED MOLECULAR DYNAMICS

Korobka A. Cullinan D. Cosman M. Grollman AP. Patel DJ. Eisenberg M. Delossantos C.

Biochemistry. 35(41):13310-13318, 1996 Oct 15.

Abstract

The d(C-G-T-A-C-epsilon C-C-A-T-G-C). d(G-C-A-T-G-A-G-T-A-C-G) oligodeoxynucleotide duplex containing the 3,N-4-etheno-2'-deoxycytidine adduct positioned opposite 2'-deoxyadenosine in the center of the helix has been analyzed by proton NMR spectroscopy and restrained molecular dynamics, The spectroscopic data establish a right-handed duplex, with sugar puckers in the C2'-endo/C3'-exo range, residues adopting an anti conformation around the glycosidic torsion angle and, with the exception of epsilon C . dA, Watson-Crick hydrogen bond alignment for all base pairs. Molecular dynamics simulations, restrained by the full relaxation matrix approach, produced a three-dimensional model with an NMR R-factor of 7%. The duplex structure shows no significant perturbation of the sugar-phosphate backbone, which remains in B-form. The exocyclic adduct and its partner dA are incorporated into the helix without producing a noticeable kink. The epsilon C . dA alignment adopts a staggered conformation with each residue displaced toward the 5'-terminus and intercalated between bases on the opposite strand, without increase of inter-phosphate distances. The partial intercalation of the epsilon C(anti). dA(anti) alignment allows stacking between the aromatic rings of epsilon C and dA and with base pairs adjacent to the lesion, suggesting an important role played by hydrophobic forces in the stabilization of the solution structure.

BIDIRECTIONAL SIGNALLING THROUGH THE EPH-FAMILY RECEPTOR NUK AND ITS TRANSMEMBRANE LIGANDS

Holland SJ. Gale NW. Mbamalu G. Yancopoulos GD. Henkemeyer M. Pawson T.

Nature. 383(6602):722-725, 1996 Oct 24.

Abstract

Receptor tyrosine kinases of the EPH class have been implicated in the control of axon guidance and fasciculation(1-7), in regulating cell migration(8), and in defining compartments in the developing embryo(9-11). Efficient activation of EPH receptors generally requires that their ligands be anchored to thr cell surface, either through a transmembrane (TM) region or a glycosyl phosphatidylinositol (GPI) group(12). These observations have suggested that EPH receptors can transduce signals initiated by direct cell-cell interaction. Genetic analysis of Nuk, a murine EPH receptor that binds TM ligands, has raised the possibility that these ligands might themselves have a signalling function(6). Consistent with this, the three known TM ligands have a highly conserved cytoplasmic region, with multiple potential sites for tyrosine phosphorylation(12-17). Here we show that challenging cells that express the TM ligands Elk-L or Htk-L with the clustered ectodomain of Nuk induces phosphorylation of the ligands on tyrosine, a process that can be mimicked both in vitro and in vivo by an activated Src tyrosine kinase. Coculture of cells expressing a TM ligand with cells expressing Nuk leads to tyrosine phosphorylation of both the ligand and Nuk. These results suggest that the TM ligands are associated with a tyrosine kinase, and are inducibly phosphorylated upon binding Nuk in a fashion reminiscent of cytokine receptors(18). Furthermore, we show that TM ligands, as well as Nuk are phosphorylated on tyrosine in mouse embryos, indicating that this is a physiological process. EPH receptors and their TM ligands therefore mediate bidirectional cell signalling.

INTERACTION OF PYRIDINE NUCLEOTIDE SUBSTRATES WITH ESCHERICHIA COLI DIHYDRODIPICOLINATE REDUCTASE - THERMODYNAMIC AND STRUCTURAL ANALYSIS OF BINARY COMPLEXES

Reddy SG. Scapin G. Blanchard JS.

Jiochemistry. 35(41):13294-13302, 1996 Oct 15.

Abstract

E. coli dihydrodipicolinate reductase exhibits unusual nucleotide specificity, with NADH being kinetically twice as effective as NADPH as a reductant as evidenced by their relative V/K values. To investigate the nature of the interactions which determine this specificity, we performed isothermal titration calorimetry to determine the thermodynamic parameters of binding and determined the three-dimensional structures of the corresponding enzyme-nucleotide complexes. The thermodynamic binding parameters for NADPH and NADH were determined to he K-d = 2.12 mu M, Delta G degrees = -7.81 kcal mol(-1), Delta H degrees = -10.98 kcal mol(-1), and Delta S degrees = -10.5 cal mol(-1) deg(-1) and K-d = 0.46 mu M, Delta G degrees = -8.74 kcal mol(-1), Delta H degrees -8.93 kcal mol(-1), and Delta S degrees = 0.65 cal mol(-1) deg(-1), respectively. The structures of DHPR complexed with these nucleotides have been determined at 2.2 Angstrom resolution. The 2'-phosphate of NADPH interacts electrostatically with Arg39, while in the NADH complex this interaction is replaced by hydrogen bonds between the 2' and 3' adenosyl ribose hydroxyls and Glu38. Similar studies were also performed with other pyridine nucleotide substrate analogs to determine the contributions of individual groups on the nucleotide to the binding affinity and enthalpic and entropic components of the free energy of binding, Delta G degrees. Analogs lacking the 2'-phosphate group bound with a 4-5-fold higher affinity to the protein compared to their 2'-phosphate containing homologs. For all analogs, the total binding free energy can be shown to include compensating enthalpic and entropic contributions to the association constants, The entropy contribution appears to play a more important role in the binding of the nonphosphorylated analogs than in the binding of the phosphorylated analogs.

NEGATIVE-STRAND RNA VIRUSES - GENETIC ENGINEERING AND APPLICATIONS

Palese P. Zheng HY. Engelhardt OG. Pleschka S. Garciasastre A.

Proceedings of the National Academy of Sciences of the United States of America. 93(21):11354-11358, 1996 Oct 15.

Abstract

The negative-strand RNA viruses are a broad group of animal viruses that comprise several important human pathogens, including influenza, measles, mumps, rabies, respiratory syncytial, Ebola, and hantaviruses. The development of new strategies to genetically manipulate the genomes of negative-strand RNA viruses has provided us with new tools to study the structure-function relationships of the viral components and their contributions to the pathogenicity of these viruses. It is also now possible to envision rational approaches-based on genetic engineering techniques-to design live attenuated vaccines against some of these viral agents. In addition, the use of different negative-strand RNA viruses as vectors to efficiently express foreign polypeptides has also become feasible, and these novel vectors have potential applications in disease prevention as well as in gene therapy.

CALENDAR OF SEMINARS,

DEC 2-4

Dec 2: "Evolution of African Cichlid Fishes: Seductive Scenarios, Magic Bullets, and Reality Checks," Irv Kornfeld, Dept. of Zoology, University of Maine, 4:00, Biology Department, Main Building, Room 101-A, New York University

Dec 2: "Bidirectional Synaptic Plasticity in the Cerebral Cortex," Mark F. Bear, Brown University,12:00, Jacob Bleibtreu, Skirball Institute, 4th floor, NYU Medical Center, New York University

Dec 2: "Special Values of Derivatives of L-functions," Nikolaos Diamantis, Columbia, 4:00, Room 507 Math, Columbia University

Dec 2: "Modular Muhler Measures," Fernando Rodriquez-Villegas, Princeton University, 5:30, Room 507, Math, Columbia University

Dec 2: "Signal Transduction of Phagocytosis," Dr. Steven Greenberg, Columbia University, 12:00-1:00, Life Sciences Building, room 038, SUNY at Stony Brook

Dec 2: "Quantum Chaology: The Photoeffect and Beyond," B. Sandaram, CSI-CUNY, 2:00-4:00, Meyer Hall Room 102, New York University

Dec 3: "Structural and Functional Heterogeneity of Nicotinic Acetycholine Receptors in the Visual System," Kent T. Keyser, Department of Physiological Optics, University of Alabama, 4:00, Life Sciences Building, Room 038, SUNY Stony Brook

Dec 3: "Molecular mechanisms of TCR-mediated Cell Death," Dr. Yongwon Choi, Rockefeller University, 12:00, Cell Biology Library, MSB-657, New York University

Dec 3: "Back to the Original Form of Matter (The First Few fm/c of a Heavy Ion Collision)," Dr. Che Ming Ko, USB, 4:15, Harriman Hall, Room P-137, SUNY at Stony Brook

Dec 3: "Dense pure Point Spectrum: Random and Deterministic Models," Gunter Stolz, University of Alabama, Birmingham, 3:30, Warren Weaver Hall, Room 1302, New York University

Dec 3: "Projection of Bodies and Hereditary Properties of Hypergraph," Bela Bollobas, Institute for Advanced Study, Memphis and Cambridge, 6:15pm, Warren Weaver Hall, Room 613, New York University

Dec 4: "Six 10 Minute Stories in the History of Neuroscience," Dr. Harry Whitaker, Laboraoire De Neuroscience De La Cognition, Univ. Quebec a Montreal, 12:00, Black Building, Room 1222, Columbia University

Dec 4: "Molecular Mechanisms of Fragile X Syndrome: Characterization of FMR1and the FXR Proteins," Dr. Haruhiko Siomi, University of Pennsylvania School of Medicine, 4:00, Room MSB 393, New York University

DEC 4-5

Dec 4: "Fish Species Flocks: Observations, Predictions, and Dilemnas," Prof. Irv Kornfield, University of Maine, 3:30, Life Sciences Building, Room 038, SUNY at Stony Brook

Dec 4: Lecture XI: "Ricci Flow," Richard Hamilton, University of California, San Diego and Visiting Professor, Columbia University, 4:30, Mathematics Building, Room 312, Columbia University

Dec 4: "Collapsed Manifolds with Pinched Positive Sectional Curvature," X. Rong, Rutgers University, 1:00, Warren Weaver Hall, Room 813, New York University

Dec 4: Magneto-Fluid Dynamics Seminar, Michael Beer, Princeton Plasma Physics Laboratory, 1:30, Warren Weaver Hall, Room 1013, New York University

Dec 4: "Turbulence in Rotating Shallow Water and Its Applications to Planetary Atmospheres," Lorenzo Polvani, Columbia University, 3:30-5:00, Warren Weaver Hall, Room 1302, New York University

Dec 5: "Physical Properties of Partly Melted Theoleiitic Basalt and Their Role in Crystal Fractionation," Tony Philpotts, University of Connecticut, 4:00, Earth and Space Sciences Building, Room 123, SUNY at Stony Brook

Dec 5: "A Building Block Approach to Organic Nanostructures," Prof. Jeffrey Moore, University of Illinois, 4:30, Havenmeyer Hall, Room 309, Columbia University

Dec 5: "Control of Proliferation and Differentiation in the Neuromuscular System by bHLH Proteins and FGFs," Thomas Braun, MD, PhD, Dept. of Cell and Molecular Biology, Institute of Biochemistry and Biotechnology, Technical University of Baunschwieg, Germany, 12:00, Annenberg, 25-51, Brookdale Center for Molecular Biology

Dec 5: "Body Size and Biological Inference in Comparative Biology," Dr. William Jungers, SUNY Stony Brook, 8:00PM, Dept. of Anthropology, Room 208, New York University

Dec 5: "Burger's Inviscid Equation with Random Force and Dynamical Systems," Yakov Sinai, Princeton University, 3:15, Room 507 Math, Columbia University

Dec 5: " New Developments in Motion of Surfaces by Mean Curvature," Tom Ilmanen, Northwestern University, 2:00, Room 507 Math, Columbia University

Dec 5: "KAM for Partial Differential Equations-A Survey," Jean Bourgain, IAS, 4:30, Room 507 Math, Columbia University

Dec 5: "Investigations on DNA Damage and Repair," Prof. Francis Johnson, USB, 4:00 Graduate Chemistry Building, Room 412, SUNY Stony Brook

DEC 5-9

Dec 5: "Translational Regulation and Control of Drosophila Body Pattern," Robin Wharton, Duke University, 4:00, HHSC, Room 301, Columbia University

Dec 6: "Particle Physics Beyond Perturbation Theory," Prof. Robert Mawhinney, Columbia Univ., 2:10, Pupin Hall, Room 428, Columbia University

Dec 6: "Learning from Evolution to Predict Protein Structure," Burkhard Rost, EMBL, Heidelberg, 12:00, Black Building, Room 523, Columbia University

Dec 6: "Semi-Conjugacies Between Kleinian Group Actions on the Riemann Sphere," Erica Klarreich, SUNY Stony Brook, 3:00, Room 520, Math, Columbia University

Dec 6: "Plasma Interactions with Spacecraft," Prof. Daniel Hastings, Massachusetts Institute of Technology, 2:00, S.W. Mudd Building, Room 214, Columbia University

Dec 6: " A Theorem of Gordon and Luecke: Knots are Determined by Their Complements," Elizabeth Finkelstein, Hunter College, 1:00, Room 507, Math, Columbia University

Dec 6: "Impulse Methods in Fluid Dynamics," Ricardo Cortez, CIMS, 10:00, Warren Weaver Hall, Room 1302, New York University

Dec 6: "Defect Structures at Thin Film-Substrate Interfaces," Perry Leo, University of Minnesota, 2:00, Warren Weaver Hall, Room 1302, New York University

Dec 9: "Bicombable Groups That Are Not Liautomatic," Martin Bridson, Princeton University, 3:00, Math Building, Room 417, Columbia University

Dec 9: " The Gross-Zagier Limit Formula," Shou-Wu Zhang, Columbia, 4:00, Math Building, Room 507, Columbia University

Dec 9: "Endoscopic Transfer of Unipotent Orbital Integrals," Magdy Assem, IAS, 5:30, Math Building, Room 507, Columbia University

Dec 9: "A Geometric Picture of Monopole Decay," Prof. Philip Argyes, Cornell University, 2:10, Pupin Hall, Room 831, Columbia University

Dec 9: "Regulation of the G Protein-Coupled alpha-Factor Receptor," James Konopka, Department of Molecular Genetics and Microbiology, SUNY Stony Brook, 4:00, Biology Department, Main Building, Room 101-A, New York University

Dec 9: "Ensembles of Hippocampal Neurons Encode Task-Relevant Events," Sam Deadwyler, Wake Forest University, 12:00, Meyer Building, Room 122, New York University

COLLOQUIA, & SYMPOSIA

DEC 9-11

Dec 9: "Thought and Language Disturbances in Schizophrenia: Cognitive and Neural Mechanisms," Dr. Deanna Barch, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical School, and Carnegie Mellon University, 3:30, Psychology-A Building, Room 109, SUNY at Stony Brook

Dec 9: "The Heritage of Marconi's Invention and the Future of Telecommunication," An All-Day Seminar, 8:30-5:00, Casa Italiana, 1161 Amsterdam Ave. and West 116th Street. Contact Bob Nelson at (212)-854-5573 for entire schedule of events and times.

Dec 10: "The Cognitive Neuroscience of Illusory Memories," Dr. Daniel Schacter, Harvard University, 3:00-4:30, Psychology Dept., New York University

Dec 10: "Structural Biology," Dr. Xiaodong Cheng, Cold Spring Harbor Laboratory, 4:15, Harriman Hall, Room P-137, SUNY at Stony Brook

Dec 10: "Molecular Targeting of PKC Isozymes," Dr. Susan Jaken, W. Alton Jones Cell Sciences Center, Inc., 12:00, Cell Biology Library, MSB-657, New York University

Dec 10: "Piecewise Linear Homeomorphisms and Isomorphic Triangulations," Rephael Bartello, Recherche en prevision Numerique, Environment Canada, 3:30-5:00, Warren Weaver Hall, Room 1302, New York University

Dec 11: " Aboveground and Belowground Plant Population Dynamics: Effects of Nutrient Heterogeneity and Population Density," Brensa Casper, University of Pennsylvania, 3:30, Life Sciences Building, Room 038, SUNY at Stony Brook

Dec 11: "The Dead and the Homage We Pay Them: Politics at Martyrdom in Guatemala," Prof. Dave Stoll, Wilson Center, 4:00, 465 Schermerhorn Ext., Murphy/Fried Lounge, Columbia University

Dec 11: "Introduction to D-branes and String Duality-Part III," Dan Kabat, New York University, 10:30, Room 507, Math, Columbia University

Dec 11: "Molecular Genetics of Circadian Rhythms in Drosophila," Dr. Michael Myers, Laboratory of Genetics, The Rockefeller University, 4:00, Room MSB 393, New York University

Dec 11: "Aerosol Forcing of Climate," Stephen Schartz, Brookhaven National Laboratory, 12:30-1:30, Endeavour Hall, Marine Sciences Research Center, SUNY at Stony Brook

Dec 11: "Examining the Etiology of Alcoholism from an Epidemiological and Behavioral Genetic Perspective," Dr. Wendy Slutske, Dept. of Psychiatry, Washington University School of Medicine, 3:30, Psychology-A Building, Room 109, SUNY at Stony Brook

DEC 11-13

Dec 11: "Mental Phenomena: Is a New Revolution in Physics Needed?" Prof. Roger Penrose, Oxford University, 4:30, Warren Weaver Hall, Room 109, New York University

Dec 11: "Self-Similarity in Decaying Quasigeostrophic Turbulence, Peter Bartello, Recherche en prevision Numerique, Environment Canada, 3:30-5:00, Warren Weaver Hall, Room 1302, New York University

Dec 12: "A Unique Post-Transcriptional Regulator: The Influenza Virus NS1 Protein," Robert Krug, Rutgers University, 4:00, HHSC, Room 301, Columbia University

Dec 12: "Perspectives on the Seismic Hazard of the Northeastern United States," John Ebel, Boston College, 4:00, Department of Earth and Space Sciences, Room 123, SUNY at Stony Brook

Dec 12: "Hollywood's View of Computers," Robert Dewar, Dept. of Computer Science and Associate Director, CIMS, 2:30, Warren Weaver Hall, Room 109, New York University

Dec 12: "Dynamic Nuclear Polarization, Decoupling, and Recoupling, in Rotating Solids," Prof. Robert Griffin, Massachusetts Institute of Technology, 4:30, Havenmeyer Hall, Room 309, Columbia University

Dec 12: Homoclinic Points and Intersections of Lagrangian Submanifolds," Jeff Xia, Northwestern University, 3:15, Math Building, Room 507, Columbia University

Dec 12: " Selected Topics in Hamiltonian Dynamics," Michael R. Herman, CNRS and Visiting Prof. Columbia, 4:30, Math Building, Room 507, Columbia University

Dec 12: "Foreign DNA in Mammalian Systems," Dr. Walter Doerfler, University of Cologne, 12:00-1:00, Life Sciences Building,Rroom 038, SUNY at Stony Brook

Dec 12: "Supramolecular Coordination Complexes as Enzyme Models and Molecular Sensors," Prof. James W. Canary, New York University, 4:00 Graduate Chemistry Building, Room 412, SUNY Stony Brook

Dec 12; "Sex Determination in Drosophilia; Regulatory Strategies in Initiation and Maintenence, Paul Schedl, Princeton University, 4:00-5:00, Life Sciences Building, Room 038, SUNY at Stony Brook

Dec 13: "Low Dimensional Topology and Algebraic Geometry Over Groups," Zlil Sela, Columbia Univ., 1:00, Math Building, Room 507, Columbia University

Dec 13: "Hyperplace Sections of Severi Varieties: The Reducible Case," Marie-Amelie Bertin, Columbia Univ., 2:30, Math Building, Room 507, Columbia University

DEC 13-18

Dec 13: "The Arithmetic of Laminations of r3\H and the Markoff Uniqueness Conjecture," Mark Sheingorn, CUNY Baruch, 3:00, CUNY Graduate Center

Dec 13: "A Necessary and Sufficient Criterion for Unique Extremality," Nikola Lakic, Cornell University, 4:00, CUNY Graduate Center

Dec 13: " Non-Oscillatory Central Schemes for the Incompressible 2D Euler Equations," Doron Levy, Tel-Aviv University, 10:00, Warren Weaver Hall, Room 1302, New York University

Dec 13: "Testing Finite State Machines: Theory and Applications," David Lee, Bell Laboratories and Lucent Technologies, 11:30, Warren Weaver Hall, Room 1302, New York University

Dec 13: "Lattice Models with Non-Periodic Long Range Order," A. van Enter, University of Gronigen, 12:45, Warren Weaver Hall, Room 1314, New York University

Dec 13: "Cohomology of Moduli Spaces of Holomorphic Bundles of a Riemann Surface," Lisa Jeffrey, McGill University, 1:00, Warren Weaver Hall, Room 1013, New York University

Dec 13: "Lagrangian Transport in Mesoscale Ocean Structures," Chris Jones, Brown University, 2:00, Warren Weaver Hall, Room 1302, New York University

Dec 16: "Cell Adhesion Molecules in Yeast: Models for Vertebrate Systems," Dr. Peter Lipke, Hunter College, 12:00-1:00, Life Sciences Building, room 038, SUNY at Stony Brook

Dec 16: " Effects of Outcome Expectancies and Disinhibition on Ad Lib Alcohol Consumption," Dr. Erica Sharkansky, Women's Health Division, National Center for PTSD, Boston VA Medical Center, 3:30, Psychology-A Building, Room 109, SUNY at Stony Brook

Dec 17: "Peripheral T Cell Tolerance and Auto Immunity," Dr. Abul K. Abbas, Harvard Medical School, 12:00, Cell Biology Library, MSB-657, New York University

Dec 18: "Dynamics of the Nuclear Envelope During the Cell Cycle," Dr. Jean-Claude Courvalin, Dept. De Biologie Celluliar, Institut Jacques Monod, 12:00, Black Building, 1222, Columbia University

Dec 18: "Surface Physics," Ben Ocko, Physics Department, BNL, 4:00, Berkner Hall Auditorium at Brookhaven National Laboratory

EXPRESSION OF SYNAPSIN I CORRELATES WITH MATURATION OF THE NEUROMUSCULAR SYNAPSE

Lu B. Czernik AJ. Popov S. Wang T. Poo MM. Greengard P.

Neuroscience. 74(4):1087-1097, 1996 Oct.

Abstract

Synapsins are a family of neuron-specific phosphoproteins that are localized within the presynaptic terminals in adult brain. Previous work has demonstrated that introduction of exogenous synapsins I(a + b) or IIa into Xenopus spinal neurons promoted maturation of the neuromuscular synapse in a nerve-muscle co-culture system. We have now studied the expression of endogenous Xenopus synapsin I during synaptic maturation in vivo and in culture, using a polyclonal antibody raised against Xenopus synapsin I. Immunoprecipitation experiments indicated that synapsin I was not detectable during the early phase of synaptogenesis in vivo, and exhibited a marked increase during the period of synaptic maturation. In contrast, the expression of synaptophysin, another synaptic vesicle protein, was detected at the start of nervous system formation, and remained at a high level thereafter. Similar expression profiles for the two proteins were also observed in immunocytochemical studies of Xenopus spinal neurons in culture: intense staining of synaptophysin was found on the first day, while synapsin I was not detected until after three days in culture. The expression of synapsin I correlated very well with the appearance of a bell-shaped amplitude distribution of spontaneous synaptic currents, a physiological parameter which reflects functional maturation of the neuromuscular synapse. In one-day-old cultures grown in the absence of laminin, an extracellular matrix protein known to be present at the neuromuscular junction, the amplitude distribution of virtually all synapses was skewed towards smaller values. In contrast, when laminin was used as a culture substrate, many synapses exhibited a bell-shaped amplitude distribution. Laminin treatment also induced synapsin I expression in one-day-old cultures.

These results suggest that the expression of endogenous synapsin I may regulate synaptic maturation at neuromuscular synapses.

LABORATORY MEASUREMENTS OF FE XXIV L-SHELL LINE EMISSION

Savin DW. Beiersdorfer P. Lopezurrutia JC. Decaux V. Gullikson EM. Kahn SM. Liedahl DA. Reed KJ. Widmann K.

Astrophysical Journal. 470(1 Part 2):L 73-L 76, 1996 Oct 10.

Abstract

Recent ASCA spectra exhibit discrepancies with the relative line intensities of various Fe XXIII and XXIV L-shell emission lines predicted by standard plasma emission codes. To address this issue, we have carried out a series of high-resolution, broad-band measurements of Fe XXIV line emission using an electron beam ion trap facility. X-ray lines produced in the trap are detected and resolved using Bragg crystal spectrometers. We report measurements of 3 --> 2 and 4 --> 2 transitions, which result primarily from electron impact excitation. Overall, good agreement is found with distorted wave calculations.

CRITICAL ROLE OF REVERSE TRANSCRIPTASE IN THE INHIBITORY MECHANISM OF CNI-H0294 ON HIV-1 NUCLEAR TRANSLOCATION

Popov S. Dubrovsky L. Lee MA. Pennathur S. Haffar O. Alabed Y. Tonge P. Ulrich P. Rexach M. Blobel G. Cerami A. Bukrinsky M.

Proceedings of the National Academy of Sciences of the United States of America. 93(21):11859-11864, 1996 Oct 15.

Abstract

HIV-1 replication requires the translocation of viral genome into the nucleus of a target cell. We recently reported the synthesis of an arylene bis(methyl ketone) compound (CNI-H0294) that inhibits nuclear targeting of the HIV-1 genome and thus HIV-1 replication in monocyte cultures. Here we demonstrate that CNI-H0294 inhibits nuclear targeting of HIV-1-derived preintegration complexes by inactivating the nuclear localization sequence of the HIV-1 matrix antigen in a reaction that absolutely requires reverse transcriptase. This drug/reverse transcriptase interaction defines the specificity of its antiviral effect and is most likely mediated by the pyrimidine side-chain of CNI-H0294. After binding to reverse transcriptase, the carbonyl groups of CNI-H0294 react with the nuclear localization sequence of matrix antigen and prevent its binding to karyopherin alpha, the cellular receptor for nuclear localization sequences that carries proteins into the nucleus. Our results provide a basis for the development of a novel class of compounds that inhibit nuclear translocation and that can, in principle, be modified to target specific infectious agents.

MONOCLONAL ANTIBODIES TO SURFACE ANTIGENS OF MYCOBACTERIUM TUBERCULOSIS AND THEIR USE IN A MODIFIED ENZYME-LINKED IMMUNOSORBENT SPOT ASSAY FOR DETECTION OF MYCOBACTERIA

Glatmanfreedman A. Martin JM. Riska PF. Bloom BR. Casadevall A.

Journal of Clinical Microbiology. 34(11):2795-2802, 1996 Nov.

Abstract

Three monoclonal antibodies (MABs) were generated from splenocytes of a BALB/c mouse immunized with heat-killed Mycobacterium tuberculosis. All three MAbs bound to surface epitopes of M. tuberculosis as shown by whole-cell enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence, and immunoelectron microscopy. One immunoglobulin M (IgM) MAb bound to lipoarabinomannan, the second IgM MAb bound to mycolyl-arabinogalactan-peptidoglycan complex, and the third MAb, an IgG3, bound to a surface epitope of an uncertain nature. The MAbs demonstrated different cross-reactivity patterns with other mycobacteria. Two of the MABs were used to develop a modified ELISA spot assay for the detection of mycobacteria.

CALCIUM DEPENDENCE OF NEUROTRANSMITTER RELEASE

Matthews G. Vongersdorff H.

Seminars in the Neurosciences. 8(5):329-334, 1996 Oct.

Abstract

Neurotransmitter is released from synaptic terminals by rapid and highly targeted fusion of synaptic vesicles with the presynaptic membrane. Several lines of evidence suggest that the trigger for vesicle fusion is the large increase in internal [Ca2+] (up to hundreds of micromolar) achieved within the submicroscopic domain of elevated calcium near open calcium channels. The rapid vise and fall of [Ca2+] in this microdomain, together with the fast kinetics of the calcium-triggered fusion machinery, account for the speed of synaptic exocytosis.

METASTABLE BOSE CONDENSATE MADE OF ATOMS WITH ATTRACTIVE INTERACTION

Shuryak EV.

Physical Review A. 54(4):3151-3154, 1996 Oct.

Abstract

Recent experiments with trapped cooled atoms have produced evidence for Bose-Einstein condensation (BEG). Among the atoms used are Li-7, with attractive low-energy interaction. A potential barrier separating the condensed part from the collapse is studied and stability limits are established. The lifetime due to tunneling is estimated and is found to be very small. We further argue that BEC should have significant angular momentum L/N similar to 1h and thus both stares with angular momentum I-z=0,1 should be "macroscopically" populated. Eventually, as rotation is slowed down, collapse and strong reheating should occur, in amusing resemblance to a supernova explosion.

MESENCHYMAL CELL ACTIVATION IS THE RATE-LIMITING STEP OF GRANULATION TISSUE INDUCTION

Mcclain SA. Simon M. Jones E. Nandi A. Gailit JO. Tonnesen MG. Newman D. Clark RAF.

American Journal of Pathology. 149(4):1257-1270, 1996 Oct.

Abstract

During wound repair a 3-day lag occurs between injury and granulation tissue development When full-thickness, 8-mm-round, excisional wounds were made in the paravertebral skin of outbred Yorkshire pigs and harvested at various times, no granulation tissue was observed before day 4, Day 4 wounds were 3% filled with granulation tissue, day 5 wounds 48% filled, and day 7 wounds 88% filled. The prerequisites for granulation tissue induction are not known but hypothetically include fibrin matrix maturation or cell activation, To examine whether matrix maturation was necessary, wounds were allowed to heal for 5 or 7 days and then aggressively curetted, resulting in the formation of fresh fibrin clots in the newly formed wound spaces, In contrast to original wounds, mo lag phase teas observed wounds curetted on day 5 were 23% filled with granulation tissue 1 day later and 99% filled 3 days Inter, whereas wounds curetted on day 7 were 47% filled 1 day later and completely filled within 2 days, Thus, granulation tissue formation resumed promptly and independently of fibrin clot matrix maturation, This observation suggested that mesenchymal cell activation might be the rate-limiting step in granulation tissue-formation, To address this hypothesis more directly, cultured porcine or human fibroblasts, grown to 80% confluence in Dulbecco's minimal essential medium plus 10% fetal calf serum, were added to new wounds, These wounds were sealed with a freshly made exogenous fibrin clot, In some wounds, platelet releasate was added to the fibrin clot, Granulation tissue did not form in day 3 wounds, which had received either fibrin alone, fibrin and platelet releasate, or fibrin and fibroblasts. In contrast, granulation tissue was observed in wounds receiving fibrin, human fibroblasts, and platelet releasate, By day 4, wounds receiving cultured human fibroblasts, fibrin, and platelet releasate were 14% filled with granulation tissue compared with less than 4% granulation tissue in control wounds, Thus, fibroblast activation is a limiting step of granulation tissue formation, and continued cell stimulation is required for accelerated development.

EVIDENCE THAT A RAPIDLY TURNING OVER PROTEIN, NORMALLY DEGRADED BY PROTEASOMES, REGULATES HSP72 GENE TRANSCRIPTION IN HEPG2 CELLS

Zhou MY. Wu XJ. Ginsberg HN.

Journal of Biological Chemistry. 271(40):24769-24775, 1996 Oct 4.

Abstract

Heat shock protein 72/73 (Hsp70) is a cytosolic molecular chaperone that carries out fundamental roles under both normal and stress situations, There is great interest in delineating the mechanisms whereby Hsp70 levels are regulated. We observed that N-acetyl-leucyl-leucyl-norleucinal (ALLN), a synthetic aldehydic tripeptide that inhibits proteasomes, markedly induced Hsp70 levels (up to 30-fold above base line in HepG2 cells and human endothelial cells). Induction of Hsp70 by ALLN was dose-dependent and not related to cell toxicity. ALLN selectively increased Hsp70 levels without affecting Hsp25, Hsp27, Hsp60, Hsp86, Hsp90, Hsp104, or Bip (immunoglobulin heavy chain binding protein) in HepG2 cells. ALLN induced Hsp70 not only by stabilizing the protein but also by dramatically increasing its synthesis. The modulation of Hsp70 synthesis by ALLN resulted from a rapid and marked increase in transcription of the hsp72 gene, since the induction of hsp72 mRNA was blocked in cells co-treated with actinomycin D. hsp72 mRNA levels were affected in a time-dependent manner by exposure to ALLN; significant elevations occurred within 60 min of treatment, and a decline to background levels was observed by 7 h of recovery. The ALLN-induced increase in hsp72 gene expression was associated with trimerization of the heat shock transcriptional factor (HSF1). ALLN did not affect the steady-state level of HSF1 protein. The effects of ALLN appeared to require de novo protein synthesis, since the induction of both HSF1 trimerization and hsp72 transcription was blocked by co-treatment with cycloheximide. When we tested a series of protease inhibitors, only the related aldehydic tripeptides, N-acetyl-leucyl-leucyl-methioninal and the proteasome inhibitor. Cbz-leucyl-leucyl-leucinal, induced Hsp70 levels. The specific proteasome inhibitor, lactacystin, which has a different structure, also induced Hsp70 levels. Overall, our results suggest that a rapidly turning over protein that is normally degraded by proteasomes may be involved in the regulation of Hsp70 synthesis via effects on the hsp70 transcriptional factor, HSF1.

UNC-40, A C-ELEGANS HOMOLOG OF DCC (DELETED IN COLORECTAL CANCER), IS REQUIRED IN MOTILE CELLS RESPONDING TO UNC-6 NETRIN CUES

Chan SSY. Zheng H. Su MW. Wilk R. Killeen MT. Hedgecock EM. Culotti JG.

Cell. 87(2):187-195, 1996 Oct 18.

Abstract

UNC-6 netrin, a laminin-related protein secreted from neuroglia and neurons along the ventral midline, orients migrating cells and pioneering growth cones on the nematode epidermis. UNC-5, a cell surface protein expressed on motile cells and pioneer axons, orients movements away from UNC-6 sources. UNC-40, a homolog of the cell surface proteins DCC (Deleted in Colorectal Cancer) and neogenin, is also expressed on motile cells and pioneer neurons. UNC-40 acts cell autonomously to orient movement toward UNC-6 sources. For cells coexpressing UNC-5, it helps orient movement away from UNC-6 sources. Finally, UNC-40 helps determine the dorsoventral position of cells undergoing purely longitudinal migrations. Together with the recent report that DCC is a netrin receptor in vertebrates, our results suggest that UNC-40 is a component of UNC-6 receptors on motile cells.

MUTATIONS AND INFINITY - IMPROVED STATISTICAL METHODS FOR ESTIMATING SPONTANEOUS RATES

Nadas A. Goncharova EI. Rossman TG.

Environmental & Molecular Mutagenesis. 28(2):90-99, 1996.

Abstract

Certain mathematical artifacts which had been appended by others to Luria and Delbruck's [Genetics 28: 491-511, 1943] model of spontaneous mutagenesis in bacterial populations have added confusion to the modeling and measurement of spontaneous mutation rates. Additional confusion arises when models which had been tuned for experiments with bacterial cultures grown from a small inoculum are adapted for use with mammalian cell cultures grown from a large initial population. As one consequence, biologists still tend to grow the large number of parallel cultures required by the fluctuation test in order to avoid large errors due to the high variability in the number of mutants in a growing culture. By avoiding models with infinite mean values and certain mathematical approximations that lead to conceptual and practical difficulties, the large variance of the number of mutants can be avoided (and the precision of the estimated mutation rate controlled) through the use of sufficiently large initial cell populations. A direct consequence is that simpler experiments with fewer cultures may suffice. In this paper, after a discussion of the confusions, we extend our previous approach [Rossman et al.: Mutat Res 328:21-30, 1995] by giving improved formulas for the standard error of the estimated mutation rate. The improvement results from using a more inclusive model based on consideration of the variability due to both the biological phenomenon of the growing culture (growth and mutation) and the protocols used for selection (sampling and plating efficiency). Also included is the situation where the initial cell population is not assumed to be free of mutants but the initial mutant fraction is measured instead. These standard error formulas are useful in planning experiments that yield mutation rate estimates with planned precision and for comparing and testing hypotheses about mutation rates in two or more populations which are grown under different conditions. (C) 1996 Wiley-Liss, Inc.

DIRECT DYNAMICS SIMULATION OF THE LIFETIME OF TRIMETHYLENE

Doubleday C. Bolton K. Peslherbe GH. Hase WL.

Journal of the American Chemical Society. 118(41):9922-9931, 1996 Oct 16.

Abstract

A direct trajectory method was employed to investigate the intramolecular dynamics and unimolecular decay of the trimethylene biradical over a range of energies. This method proved to be computationally viable when the internuclear forces were determined by semi-empirical molecular orbital theory. The trimethylene decay is double exponential at low energies, but becomes single exponential with a statistical rate constant as the energy is increased. The non-statistical behavior at low energies arises from incomplete intramolecular vibrational energy redistribution (IVR). The simulated results are in good agreement with the available experimental data.

A LINEAR EQUIVALENT BAROTROPIC MODEL OF THE ANTARCTIC CIRCUMPOLAR CURRENT WITH REALISTIC COASTLINES AND BOTTOM TOPOGRAPHY

Krupitsky A. Kamenkovich VM. Naik N. Cane MA.

Journal of Physical Oceanography. 26(9):1803-1824, 1996 Sep.

Abstract

A linear equivalent barotropic (EB) model is applied to study the effects of the bottom topography H and baroclinicity on the total transport and the position of the Antarctic Circumpolar Current (ACC). The model is based on the observation of Killworth that the time mean velocity held of the FRAM Model is self-similar in the vertical.

A realistic large-scale topography (H) over bar is constructed by filtering 5-minute resolution data with an appropriate smoothing kernel. It is shown that the asymptotic behavior of the solution of the barotropic model (a particular case of the EB model) in the limit of very small bottom friction depends on subtle details of topography and basin geometry. Given the uncertainties of the smoothing procedure the authors conclude that the barotropic model is not robust with respect to possible variations of model topography.

The authors found that the EB model with a vertical profile function similar to that of Killworth reproduces the major features of the time- and depth-averaged FRAM solution, including the position and the transport of the ACC, reasonably well. The solution is robust with respect to uncertainties in (H) over bar. The EB model is much improved by a parameterization of the bottom friction via near-bottom velocity, which tends to shut off the flow in the shallow regions.

A GENE MAP OF THE HUMAN GENOME

Schuler GD. Boguski MS. Stewart EA. Stein LD. Gyapay G. Rice K. White RE. Rodrigueztome P. Aggarwal A. Bajorek E. Bentolila S. Birren BB. Butler A. Castle AB. Chiannilkulchai N. Chu A. Clee C. Cowles S. Day PJR. Dibling T. Drouot N. Dunham I. Duprat S. East C. Edwards C. et al.

Science. 274(5287):540-546, 1996 Oct 25.

Abstract

The human genome is thought to harbor 50,000 to 100,000 genes, of which about half have been sampled to date in the form of expressed sequence tags. An international consortium was organized to develop and map gene-based sequence tagged site markers on a set of two radiation hybrid panels and a yeast artificial chromosome library. More than 16,000 human genes have been mapped relative to a framework map that contains about 1000 polymorphic genetic markers. The gene map unifies the existing genetic and physical maps with the nucleotide and protein sequence databases in a fashion that should speed the discovery of genes underlying inherited human disease. The integrated resource is available through a site on the World Wide Web al http://www.ncbi.nlm.nih.gov/SCIENCE96/.

KAP104P - A KARYOPHERIN INVOLVED IN THE NUCLEAR TRANSPORT OF MESSENGER RNA BINDING PROTEINS

Aitchison JD. Blobel G. Rout MP.

Science. 274(5287):624-627, 1996 Oct 25.

Abstract

A cytosolic yeast karyopherin, Kap104p, was isolated and shown to function in the nuclear import of a specific class of proteins. The protein bound directly to repeat-containing nucleoporins and to a cytosolic pool of two nuclear messenger RNA (mRNA) binding proteins, Nab2p and Nab4p, Depletion of Kap104p resulted in a rapid shift of Nab2p from the nucleus to the cytoplasm without affecting the localization of other nuclear proteins tested, This finding suggests that the major function of Kap104p lies in returning mRNA binding proteins to the nucleus after mRNA export.

Selected Funding Updates

Compiled by Peter M. Saal

OFFICE OF THE VICE-PRESIDENT FOR RESEARCH—SUNY STONY BROOK

Department of Agriculture: US - Israel Binational Research & Development Fund

BARD Postdoctoral Fellowship Program: awards provide a $27,000 stipend, plus a $3,000 research allowance, for one year of cooperative research between postdoctoral fellows from one country (U.S. or Israel) and senior scientists from the other in areas of agricultural research of mutual interest to the U.S. and Israel. Applicants must be U.S. or Israeli citizens who have completed a Ph.D. degree within the past three years. Contact: Lynn Gipe, Intl. Pgm. Specialist; 301-504-5616. Deadline: 01/15/1997

BARD Research Fellowship Program: awards provide a stipend of up to $3,000 per month for a maximum of twelve months of cooperative agricultural research between fellows from the U.S. and scientists from Israel in areas of mutual interest to the U.S. and Israel. Applicants must be U.S. citizens who are established research scientists affiliated with U.S. non-profit research institutions, universities, or federal and state agencies. Contact: Lynn Gipe, Intl. Pgm. Specialist; 301-504-5616. Deadline: 01/15/1997

Marine Biological Laboratory: Summer Research Fellowships Program

The Marine Biological Laboratory announces the 1996 Summer Research Fellowships Program. Program focus is on younger investigators. Both Full and Partial Fellowships are offered. Full fellowships cover most costs of conducting summer research, and provide living and travel expenses. Partial Fellowship funds cover many of the costs of conducting summer research, including living and travel expenses. One full and twenty partial fellowships are available. Each is individually named, and information is provided on the specific research area involved.

The Marine Biological Laboratory is a significant part of the scientific and research community of Woods Hole, MA, serving as the summer home of American and international marine biology, and year-round, hosting research programs in cell and developmental biology, ecosystem studies, molecular evolution, neurobiology, and sensory physiology. A variety of Fellowships and Awards are available to qualified graduate students, postdoctoral fellows, and young faculty selected to participate in MBL programs.

Contact: Fellowship Coordinator, Office of Research Administration, Marine Biological Laboratory, Woods Hole, Massachusetts 02543. Telephone: 508-289-7441. Deadline: 01/15/97

National Center for Atmospheric Research: Postdoctoral Appointments

Two-year postdoctoral appointments are provided for research in the atmospheric sciences at the National Center for Atmospheric Research. Stipends are $35,000 in the first year, and $37,000 in the second year. Recent Ph.D.s (or equivalent) and scientists with no more than four years of experience past the Ph.D. are eligible. There are no citizenship restrictions.

Contact: Barbara Hansford, Coordinator; 303-497-1601. Deadline: 01/05/1997

National Research Council: Collaboration in Basic Science and Engineering (COBASE)

Grants are provided to U.S. scientists who wish to collaborate with their foreign colleagues in Central/Eastern Europe and the Newly Independent States, to conduct research projects in science and engineering. Both short-term project development grants of up to $2,500 for two weeks, and long-term research grants of up to $15,300 for up to six months, are offered.

Contact telephone: 202-334-3680. Deadlines: December 30, 1996 for Short-Term activities; July 7, 1997 for Long-Term activities.

NASA: NRA-96-HEDS-01 - Microgravity Fluid Physics - Research & Flight Experiment Opportunities

The National Aeronautics and Space Administration (NASA) is interested in receiving proposals for basic experimental and theoretical research using microgravity to advance scientific knowledge and technology in fluid physics, including fluid dynamics and heat and mass transfer of relevance to microgravity research. In addition, proposals are sought to provide a fundamental understanding of physical and chemical processes in extraterrestrial environments, such as local resource utilization, bio-fluids and spacecraft and life support systems. The areas of low temperature and fundamental physics will be addressed in a separate announcement.

A more detailed description of this opportunity with specific guidelines for proposal preparation is available from: Alexander D., Pline, Microgravity Science and Applications Division, Code UG, NASA Headquarters, Washington, DC 20546. Telephone: 202/358-0820; e-mail: alexander.pline@hq.nasa.gov
Proposal due date is March 18, 1997.

NASA: NRA-96-HEDS-02 - Microgravity Materials Science - Research & Flight Experiment Opportunities

The National Aeronautics and Space Administration (NASA) is interested in receiving proposals for basic experimental and theoretical research using microgravity to advance scientific knowledge and technology in materials science. In addition, proposals are sought to provide a fundamental understanding of physical and chemical processes in extraterrestrial environments, such as local resource utilization, radiation protection materials, welding and joining, and energy conversion and storage. A more detailed description of this opportunity with specific guidelines for proposal preparation is available from: Dr. Michael J. Wargo, Microgravity Science and Applications Division, Code UG, NASA Headquarters, Washington DC 20546. Proposal due date is March 11, 1997.

NASA: NRA-96-HEDS-03 - Fundamental Physics in Microgravity - Research & Flight Experiment Opportunities

The National Aeronautics and Space Administration (NASA) is interested in receiving proposals for basic experimental and theoretical research using microgravity to advance scientific knowledge and technology in fundamental physics. Specifically, proposals are being sought to provide fundamental understanding in the research areas of Low Temperature and Condensed Matter Physics, Laser Cooling and Atomic Physics and Gravitational and Relativistic Physics.

A more detailed description of this opportunity with specific guidelines for proposal preparation is available from: Dr. Mark C. Lee, Microgravity Science and Applications Division, Code UG, NASA Headquarters, Washington, DC 20546. Telephone: 202/358-0816, mark.lee @hq.nasa.gov This NASA Research Announcement is also available electronically at: http://microgravity.msad.hq.nasa.gov Proposal due date is March 25, 1997.

NASA: NRA 96-OSS-13 - Long-Term Space Astrophysics

The National Aeronautics and Space Administration, Office of Space Science, solicits basic and applied research proposals related to the analysis of data from Space Astrophysics observations for the Long-Term Space Astrophysics (LTSA) Research Program. The dominant objectives of the LTSA program, which was initiated in 1990, are to enhance the scientific return from space astrophysics missions by supporting long-term (up to five years) funding and to strengthen the U.S. long-term research base in space astrophysics. Participation in this program is open to all categories of organizations, domestic or foreign, including educational institutions, for-profit and not-for-profit organizations, NASA centers, and other Government agencies. This announcement will be available on the OSS Homepage on November 26, 1996, at URL: http://www.hq.nasa.gov/office/oss/research.htm.

Scientific inquiries should be addressed to: Dr. Guenter Riegler, Research Program Management Division, Code SR, Office of Space Science, NASA Headquarters, Washington, DC 20546-001. Telephone: 202-358-1588, E-mail: guenter.riegler@hq.nasa.gov. This announcement will be released on November 26, 1996, and proposals are due February 26, 1997.

NASA: NRA 96-OSS-14 - Ancient Martian Meteorite Research Program

The National Aeronautics and Space Administration, Office of Space Science, solicits basic and applied research proposals related to the study of ancient Martian meteorites for the Ancient Martian Meteorite (AMM) Research Program. The objectives of the AMM program are to further investigate and resolve, to the extent possible, recent claims of a biological origin of certain phenomena within meteorite ALH84001. The AMM program is a joint program with the National Science Foundation (NSF), which will issue a separate solicitation (Dear Colleague Letter) for participation in their part of the effort.

This announcement will be available at URL: http://www.hq.nasa.gov/office/oss/research.htm. Scientific inquiries should be addressed to: Mr. Joseph M. Boyce, Research Management Division, Code SR, Office of Space Science, NASA Headquarters, Washington, DC 20546-0001. Telephone: 202-358-0302, E-mail: joseph.boyce@hq.nasa.gov. Proposals are due January 29, 1997.

PA-97-004: Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer

The National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute (NCI) wish to encourage experienced and new investigators to pursue basic and clinical investigations into the molecular genetics of acute and chronic pancreatitis as well as the "preneoplastic" genetic changes that occur and predispose individuals to adenocarcinoma of the pancreas. Basic studies include the generation of transgenic animal models of pancreatitis which show inherited forms of pancreatitis. Particularly, organ-specific transgenic mice are sought that exhibit acute or chronic pancreatitis. Alternatively, for pancreatic cancer, the fifth most common cause of death from cancer, basic science studies are sought which identify the numerous genetic alterations that are involved in this form of carcinogenesis. Such studies could utilize transgenic mice or gene knockout mice to systematically determine pancreatic preneoplastic genetic events.

Clinical studies are also sought that increase our knowledge in the early detection and diagnosis, prognostication, prevention and treatment of pancreatitis and pancreatic cancer. These studies could utilize the recent advances in the field

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largest redshift estimates that has been spectroscopically confirmed are as high as four."

A second reason the team feels they have identified galaxies with redshifts as high as six is that their spectra exhibit the same properties as other remote objects of known distances such as quasars. Although no one is certain just what a quasar is, Lanzetta suggests it is probably a massive black hole that swallows up material with such great force that it emits a tremendous amount of energy as a result. Quasars have always been the farthest objects observed because they tend to be brighter than galaxies, and frequently exhibit redshift values as high as four or five.

"Astronomers have been using quasars over the last twenty five years to study intergalactic gas that, by chance, lies along the line-of-sight between the quasar and earth. Quasars act as lamps that light up the gas so that we may see it," said Lanzetta. As a result, astronomers have been able to determine that most of this intergalactic gas is made up of hydrogen clouds. They have also found that the concentration of hydrogen clouds along the line of sight increases for remote galaxies at greater redshift values. Lanzetta concludes that "we can use the spectral signature imprinted by these hydrogen clouds as markers of high redshift objects." The team performed spectral-energy distributions for their six newly-discovered galaxies, and found very strong hydrogen spectroscopic imprints, further reinforcing their contention that they have identified very distant galaxies.

Some astronomers suggest that a nearby galaxy could, in fact, exhibit a false high redshift value due to the presence of dust lying along the line of sight. Such dust could preferentially absorb and scatter the characteristic blue light emitted by a low redshift galaxy while passing the red light through unimpeded, so that it appears to be at high redshift. "If this were true," said Lanzetta, "then our six candidate galaxies should be very bright at infrared wavelengths. We have eliminated this argument by obtaining deep infrared images from a colleague using the KECK telescope in Hawaii and found that none of our high redshift galaxies were detected in the infrared wavelengths".

THE SHAPE OF THE UNIVERSE PROVIDES CLUES TO ORIGIN AND FATE

It has been estimated that the age of the universe can range anywhere from 8 to 20 billion years. Prior to the Stony Brook team's findings, astronomers were able to look back to a time when the universe was approximately 13% of its present age. If the team's findings of these very distant galaxies are confirmed, estimates of the age and shape of the universe could be significantly changed. Although the team acknowledges the importance of finding galaxies with high redshift values of six, they are equally intrigued by the lack of observation of distant galaxies originally predicted by galaxy formation theories.

"The things that we can directly draw from our analysis of the Hubble images is that we have good evidence that we really have seen the most distant objects in the universe — we know something about their appearance, we know something about how luminous they are, and we know something about how many there are," said Lanzetta. "Even the most pessimistic people who disagree with our redshift estimates would not argue with our claim that we have established an absolute upper limit to the amount of distant galaxies there are — and that there are fewer than what naive expectations would predict," adds Lanzetta.

The team argues that this lack of observed distant galaxies, and the consequent lack of expected amounts of mass, implies the universe is precariously balanced between eternal expansion and eventual collapse. Hence, one important question before astronomers today is to predict whether the universe will continue to expand, or is bound by its own mass and will eventually collapse upon itself. Yahil suggests that the lack of observed distant galaxies means that we are seeing less volume in the distant universe; this finding could mean that the universe itself has a concentrated, high mass density. If this is true, then the universe is likely to collapse upon itself due to its own gravitational forces, or perhaps, to hang precariously between expansion and recollapse — a scenario referred to as the Einstein-deSitter model of the universe. Yahil intends to research this very complex issue in the future, hoping to gain better insight into the fate of the universe. "Our results have implications bearing not only on the formation and evolution of galaxies, but also on the ultimate fate of the universe," said Yahil.

Presently, the team is working on a cosmological model that would advance understanding of how galaxies progressed through various stages, and sort out just what happened since the Big Bang — time slice by time slice — that has ultimately shaped the universe as we know it.■

– Funding Updates –

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that identify a genetic locus on human chromosome 7 that exhibits linkage to hereditary pancreatitis as well as the recent observation of allelic loss of tumor suppressor gene(s) on human chromosome 18 as a early event in human pancreatic carcinogenesis.

The support for this program announcement will be through the NIH research project grant (R01) award, the FIRST (R29) award and the small grants (R03) award.

PAR-97-006: Small Grants for Therapeutic Clinical Trails of Malignancies

The Division of Cancer Treatment Diagnosis and Centers, National Cancer Institute (NCI) announces a small grants program to encourage the submission of small grant applications for new therapeutic clinical trials of malignancies that take advantage of recent laboratory developments. New and experienced investigators in relevant fields and disciplines (clinical, surgical, and radiation oncology) may apply for small grants to test new treatment strategies in patients or do pilot clinical studies. Application Receipt Dates: May 15, September 15, and January 15.

DA-97-003: Discovery of Novel Pharmacotherapies for Cocaine Dependence

The purpose of this Request for Applications (RFA) is to encourage applications combining medicinal chemistry and preclinical pharmacology to design, synthesize and test compounds leading to the identification of candidates for advanced preclinical and clinical evaluation as potential pharmacotherapies for cocaine dependence. Pharmacological testing may be conducted using in vitro and/or non-human in vivo procedures. It is anticipated that approximately $1.5 million will be available to fund between five to seven research project grants (R01) and FIRST (R29) awards. Letter of Intent Receipt Date: February 13, 1997; Application Receipt Date: March 13, 1997.

HL-96-021: Sleep Academic Award

The primary objective of this initiative is to encourage the development and/or improvement of the quality of medical curricula, physician/patient/nurse and community education, and clinical practice for the prevention, management, and control of sleep disorders. A secondary objective is to promote high quality clinical research in sleep. A candidate for the Sleep Academic Award must have knowledge and skills in sleep and sleep disorders medicine and be a member of the faculty in an accredited school of medicine or osteopathy in the United States, its territories or possessions. The candidate must also have sufficient experience and training in clinical sleep research, clinical practice, and/or medical education to implement a high quality curriculum in sleep and sleep disorders as well as the unqualified support from the Dean and the educational leadership of the institution is also required. The mechanism of support is the Academic Award Program (K07) of the National Heart, Lung, and Blood Institute. The total project period may not exceed five years and is non-renewable.

The estimated funds (total costs) available for fiscal year 1997 will be $300,000. It is anticipated that three to four grants will be awarded this year and in an additional competition to be held during fiscal year 1998. Letter of Intent Receipt Date: December 9, 1996; Application Receipt Date: January 23, 1997.

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

The National Institute on Aging, National Institute of Child Health and Human Development, National Institute on Deafness and Other Communication Disorders, National Institute of Dental Research, National Institute of General Medical Sciences, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, and National Institute of Nursing Research are jointly sponsoring a new neuroscience predoctoral research training program.

The aim of the program is to encourage and support broad training in the neurosciences by offering institutions a single comprehensive training grant. Support through the program is focused on the early years of training before full-time thesis research is started. Trainees are expected to be participants in a formal predoctoral curriculum offering broad and fundamental training in the neurosciences. For institutions that presently have multiple training grants with predoctoral trainees in the neurosciences, predoctoral training positions can now be consolidated into a single training grant jointly sponsored by the participating NIH Institutes.

Applications will be also accepted from institutions without current training grant support. Existing training grants that have postdoctoral positions may continue, less any predoctoral positions moved to the consolidated application. Depending on the policies of the awarding NIH Institute, other training grants at the applicant institution may continue to support predoctoral trainees involved in thesis research. The training grant will support stipend and other training costs according to the current NRSA guidelines.

It is expected that the new training programs will act as a source of trainees and activities that will enhance basic and disease-related neuroscience research that is relevant to the participating NIH Institutes. It is important that the administration of the applicant institution as well as all participating academic units and departments indicate their willingness to support the training goals of the program. Letter of Intent Receipt Date: March 1; Application Receipt Date: May 10.■

Resolving Physician-Patient Impasse in Chronic Illness

"Non-Difinitive" Solutions May Be the Answer

by Elizabeth Kelso

Chronic illnesses are a major challenge to contemporary medicine, representing more than 60% of office visits to general and family practitioners for middle aged and geriatric patients. Patients living with chronic illnesses are also often deemed "difficult" by physicians because they frequently place heavy demands on their physicians. In some instances, patients seek help from a physician but then neglect to follow a prescibed course of treatment, fostering an impasse that reveals itself in the examination room as poor communication between the patient and physician, "doctor-shopping," and in frequent visits displaying mounting patient frustration.

Raja Jaber, MD, Medical Director of the Family Practice Center at University Hospital & Medical Center at SUNY Stony Brook, and Jeff Trilling, MD, Vice Chair of the Department of Family Medicine at SUNY Stony Brook, have developed a consultation model aimed at resolving this sort of physician/patient impasse. In 1992, they implemented a pilot study utilizing the outpatient population of the Family Practice Center, affiliated with the medical school at Stony Brook and a training site for residents in Family Medicine, to test the effectiveness of their procedures in ameliorating impasses between physicians and chronically ill patients.

Incidents of patient/physician impasse were identified by attending physicians invited to refer patients to the Chronic Illness Consultation Team, comprised of Drs. Trilling and Jaber, plus a family therapist, the patient, their own attending physician, and sometimes medical residents as well. The Chronic Illness Consultation Program tested the "Circle of Change" model developed by Trilling and Jaber.

Dr. Raja Jaber(l), and Dr. Jeff Trilling(r), Family Medicine, SUNY SB

This model addresses impasse in the primary care setting by identifying the physician/patient dynamics that maintain, reduce, or aggravate difficult interactions, and by providing strategies vital to the resolution of the impasse. The "Circle of Change" takes into account the fact that each patient enters the examination room with experiences, perceptions, and expectations that give shape to how they interpret and assess their illness. Physicians introduce their own presumptions and expectations into the encounter. The clash of these differing assumptions and expectations can formulate an impasse that prevents adequate treatment and relief for the patient.

An example of the "Circle of Change" approach:

At the onset of any meeting the team dialog is informal, but it then evolves into a semistructured interview where patients' and physicians' explanatory models of illness and their assumptions about each other are elicited using open-ended questions. (The interview was based on a set of questions introduced by Arthur Kleinman, MD, and published in a 1978 *Annals of Internal Medicine* article, "Culture, Illness, and Care." Kleinman reveals patients' hesitancy to disclose their own explanatory models of their illness, and reiterates that physicians must be persistent in demonstrating earnestness and interest in under-

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Career Opportunities

Technology Development Internship Available

New York Biotechnology Association, Inc.

The New York Biotechnology Association is seeking qualified applicants for a technology development intenship for NYBA's NYC office. Will work with Director of Technology Development to build and expand relationships and collaborations between biotech companies and academic laboratories in the region. Will also conduct outreach programs to assist biotechnology entrepreneurs.

Qualified candidates must have a Ph.D. (or equvalent) in life sciences or chemistry, 0-3 years of postdoctoral research experience, and excellent communication skills. To apply, please fax your resume to: Director of Technology Development. Fax: (212)-327-0915

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standing the patient's beliefs.)

The following questions are a few offered to facilitate a conversation eliciting patients' explanatory models of illness.

What do you think has caused your problem?

Why do you think it started when it did?

What do you think your sickness does to you?

How severe is your sickness?

For example, such questions elicited the following comments from a patient with arthritits:

Patient: Back in 1990, I had spinal meningitis. I feel that it somehow stems from there. Because it is since then I really started having bad joint pains. I mean there might be no connection, but I feel there is.

Physician: "What do your husband and children think about your arthritis? What do they think it is due to?"

Patient: "I feel my children are getting very worried about me. Nine out of ten times I'm walking with a cane in the house. Plus I'm having a bad day or something."

Spouse: Now we are limited. You got to be very very careful. You can't go near her, you can't touch her, she's in pain. It's the circle of what's happening.

Physician: So your relationship has really been shaken since the meningitis. I understand very well how your relationship has been shaken by this illness.

In the "Chronic Illness Consultation," the team is interested in the patterns of interactions between patients and family members as they relate to their differing perceptions about illness. Chronic illnesses frequently strain relationships in an extended family. Further, the physician's focus is frequently on the specific biomedical aspects of the patient's illness, while the "consultation team's" intention is the whole patient, including understanding the impact of illness on the whole family.

Such a team focus elicited comments such as this:

Spouse: You guys did something good here. You got me thinking another way now. I've got to stop jumping down her throat. If I take one problem away, it might help her a little bit. Am I thinking all right.

Physician: Yes, I think you can help. Even so, anybody who lives with a chronically ill person becomes upset. It's very hard to live with somebody who is losing their functioning.

As facilitators of change, physicians can consider providing information and choices, rather than definitive specific solutions. Sympathetic physicians who discontinue pursuit of a precise, given change of behavior in the patient as their sole purpose can subsequently make the doctor/patient interaction a more flexible one. When the illusion of "the cure" disappears, accepting that compassion may be an important intervention in and of itself enables the physician to feel more comfortable with their own sometime inability to provide definitive cures. They can offer some degree of hope to a patient, important in itself:

Physician: With proper medical care, I think you'll get better.

Patient: You do think I'll get better? Nobody's actually said that. I'm just assuming that I'm gradually getting worse and worse. You're giving me a ray of hope.

The "Chronic Illness Consultations" were videotaped, and a curriculum for working with residents to resolve such clinical impasse was developed. In 1993, Jaber and Trilling examined the formulation of the physician/patient impasse, and recently developed a follow-up on their conceptual model, "The Circle of Change." Their work in this area extends further to an active interest in complementary medical therapies.

The basic tenets of the Jaber and Trilling work views each individual coping with chronic illness in the context of family and society, emphasizing lifestyle changes, and general enhancement of the body's inherent capability to heal. These ideas are highly compatible with the ideas offered in the "Circle of Change" based on a biopsychosocial model and family systems theories. Further exploration of ways of integrating beneficial aspects of complementary medicine into accepted clinical practice are currently being spearheaded at the State University of New York at Stony Brook by Trilling and Jaber, and by Stanley Altman, Director of the Center for Health, Policy and Management.■

The author is a Project Assistant in the Department of Family Medicine, State University of New York at Stony Brook.

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vitro using purified factors. The difficulty in this task lies in the large number of proteins and RNAs likely to be involved in splicing, conservatively estimated in yeast to be encoded by at least 100 different genes (about 2% of the yeast genome).

A number of snRNAs—U1, U2, U4, U5, and U6—have been identified as essential for splicing. These RNAs appear to be involved in the recognition of the 5' and 3' splice sites. The exon/intron boundaries in mammalian genes are marked by canonical sequences that determine the location of the splicing events. One significant area of Manley's work has been the identification of the importance of base pairing in recognizing the splice sites in mammalian genes, particularly between the U2 and U6 snRNAs and the pre-mRNA. Manley's approach has been to test the effects of base substitutions in the 3' splice site—usually called the branch site—on the splicing of the SV40 small t gene when a plasmid containing this sequence is introduced into a human cell line.

Through such experiments he and his colleagues have found that mutations in the branch site sequences inhibit splicing. Moreover, when a cloned human U2 gene containing mutations designed to allow binding to the mutated branch site is introduced simultaneously, splicing is restored, suggesting that base pairing between the pre-mRNA branch site and the U2 snRNA is essential. This kind of assay has been exploited to identify a base pairing interaction between the U6 snRNA and the 5' splice site as well. Manley writes, in a 1995 paper published in *Genes and Development,* that "the existence of these dynamic RNA-RNA interactions strengthens the view that pre-mRNA splicing is RNA catalyzed."

His current model of U2/U6/pre-mRNA interactions, outlined in the aforementioned paper, proposes a series of three separate base pairing interactions, or helices, that allow for recognition of the splice sites and, potentially, for the catalysis of the first step of the splicing reaction. One notable feature of the model is the intriguing similarity in secondary structure between the U2/U6/pre-mRNA complex and the self-splicing hairpin ribozyme of tobacco ring spot virus. Manley comments, "The components at the heart of the catalytic machinery (for pre-mRNAs) may have evolved features from self-cleaving RNAs," although he adds that there are significant differences in the chemistries of the two reactions.

Another aspect of splicing under study in Manley's laboratory is the role of the protein components of the spliceosome. The splicing proteins typically contain a sequence-specific RNA binding domain and an arginine/serine-rich domain that probably promotes protein-protein interactions in the spliceosome. Manley and co-workers have been characterizing one such factor, ASF/SF2, demonstrating that it can be UV crosslinked efficiently to a 32P-labeled RNA containing a consensus 5' splice site, but binds less well to an RNA containing a mutated 5' splice site. ASF/SF2, the first protein splicing factor shown to recognize 5' splice sites, has also been found to exhibit concentration-dependent differential splice site utilization, leading Manley to propose that alternative splicing in vivo might depend on variations in the concentrations of such splicing factors. Several investigators in the splicing field, including Manley, have further proposed that additional factors will be identified that have distinct RNA binding specificities and that promote specific protein-protein interactions in the spliceosome, filling out the picture of how splice sites are recognized and introns accurately excised.

Of course, the end result of an alternative splicing event is presumably the production of a protein with a different activity that either a differently spliced RNA or the unspliced precursor. In Drosophila, the classic example of alternative splicing affecting biological function is the series of splicing events that culminates in sex determination. While Manley points out that "nothing comparable exists right now in mammals," he adds that "eventually there will be specific examples of regulated splicing in development and differentiation." In the case of human disease he notes that "a lot of genetic diseases—sickle cell, for example—are caused by alterations in splicing. There are also examples of oncogenes undergoing alternative splicing, although there has been no clear documented change (in splicing) that leads to a tumor. When we understand more about splicing factors it may be possible to address problems related to splicing in human disease." Toward this end, he says that his own laboratory will continue its work on the identification of protein splicing factors and on the mechanism of catalysis in the spliceosome. Additionally, he suggests that the regulation of splicing factor activity will become an important area of research, particularly "the identification of kinases that activate splicing factors by phosphorylation."

Dr. Crick once remarked that what he meant to convey by his "central dogma" comment was that "once information gets into a protein, it can't get back out again." If so, then the study of RNA splicing factors—the managing editors of the process—addresses one of the most fundamental questions in molecular biology: how are the discrete units of genetic information found in individual exons assembled into different translatable messenger RNAs in a context-dependent manner? The identification of such factors by Dr. Manley and his colleagues in the splicing field should yield new insights into this important and intriguing problem.■

December 1996

Center for
Biotechnology
A New York State Center for Advanced Technology

Biotechnology Seminar Series

The Center for Biotechnology is establishing a forum to increase interactions between research scientists in New York Biotechnology companies and research scientists at SUNY -- Stony Brook. We are initiating a series of seminars in which industry scientists can present their research to members of academic departments at SUNY -- Stony Brook. The seminar will be followed by an informal gathering where individuals can discuss mutual interests in greater detail. The goal of the seminars is to encourage research collaborations that will lead to new products or services for the company and funding for academic research. The Center for Biotechnology, through its Innovative Technology Grants (ITG) and other programs, can provide financial support for these collaborations. Industry scientists who would like to present seminars, or academic scientists who would like to suggest speakers, should contact Dr. Robert Lewis (516-632-8521, rlewis@life.bio.sunysb.edu).

December 2, 1996, 4:00 p.m.: Richard Powell, Ph.D., Research Chemist, Technical Services, Nanoprobes, Inc., "Molecular Microscopy: Metal Clusters as Better Biological Probes", Room 038, Life Sciences Bldg., SUNY -- Stony Brook.

December 9, 1996, 4:00 p.m.: James Maioriello, Ph.D., Manager, Chemical Services, Collaborative Laboratories, Inc., "Conjugation of Enzymes to Polymers for Use in Personal Care Products", Room 412, Chemistry Bldg., SUNY -- Stony Brook.

Undergraduate Biotechnology Internships (Deadline for Summer -- January 31,1997)

The Center for Biotechnology is beginning its active recruitment for students who wish to participate in the Undergraduate Biotechnology Internship program. The program is designed for students beginning their junior or senior year at SUNY who are considering a career in biotechnology. Having workplace experience will increase your chances for employment far beyond what any grades or standardized exams will provide. Participating companies sometimes hire interns when they graduate. Interns are placed as employees under the direction of senior scientists in local biotechnology companies, where they participate in the company's research, production or services activities. Interns work full-time (40 hours per week) for the Summer semesters, and part-time (12-15 hours per week) for the Fall and Spring semesters. A stipend of $3000 is paid for the entire summer, and $1500 is paid for each of the fall and spring semesters. Students sign up for three credits (CHE488 or BIO488) for each of the fall and spring semesters; taking the summer session for credit is optional. Additional information and applications can be obtained from the Center (130 Life Sciences Bldg.) or from our Web site (http://life.bio.sunysb.edu/biotech).

Innovative Technology Grants (Deadline February 10, 1997)

The Innovative Technology Grants provide seed funding for biotechnology research projects with potential commercial applications. The awards are granted to faculty scientists, and can be used to develop the projects in collaboration with New York state biotechnology companies. PIs planning projects with a corporate cosponsor should be in contact with the company now. If you need help in finding a corporate sponsor, please contact the Center. Information and application forms can be obtained from our Web site (http://life.bio.sunysb.edu/biotech), or directly from the Center (130 Life Sciences Bldg.). The final deadline for the receipt of applications is February 10, 1997.

Job Fair: Alternate Careers in Biotechnology (March 20, 1997)

The Center is sponsoring its annual Biotechnology Job Fair on March 20, 1997. Students are encouraged to bring their résumés and meet with representatives of local biotechnology and pharmaceutical companies looking for employees. The Center is also hosting a panel of professionals who will discuss alternate careers in biotechnology. This panel is designed for students with scientific training who do not wish to pursue a career at the lab bench. This is your opportunity to ask questions and learn how to develop a career that matches your interests. For more details and updates, watch our Web site (http://life.bio.sunysb.edu/biotech).

Biotech Expo (April 24, 1997)

The Center is hosting its annual Biotech Expo at SUNY -- Stony Brook. Companies will be showcasing the latest in research and medical equipment and supplies. Check our Web site (http://life.bio.sunysb.edu/biotech) for details and updates.

Regulatory Affairs Seminar

A seminar covering aspects of regulatory affairs for biotechnology companies is being planned for May 1996. Please contact the Center (rlewis@life.bio.sunysb.edu) with suggestions for topics, or to be placed on the mailing list for the seminar announcement. Check our Web site (http://life.bio.sunysb.edu/biotech) for updated information.

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