Open-Source Molecular Biology: Will Open-Source Biotech Stimulate Innovation in Health Care?

As the costs of innovation rise, many in the pharmaceutical and biotech industries see the value of more open access to intellectual property, along the lines of the open-source movement in software. Such a move toward "open-source biology" may spur other profound changes—new cures for neglected diseases in the developing world, and new business models and pathways for innovative drugs. Experimental organizations have already entered hybrid public–private collaborations, often turning to open-source intellectual property (IP) agreements to spur innovation and make drug development more affordable. Indeed, the pharmaceutical and biotech sectors may be forced to adopt open-source practices to stay in business. At the same time, open-source biotech could make public health systems far more responsive to global pandemics and other health emergencies.

This memo is the first in a series of Health Horizon's *Signals:* Quick hit forecasts of big-picture topics designed to stimulate long-term strategic thinking. Each *Signal* includes an overview of pertinent data and expert interviews, and is intended to point to important trends likely to emerge over the next decade and beyond.

The biotech industry arose in the late 1970s when new intellectual property arrangements came together with venture capital and developments in life sciences such as monoclonal antibodies. Twenty years later, new norms are emerging in response to the evolution of life sciences and the innovation drought in pharmaceuticals and biotech. Although we now speak of "globalized life sciences," less than 10 percent of the world's health research dollars go toward problems that affect 90 percent of the world's population—the poor in developing countries.[1] Meanwhile, industrialized nations face rising demand for expensive new vaccines and other drugs, the costs of which threaten the sustainability of their health care systems. Open-source biology may help bridge the allocation gap and make the development of new drugs more affordable.

THE INNOVATION DROUGHT

The biotech industry is encountering rising costs due to restrictive IP arrangements created early in the biotech age. Under such arrangements, companies are claiming patents on such things as genetic code and proteins. As a result, investment in IP management is significant, and litigation in biotechnology is almost as common as in the medical-device industry.

To recoup these soaring costs, companies develop only the most profitable drugs. In the past 30 years, only one percent of the drugs produced by the pharmaceutical industry were for diseases that mainly affect the world's poor.[2] What's more, nearly 70 percent of new drugs are considered "me-too drugs" that differ little from existing drugs and involve little or no innovation. At the same time, studies show that scientists are increasingly withholding data due to the ethos of secrecy that is part of the pharmaceutical and biotech industries' culture.[3] In this way, our current patent-centered IP regime may be a significant barrier to innovation because it stifles the creation of goods beneficial to the public's health rather than stimulating innovation as patents were designed to do.

While interest in biotech's promise has grown, investors have become impatient given that the collective profits of the industry amount to a loss of nearly $40 billion over the last 25 years.[4] Adding impetus to the search for new models for innovation are the rise of computational biology and the influx of computer scientists and engineers into the life sciences. These professionals are familiar with the success of open-source software. As a result, the use of open-source bioinformatics and databases has already increased significantly in the biotech field.

GLOBAL HEALTH
HEALTH HORIZONS PROGRAM
SR-978A

The anti-retroviral debates of the late 1990s have also had an impact on IP norms. When Yale University, the holder of the IP for stavudine, loosened its rights, the price of the drug declined in developing countries by 30-fold. In this way, the humanitarian needs of the poor are beginning to affect norms in the science and technology sectors. But even when humanitarian concerns are not their primary goal, pharmaceutical companies such as Eli Lilly, Merck, Aventis, Johnson & Johnson, and Novartis are taking part in open-source initiatives such as the Cell Signaling Network to get a jump on innovative drug discovery.

WHAT IS OPEN-SOURCE BIOLOGY?

Many of those involved in open-source biology question whether the metaphor is accurate given the differences between software and biotechnology. Drew Endy of the Molecular Sciences Institute describes open-source biology simply as the free distribution of biological information and methods in the service of mankind.

There are already several open-source or open-access scientific journals, such as *Hinari* (http://www.who.int/hinari/en/) and the *Public Library of Science* (http://www.plos.org). These provide the foundation for free exchange of biological knowledge; however, there is an obvious need to link computational biology and wet labs to bring drugs to the marketplace.

Most open-source biology works with a range of licensing mechanisms to create a common pool such as the Creative Commons in software. There are also peer-to-peer and open collaborations for a wide range of open-source biotech tools. The BIOS initiative at CAMBIA is a public research institution that uses distributed IP to support agriculture in developing countries. The *Centro Internacional de Agricultura Tropical* in Colombia has developed apomictic seeds (seeds that don't need to be fertilized to reproduce) for poor farmers in Latin America. On the health front, the Institute for One World Health and several other public–private partnerships have numerous drug and vaccine candidates in various stages of clinical trial. The Molecular Sciences Institute in Berkeley, California, is a basic science laboratory that is committed to making its research and technology available to benefit the public by using wide licensing to industrial partners to foster commercial application of its biological technology among many other methods.

Rob Carlson is an Associated Fellow at the Molecular Sciences Institute in Berkeley, California. MSI's mission is to predict the behavior of cells and organisms in response to defined genetic and environmental changes, and it seeks to widely disseminate its research results using a variety of open-source methods.

Q | What are the key factors in the emergence of open-source molecular biology? Is this a movement?

Open-source molecular biology is actually not novel. Life sciences have always had a tradition of sharing reagents, knowledge, and biological materials. What is new is that much of the applied technology is owned by someone and is becoming more expensive to use. But we're seeing a shift in the costs associated with manipulating the genome, and the skills required to accomplish this are more widespread. Countries that traditionally have not had the resources to develop their own life sciences are beginning to find it easier. Some, such as India, have adopted more open approaches to intellectual property, but whether this will remain so is a question since India recently joined WIPO [the World Intellectual Property Organization], and more pharmaceutical companies are moving into the Indian market. Whether open-source practices constitute a movement is still too early to know.

Q | What are the differences between open-source software and open-source life sciences? Are there obstacles in the life sciences that could make this much more difficult to accomplish?

I'm not sure what open source really means. When Drew Endy and I started kicking these ideas around in 2000, it had a different meaning. I'm really using it as an analogy. Molecular biology isn't software and DNA is not code. The means of production in biology are really quite different from software, and you cannot transmit data the same way. I think that someday biology may feel like software and you'll be able to write code for DNA or proteins and design things, but that's not where we're at right now. At the moment we still rely on evolution.

Q | Have any ethical issues emerged?

Beyond the obvious bioterrorism issue, we have the problem of bio-error. We make mistakes, mistakes have already been made, so what we do to fix them will be important. It isn't useful to demand a certain behavior from scientists without having mechanisms to guarantee it. Biology isn't like medicine and engineering, where you have licensing and regulatory mechanisms. In both cases, you have to go to someone who knows far more than you do, and if they screw up, the consequences are fairly obvious. In biology, if something dangerous gets out you often won't be able to find out who did it, but you'll still have to find a remedy. If we try to control the science, we may find that unethical participants will just create a black market. The best strategy will be to have as many scientists with excellent training as possible and good communication networks.

Q | What efforts exist outside the global health arena and what is their promise?

The BioBricks project at MIT has its Genetically Engineered Machines Competition, where they're building circuits and students are getting an excellent education. It's modeled on the integrated circuits programs of the early 1970s. During that era, companies each had their own fabrication house and design software. DARPA funded classes for students to learn to use the same design software. Now we have MIT, Berkeley, Stanford, and the University of Texas at Austin all building on this model. The fundamental problem is that we don't have good technologies to support engineering in the life sciences. If we have more trained people and an open structure, we may see more innovation. This will be increasingly important as we face threats such as SARS, West Nile Virus, and pandemic influenza. We have no rapid response for vaccine production. The technologies exist, but we're not investing in them. Rather than stockpiling Tamiflu, we could focus on DNA vaccines. These are potentially much less expensive and could be distributed more rapidly. Distributed manufacturing of DNA vaccines would be far more effective at the local level and could further lower costs.

Q | Do you think that open-source molecular biology could promote new business models? On the other hand, is the current IP framework such a hindrance that open-source IP will be necessary for innovation?

The business models for biology stink at the moment. Good tools simply are not available, and our ability to use biology to solve problems is not good. But this is changing. Right now you can order a DNA fragment or protein over the phone. And we're getting our hands around important mechanisms at the molecular level such as RNA interference. Now we know RNA interference is an important part of viral and bacterial pathogenesis. If we know the sequences that interrupt RNA circuits in an influenza virus, for example, we may be able to address pathogens at the molecular level. Developments such as this may alter the business model in pharmaceuticals and biotech now characterized by libraries of small molecules and lead compounds screened for the best fit rather than the more engineering-like approach RNA interference may offer. In the next 20 years we may see progress in really unexpected ways as the cost of doing science decreases, and we see countries in Africa, for example, finding novel ways to fight infectious diseases with these tools.

Q | What are the implications of DIY [do-it-yourself] molecular biology and biohacking? How will they affect the public perception of biotech?

This is all very early just now. The Amateur Scientist column in *Scientific American* used to explain how to build simple lab equipment at home, but if you relied on that you would be very limited in your capabilities. Unless you really know what you are doing, you wouldn't get very far. But eBay and its progeny have completely changed access to truly useful equipment. The Web also provides access to reagents, genome sequences, and protocols. That said, just like anything else, doing biology takes skill and practice. I doubt that most biohackers have been at it long enough to do anything interesting. Professionals either have all the toys they need or go to a VC to start a company. But the opportunity for the hacker is there. It's just a matter of time before we start getting surprised on a regular basis. As to the public's response, well, you could decide to be afraid or you could see this as an opportunity. I don't know that a garage hacker is any more likely to cause something nasty than a Ph.D. in a government or corporate lab—remember that the anthrax attacks used a strain developed by the U.S. government.

VIRTUAL PHARMA: THE TROPICAL DISEASE INITIATIVE

One model of open-source drug discovery is the Tropical Disease Initiative (TDI) of Stephen Maurer, Arti Rai, and Andrej Sali, funded by the World Health Organization and the Rockefeller Foundation.[5] TDI is a Web-based network that mobilizes volunteers with expertise in drug discovery, proteomics, and compound libraries to find the best drug candidates for tropical diseases and reduce the costs of developing them. In this way, a consortium of scientists and institutions working under open source licenses produces freely available knowledge that companies can use to manufacture drugs (see Figure 1).

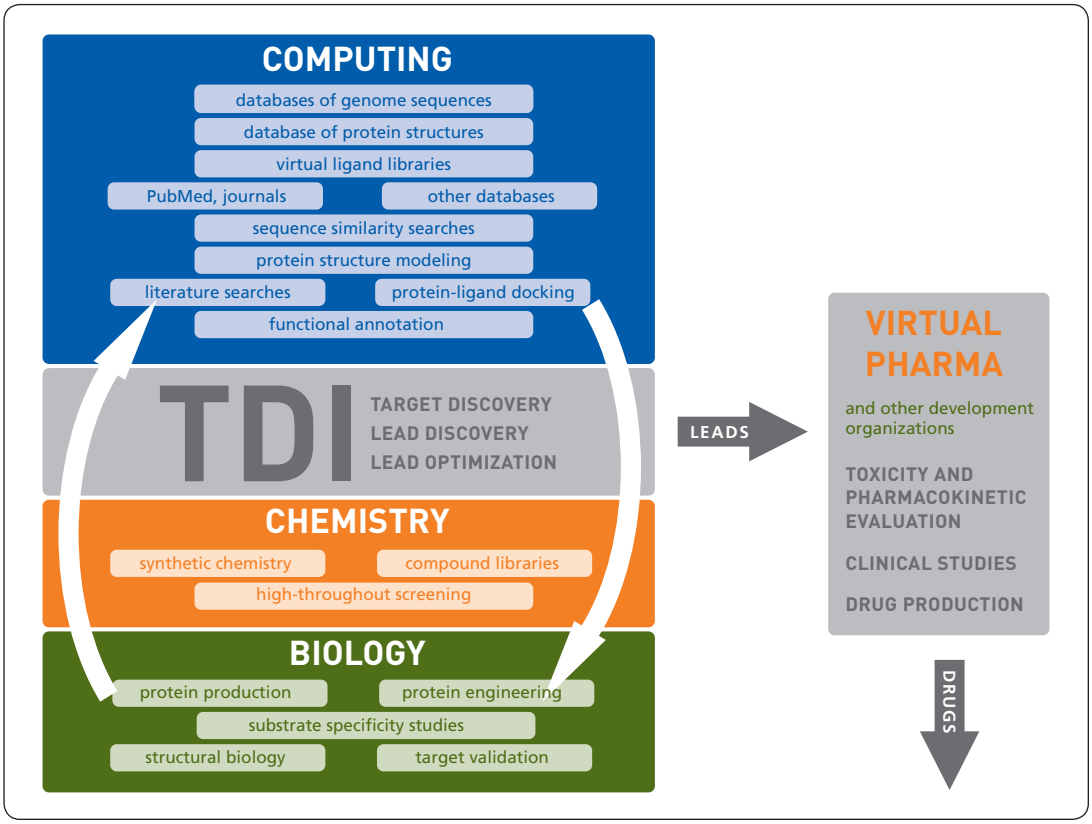
Rather than the substantial financial incentives that traditional pharmaceuticals offer, the rewards under this framework are non-monetary: advertisement of expertise, satisfaction of working on humanitarian causes, acquisition of new skills, peer recognition, and so on. The model helps lower costs by bringing competition back into the marketplace, since patents can actually decrease competition by granting monopoly rights for a given term. Competitive bidding to manufacture the leading drug candidates also works to keep costs down. At the same time, the manufacturers of generics can find their own new drug candidates, decreasing overall costs even further.

LICENSING AND OPEN SOURCE

As with open-source software, licensing arrangements are critical to open-source biology. In software, recent projects such as the Creative Commons use various licensing agreements to encourage open access to copyrighted materials. While there are important differences between software and the life sciences, open-source biology can draw on a variety of licensing options as well: [6]

- **Public Domain License**—permits anyone to use the material for any purpose.
- **Creative Commons Attribution License**—permits anyone to use the material for any purpose providing proper attribution is given.
- **General Public License (GPL)**—gives the user the right to use or modify the material in any way but prohibits users, by means of *copyleft licenses*, from seeking intellectual property rights on the derivative material.

1 | The TDI Model of Online Collaboration



Source: Maurer, S., Rai, A., Sali, A., Finding Cures for Tropical Diseases: Is open source an answer? *PLoS Medicine* 2004; 1,3

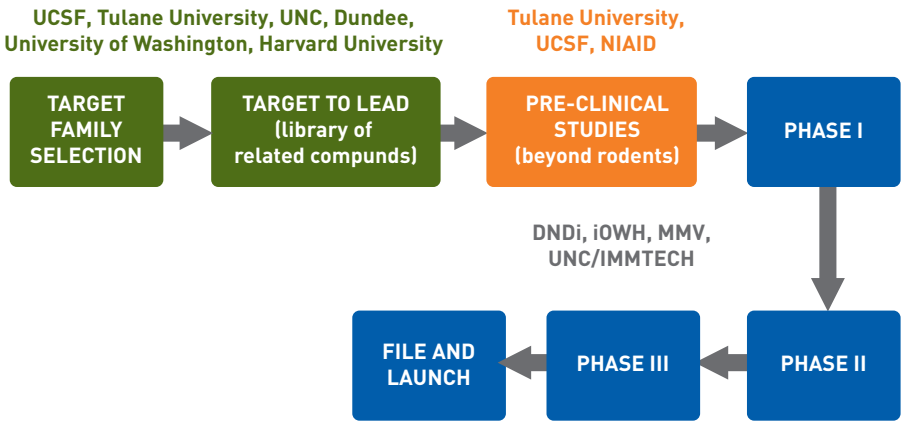
» **Copyleft License**—puts the product in the public domain for free under a GPL; all subsequent modifications remain free under the same GPL.

» Licenses that permit commercial companies to obtain and exploit patents outside the developing world. Often used in tiered marketing and pricing structures.

Participants in the drug-development process can use these mechanisms to foster collaboration and creativity.

Another model proposed by James McKerrow of the University of California, San Francisco, consists of a consortium of academic and industry partners that moves lead compounds from the bench to clinical trials to the marketplace by involving different partners at each stage. Open access figures prominently in this model and gives drug manufacturers a financial incentive to get involved in global health efforts. For example, "unprofitable" anti-parasitic drugs for global health problems such as African trypanosomiasis could be developed by firms interested in crossover anti-fungal drugs for more profitable industrialized markets. Figure 2 outlines how this kind of academic–industry collaboration might work.

Such a consortium could be funded by a range of philanthropies, government research organizations such as the NIH, and other groups such as the Institute for One World Health, a nonprofit pharmaceutical company devoted to neglected diseases. This network of collaborators focusing on different stages of development could bring lead drug candidates to the marketplace more quickly and at a more reasonable cost.



UCSF: University of California, San Francisco
NIAID: National Institute of Allergy and Infectious Diseases
DNDi: Drugs for Neglected Diseases initiative
IOWH: Institute for One World Health
MMV: Medicines for Malaria Venture
UNC: University of North Carolina
IMMTECH, Inc: Pharmaceutical company

2 | Academic–Industry Collaboration for Drug Development

Source: McKerrow, J., Designing Drugs for Parasitic Diseases of the Developing World, *PLoS Medicine* 2005; 2,8

PEER-TO-PEER PRODUCTION MODELS

Innovation in biotechnology depends heavily on creating the right biological tools to facilitate research. In the late 1980s, for example, polymerase chain reaction (PCR) revolutionized the way biological sciences are practiced. Creating new tools can be facilitated by leveraging industry, state, and philanthropic funds and expertise to create peer-to-peer networks that can reduce the amount of time required to innovate. New social technologies such as wikis—user-maintained databases such as Wikipedia that are easy to use and update—that enable such networks to emerge, combined with the new licensing mechanisms outlined above, can facilitate open collaboration. Such open-source, peer-to-peer networks are proliferating, and include DARPA's BioSpice program, BioBricks, the SynapticLeap, BioForge, and InnoCentive.

Community computing grids such as the well-known SETI@home are developing in the life sciences as well. The World Community Grid under the direction of Arthur Olsen at the Scripps Institute has recently created FightAIDS@Home using a software program called "AutoDock." AutoDock "is a suite of tools that predicts how small molecules, such as drug candidates, might bind or 'dock' to a receptor."[7] The group hopes to use such community computing grids on a massive scale to test how different small molecules dock to HIV protease and thus find the ones that work more quickly than existing market-based or competitive strategies.

OPEN-SOURCE BIOLOGY OF THE FUTURE: BIOHACKING OR DIY BIOLOGY

The rise of computational biology and public access biotech databases has created opportunities for "biohacking." There is already an online magazine called *Biotech Hobbyist* for biotech hobbyists and DIY biotech hackers.[8] In addition, Natalie Jermijenko and Eugene Thacker have written *Creative Biotechnology: A User's Manual*, where readers can learn how to clone a tree or start a culture of their own skin.[9]

Biohacking brings up concerns about ethical responsibility along with fears that open-source methods may be exploited by bioterrorists. While posing important ethical dilemmas, however, the ethos of biohacking may also provide new ways of thinking about the body, health, medicine, and even art.

Indeed, "bioart" has come into prominence in recent years. Bioart calls into question the basic assumptions of the biotech industry to create new meanings about biotech, life, and intellectual property. The Critical Arts Ensemble has developed a "contestational biology" project that seeks to challenge prevailing industry norms.[10] By means of art that appropriates biotechnologies, this group attempts to move beyond the dominant ways of looking at science by doing such things as creating a new version of Monsanto's herbicide-resistant Roundup Ready seeds. While one may disagree with the politics of the Critical Arts Ensemble, one can get important signals about the possibilities of moving beyond the "technology as a tool" or the "master molecule" narrative of genetics that may hinder future innovation as our knowledge of biological systems becomes more complex.[11]

—Jody Ranck

For more information on this topic, contact:

Jody Ranck
Co-Director, Health Horizons Program
650-233-9518
jranck@iftf.org

BioBricks (http://www.biobricks.org)—attempts to create a bio or scientific commons that can provide the next platform for new biotechnology tools.

BioForge (http://www.bioforge.net)—a project of the CAMBIA BIOS largely to develop new tools and agricultural products for farmers in developing countries.

Molecular Sciences Institute (http://www.molsci.org)—a cell biology research institute founded by Nobel Laureate Sydney Brenner and Roger Brent, which has been at the forefront of fostering a culture of open-source molecular biology.

Alliance for Cell Signaling (http://www.signaling-gateway.org/aboutus/)—a joint project between the Alliance for Cell Signaling and *Nature*, funded by a number of pharmaceutical companies, to provide open access to developments in cell signaling that are important to the development of new products..

Science of Collaboratories (http://www.scienceofcollaboratories.org/)—an organization devoted to studying the behavioral aspects of scientific collaborations.

International HapMap Project (http://www.hapmap.org/abouthapmap.html)—an international collaboration to develop a haplotype (closely linked alleles that tend to be inherited together and can be associated with diseases such as asthma, arthritis, diabetes, and heart disease) map of the human genome. The HapMap is expected to be a key resource for researchers to use to find genes affecting health, disease, and responses to drugs and environmental factors.

BioSpice (https://biospice.org/index.php)—an open-source collaboration developed by DARPA to develop tools for systems biology. The University of California at Berkeley also has an important node in this research collaboration at http://biospice.lbl.gov/.

Low Hanging Fruit (Sandler Center Open-Source Database) (http://itsa.ucsf.edu/~schisto/fruit.html)—a UCSF–based high-throughput screening database on parasitic diseases.

ENDNOTES

1 Global Forum for Health Research, *Monitoring Financial Flows for Health Research: Behind the global numbers*, Geneva 2006; see http://www.globalforumhealth.org/Site/000__Home.php.

2 Médecins Sans Frontières, *Fatal Imbalance: The crisis in research and development for drugs for neglected diseases,* Geneva, 2001; http://www.msf.org/source/access/2001/fatal/fatal.pdf.

3 Campbell, E.G. et al., Data Withholding in Academic Genetics: Evidence from a national survey, *Journal of the American Medical Association* 2002; 287,4:473–479.

4 Hamilton, David. P., As Scientists Search for Cures, They Gobble Investor Cash; A handful hit the jackpot. *Wall Street Journal*, May 20, 2004.

5 Maurer, S., Rai, A., Sali, A., Finding Cures for Tropical Diseases: Is open source an answer? *PLoS Medicine* 2004; 1,3.

6 This overview is based on Maurer et al., op. cit., and Hope, J., *Open Source Biotechnology*, Doctoral Thesis for The Australian National University, Canberra, Australia, 2004; http://rsss.anu.edu.au/~janeth/OpenSourceBiotechnology27July2005.pdf.

7 World Community Grid, *FightAIDS@Home* Web site, http://www.worldcommunitygrid.org/projects_showcase/viewFaahResearch.do.

8 *Biotech Hobbyist* Web site, http://xdesign.ucsd.edu/biotechhobbyist/.

9 Jermijenko, N., and Thacker, E., *Creative Biotechnology: A user's manual*, Newcastle, UK, 2004; http://www.locusplus.org.uk/biotech_hobbyistNJ.html. See the *Cool Tools* Web site by Kevin Kelly for more details, http://www.kk.org/cooltools/archives/000582.php.

10 Critical Arts Ensemble, *Contestational Biology* Web site, http://www.critical-art.net/biotech/conbio/index.html.

11 Thacker, E., Open Source DNA? *Haus der Kulturen der Welt*, Berlin, October 10–13, 2001; http://www.mikro.org/Events/OS/text/Eugene-Thacker_OSDNA.htm.

WILL OPEN-SOURCE BIOTECH STIMULATE INNOVATION IN HEALTH CARE?

2006 Fall Conference

NEW BUSINESS MODELS IN THE GLOBAL HEALTH ECONOMY

October 11–12

For more information contact:

Lea Gamble
650-233-9573
lgamble@iftf.org

INSTITUTE FOR THE FUTURE

HEALTH HORIZONS PROGRAM

Institute for the Future

650-854-6322
www.iftf.org