



David Jolley, hornist, to perform at the next Peggy Rockefeller Concert



David Jolley will perform at the next Peggy Rockefeller Concert, Wed., Feb. 23. Photo courtesy of Herbert Barrett Management.

The next Peggy Rockefeller concert on Wed., Feb. 23, will feature a chamber artist of unusual sensitivity and range: David Jolley was described by The New York Times as a hornist of "remark-

able virtuosity." His performances have taken him all over North and South America, Europe, East Asia and the Middle East.

He has collaborated with such groups as the Kalichstein-Laredo-Robinson Trio, the Guarneri Quartet, the American String Quartet, the Beaux Arts Trio, Musicians from Marlboro and the Chamber Music Society of Lincoln Center. Jolley is a member of the virtuoso woodwind quintet Windscape, and of a newly formed trio with violist Michael Tree and pianist Leon Fleischer, and he is hornist with the Orpheus Chamber Orchestra.

Summer festivals at which Jolley has appeared include the Marlboro Festival, Bravo! Colorado, Music from Angel Fire, the Aspen Music Festival, the Mostly Mozart Festival, the Dartington Hall Festival in Great Britain, the Kuhmo and

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RU Neuroscience blooms at New York Academy of Sciences Spring lecture series

Brain cells rebloom this spring at a lecture series presented by The Neuroscience Section of the New York Academy of Sciences, The New York Section of the Society for Neuroscience and The Neuroscience Therapeutic Division of Parke-Davis/Warner Lambert. The free lectures will feature talks by three Rockefeller faculty members, Fernando Nottebohm, Arturo Alvarez-Buyulla and Bruce McEwen. All of the featured lectures will focus on the basic biology and potential clinical implications of the discovery that brain nerve cells

have the capacity for rebirth and regeneration throughout the human life span. Along with the RU presenters, other speakers include international experts responsible for breakthroughs in neuronal stem-cell science. The talks will review the origins of the work, the present state of the art, the future directions and the clinical and ethical implications for this line of groundbreaking research. The first lecture on Wed., Mar. 3 at 6:00 p.m. will be given by Nottebohm. The series will be held at the New York Academy of Sciences, 2 East 63rd St.

WEDNESDAY, MARCH 1

- 5:00 p.m. **Press backgrounder and panel for the general public**
Fernando Nottebohm, The Rockefeller University,
Elizabeth Gould, Princeton University
- 6:00 p.m. **Neuronal Replacement in the Adult Vertebrate Brain: Hope for a New Neurology**
Fernando Nottebohm, The Rockefeller University
- 7:00 p.m. **Neurogenesis in the Adult Mammalian Brain**
Elizabeth Gould, Princeton University

WEDNESDAY, APRIL 5

- 6:00 p.m. **Identification and Regulation of Stem Cells for Adult Neurogenesis**
Arturo Alvarez-Buyulla, The Rockefeller University
- 7:00 p.m. **The Birth and Death of Neurons, from Stem Cells to Functional Circuits**
Ronald McKay, National Institutes of Health

WEDNESDAY, MAY 3

- 6:00 p.m. **From Stem Cells to Brain Tumors: Gli Proteins and Hedgehog Signaling in CNS Development and Disease**
Ariel Ruiz I Altaba, New York University School of Medicine

WEDNESDAY, MAY 31:

- 6:00 p.m. **Resilience and Vulnerability of the Adult Brain: From Serendipity to Clinical Relevance**
Bruce McEwen, The Rockefeller University

All lectures will take place at the New York Academy of Sciences, 2 East 63rd St. For more information contact Henry Moss at 212-838-0230 or hmoss@nyas.org.

Robert Darnell to discuss tumor immunity at today's Friday Lecture

Robert Darnell, associate professor and head of the Laboratory of Molecular Neuro-Oncology, will discuss "Tumor Immunity and Neuronal Function: New Insights from the Study of Paraneoplastic Neurologic Degeneration" at the Friday lecture today (Feb. 18).

Darnell's lab studies a group of rare brain diseases called paraneoplastic neurologic disorders (PNDs). These diseases occur when tumor cells in the body express proteins that are normally made only in the brain. Proteins in the brain are not normally seen by the immune system; thus when the immune system sees neuronal proteins in cancer cells, it mounts what the Darnell laboratory has helped define as the best-understood instance of naturally occurring effective tumor immunity. In PND, this attack makes its way across the blood-brain barrier and causes autoimmune damage to neurons, bringing patients to clinical attention, and allowing a careful study of both the processes underlying their tumor immunity and autoimmune neurologic disease.

Darnell's laboratory has focused on two PNDs in which the patient's autoimmune antisera allowed cDNAs encoding the target tumor-brain antigens to be cloned. Such clones have opened the door to a detailed understanding of both the biological role these normally neuron-specific proteins play in cells and of the biological mechanisms underlying the disorders. In a disease called paraneoplastic cerebellar



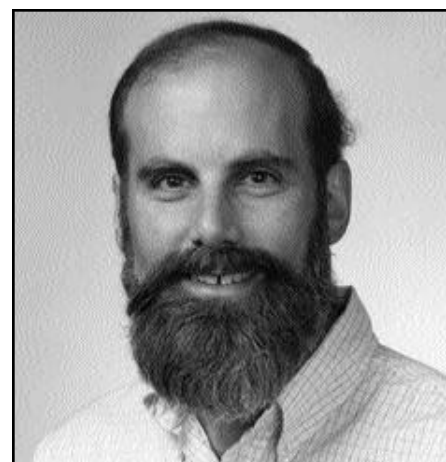
RU Associate Professor Robert Darnell will present today's Friday lecture (Feb. 18). Photo by Robert Reichert.

degeneration (PCD), the immune system keeps tumors in check by targeting a protein called cdr2, an antigen that is usually expressed only in the cerebellum by Purkinje neurons, cells responsible for coordinating movement. Darnell's lab reported in the August 1999 issue of *Genes & Development* that cdr2 down regulates activity of the c-myc proto-oncogene in Purkinje neurons, work that suggests cdr2 may function in neurons and tumor cells to block programmed cell death. In studies performed at the RU Hospital, Darnell's group reported in the November 1998 issue of *Nature Medicine* that PCD patients harbor killer T cells that are the likely mediators of tumor immunity. In

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Next week's Friday Lecture: "Antagonists of Hedgehog and Wnt signalling"

Matthew P. Scott, professor of developmental biology and genetics at Stanford University School of Medicine and an investigator at the Howard Hughes Medical Institute, will present next week's Friday lecture (Feb. 25). The topic will be "Antagonists of Hedgehog and Wnt Signalling."



Matthew P. Scott will present next week's Friday Lecture (Feb. 25). Photo courtesy of Matthew P. Scott.

Errors in signalling systems cause reversals of polarity and duplications in structures, such as a fly with three sets of wings.

In next Friday's lecture, Scott will focus on the Wnt and Hedgehog signalling systems. These two pathways are used repeatedly to control pattern formation in the developing nervous system, limbs, skeleton, musculature and many organs.

Scott's lab has done extensive research on a receptor of the Hedgehog signal, a membrane protein called Patched. The lab's research shows that in multiple tissues, Hedgehog appears to stimulate growth by opposing the growth-restraining actions of Patched. The lab has also demonstrated that a balance between hedgehog and patched protein activities is essential for cells to assume their proper fates and for tissues to form correctly. The

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December 1999, the lab reported that cytotoxic T lymphocytes (CTLs) are at least partly responsible for PCD, having found these "killer" immune cells in the cerebrospinal fluid of women suffering from the disease. The researchers also found that the neurological damage from these cells might be lessened by giving patients an immunosuppressant drug. In addition to suggesting a treatment for PCD, the finding could have wide significance for common autoimmune diseases like multiple sclerosis.

Darnell's group is extending these studies to look at two RNA binding proteins that are target antigens in paraneoplastic opsoclonus myoclonus ataxia (POMA) and the paraneoplastic Hu syndromes, disorders associated with gynecologic and lung tumors. Darnell's laboratory has completed a series of biochemical, structural and genetic studies demonstrating that Nova functions to regulate RNA splicing in neurons. These studies are being applied to both the basic and clinical biology of RNA binding proteins, which appear to play critical roles in both tumor immunity and neurologic function, including both mental retardation and autoimmune neu-

rologic disease.

Darnell earned his B.A. in biology and chemistry from Columbia University in 1979. He received a medical degree and a doctoral degree in molecular biology in 1985, both from the Washington University School of Medicine. He was an intern and resident in internal medicine at Mount Sinai Hospital in New York City and then resident and chief resident in neurology at New York Hospital. Darnell came to RU in October 1992 and was promoted to associate professor in 1997. He has been honored with the Irma T. Hirsch Career Scientist Award and the Derek Denny-Brown Young Neurological Scholar Award. He holds the rank of physician at the RU Hospital, where he has been associate program director of the GCRC since 1996. He also teaches at Memorial Sloan-Kettering Cancer Center, where he is an attending physician in the neuro-oncology department, and at Cold Spring Harbor Laboratories, where he has been director of the Molecular Cloning of Neural Genes course since 1996.

The lecture will take place in Caspary Auditorium at 3:45 p.m. and will be preceded by a tea in Abby Aldrich Lounge. All are welcome.

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lab showed that mutations in the human Patched gene cause basal cell nevus syndrome (BCNS); basal cell carcinoma, the most common form of human cancer; and medulloblastoma, a malignant tumor of the cerebellum. To further understand the molecular biology of the Hedgehog signaling system, the lab is studying the mechanism of action of the Costal-2 protein complex, which may repress the transcription of Hedgehog target genes.

The Wnt signaling pathway is equally critical in animal development and human cancer. Scott's lab has identified a gene in

the fly, Naked, that encodes a novel protein (Naked cuticle) which appears to antagonize and therefore restrain Wnt signaling.

Scott received a bachelor of science in life sciences and a Ph.D. in biology from the Massachusetts Institute of Technology. He began working on homeotic and signalling pathways with Thomas Kaufman and Barry Polisky as a postdoc at Indiana University. From 1985 to 1989, he was a Searle Scholar, and in 1990 he was awarded the Passano Foundation Young Investigator Award.

His talk will begin at 3:45 p.m. in Caspary Auditorium and will be preceded by a tea in Abby Aldrich Lounge at 3:15 p.m.

Potpourri

Abby Aldrich Dining Room Schedule

The Abby Aldrich Dining Room will be closed Wed., March 8, due to a Board of Trustees meeting. The dining room will open again Thurs., March 9.

1999 FSA participants

If you participated in the Flexible Spending Account benefit in 1999, please be aware that all claims for expenses incurred in 1999 must be made before Sat., Apr. 15, 2000. Claim forms are available in Human Resources. If you have questions regarding flexible spending accounts, call Human Resources, x8300.

Call to authors

If you have recently published a book, journal article or other piece, News&Notes would like to know about it. Please send your publication particulars, along with a summary or copy of the piece to Ann-Marie Blaber at Box 68 or fax x7876.

92nd Street Y Lecture

The 92nd Street Y will present a panel discussion on the legacy of Marilyn Monroe in Caspary Auditorium on Tues., Apr. 11. Panelists include authors Joyce Carol Oates and Dominick Dunne, columnist Liz Smith and film critic Molly Haskell. Tickets are \$20 and can be purchased

at the 92nd Street Y's box office or through Y charge at 996-1100. A number of free tickets will be available for RU students. Call x8072.

Squash anyone?

If you enjoy the fine sport of squash, why not join RU's newly formed squash ladder? It should be up and running by March. To sign up or to learn more about the ladder, visit <http://guitar.rockefeller.edu/~fmelo/squash/>.

News&Notes Schedule

The next issue of News&Notes will be published, Fri., Mar. 3. Happy Presidents' Day.

Sponsored Research News

Terry Gaasterland, associate professor and head of the Laboratory of Computational Biology recently received an early career development grant from the National Science Foundation. The grant, which will sponsor her research for the next four years, totals \$497,918 and is titled "Automated Annotation of Functional Pathways Using Eukaryotic cDNA Sequence Data."

Australian funk band Fruit to play at this Friday's Tri-Institutional Noon Recital

Today's Tri-Institutional Noon Recital will feature Australian music sensation, Fruit. Operating independently since 1995, this music and performance group has grown in five years from a popular local outfit based in Adelaide, Australia, to an internationally renowned and sought-after festival act. With three main vocalists and songwriters, the sound is dynamic. The group describes its music as acoustic-based pop and funk, flavored with an occasional twist of Latin or squal of punk aggression.

During a four-month tour Fruit played 17 shows throughout Brazil, 23 across the United States and 25 shows across Germany. They then performed at the Edinburgh Fringe Festival for five sold-out shows at the Beck's Famous Spiegeltent.

Today's noon performance is the second in the band's seven-week return stint to North America. Following their American tour, Fruit will appear at select festivals and venues, including WOMAD Germany and WOMAD UK. With 3 CDs to their name, Fruit anticipates a full-length album for 2000.

The group features Yanya Boston on drums; Susie Keynes on acoustic/electric guitar and vocals; Sam Lohs on acoustic guitar, percussion and vocals; Catherine Oates on bass guitar and vocals; and Mel Watson on vocals, horns and guitar.

Boston has performed at many major music festivals such as WOMADelaide 95 with Rough Image and the Southern Hemisphere leg of WOMAD 99 with Maori Band KAH. Keynes is the recipient of many music industry accolades including co-winner of the SCALA FOOM Songwriting Award in 1996 and SAMIA Award nomination for Most Outstanding Female Vocalist in 1997 and 1998. Lohs began her musical career as a busker in Canberra, Australia at age 17. She has since been nominated for 1997-98

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Mustasaari Festivals in Finland and the Epidavros Festival in Greece. Jolley has numerous recordings.

Pianist Morey Ritt, who will accompany Jolley, has been recognized for her artistry in solo recitals and chamber music concerts in North and South America, Europe, and Australia.

After attending Queens College and graduating from the Mannes College of Music, Ritt studied in Paris with Yvonne Lefebvre under the Fulbright program and toured as a recipient of a Rockefeller grant. She was then appointed to the faculties of both Mannes and Queens College; at the latter she earned a Master of Arts degree in musicology. Ritt has taught in Australia, where she served as Exchange Senior Lecturer in Piano at the Queensland Conservatorium of Music in Brisbane while performing in chamber music and solo recitals and appearing as soloist with the Queensland Symphony. Teaching and playing also have taken her to the Spoleto, Evergreen, Weathersfield and Round Top Festivals and to the Chamber Music Conference at Bennington.

The performance on Wed., Feb. 23 at 8 p.m. in Caspary Auditorium will consist of works by Paul Dukas, Daniel Schnyder, Emmanuel Chabrier, Francis Poulenc and Eric Ewazen.



Australian band, Fruit will perform at today's Tri-Institutional Noon Recital. Photo by Randy Larcombe.

songwriter and 1998 vocalist at the SAMIA awards and has also played with the Indigo Girls. Oates' percussive ability saw her win a SAMIA Award for Most Outstanding Drummer in 1997 and 1998. She has recently begun playing bass guitar for the group. Watson has won over a dozen awards for her musical achievements, event and video production and performance on horns.

The performance takes place at noon today (Feb. 18) in Caspary Auditorium. Admission is free for members of the tri-institutional community and their guests.

The American Association for the Advancement of Science's Annual Meeting and Science Innovation Explosion February 17 to 22, Washington, D.C. presents:

Science in an Uncertain Millennium

with RU presenters:

Fernando Nottebohm and Arturo Alvarez-Buylla

Sat., Feb. 19, 9 a.m.
Production and Replacement of Neurons in the Adult Brain (Nottebohm)
The Origins of New Neurons in the Adult Brain (Alvarez-Buylla)

Andrej Šali
Sun., Feb. 20, 3 p.m.
Comparative Protein Structure Modeling of Genes and Genomes

Atallah Kappas
Mon., Feb. 21, 8 a.m.
Production and Replacement of Neurons in the Adult Brain

Joshua Lederberg with Lindley Darden of the University of Maryland-College Park
Mon., Feb. 21, 3 p.m.
Reasoning Strategies in Error-Correction in Science

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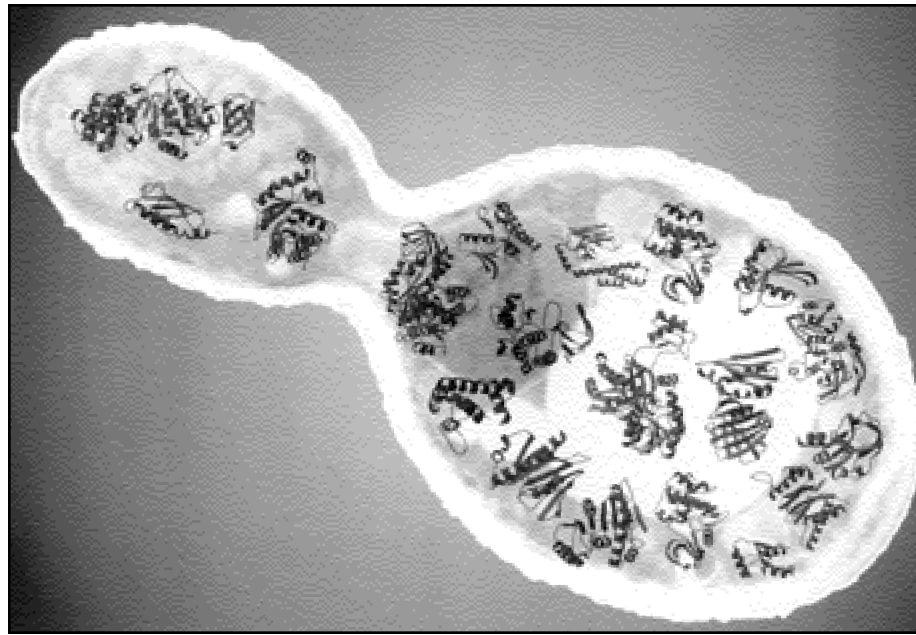
Structural genomics: a new science for an exploding field

by Jim Stallard

While the Human Genome Project (HGP) is often portrayed as an end in itself, most scientists recognize that the information gleaned from it is merely a starting point from which to ask questions about gene expression, translation and replication. With completion of the HGP in sight, scientists are carrying genomic research to the next step—studying the structures and functions of proteins that the genes encode.

Genes may be the blueprints for life, but proteins are the true builders, carrying out virtually all of life's essential functions through chemical reactions. These long chains of amino acids fold into compact but flexible shapes that are determined by the amino acid sequence. When it comes to proteins, function follows form; the shape is the very definition of what task it will perform.

However, analyzing and cataloguing information about proteins, often called "proteomics" is easier said than done. The HGP, a straightforward task of determining the sequence of chemical letters, will have taken barely more than 10 years when completed. By contrast, it would take decades to determine every three-



Approximately 1100 of the 6200 yeast proteins were modeled relatively accurately with the MODELLER program. Here, some of these models are superimposed on an image of a yeast cell. *Diagram courtesy of the Sali lab.*

Medical College of Cornell University, Brookhaven National Laboratory and the Albert Einstein College of Medicine.

"The initiative represents an attempt by scientists to get a handle on the huge amount of new genetic information that has been generated by genomic sequencing projects as part of the HGP," Burley says.

tium of scientists introduced a pilot study for structural genomics. As their first target organism, the group selected a simple, well-studied type of yeast called *Saccharomyces cerevisiae* (bakers yeast) and focused on 12 of its proteins for which no structural information was available or predicted. They also selected four domains for which structures had been predicted with high confidence. Within one year the study showed that the techniques the group implemented could support a structural genomics initiative.

Positive Repercussions

The scientists maintain that choosing medically relevant targets will provide benefits whether a protein's folds are "new" (i.e., different from those in other proteins already solved) or "old" and whether its function is already known or is unknown. They also believe choosing these targets will have important consequences for disease and patient-oriented research.

Burley says, "One could imagine that some future NIH grant applications would include both a request for funds and a request for a supply of a particular purified protein deposited in a centralized cold-storage facility."

The researchers reject claims that structural genomics will put X-ray crystallographers and nuclear magnetic resonance (NMR) spectroscopists out of business, contending that technological advances

Scientists are carrying genomic research to the next step—studying the structures and functions of proteins that genes encode.

will improve the efficiency of all structural biologists. They also argue that structural genomics may even provide the means to address "one of the great unsolved problems in molecular biology"—the relationship between one-dimensional sequence information (the order of amino acids in a protein) and three-dimensional structure (the folds of the complete protein).

"If proven effective, the structural genomics approach could provide a way for researchers to come to grips with the impending flood of genetic data and speed its translation into therapeutic use," Burley says.

Funding for the research was supported in part by Rockefeller University, the National Institutes of Health, Center for Research Resources, the Department of Energy, the Albert Einstein College of Medicine, Mount Sinai School of Medicine, Weill Medical College of Cornell University, Brookhaven National Laboratory and the Albert Einstein College of Medicine.

The RU world of proteins

Structural genomics is merely one aspect of the study of protein function. Rockefeller's history of making breakthrough discoveries in protein and peptide chemistry stems from its strength in such fields as biochemistry, biophysics, chemistry and cell biology.

Rockefeller's leadership in protein research was demonstrated once again in October 1999, when RU Professor and HHMI Investigator Günter Blobel received the Nobel Prize for Physiology or Medicine. Blobel, who made the seminal discovery that proteins have intrinsic signals that govern their transport and localization in the cell, was the 20th scientist associated with the university to receive the award.

Blobel acknowledged the essential contributions of previous Nobel Prize winners at Rockefeller, including those by cell biologist George E. Palade, who discovered the ribosome and the secretory pathway; Stanford Moore and William H. Stein, who worked out the chemical composition of an enzyme that breaks down RNA; and Professor Emeritus Bruce Merrifield, who developed a simple method of synthesizing peptides and proteins.

The task of teasing out protein function requires the kinds of collaborations that Rockefeller University encourages. Blobel, describes these interactions as "tremendously rich soups."

"There is a tremendously rich soup of biochemistry and cell biology, and these disciplines try to focus on the function of the proteins," says Blobel, an HHMI investigator. "And then there is the tremendously rich soup of structural biology, which looks at high-resolution structures of the proteins. There is also chemistry to modify the structure of the proteins and information biology to see whether you can, from the sequence, perhaps get information on the function of the protein by comparing sequence families."

As an example of the complexity of the protein problem, Blobel points out that the *E. coli* genome is completed, but half of the proteins coded by these genes and their functions are still unknown. "The challenge is to identify the functions of proteins," Blobel says. "The sequence is there, and by comparing sequences we can determine protein function, but we also need to develop new assays. We have to think in terms of 'How can you get the function out of the proteins?'"

The University continues to lead the field of inquiry into how proteins are synthesized, from the initial step, in which the genetic information stored in DNA is transcribed to messenger RNA, through the second phase, in which the messenger RNA is translated into a protein. And increased collaboration among Rockefeller's 75 research laboratories is allowing its newest generation of scientists to ask innovative questions about proteins.



From left: Professor Stephen Burley, Assistant Professor Terry Gaasterland, and Assistant Professor Andrej Šali together work on the structural genomics initiative. *Photos by Robert Reichert.*

dimensional structure of every protein encoded by the human genome. Such an exhaustive effort also would yield a large number of redundant shapes, since scientists estimate there are only 1,000 to 5,000 distinct spatial arrangements of proteins in nature.

Targeting likely suspects

Because the task of analyzing proteins dwarfs the HGP in terms of complexity, researchers at The Rockefeller University and the Howard Hughes Medical Institute and colleagues at other New York City institutions, have proposed a "structural genomics initiative," which would guide scientists toward tackling the most significant proteins first. The initiative suggests focusing on proteins that cause disease in humans as well as those that are used in treating disease. As the scientists explained in a commentary that ran in the October 1999 issue of the journal *Nature Genetics*, focusing on these "likely suspects" will bring a quicker payoff.

"This program aims to develop a comprehensive, mechanistic understanding of normal and abnormal human and microbial physiology at the molecular level," says Stephen Burley, RU's Richard M. and Isabel P. Furlaud Professor and an investigator with the Howard Hughes Medical Institute (HHMI). "This strategy should lead us to medically relevant data more quickly."

Collaborating with Burley in the initiative are John Kuriyan, Patrick E. and Beatrice M. Haggerty Professor and HHMI investigator, RU Assistant Professor Andrej Šali, RU Assistant Professor Terry Gaasterland, and researchers from the Mount Sinai School of Medicine, Weill

Gene-centered medicine

The discovery of the double-helical structure of DNA by Watson and Crick in the 1950s ushered in the modern field of molecular biology, and since then molecular and cell biologists have become proponents of the "gene product theory of human disease." Instead of examining microbial invaders, for example, the biomedical research community studies the consequences of introducing foreign proteins—such as fungal, bacterial and viral virulence factors—into humans or the results of genetic mutations that disrupt the function of normal genes.

This molecular view of disease has contributed to the importance of studies of the three-dimensional structure of proteins using techniques such as X-ray crystallography and nuclear magnetic resonance spectroscopy, which allow researchers to visualize the various shapes that enable proteins to perform their vital functions. Other dramatic advances in computational biology—most notably, specially designed software that finds all the protein-coding regions in a genome—now help researchers to predict protein function.

Šali and Gaasterland themselves have made important contributions to computer methods. Šali designed a software program called MODELLER that allows scientists to use existing knowledge about protein structures to extrapolate the structure of other proteins. Gaasterland has developed a program called MAGPIE that finds all protein-coding regions in the genome and also predicts protein function according to sequence homology with other proteins.

To demonstrate that a targeted effort involving proteins is feasible, the consor-