

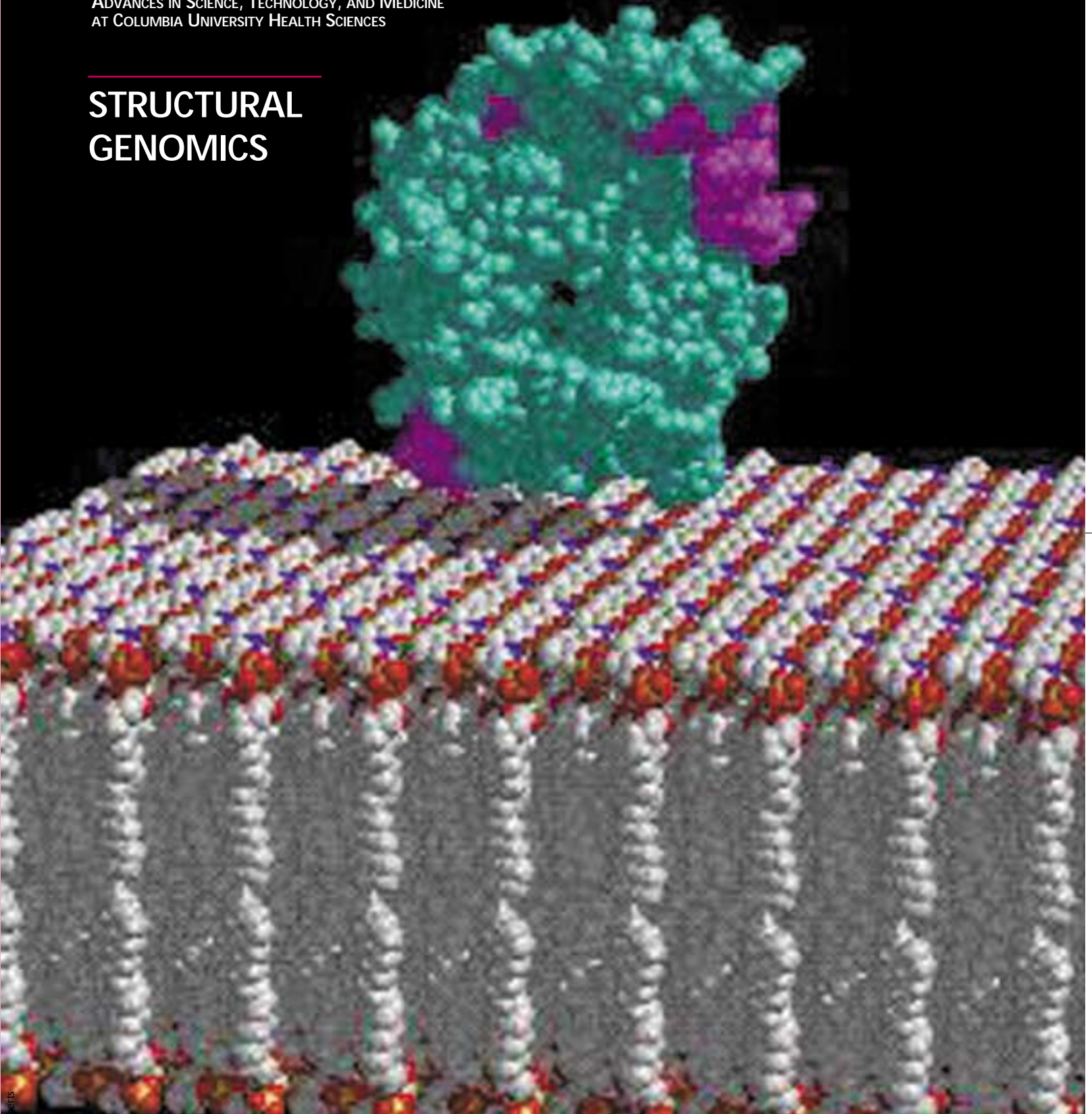
BIOMEDICAL

WINTER/SPRING 2001
VOL. 8, ISSUE 1

FRONTIERS

ADVANCES IN SCIENCE, TECHNOLOGY, AND MEDICINE
AT COLUMBIA UNIVERSITY HEALTH SCIENCES

STRUCTURAL GENOMICS



VEGF and angiogenesis,	p. 3
Synapses and spines,	p. 8
Neuroprotective effects of estrogen,	p. 10

Reshaping Health Care

FRANÇOISE SIMON, PH.D.
PROFESSOR, COLUMBIA BUSINESS SCHOOL

Health care is facing an unprecedented number of disruptive forces, from post-genomic discovery to consumerism and government cost containment. These forces are driving the biopharmaceutical industry to reinvent itself radically.

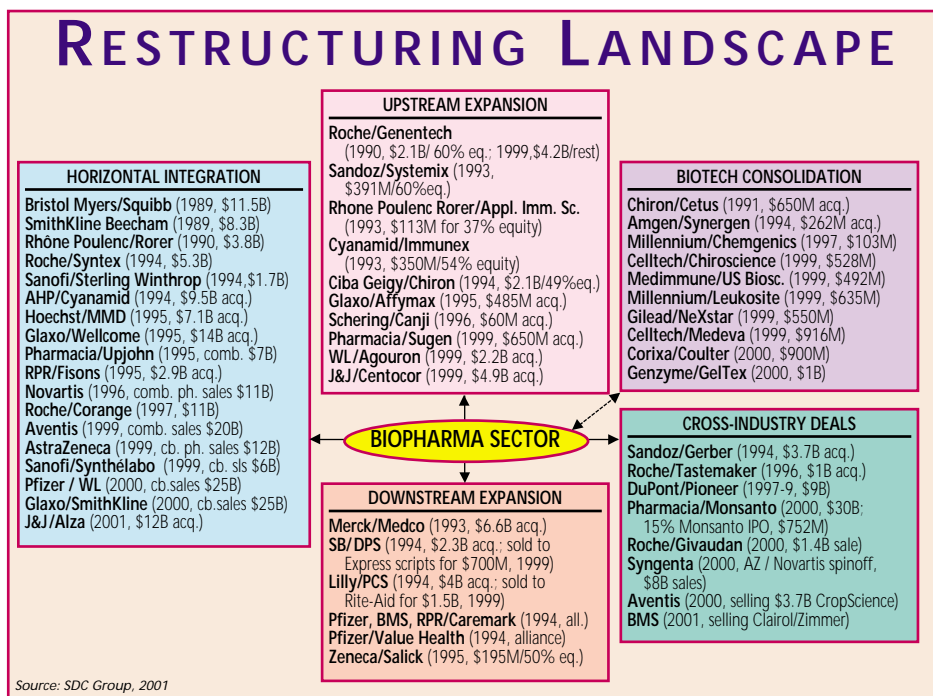
This is occurring on two parallel levels. First, a 10-year trend of mega-mergers is escalating, even though most merged firms have shown lower economic return and research investment than their solo counterparts. Second, new structures are emerging to fill the innovation gap, ranging from virtual networks to academic/industry hybrids and genomics or proteomics consortia.

The past decade has seen a massive consolidation wave, from the \$12 billion merger of Bristol-Myers and Squibb in 1989 to the twin, \$25 billion Pfizer/Warner-Lambert and GlaxoSmithKline deals in 2000. This trend is likely to continue since the industry is fragmented. The largest firm, Pfizer, still has only a 7 percent global share.

The first factor driving consolidation is global scale. The cost of developing a new drug now averages \$500 million, which must be offset by a rapid penetration of key global markets. The world's largest brand, AstraZeneca's \$6.3 billion proton pump inhibitor Prilosec, took three years to reach more than 30 countries, while Pfizer's Viagra was introduced in more than 40 countries in its first year on the market. Mega-mergers combine the geographic scale and marketing power needed to develop a portfolio of "megadrugs" (products with more than \$1 billion in sales).

A second consolidation factor is the need to refill R&D pipelines. A looming wave of major patent expirations makes the need for pipeline renewal acute. Over the next six years, Merck, Bristol-Myers Squibb, and Pfizer alone will lose patents on 25 products totaling \$18 billion in sales.

The third consolidation factor is a fundamental shift in



research from chemical screening to an understanding of the pathogenetic pathways of disease. The complexity of proteomics research requires massive R&D resources, such as the \$4 billion budget of the new GlaxoSmithKline. This also increases the scale of pharma/biotech acquisitions.

Five major restructuring models have seen varying degrees of success. Vertical integration includes expansion upstream to increase R&D capacity and expansion downstream to enhance distribution through PBMs (pharmacy benefit management firms). Upstream acquisitions can be successful if a biotech firm's autonomy is preserved to avoid the erosion of innovation by the parent company bureaucracy. By contrast, pharmaceutical downstream forays have largely been disastrous. Two of the three key PBM acquisitions were divested at losses totaling \$4 billion (see figure).

The horizontal integration models are pharma/pharma, biotech/biotech, and cross-industry deals. The latter were driven by a life sciences model that assumed blurring boundaries among pharmaceuticals, consumer goods, and agrochemicals. New hybrid product categories such as nutraceuticals showed promise, but they collided with consumer fears about genetically modified organisms. Research benefits were envisioned in applying genomics across several fields, but R&D costs, distribution channels, and—most importantly—profit margins were too different to yield the expected synergies. As a result, most non-core acquisitions were divested.

The highest success potential may belong to the biotech/biotech integration model. Acquisitions are reaching

continued on page 12

BIOMEDICAL FRONTIERS is published by the Office of External Relations in the Columbia University Health Sciences Division of the Columbia-Presbyterian Medical Center, 630 West 168th Street, P&S Box 37, New York, NY 10032 (212-305-7131; fax 212-305-4521). Please contact External Relations regarding subscription, mailing list, or any other inquiries.

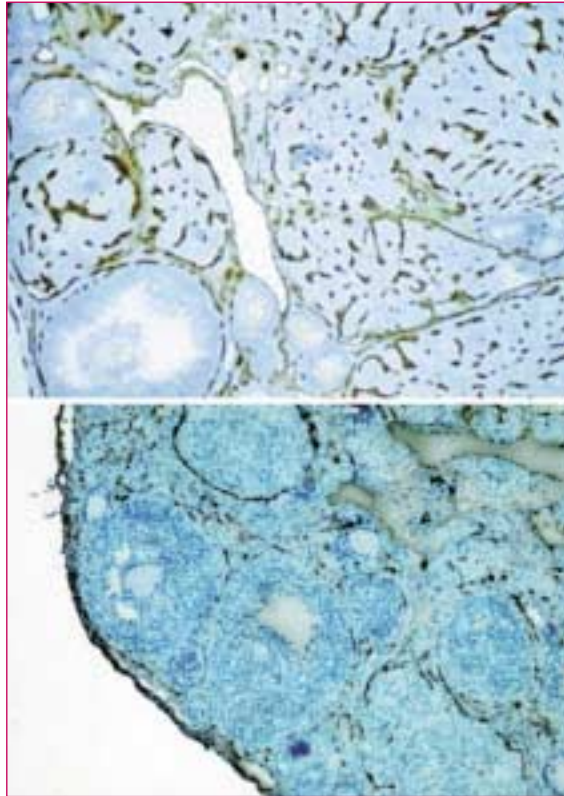
Bonita Eaton Enochs
Assistant Vice President

Howard R. Roberts/H Roberts Design
Art Director, Biomedical Frontiers

Signals that Form Blood Vessels

forming the many elaborate structures that make up an organism is too complicated a task to be completely predetermined within each cell. Instead, a recurrent theme in development involves communication with neighboring cells. Dr. Jan Kitajewski, associate clinical professor of pathology and obstetrics and gynecology, and colleagues are looking at the importance of such interactions in reproductive vasculature. Their findings may be important for understanding growth of vasculature in tumors and the adult ovary, as well as in embryos. By testing ways to disrupt this communication, their work may lead to development of anti-tumor therapies.

Angiogenesis, the formation of new blood vessels, principally occurs in the embryo. A notable exception is the adult female reproductive system, where angiogenesis occurs cyclically with the menstrual cycle. Because angiogenesis is also involved in the growth of cancerous tumors, cancer researchers pursue the factors that control blood vessel formation in the hopes of limiting tumor growth by interfering with angiogenesis. Several signaling pathways are involved in angiogenesis. One important signal is vascular endothelial growth factor (VEGF). To respond to this signal by initiating blood vessel formation, cells must have an appropriate receptor; one receptor for VEGF is VEGF receptor 2, also known as Flk-1. Learning how to block this interaction to fight



Two mouse ovaries stained for endothelial cells (shown in brown) provide a visualization of the vasculature in the ovary. The top panel shows a normal ovary with brown stained vessels in the corpus luteum and other areas. The bottom panel shows an ovary from a mouse treated with antibodies that block VEGF receptor activity and, therefore, VEGF-mediated angiogenesis. The corpus lutea no longer have brown staining, meaning no new blood vessels. The vessels surrounding the corpus lutea are still present because they are not actively growing.

tumors is the focus of one of Dr. Kitajewski's projects.

"In adults, normal angiogenesis also occurs mainly in the female reproductive system. We're interested in studying the regulation of ovarian vasculature. Our research looks at various angiogenic factors and compares their roles in tumor and ovary," says Dr. Kitajewski.

Dr. Kitajewski and Dr. Ralf Zimmermann, assistant professor of ob/gyn, use mouse models to test the effects of anti-angiogenic agents, such as antibodies, on ovarian angiogenesis. Aside from shrinking or blocking growth of tumors, the action of these agents block ovarian angiogenesis. This raises the concern of possible long-term effects on female reproduction. "If therapeutics are to be used, we need to assess the long-term effect of antibodies on the reproductive tract."

Preliminary results from experi-

ments by Dr. Zimmermann and Dr. Michel Ferin, professor of ob/gyn, show evidence that in female monkeys, administering an antibody that neutralizes VEGF can interfere with the reproductive cycle. However, the monkey's cycle recovers when treatment is discontinued. Anti-VEGF antibodies are now in phase I and II clinical trials for various cancers.

A similar approach employs antibodies directed to receptors for angiogenic signals. "A company called InClone Systems specializes in antibodies to cell-surface receptors like Flk-1, the receptor for VEGF. Several other biotech companies are developing neutralizing antibodies or drugs to block angiogenesis. We looked in monkeys to assess effects on primate reproductive cycle, as well as mice. Antibodies to these receptors can actually block luteal development, as well as tumor growth," says Dr. Kitajewski. "VEGF receptor action is associated with growing blood vessels and not pre-existing vessels. This means we can block angiogenesis and follicle development without affecting other blood vessels in the body," Dr. Zimmermann explains. □

Reducing Tissue Damage Caused by Ischemia

Tissue damage resulting from oxygen deprivation following vessel blockage, or ischemia, can be lethal, especially when the blockage occurs in the brain or heart. Destructive processes that follow ischemia may continue even after the interrupted blood supply is restored to the oxygen-starved tissues. Low oxygen, or hypoxia, triggers inflammation, blood coagulation, and immune responses, all of which may contribute to tissue damage.

Dr. Shi-Fang Yan, assistant professor of surgery, and colleagues at Columbia and Scripps Research Institute have identified a protein called Egr-1 as a master switch that unleashes blood clotting and immune and inflammatory responses by turning on a host of genes involved in these destructive processes. In the December 2000 issue of *Nature Medicine*, the researchers reported that mice lacking the gene for Egr-1 showed less tissue damage and better recovery of organ function after oxygen deprivation than normal mice. Because the mice seem largely unharmed by deletion of the Egr-1 gene, the authors suggest that temporarily blocking Egr-1 might be an effective therapeutic approach for reducing damage after a stroke or heart attack.

Dr. David Stern, the Carrus Professor of Surgical Science at P&S, was the co-author. "Among the first cells to see a change in oxygen are the cells of the blood vessel walls and blood. When there's low oxygen, there's a greater chance of developing a blood clot. Starting at the earliest times during hypoxia, the Egr-1 gene is turned on. What Dr. Yan studied is a pathway in which Egr-1 triggers production of tissue factor, which leads to thrombosis. Knockouts of this gene showed low production of tissue factor under hypoxia. In knockouts, for-

ward flow is restored much better compared with wild-type (genetically normal) mice, who died more easily, with more fibrin formation."

"There are a lot of things that we target in ischemia," says co-author Dr. David Pinsky, associate professor of medicine. "The great thing about this transcription factor is that it is the 'grandfather' of a cascade of other factors. If you can just target one trigger that has a lot of outcome downstream, you'll be in a much better position to counteract inflammation."

Dr. Yan and colleagues looked at Egr-1's role in responses of lung tissue to ischemia, but the researchers hope that damage in other tissues also involve the pathway they identified. "We're trying to show that it's in macrophages and smooth muscle cells of the blood vessel walls. It's reasonable to look at whether it's generalizable," says Dr. Stern.

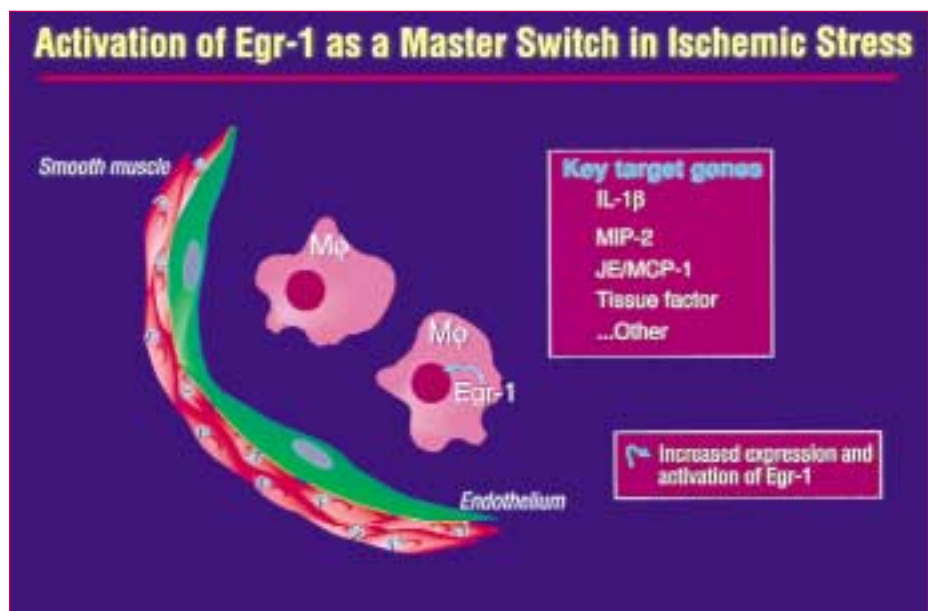
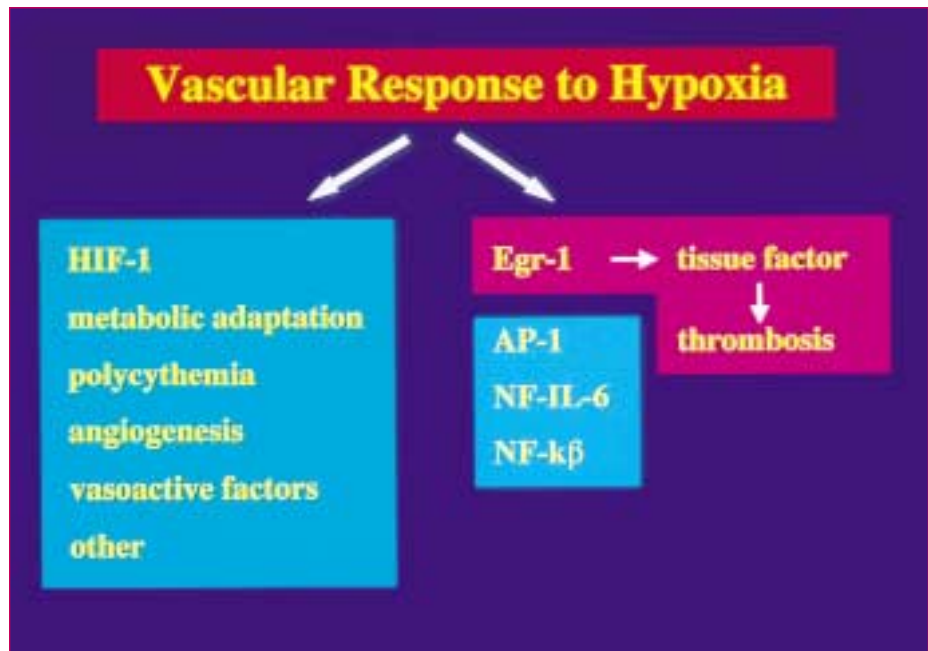
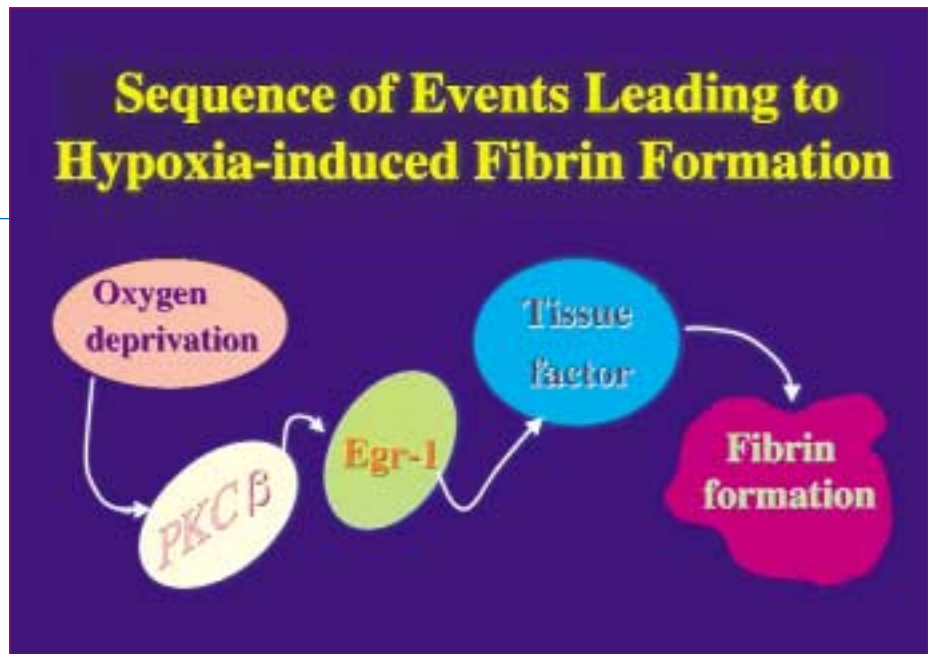
"This pattern is common to a number of tissues other than the lungs. Both in heart and brain ischemia, when blood flow ceases, certain things are triggered. The cells change characteristics to promote coagulation and edema," says Dr. Pinsky. The endothelial cells that make up blood vessel walls are among the first to respond to hypoxia. "Endothelial cells are normally tightly juxtaposed. In ischemia, hormones, cytokines, and also VEGF have a permeability-inducing function, making the vessels leak excess fluid to surrounding tissues." Why should such apparently maladaptive responses be so widespread? "It's possible that these may have been very primitive protective mechanisms," suggests Dr. Pinsky.

He and others have successfully targeted other culprits of ischemic damage in the brain. By upregulating their expression of a surface protein, C1q, neurons affected by the ischemia label themselves

for destruction by the complement-mediated immune system. Damaged endothelial cells lining microvessel walls also express an adhesion receptor protein, P-selectin, which recruits leukocytes from the blood, causing them to adhere to vessel walls and promoting clot formation. This clot formation can further hinder efforts to restore the flow of blood to ischemic tissues.

These two immune molecules, C1q and P-selectin, demanded a two-sided therapeutic attack. In 1999, along with scientists at Avant Immunotherapeutics and others at Columbia and the University of California at Berkeley, Dr. Pinsky reported in *Science* on such a bipartate attack. With a hybrid molecule produced at Avant, they were able to dramatically reduce tissue damage in a mouse model of stroke.

In general, expression of C1q on a cell's surface flags the cell for engulfment by cells that bear a receptor for the surface marker. Membrane receptors on the attacking cells could be prevented from reaching their C1q targets by adding lots of a soluble version of the receptor, called soluble complement receptor 1 (sCR1), to protect C1q-bearing cells from immune attack. A second strategy addressed selectins, cell-adhesion molecules that are upregulated in stroke and trigger clot formation and white blood cell adhesion. Sugars were added to sCR1 in a special configuration via a chemical procedure called sialyl Lewis x (sLe^x) glycosylation. The glycosylated protein could now also function to block selectin's stickiness, keeping blood cells from adhering to vessel walls and forming a clot. Within brain microvessels, the hybrid sCR1-sLe^x was highly effective at reducing clotting and greatly cut down on the volume of brain tissue damaged by a stroke. □



Structural Genomics

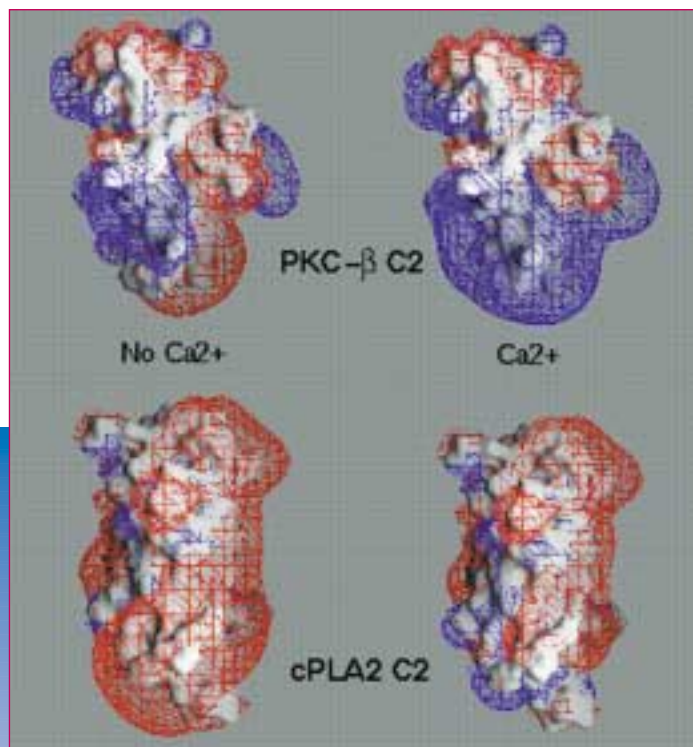
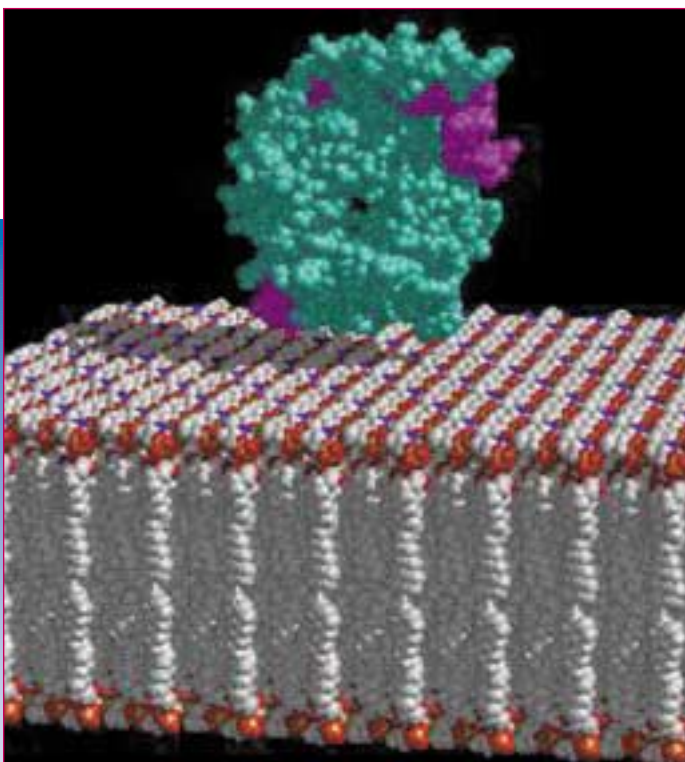
The Human Genome Project has yielded the sequences of genes for a vast number of proteins, but the structures of most of these proteins have yet to be determined. Structural genomics is the field of research that attempts to use high throughput methods to determine as many 3-D structures of proteins as possible. The effort may reveal rules that could be used to predict the shape of a protein from its sequence.

Determining the structure of a protein may help explain its function as well as how it's affected by both normal physiological processes and disease. Detailed structural information also enables researchers to model a protein's interactions with a drug candidate, greatly aiding in pharmaceutical design. To maximize the number of structures that can be obtained, a team of 10 Columbia researchers led by Dr. Wayne Hendrickson, University Professor and professor of biochemistry and molecular biophysics, will develop procedures to speed up techniques like X-ray crystallography that are used to determine the actual shapes of isolated proteins. (See accompanying article.)

"The goal is to determine as many structures as possible. But even then, we'll still have many fewer structures than primary sequences," says Dr. Barry Honig, professor of biochemistry and molecular biophysics. While exhaustive crystallography on every protein encoded by known gene sequences may be impractical, bioinformatic computing approaches using sophisticated sequence comparisons and modeling of unknown structures such as those used by Dr. Honig may greatly extend the benefits of structurally analyzing a set of representative proteins. "Our research is designed to develop methods to predict

structures based on experimentally determined related structures. Our goal is to be able to do homology modeling—building a model of the 3-D structure of a protein based on similarities to a protein of known structure." By recognizing patterns between gene sequences and the structures of proteins they encode, the researchers hope to deduce rules to predict an unknown protein structure based on its sequence.

The fruits of their work won't be merely academic: Predicting interactions between molecules may be important to understanding diseases and ways to fight them. "One problem with drugs is specificity. For instance, how do you design a drug that binds to one kinase and not others? This all comes down to specific interactions between proteins and between proteins and drugs," says Dr. Honig. "Three-dimensional structure is a starting point, but not enough. Other properties are important. For example, we use computer-based calculations of electric fields to predict how they interact electrostatically," says Dr. Honig. Dr. Diana Murray, a postdoctoral research fellow in Dr. Honig's lab who recently joined the Weill Medical College at Cornell as an assistant professor, is focusing on one structural motif common to many proteins, the C2 domain. "There are more than a hundred C2 domain sequences, but structures for only a dozen have been determined," says Dr.



Electrostatic potential of two C2 domains in the absence (left) and presence of the bound calcium ions (right). Red denotes negative and blue denotes positive potentials. The C2 domain of PKC β becomes positive upon calcium binding while the C2 domain of the PLA2 becomes neutral.

From the cover: Model of the β , γ heterodimer of the G protein, transducin, at the surface of a lipid bilayer

Murray. "We're constructing homology models for the C2 domain sequences of unknown structure and comparing their electrostatic properties with those of the C2 domains of known structure and looking for correlations with function." Although similar in overall sequence, slight differences in regions corresponding to surface loops confer important functional differences in behavior of the proteins. "The structures are highly similar but the biophysical properties of the different domains can be dramatically different. We're examining how different C2 domains target different membranes in response to binding calcium." The membrane surfaces in a cell are not all alike. The cytoplasmic side of the plasma membrane is more negatively charged, while internal membranes, such as the endoplasmic reticulum, is enriched in phosphatidylcholine which is electrically neutral. "We've found in many cases that the change in electrostatic potential of C2 domains upon binding calcium dictates their membrane-binding behaviors. For example,

the C2 domain from PKC β becomes highly positively charged and targets the plasma membrane, while the C2 domain from cPLA2 becomes overall neutral and targets the endoplasmic reticulum."

So slight differences in sequence can determine whether a given C2-containing protein sticks or falls off of a membrane. By carefully comparing computer models of the charges on each version of the C2 domain, Dr. Murray hopes to learn to predict how a given C2 domain from a new sequence will behave in real life. □

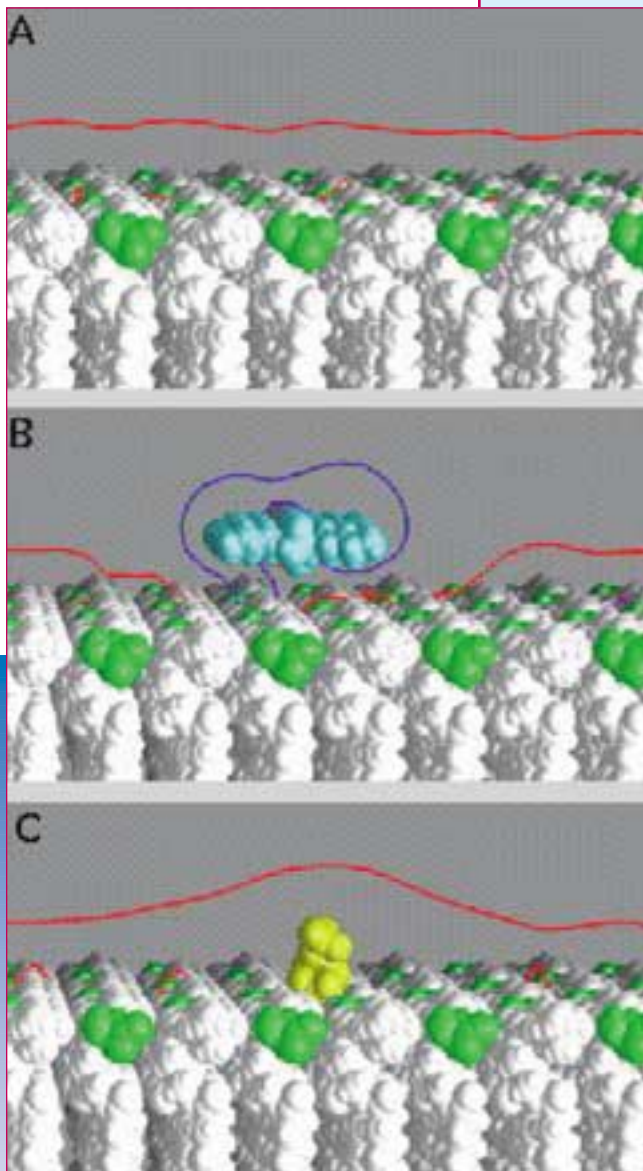
THE STRUCTURAL GENOMICS EFFORT

The structural genomics program funded by the National Institute of General Medical Sciences (NIGMS) has as its goal identifying 10,000 3-D structures of the human genome's proteins in 10 years. "The optimism for being able to do this is based on advances in techniques," says Dr. Wayne Hendrickson, University Professor, professor of biochemistry and molecular biophysics, and leader of the Columbia structural genomics team.

"It's a cross-disciplinary project. The idea is to carry out analysis of protein structure on a pan-genomic scale, bringing together capability in experimental determination of structure and bioinformatics," says Dr. Hendrickson. Other Columbia faculty involved in the research are Barry Honig, Eric Gouaux, Arthur Palmer, and Burkhard Rost (biochemistry and molecular biophysics); John Hunt and Liang Tong (biological sciences); Andrew Laine (biomedical engineering); Peter Allen (computer science); and Ann E. McDermott (chemistry, biological sciences, chemical engineering, and applied chemistry).

The Columbia team is part of the Northeast Structural Genomics Consortium with other researchers from New York, New Jersey, Connecticut, Washington, and Ontario, Canada. The consortium is one of seven pilot structural genomics research centers awarded five-year research grants by NIGMS. The grant enables researchers to develop techniques in X-ray crystallography and NMR spectroscopy to determine protein structures on a large scale. In the first round of funding, announced Sept. 26, Columbia received \$8.5 million, the largest individual share for the Northeast Consortium.

"One structure method is X-ray crystallography," Dr. Hendrickson says. This first requires purifying enough of a protein to form a crystal, an ordered stacking of the protein molecules. A beam of X-rays is then directed toward the protein crystal. The X-rays are bent, or diffracted, by features of each protein molecule in a predictable way. Analyzing the resulting X-ray diffraction patterns yields the protein's structure. Because efforts to determine protein structure are limited by researchers' abilities to obtain and purify enough of the protein for a sizeable crystal, Dr. Hendrickson outlines a number of technical innovations that boost researchers' ability to determine structures. "With minor adaptations, the main plan is to use selenomethionine with multiple-wavelength anomalous dispersion (MAD) phasing. MAD phasing enhances the amount of data that can be obtained from a protein sample. It takes advantage of interactions between X-rays and electron orbitals. In order to do MAD phasing, relatively heavy atoms are required." Living cells are used to make proteins that incorporate selenomethionine, which has selenium in place of the sulfur atom in methionine, one of the amino acids that make up proteins. The switched elements in the amino acid do not appear to affect the protein's shape or physiological function. □

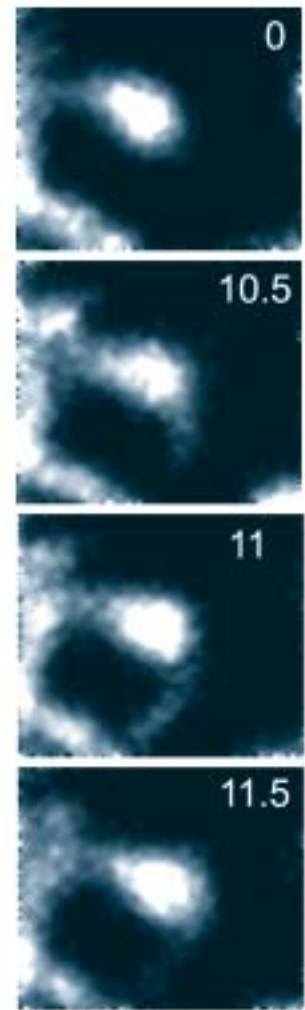


Electrostatic potentials above a charged membrane (top panel) and the membrane in the presence of a positively charged peptide (central panel) and in the presence of a highly charged PIP2 phospholipid (bottom panel)

Neurons with Spine

Neurons form special contacts called synapses, through which they change the activity of neighboring cells. In brain development, more than 1 trillion neurons must form a greater number of specific connections. An important question in developmental neurobiology contemplates how these contacts are made. And, once a particular connection is formed, what decides whether it is kept as a permanent synapse?

Synapses typically form on dendrites, the branch-like protrusions of a neuron's cell body. Most of the excitatory input occurs on spines, short, spiky outgrowths from the dendrites. Spines are believed to act as biochemical compartments and are important sites for encoding the changes in synapses that might underlie certain types of learning. Far from being completely passive or rigid structures, however, spines are now known to be quite active. This revelation has come partly as a result of methods that allow imaging of the tiny spines in living neurons of various brain regions, says Dr. Anna Dunaevsky, a postdoctoral research scientist in the lab of Dr. Carol Mason, professor of pathology and of anatomy & cell biology in the Center for Neurobiology and Behavior. Drs. Mason and Dunaevsky collaborate with Dr. Rafael Yuste, assistant professor of biological sci-



Dendritic spines are highly motile structures and change their form. Left: A low magnification image of Purkinje cell from a postnatal day 22 mouse, labeled with a green fluorescent protein. Right column: A spine on a Purkinje cell from a postnatal day 10 mouse photographed at four time points (time shown in minutes), showing a process that emerges from the spine head and retracts.

ences at Columbia's Morningside campus, who pioneered imaging of living dendrites and spines.

"We're observing dynamic properties of Purkinje cell dendritic spines as the first step towards understanding the interactions between two neurons during synapse formation," says Dr. Mason. The Purkinje cells are the primary output neuron of the cerebellar cortex, which is known for motor coordination and also thought to be a site for certain kinds of learning. Thick slabs of living cerebellum from postnatal day 10 mice are cut and kept alive in a

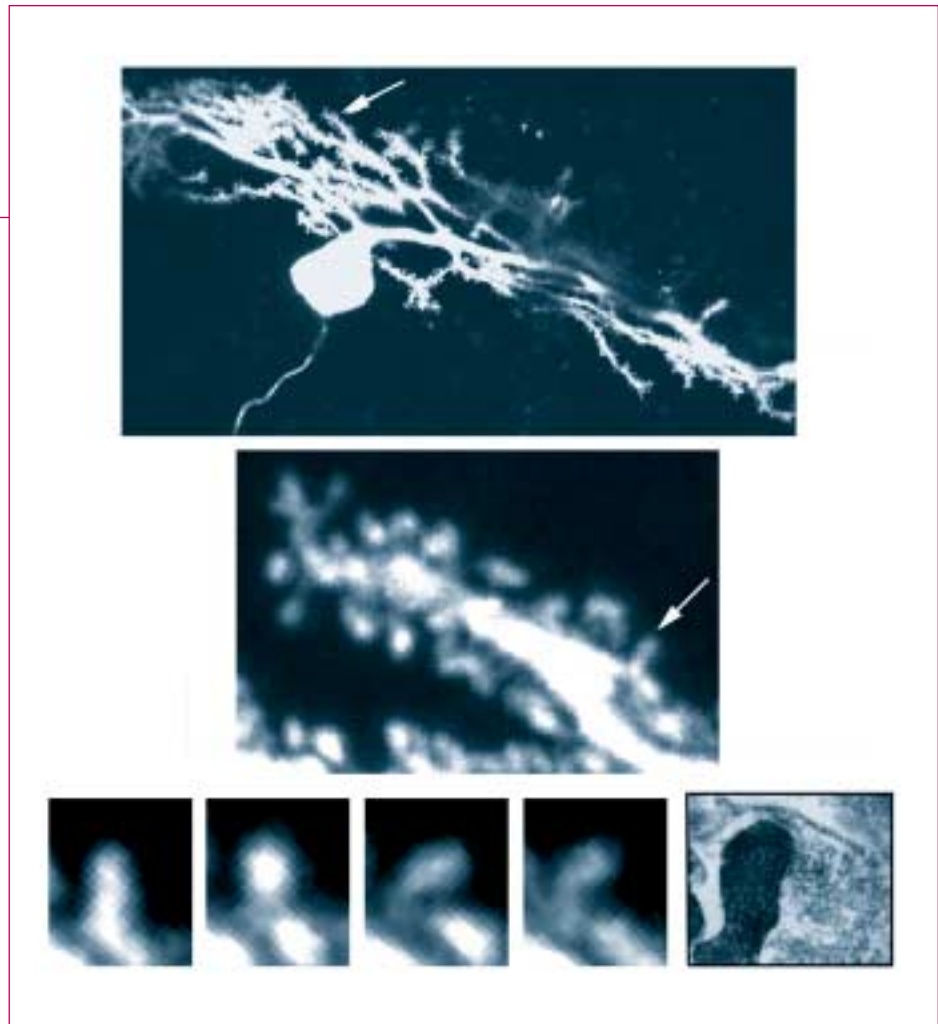
dish for long-term observation. "We label Purkinje cells by injecting gold particles laden with DNA encoding green fluorescent protein and watch them with 2-photon time-lapse microscopy," says Dr. Dunaevsky. The 2-photon microscope uses light with low energy; the combined energy of two photons at the plane of focus excites the green fluorescent protein, resulting in very localized excitation and views of structures in sharp focus.

This novel type of microscopy allows prolonged live imaging of neurons in intact tissue. Images obtained

over time reveal that the dendritic spines of Purkinje cells are anything but static; they rapidly change shape and appear to be wiggling around. "Spines that were traditionally studied and classified in static tissue sections as belonging to different size and shape categories could be the same spines that are morphing and moving over the course of seconds to minutes," says Dr. Mason.

Dr. Dunaevsky has found that construction of actin filaments, the structural proteins involved in many types of cell motility, is necessary for the spines to wiggle. In contrast to some changes of synapses during development, the active behavior of the spines seems unaffected by generally exciting or blocking activity of the Purkinje neurons.

Like humans, the spines tend to slow down with age. "At postnatal day 10, the peak time of synaptogenesis, 75 percent of spines show some motility. In slices from an older animal, only about 40 percent are motile. Because we saw these developmental changes, we wondered if the increased number of synaptic inputs as the brain matures might arrest motility," says Dr. Dunaevsky. To see if synapses had formed on spines that took up sedentary lifestyles, Dr. Dunaevsky chemically preserved the cells for examination with electron microscopy. Carefully piecing together a picture of each spine from sequential sections allowed the researchers to identify many individual spines that they viewed in the living state. "This gives us the ability to correlate motile activity with synaptic contacts. We see that spines move even if they have



Dendritic spines can be motile even when contacted by a synaptic terminal. Top: A Purkinje cell labeled with a green fluorescent protein. Arrow points to a portion of the cell that is shown in higher magnification (middle) and which was imaged by 2-photon microscopy in the living state then analyzed by electron microscopy. Bottom: A spine that was motile (arrow in the middle panel) is contacted by a synaptic terminal (right most panel).

formed a synapse with another cell," says Dr. Dunaevsky. How can spines wiggle while still holding on to a synapse? Is the cell that makes the synapse onto the spine wiggling as well? The researchers can watch the long processes that form synapses onto the Purkinje cells. The structures on the adjacent neuron that make synapses don't seem to move much. They believe that during spine motility, either synapses quickly form and break apart or, more likely, the spines manage to perform their acrobatic maneuvers while remaining attached. Labeling two cells with two different color fluorescent labels will enable

the investigators to differentiate between those two possibilities.

To understand more about spine motility and its function, especially as the brain matures, the researchers will use factors known to affect other developmental processes. Brain-derived neurotrophic factor is known to increase the number of spines, so the researchers plan to see if motility also is affected by this growth factor. The researchers also plan to examine spine motility in mutant mice that have defects in Purkinje cell survival and development and in other mouse genetic models for neurological disease. □



Estrogen Receptor and Alzheimer's

To be effective—in a textbook sense—the steroid hormone estrogen must diffuse through a cell's plasma membrane and bind to estrogen receptors, which then move to the cell nucleus, bind to DNA, and turn transcription of specific genes on or off. But scientists have long known that some of estrogen's effects are much too rapid to require all these steps. "There are many actions of estrogen that are genomic, but there are others that happen within seconds to minutes," says Dr. Dominique Toran-Allerand, professor of anatomy & cell biology and neurology, who was among the first researchers to try to answer this enigma.

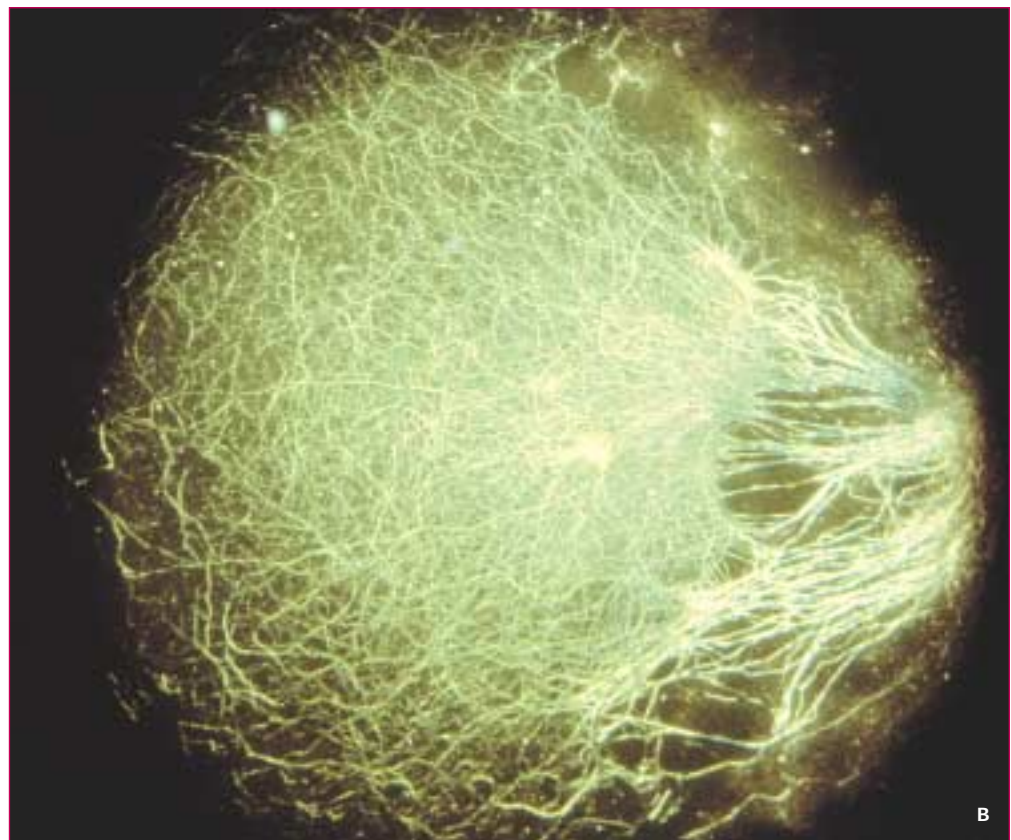
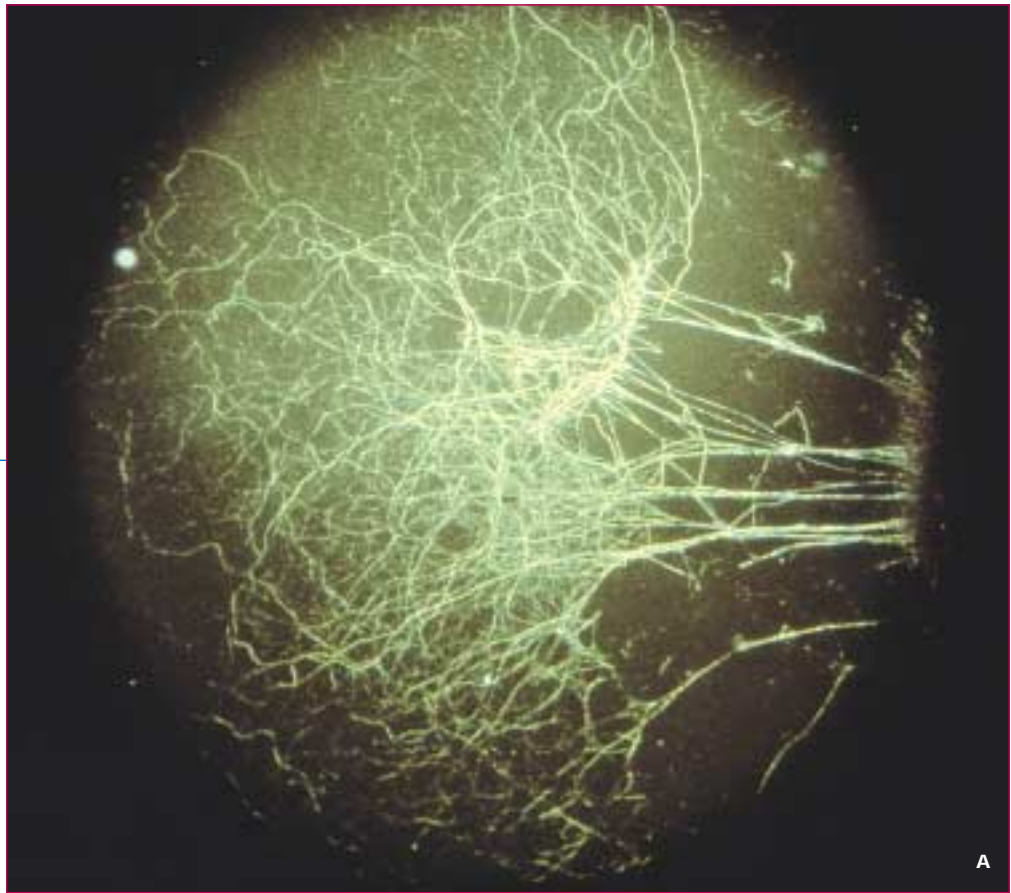
"The dogmatic view is that estrogen is a transcriptional enhancer that acts directly on its receptors in the nucleus, but here were effects that were too rapid to be mediated by transcription. What we're working on is the possibility of an estrogen receptor associated with the plasma membrane rather than the nucleus."

Estrogen stimulates growth of axons and dendrites. "I became interested in the cellular and molecular mechanisms underlying this estrogen-enhanced growth of neuronal processes," says Dr. Toran-Allerand. Her research has focused on whether estrogen affects responses of nerve cells by interacting with growth factors called neurotrophins. "Many of the regions where people had shown responses to neurotrophins were not only also estrogen responsive, but neurotrophin and estrogen receptors were found in the same nerve cells." By binding the neurotrophins, neurotrophin receptors trigger a cascade involving activation of the MAP kinase cascade, a cell signaling pathway that influences cell division, cell differentiation, and cell survival. Dr. Toran-Allerand found that estrogen can activate the MAP kinase cascade in a similar fashion and in this manner influence neuronal development and neuroprotection.

"The cell membrane has specialized microdomains called caveolae—little caves—which are invaginations of the plasma membrane. A wide variety of receptors and signaling proteins, referred to as kinases and phosphatases, are found in these little caves. It is believed that this pre-organization facilitates signaling," Dr. Toran-Allerand says. "We found an estrogen receptor located within caveolae which is also physically associated with components of the MAP kinase cascade. I've been trying to characterize this novel estrogen receptor."

In mice lacking one of the two known nuclear estrogen receptors, ER α , Dr. Toran-Allerand showed that the estrogen estradiol was still able to trigger the MAP kinase cascade. However, estrogenic substances specific for either ER α or the other receptor, ER β , were unable to turn on the MAP kinase cascade. "We propose that this new receptor actually mediates activation of the MAP kinase cascade," says Dr. Toran-Allerand.

If the new protein proves to function as an estrogen receptor, the findings may go beyond simply crushing the dogma that estrogen acts only via nuclear receptors. Structural changes in nerve cells are thought to contribute to mental deterioration that accompanies Alzheimer's disease. Some evidence suggests that therapeutic replacement of estrogen, which is lost with age, can help prevent this deterioration. Controversy exists over whether estrogen treatment may increase the risk for certain cancers. If the putative estrogen receptor studied by Dr. Toran-Allerand's team is involved in the neuroprotective effects of estrogen, drugs that specifically target it in the brain might be able to fight estrogen loss and its consequences without increasing cancer risk. □



Neurons from slices of the brain maintained in culture, when exposed to high concentrations of estrogen (A), exhibit much more growth of neurites (axons and dendrites) than do neurons exposed to much lower concentrations of estrogen (B).

CPMC *ON THE WEB*

Audubon Center
www.auduboncenter.org

Clinical Trials
cpmcnet.columbia.edu/dept/ctrials

Columbia Innovation Enterprise
www.columbia.edu/cu/cie

Grants and Contracts
cpmcnet.columbia.edu/research

Executive Vice Provost
www.columbia.edu/cu/research/admin.html

continued from page 2

the \$1 billion level, and culture clashes and loss of key scientists are less likely than in pharma/pharma deals.

The link between consolidation and performance has been best studied in the pharma/pharma model using the decade of data available. The three main performance measures are market share, economic return, and research productivity. By all three measures, most non-merged companies performed better than merged firms. In a 1999 study by Pharma Strategy Consulting, all but two of the non-merged firms registered market share gains ranging from 12 percent (Lilly) to 110 percent (Astra). By contrast, merged companies (with the exception of Bristol-Myers Squibb) all lost market share since their mergers. Another study by AT Kearney and the author showed a similar trend in terms of economic return. All merged firms (except BMS) had lower returns than their solo counterparts.

Research productivity is the most elusive indicator because of the 10-year minimum lag between research investment and introduction of new drugs. However, the high opportunity costs of acquisitions (as they displace research dollars and lead key scientists to depart) are evident. A 2000 Lehman Brothers study compared cumulative R&D spent from 1990 to 1994 vs.

1995 to 2000. Again, the R&D spending increase at solo firms such as Pfizer and Lilly was three to four times that of merged firms such as Glaxo Wellcome.

In parallel with consolidation, new structures are forming. Virtual networks now link biotech and pharmaceutical firms, the latter relying on webs of hundreds of R&D alliances.

The complexity of post-genomic research is also spurring the development of academic/industry hybrids and consortia. Leading universities are moving from early contract forms, such as licensing, to their own venture capital funds and to full public-private partnerships.

Finally, large-scale systems approaches to biology are emerging as the dominant form of post-genomic research. The SNP Consortium, set up in 1999 to identify the gene markers (single nucleotide polymorphisms) that predispose some individuals to disease and protect others, linked the Wellcome Trust and 10 pharmaceutical firms through a \$45 million two-year endowment. Regional consortia are also being formed, such as the Northeast Structural Genomics Consortium (described in this issue) linking Columbia with other East Coast centers.

Through these structures and consolidation, health care is reshaping itself to address post-genomic discovery. An emerging scenario is linking pharma mega-marketers to a web of biotech and academic innovation engines. □

**FOR
MORE
INFORMATION**

**BIOMEDICAL
FRONTIERS:**
212-305-7131
biofrontiers@columbia.edu

**AUDUBON
CENTER:**
Mitch Gipson
Executive Director
212-342-7067
ig34@columbia.edu

CLINICAL TRIALS:
Michael I. Leahey
Director
212-305-5063
mil7@columbia.edu

PATENTS AND LICENSES:
**COLUMBIA
INNOVATION
ENTERPRISE**
Ofra Weinberger, Ph.D.
Director, Health Sciences
212-305-5198
ow1@columbia.edu

MEDIA REQUESTS:
Carolyn Conway-Hoare
*Director of
Public Relations*
212-305-3900
cc328@columbia.edu

**GRANTS AND
CONTRACTS:**
Richard Sohn, PhD
Director and Assoc. Dean
212-305-4191
rjs6@columbia.edu

Columbia University
Health Sciences Division
BIOMEDICAL FRONTIERS
P&S Box 37
630 West 168th Street
New York, NY 10032

Non Profit Org.
U.S. Postage
PAID
New York, NY
Permit No. 3593