FasterCures
The Center for Accelerating Medical Solutions

ENTREPRENEURS FOR CURES:

The Critical Need for Innovative Approaches to Disease Research

The measure of our success is lives saved and suffering diminished – not the number of grants awarded, publications presented, or laboratory space acquired.

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I. The Bottom Line is Curing Disease

Innovation. Business leaders obsess about it endlessly. A search on Amazon.com™ for books about innovation yields more than 200,000 items. What does it mean to innovate in the search for cures for disease?

The irony about medical research is that its *outcomes* are often innovative – new knowledge about biology and disease, and new products to treat disease – but its *processes* in many cases are not.

What if you were in the business of curing a disease – not "discovery" or "research," or of selling a product – but of curing a disease? What would your business model be?

It probably wouldn't be to create an environment in which the researchers whose work was central to your success pursued their individual interests or career goals and not necessarily yours. Or one in which you were interested in funding only the earliest or latest stages of product development and nothing in the middle.

It probably wouldn't be to invest increasingly large sums of money for increasingly smaller returns, to get a product to your customer 15 years after you started.

But that's effectively the system we have in charge of finding cures for the diseases that affect us all.

The past few decades have brought enormous breakthroughs in the fundamental knowledge necessary to understanding, preventing, diagnosing, and treating many diseases – advances such as the sequencing of the human genome, the application of RNA interference to inhibit gene expression, and the ability to use stem cells to treat human disease.

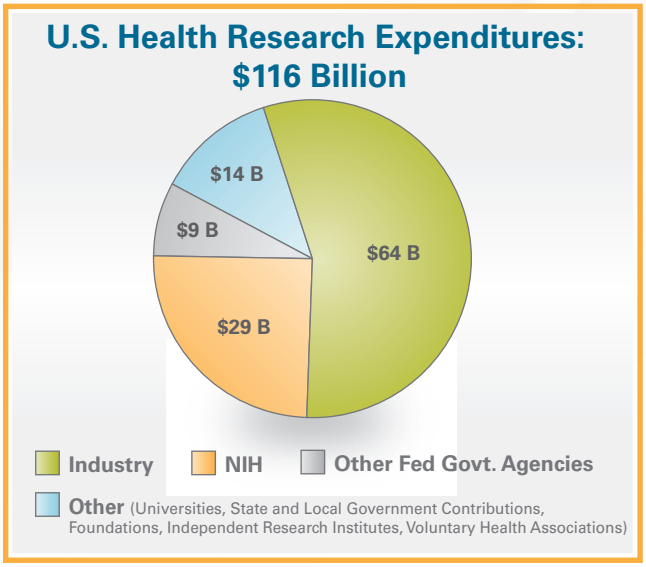
But our ability to translate exciting new discoveries into products that can help patients is severely lagging behind the pace of discovery. There remains a formidable list of diseases for which there are no cures or even meaningful treatment options.

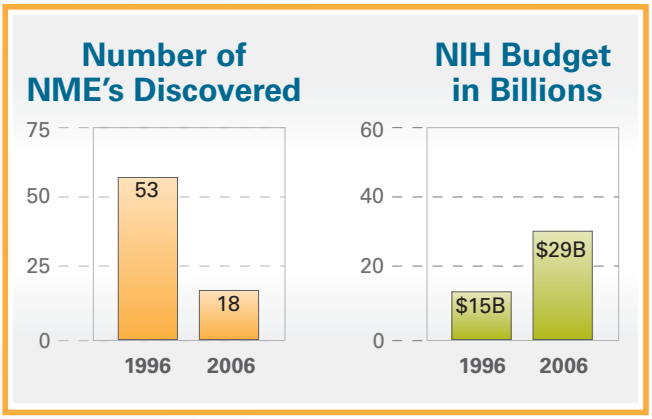
Since 2004, *FasterCures* has worked to identify the elements of innovation that could accelerate progress in curing disease across the board. This white paper is a summary of what we have learned to date.

II. The High Costs of Business as Usual

Along with the moral imperative to conquer disease and relieve suffering comes the economic reality that illness and its costs are debilitating to our economy. According to the Centers for Medicare and Medicaid Services, the United States spent $2.1 trillion on healthcare in 2006, or more than $7,000 per person.[1]

In the United States alone, $116 billion was spent on biomedical research in 2006—nearly $29 billion by the National Institutes of Health (NIH) and more than $64 billion in 2006 by industry.[2] These are substantial investments, but in reality they are miniscule when one considers that only 5.5 cents of each American health dollar is invested in research to cure costly conditions such as obesity, heart disease, cancer, diabetes, and Alzheimer's.





Moreover, after years of rapid growth and record profits in the pharmaceutical industry, the era of blockbuster drugs seems to be coming to an end. Fewer unique molecules are being discovered, and only a small percentage of these ever make it into clinical trials and through the regulatory approval process. For example, the number of "new molecular entities" approved by the Food and Drug Administration (FDA) fell from 53 in 1996 to 18 in 2006, over a period when the budget for the NIH was almost doubled, from less than $15 billion to $29 billion, and industry's investment increased significantly as well. In addition to the reduced pipeline, it still takes far too long, as long as 15 years[3], to take an idea through development, testing, and regulatory approval.

"If you think research is expensive, try disease."

– Mary Lasker
Founder, Lasker Foundation

[1] http://www.cms.hhs.gov/NationalHealthExpendData/downloads/highlights.pdf (Accessed 05/28/08)

[2] http://www.researchamerica.org/uploads/healthdollar2006.pdf. The remainder was spent by federal government agencies other than NIH, and by other institutions such as universities, state and local governments, and foundations. (Accessed 05/28/08)

[3] http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=4 (Accessed 05/28/08)

It's not just love that money alone can't buy – it's cures, too. We need to be more strategic about how resources are used; address the growing gap in the research continuum between basic discovery and commercial development; foster collaboration among researchers, institutions, disciplines, and sectors; and apply some management to the science that can help drive progress along the continuum.

Shortly after World War II, the NIH created a research enterprise system whose central organizing principle was the study of human biology. In addition to this system of *studying diseases*, we need to create a medical research enterprise whose central organizing principle is *curing diseases*.

"Innovation has nothing to do with how many R&D dollars you have. When Apple came up with the Mac, IBM was spending at least 100 times more on R&D. It's not about money. It's about the people you have, how you're led, and how much you get it."

– Steve Jobs
Co-Founder and Chairman, Apple, Inc.

III. Addressing Challenges Within the Traditional Research System — *No One Said It Would Be Easy*

What's behind the slow momentum in clinical discovery and application? There are many factors, but among them are structural obstacles that have arisen from the ways in which the biomedical research enterprise has grown and evolved along with the nation's increasing investment in science over the past 50 years.

In the simplest terms, there are three stages of medical research:

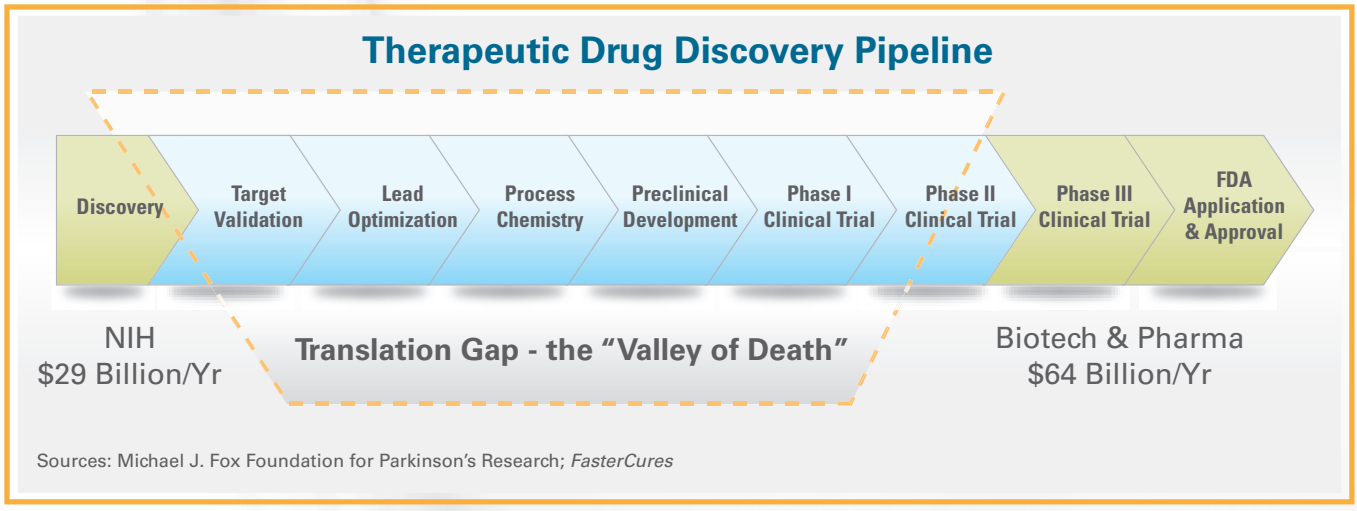
1. ***Basic research or basic discovery*** is the earliest stage of research, carried out for the advancement of knowledge, without necessarily any regard to its application to practical problems.

2. ***Translational research*** is the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment and prevention of human disease – the critical bridge between basic research and clinical research. It includes intermediate steps such as identification of biomarkers, target and pathway validation, and development of and testing in animal models.

3. ***Clinical research*** is research in human subjects aiming toward approved treatments for patients.

Our current publicly-funded academic research infrastructure, as guided by the policies and practices of NIH – the single largest sponsor of biomedical research in the world – has focused primarily on unlocking the underlying questions of biology, that is, *basic research*. This has been a critical approach, leading to many advances in our understanding of human and disease biology, but it is not sufficient to develop a therapy for a patient.

The biopharmaceutical industry funds primarily clinical research – and as costs have grown and uncertainty increased, companies are in many cases investing later along the research continuum and becoming more conservative in their decisions about what to fund. The average cost to research and develop a successful drug is estimated to be more than $800 million, which includes the cost of thousands of failures.[4]



[4] http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=5 (Accessed 05/28/08)

The result is an ever-widening gap – referred to by some as a "valley of death" – in funding and support for the kind of research that moves basic science down the path toward treatments.

Translational and clinical research—which aim to apply fundamental knowledge to the human condition—are far more difficult and expensive to conduct than basic research because they often involve complex organisms (i.e., animal models, humans) living in multifaceted environments. Translational and clinical research are typically conducted under strict regulatory regimes, for example, for the protection of laboratory animals or human subjects, or to protect against conflicts of interest. Thus, structural and intellectual barriers have made it difficult to quickly or easily translate basic research into clinical applications.

Aside from this gap or "leak" in the research pipeline, there are significant cultural barriers to accelerating progress toward patient-relevant outcomes.

Making change to the infrastructure and reward systems within academic research institutions is difficult. An entire bureaucracy has grown up around research publications, grant seeking and grant making, academic empire building, and intellectual property protection.

Fierce competition for funds, publications, and patents serves as a disincentive to institutionalized communication and data exchange between basic and clinical researchers and among research institutions. Scientists wanting to tackle complex research problems using cross-disciplinary approaches often face obstacles within their institutions and from funding sources.

Key Issues Affecting Progress in the Traditional Academic Research System

Infrastructure

- Institutional stakeholders' resistance to changing infrastructure and rewards systems – in areas such as publication, tenure, grants, and intellectual property – to promote collaboration and innovation;
- Lack of institutionalized communication and data exchange between basic and clinical researchers; and
- Inadequate opportunities for cross-disciplinary training and practice.

Research Environment

- Highly specialized, reductionist approach to scientific inquiry;
- Little funding or reward available for high-risk research;
- Focus on individual organizational challenges instead of collaborative approaches to "big picture" problems;
- Increasing conflict-of-interest challenges arising in public-private partnerships;
- Lack of public understanding of the challenges facing the disease research endeavor;
- Insufficient focus on translating basic research into clinical application;
- Inadequate dissemination of previous research efforts – especially failures; and
- Failure to aggregate funding across organizational lines to achieve larger scale impact.

Moreover, our current systems for reviewing and funding research are highly conservative, placing heavy emphasis on established researchers and high success rates in research outcomes rather than in clinical outcomes. Novel, high-risk proposals do not fare well in a system driven to maximize positive results in the face of limited fiscal resources. The peer-review system is also oriented around evaluating individual proposals and identifying flawed ideas – not around prioritizing research projects for a particular field or funding team science.

Individual researchers have a strong professional stake in the current system, but perhaps more importantly, institutions have powerful stakeholder interests that make change difficult to achieve. In 2005 the top ten universities awarded NIH funds received almost 10,000 grants providing more than $4.2 billion to their budgets as well as prestige to their faculties.[5] Grants went to almost 3,500 institutions located all over the United States, creating widespread political support.

"Why can't we continue to answer the underlying questions in biology while also addressing those questions critical to specific diseases? Why can't we do both?"

- David Baltimore
Nobel Laureate, Professor of Biology
California Institute of Technology

Universities and hospitals have devoted increasing amounts of time and resources over the last decade trying to maximize the benefits of the intellectual property created by their researchers. Staffing at technology transfer offices of U.S. universities, hospitals, and other research institutions doubled between 1997 and 2006, and the number of new patent applications filed by these institutions almost doubled between 2001 and 2006 (though the number of patents issued has remained static). Licensing income is worth millions of dollars annually to many of these institutions.[6]

For all the money flowing through the system, there is remarkably little emphasis on specific goals or milestones to cure disease or achieve specific clinical results. Researchers often insist that "science cannot be managed," and that the role of sponsors is to provide ever-increasing funds without directing how those funds will be used. The definition of accountability is customarily that funds are used as proposed and that reporting requirements are met. As a result, emphasis on speed or direct responsiveness to health needs is spotty, and the time from initial discovery to dissemination and commercialization can sometimes be measured in decades—an outcome that is simply unacceptable to the citizens who fund this research and expect to benefit from it.

Traditional research institutions designed around the goal of advancing our knowledge of basic biology are not easily redirected to undertake the innovative efforts needed to accelerate the development of new medical solutions. It's not that the medical research system has failed its original purpose. But years of discovery, which has included the genome and information revolutions, the doubling of our national investment in research through NIH, and a new sense of urgency for progress in curing diseases, have created a changed research environment that demands a system with greater flexibility, efficiency, and accountability.

The measure of our success is lives saved and suffering diminished – not the number of grants awarded, publications presented, or laboratory space acquired.

[5] http://report.nih.gov/award/trends/Rnk_05_All.xls (Accessed 05/28/08)

[6] http://www.autm.net/events/file/AUTM_06_US%20LSS_FNL.pdf (Accessed 05/28/08)

IV. Finding Big Ideas in Small Spaces — *New Business Models to Accelerate Research*

"What we call 'innovation' really isn't innovative at all; it's usually just another way of revving up, lubricating or refueling the machine."

- Douglas Rushkoff
"Get Back in the Box:
Innovation from the Inside Out"

Pressures to reform the academic research system to be more problem-oriented, to establish and regularly reassess priorities, and to leverage research funding to accelerate progress in translational and clinical research have yielded incremental changes.

In recent years, NIH has adopted several new initiatives to advance translation of basic discovery to research with clinical relevance – for example, through its Roadmap for Medical Research.[7] The Roadmap set many of the right goals: fostering more collaborative research; linking together existing clinical research networks; providing core services to aid those conducting translational research; and supporting the training and career development of physician-investigators. There are examples of NIH initiatives that successfully support these goals. But at less than $500 million, the Roadmap represents an investment of less than 2% of NIH's budget.[8]

Change is slow, and innovative efforts outside NIH and industry are needed now more than ever to create a parallel track of disease research that complements existing efforts while aggressively pursuing innovative research agendas and approaches.

Components Essential to Successful Innovation in Disease Research

Research Resources

- Research roadmaps to facilitate prioritization of research projects in a disease area;
- Application of new technological advances to the biomedical research endeavor (such as bioinformatics and high-throughput genomic analyses);
- A better system to collect and use patient data in research;
- More human capital focused on the translational research gap;
- Clear guidance documents and regulatory pathways for new technologies and approaches from the federal government;
- Guidelines for establishing and maintaining successful public-private partnerships;
- A global perspective of the drug discovery and development process; and
- Collaboration on patient registries and recruitment for clinical trials.

Research Infrastructure

- Organizational transformation to address emerging research needs;
- Risk-sharing on pre-competitive tools such as biomarker development;
- Integration of patient health records and electronic medical records for research into the Nationwide Health Information Network (NHIN);
- A more pervasive focus on translational research at NIH;
- Increased funding and predictable rewards structure for very novel, high-risk research; and
- Standardization of clinical terms.

Research Environment

- Online tools to facilitate collaboration among researchers and interaction with data;
- Increased awareness of the importance of translational research programs;
- Effective communication of the complexity and value of medical research to the lay public and the media;
- Unified advocacy behind key public policy issues (such as privacy, intellectual property, and ethical issues);
- Development of an information portal for disease research organizations to exchange best practices; and
- Goal-oriented intellectual property arrangements.

[7] http://nihroadmap.nih.gov/ (Accessed 05/28/08)

[8] http://officeofbudget.od.nih.gov/ui/2008/Final%20Roadmap.pdf (Accessed 05/28/08)

Models of Innovation

FasterCures has often found models of innovation in the conduct of medical research outside the traditional establishment. *The Redstone Acceleration and Innovation Network (TRAIN)* is a group of unique nonprofit foundations that fund and conduct medical research across a spectrum of diseases, from breast cancer to Parkinson's disease – organizations such as the Cystic Fibrosis Foundation, the Michael J. Fox Foundation for Parkinson's Research, and the Multiple Myeloma Research Foundation. In some circles these groups are becoming known as *"venture philanthropies"* – or as we like to say, sources of *"passion capital."*

TRAIN has come together under the auspices of *FasterCures* to help its members more easily and effectively support each other's efforts to produce better and faster results, and to bring their sense of urgency about conducting bench-to-bedside translational research to the medical research community as well as to the public at large.

In many cases, these disease research organizations were created by patients and their families, who were frustrated by the slow pace or inadequate attention of the traditional medical research system. Collaborative, mission-driven, results-oriented, and strategic in their use of capital, these groups are motivated solely by moving promising therapies from the laboratory bench to the patient's bedside as rapidly as possible – even those that do not directly fund therapy development. Supporting translational research is a critical part of their mission.

Nonprofit organizations can support alliances that typically would not be supported through public investments, such as with for-profit companies. They can bridge disciplines, institutions, and ideas when the opportunity arises and in record time. With financial incentives, they can change the culture and structure of research.

"For too long, our national research enterprise has been dominated by long-term investment in low-risk, low-yield, but reliable bonds. These new disease research organizations represent a diversification of our national research portfolio with a variety of high-risk, high-reward ventures."

- Greg Simon
President, FasterCures

Even though private contributions cannot match those of the federal government or industry, nonprofit disease research organizations play a special role. Because of their close relationships with the patient communities, their ability to move quickly to address emerging translational and clinical opportunities, and their capacity to leverage public investment, these organizations can catalyze and jump-start innovation. Moreover, they can serve as a reliable source of funds for novel, high-risk research that might not be able to compete successfully for public funds.

Because they are closer to the patients and therefore closer to the problems needing solutions, innovative nonprofit funders have heightened awareness of the importance of translational and clinical research programs. Increasingly, they are forming a unified advocacy front on key public policy issues affecting the pace of research, such as privacy regulations, intellectual property challenges, and the resolution of ethical issues.

Venture philanthropies' innovative practices fall into four general categories:

1. ***Strategic use of capital.*** Most of these organizations have in some way conducted a rigorous process to determine where they can have greatest impact, in light of their small size relative to government or industry research and development efforts. Like any entrepreneurial company, each has sought a niche to fill that addresses a need in the marketplace.

   Their strategies include:
   - using a "venture capital model" of philanthropic investing, providing initial funding for high-impact, early-stage projects;
   - targeting the most rewarding areas for research, creating a research "portfolio" (i.e., taking a proactive planning approach rather than being entirely investigator driven);
   - prioritizing research projects for the field as a whole, not just for the individual organization;
   - placing a high degree of emphasis on translational research, clinical trials, and drug development; and
   - convening management and business advisory boards to supplement scientific advisory boards.

2. ***Building collaborations.*** Collaboration is central to the philosophy of virtually all of TRAIN's disease research organizations — among researchers of different disciplines, among institutions, and among sectors. Most of these organizations have created formal consortia of medical research centers to team on disease research and share information. Increasingly, they are collaborating with the pharmaceutical and biotechnology industries to advance clinical trials and drug development. The existence of these academic research consortia are often a motivator for industry to develop drugs, since the networks are available to help quickly advance clinical development of promising compounds.

   Collaborative efforts include:
   - linking partners through common informatics systems, allowing them to centralize and share study data and resources;
   - training partners in the design, standardization, and conduct of clinical trials; and
   - showcasing exciting ideas from academia to industry.

3. ***Streamlining the grantmaking process.*** Many of these organizations have radically streamlined the grantmaking process, simplifying the paperwork involved, and letting researchers get on with their research. Several, for example, limit applications to five pages, make grant decisions within 60 days, and fund approved projects within 90 days. NIH takes 9-10 months from submission of application to award (in the rare event that a researcher receives an award on the first try), and applicants are advised to set aside a week just to fill out the application forms.

4. ***Sharing information.*** Another central organizing principle for most of these disease research organizations, which are more concerned about collaboration than competition, is the need to share information and resources. These groups operate on the expectations that scientists must share results and strategies with their funders and peers far in advance of publication; data and products from studies should be centralized and shared; tissue banks should be established and accessible to the research community; and clinical trials databases should be widely available.

Free of the pressures of publication and career advancement in academia and the bottom-line imperatives of the private sector, nonprofit foundations are ideally positioned to make relatively high-risk investments that could significantly move a field of research forward and increase the likelihood that other parties also will invest.

Some of the ways foundations are already doing this are:

- developing pre-clinical tools that benefit everyone in a disease area;
- targeting research in areas that will help translate basic scientific discoveries into therapies – such as biomarkers, target and pathway validation, animal models, and small pilot clinical trials;
- creating funding mechanisms that enable or even require academic researchers to work with industry partners;
- bringing focus, management, and accountability to academic research;
- providing access to a patient community and resources by creating patient registries, biorepositories, and networks of trained clinical trials sites;
- working with companies to explore new indications for existing drugs;
- employing high-throughput screening to help industry identify better investment opportunities;
- facilitating industry access to academic scientific experts and clinicians;
- advocating with the FDA for the approval of new treatments; and
- serving as a "Good Housekeeping Seal of Approval," validating particular researchers, paths of inquiry, clinical trial designs, endpoints, or targets for follow-on industry investment.

Philanthropic funders of disease research can play an absolutely critical role in stimulating research in under-resourced disease areas, and helping bridge the widening "valley of death" in research funding between basic discovery and later-stage research.

Collaboration Is Critical

Some of the most exciting work to come in biomedical science lies at the intersection of disciplines. For example, genomics, proteomics, behavioral science, and epidemiology all have something to add to our understanding of cancer, schizophrenia, diabetes, obesity, and heart disease. Research is becoming more interdisciplinary and multi-institutional, and this requires:

- team-based science;
- well-understood challenges, concrete, attainable goals, and clear action plans for translation;
- effective management to drive progress toward milestones;
- risk-sharing;
- tools for collaboration (such as structured communications and data-banking for research purposes);
- improvement in how research results are reported, published, and disseminated;
- shared commitment and accountability;
- openness to organizational change and consolidation to facilitate research progress and efficiency;
- trust; and
- an agreed approach to intellectual property that maximizes collaboration in research.

"Much is known, but unfortunately in different heads."

- Werner Kollath nutritionist

V. *FasterCures:* Linking Entrepreneurs for Cures

Recognizing that a collective approach is needed to successfully address the barriers to innovation, *FasterCures* has:

- created *The Redstone Acceleration and Innovation Network* to accelerate innovative disease research;
- developed the *Philanthropy Advisory Service* to provide professional research and evaluation of potential nonprofit investments for philanthropists, estate planners, and financial advisors;
- promoted medical record and biological material databases that are readily available for research through its *Think Research* and *BioBank Central* initiatives;
- shared case studies of successes and failures in novel disease research approaches;
- hosted regular information exchanges between disease research groups and targeted audiences to continue the innovation discussion;
- worked with the Biotechnology Industry Organization to create an information clearinghouse to accelerate the exchange of information between the financial community and nonprofit research groups;
- increased participation and visibility of nonprofits at investor conferences to help match research efforts with appropriate investors; and
- advocated on behalf of disease research/patient groups with FDA on matters of product safety and risk.

VI. Closing Thoughts by Greg Simon

"It's very difficult for large organizations to change. My own advice is to form small organizations that will change the big ones."

- Michael Milken
Chairman, FasterCures

Medical research is badly in need of entrepreneurship. It can and does exist in small nonprofit disease research organizations that see themselves as accountable to their stakeholders – patients – for finding a cure for their disease. But nonprofit foundations that are increasingly focusing their efforts on translational and clinical research cannot fill this role alone; their investment represents a small fraction of the total national investment in medical research. The success of the bench-to-bedside translation depends on the joint efforts of NIH, academic institutions, nonprofit foundations, and the pharmaceutical and biotechnology industries.

There is an urgent need for more creative thinking about and models for financing large, high-risk, long-term investments that could lead to biomedical breakthroughs (including within the biopharmaceutical industry). There is an urgent need for rigorous research and trusted evaluation of the work being done by medical researchers to help guide funding decisions, and for performance measures and standards for accountability in all sectors that give confidence to taxpayers, investors, and philanthropists that their resources are being well used.

All sectors – government, industry, and nonprofit – have critical roles to play in this most important of enterprises. All can benefit from the lessons we've learned about innovation in every other facet of our lives – and from thinking of themselves as ***"entrepreneurs for cures."***

For further reading on innovation in medical research and the barriers to it, please see the following reports on the *FasterCures* Web site:

1. "*Lake Tahoe Retreat*," www.fastercures.org/pdf/Tahoe.pdf
2. "*Summit on Innovation in Disease Research*," www.fastercures.org/pdf/Innovation_Report.pdf
3. "*Investing in Innovation: Accelerating Disease Research Through Philanthropy and Business*," www.fastercures.org/pdf/Investing_in_Innovation.pdf

Through our SmartBrief publication and quarterly newsletter *FastTrack*, *FasterCures* enables its growing subscriber base to stay on top of the latest news in the search for cures.

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FASTTRACK
Quarterly Newsletter

To sign up for our free, quarterly newsletter with the latest news stories from *FasterCures*, visit: www.fastercures.org

FasterCures is dedicated to saving lives by saving time. Our mission is to identify and implement global solutions to accelerate the process of discovery and clinical development of new therapies for the treatment of deadly and debilitating diseases. FasterCures was formed under the auspices of the Milken Institute.

FasterCures

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FasterCures
1101 New York Ave, NW Suite 620
Washington, D.C. 20005
(202) 336-8900
www.*FasterCures*.org