

# Discovery Medicine

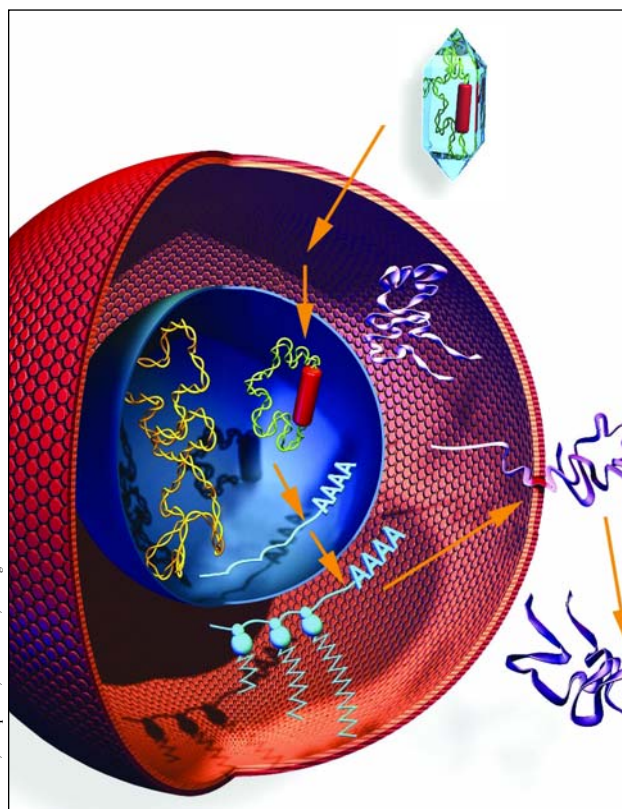
*Medicine on the Leading Edge*

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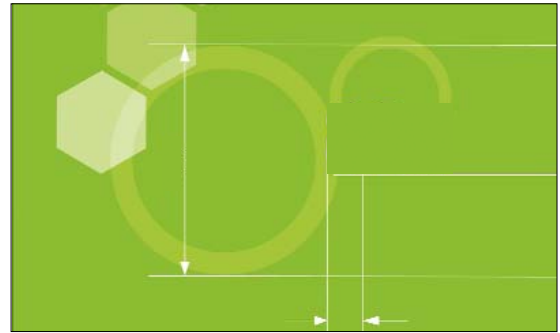


## Gene Therapy for Heart Disease, Cancer and AIDS

Pages 4, 18, 25, 37 and 58

## Editor's Note

**F**or many of the difficult-to-treat diseases, gene-based therapies and gene-based drug deliveries offer hope and excitement. In this issue of *Discovery Medicine*, articles describe the use of gene therapy to manipulate stem cells for treating heart diseases (Dr. Rosen et al. on page 18), to produce vaccines for the immunotherapy of cancer (Dr. Acres et al. on page 25 and Dr. Stevenson on page 37), and to fight HIV-1 infection (Dr. Egan on page 58).



However since their first use about two decades ago, gene therapies have remained experimental. Genes with therapeutic potential have been injected into test animals and patients in various forms -- naked or "clothed" delivered by (gene) guns, cassettes, shuttles, viruses, etc.

The efforts have been heroic. But it is time to reflect on why the gene therapy research enterprise has not been as successful in patients as scientists and physicians had hoped. To be sure, the natural barriers are formidable. Following introduction into the human body, the therapeutic genes have to battle the body's complexity, establish a hold in a hostile environment, and confront outright rejection by the body's immune system. Looking introspectively, it is clear that the vectors that have so far been used to deliver the genes are mostly inadequate to carry gene therapy onto a more successful conclusion. Their limitations have restricted us to the level of success at which we now stand.

It seems logical that the investigators in the gene therapy community first need to devote substantially more effort and resources to devising a powerful, modular, controllable, and safe gene delivery vehicle. The NIH should organize and fund "Project Gene Vector" in proportion to that applied to the "Human Genome Project." With the right tools, successful gene therapy is attainable.

*Benjamin Yang, M.D., Ph.D.*  
Executive Editor  
*Noel R. Rose, M.D., Ph.D.*  
Editor-in-Chief

<b>Editor-in-Chief</b>	<b>Noel R. Rose, M.D., Ph.D.</b> Professor of Pathology, Molecular Microbiology, and Immunology Director, Johns Hopkins Center for Autoimmune Disease Research The Johns Hopkins University Schools of Medicine and Public Health, Baltimore, MD
<b>Senior Editors</b>	<b>Jacques Banchereau, Ph.D.</b> Professor of Immunology Director, Baylor Institute for Immunology Research and Baylor/ NIAID Center for Translational Research on Human Immunology and Biodefense, Baylor Health Care System, Dallas, TX  <b>David Borchelt, Ph.D.</b> Associate Professor of Pathology The Johns Hopkins University School of Medicine, Baltimore, MD  <b>Eugene Braunwald, M.D.</b> Distinguished Hersey Professor of Medicine Chairman, TIMI Study Group Editor, <i>Harrison's Principles of Internal Medicine</i> Brigham and Women's Hospital, Harvard Medical School, Boston, MA  <b>C. Garrison Fathman, M.D.</b> Professor of Medicine, Immunology, and Rheumatology Director, Center for Clinical Immunology at Stanford Director, Division of Immunology and Rheumatology Stanford University School of Medicine, Stanford, CA  <b>John D. Gearhart, Ph.D.</b> C. Michael Armstrong Professor of Gynecology & Obstetrics, Physiology, and Comparative Medicine Investigator, Institute of Cell Engineering The Johns Hopkins University School of Medicine, Baltimore, MD  <b>Donald L. Price, M.D.</b> Professor of Pathology and Neuroscience Director, Division of Neuropathology The Johns Hopkins University School of Medicine, Baltimore, MD  <b>Stanley B. Prusiner, M.D.</b> Professor of Neurology and Biochemistry Director, Institute for Neurodegenerative Diseases University of California, San Francisco, CA  <b>J. Craig Venter, Ph.D.</b> President J. Craig Venter Institute, Rockville, MD  <b>Bert Vogelstein, M.D.</b> Clayton Professor of Oncology and Pathology Investigator, Howard Hughes Medical Institute Sidney Kimmel Comprehensive Cancer Center The Johns Hopkins University School of Medicine, Baltimore, MD
<b>Executive Editor</b>	<b>Benjamin Yang, M.D., Ph.D.</b> President, <i>Discovery Medicine</i>
<b>Associate Editors</b>	<b>Patrizio Caturegli, M.D.; David Eve, Ph.D.; Yang Lu, Ph.D.; Philip Musk, Ph.D.; Max Oppenheimer, Esq.; James J. Wang, M.D., Ph.D.</b>
<b>Copy Editor</b>	<b>Karen Hudson, Rebecca Zerzan</b>
<b>Art Illustration</b>	<b>Karen Peng, Kaite Yang</b>
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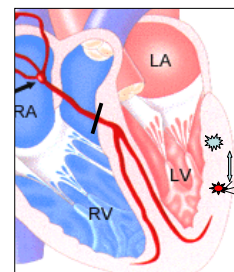
**Contact/Service**  
57 W. Timonium Rd., Ste. 207  
Timonium, MD 21093, USA  
Phone: 410-252-3631  
Fax: 410-252-3634  
service@discoverymedicine.com  
www.discoverymedicine.com

#### 4 **Editor's Note**

### 11 **Restoration of Heart Functions Using Human Embryonic Stem Cells Derived Heart Muscle Cells**

*Lior Gepstein and Izhak Kehat*

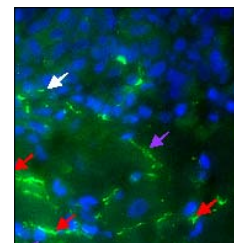
Stem cells have a great potential in regenerative medicine. Among their many capabilities, for example, they can become heart muscle cells when they are grown in a specially formulated "juice" in culture. These stem cells-derived heart muscle cells can be transplanted into the heart where they integrate into resident heart muscle and function as a pacemaker. Many technical issues remain to be addressed before stem cells can be used therapeutically.



### 18 **Adult Human Stem Cells as a Platform for Gene Therapy: Fabricating a Biological Pacemaker**

*Michael R. Rosen, Peter R. Brink, Ira S. Cohen, Richard B. Robinson*

Many people carry electronic pacemakers and, generally speaking, these devices work quite well. However, they do not automatically adjust heart rates in response to special circumstances, like exercise or emotion. Stem cells isolated from adult bone marrow can be genetically engineered to behave like the heart's own natural pacemaker cells. These stem cells can grow and integrate with native surrounding heart muscle cells, allowing the heart to react more naturally to their surroundings.



### 25 **Gene-based Cancer Immunotherapy and Vaccines**

*Bruce Acres, Patrick Squiban, and Margaret Liu*

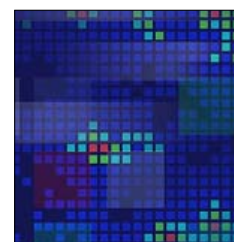
Cancer treatment has been hampered by the fact that most drugs target cancer cells as well as normal cells. Gene therapy is one of a handful of methods that will make cancer cells "stand out," allowing drugs or the host's immune system to selectively target cancer cells.



### 30 **Pharmacogenomics: Bench to Bedside**

*Richard Weinshilboum and Liewei Wang*

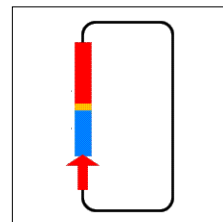
Pharmacogenetics, or pharmacogenomics, studies how a person's genetic makeup affects the person's response to drugs, holding out promise for medicine that caters to an individual's genomic makeup. Individualized medicine would be a paradigm shift from the current, centuries-old industry practice. Science, growing awareness of patients' needs, the hesitant but increasingly interested pharmaceutical industry, and government agencies are forging a movement towards personalization of drug treatments.



## 37 Turning Genes Into Cancer Vaccines

*Freda K. Stevenson*

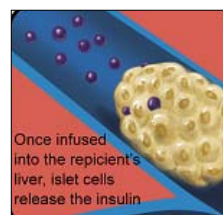
DNA vaccines are selected DNA sequences usually contained in barebone circular plasmid DNA. These vaccines can be injected into muscle or skin where they can be taken up by cells and expressed into proteins. Though its effectiveness needs improvement, it is a relatively simple, convenient, and inexpensive way of formulating a cancer vaccine.



## 43 Islet Transplantation and the Challenges of Treating Type 1 Diabetes

*Eric H. Liu, Kristina I. Rother, and David M. Harlan*

There are 18 million people suffering from diabetes in the United States alone, with 1 million of these have type 1 kind caused by autoimmune attacks against pancreatic islet cells. Islet transplantation is one way to treat type 1 diabetes, but it is far from an ideal treatment.



## 50 BRCA1 and BRCA2 in 2005

*Steven A. Narod*

The discovery of BRCA1 and BRCA2 is one of those events that immediately change people's lives. Women who test positive for one or both of the genes have options to confront the high probability of developing breast cancer. Dr. Narod gives an update.



## 55 Radiation for Early Breast Cancer: Is Less More?

*Anthony Fyles, Lee Manchul, David McCready, Maureen Trudeau, and Sasha Olsson*

For women who are diagnosed with breast cancer while still in the early stages without spreading to nearby lymph nodes, treatment can be very effective. Cancer treatment in these cases is usually a combination of lumpectomy, radiation, and tamoxifen. Radiation reduces the chance of recurrence and should be used for patients who can overcome its side effects and its inconvenience.



## 58 Actively Immunizing Patients with HIV-1: Progress on the Development of a Therapeutic Vaccine

*Michael A. Egan*

HIV-1 is a tough virus to beat. It invades and disables the body's primary defense system; it hides; it integrates itself into the host cell's genome; and it mutates. "The path towards the development of an effective therapeutic vaccine for the treatment of HIV-1 infection is littered with disappointments." Scientists keep trying.



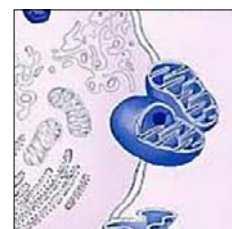
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**64 Seasonal Variation of Rheumatic Diseases***Naomi Schlesinger and Michael Schlesinger*

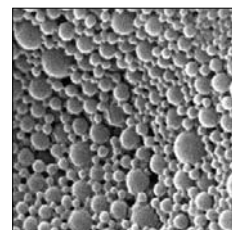
Rheumatic diseases vary by season in severity. Of course, environmental factors, such as temperature and moisture, contribute to the seasonality of some diseases. But other important factors, including as levels of hormones, antibodies, inflammatory factors, and immune response readiness, could greatly contribute to disease seasonalities.

**70 Selective Targeting of Mitochondria for the Treatment of Cancer***Pierre J. Dilda and Philip J. Hogg*

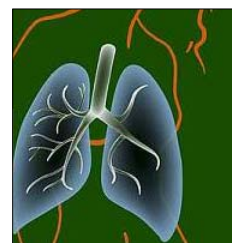
Mitochondria are a cell's fuel generators, providing ATP which power cellular activities. Drugs that target mitochondria are less likely to be compromised by drug resistance because mitochondria do not offer alternatives for cells to bypass drugs' therapeutic effects. A number of promising drugs are currently being developed to attack cancer cell mitochondria, sparing those in normal cells.

**74 Pharmacokinetics of Drugs Administered in Nanosuspension***Barrett Rabinow*

Nanotechnology is all the rage these days. In medicine, nanotechnology is being studied for, among other uses, effective drug delivery, which would serve both diagnosis and therapy. When nearly insoluble drugs are made into nano-sized particles and delivered orally or intravenously, they are dissolved faster because of their greater surface-to-mass ratio and hence the bigger exposure to "solvents" in the body.

**80 Mechanism of Disease: Pulmonary Hypertension***Harrison W. Farber and Joseph Loscalzo*

Pulmonary hypertension is a disease that eventually leads to lung and/or heart failure. Because the causes were largely unknown, it has been called "idiopathic" pulmonary hypertension. Armed with new research tools and technologies, such as genetic and genomic analyses, scientists are now uncovering the causes and pathogenesis of the disease. New understandings of mechanisms of the disease are summarized.



**88 Global Gene Expression Profiles Reveal Pathways Related to the Pathogenesis of Chronic Obstructive Pulmonary Disease**

*Wen Ning, Chao-Jun Li, and Augustine M.K. Choi*

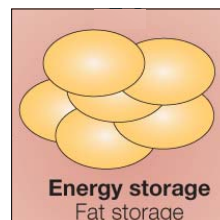
Chronic Obstructive Pulmonary Disease is primarily caused by smoking, but it does not afflict all smokers. Studies indicate that genes may determine whether or not a smoker will develop COPD. Genetic profiles of smokers who have COPD and those who don't are compared by genomic analysis.



**94 Obesity: A Chronic Disease in Need of Drug Targets and Safe Medicines**

*Leo Seman, Alex S. Burn, and Paul Burn*

Obesity afflicts 300 million people worldwide, a condition described by the World Health Organization as a major chronic disease of pandemic proportion. Obesity invites many health hazards, including type 2 diabetes, coronary heart disease, and stroke. In addition to advocating a controlled energy intake, there is an urgent need to develop new drugs to prevent and treat obesity, as the only few drugs currently available have side effects that limit their long-term use.



**104 A Change of Heart. How the People of Framingham, Massachusetts, Helped Unravel the Mysteries of Cardiovascular Disease (Book Summary)**

*Book by Daniel Levy, M.D., and Susan Brink; Summary by David Eve*

For more than 50 years, Framingham Heart Study has produced over 1,000 scientific papers and identified major risk factors associated with heart disease, stroke, and others. It changed America's heart. Cigarettes were no longer advertised as "your doctor's favorite brands." We knew, from the Study, that LDL is a "bad" cholesterol and HDL is a good one.

