

BY MARTHA AMRAM, TERESA MAGULA AND GLENN YAGO

**It is a sad irony** that, while it is widely acknowledged that the potential to cure disease and improve global health standards has never been greater, both public and private funding for biomedical research are now in decline. Since 2004, National Institutes for Health funding has stagnated. In fact, the budget cut in 2006 was steep enough to bring NIH R&D below the 2003 funding level in real terms. Arguably even more troubling, the major pharmaceutical houses have responded to their relative lack of success in developing blockbuster drugs by pulling back from high-risk, early-stage R&D.

The Milken Institute organized two day-long financial innovation “labs” – brainstorming sessions bringing together experts from a variety of fields – to explore new channels for attracting capital to drug development. The primary goal was to identify market vehicles that could leverage private philanthropic resources to reduce credit risk, attract investors and accelerate commercialization in a broad range of disease areas. Lab participants included foundation executives, patent brokers, intellectual property lawyers, private equity investors and analysts, insurance consultants, biotech entrepreneurs, and academics specializing in finance, entrepreneurship and risk analysis.

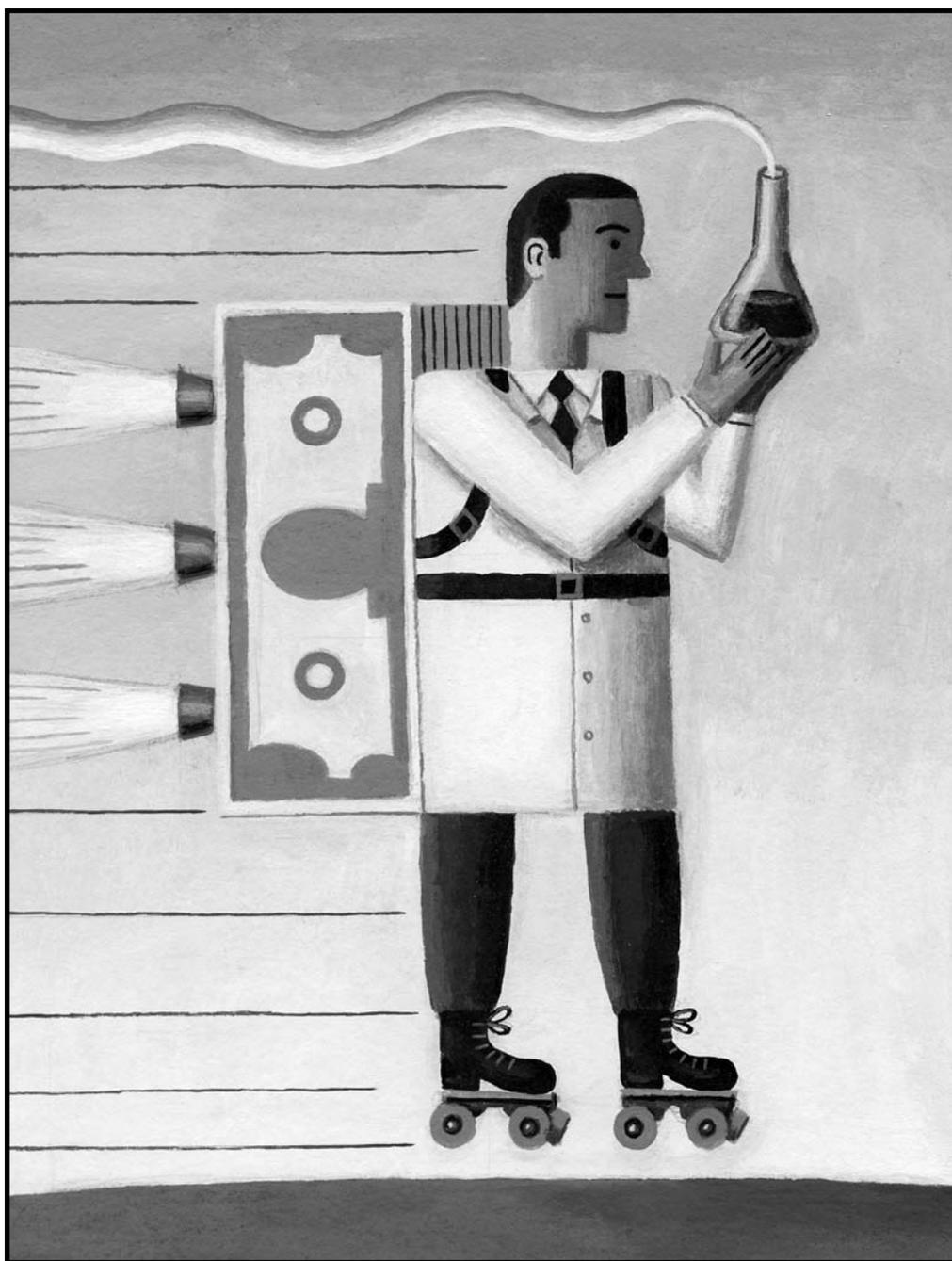
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This partial withdrawal of pharmaceutical companies as integrated developers has had serious consequences. Promising discoveries in cancer and other disease areas languish for lack of capital and expertise, and developed products fail as a result of inadequate access to marketing platforms.

What’s more, other trends are working against a comeback. The average cost of bringing a new drug through development, clinical trials and market launch has reportedly passed \$800 million. And merely making it to market is no guarantee of success: of products that do reach consumers, 70 percent fail to recoup their R&D investments – let alone offset the costs of all the new compounds that never make it beyond clinical trials.

In this environment, it is no surprise that the pace of medical innovation is far below its potential. There is virtually no venture capital available for innovative ideas that lack very substantial clinical data. One lab participant, Joe Daniele, chief operating officer of Acorn Technologies, currently controls rights to key

MARTHA AMRAM, TERESA MAGULA and GLENN YAGO are, respectively, senior fellow, research associate and director of capital studies at the Milken Institute.



JAMES KACZMAN (ALL)

discoveries for epilepsy, complete with positive early-stage results. “But finding a buyer for these discoveries” – even among big pharmaceutical companies with deep pockets and

few new drugs of their own in the works – “has been nearly impossible,” he explained.

Funding development of the next Prozac, Viagra or Claritin is thus hard. What’s even

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harder is funding development of drugs for which the primary market would be poor countries: less than 10 percent of global investment in pharmaceutical R&D is devoted to diseases of poverty that affect hundreds of millions.

### FINANCIAL INNOVATION AS A PARTIAL SOLUTION

The cost and risk associated with developing a new medication escalate dramatically as soon as the drug candidate reaches the clinic. The cost varies according to scientific complexity, but generally follows the pattern illustrated in the table.

STAGE OF PRODUCT DEVELOPMENT	APPROXIMATE COST (MILLIONS)
Discovery – preclinical validation	\$5–\$25
Phase I	\$2 - \$12
Phase II	\$8 - \$30
Phase III	\$75 - \$250+

The funding crisis occurs at the point of transition from preclinical to clinical stage development. Very few sources of funding are available to support early-stage work. In fact, most sources will not invest until the compound has been exposed to humans in Phase I safety trials. Others wait for the results of rigorous Phase II trials to demonstrate efficacy. While this strategy has been fairly effective in reducing private risk, it stifles innovation.

The most natural analogy with past innovations in the financial markets comes from the corporate bond market. At one time, no one would invest in below-investment-grade debt. But once given a transparent valuation model and market liquidity, investors flocked to the new market segment. The odds hadn't suddenly changed, but transparency made those odds understandable, while increased liquidity enabled investors to pool risk. In the pharmaceutical industry, transparent valua-

tion models should be able to play an important role in closing the Phase II funding gap, particularly as those models could help attract new sources of funding.

### SIX POSSIBLE SOLUTIONS

#### 1. Reduce scientific risk by pooling intellectual property

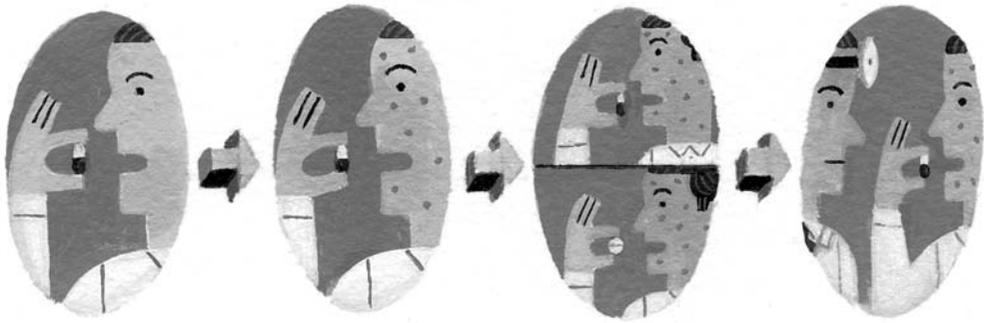
The notion of bundling patents or early-stage drug prospects to remove risk through diversification has been cited in numerous academic studies. Early attempts were made to monetize drug development opportunities by exchanging future royalties from the patent pool for an upfront sum. Peter Walsh of Harris Nesbitt identified four early transactions that pooled as many as 23 medical solutions. Each transaction required a rating by Standard & Poor's and/or Moody's; the ratings ranged from AAA to BB. Two of the deals also had credit insurance.

**BioPharma Royalty Trust (2000).** In conjunction with Royalty Pharma AG and BancBoston Capital, Yale University agreed to pay royalties on an HIV-AIDS drug discovered at Yale to Bristol-Myers Squibb in exchange for \$79 million.

**Royalty Pharma (2003).** Memorial Sloan-Kettering Cancer Center in New York City agreed to pay royalties to Royalty Pharma AG on two drugs used during chemotherapy treatments in exchange for \$225 million.

**Royalty Securitization Trust I (2004).** Royalties from 23 biopharmaceutical products, medical devices and diagnostics from 19 companies were securitized for \$228 million. The Paul Royalty Fund had invested in the young companies and then exchanged a portion of its royalty rights for an upfront payment.

**Drug Royalty LLC (2005).** The royalties from eight drugs that had been in the market an average of seven years were collateralized for \$68.5 million. The drugs were owned by a



## THE R&D PROCESS IN PHARMACEUTICALS

### PHASE I

Phase I is the first time a drug is tested on humans. Usually between 20 and 80 healthy human volunteers take the drug to test it for toxicity and its effect on people of varying races and genders.

### PHASE II

The volunteers this time are people who suffer from the disease the drug aims to help. About 100 to 300 patients are involved, and the trial can last up to two years. This phase is used to determine the drug's therapeutic effects and the dosage required.

### PHASE III

Phase III is the main clinical trial, usually involving between 1,000 and 3,000 patients. If there are established drugs for the disease, the new drug is tested against the best on the market. If there is no existing drug, the new drug is tested against a placebo.

### PHASE IV

Phase IV is carried out after the drug has been registered with the FDA. The trial is conducted to allow local doctors to become familiar with the drug and to gain their trust.

subsidiary of Drug Royalty LLC.

To better understand the risk-reward trade-off, it is useful to walk through the Yale University deal. In 1985, Yale received a patent for a treatment for HIV-AIDS. The university then granted an exclusive license to Bristol-Myers Squibb to develop the drug Zerit. In 1994, Zerit received FDA approval. In 2000, a private company, BioPharma Royalty Trust, purchased Yale's royalty stream for Zerit. A trust was created to fund the purchase payment. Yale University, Royalty Pharma and BancBoston participated in the trust. When the deal closed, Yale received a cash payment and equity in the trust.

Each quarter, the trust was to receive a payment from Bristol-Myers Squibb and, in turn, would redirect 30 percent of the payment to the inventors, per university policy. The remainder was to be used to service the loan payments, and the surplus distributed to the equity partners. Yale University got \$79 million from the trust and used the funds to

finance a new classroom and research complex at Yale Medical School. The senior debt in the transaction was rated A by Standard & Poor's, and subordinated debt was rated AA, after a credit enhancement by a reinsurance company.

Just two years later, the trust began an early write-down due to lower than expected sales for Zerit. Payments to Yale University continued, however, as there was a \$22 million line of insurance on the trust.

In retrospect, those close to the deal believed that three significant issues weakened the transaction structure. First was overreliance on a single drug for the trust's revenues. Second were excessively optimistic estimates for sales of Zerit. Finally, during the second half of 2001, Bristol Myers-Squibb dumped its entire inventory of the drug at a discount to wholesalers, stalling sales thereafter.

The Yale transaction was the earliest of the four, and the least diversified. In 2003, Royalty Pharma AG closed another transaction,

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with New York's Memorial Sloan-Kettering Cancer Center, which monetized drug royalties. Royalties from nine proven drugs were included in the transaction, as were four additional drugs in the late stages of the FDA approval process. Moody's rated this transaction AAA.

### **2. Use foundation funds to enhance credit quality and attract potential investors**

Foundations generally limit their financial participation in drug development either to providing modest funding to early research or to giving reimbursable grants with the expectation of a return from royalties on sales. In both cases, the foundations hope their early commitment will spur follow-on funding from other investors. Glenn Yago, director of capital studies at the Milken Institute, suggested two alternative roles for foundations: playing the role of credit enhancers so that debt and equity capital can be raised more cheaply, and facilitating the sharing of research for a specific disease.

In a discussion of credit enhancement, Nir Kossovsky, founder and CEO of Technology Option Capital, said it is not enough for IP holders and capital providers simply to join forces. They need a legal structure to capture the governance, obligations and payouts of their collaboration. Several foundation participants argued, moreover, that their charters required smooth spending on projects so as to conform to the budgets arising from returns on the endowment, and thus could not support the intermittent calls on their capital from a guarantee.

As for the role of foundations as facilitators of information sharing, John Wilbanks, executive director of Science Commons, said they could design funding agreements to "create a commons for a single rare disease

foundation." For example, the Huntington Disease Society of America, which currently funds a number of universities at \$25 million a year, found that it must negotiate with each university's technology transfer office if professors from different universities want to work on the same stem cell lines and reagents. The commons is a mechanism comprising contracts, definitions and funding agreements that allow funded researchers direct access to the research materials of other researchers funded by the foundation. The nonprofit Science Commons, based in Cambridge, Mass., has six rare neurological disease foundations ready to adopt its legal and contractual tools.

### **3. Use directors and officers liability insurance to enhance credit quality**

Directors and officers (D&O) insurance covers the actions of senior corporate management and board members, and includes actions pertaining to intellectual property and product development. For a premium increase, suggested Robert Block of Technology Option Capital, this coverage could be expanded to the scientific and commercial risks of biotech product development.

As a commercial entity, a special purpose vehicle (SPV) could carry D&O insurance, which would serve as an additional credit enhancement. Block pointed to a recent court ruling in which members of the Abbott Laboratories board of directors were obligated to acquaint themselves with the manufacturing process pertaining to technology development. The D&O policy was used to settle the matter out of court. Thus, Block argued, the D&O policy already insures against actions the board may take that could harm the value of the firm, including technology management, in general, and drug development failure, in particular. Insurers, he said, are already exposed to technology risk, and because the

proposed SPV governance structure increases transparency, they should be willing to provide extra coverage for extra premium.

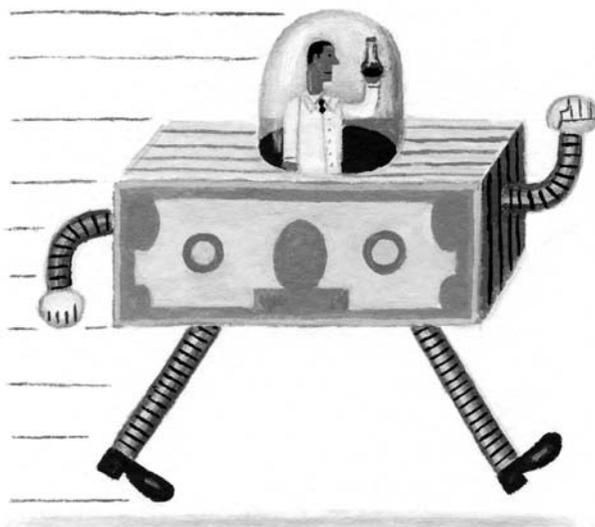
#### **4. Tap into the emerging market for IP-backed securities**

Several lab presenters were active participants in the emerging market for IP-based lending, a growing segment of the asset-backed securitization market. Robert D'Loren, CEO of New York-based UCC Capital, spoke of the large share of corporate value created by intangible assets. UCC's due diligence for intellectual property securitization includes addressing the strategic risks, such as competitor moves and bankruptcy risks that could disrupt the value of the company.

Many companies are eager to monetize their IP, said Keith Bergelt, president and CEO of IP Innovations, based in Charlotte, N.C. Recent data from Ocean Tomo, a merchant bank specializing in intellectual property, shows that, on average, 87 percent of corporate value comes from intangible assets. Bergelt's firm however, does not lend solely on the value of intellectual property. The company addresses the market with two complementary transactions: it provides financial guarantees for revenue streams attached to IP so as to remove some of the risk for traditional commercial bank and asset-financing lenders, and it makes direct loans to IP-rich companies with unused debt capacity.

Several Lab participants wondered if asset-backed or IP-secured financing actually could play a role in funding drug discovery, given industry practices. Lenders were willing to make loans for successful drugs, but not for

drugs that faced significant scientific and commercial risks. One participant suggested that if the loan-to-value ratio was 25 percent and an early-stage drug prospect is worth \$3 million to \$4 million, a loan of \$1 million might be possible. This does not reduce the need to raise significant equity capital; nor would the debt funding be sufficient to close the Phase II funding gap.



#### **5. Use donor bonds to underwrite medical research and drug delivery to underfunded patient groups**

The partnership between Bayer Healthcare AG and the Global Alliance for TB Drug Development (the TB Alliance) illustrates why there has not been a private-market solution to the fight against tuberculosis. The TB Alliance estimates that the tuberculosis drug market is currently just \$600 million per year, and is not expected to exceed \$700 million in 2010. But the cost of developing a single anti-TB drug is estimated to be near \$100 million.

The relatively small size of the market plus the economic and geographic considerations of this disease have made this effort

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unattractive for any single company. That's where the nonprofit TB Alliance fits in: to catalyze a global solution that depends on public-private partnerships. The Alliance pursues intellectual property rights in the area of TB research, as well as coordinating drug trials and research efforts. It is funded through country donations (primarily Europe and the United States), as well as by the Bill & Melinda Gates and Rockefeller foundations.

The goal of the Bayer/TB Alliance partnership, announced in October 2005, is to coordinate clinical trials to study the potential of an existing antibiotic, moxifloxacin, in the treatment of TB. The TB Alliance will coordinate and help cover the cost of the trials, leveraging substantial support from several U.S. and European government agencies. The partnership's goal is to make an anti-TB drug available at cost. If the drug development process is successful, Bayer will receive approval from the FDA for an additional prescriptive use for moxifloxacin.

A second public-private partnership discussed was that between GlaxoSmithKline Biologicals (GSK) and the International AIDS Vaccine Initiative (IAVI). GSK and IAVI will collaborate to try to develop an AIDS vaccine. IAVI, which will contribute funding, is in turn funded by donations from countries (primarily from Europe and the United States), as well as the Gates and Rockefeller foundations. The goal is for GSK to make a sustained supply of an AIDS vaccine available at cost.

In June 2005, before the G8 Summit, GSK and Bayer joined with other large pharmaceuticals and nonprofits to ask the G8 ministers for help. The public-private partnership model was working, the letter from the pharmaceuticals to G8 ministers acknowledged, but most drugs would not finish development

without greater financial support. In response, Britain announced that it would commit to purchasing 200 million to 300 million doses of the AIDS vaccine, if and when it was developed. Britain made a similar commitment for a malaria vaccine.

Health economists have argued that such guarantees can create a market as robust as that for pharmaceutical products in developed countries. In a recent study, economists at the National Bureau of Economic Research calibrated the potential for such advance-purchase agreements. It concluded that biotech and pharmaceutical companies are motivated to pursue drug prospects for markets of \$3 billion in revenue or larger – which would require a \$15-per-dose guarantee for the first 200 million doses and \$1 per dose thereafter. This approach, according to the research, would be several orders of magnitude more cost effective than current methods of funding vaccines for poor countries.

A critic of the advance-purchase commitment, Andrew Farlow of Oxford University, has argued that the program design will not lead to the most effective cure for malaria because it rewards the first pharmaceutical solution to market. What if the second vaccine to market is the better cure? Program supporters say that not all funds will be spent at once, so there will be purchasing power left for the second to market. Farlow also argues that the program design is rife with potential corruption, as the host government is asked to contribute \$1 per vaccine while donors pay \$14. An unscrupulous firm could potentially bribe government officials to allocate millions of dollars in revenue.

### **6. Use donor bonds to underwrite medical research and drug delivery to underfunded patient groups**

In March 2005, six European governments

## PARTICIPANTS IN THE MILKEN INSTITUTE FINANCIAL INNOVATION LABS

### SESSION 1: SANTA MONICA, CALIF.

**Shai Aizin**, Consul for Economic Affairs, Government of Israel Economic Mission

**Martha Amram**, Senior Fellow, Milken Institute

**Robert Block**, Chief Operating Officer, Technology Option Capital LLC

**Jerry Cacciotti**, Managing Director (Life Sciences), Strategic Decisions Group

**David A. Cohen**, Principal, GKM Capital

**Lee Cole**, Chairman, Bioaccelerate

**Joe J. Daniele**, Chief Operating Officer, Acorn Technologies Inc.

**Roy Doumani**, Professor of Molecular and Medical Pharmacology, UCLA School of Medicine, Department of Molecular and Medical Pharmacology

**Stockton Gaines**, Chairman, Acorn Technologies Inc.

**Judith Giordan**, Managing Director, Alerion Partners

**James Gore**, Chief Operating Officer, Seattle Biomedical Research Institute

**Cindy Gustafson**, Chief Financial Officer, Seattle Biomedical Research Institute

**Nir Kossovsky**, Founder, President, and CEO, Technology Option Capital, LLC

**Joel Kurtzman**, Senior Fellow, Milken Institute

**Laura Martin**, Soleil/Media Metrics

**Victor Martinez**, Director, Guggenheim Partners

**Gary Michelson**, Karlin Technology Inc.

**Dale S. Miller**, Executive Chairman, Proneuron Biotechnologies Inc.

**Peter Passell**, Senior Fellow, Milken Institute

**Tomas Philipson**, Senior Fellow, Milken Institute and University of Chicago

**Gilbert Rishton**, Founder and Director, Channel Islands Alzheimer's Institute

**Howard Soule**, Managing Director, Knowledge Universe

**Alison Sowden**, Chief Financial Officer, Huntington Library

**Glenn Yago**, Director of Capital Studies, Milken Institute

### SESSION 2: NEW YORK CITY

**Martha Amram**, Founder, Growth Options Insights

**Tom Benthin**, Milken Institute

**Keith Bergelt**, President and CEO, IP Innovations

**Robert Block**, Chief Operating Officer, Technology Option Capital LLC

**Jeffrey Brandt**, Principal, JLB Consulting Inc.

**Jared Carney**, Director of Marketing and Project Development, Milken Institute

**Lee Cole**, Chairman, Bioaccelerate

**Robert D'Loren**, President and CEO, UCC Capital

**Jay Eisbruck**, Managing Director, Moody's Investors Service

**Gargee Ghosh**, Program Officer and Economist, Bill & Melinda Gates Foundation

**Judith Giordan**, Managing Director, Alerion Partners

**Steve Hartman**, General Counsel, Andersen Partners

**Michael Klowden**, President and CEO, Milken Institute

**Nir Kossovsky**, Founder, President, and CEO, Technology Option Capital LLC

**Joel Kurtzman**, Senior Fellow, Milken Institute

**Ellen Lubman**, Celtic Pharma Management L.P.

**Laura Martin**, Soleil/Media Metrics

**Molly McGuire**, Special Projects Coordinator, Alpha-1 Foundation and COPD Foundation

**Eytan Mesznik**, Managing Director, Mesco LTD

**CB Mulhern**, Vice President, Deutsche Bank Securities Inc.

**Jean Nichols**, President, J. Nichols Inc.

**Ilya Oshman**, Vice President and General Manager, Pfizer Strategic Investments Group

**Eric Silvergold**, Guggenheim Partners

**Gregory Simon**, President, FasterCures

**Peter Walsh**, Managing Director, Harris Nesbitt

**John Wilbanks**, Executive Director, Science Commons

**Glenn Yago**, Director of Capital Studies, Milken Institute

announced donor bonds, a financial innovation designed to accelerate the delivery of medicines to Africa. Donor bonds imitate the practice of credit card companies that use future customer repayments as the collateral for borrowing. With donor bonds, future gifts are the collateral for borrowing.

The first donor bonds were issued in April 2006, backed by donation commitments from the U.K., France, Italy, Norway, Sweden, South Africa and Spain. (The U.S. government declined to participate, saying that the federal budget process does not allow for the long-

term commitments required by this securitization structure.) The bonds will be issued by a special purpose vehicle known as the International Finance Facility for Immunization. The programs financed by the bonds will be managed by the Global Alliance for Vaccines and Immunization (GAVI), which has received a pledge of \$750 million over 10 years from the Bill & Melinda Gates Foundation. GAVI expects that the acceleration of immunizations through donor bonds will "save the lives of 5 million children and protect another 5 million as adults." **M**