EINSTER

NewsReel



Seated, left: Dan de Roulet, Chairman of the Board of Trustees, North Shore-LIJ, and Ira Millstein, Chairman of the Board of Overseers, AECOM; standing, left to right: Lawrence Scherr, M.D., Senior Vice President of Academic Affairs and the Betsey Cushing Whitney Dean and Chief Academic Officer, North Shore-LIJ; Michael J. Dowling, North Shore-LIJ CEO and President; Dominick P. Purpura, M.D., The Marilyn and Stanley M. Katz Dean, AECOM; and Michael Reichgott, M.D., Ph.D., Associate Dean for Clinical Affairs and Graduate Medical Education. AECOM

"They are coming into a major

population, offers expertise in virtually all clinical fields, gives

health system that treats a diverse

students the opportunity to work

alongside some of the region's best

physicians, and provides access to a

range of patient-oriented research

enhanced their institutional bond

by creating joint graduate opportu-

"In 2002, Einstein and the North

projects." said Scherr.

Shore-LIJ Research Institute

nities for the medical school's

doctoral candidates, focusing on

disease-oriented research." said

Michael J. Dowling, the health sys-

officer. "This new agreement fur-

ther strengthens our relationship

and gives us an opportunity to

pursue academic areas of mutual

ical students two major teaching

approach to their education and

help broaden their experience in

provide a more well-rounded

treating patients with a range

of illnesses."

interest. By offering Einstein med-

hospitals for their training, we can

tem's president and chief executive

New Einstein, North Shore-LI Partnership Announced

Since 1988, LIJ has served as the Long Island campus for Einstein medical students and faculty, with approximately 180 students training annually. Under a new agreement, announced this past summer, medical students at Einstein will now be able to complete clinical rotations at North Shore University Hospital in Manhasset as well as at LIJ Medical Center in New Hyde Park, which includes the Zucker Hillside Hospital and Schneider Children's Hospital.

"This new collaboration will ensure that our students will continue to receive outstanding educational experiences and, by their presence, further enhance the academic excellence of the North Shore-LIJ Health System," said Dean Dominick P. Purpura at the signing of the agreement. "One could not imagine a more desirable union of common cause," he added.

Approximately one-third of graduates from Einstein already receive some training at LIJ. "We expect this new agreement will provide even greater opportunities for Einstein medical students," said Lawrence Scherr, M.D., senior vice president of academic affairs, and the Betsey Cushing Whitney Dean and chief academic officer of the North Shore-LIJ Health System.

Alumnus Mark Mehler Named Chair of Neurology

Dr. Mark F. Mehler, Class of '80, has been appointed chair of the Saul R. Korey Department of Neurology, succeeding Dr. Herbert Schaumburg, who held that position for nearly 20 years. Dr. Mehler, professor of neurology, neuroscience and of psychiatry and behavioral sciences, is also the Alpern Foundation Professor of Cerebral Palsy Research.

In addition to earning his M.D. degree at Einstein, he was the first student at the medical school to undertake a research project to earn an M.D. with Special Distinction for Research (in neurochemistry).

Following graduation, he left Einstein temporarily to complete a residency in internal medicine at Boston's Beth Israel Hospital and a clinical fellowship in medicine at Harvard Medical School. He then returned to the College of Medicine, where he completed a residency in neurology and served as chief resident. From there, he began his career at Einstein, where he is now marking his 20th year on the faculty.

Among the many positions he has held, Mehler has served as director of the Mental Retardation & Developmental Disabilities Research Center/NICHD Core Tissue Culture Facility of the Kennedy Center, as well as chief of the center's Laboratory of Molecular and Developmental Neurosciences. He also is director of Einstein's Institute for Brain Disorders and Neural Regeneration.

As an investigator in both the Kennedy Center and the Cancer Center, Mehler conducts research related to pregenitor cells of the nervous system and the influence of cytokines on nerve tissue development

He is widely published, has been a journal reviewer for every major journal in his field, and has served as a scientific reviewer for the NIH, the NSF, and the International Brain Research Organization.

In addition to his research activities, Mehler is an attending neurologist at both Jacobi Medical Center and Montefiore Medical Center. Since 2000, he has been chairman of neurology at Jacobi, as well as at North Central Bronx Hospital and North Bronx Healthcare Network.

Since joining the faculty in 1984, Mehler has been very active in the educational life at Einstein, serving in a variety of capacities relevant to medical student curriculum, the medical student scientist training program, and the graduate neuroscience program. He also serves as a mentor to both predoctoral and postdoctoral students, as well as



Dr Mark F Mehler

to junior members of the Einstein faculty.

Of his new role he notes, "Saul R. Korey, the namesake of our department, was visionary in that he sought to integrate the lab bench with the bedside while building interdisciplinary alliances. We will emulate the Korey model, bringing together disciplines as disparate as bioengineering, genetic epidemiology, stem cell biology, molecular biology, and psychiatry to enlarge the bounds of our knowledge in understanding nervous system diseases and to develop innovative ways for addressing them."

Kalnicki Appointed Chair of Radiation Oncology

Dr. Shalom Kalnicki has been named Chairman of Radiation Oncology. The appointment marks his return to Einstein, where he completed a residency in radiotherapy and then served as chief resident and a fellow.

Most recently, Kalnicki has been director of radiation oncology at the University of Pittsburgh Cancer Institute and vice chairman of clinical affairs of the department of radiation oncology at the University of Pittsburgh School of Medicine, as well as director of the department's residency program.

An expert in brachytherapy for lung and prostate cancer, Kalnicki recently developed expertise with sterotactic radiosurgery on intensity modulated radiation therapy, more commonly known at IMRT. He possesses a broad background using state-of-the-art technology and a strong commitment to clinical research. He has been co-principal investigator of numerous federally funded radiation therapy trials and also holds several major industry grants relating to new, cutting-edge therapies in the field.

continued on page 18







DEAN PURPURA

October 13, 2004 – A Monumental Day



LEFT TO RIGHT: DR. LAWRENCE STURMAN, JOSEPH ORLANDO, DR. BENJAMIN CHU, MICHAEL PRICE, SAMUEL WEINBERG, MURIEL BLOCK, IRA MILLSTEIN, DEAN PURPURA, PRESIDENT JOEL, MORRY WEISS, BURTON RESNICK, ROBERT BELFER.



n a day bursting with sunshine and an aura of good feeling and pride, and with an audience of nearly 500 looking on, the College of Medicine broke ground for its new Michael F. Price Center for Genetic and Translational Medicine/Harold and Muriel Block Research Pavilion.

The new \$200 million, 201,000 square-foot, five-story research building is named in honor of Michael F. Price and Muriel Block and her late husband Harold. Mr. Price, Chairperson of Einstein's Executive Committee, and a pioneer in the mutual fund industry, made a donation of \$25 million toward the creation of the Center. Mrs. Block's gift, valued at \$21 million, is the second largest donation ever received by the medical school.

"We are blessed to be living at a time when nature's most carefully guarded secrets are being revealed ..."

-Dominick P. Purpura, M.D.

The new building represents the largest medical research facility to be constructed in the Bronx since the College of Medicine opened in 1955 and effectively doubles the size of the Einstein campus. It is being built on 10 acres of land leased from the New York City Health and Hospitals Corporation for a period of 99 years and represents an unusual collaboration between a private institution and a public entity, Iacobi Medical Center.

The Price Center/Block Pavilion, which is expected to open in 2008, will house 40 state-of-the art laboratories, in addition to research support facilities and a 100-seat auditorium. The building's design will further advance Einstein's long-standing emphasis on fostering scientific collaboration among its faculty and researchers.

On the theory that one picture is, indeed, worth a thousand words, the editors are pleased to tell the story of this magical day through many pictures, and just a few words.

"We are blessed to be living at a time when nature's most carefully guarded secrets are being revealed in studies of basic life processes. Einstein must be an active participant in this century of revelation, the understanding of life and its disorders. To achieve this lofty goal, there will arise on these grounds a new state-of-the-science facility." -Dominick P. Purpura, M.D.



EINSTEIN COLLEGE OF MEDICINE OF Y PRICE CENTER FOR GENETIC AND TRANS HAROLD AND MURIEL BLOCK RESEARCH BREA CER

GRO

"For many of us who have been with Einstein for 30 or more years, the construction of the Price Center housed in the Block Pavilion represents the culmination of a dream. But it also marks an important beginning, a revolutionary future of expansion and of success. We have set in motion a new phase in our history, a phase that will raise Einstein to another level. We are entering an era of great growth, increased space for research, additional amenities for students. We will be doubling the size of our campus. There will be more space for virtually everything we want to do.

Many people worked very hard to bring about this day and many people deserve credit. But none deserve credit more than Michael Price and Muriel Block, whose generosity has been overwhelming, and on behalf of the Board, the faculty, and all of us here, I thank you both."

-Ira Millstein, Chairperson, **Board of Overseers**

MILLSTEIN AND PURPURA

"We have set in motion a new phase in our history, a phase that will raise Einstein to another level. We are entering an era of great growth, increased space for research, additional amenities for students. We will be doubling the size of our campus. There will be more space for virtually everything we want to do ..." -Ira Millstein

"The founders of this College of Medicine had a vision of a medical school that breached the barriers of bias. And it came to pass. Today we enlarge this vision to encompass the role the College must play in the revolution of medical science. Albert Einstein once famously said, 'The distinction between past, present and future is only an illusion.' He could not have been more prescient in regard to our quest for excellence. As it was in the beginning so shall it be now and in the future. On this occasion of renewal, we reaffirm the expectation that the research carried out in the Center for Genetic and Translational Medicine will meet this tradition of excellence that characterized the Albert Einstein College of Medicine since its founding a half-century ago."

-Dominick P. Purpura, M.D.

-Michael F. Price

a lasting impression." -Muriel Block





"I'm here because of Dom [Purpura]. His vision, his ability to look forward to where the institution can go, to where the science can go, is amazing. He told me what Einstein could deliver-the people, the science, the know-how. To know that we're going to translate from across the street to over here some of that basic knowledge into new science, new cures, is a very exciting thing. I believe that whatever we do, we're going to succeed. And there is no better place to do it than here in New York, in the Bronx."

"On this auspicious occasion, my heart swells with pride to be part of a research project established for the good of mankind. It makes



PRESIDENT, YESHIVA UNIVERSITY

"Scientific exploration, medical and moral discovery, is more than prose; it is poetry. We're here to celebrate the "poetry" that gets produced at this wonderful place, with these wonderful partners. We celebrate the advance of the "lyric poem" that is the Albert Einstein College of Medicine of Yeshiva University."

-President Richard Joel



DR. MARK CHANCE, DEAN PURPURA, MICHAEL PRICE, DR. MATTHEW SCHARFF





MURIEL BLOCK



PRESIDENT JOEL, MORRY WEISS, BURTON RESNICK

"Scientific exploration, medical and moral discovery, is more than prose; it is poetry. We're here to celebrate the "poetry" that gets produced ... at the Albert Einstein College of Medicine of Yeshiva University." -President Richard Joel

"On behalf of the residents of New York City, I commend Einstein's dedicated team for making this day possible. This new facility will further the important role you have played in the medical community of our great city and will bring hope and improved care to so many living with debilitating diseases. It is always gratifying to unite with people and organizations committed to making a difference in their communities and in the lives of others." -Mayor Michael R. Bloomberg

"This state-of-the-art facility will not only be the largest medical research investment ever in the history of the Bronx, but it will also be a catalyst for the entire East Bronx community. The jobs involved in the construction of this facility, the people who will train in it, and the 400 additional jobs that will be created to staff this new enterprise, demonstrates the depth of Albert Einstein College of Medicine's dedication to this borough and this community."

-Congressman Joseph Crowley

"This Center will certainly be in the forefront of biomedical research. The work that will be conducted here will help to improve the health and quality of life of all residents of the Bronx and of New York City. I appreciate the efforts of all those involved in working out the lease agreement, including the Bloomberg Administration, the Health and Hospitals Corporation, and, of course, the leadership of Jacobi Medical Center. Congratulations to all."

- City Councilwoman Madeline Provenzano



THE HON. JEFFREY KLEIN NEW YORK STATE SENATOR-ELECT



MICHAEL CARDOZO CORPORATION COUNSEL CITY OF NEW YORK

"This is a great day for the Morris Park community and a great day for the Bronx. Einstein is a world-class health institution that provides the kind of services to our citizens that can't be duplicated. I look forward to many, many more groundbreakings with Einstein because what's good for Einstein is good for the Bronx."

-State Senator-Elect Jeff Klein

"This city is known for a lot of things. It's known for dreamers, it's known for doers, it's known for people with extraordinary imagination. It's known for outstanding research. Today what we're celebrating is the success of the dreamer, the doer, the researcher, as well as the cooperation of the public/ private partnership that brought us to this moment." -Michael Cardozo

Corporation Counsel City of New York

"The Bronx is in a period of revival that is really unprecedented, and this day is emblematic of where we are and where we are going. This new building will accrue to the benefit of all Bronxites, all New Yorkers, all Americans, and, indeed, all of humanity." -Bronx Borough President

Adolfo Carrion, Jr.

MURIEL BLOCK, (C) WITH HER GRANDSON (L) AND IRVING BAUMRIND



THE HON. ADOLFO CARRIÓN, BRONX BOROUGH PRESIDENT



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Michael - Cinstein	Con comonies o
Harold F. Price C.	College of M
and Muriel	nter for Generatione of the
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M.D., Ph.D.

12:30 P.M.

4:15 P.M. Closing Reception

MICHAEL F. PRICE



"I believe that whatever we do, we're going to succeed. And there is no better place to do it than here in New York, in the Bronx."











(FROM L): MURIEL BLOCK, PENNY PURPURA, DR. DEBBY KLIEGLER, AND ABBY BELKIN



THE STAGE WAS SET FOR A PERFECT DAY.



LAWRENCE STURMAN, M.D., PH.D. DIRECTOR, WADSWORTH CENTER NEW YORK STATE DEPT. OF HEALTH



LEFT TO RIGHT: TOM PAYETTE, SAMUEL WEINBERG, AND DAN TISHMAN



Spelunking the Nano Caves Caveolae give up their secrets

he trend in biomedicine today is decidedly towards "disease focused" research. Just consider the centers here at Einstein devoted to cancer, AIDS, diabetes, liver disease, and sickle cell anemia. Not surprisingly, such research breeds specialization: an AIDS researcher won't generally dabble in diabetes, and the findings of a colon-cancer researcher are unlikely to turn up in a rheumatology journal.

All of which makes Dr. Michael Lisanti, professor of molecular pharmacology, a Renaissance researcher. In a recent sevenmonth period, he published articles on skin cancer, angiogenesis, embryogenesis, bladder cancer, cardiomyopathy, atherosclerosis, diabetes, muscular dystrophy, life span and cell signaling.

"I've always been interested in diverse issues of basic biology and in investigating the causes of human disease," says Lisanti. "But all our work ultimately has one central theme-the caveolae."

Caveolae are tiny (50-100 nanometers in diameter) flaskshaped infoldings that pock, or dimple, the surface of most cells but are especially abundant in fat cells, endothelial cells and

muscle cells. Nobelist George Palade first described these structures in 1953, based on electron micrographs of endothelial

cells. Two years later, Japanese electron microscopist Eichi Yamada dubbed them caveolae (Latin for "small caves"). Only in the past few years, however, have researchers made strides in understanding their structure and myriad functions. Lisanti has been a leader in those efforts.

THE CAVEOLAE IMAGES ON THIS PAGE WERE ADAPTED FROM OUICK-FREEZE. DEEP-ETCH IMAGES OF CAVEOLAE PROVIDED BY DR. IOHN HEUSER OF WASHINGTON UNIVERSITY IN ST. LOUIS.



 \mathbf{T} n 1992, while working as a research fellow at the Whitehead Institute for Biomedical Research in Cambridge, Lisanti isolated caveolae from the surface of cells-the key breakthrough in showing that caveolae were indeed unique cellular organelles. Looking for the proteins that give caveolae their structure, he and his colleagues found three-identified as caveolins 1, 2 and 3–and then established that the caveolin proteins "build" caveolae through oligimerization. i.e., the combination of caveolin proteins with each other to form the caveolar structure.

"Our research showed that it was possible to make an organelle with a single protein by overexpressing it," notes Lisanti. The three genes that code for the caveolin proteins are Cav-1, Cav-2 and Cav-3. These Cav genes are referred to as a gene "family' and, in the mouse, are all located on the same chromosome (chromosome 6). Lisanti's group at the Whitehead Institute was the first to clone Cav-1 in mice and to clone Cav-2 and Cav-3 in rats and humans.

Based on the shape of caveolae and their abundance in endothelial cells, Palade speculated more than 50 years ago that caveolae were involved in endocytosis, the transport of extracellular proteins into the cell-a role confirmed by later studies. But more surprising functions awaited discovery. While analyzing his newly isolated caveolae in 1993, Lisanti found not only caveolins but also numerous proteins known

caveolae as "signaling organelles"

or "signalosomes" that selectively

recruit and sequester signaling

molecules. Indeed, the caveolar

concentrations of some of these

molecules were many-fold higher

than their levels in other portions

In their "caveolae signaling

hypothesis," Lisanti and his

colleagues proposed that

signaling proteins within

caveolae confers clear bene-

fits to cells: It allows cells to

regulate signaling events by

bringing interacting molecules

close to each other and also facili-

compartmentalizing

of the plasma membrane.



metastasis.

atherosclerosis.

tates "cross-talk" among different signaling pathways. According to this hypothesis, the caveolins function as the scaffolding proteins that "build" caveolae and also help to organize and concentrate specific signaling molecules within these organelles. A wide array of signaling proteins are now known to preferentially localize to the caveolae, including G-proteins, H-Ras, Src family tyrosine kinases, PKC isoforms, EGF-R, Neu and endothelial nitric oxide synthase.

isanti's research has focused primarily on caveolin-1, the most plentiful and widespread of the three caveolin proteins and arguably the most important. His work has provided the best evidence to date that caveolin-1 functions as a tumor suppressor in mammalian cells. "One of our observations at the Whitehead Institute, in a collaborative effort with Dr. David Baltimore, was that caveolin-1 is downregulated in cancer cells-it disappears in transformed cells and so do the caveolae," says Lisanti. "We thought this might be related to the fact that caveolin-1 is both an inhibitor of signal transduction and a negative regulator of cell proliferation." Conversely, the protein may also help to nourish tumors: Lisanti recently presented the first in vivo evidence that caveolin-1 and caveolae help to support the pathological angiogenesis needed for both tumor growth and

Since coming to Einstein in 1997, Lisanti and his colleagues have worked with associate professor of biology Winfried Edelmann to create numerous caveolin-gene knockout mice to determine the function of caveolins in various tissues and organs. Research on these knockouts has established caveolin-1's importance in a wide variety of physiological processesnot only cancer and angiogenesis but also diabetes, cardiomyopathy and lifespan. And in a study published last January, Lisanti showed that deleting caveolin-1 could be a new strategy for preventing

"The standard theory attributes atherosclerosis to some sort of mysterious injury to the endothelial cells lining the coronary arteries, which allows lipoproteins to get underneath these cells," says Lisanti. "But a less popular theory posits that atherosclerosis results from caveolar transcytosis, meaning that caveolae in endothelial cells act as "shuttle buses" that move atherogenic lipoproteins out of the bloodstream, across the cell and into the subendothelial space, where they build up and eventually obliterate the vessel's lumen." The endothelial cells are certainly rich in caveolae: Each has between 5,000 and 10,000 of them, with

because it lacks both copies of the apolipoprotein E gene. (This latter knockout, known as ApoE-/-, has an abnormally high plasma cholesterol level and is the "gold standard" in studies of atherosclerosis and the genes implicated in causing it.)

The interbreeding yielded "double knockout" mice lacking both ApoE and caveolin-1. These double knockouts were compared with mice from a different interbreeding effort that were deficient in ApoE alone (ApoE-/-Cav-1+/+ mice). Both groups of atherosclerosis-susceptible mice were then fed a high-fat, high-cholesterol "Western" diet. After five months,



LOST CAVEOLAE MEANS CLEAN ARTERIES: ApoE (-/-) knockout mice (which spontaneously develop atherosclerosis) were bred with knockout mice devoid of caveolin-1 to yield "double knockout" mice lacking both ApoE and caveolin-I. The double knockouts were put on a high-fat, high-cholesterol "Western" diet along with mice deficient in Apo E but possessing caveolin-I. After five months, the aortas in the double-knockout mice (upper picture) had 70 to 80 percent less plaque than mice possessing caveolin-I (lower picture). (Photos courtesy of Phillipe Frank)

adipocytes (fat cells) the only cell type containing more.

"So we were interested in seeing if mice could be made resistant to atherosclerosis if they didn't have caveolae," Lisanti continued. "Phillipe Frank, an instructor in my lab, worked at the Ottawa Heart Institute before coming here and was very interested in doing this experiment. But first we needed a mouse model that lacked caveolin-1." So Lisanti, Frank and their colleagues developed a caveolin-1-knockout mouse (Cav-1-/-), which was devoid of caveolae. They bred this mouse with a knockout mouse that spontaneously develops atherosclerosis

blood levels of cholesterol and triglycerides were measured in the mice, and their aortic arteries were assessed for plaque deposits indicating atherosclerosis.

Based on blood lipids alone, things didn't look good for the mice lacking caveolin-1: Compared with their brethren who had the protein, the caveolin-1-deficient mice had dramatically elevated levels of cholesterol and triglycerides. Yet despite their unfavorable lipid status, these caveolin-1-deficient mice had much healthier arteries than their counterparts. In fact, the mice lacking caveolin-1 had a startling 70 to 80 percent reduction in atherosclerotic plaque area compared with mice possessing caveolin-1.

How does a lack of caveolin-1 protect arteries from atherosclerosis? Probably by preventing endothelial cells from swallowing up lipoproteins from the blood stream. "Caveolin-1 appears necessary for the normal functioning of CD36, a cell-surface "scavenger" receptor that pulls "bad" LDL cholesterol into endothelial cells," says Lisanti. "With caveolin-1 absent, we found that the presence of CD36 on cell surfaces was reduced by 85 to 95 percent."

These results provide strong evidence in support of the caveolar transcytosis theory of atherosclerosis. They also suggest a radically new strategy for preventing or treating the disease: target drugs to the coronary endothelium, where they would prevent plaque buildup by inhibiting the formation of caveolin-1. "This approach would basically nullify the effect of cholesterol as a cause of atherosclerosis," says Lisanti. "So you could continue to eat a high-fat McDonald's diet and just take a pill to inhibit caveolae formation."

n addition to his research with caveolin-1, Lisanti's has also L done important work on the caveolin-3 protein, which is found only in muscle cells. And for a selfprofessed "mouse genetics guy," this work is taking him down an unlikely path: towards a possible treatment for muscular dystrophy. Collaborating with Italian researchers in the late 1990's, Lisanti identified two different Italian families with a form of limbgirdle muscular dystrophy caused by Cav-3 mutations. These cases revealed a novel mechanism for transmitting the disease.

Most loss-of-function congenital disorders-including most cases of limb-girdle muscular dystrophyare autosomal recessive: The child inherits a mutated gene from both parents, neither of whom has the disease. But limb-girdle muscular dystrophy in these families was autosomal dominant: Just one mutated allele was sufficient to cause disease. Such a "dominant negative" inheritance produces a protein that is structurally similar to the wild-type protein and able to competitively inhibit normal protein function.

continued on next page

The expression of the wild-type caveolin-3 protein in these patients was reduced by 95 percent, and tissue-culture studies soon showed why: mutated caveolin-3 protein was oligimerizing with wild-type caveolin-3 protein during caveolar biosynthesis to form unstable aggregates that were degraded before reaching striated musclecell membranes, where they would normally localize.

Since the absence of caveolae is the direct cause of this form of limb-girdle muscular dystrophy, it would be useful to know what was degrading their protein components. Prime suspect were proteasomes, enzyme-rich organelles found in large numbers in the cytoplasm and nucleus of all plant and animal cells.

noteasomes perform an important quality-control function in the cell: They digest damaged intracellular proteins and recycle their constituent amino acids. Defective proteins are first ubiquitylatedmarked for degradation by being tagged with the protein ubiquitin-and then digested by proteasomes. Proteasomes received publicity last Fall when three scientists were awarded the 2004 Nobel prize in chemistry for revealing the mechanism by which ubiquitin marks proteins for proteosomal destruction.

Lisanti realized that if proteasomes were destroying the wild type/mutant caveolin-3 complexes, one way to find out would be to administer a proteasome inhibitor to caveolin-3 mutant cells and see what happens.

Researchers have found a number of natural and synthetic drugs that can inhibit proteasome activity. Several have shown promise in combating cancer, apparently by stabilizing short-lived proteins that inhibit the cell cycle, resulting in cell-cycle arrest and apoptosis. The proteasome inhibitor Velcade was approved in 2003 by the Food and Drug Administration for treating multiple myeloma.

In a paper published in 2000 in the Journal of Biological Chemistry, Dr. Lisanti showed that defective caveolin-3 proteins did undergo ubiquitination/proteasomal degradation, since treatment with any one of four different proteasomal inhibitors prevented their destruction. Perhaps even more important: In cells expressing both wild-type and mutant forms of caveolin-3, one proteasome inhibitor in particular-MG-132-"rescued" the wild-type caveolin-3 so that it was able to reach the plasma membrane.

Proteasome inhibition, therefore, could potentially help those rare patients with limb-girdle muscular dystrophy caused by Cav-3 mutations. But to Dr. Lisanti, these results also suggested something even more important: a new way to

THREE-DIMENSIONAL RENDERING OF A "MOLECULAR MACHINE": Proteasomes are found in the cells of all forms of life, where they digest misfolded or damaged proteins. The proteasome consists of a cylindrical core composed of four stacked rings, each of which contains seven proteins. On each end of the proteasome's core is a regulatory protein "cap" responsible for recognizing proteins tagged by ubiquitin and fated for destruction. In a process requiring energy (ATP), tagged proteins are first unfolded and then fed into the proteasome's core. There the proteins are digested by several active sites on the inner surface of the core's two middle rings, producing peptides averaging eight amino acids in length that can then be recycled.

(Illustration:Tatyana Harris)

treat Duchenne muscular dystrophy, the most common form of the disease and one of the most prevalent of all severe inherited childhood diseases, affecting one of every 3,500 children.

s with limb-girdle muscular dystrophy caused by Cav-3 **L** mutations, the Duchenne variety also involves a single defective protein-dystrophin-which fails to insert into the membranes of muscle cells, causing muscle fibers to atrophy. "I started to think that if dystrophin is degraded similarly to what we observed with limb-girdle muscular dystrophy's caveolin-3, then perhaps we could apply the same proteasomeinhibition approach to Duchenne," Lisanti recalls. "Surprisingly, nobody had looked at proteasomal degradation of dystrophin as a possible cause of the atrophy in Duchenne muscular dystrophy. So there was very little information in the literature on the fate of these proteins, and most of the existing data was very poor or inconclusive.'

To learn whether proteasome inhibitors could help against Duchenne muscular dystrophy, Lisanti tested the proteasome inhibitor MG-132 on the mdx mouse, the standard mouse model for studying the disease. The mdx mouse results from a naturally occurring premature stop

codon mutation that causes a highly truncated version of the dystrophin protein to be formed.

The researchers first administered MG-132 locally, injecting it into the mdx mouse hind limb along with India ink to visualize the injection area: the muscle from the other hind limb of each animal served as an internal control. Twenty four hours later, the muscle was isolated for further study. Frozen tissue sections were immunostained, using antibodies directed against dystrophin, and were then examined by immunofluorescence.

As expected, dystrophin was absent in skeletal muscle from untreated mdx muscles. But results for treated muscles showed that the proteasome inhibitor "rescued" the expression level of dystrophin (which would normally be degraded) and enabled it to localize in cell membranes. Results were confirmed using Western blot analysis, which showed a strong dystrophin protein band in gels from treated muscles and no dystrophin band from untreated muscle.

To see if MG-132 would work systemically, the researchers filled osmotic pumps with MG-132, implanted the pumps beneath the

Surprisingly, nobody had looked at proteasomal degradation of dystrophin as a possible cause of the atrophy in Duchenne muscular dystrophy...

skin of mdx mice and allowed the drug to diffuse at a constant rate for eight days. Vital staining of diaphragm and hind limb muscle using Evans blue dye showed no muscle-fiber damage in mice receiving MG-132 compared with significant muscle damage seen in control mdx mice.

The results, published in October 2003 in the American *Journal of Pathology*, showed that both local and systemic administration of MG-132 prevented dystrophin from being degraded. The rescued dystrophin protein-despite being in truncated form– was able to reach the cell membranes of skeletal muscles and greatly enhance muscle quality.

"We were very shocked and surprised that this simple approach actually worked," says Lisanti. "People had been looking for a pharmacological treatment for Duchenne muscular dystrophy for a very long time." Next up: studies with mdx mice to see if proteasome inhibitors improve muscle function and, eventually, clinical trials to assess the effects of proteasome inhibitors on muscular dystrophy patients.





the controversy.

cantly to our understanding of the

Neither a "Tauist" nor "Baptist" Be Alzheimer's Researcher Peter Davies Just Follows the Science

What causes Alzheimer's disease? The question has triggered one of medicine's most heated controversies, arousing deep antagonisms in the Alzheimer's research community and prompting growing media attention: *"Fevered Debate Over Alzheimer's* Origins Causes Deep Division," proclaimed a Wall Street Journal headline in early August. Sitting somewhat uneasily in the eye of this media storm is Einstein's Peter Davies. Resnick professor of Alzheimer's disease research, who was quoted in this and most other press reports on

The debate centers on whether Alzheimer's is caused by "plaques," made of the protein beta amyloid, that accumulate around nerve cells in the brain, or whether the real culprit is a protein called tau, which forms "neurofibrillary tangles" within nerve cells. Believers in beta amyloid protein are referred to as "baptists," while tau's proponents are, understandably, known as "tauists". In the midst of a battle rife with religious overtones and marked by near-religious fervor, Dr. Davies can best be described as an agnostic. "As Time Magazine quoted me," says Peter, "'I'm not a baptist or a tauist-I'm a Roman Catholic." Davies ranks as one of the nation's most distinguished Alzheimer's experts. Discoveries he has made during his 27 years at Einstein have added signifi-

disease. Recently, the editors of EINSTEIN sat down with him to discuss not only the cause of Alzheimer's but also to talk about more basic issues-such as how this Welshman from the town of Tredegar ended up in the Bronx in the first place.

You are one of Einstein's most illustrious researchers-a senior scientist and recipient of two MERIT awards from the National Institutes of Health. What induced you to leave Great Britain in 1977 and come here? At that time, Alzheimer's disease was a backwater in science. Very, very few people were studying it. There was only one truly outstanding research group in the world, and that was here at Einstein, headed by Bob Terry and Bob Katzman. I had written to Bob Terry in 1976 and described my research. He wrote back, and it was obvious that he saw the implications of my work even more clearly than I did. He said, 'Why don't you come and spend a year or two with us, and we'll see what we can arrange.' I remember thinking at the time that I needed to study under somebody like him-somebody who was really at the top of field. We hit it off from day one. It was a fantastic environment, with Terry and Katzman and also Leon Thal and Herman Buschke. A truly vibrant group.

So it was the group that put Alzheimer's on the map?

That's right, this place was truly the powerhouse in Alzheimer's disease. And the longer I was here, the more good people I found, including Bill Norton, Bob Levine, the Suzukis in the Kennedy Center. It was tremendous for a young scientist who'd been in this little British system to be working with these superb people.

Bob Terry is kind of a legend around here. How would you describe him? Terry (who left Einstein in 1983 for the University of California at San Diego and has since retired) was the most critical person I've ever met. He would question everything—an approach that some people interpreted as hostile but

that he never intended that way. 'Tell me what you mean. I don't understand what you're saying, I think that's wrong'—he would push you to explain what you really meant, to justify what you think. It was a wonderful environment for me to be in at that time.

Why have you stayed here? I've been around a lot of institutions in the 27 years I've been at Einstein, and I don't know of any place that can rival the academic and intellectual environment we have here—not in this country and not anyplace else in the world, that I know of. Here I can walk down the hall, talk to somebody who knows what they're talking about and they'll spend time with me telling me exactly what I need to know. My students do the same thing. That's just the way it works around here, and the surprise for me is that it doesn't work this way at other institutions, where people are too turf-conscious or perhaps paranoid about others stealing their ideas.

You've developed the first mouse model for Alzheimer's-an achievement that earned you your second MERIT award from the NIH. Did the NIH fund that research? Unfortunately, the NIH will not give you a grant to make a mouse model. Instead, you have to have made the model and then tell them what you're going to do with it once you've made it. So the NIH award came only after the nearly

two years it took to make the mouse model-work that had absolutely no NIH funding. Until the NIH grant actually materialized, the research relied entirely on income I received from Judy and Burt Resnick as the Resnick Professor of Alzheimer's Disease Research and from other supporters such as Einstein board member Fred Tepperman. I couldn't have done it without them.

Could you describe this animal model? To be accurate, this is not an animal model of Alzheimer's disease

but rather a model of tangle formation. As you know, the two hallmarks of Alzheimer's disease are the accumulation in the brain of neurofibrillary tangles and plaques made of the protein betaamyloid. You could call this a partial model of Alzheimer's disease, since there are tangles but no plaques.

How did this model come about? We were collaborating with Karen Duff of the Nathan Kline Institute, and Karen had made a transgenic mouse that possessed a single copy of the normal human tau gene along with the customary two mouse tau genes. Tau codes for the protein that ends up forming the tangles of Alzheimer's disease. Karen asked me to characterize these mice, to see if they developed any pathology. We spent two years, from 1998 to 2000, doing that and found no pathology– nothing. We were disappointed,



but we had seen hints that these mice were on the edge of pathology.

Meanwhile, Cathy Andorfer of my laboratory had attended a meeting where a Swiss scientist said he had knocked out both copies of the mouse tau gene. Cathy said, 'I want to cross his knockout mouse with our mouse containing both mouse and human tau genes so that we can breed a mouse containing only human tau. continued on page 16

A Meeting of Minds & Hearts Einstein and Israeli Researchers Share Science and Support

by Edward R. Burns, MD wo driving forces motivated 19 Einstein faculty to travel to Israel this past spring and meet up with a distinguished complement of investigators at the Weizmann Institute of Science in Rehovot. First was the natural tendency of scientists to share their knowledge and learn from distinguished colleagues. Second was the desire to show support for a beleaguered faculty who are being shunned on the world stage simply because they happen to be Israelis. In several well publicized cases and in many more secretive ones, the European community has virtually ostracized Israeli academicians for frankly political reasons. Einstein faculty wanted to show their colleagues in Israel that they are respected and admired for the people they are and the work they do.

The genesis for the idea came over a year ago when John Hardin, our former chairman of medicine, suggested that we invite some Weizmann scientists to New York. John is friendly with Dr. David Mirelman, the chair of biochemistry at Weizmann, and thought that the two institutions could find common ground for collaboration.

At an initial meeting, Dr. Purpura and Martin Kraar, Executive Vice President of the American Friends of the Weizmann Institute, agreed to share the expenses for the trip. The increased pressure of the intifada on civilian life in Israel put a damper on the idea, and concrete planning languished. Meanwhile, reports of academics refusing to visit Israeli universities or invite Israeli professors continued to punctuate the news.

About eight months ago Rob Singer, co-chairman of anatomy and structural biology, asked to become involved in the project. Concomitantly, because of other commitments, John Hardin asked Rob to take

Dr. Burns is Associate Dean for Academic Affairs.



his place. Rob and I began to work together and formed a small working group of AECOM scientists including David Shafritz, Robbie Burk and Irving Listowsky to revitalize our efforts. We compiled a description of the scientific work of the Weizmann faculty for biologic sciences and sent it to our investigative faculty. Some twenty P.I.'s responded with interest in meeting and potentially collaborating with specific Weizmann faculty.

With this major interest brewing, our working group made a major decision. Rather than inviting the Israelis to New York, we decided to make the trip ourselves to Rehovot.

We reasoned that the morale of the Israeli scientists was at an all-time low and that a visit by a contingent of American scientists would provide a major emotional boost. To our delight, 19 of the AECOM scientists who initially expressed interest agreed to go. We were off.

I credit Rob Singer with putting together a spectacular scientific program. Through intensive discussions with senior Weizmann faculty, Rob and his Israeli colleagues paired talks on complementary topics, scheduling AECOM and Weizmann investigators back to back on such topics as angiogenesis, tumor metastases, cell adhesion and signaling, genomics, tumor suppression, stem cells and neurologic diseases.

e left en masse from Kennedy Airport on May 7th and arrived the next day. Our group comprised Steven Almo, Gary Bassell, Felix Bukauskaus, Robbie Burk, Winfried Edelmann, Marshall Horwitz, Susan Horwitz, David Lawrence, Irving Listowsky, Phillip Scherer, Nicole Schreiber-Agus, Jeff Segall, Yoran Shav-Tal, David Shafritz, Dennis Shields, Bruce Terman, Jon Warner, Rob and me. The Weizmann people arranged a bus to pick us up from Ben Gurion airport. About half of our group had never been to Israel and a quarter were not Jewish. Expectations of such a group naturally mirrored the view of nightly television news, namely that the country would be in turmoil with soldiers and barbed wire everywhere. We were in for a pleasant surprise. After a short ride from the airport, we entered the oasis, 14 miles south of Tel Aviv, that is the Weizmann Institute of Science. The campus is extraordinary in its size, beauty and diversity of architectural styles. Thousands of species of

Einstein faculty wanted to show their colleagues in Israel that they are respected and admired for the people they are and the work they do.

flora festoon and blanket hundreds of acres of lush green land. Rather than a war zone, we seemed to have entered paradise. The Weizmann organizers (including Avri Ben-Zeev, Benny Geiger, and Varda Rotter) had arranged for us to lodge and dine at the hotel on campus. Our first evening of meet and greet was a pleasure.

On Monday morning the scientific program began in earnest. Dr. Ilan Chet, President of the Weizmann Institute, greeted the group and profusely thanked us for coming. He stated that Einstein's was the largest contingent of scientists to visit in more than five years and that our efforts had gone a long way to disperse the cloud of pariahdom that has hung over their faculty.

Representing AECOM, I then presented an overview of Einstein's history and described in detail our

faculty, students and facilities. But the clear highlight, as well as the objective of the day, was the science. And great science came next. Nine exciting talks were presented that day and attended by Weizmann faculty, graduate students and post-docs.

thousands of years.





Monday evening proved to be the social highlight of the trip. President and Mrs. Chet invited the entire Einstein contingent and the Weizmann organizing committee to their home for dinner. To the elegant strains of Carl Phillip Emmanuel Bach's Sonata for Harp performed by a student of the Conservatory of the Jerusalem Academy of Music and Dance, we dined in elegance in a classic home of Mid-Eastern style with terrazzo floors, shaded verandas and stunning collections of Israeli art. Professor Chet, a talented raconteur, regaled the group with vignettes of his meetings with famous scientists from around the world. We were also enthralled by his private collection of archeological artifacts from Mesopotamia, with some pieces dating back

A total of 36 scientific talks were presented over a four-day period, half by Einstein faculty and half by Weizmann's. I would estimate that more than 500 people attended the various talks, each of which generated intense discussion and excitement. The quality of the science on both sides was terrific. The Weizmann



people clearly have the resources and equipment to do first-rate innovative work that rivals any institution in the world. During the coffee breaks I noted the enthusiasm of our faculty as they plied their new Israeli colleagues with probing questions and suggestions for future work. Clearly, our objectives were achieved.

During the afternoon breaks, many of us took the time to tour the Weizmann campus. In addition to scores of modern sculptures and gardens, the campus boasts some 60 buildings including a few named by families familiar to Einstein. There is an Ullmann building for Biological Chemistry, a Lubin building that houses food services, and a brand new Belfer Building for Molecular Genetics. Several of us toured Chaim Weizmann's house.

r. Chaim Weizmann was a distinguished chemist who became Israel's first President. An ardent young Zionist, he was instrumental in obtaining the Balfour Declaration from the British government in 1917, which recognized the right of the Jewish people to establish a national home in the land of Israel. In 1934 he established the research institute in Rehovot that now bears his name and served as its first President. The Weizmann house was built in 1936 by Erich Mendelsohn, the famous German architect and master of the International Style. The house is magnificent in its simplicity. The library contains numerous signed photos of Weizmann with world figures such as Albert Einstein, Winston Churchill, Franklin Delano Roosevelt and Harry Truman. In the garden we found a magnificent 1950 vintage Royal Lincoln Cosmopolitan car, one of 18 in the world, presented to Weizmann that year by Henry Ford II in honor of Israel's independence two years earlier. The experience was a window into some remarkable history.

While all of the heavy-duty science exposition was taking place, I arranged for several of our faculty who had never been to Israel to take a short tour of Jerusalem. Jon Warner, Phil Scherer, Winfried



Edelmann and Felix Bukauskas stole away for a few hours of living history. They toured the old city of Jerusalem including the Moslem, Christian, Armenian and Jewish guarters. They visited the church of the Holy Sepulcher, the Via Dolorosa, the Dome of the Rock and the Western Wall. On their return to Weizmann they were filled with the wonder and appreciation of having seen historically meaningful places they had heard about all of their lives.

Our visit wrapped up on Thursday afternoon. Emotional farewells and promises of "we'll work together on projects" punctuated loads of hugs and hand shakes. Together with Rob and the Israeli organizing committee, I wrote a mission statement that promised that Einstein and Weizmann would work together collaboratively and exchange scientists, graduate students and post-docs. The statement was presented to President Chet, and I brought back copies for Dean Purpura and President Richard Joel. President Chet asked me to extend his personal invitations to the Dean and the President to visit him at the Institute.

s our return flight was A not until 1:00 am, the whole group had a few hours to grab some sightseeing. We sped off to Jerusalem to visit the Western Wall and the Valley of the Communities. This mammoth 2.5 acre holocaust memorial was dug out of bed rock and contains 107 walls towering 30 feet each. On these walls are carved the names of more than 5,000 Jewish communities that existed in Europe before World War II and were destroyed by the Nazis. As we walked through the labyrinth of cavernous rock, 30 feet below ground, we were awed into silence. The emotional impact of seeing the names of so many well-known cities, representing over a thousand years of Jewish communal life, was sobering. At the Western wall, we saw several hundred soldiers being initiated into the Israeli army. These frightfully young men and women each spent a few moments of prayer at the wall, pledging to serve their country honorably and in a manner consistent with the humane traditions of their people. It was especially touching as virtuallynone of these teenagers was particularly religious. They did, continued on page 20

The Innovation Laboratory Unlocking the Secrets of Cells

arlier this year, the National Institutes of Health released a ranking showing that Einstein's Department of Anatomy and Structural Biology was awarded more NIH funding than any other anatomy/cell biology department in the nation for FY2002–a total of \$19,028,666. (Second-place Harvard Medical School received about one million dollars less.) The co-chairs of anatomy and structural biology–Drs. John Condeelis and Robert Singer–credit a change in research emphasis as a major reason for their department's success in attracting grants.

"We decided to focus the department's research on two areas: the imaging of single cells and single molecules as they relate to cancer as well as the basic biological processes that operate at the level of single molecules," says Condeelis. "I think this is really what accounts for the big increase in our funding. And while our number one ranking is for FY2002, in FY2003 we actually received a significant increase over FY2002. So we expect that we'll hold on to our number one ranking for awhile."

ccompanying this new focus in the department is a strong desire for technological innovation. "John and I share this vision of developing new technology through pushing the envelope in microscopy and using it to see things we've never been able to see before, particularly in living tissues in animals," says Singer. "Our emphasis is on looking at things in the living world, because most everything that's been done in biology up until now has been done on dead things, which don't always provide reliable information.



Cutting-edge research is not only "new and exciting," Singer notes, but also provides access to new funding initiatives at the NIH: "The agency has been issuing research proposals for new, innovative technology development, and we've been applying for and receiving them. These are large, bigbudget grants, and I think that's

what has pushed us over the top." One of the department's recent breakthroughs is a light-microscope technology that reveals the geneexpression profile of a single cell–a development that could help alter the way biologists carry out genetic profiling.

"Basic medical science has traditionally looked at a whole organ system or a whole tissue," says Condeelis. "This involves grinding up the tissue and then obtaining a gene-expression pattern that essentially averages the behavior of the many different cells in that tissue.

But now there's a real revolution in biology where it's possible to use the light microscope to look at actual biochemical and geneexpression pathways inside single cells rather than settling for tissue averages."

This work, says Condeelis, has already led to the realization that organ systems are not homogeneous structures—and that research that assumes tissue homogeneity can lead to extremely misleading results.

"You're no doubt familiar with microarrays, the "chips" that provide a tissue's genetic fingerprint by quantifying the expression of thousands of genes," says Condeelis. "Microarrays are powerful, but it's now clear that when you look at a microarray of a whole tumor, you're really getting just a crude averaging of the tumor's

genetic behavior. We now know that a single tumor is extremely diverse genetically, containing many different cell populations with completely different functions. To find differences among tumors that are useful therapeutically, you really have to look at individual cells."

Representation of the second s the "personalized medicine" that will soon be the way that major diseases are treated.

"Now, for example, we can go back and look at colon-cancer patients who responded or didn't respond to a particular drug," he says. "Focusing on individual tumor cells, we can look at both groups of patients and ask, 'What genes were they expressing after they got the drug?' We can then use this information as a predictive



marker to say, 'These patients won't respond to chemotherapy but should get radiation instead." Arguably the most important of all tumor cells are the tiny sub-population of cells that migrate from the primary tumor and metastasize to other parts of the body. In a major advance, researchers in Einstein's Department of Anatomy and Structural Biology have devised a light-microscope technology that isolates and captures these invasive cells. Tumor cells are made to express green fluorescent protein, allowing researchers to readily spot those cells that are moving. Then, making use of chemotaxis (the process by which cells follow a chemical gradient), the researchers collect these cells in an artificial blood vessel that they insert into the tumor. "If you go the traditional route and grind up the tissue, you'll never see these motile cells because they comprise less than one percent of the total cells in the tumor," says Condeelis. "But isolating these cells and looking at their gene expression tells you why that tumor is special and is different from someone else's tumor."

he department's aim, says Singer, is to make Einstein's imaging center "the most advanced in the country." To achieve that goal, the researchers will be relying heavily on their Innovation Laboratory, created last year and currently housed in the Forchheimer basement. It will be the department's core facility, the place where current and future investigators-scientists, engineers



EINSTEIN'S DEPARTMENT OF ANATOMY AND STRUCTURAL BIOLOGY uses fluorescent nucleic acid probes to reveal the gene expression patterns of individual cells. Figures I (left) and 2 (right) show the transcription sites for two genes specific for prostate tissue, Androgen Receptor (AR) and Jagged 1 (JAG1). In Figure 1, AR appears light blue, Jag1 appears orange, and nuclei are stained pinkish white. In Figure 2, the data shown in Figure have been analyzed using software that automatically detects the AR and JAG1 transcription sites and then labels each of those sites with the appropriately colored square. The nuclei in Figure 2 are stained blue. (Images courtesy of Dr. Robert Singer and Shailesh Shenoy)

and software writers-will develop the microscope technologies of the future.

"By allowing us to ask questions about single cells and single molecules and genes within those cells, microscopes are expanding our vision of organ systems, tissues and

Arguably the most important of all tumor cells are the tiny sub-population of cells that migrate from the primary tumor and metastasize to other parts of the body. In a major advance, researchers in Einstein's Department of Anatomy and Structural Biology have devised a lightmicroscope technology that isolates and captures these invasive cells.

the diseases that affect them," says Condeelis. "The Innovation Laboratory is all about pushing this effort to the next level. We figure out what we need to do in order to advance our research, and then we invent the technologies that will help us achieve those aims."

Then the Price Center is completed, the Innovation Laboratory will be teamed with the department's Analytical Imaging Facility (containing microscopes already developed and being used in research) to comprise the tentatively titled Biophotonics Center, which will occupy an entire floor of the new building.

"Two years from now," says Condeelis, "our whole department could be using a breakthrough technology that hasn't even been invented yet. That's the beauty of an Innovation Laboratory, that it can lead to developments that can't possibly be predicted."

> THIS MICROSCOPE IMAGE OF BREAST CANCER in a mouse shows cancer cells (in green) that have migrated from the tumor. The arrow shows some of these cancer cells attaching to and crawling along extracellular matrix fibers (in purple).

Neither a "Tauist" nor "Baptist" Be ontinued from bage 1

So we got the mice from Switzerland and mated them with our miceand then endured a terribly slow and frustrating period during which the mice just would not interbreed. But finally it worked and we got mice with just the human tau gene.

When the mice were about four months old, Cathy took the first look at their brains and said, 'These mice definitely have pathology.' After we had followed several mice up to one year of age and saw a progression in pathology, I knew we had enough data to write the grant to the NIH.

It's amazing when you think about it: Our hTau mouse model, with just the one human tau gene, develops pathology—and yet the mouse with three tau genes does not.

Since your tau mouse model produces only tangles, are you trying to get plaques in there too?

No, I don't care to do that at this point. I actually have done that with a collaborator–using genetic manipulation to make a mouse with plaques and a mouse with tangles and then mating them and ending up with progeny that have both plaques and tangles. But these mice don't get plaques and tangles the way a patient with Alzheimer's does. Instead, you have two artificial pathologies that are present for unrelated reasons.

I wanted a marker for the disease process, and tau is fantastic for that. One of the first things you see in the brain of a patient with early Alzheimer's disease are abnormalities of tau, which progress to tangle formation. These abnormalities tell you right away that the disease pathway has begun. Are tau abnormalities necessary for causing the disease? I don't know, but I think they are. Some of the recent data in mice strongly suggest that the abnormalities resulting in tangle formation may kill brain cells or at least cause severe dysfunction.

Our model is probably the best tangle model available right now. But is it perfect? No. As yet there is no true animal model of Alzheimer's.

What's happening in the search for Alzheimer's treatments? The bulk of the money in Alzheimer's research has pursued the amyloid hypothesis—the notion

that formation of amyloid plaque causes all the rest of the problems in Alzheimer's. As a result, we now have a good understanding of how plaque forms. Many pharmaceutical companies have already developed compounds that will prevent amyloid formation. They've done the toxicological testing, and the drugs look very safe. One company, Neurochem, announced in June that it would start recruiting patients to test the effectiveness of such a drug. But the other companies are sitting on the sidelinesfor two reasons. Testing such a drug on Alzheimer's patients would be very, very expensive-somewhere around \$200 million. And it's still unclear whether amyloid formation is the real key to this disease. I don't think it is. Rather, I think it's a downstream event, and the critical

Alzheimer's research is clearly a polarized field, divided between the "tauists" and the "baptists". Is it accurate to call you a committed taoist? We've done a lot of work on tau and tangle formation so people think we're tauists, but we're really not. This polarization between tangle and plaque proponents is really shortsighted and destructive, because you cannot have Alzheimer's disease without having both. We have to remember that our goal is to understand Alzheimer's disease, which means finding how both pathologies result from some basic insult.

abnormalities are really upstream

of amyloid production.

Are there any signs of détente? Things are slowly getting better. Four or five years ago, when I would stand up at meetings and suggest that the amyloid hypothesis was wrong, I would be attacked like crazy. Now when I say that, they'll argue with me but with not nearly the same vehemence. Also, a lot of the amyloid people have started doing some small projects on tau, and vice versa. And my lab is actively exploring how a single pathway in the brain might give rise to both plaques and tangles. If I knew what that pathway was, perhaps I could trigger it in the mouse and then get both plaques and tangles from a single manipulation.

Could you describe this research effort? There's an enzyme that we think might be important in a pathway

that may generate both pathologies. I have a student who has cloned the gene that codes for this enzyme, and we're exploring in cell culture and in the brain what this enzyme does

Is a single pathway for causing Alzheimer's really essential? In coronary heart disease, for example, you've got several mechanisms-hypertension, elevated blood cholesterol, cigarette smoking-that are all implicated in causing plague buildup in the arteries. You're absolutely correct—there is almost certainly more than one pathway in Alzheimer's. But here's the way I look at it: About twothirds of Alzheimer's patients clearly have the same disease– a single disease entity. These are the cases I'm interested in. For these people, I can look at a single section of the brain and, based on that one section, I can correctly predict what the entire rest of the brain will look like. In my view, the same biochemical pathway is involved in these 'classic,' simple Alzheimer's cases. Now, there are probably multiple reasons why the pathway got going, but I don't really care about them at this point. I want to define this pathway in a very, very predictable way so that once it's turned on, we know exactly what is going to happen to the brain: where the plaques will be, where the tangles will be, where in the brain the cells will die, which cells are going to be affected.

Are you involved in efforts to produce an Alzheimer's vaccine? Only in the sense that I've said on numerous occasions that this is a very bad idea. Stimulating antibodies against amyloid protein is a great piece of science to do in mice but a bad idea for humans for the reason we now all recognize: You run the risk of provoking an autoimmune response in the brain.

A vaccine trial was halted in 2003 because it caused severe inflammation in the brains of several participants. In the one patient where we know the details, a woman with fairly mild Alzheimer's was given her third injection and within a week had become bedridden and reduced to a vegetative state: she died in that state 10 months later. Yet I've heard researchers involved with this study say publicly, 'Oh, yes, some patients developed a mild encephalitis that

resolved after a few weeks'– well [expletive deleted]! This lady appeared to die from the vaccine, and we still don't know exactly how many other patients were harmed.

In the late 1970's you hypothesized that the symptoms of Alzheimer's result from a deficiency in the neurotransmitter acetylcholine and that this deficiency should be correctable with drugs that inhibit cholinesterase, the enzyme that breaks down acetylcholine in brain synapses. How do you view your "cholinergic hypothesis" in hindsight? I'm perfectly comfortable with the idea that it was a reasonable hypothesis to propose based on what we knew then. But it was wrong-or, perhaps, a little right and a lot wrong—which is okay. That's the scientific method: You put up the best hypothesis you can, and then you look for the holes in it. On the plus side, it stimulated a tremendous amount of work in the field and led to the four cholinesterase-inhibitor drugs including Aricept and Reminyl, that have been approved in the past few years for treating Alzheimer's symptoms.

Treating the acetylcholine deficit with these drugs helps a little bit you get some improved quality of life-but it doesn't affect the ongoing disease process. The deficit is too much of a downstream consequence of the real problem that remains to be discovered. I want to find the upstream pathway responsible for the acetylcholine deficit so that we can intervene as high up as possible and stop the disease process. That's the only thing that will make a difference. The disease progression is what destroys patients and, all too often, destroys families too.



the 'why'."

was very determined."

The Return of the Prominent Son Ron DePinho, M.D., Class of '81

he very same year that the Albert Einstein College of Medicine opened its doors to its first class of medical students. Celeste and Alvaro DePinho welcomed the arrival of their first son and third child, whom they named Ronald. Young Ronald DePinho (Class of '81) grew up in the Bronx and Yonkers, attending Mount St. Michael's High School and Fordham University.

At Mount St. Michael's, he developed a love of and fascination with biology. The subject would become his major at Fordham, and it remains the foundation for his research interests today. "When I was in high school," DePinho remembers, "my exposure to biological sciences fueled a deep desire to understand the inner workings of complex biological systems. This orientation towards mechanistic, as opposed to descriptive, science continued into my medical training during which time my thoughts in patient care were often dominated by an interest in understanding the basis for the affliction. I wanted to know

DePinho graduated Salutatorian and Summa Cum Laude from Fordham in 1977 and then ventured several miles east to attend Einstein. His medical education thrilled his parents, who had limited education. "My dad believed there was no higher calling than becoming a physician and taking care of people," says DePinho. "When he was 17, his family, which was poor and starving in fascist Portugal, sent him to Brazil so that he could earn money to send home. Even though he knew no one, he had a restaurant and an ice business by the time he was 21. He had a high degree of innate intelligence and

The senior DePinho eventually stowed away on a ship out of Rio that was bound for New York, hiding in a cargo box for 13 days. Although he almost died by the voyage's end, Alvaro DePinho

regained his health and found work as a laborer, working in construction. Believing in this country's ideals, he volunteered for World War II and returned as a US citizen and decorated veteran. He continued to learn many aspects of the construction

industry. Ultimately, his accumulated knowledge and determination led him to establish his own company.

"My dad's company participated significantly in the rebuilding of Stamford and Greenwich, Connecticut," DePinho notes with pride. "But his greatest focus, and that of my mom's, was insuring that his children secured a firstrate education."

While DePinho chose to attend Einstein, it was not because of its proximity to home. "I came to Einstein because I admired the tremendous tradition of excellence the school had, particularly in the neurosciences," he says. "I also liked the fact that Einstein celebrated the individual, accepting people who were a little out of the mainstream and who were not

During his first year, DePinho founded the school's Tae Kwon Do Club, which, he proudly notes, continues to meet. He was introduced to the martial arts discipline during high school and credits it with instilling a philosophy of discipline, respect and courtesy that still guides him today.

These core attributes of martial arts still influence him. And they also are reflected in the individuals he credits with helping to shape and guide his career as a scientist: Dean Purpura; Dr. Frederick Alt, professor of bio-chemistry at



afraid to think outside the box."

Harry Eagle Professor of Cancer Research, and professor of cell biology and of medicine at Einstein. DePinho notes, "Dom Purpura is another of the reasons I came to Einstein. At that time, he headed

program and I had tremendous respect for Dom, as well as a serious interest in neuroscience."

Following graduation from Einstein and the completion of his medical residency in 1984, DePinho pursued an interest in basic research, working simultaneously as a postdoctoral fellow in the laboratories of Dr. Alt, at Columbia, and Dr. Scharff, at Einstein. He joined the Einstein faculty in 1988 where he began his work on cancer genetics. At the same time, he also served as an attending physician at Jacobi, an assistant professor of microbiology and immunology, and director of the medical school's new Transgenic Mouse and Gene Targeting Facilities.

"I was very fortunate to work with Matty, both as a trainee and later as a faculty member. I learned not just about how to be a sound scientist but the importance of being a good mentor."

Of Scharff he adds, "To this day, Matty's tutelage continues to have a major impact on how I mentor trainees and and how I conduct science. He is extraordinarily generous, giving so much to others and never asking for anything in return. He demonstrates how your impact on others can carry work further. As scientists, he instilled in us the belief that mentoring is the most important thing we do."

The demands of his basic research program prompted DePinho to stop attending on the wards in 1998 and to devote all his time on disease mechanisms in the laboratory. "I felt that to make a lasting impact, I needed to pursue a pure science track and immerse myself in it completely," he explains. "Even so, my science is intimately connected to what I learned in medicine, since I work at an organismal level."

His primary focus is molecular oncology, studying how oncogenes and chromosomal instability mechanisms govern the development of cancer.

"My goal is to transform molecular insights into medicine that can impact the survival of patients with cancer. I'd also like to help further our understanding of the link between advancing age and cancer, and to harness that information to identify therapeutic treatments."

DePinho spent the first 10 years of his career pursuing such knowledge at Einstein, but in 1998 he left for the Dana Farber Cancer Institute and Harvard Medical School, in Boston. "It's the only mistake he's made in his entire career," chides Dr. Purpura goodnaturedly.

DePinho's work with transgenic mice has led to numerous discoveries and honors. Most recently, he was named Einstein's 2004 Distinguished Alumnus and presented the John M. Lewis Annual Memorial Lecture of the Irma T. Hirschl Trust at Einstein.

At the conclusion of his presentation, he talked about both his dad and Einstein. He said, "My dad dug lots of ditches as a laborer in the Bronx. Einstein is about what my dad was. They take someone, maybe a little rough around the edges, and give them a chance. They give them what they need to achieve their full potential. And they helped this kid from the Bronx to do a little good."

NEWSREEL continued from page 2



DR. SHALOM KALNICKI

Born in Israel, Kalnicki received his education in Brazil and his M.D. degree from the Medical School of the University of Sao Paulo. Following his internship in Brazil, he completed a residency and a fellowship at Einstein/Montefiore, where he served as chief resident. He then returned to Brazil, where he spent a few years in radiation oncology at "The Albert Einstein Hospital in Sao Paulo" and at the Oswaldo Cruz Radiotherapy Institute, also in Sao Paulo.

In 1988, Kalnicki joined the faculty of the University of Pittsburgh School of Medicine and became director of radiation oncology at McGee Women's Hospital and Shadyside Hospital of the Joint Radiation Oncology Center at the University of Pittsburgh Medical Center. From there, he went to the Allegheny Campus of the Medical College of Pennsylvania, where he was director of the Division of Radiation Oncology at Allegheny General Hospital, MCP-Hanneman School of Medicine, and Allegheny University of the Health Sciences.

Dr. Susan Horwitz Receives New York City's Highest Scientific Honor From Mayor Bloomberg

Dr. Susan Horwitz, professor and co-chair of molecular pharmacology, has received the City of New York's highest honor for achievement in biology and medicine.

On October 13, Mayor Michael R. Bloomberg presented Horwitz with the Mayor's Lifetime Achievement Award for Excellence in Biological & Medical Sciences at a ceremony held at City Hall.

The mayor's awards have been given annually since 1992 and are administered for the City of New York by the New York Academy of Sciences. Previous recipients have included four Nobel Prize winners.

Horwitz, who also is a professor of cell biology and the Rose C. Falkenstein Professor of Cancer Research, joins three other Einstein faculty members who have received the award since its inception. In 1992, the award went to Dr. Barry Bloom, then chairman of the department of microbiology and immunology and now Dean of the Harvard School of Public Health. In 2001, Dr. Dominick P. Purpura received the honor, and last year, Dr. Matthew Scharff, Harry Eagle Professor of Cancer Research and professor of cell biology, was among the mayor's honorees.

The award recognizes Horwitz's pioneering cancer research that led to the development and eventual approval of Taxol as a treatment for ovarian, breast, and lung cancers. A drug isolated from the yew tree, Taxol is considered one of the most effective cancer-fighting therapies developed in recent years. Her work has influenced both basic and clinical research into antitumor drugs, and she is currently focusing on the problem of drug resistance and on natural products as a source of new drugs for cancer treatment.



MAYOR MICHAEL BLOOMBERG & DR. SUSAN HORWITZ

The Mayor's Lifetime Achievement Award for Excellence in Biological & Medical Sciences is the latest of numerous honors Horwitz has received during her illustrious career. Earlier this year, the National Foundation for Cancer Research (NFCR) named her an NFCR Fellow-the foundation's highest distinction-and last year, she received the Barnard Medal of Distinction, the highest honor given by Barnard College. She also is the recipient of the AACR-Bruce F. Cain Memorial Award, has been elected to membership in the American Academy of Arts and Sciences, and is past president of the American

Association for Cancer Research. She is also on the board of scientific advisors of the National Cancer Institute

Horwitz's scientific and academic skills have been richly evident since she joined the Einstein faculty in 1968. She was named professor of cell biology and of molecular pharmacology in 1980 and appointed co-chair of molecular pharmacology in 1985. She was appointed Associate Director for Drug Development at the Albert Einstein Cancer Center in 2000. ■

Laurels

Dr. Gary Bassell, associate professor of neuroscience, has been invited to serve as a regular member of the Neural Differentiation, Plasticity, and Regeneration study section at the Center for Scientific Review of the NIH.

Dr. Arnold Melman, professor and chair of urology, received the John Kingsley Lattimer Award in Urology presented by the Kidney & Urology Foundation of America. The award recognizes Melman's life-long commitment to improving the care of people with urologic problems, particularly those affected by erectile dysfunction.

Dr. Peter Mundel, associate professor of medicine (nephrology) and of anatomy and structural biology, served on the organizing committee of the Fifth International Podocyte Conference, held in Seattle.

Dr. Todd Olson, professor of anatomy and structural biology, was an invited panelist at a meeting of the U.S. Department of Health and Human Services' Advisory Committee on Transplantation. Olson addressed the committee about the problems associated with acquiring, using, and disposing of human remains in medical education and research.

Dr. Luciano Rossetti, the Judy R. and Alfred A. Rosenberg Professor of Diabetes Research, was a featured speaker at the "Days of Molecular Medicine 2004" Symposium, hosted by the Wellcome Trust and Nature Medicine in England. Rossetti, who is also professor of medicine (endocrinology) and of molecular pharmacology, spoke on "Hypothalamic Mechanisms for Nutrient Sensing" at the scientific session on Syndromes of Insulin Resistance and Obesity: Lessons from Genetics.

Dr. Gary Schwartz, professor of medicine and of neuroscience, has been invited to serve on the Neuroendocrinology, Neuroimmunology, and Behavior Study Section of the Center for Scientific Review at the NIH.

Dr. Victor Sidel, distinguished university professor of social medicine, received a Doctor of Humane Letters from the University of Massachusetts at Lowell.

Dr. Yuxun Wang, a postdoctoral fellow in the laboratory of Dr. Winfried Edelmann, professor of cell biology, received a Scholar-In-Training Award from the American Association for Cancer Research (AACR) and Astra Zeneca for his research exploring the mechanisms of tumors and their development, as well as the role that genomic instability plays in causing cancer. As part of his award, Wang presented his abstract describing his most recent research at the 95th annual meeting of the AACR. His abstract received the additional honor of "best abstract plenary" of the oral presentations at the annual meeting, which was attended by more than 15,000 researchers.

Health Commissioner Dr. Thomas Frieden recently appointed **Dr**. Thomas K. Weber to the New York City Health Department Board of Advisors. Weber, who is associate professor of surgery and of molecular genetics, also was elected to the Board of Directors of the Eastern Division of the American Cancer Society and was nominated to the National Colorectal Cancer Round Table.

Dr. Allan Wolkoff, professor of medicine and of anatomy & structural biology, has been invited to serve as chairperson of the Hepatobiliary Pathophysiology Study Section at the National Institutes of Health's Center for Scientific Review. Wolkoff also is director of the Belfer Institute for Advanced **Biomedical Studies.**

Dr. Zhong-Yin Zhang, professor in the departments of molecular pharmacology and biochemistry, was among the presenters who discussed "Chemical Biology as Related to Neurodegenerative Diseases" at the New York Academy of Sciences' "Frontiers of Science" meeting.

In Memorium

Dr. Marx.

of Germany.

"ready for a change."

Einstein.

Over the course of her 45-year career at Einstein, Dr. Marx-as described by her long-time friend and colleague, Dr. Paul Goldiner-"single-handedly pushed the development of obstetric anesthesiology as a specialty." She founded both the Society for Obstetric Anesthesiology and Perinatology and the Obstetric Anesthesia Digest. There were two accomplishments

achievement.

The editors wish to thank Dr. Ronald Simon and Dr. Jill Maura Rabin for providing this remembrance of

Dr. Gertie F. Marx began her journey to the Albert Einstein College of Medicine while still a young medical student in Germany in the 1930s. While attending a rally, where the featured speaker was a still relatively obscure Adolf Hitler, she quickly realized that her future and that of her family lay outside

Subsequently, she completed her medical training at the University of Bern, in Switzerland, in 1937 and immigrated to the United States. After completing an internship and residency in anesthesiology at the Beth Israel Hospital, she served as an attending anesthesiologist at that institution for 11 years. By 1955, in Dr. Marx's own words, she was

Dr. Marx's expectations for her career at Einstein were lofty, but they did not include the police escort she received on her first day. While making her way from her Manhattan apartment to Einstein, she apparently got lost in the South Bronx. In her haste to get to Einstein, she made an illegal U-turn directly in front of an unmarked police car. When confronted by the officer, she stated, "Give me the ticket fast because I'm supposed to start an anesthetic in 45 minutes at the new hospital and I don't know where it is." The officer then proceeded to give her a high-speed escort to Einstein, sans the ticket. And she arrived in time to give the first of her many spinal blocks at

in particular of which Dr. Marx was most proud. In 1989, she joined Dr. Virginia Apgar as the only women ever to receive the Distinguished Service Award from the American Society of Anesthesiologists. And in 1993, Queen Elizabeth II presented her with the College Medal from the Royal College of Anesthetists, in recognition of her lifetime

In addition to her many academic accomplishments, Dr. Marx was one of those rare individuals who could instantly cut through the superfluous straight to the heart of things. She became a trusted advisor and confidante to many medical students, residents, and colleagues. Her opinions were widely sought on issues as diverse as anesthetic management, global politics, immigration law, opera, and personal and family relationships. She will be missed by her family, many friends, and colleagues. Dr. Marx died in January, 2004, at the age of 91.

The editors wish to thank Dr. Ernst R. Jaffé for providing this remembrance of Dr. Eder.

Dr. Howard Eder paid his first formal visit to Einstein in about 1955, when Irving London invited him to study Grand Rounds in Jacobi Hospital's fourth floor auditorium. His erudite talk on lipids and his work on lipoproteins was certainly impressive and very important for the future studies of heart diseases, even though well beyond my comprehension at that time.

Howard provided me with my entry into the research topic that occupied much of my investigative efforts at Einstein. I had been asked to consult on a pregnant woman in Jacobi because of her very odd and unexplained cyanosis. The cause turned out to be hereditary methemoglobinemia, the subject to which I then devoted much of my research activities while I was still in the laboratory. Howard gave me a reprint of the article he wrote with Clement Finch and a Dr. McKee, which was published in the Journal of Clinical Investigation (28:265, 1949), entitled "Congenital Methemoglobinemia: A Clinical and Biochemical Study of a Case." Thus, I owe him a deep debt of gratitude.

We maintained a very friendly association over the years, even when our interactions became less frequent after I became Acting Dean and Senior Associate Dean. My wife and I also enjoyed the privilege of a friendship with Howard and his wife, Barbara, outside of Einstein.

I know that I and his many colleagues at Einstein will not forget him or his academic contributions. Dr. Eder died in January, 2004, at the age of 86. ■

The editors wish to thank Dr. Sam Seifter for providing this remembrance of Dr. Daly.

Dr. Marie M. Daly was an outstanding member of the departments of biochemistry and medicine at the Albert Einstein College of Medicine from 1960 to 1986.

Born in New York, Dr. Daly received her B.S. degree, magna cum laude, in chemistry in 1942 from Queens College. In 1943, she received her M.S. degree in chemistry from New York University, and in 1947, she received her Ph.D. degree in chemistry from Columbia University. She was probably the first African-American woman in the United States to be awarded a Ph.D. degree in chemistry.

Dr. Daly was on the research and teaching staffs of Queens College, Howard University, the Rockefeller Institute, and Columbia University College of Physicians and Surgeons. She collaborated with Dr. Quentin Deming at the Goldwater Memorial Hospital in New York, and she came to Einstein with Dr. Deming in 1958.

Her research centered largely on four areas. At the Rockefeller Institute she collaborated with Drs. A.E. Mirsky and V.G. Allfrey on the chemistry of histones, work that was fundamental in the field. With those investigators she also did important work on protein synthesis. Then, at Goldwater, and in her early years at Einstein, she did significant work on the biochemistry of cholesterol and its relation to hypertension. In her last years at Einstein, she contributed significantly to the understanding of the uptake of creatine by muscle cells. (Creatine is an important compound in the bioenergetics of muscle.)

Dr. Daly was engaged in teaching medical and graduate students at Einstein and was especially involved in recruitment and training of minority students. For many years she guided the careers of African-American students at Einstein.

Dr. Daly retired in 1986. She is remembered as a wonderful and generous person with a winning smile and dignified bearing. She was highly cultured and especially devoted to playing the flute. In later years, when cancer interfered with her ability to play the flute, Dr. Daly learned to play the guitar. She also was an excellent gardener and was devoted to her dogs.

Dr. Daly was married to Vincent Clark, who died several years ago. She is survived by members of the Daly and Clark families. Dr. Daly died in October, 2003. ■

Dr. Labe Scheinberg was a unique neurologist who specialized in the degenerative nervous disorder, multiple sclerosis, and was known to his patients for ensuring the best possible medical treatment for their needs.

In his long association with Einstein, starting in 1956, Dr. Scheinberg was among the earliest advocates for bringing neurologists, psychologists, physical therapists and other members of the medical staff together to attend to the problems of patients with MS. As a result, he was instrumental in helping Einstein create the first comprehensive care center focused on multiple sclerosis. Established in the 1970s, the center became a prototype for similar multidisciplinary centers throughout the U.S.

"He developed the notion that MS was a disease where patients had many needs," said Dr. Herbert Schaumburg, who succeeded Dr. Scheinberg as chair of neurology.

Dr. Scheinberg joined the Einstein faculty as an instructor in medicine (neurology), following an appointment at Columbia. He rose quickly through the academic ranks at Einstein, receiving his appointment as a professor of neurology in 1964. That same year, he became co-chairman of the Saul R. Korey department of neurology as well. During his career at the medical school, he also served as Assistant Dean, Associate Dean, and Dean, as well as director of Einstein's Research & Training Center in Medical Rehabilitation of Multiple Sclerosis. Dr. Scheinberg died in February, 2004, at the age of 78.

Mideast Meeting continued from page 13



however, wish to join their commitment to military service to a greater moral purpose.

Our mood naturally lifted as we ended our stay with dinner in an authentic Moroccan restaurant, replete with cushioned divans and fez-capped waiters. The fact that each of us had to be searched by a security guard for bombs and weapons before entering the restaurant brought home the message that terrorism in Israel is an everpresent danger. But like the Israelis who live with terrorism everyday, we quickly dismissed reality and threw ourselves into Middle Eastern cuisine and drink with gusto. We finally headed back to the airport and the safe haven of the USA in good spirits.

Back home, in June, we gathered the AECOM participants together to plan future collaborations. We are now planning the Second Annual Weizmann-AECOM meeting, to be held in the Bronx May 16-19, 2005.

In addition to the exchanges and visits mentioned in our mission statement, we want to see If successful, this will lead to good science, good fellowship and much needed support of a premier institute of science in Israel. These are lofty goals, but Einstein's faculty wish to pursue them with a passion.

if specific collaborative projects can be developed between scientists in the two institutions. Our intent is to undertake pilot projects that build on the synergy of investigators at the two institutions. The ultimate goal of successful projects would be for AECOM investigators to apply for NIH program projects and sub-contract appropriate parts to Weizmann. If successful, this will lead to good science, good fellowship and much needed support of a premier institute of science in Israel. These are lofty goals, but Einstein's faculty would like to pursue them with a passion. \blacksquare



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