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CHILDREN WITH AIDS

THE REMARKABLE STORY OF AN AMERICAN EPIDEMIC PREVENTED
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This issue of Einstein contains articles that cover the full spectrum of research currently performed by faculty of the Albert Einstein College of Medicine, as well as by the postdoctoral fellows who work in their laboratories. The pieces also illuminate major achievements from our past and offer glimpses of potential achievements in the future. An article describing the Center for AIDS Research, under the direction of Dr. Harris Goldstein, shows how basic science discoveries are translated into novel therapeutics, and how interventions first applied in Bronx neighborhoods are translated to African countries ravaged by AIDS such as Rwanda.

The story of pediatric AIDS and the pioneering work of Dr. Arye Rubinstein highlights the importance of careful patient observation and the unique skills of a dedicated clinician-scientist. While pediatric AIDS is now fortunately on the wane in the United States, new challenges such as the apparent rise in the prevalence of autism have appeared. A conversation with Dr. Isabelle Rapin offers an insightful perspective from a major figure in the field of pediatric neurology who helped define the spectrum of autism disorders.

Einstein’s contributions to the field of stem cell research are detailed in articles on Drs. Mark Mehler, Eric Bouhassira, Sanjeev Gupta, Carl Schildkraut, and Art Skoultchi. For me, this story, touching on the controversy surrounding human embryonic stem cell (hESC) research, evoked memories of my meeting in the Oval Office with President Bush on August 2, 2001 to present the case for the importance of hESC research in helping develop a cure for type 1 diabetes. Although President Bush, one week later, approved use of Federal funds to support hESC research, support was limited to hESC lines derived before his speech delivered at 9 P.M. on August 9, 2001. Because of the limitations of the few available “Presidentially-approved” hESC lines, much of the vital research that needs to be performed must be supported by private funds. Such funding is critically needed at Einstein to support our own outstanding stem cell research program. This is but one imperative emerging from an ongoing strategic research planning process that I have initiated whose overarching theme is enhancing the linkage between Einstein’s superb basic science research and the clinical research needed to bring basic discoveries to patients. Einstein can certainly take pride in the past accomplishments of great physician-scientists like Rubinstein and Rapin, and the work of Harris Goldstein, Mark Mehler, Eric Bouhassira, and Sanjeev Gupta. Bodes well for Einstein’s continued prominence as a place where physician-scientists make important biomedical research advances. Collaborations between these physician-scientists and superb basic science colleagues such as Art Skoultchi and Carl Schildkraut will help realize my vision of a strong linkage between basic and clinical research leading to advances in diagnosis, treatment and prevention of disease.

Collaborations between physician-scientists and superb basic science colleagues ... will help realize my vision of a strong linkage between basic and clinical research leading to advances in diagnosis, treatment and prevention of disease.
Twenty-five years into the AIDS epidemic, these worldwide statistics stand above the rest: 65 million infected, 25 million dead, 0 cured. They are a sobering reminder of the suffering that continues and the challenges that remain, especially in the developing world.

But there is a different—and happier—story to be told about pediatric AIDS in America. In 1992, the Centers for Disease Control and Prevention reported 942 new cases of pediatric AIDS (defined as children under 13) in the United States. Tens of thousands of additional cases were expected in the years ahead, threatening to overwhelm hospitals and social service agencies. Thankfully, this doomsday scenario for children never materialized. In fact, pediatric AIDS has almost disappeared in this country, dwindling to a total of only 48 new cases in 2004.

A significant portion of the credit for this remarkable turnaround belongs to one institution, Albert Einstein College of Medicine, and to one physician, Arye Rubinstein, M.D., Professor of Pediatrics and Microbiology and Immunology.

Dr. Arye Rubinstein during the early days of the pediatric AIDS crisis.
Although Rubinstein was an eminent immunologist, he could not get anyone else to believe his unlikely analysis... word quietly circulated that the Israeli-born researcher had gone a little batty.

FEAR AND LOATHING
Dr. Rubinstein kept at his seemingly quixotic quest. A scientist as well as a clinician, he knew that if he compiled enough data to support his hunch, the medical establishment would have to respond. A big break came in 1982, when he was awarded the first National Institutes of Health (NIH) grant to study AIDS in women and children, focusing on the epidemiology, immunology, and pathogenesis of the disease.

From this work flowed a wave of findings, including evidence of links among the various immune disorders affecting infants, mothers, and homosexuals. One piece of evidence, found in the blood of patients from all three groups, was a common antibody that reacted with T cells, a type of immune cell, the presumed target of the infection. Cynically, Dr. Rubinstein found the same antibody in hemophiliacs who had come down with a mysterious immune disorder. The implication was that the blood supply was tainted. Again, no one in the United States wanted to hear of it, although his data did convince Japan to start screening its blood donors. Unfortunately, Dr. Rubinstein found that hIV was not transmitted through casual contact. The parents got very upset, but I testified that hIV was not transmitted through saliva. There were no precautions taken whatsoever, and none of us got infected.

As time went on, Dr. Rubinstein published numerous papers documenting that sexual transmission did not occur. In the beginning, everyone threw the blame at drug users, but as Dr. Rubinstein and his colleagues in the Division of Allergy and Immunology were the first to clarify the epidemiology of the disease and recognize that it was a major route of transmission: from mother to fetus, through sexual activity, and through blood products. “We also suspected transmission through sharing needles and other infectious drug paraphernalia,” Dr. Rubinstein recounted in his book And the Band Played On, which detailed the early years of the AIDS epidemic, being written by a famous immunologist, he could not get anyone else to believe his unlikely analysis... word quietly circulated that the Israeli-born researcher had gone a little batty.
hour in your own clinic and say good-bye and assume that there will be compliance... It was clear from the beginning that you have to go much more into the socioeconomic situa-
tion of those families... And that’s why I started this social medicine program here very quickly. At this
point, we have social workers. We have outreach workers that go to the houses. Ward workers are
children without having this kind of outreach. It’s a futile exercise.”

OVERWHELMED

The first of those social workers was Dr. Anita Septimus, who arrived at Einstein in 1985. Relatively new to
social work and admittedly naive about HIV/AIDS, Dr. Septimus was overwhelmed. “In the first month, we
lost four babies. I told Dr. Rubinstein, ‘I didn’t come here to bury children. ’” she says. The work
was infinitely heartbreaking, espe-
cially for a mother with four children
who had to continuously treat her
six-year-old twins for the AIDS virus
that was killing their baby brother. “I
came from a different world,” she
says. “I think there’ll come a time when AIDS
will have passed into history. There
will have been a cure and a vaccine.
There are so many children who
died...”

Dr. Rubinstein’s laboratory would
begin to see progress around 1987. That year, the first antiretroviral therapy became available:
AZT was approved for use in adults
and children under age 15. Dr. Rubinstein explains that this was a “leap forward. It was the first time
we had something that could save these kids.” By 1988, AZT was approved for use in children over age 3.

In the meantime, outreach and home visits were vital for treating the children who had been exposed to
HIV. “Once you got the diagnosis, there were outreach visits to the children and families. But our
resources were very limited,” said Dr. Septimus. “We learned what we learned the hard way.”

Despite all these accomplishments in the United States, the real work in pediatric AIDS is just getting started at
the global level. At the most recent International AIDS Conference, experts noted that 2.5 million children
under age 15 worldwide are infected with HIV.

Dr. Arne Rubinstein and Dr. Anita Septimus, still working together more than 25 years after pediatric AIDS
was first identified at Einstein. ... the real work in pediatric AIDS is just getting started at the global level.
AIDS IN THE 21ST CENTURY: Confronting the Challenge at Home and Abroad

A decade ago, highly active anti-retroviral therapy, also known as HAART, revolutionized the treatment of AIDS, transforming infection with HIV from a fatal illness into a manageable chronic disease. What the next breakthrough will be is not clear, but a highly promising candidate is radioimmunotherapy, in which antibodies are used to ferry a lethal dose of radiation directly to cells infected with HIV.

Left alone, HIV infection progresses as the virus hijacks T cells—which orchestrate the body’s response to intruders—and turns them into factories for making HIV. New copies of the virus are then released into the bloodstream, where they infect more T cells, steadily weakening the immune system. HAART breaks this vicious cycle by blocking viral replication in newly infected T cells. Established T cell infections, however, are left untouched. Thus, HAART can control HIV infection, but it cannot cure it. “You can treat patients with anti-viral drugs for years and they will have no detectable virus in the bloodstream,” says Harris Goldstein, M.D., Professor of Pediatrics and Microbiology & Immunology. “But within weeks after stopping therapy, the virus comes right back because there are all these pockets of HIV-infected cells. It’s like the Taliban hiding in the caves in Afghanistan. When you stop bombing, they come right out and start fighting all over again. So, the question is, can we come up with a therapy that can specifically target HIV-infected cells and eliminate those reservoirs of HIV?"

One answer may be radioimmunotherapy, or RIT, which harnesses the specificity of antibodies with the destructive power of radiation, in the form of a few molecules of a radioactive isotope. Because each type of antibody is specific for only one type of antigen, the radiation can be targeted with great precision, minimizing collateral damage to healthy cells. It’s the medical equivalent of a smart bomb.

RIT was originally developed as a treatment for cancer. Two RITs were recently approved for treating lymphoma. Now, researchers at Einstein are trying to adapt this technology for fighting infection with HIV. Since viruses are much different from cancer cells, the creation of a radioimmunotherapy for HIV posed significant challenges. Viruses are mere wips of DNA or RNA wrapped in a thin protein coat. Simple, tough, and resilient, they sough off radiation like rainwater and can readily repair any damage that might occur. What’s more, HIV can hide in T cells, beyond the reach of antibodies.

“Now, our approach is not to target the viral particles but rather T cells that host the virus,” says study leader Ekaterina Dadachova, Ph.D., Associate Professor of Nuclear Medicine and Microbiology & Immunology. “The good thing is that T cells are among the most radiosensitive cells in the body. We found that by using a cocktail of antibodies, one of which is specific for only one type of cell and another for only one type of antigen, it is possible to destroy the virus in T cells and prevent its spread.”

Dr. Dadachova’s immunotherapy consists of an antibody for glycoprotein 41 (gp41) and a radioactive isotope called Bismuth-213, bound together with a special molecule known as a ligand. The gp41 antibody was selected because its corresponding glycoprotein is reliably expressed on the surface of T cells infected with HIV and, unlike other HIV-related glycoproteins, it usually doesn’t shed into the bloodstream. Bismuth-213 was chosen because of several characteristics, including a half-life of 46 minutes. Such a decay rate is just enough time for the treatment to be prepared and administered and for the radioactively labeled antibodies to do their job, but not so much time that the patient would have to be quarantined for very long. After four hours, Bismuth-213’s radioactivity falls to negligible levels.

The treatment, given as an intravenous infusion, would be complemented with a dose of HAART, so as to destroy the viruses when they are flushed out of their “caves.”

With so many pieces needed to make this puzzle, Dr. Dadachova has had to call on the expertise of a wide variety of researchers. Her collaborators at Einstein include Arthur Casadevall, M.D., Ph.D., the Leo and Julia Forchheimer Professor of Microbiology & Immunology and Chair of the department, who is also collaborating with Dr. Dadachova on developing RITs for melanoma, fungi, and bacteria; Dr. Goldstein, who specializes in mouse models of HIV and in the pathogenesis and treatment of HIV disease; and Mahesh Patel, M.D., Assistant Professor of Medicine, a researcher in the department of radiation oncology at the College, who is also collaborating with Dr. Dadachova. In addition, the human monoclonal antibodies were provided by Susan Zolniker-Pamer, Ph.D., an immunologist at NYU School of Medicine, the ligand by Martin Brechbiel, Ph.D., on the investigator-driven immunotherapy branch at the National Cancer Institute, and the isotope by Alfred Morgenstern, Ph.D., and Christos Apostolidis, Ph.D., nuclear chemists at the institute for Transuranium Elements in Germany. In an encouraging start, Dr. Dadachova and her colleagues, supported by a CAIR pilot project award, have demonstrated that the treatment is effective at killing T cells both in vitro and in vivo, the latter involving two different models of mice with HIV.

Results of their proof-of-principle study were published in PLoS Medicine. The technology has already been licensed to a commercial partner, which is working to make large quantities of clinical-grade antibodies. Clinical trials are perhaps a year or two away.

Dr. Dadachova predicts that RIT can also be developed for other infectious diseases, including those caused by antibiotic-resistant microbes.

A SMART BOMB AIMED AT HIV

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CUSTOM-MADE IMMUNITY

One of nature’s most crafty viruses, HIV is able to dodge just about everything that the immune system can throw its way. But a small percentage of people infected with HIV manage to keep the virus in check without any medications. The secret to these “elite controllers,” who number about one out of 300 people with HIV, may be in having T cells that are highly efficient at eliminating cells infected with the virus.

Unfortunately, these super T cells cannot be transplanted from one patient to another. “Your own T cells would reject them, or they would attack your cells,” explains Dr. Goldstein.

But the researcher may have discovered a way to get around this immunological roadblock. It appears that some T cells from elite controllers have a receptor that is particularly adept at recognizing cells infected with HIV, which express unique epitopes (antigenic fragments of the virus) on their surface. Based on that insight, Dr. Goldstein surmised that it might be possible to confer immunity to HIV by transplanting into patient’s T cells the genes that code for this receptor.

The first step in creating this therapy was to clone the genes for the receptor. Next, the cloned copies... the question is, can we come up with a therapy that can specifically target HIV-infected cells and eliminate those reservoirs of HIV?"

The technology has already been licensed to a commercial partner, which is working to make large quantities of clinical-grade antibodies. Clinical trials are perhaps a year or two away. Dr. Dadachova predicts that RIT can also be developed for other infectious diseases, including those caused by antibiotic-resistant microbes.
Certain AIDS patients can keep HIV at bay without drugs. Some of their T cells have a cell-surface receptor that recognizes HIV-infected cells. Dr. Goldstein is developing an AIDS therapy to equip patients’ T cells with cloned copies of the gene for the receptor. This illustration shows a T cell (lower right) with a receptor that is binding to a cell infected with HIV.

Like radiosensitization, the effectiveness of the gene therapy is greatly improved by the use of an antigen that targets HIV-infected cells. Moreover, the treatment can be used to cure HIV infection, not just to suppress it.

A similar broad-spectrum approach is used in HAART, where a variety of antiretroviral drugs are thrown at HIV at once, reducing the chances that the virus will happen upon a successful mutation. Dr. Goldstein does not imagine that a single protein can cure all patients infected with HIV. But it could prove to be a life-saving immune-system boost for the 20 to 30 percent of HIV patients who don’t respond well to antiretroviral medications.

The treatment might also be useful in preventing infection following acute exposures to HIV—for example, after needle-stick injuries (which are distressingly common among healthcare workers) or after high-risk sex. “If you attack the virus very rapidly and eliminate it, you may prevent infection,” he says.

Assuming prefabricated immunity is shown to be effective in clinical trials, Dr. Goldstein expects that it will move rapidly through the approval process. “Our approach uses tools that have already been approved for patient use, so we wouldn’t have to get approval for a whole new therapy, just a variation,” he says. “Therefore, I am hopeful we are taking in terms of years as opposed to decades.”

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HELPING RWANDA HEAL

For the map of the word “humanitarian” doesn’t seem strong enough to describe the recent history of women in Rwanda.

In a hundred-day period in 1994, Rwandan soldiers and Hutu gangs slaughtered 800,000 to a million civilians, mostly Tutsis and other Hutus. A quarter-million women were raped, and tens of thousands were infected with HIV. A decade later, many of them are dying of AIDS.

The story gets worse. Before inexpensive antiretroviral therapy arrived in Rwanda in mid-2004, the drugs were given to the alleged rapists in international prisons, but not to their victims. Some 100,000 victims of rape are now being rectified. In 2004, two

physicians and an activist-journalist from America teamed with a group of the survivors, Rwandan officials, and a handful of nongovernmental organizations (NGOs) to create Women’s Equity to Access to Care and Treatment, or WE-ACTx, which delivers a wide range of services to women in Rwanda.

One of those physicians is Kathryn Anastos, M.D., Professor of Medicine and Epidemiology & Population Health, a specialist in public health for urban minorities with HIV. Soon after hearing the survivors’ pleas for help, Dr. Anastos and WE-ACTx’s two other founders—Dr. Maryanne Cohen and Anne-Christine Akesly—an American who works in Africa both for WE-ACTx and to Africas to see what they could do. “The women told us, ‘A lot of people come, and nobody comes back,’” says Dr. Anastos. “So, we did go back. We went back really, really fast. It was too heartbreaking. Plus, I’m a doctor. I knew we could turn things around.”

Back in 1993, she faced a similar situation in the South Bronx, one of the nation’s first communities to be ravaged by HIV and one of the last to get appropriate treatment. At Bronx-Lebanon Hospital and then at Montefiore Medical Center, Dr. Anastos played a central role in building HIV clinics and services for the underserved neighborhoods and, when effective drug therapy became available, reversing the course of the disease in those living with HIV.

The fact that government agen-

cies, health-care providers, and society at large ignored this population for so long, ranks her still. “I was outraged at how my patients were described in both the lay and medical literature, as if they were perpetrators and not victims,” she says. “This was especially true for the women.”

A self-described child of the ’60s, Dr. Anastos decided early in her career to change the system from within. In 1993, while working at Bronx-Lebanon, she won a grant from the National Institutes of Health to lead the New York consortium of the Women’s Interagency HIV Study (WHIS), a study of the natural history of HIV infection in women at six sites around the country. “I learned that there was no information about how to treat my patients, especially the women, and there is still little information about men of color,” she explains. Thirteen years on, WHIS continues, now at Montefiore.

In Rwanda, half a world away, Dr. Anastos found a similar challenge: a large number of women with HIV living in communities with scant health-care resources. However, the WE-ACTx project was wound up not to impose Western solutions on an African population, an approach that has failed in numerous efforts. Instead, the team simply asked what the women and the government wanted. “We’ve succeeded without the government—without the grassroots organizations or the women themselves. We have to empower the women themselves,” she says.

“We need to empower women, the greater the community cohesiveness, and the greater the community’s ability to take care of itself.”
Human Embryonic Stem Cells: Investigating the Origins of the Species

Nanogram for nanogram, human embryonic stem cells are certainly the most controversial of biological entities and may rank as the most valuable as well. With their unique ability to multiply indefinitely and to develop into virtually any cell type, embryonic stem cells offer limitless potential for regenerating tissues and curing disease.

Unfortunately, the hype and controversy obscure some key facts: Very little is known about the basic biology of these cells, which were first isolated only nine years ago. And from a therapeutic standpoint, embryonic stem cells themselves are useless. “Human embryonic stem cells can’t cure anything,” notes Dr. Eric Bouhassira, Professor of Medicine (hematology) and Cell Biology at Einstein. “To cure diseases, you need to change embryonic stem cells into more specialized cells that can then be transferred to patients.”

Dr. Bouhassira has been studying human embryonic stem cell at Einstein since 2001. He was the organizing force behind the three-year, $3 million center grant for human embryonic stem cell research that Einstein received from the National Institutes of Health in 2005, one of only six such grants awarded. Fully half the federal money goes to the Center’s core facility, where a lab manager and two technicians culture two lines of human embryonic stem cells.

President Bush has restricted federal funding to human embryonic stem cell lines created before August 9, 2001. The two cell lines being studied at Einstein were provided by Dr. James Thomson of the University of Wisconsin, the researcher who first isolated human embryonic stem cells and grew them in tissue culture. Dr. Bouhassira directs the new center, called the Einstein Center for Human Embryonic Stem Cell Research. He and three other Einstein researchers—Dr. Sanjeev Gupta, Professor of Medicine (Liver) and Pathology; Dr. Carl Schlootkraut, Professor of Cell Biology; and Dr. Arthur Skoulitchi, Professor and Chair and Judith and Burton P. Resnick Professor of Cell Biology—serve as the center’s principal investigators. All four are working to advance fundamental knowledge of human embryonic stem cells. “You have to remember that we’ve only known since 1998 how to grow human embryonic stem cells,” says Dr. Bouhassira. “So there is a great need to gain insights into the basic biology of human embryonic stem cells if we’re ever going to use them clinically in patients. This fundamental knowledge will help us to maintain these cells in an undifferentiated state, to determine which cell lines are suitable for use in patients and—perhaps most important—to control when stem cells differentiate and what types of cells they become.

“For example,” Dr. Bouhassira asks, “what are the signals that tell an embryonic stem cell to stop making identical copies of itself and instead begin differentiating into a muscle, blood or other type of cell? Learning the answer will improve our ability to induce stem cells to differentiate in the first place and then, hopefully, help us coax them to differentiate into the particular cell types we want.”

Changing Stem Cells Into Red Cells

Human embryonic stem cells are “pluripotent”—able to form all cell lineages in the body. They differentiate into more specialized progenitor cells referred to as “multipotent” stem cells that can form several different cell lineages. Dr. Bouhassira’s
work focuses on directing human embryonic stem cells to differentiate into multipotent hematopoietic stem cells that, in turn, differentiate into red cells, T cells, platelets and all the other cell types that comprise the blood.

One possible practical application of this research: providing patients with immunologically compatible bone marrow transplants.

Successful bone-marrow transplants provide patients with a fully functioning bone marrow—evidence that some of the donated marrow cells successfully survived the needs of the patients’ blood and immune systems. A 1996 study in Science showed that lethally irradiated mice could be “rescued”—their blood and immune systems entirely restored—with just a single hematopoietic stem cell from the marrow or form adult red blood cells,” says Dr. Bouhassira. “That’s an important consideration when we think about using human embryonic stem cells to develop human therapies.”

CA R L S C H I L D K R A U T, Ph.D.

Inducing human embryonic stem cells to develop into hematopoietic stem cells...
SMAD4
TGFB2
SMAD4
3
D
0
K71
EP300
D
K71

ated cassette exchange (rCMe), it

gene 1, 5 or 10—and, depending

viruses or plasmids as vehicles for car

greatly improves on previous genetic

Bouhassira developed several years

using a purposely messed-up gene,

removed anyway? This experiment,

are present on human embryonic

does it really matter if epimutations

and other epigenetic “marks” are

observe the consequences.

into human embryonic stem cells and

mutate” a gene by studding it with

stem cells. he will also purposely “epi

globin genes that are expressed

themselves.

replication, Dr. Bouhassira is focus

cells. But rather than studying DnA

the health of human embryonic stem

Bouhassira is interested in epigenetic

his laboratory will determine the

“We know that methylation

epigenetically silenced gene into

rCMe allows researchers to precisely

two different pathways that recapitulate how red blood cells develop

in vitro

are suitable for transfusion.

Production of adult red blood cells, similar

to fetal liver red blood cells vs. less complex networks in

stem cells and fetal liver progeni

ated genes in human embryonic

software that examines “biological

ation—can be assessed using special

ing hepatocytes and pancreatic

embryonic stem cells, partially dif

types of cells: undifferentiated human

and liver can be considered cousins

stem cells and fetal pancreatic
tissues, such as

Dr. Gupta will

on this success,

stem-cell differentiation as well: Drs.

Gupta and Bouhassira obtained

on human embryonic stem cells on human

human studies. So the goal is to cul

ture embryonic stem cells on human

tissues—and Dr. Bouhassira has shown that

these epimutations are truly permanent.

between which two genes—the

new gene will reside. Just as important,
rCME allows researchers to precisely

calibrate the expression level of the

newly inserted gene. Dr. Bouhassira will completely

methylate the globin gene in vitro

and then, using rCME, insert this
epigenuically silenced gene into a human embryonic stem cell. For

comparison, he will do a similar inser

tion using a normal (unmethylated)

version of the globin gene. A

major remodeling of epigenetic

information occurs as embryonic

cells differentiate into red blood cells;” says Dr. Bouhassira. By following

the fate of this purposely epimutated globin gene, we can learn whether

remodeling includes erasing epimutations. If the embryonic stem cell can

restore the globin gene to normal function by unmethylating it, then

we won’t need to worry so much about the epigenetic status of human

embryonic stem cells, because these

epimutations may be temporary.”

The second aspect of Dr. Bouhassira’s basic research on human embryonic stem cells involves coas

ting them to differentiate into mature red blood cells. As noted on

page 16, he has successfully redirected embryonic stem cells to differentiate

into fetal red cells but not yet into adult red cells mature enough for trans

uation. To try to overcome this hurdle, Dr.

Bouhassira will use his rCME tech

nique to insert into embryonic stem

cells the adult globin gene along with

promoter and enhancer regions that

allow for globin expression in fetal

red blood cells. This insertion should

result in red blood cells that express

adult hemoglobin along with fetal

hemoglobin. “We hope that this

technique can supply a ready source of blood cells that are suitable for use

in transplantation,” says Dr. Bouhassira.

SMAD
TGFB
MAP3K7
MADH2
SMAD4
TGFB1
TGFB3
TGFB2
TGFB1
TGFBR2
TGFBR1
MAP3K
P3
K71

BA

MA

P3
K71

P1ER
K

activator
kinase
MA
D
HI
P
SKIL
MA
P
K3

Sanjeev Gupta, M.D.

Embryonic stem cells are the

ultimate mixed blessing: they can form more than 200 cell types in the human body—but how do

you push them in any one direction? Dr. Sanjeev Gupta is comparing the gene expression profiles and genetic

networks of embryonic stem cells and the cells into which they differentiate; that’s a way to understand

specific signaling pathways. These approaches offer the exciting poten

for identifying transcriptionally active or inactive networks in various cell types.”

Dr. Gupta. Dr. Gupta is also developing strate

ges for manipulating stem cells into fetal hepatic progenitor/stem cells—

and then into either hepatocytes or pancreatic beta cells. “The pancreas and liver can be considered organs

under the skin, since they both arise from the same progenitor cell during embryonic development,” says

Dr. Gupta.

Making embryonic stem cells dif

ferentiate in the desired directions

involves exposing them to the proper

chemical environment. Based on his

gene-expression findings, Dr. Gupta

will use his rCME technique to insert

the adult globin gene along with

promoter and enhancer regions that

allow for globin expression in fetal

red blood cells. This insertion should

result in red blood cells that express

adult hemoglobin along with fetal

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technique can supply a ready source of blood cells that are suitable for use

in transplantation,” says Dr. Bouhassira.

embryonic stem cells. The

same genes can also be grouped

according to cell process (receptor

activity or protein binding, for exa

mple) to indicate their participation in specific signaling pathways. “These approaches offer the exciting poten

for identifying transcriptionally active or inactive networks in various cell types,” says Dr. Gupta.

stem cells for treating type 1 diabetes.

transplants that involves implanting

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technique can supply a ready source of blood cells that are suitable for use

in transplantation,” says Dr. Bouhassira.

while keeping the globin gene silenc

in embryonic stem cells. Bouhassira

reached this goal by using strategies

that involved introducing the gene for the catalytic

domain of telomerase into fetal

tissue. This led to the telomerase enzyme being

expressed in fetal cells, which in turn led to the telomeric repeats being

maintained and therefore preventing the cells from undergoing chromosomal shortening and eventu

ally stopping cells from dividing further. These so-called Hi-B cells not only support the growth of human

embryonic stem cells but can trigger stem-cell differentiation as well. Dr. Gupta and Bouhassira obtained

embryonic stem cells by co-culturing

human embryonic stem cells with immor

talized fetal tissue containing the telomerase enzyme. By successfully culturing these cells, Dr. Gupta

was able to show that his technique could be used to generate fetal liver progenitor cells that were capable of
differentiating into liver cells and that this resulted in the generation of fetal liver cells with characteristics of

embryonic stem cells.
To replicate themselves, embryonic stem cells and other cells must increase in size, duplicate their DNA, and then go through divisions resulting in two daughter cells, each containing one complete copy of the entire genome. These processes are controlled in the cell cycle, pictured here, which has several phases: G1, cell becomes larger, protein P21 (and synthesis-proliferation). G2 (DNA replication occurs). G2 cell checks that DNA replication is complete and prepares for cell division; and M (mitosis, when chromosomes are separated and the cell divides into two daughter cells).

**ARTHUR SKOULTCHI, Ph.D.**  
Dr. Skoultchi focused on erythroleukemia—specifically, a type of leukemia that involves red cells—Dr. Arthur Skoultchi traced this phenomenon to communication. Our recent work “is a cell’s proliferation program and its differentiation program,” he says. Now, he hopes to learn whether such mechanisms—where cell proliferation is blocked and re-entry into differentiation is triggered. Also, studies involving mouse embryonic stem cells indicate that certain G1 cell-cycle regulators are missing—causing the cells to make a very quick transition through the G1 phase. It almost prevents G2 from occurring, and these cells don’t want to linger in the G1 phase for fear that the decision might be made to differentiate instead.

**Dr. Skoultchi’s lab, is currently investigating whether the same phenomenon occurs in human embryonic stem cells.**

Easily in G1, a cell may decide to exit the cell cycle and enter a nondividing stage (Go). For some cells (e.g., liver cells), this may be a temporary “pause” before re-entering the cell cycle, while other cells (e.g., brain neurons) may never divide again. For embryonic stem cells, entering Go means abandoning pluripotency and begins the process of differentiation that eventually leads to a specific cell type. “We are hopeful that this work will shed light on the mechanisms by which human embryonic stem cells maintain their totipotency,” said Dr. Skoultchi.

**M phase (mitosis)**  
**G2 phase**  
**G1 phase**  
**G0 phase (apoptosis)**  
**S phase**  
**continued proliferation**

**Decision to continue proliferating or to differentiate**
In your autobiography, published in the Journal of Child Neurology, you write that in order to have it all—a career, marriage, family—one should “find a good mentor, enjoy what you do, and be lucky.” Who was your mentor?

One was Dr. Saul Korey [former chair of neurology], an absolutely extraordinary person, extraordinary both as a scientist and a department chair. To him, there was no doubt that faculty members had to do research. If you didn’t want to, goodbye. Also, he was loyal to the faculty. Once he decided that you were okay, he would support you, regardless. You could go to him at any time of the day for advice. He might be doing research in his lab, and you could talk to him about a patient problem. He always said patients come first.

He died so young, in 1963, only a few years after you came to Einstein. Why did you stay?

He created a department of such strength, that even after his death, it stayed together for 20 years. People didn’t leave, and the subsequent chairs were Korey people.

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Going back to your bio, have you been lucky?

Incredibly. I was lucky being born into an intelligent family with professional parents who fostered intellectual development. I was lucky in medical school. I met a professor of surgery who emphasized to us what medicine was all about and what your responsibility to patients is. I was lucky when I came to Einstein and met Dr. Korey. And I was lucky when I met a husband who was incredibly generous and supportive of me. He invented women’s 8 to long before the term had been coined.

When did you first get interested in autism?

I occasionally saw some classically autistic kids in clinical practice in the fifties and sixties, but it really came to a head in the seventies, when Dr. Doris Allen, who turned out to be one my major co-investigators and friends, was appointed director of a therapeutic nursery in the department of child psychiatry at Jacobi. The majority of the children were autistic. She took it over from a psychoanalyst who was analyzing the parents, and decided that treatment should focus on the children. She was trained in developmental psycholinguistics and I was trained in neurology. I educated her in the nervous system and she educated me in language, so it was a very good collaboration.

How much was known about autism at that time?

We knew nothing about the biology. Nothing, nothing, nothing.
A significant portion of your work on autism was done under your grant from the National Institutes of Health on multidisciplinary, multicenter study of higher cortical function disorders and developmental language disorders in children. How did this come about?

In the late seventies, the Child Neurology Society invited us to develop a neurological classification of developmental disorders, which led to the NIH grant in 1985. I eventually became the principal investigator and began to see a lot of autistic children.

What were some of the contributions of that study?

We published some major papers in language regression and autistic regression, using our private practice data. (I’ve always viewed every patient as a potential research subject and therefore made the data retrievable, at least in a primitive way.) When we started out, people didn’t believe that children with autism underwent a regression, and we were among the first groups to point this out.

Is the prevalence of autism increasing, or just awareness of autism? Is the prevalence of autism increasing?

I think it’s increased awareness, particularly awareness of autism in the mildly affected children—which Dr. Allen showed in her nursery that is retrievable, at least in a primitive way.) When we started out, people didn’t believe that children with autism underwent a regression, and we were among the first groups to point this out.

What have you been working on lately?

My most recent accomplishment is Autism: A Neurological Disorder of Early Brain Development (Cambridge University Press, 2006), a book on autism by neurolinguists that I conceived with Dr. Roberto Tuchman, who is one of my former residents.

So, after half a century, you’re not quite done yet?

They’ve kicked me out yet. My current boss, my former student, Dr. Solomon Moshé [professor of neurology and pediatrics], protects me. He says to the Dean, “Don’t throw her out, she’s still making contributions.” He’s the one who invented the December 19 follies. It was not my idea, I assure you.

Are there that many high-functioning people on the autism spectrum? One of the most enlightening papers, a paper I always like to quote to parents, is by a doctor in England named Simon Baron-Cohen, who developed a questionnaire for adults to identify themselves as autistic—because adults with autism are not brought in by their mothers and he wanted to study them. So, he gave the questionnaire to 800 students at Cambridge University, the crème de la crème. He interviewed those who identified themselves as autistic, and found that many of them were indeed on the autistic spectrum. They had never been identified as autistic, but they had had difficult childhoods, were observations for autism that we hear so much about? What drives me crazy are treatments that people are offering that have no basis in research and that are exploiting parents. This is terrible. But I guess quacks have been around all the time. I am sure that many of them are sincere and really believe that they are doing something good. But there is no evidence.
Postdocs are often described as the engines that drive all biomedical research.

To be a postdoc is to be in a state of transition from graduate student to independent researcher. While Principal Investigators (PI’s) direct the labs, postdocs play an indispensable role in carrying out the day-to-day research activities to achieve the lab’s mission.
A New Home for Einstein Postdocs

The Michael F. Price Center for Genetic and Translational Medicine, Harold and Muriel Block Research Pavilion, scheduled to open within a year, will ultimately house 40 new laboratories.

“Postdocs are crucial for successful laboratory research, and the influx of many additional postdocs to the Price Center will mark a big expansion of the medical school’s research enterprise,” says Dr. Allan Wolkoff, director of Einstein’s Belfer Institute for Advanced Biomedical Studies.

“Naturally, we hope to attract the best and brightest people to our laboratories. And once they’re here, we need to do everything possible to make their postdoctoral experience a positive one.”

Postdocs are vital to an institution like ours, and we need to let them know how much we value them.

Postdocs career workshops for sharpening skills such as writing a research grant and managing a lab. Dr. Wolkoff also offers a postdoctoral program, Pathobiology of Disease, which introduces Ph.D.’s to clinical research, including learning the perspective of the patient.

“Since most Ph.D.’s don’t come in contact with patients, we wanted to expose them to the clinical side, so they can consider additional possibilities for exploration and collaboration as they pursue their research,” Dr. Wolkoff says.

“Postdocs are vital to an institution like ours, and we need to let them know how much we value them,” says Dr. Dennis Shields, former Director of the Belfer Institute, and Professor of Developmental & Molecular Biology and of Anatomy & Structural Biology.

To illustrate his point, Dr. Shields holds up a copy of Nature Cell Biology that just arrived in the mail. “This has an editorial discussing how postdoctoral fellows in the U.S. and Europe often are underpaid, underemployed and have limited prospects for future employment,” he said. “It also notes steps being taken to improve these conditions, particularly satisfying to note how many of these recommendations we’ve already implemented on behalf of Einstein postdocs, and to know we have had a leadership role in establishing many of the improvements now being sought at other institutions.”

One of the important achievements pioneered at Einstein is the establishment of an organization specifically for postdocs. Founded in 1995, the Einstein Postdoctoral Association (EPA) provides Einstein’s 380 postdocs a strong voice in communicating their needs and concerns to the medical school. Members of the EPA meet periodically with Dr. Wolkoff, and their efforts have led to improved housing, health insurance, vacation benefits, and clear standards for postdoc salaries at Einstein.

“The steps we have taken have made an enormous difference, ensuring that a broader scale of important details receive appropriate attention and assuring that postdocs truly feel valued at Einstein,” says Dr. Shields.

Julie Herrick, Assistant Dean for Research Development, agrees. “When the EPA was first established, postdocs raised issues that ran the gamut from academic to quality of life, and we took them all very seriously. A Belfer Institute advisory committee composed of faculty, postdocs, and administrators was created so we could address important issues from a broader range of perspectives.”

An important step was the creation of a Belfer Institute Office, Mary Ann Clifford, administrator of the Belfer Institute, keeps in close touch with postdocs from the moment they enter Einstein and throughout their tenure here. Many postdocs come from abroad, so Ms. Clifford helps make sure that visas are obtained and that other critical details don’t fall through the cracks.

“Nationally, fewer than 50 percent of postdocs are American,” says Dr. Wolkoff. “Many American students no longer pursue science at the postgraduate level because of diminishing grant support and a dearth of good-paying jobs.

But for postdocs from abroad, coming to the United States is a popular move. “A stint in the U.S. is a good thing to have done,” says Dr. Lucy Firth, a British postdoc in the laboratory of Dr. Nicholas Baker, Professor of Molecular Genetics and of Developmental & Molecular Biology. “I wanted to come to America to study developmental processes in a model organism,” says Dr. Firth.

“Coming to Nick’s lab and studying development in the Drosophila eye has allowed me to pursue just the kind of research I had in mind,” Dr. Firth’s research centers on the extracellular signals responsible for spatially regulating proliferation in the differentiating Drosophila eye.

“I had advertised for a postdoc when Lucy wrote to me, so I was able to offer her a place in my lab,” notes Dr. Baker, who also is originally from Great Britain and completed his own postdoctorate in California before joining the Einstein faculty. “I liked the intellectual atmosphere at Einstein and I have found that other faculty from abroad were attracted to Einstein for the very same reason,” he says.

Einstein’s postdocs clearly appreciate the College’s unusual spirit of collaboration. “There are a lot of opportunities here for sharing ideas and really discussing science,” says Dr. Vivien Chevaleyre, a postdoc from France working in the laboratory of Dr. Pablo Castillo, Associate Professor of Neuroscience, who is studying the signaling molecules involved in the function of synapses in the central nervous system.

Dr. Chevaleyre’s postdoc position was initially supported by an Einstein Scholar Fellowship, awarded to one postdoc annually with the goal of attracting quality scientists to Einstein. Two years ago, the scholar fellowships were discontinued and replaced by the Outstanding Postdoctoral Research Scholar Prizes. These $5,000 prizes are awarded each year to at least five Einstein postdocs for exceptional research projects, conducted at the College of Medicine, that resulted in published papers. Postdocs Chevaleyre, Fan, Shi and Firth have won research prizes for work published respectively in Nature Neuroscience and Neuron, Cell, Science and Developmental Cell.

“Publishing in notable journals is a benchmark by which job-seeking postdocs will be judged,” says Dr. Wolkoff. “We hope that encouraging and rewarding exemplary work can have added benefits for our postdocs, because ultimately we want to help them secure a position, whether in academia, industry, or the government.” (See sidebar at right for the 2006 awards.)

Belfer Institute Recognizes Top Postdocs for Excellence in Research

On November 30, 2006, the Belfer Institute awarded five Outstanding Postdoctoral Research Scholar Prizes. The recipients presented their research and received their $5,000 awards from Dean, Allen M. Spiegel at a special event celebrating their achievements.

This year’s winners were:

Hui Feng, Ph.D., a postdoc in the laboratory of Dr. Charles Rubin, Co-Chair of Molecular Pharmacology. Dr. Feng’s winning paper was Regulation and Evolution of C elegans Protein Kinase D."

Michaela Jansen, Ph.D., a postdoc in the laboratory of Dr. Myles Akabas, Professor of Physiology and Biophysics. Dr. Jansen’s winning paper was "The Molecular Basis of the M2 and M3 Transmembrane Domains of the GABA_A Receptor."

Andong Gu, Ph.D., a postdoc in the laboratory of Dr. J. Donald Goldmann, Director of the Albert Einstein Cancer Center. Dr. Gu’s winning paper was "Identification of an Intracellular Foite Transporter and the Molecular Basis of Hereditary Foite Malabsorption."

Inna Shcherbakova, Ph.D., a postdoc in the laboratory of Dr. Michael Brenowitz, Professor of Biochemistry. Dr. Shcherbakova’s winning paper was "How Does RNA Fold?"

Vyacheslav Yurchenko, Ph.D., a postdoc in the laboratory of Dr. Moshe Edelkoch, Professor of Pathology. Dr. Yurchenko’s winning paper was "From DNA Replication to Translational Modification."
Becoming a PHYSICIAN

by Ben Brody
Class of 2007

What happened?" the patient asked. She was coming out of four hours of surgery. A weary resident cleaned dried blood and iodine from the skin around the surgical wound on her abdomen. The anesthesiologist had just removed her breathing tube. The patient, to my surprise, was staring straight at me—the medical student. She asked again: "What happened?" During my recent rotation, I had been rapidly expanding abdominal mass had developed. Early in her surgery, a frozen section had been sent to the laboratory, and 20 minutes later a voice over the intercom had confirmed what the surgeons had suspected: she had ovarian cancer. The tumor had spread through the pelvis and abdomen, attacking the uterus and loops of bowel. The surgeon and residents meticulously resected all visible disease, but the prognosis was grim and everyone in the operating room knew it—except me. Surely it was not my place to relay this news. The surgeon bailed me out.

"It was a real doctor," I said in a calm, soothing voice. He told her that she had ovarian cancer. The surgery had been successful, but the patient was alert and oriented. From the first weeks of medical school through the licensing exam, this initial encounter is the focus of medical education. Whether you’re examining an elderly woman with diabetes who has a foot ulcer, a young man having a panic attack, or a vomiting infant, instructing all these questions five times," patients forget anything," I was advised during my medicine clerkship. My training gave me a differential diagnosis and a good sense of which tests and medications might be useful. But after all my questions, the patient had one for me. "Do you think I’m crazy?"

"Just like that, I was in over my head. I had no script—only clinical judgment, that perplexing skill that can’t be reviewed in morning rounds or diagrammed on PowerPoint slides. "Well, I think you might very well be sick," I said. "But I think you can probably be helped here." I excused myself, feeling nauseated at this young patient’s prognosis, and went off to find an attending. These are the conversations I find the most difficult—and, I submit, the ones for which medical schools do the worst job of preparing students.

What happened? the patient asked ... The patient, to my surprise, was staring straight at me—the medical student!

Taking histories from real patients during the past year has made me begin to feel like a real doctor. But then the script ends. And the uncropped conversations that follow, the ones that are taken, when the patients’ questions begin, especially with patients who are angry or frustrated, that’s the stuff that we are caring for them, or simply their own failing health. Over time, I always thought I’d learn how to respond as the best clinicians did, defusing confrontational situations with a mix of compassion, authority, and carefully wielded humor. To be sure, this stuff is difficult to teach. There’s always a component of improvisation. And it’s hard, as a student, to know how much of yourself to put out there; you have to be emotionally involved enough to connect with the patient, but not so emotionally as to become overwhelmed. One physician told me, “See another 10,000 patients, and I absolutely promise that you’ll improve.” Until that happened, I figured, there would always be a wise attending handing the hall, ready to take over when I ran into trouble. But in the middle of my medicine clerkship, a patient I’ll call Mrs. Hayworth was transferred to our service. She had presented several days earlier with bizarre behavior and focal neurologic deficits. Computed tomography (CT) had revealed a brain mass and hemorrhagic stroke. Her condition had been stabilized in the intensive care unit (ICU), but eventually, the resident and intern instructed. "And send her for a CT of the chest, abdomen, and pelvis." When I reached the son on the telephone, he had difficulty appreciating the severity of his mother’s illness. “Perhaps you could come to the hospital to see your mom, and we could talk in person,” I suggested. He agreed to come in the following morning, and we could talk in person, “I’m not a doctor quite yet,” I said—returning, finally, to the script that had been laid out. “But you can call me whatever you’re comfortable with.”

Ben Brody is a fourth-year medical student at the Icahn School of Medicine at Mount Sinai. This article is reprinted, with permission, from The New England Journal of Medicine. September 7, 2006.

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A MYSTERY SOLVED: HOW A KEY DIETARY VITAMIN IS ABSORBED

Researchers led by David Goldman, M.D., Director of the Albert Einstein Cancer Center and Susan Resnick Fischer Professor, have solved a long-standing mystery: how the B vitamin folate—a crucially important dietary nutrient—is absorbed by the intestinal tract. The findings, published in the December 1, 2006 issue of the journal Cell, pave the way for a genetic test that can save the lives of infants who lack the ability to absorb folate. Since folate is water soluble, it can’t readily penetrate the fatty membrane of cells but instead needs a specialized uptake mechanism so it can be absorbed by intestinal cells and enter the bloodstream. Dr. Goldman and his colleagues identified the membrane protein, dubbed PCTF/HCP1, that transports folate molecules from the small intestine’s acidic milieu into intestinal cells. The Einstein study also showed that a mutation in the PCTF/HCP1 gene is responsible for hereditary folate malabsorption, a rare but potentially fatal disorder. Other Einstein scientists involved in the research were Andong Gu, Michaela Jansen, Antonette Sakaris, Song Hye Min, Shikhtana Chattopadhyay, Eugenia Tsai and Rongbao Zhao.

TAKING THE PULSE OF A GENE IN LIVING CELLS

Einstein scientists have observed for the first time that gene expression can occur in the form of discrete “pulses” of gene activity. Their study, published in the June Issue of Current Biology, used pioneering microscopy techniques developed by Robert Singer, Ph.D., Professor and Co-chair of Anatomy & Structural Biology, that allow scientists to directly observe the behavior of a single gene in real time. The researchers used a fluorescent marker that sticks to a gene and that becomes visible only when the gene is active. Dr. Singer notes that the pulsing observed in this gene important in the development of the social amoeba Dictyostelium would allow it to very precisely regulate development. Dr. Singer’s Einstein collaborators were Tatjana Ireck and Shailess M. Shenoy.

UNDERSTANDING DRUG-RESISTANT TUBERCULOSIS

Isoniazid is one of the most effective anti-tuberculosis drugs, and ethionamide and prothionamide are the most commonly used drugs for treating drug-resistant TB as well as leprosy. Yet the mechanism of action for all three drugs was unknown until the publication of two papers co-authored by William R. Jacobs, Jr., Ph.D., Professor of Microbiology & Immunology and Howard Hughes Medical Institute Investigator at Einstein, in the September 2006 issue of Nature Medicine. Dr. Jacobs conclusively established Isoniazid’s target by transfecting Mycobacterium tuberculosis a single point mutation within the gene suspected of encoding the drug target (the protein INH). Demonstrating that this transfer sufficient to confer drug resistance (INH is essential for mycolic acid biosynthesis in M. tuberculosis). In the January 2007 issue of the Journal of Experimental Medicine, Dr. Jacobs showed that ethionamide and prothionamide also target the INH protein. As Dr. Jacobs earlier found was true for isoniazid and M. tuberculosis, ethionamide and prothionamide form covalent adducts with nicothiamide adenine dinucleotide (NAD) that bind tightly to inhibit INH in both M. tuberculosis and M. leprae (the bacterium that causes leprosy). The identification of these drug-NAD adducts represents a new paradigm in the history of drug action.

A NEW TACTIC FOR TRANSFORMING STEM CELLS

Eric E. Boughassai, Ph.D., Professor of Medicine and Cell Biology, has developed a method for reproducibly differentiating human embryonic stem cells into mesenchymal stem cells that in turn can differentiate into osteocytes and adipocytes. This technique, described in the August issue of Stem Cells, has the advantage of not requiring a feeder layer of animal origin that could complicate the use of these cells for clinical purposes. The mesenchymal stem cells grow robustly, have a stable karyotype, are contact inhibited, can be grown in culture for about 20-25 passages and have an immunophenotype similar to mesenchymal stem cells derived from other sources. The ability to derive mesenchymal stem cells from human embryonic stem cells could have useful clinical applications, since mesenchymal cells offer considerable therapeutic potential in the areas of cell therapy and regenerative and reconstructive medicine. Dr. Boughassai’s Einstein collaborator was Emmanuel N. Olver.

LONGEVITY GENE TIED TO MENTAL CLARITY

A gene variant linked to living to 90 and beyond also helps very old people think clearly, according to research by Nir Barzilai, M.D., and colleagues that appeared in the December 26, 2006 issue of Neurology. Known as CETP VV, the variant alters the cholesterol exporter protein so that the body makes abnormally large “good” HDL and “bad” LDL lipoprotein particles. Dr. Barzilai, director of the Institute for Aging Research at Einstein, had previously shown that CETP VV helps people live longer—perhaps because larger cholesterol particles are less likely to lodge in blood vessels and cause heart attacks and strokes. This new finding indicates that CETP VV also protects the brain’s cognitive integrity—either through the same vascular “anti-clogging” benefit that contributes to longevity or through an independent protective mechanism yet to be found. Other Einstein scientists involved in the study were Gil Atzmon, Carol Derby, Jonathan Bauman and Richard Lipton.

ONE TREATMENT FOR ERECTILE DYSFUNCTION SHOWS PROMISE

A phase 1 trial of gene transfer therapy for erectile dysfunction (ED) indicates that the therapy can last for months and could one day be a treatment option for ED, according to a paper by Arnold Melman, M.D., Professor and Chair of Urology, published in the December 2006 issue of Human Gene Therapy. The study involved administering various doses of a transfer gene called hMaxiK to 11 ED patients. This gene stimulates potassium ion transfer in the smooth muscle cells of the penis by creating additional potassium channels. This relaxes the cells and allows blood flow required for an erection. The gene was transferred using “naked DNA,” a form of circular DNA that does not integrate with chromosomal DNA. Dr. Melman developed the therapy with George Christ at Einstein. Dr. Christ is now at Wake Forest University School of Medicine.

DEvising THE WoRld’S SMAllEST CANCER DETECTION DEVICE

Einstein researchers have received a $2 million grant from the National Cancer Institute to study tumor microenvironments—where tumors interact with surrounding tissues, cells and chemicals in ways that encourage cancer cells to become metastatic. The new grant allows Professor and Co-chair of Anatomy & Structural Biology at Einstein, and the principal investigator of the newly funded program, to team up with researchers at the College of Nanoscale Science and Engineering of the University at Albany. Dr. Condeelis and his colleagues will work to develop the world’s smallest cancer detection device: a microchip, assembled from nanoscale components, that will be just two to three cells in diameter and a tenth of a millimeter in length. When placed in a breast tumor, the microchip will gather information on the presence of metastatic cells that would demand more aggressive cancer therapy.

HOW ESTROGEN PROTECTS BRAIN CELLS

Profuse bleeding, open-heart surgery and cardiac arrest all cause global brain ischemia (inadequate blood flow to the entire brain). Animal studies have shown that administering estradiol at levels used for hormone therapy reduces nerve death and cognitive impairment following global brain ischemia. Estradiol is the main estrogen secreted by the ovaries. In a paper published online in November in the journal Endocrinology, Einstein researchers Anne M. Eltgen, Ph.D., B. Suzanne Zuki, Ph.D., and Teresa Jover-Mengual, Ph.D., describe the molecular mechanisms by which estradiol provides neuroprotection. The research showed that estradiol acts via the classical estrogen receptors, the ERα and ERβ, and the recent discovery that the estrogen receptor, the ERα, is located within many cancer cells and that estradiol, which is a natural estrogen, binds to the ERα to prevent its activation. The new finding indicates that estradiol is a potential therapeutic target for metastatic cancer.

News from the Labs
Patients being recruited for this trial have T-cell ALL that has recurred or proven resistant to other therapies. Since the FDA has also put the drug on its “fast track” approval schedule—reserved for drugs with the potential for treating serious or life-threatening medical conditions that are not well treated by existing drugs—the agency could approve tobrofosine following successful conclusion of this phase IIb trial.

The drug’s creation was sparked by an observation made more than 30 years ago. “Back in 1975, a baby who had lost all of its T cells by the age of two was found to be genetically deficient in the enzyme purine nucleoside phosphorylase, or PNP,” says Dr. Schramm. “The absence of that enzyme caused an immunodeficiency specific to T cells, with no other cells of the body affected. So we realized that a drug that could block PNP might be ideal for treating cancers that involve T-cell proliferation and also for treating autoimmune diseases, such as psoriasis and rheumatoid arthritis, that are caused by misdirected T-cell attacks.”

To design Immucillin-H and other immunolins, Dr. Schramm and his colleagues first used physical chemical measurements and quantum theory to determine PNP’s “transition state”—the brief (one-trillionth of a second) period in which a substrate is being converted to products at the catalytic site of its enzyme. Armed with a perfect picture of PNP’s transition state, the researchers used it as a blueprint to design an inhibitor structurally similar to PNP’s substrate but that would bind PNP much more tightly. The result: a drug that binds PNP almost a million times tighter that its natural substrate and that blocks PNP about 1,000 times more powerfully than any previously patented compound intended for that purpose.

Dr. Schramm has spent more than 20 years studying transition-state theory and six years designing Immucillin-H. The synthesis of Immucillin-H resulted from a long-term collaboration between his lab and the Carbohydrate Chemistry Team at Industrial Research Ltd., in New Zealand. He is optimistic that his efforts will soon pay off for patients. “For people who are dying of T-cell cancers, we hope that the outcome of our research will be a once-a-day pill that will halt or perhaps even cure their cancer while causing no side effects.”

As for using Immucillins in treating autoimmune diseases, Dr. Schramm notes that one of his second-generation Immucillins is now being tested against psoriasis in phase II clinical trials. The drug is being developed by BioCryst in collaboration with Roche Pharmaceuticals.

EINSTEIN Receives $10 Million NIH Grant for Landmark Study of Hispanic Health

The National Heart, Lung, and Blood Institute of the National Institutes of Health announced in October that the Albert Einstein College of Medicine was awarded a $10 million grant for an unprecedented, large-scale study of the health status of 4,000 people of Hispanic/Latino origin in the Bronx. Einstein was one of only five institutions nationwide to receive grants under this new Federal Program, and the only one in New York. Pictured at a reception held to thank the many community leaders who played an active role in working with Einstein to bring this landmark study to the Bronx are (l-r) Bronx Borough President Adolfo Camacho, Dr. Sylvia Wassertinel-Smoller, principal investigator of the project, and Einstein Dean, Dr. Allen M. Spiegel. The goal of the “Hispanic Community Health Study” is to identify the prevalence and risk factors for a variety of diseases and disorders among Hispanics in the United States. To be conducted over a 6½-year period, the project will address such health problems as heart disease, stroke, asthma, diabetes, sleep disorders, cognitive impairment, kidney and liver diseases and hearing impairment. Risk factors that will be assessed include nutrition, obesity, smoking, blood pressure, social and economic disparity, occupation, health care access, medication and supplement use, and the environment.
Center for Babies, Toddlers and Families Opens

Zaida M’Boirick, 5, had the honor of cutting the ribbon at the opening ceremony for Einstein’s Center for Babies, Toddlers and Families on November 28th. She was joined by (l-r) Dr. Robert Marion, director of the medical school’s Children’s Evaluation and Rehabilitation Center (CERC); Beverly Carrington, a community member; Dr. Susan Chinitz, director of the new Center; and Einstein Dean, Dr. Allen M. Spiegel. The Center, which is located at 1521 Jarette Place in Montefiore Medical Park, is an expansion of CERC’s Early Childhood Center. It provides a broad range of therapeutic services for young children and their families, with support from the Robin Hood Foundation and the City of New York.

Dr. Judah Folkman Delivers Inaugural Terman Memorial Lecture

World-renowned cancer researcher Dr. Judah Folkman honored the memory of the late Dr. Bruce Terman, Associate Professor of Medicine (Cardiology) and Pathology, by delivering the first Terman Memorial Lecture at Einstein on February 8th.

Andrus Professor of Pediatric Surgery and of Cell Biology at Harvard Medical School, Dr. Folkman, is credited with founding the field of angiogenesis research. His work has led to the development of “anti-angiogenic” drugs that have proven effective against cancer as well as age-related macular degeneration. Dr. Terman, whose untimely accidental death last year touched the entire Einstein community, was known for his research into the molecular regulation of angiogenesis.

Dr. Folkman spoke on “Angiogenesis: An organizing principle in biomedicine?” He is pictured here (center) with Mrs. Susan Terman and Dr. Mitch Kaufman, Dorros Professor of Cardiovascular Research at Einstein, who organized the lecture.
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