

## Finding Cures for Tropical Diseases: Is Open Source An Answer? \*

Stephen M. Maurer, Arti Rai & Andrej Sali\*\*

### I. INTRODUCTION

Tropical diseases affect more than 500 million people, one tenth of the world's population.<sup>1</sup> Malaria, for example, kills more than one million people each year.<sup>2</sup> And yet, only about one percent of new drugs treat tropical diseases.<sup>3</sup> For diseases prevalent in rich countries, patent incentives and commercial pharmaceutical houses have created health innovation systems that are the envy of the world. However, the patent system does not work for diseases in developing countries, where companies cannot sell enough patented products to cover their research and development (R&D) costs. Proposed solutions to address this problem fall into two categories: charitable adjustments to the patent system and non-profit venture capital firms.

Proposals for charitable adjustments to the patent system generally involve using subsidies to prop up drug prices and

---

\* This article is based on S.M. Maurer, et al., *Finding Cures for Tropical Diseases: Is Open Source an Answer?*, 1 PLOS MED. 3 (2004).

\*\* Stephen M. Maurer is a Visiting Lecturer, Goldman School of Public Policy, University of California, Berkeley. Arti Rai is a Professor of Law at Duke University School of Law. Andrej Sali is a Professor at the Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry and The California Institute for Quantitative Biomedical Research, University of California, San Francisco.

1. See Richard E. Davis, Parasitology and Tropical Diseases, at [http://www.library.csi.cuny.edu/~davis/faculty\\_page/Parasit\\_links/parasitology\\_links.html](http://www.library.csi.cuny.edu/~davis/faculty_page/Parasit_links/parasitology_links.html) (last visited Sept. 23, 2004).

2. WORLD HEALTH ORGANIZATION, INHERITING THE WORLD: THE ATLAS OF CHILDREN'S HEALTH AND THE ENVIRONMENT 20 (2004), available at <http://www.who.int/ceh/publications/en/07malaria.pdf>.

3. See O. Trouiller & P.L. Olliaro, *Drug Development Output from 1975-1996: What Proportion for Tropical Diseases*, 3 INT'L J. OF INFECTIOUS DISEASE 61, 61-63 (1998-1999).

restore incentives.<sup>4</sup> The problem with this approach, however, is determining how large the subsidy should be. In principle, the most cost-effective solution is to set a subsidy that barely covers expected R&D costs. However, determining drug R&D costs is difficult. Published estimates of such costs vary widely.<sup>5</sup> Set the subsidy too low and nothing will happen. Set the subsidy too high and costs skyrocket. Cost containment is an important issue, and to the best of our knowledge, no sponsor has used subsidies to prop up drug prices and restore incentives.

The second approach involving non-profit venture capital firms has started to bear fruit. Today, more than half a dozen "Virtual Pharmas" exist. Unlike conventional pharmaceutical houses, "Virtual Pharmaceutical Companies" or "Virtual Pharmas" do little or no development in-house. Instead, they develop a portfolio of promising drug candidates through a web of agreements with commercial and academic partners. Like their corporate cousins, Virtual Pharmas look for promising drug candidates and push development through clever contracts with corporate partners. Today, Virtual Pharma manages most of the world's R&D effort for tropical diseases.<sup>6</sup> They are responsible for most drug candidates currently under development. The challenge is to make them stronger. Virtual Pharmas need more upstream research, particularly in linking genomics and chemistry.<sup>7</sup> They suffer from constricted budgets,<sup>8</sup> making cost containment essential. "Open source drug discovery" could alleviate these problems.

---

4. See Michael Kremer, *Creating Markets for New Vaccines - Part II: Design Issues*, in *INNOVATION POLICY AND THE ECONOMY* 73, 73-76 (Adam B. Jaffe, Josh Lerner Lerner, & Scott Stern, eds., 2001); Mattias Ganslandt, et al., *Developing and Distributing Essential Medicines to Poor Countries: The DEFEND Proposal*, 24 *WORLD ECONOMY* 779, 792 (2001); *Helping the Poorest*, *THE ECONOMIST*, Aug. 14, 1999, at 11.

5. See Arnold S. Relman & Marcia Angell, *America's Other Drug Problem*, *THE NEW REPUBLIC*, Dec. 16, 2002, at 27, 29-30.

6. Personal Communication with Solomon Nwaka, Scientific Officer, Medicines for Malaria Venture; Personal Communication with V. Holt, CEO, OneWorld Health.

7. See Solomon Nwaka & Robert G. Ridley, *Virtual Drug Discovery and Development for Neglected Diseases Through Public-Private Partnerships*, 2 *NATURE REVIEWS: DRUG DISCOVERY* 919, 924-25 (2003).

8. See generally e.g., *MEDICINES FOR MALARIA VENTURE, ANNUAL REPORT 2002*, 31-38 (2003), available at <http://www.mmv.org/filesupld/53.pdf>; Declan Butler, *Gates Steps Up War On Malaria with Donation of \$168 Million*, 425 *NATURE* 331 (2003).

## II. ANALYSIS

### A. OPEN SOURCE DRUG DISCOVERY

To date, open source methods have made little headway beyond software.<sup>9</sup> However, computing and computational biology are converging. In the same way that programmers find bugs and write patches, biologists look for proteins (“targets”) and select chemicals (“drug candidates”) that bind to them and affect their behavior in desirable ways. In both cases, research consists of finding and fixing tiny problems hidden in an ocean of code.

What would open source drug discovery look like? In analogy with current software collaborations, we propose a Web site where volunteers could search and annotate shared databases. Individual pages would host tasks like searching for new targets, finding chemicals to attack known targets, and posting data from related chemistry and biology experiments. There would also be chat rooms and bulletin boards where volunteers could announce discoveries and debate future research directions. Over time, the most dedicated and proficient volunteers would become leaders. Just as it does today, Virtual Pharma would choose the best candidates and develop promising discoveries.<sup>10</sup> Most importantly, all discoveries would be made available without patents, in a manner that maximizes access in the developing world.<sup>11</sup>

### B. INCENTIVES WITHOUT PATENTS

Patents are not the only way to elicit innovation. Economists have shown that software collaborations appeal to a variety of motives including ideology, learning new skills,

---

9. See generally Dan L. Burk, *Open Source Genomics*, 8 B.U. J. SCI. & TECH. L. 254, 255 (2002); Kenneth Neil Cukier, *Community Property: Open-source Proponents Plant the Seeds of a New Patent Landscape*, 1 ACUMEN 54, 57-58 (2003) (noting the first seeds of an open source biology movement are emerging in bioinformatics), available at <http://www.cukier.com/writings/acumen-cukier-oct03.pdf>; Janet Hope, *Open Source Biotechnology?* (2003) (describing limitations to open source biology), available at <http://rsss.anu.edu.au/~janeth/OSBiotech.html>.

10. Personal Communication with Solomon Nwaka, Scientific Officer, Medicines for Malaria Venture; Personal Communication with V. Holt, CEO, OneWorld Health.

11. For a discussion of the different licenses under which discoveries might be available, see S.M. Maurer, et al., *Finding Cures for Tropical Diseases: Is Open Source an Answer?*, 1 PLOS MED. 3 (2004).

gaining reputation, and impressing potential employers.<sup>12</sup> These incentives may sound limited, but open source software would not exist without them. Similar incentives should motivate biologists. In fact, gaining reputation through publication is a particularly strong motive for academic biologists.

Now consider the universities and corporations who will be asked to supply people and resources. In sharing data, research tools, and other inputs, one might expect that intellectual property rights would be an issue. However, a sensible manager does not assert rights unless she expects to earn a profit. Since the commercial value of their inputs depends almost entirely on U.S. and European markets, universities and companies have little to lose by sharing their intellectual property with groups that fight tropical diseases. In fact, some private firms already do this.<sup>13</sup> Additionally, sophisticated university licensing offices tolerate open source software projects that do not have significant commercial value. We think that they will be similarly understanding of open source biology with low commercial value. Life sciences companies will probably be equally tolerant.<sup>14</sup> The main challenge will be to show donors that an open source project can keep members from diverting donated information into unauthorized commercial research.

Finally, consider the private companies whose facilities will be needed to turn open source discoveries into actual drugs. During the 1950s, the March of Dimes developed polio vaccines without any patents at all.<sup>15</sup> Instead, corporate partners received contract payments to help with development.

---

12. See Josh Lerner & Jean Tirole, *Some Simple Economics of Open Source*, 50 J. INDUS. ECON. 197, 212-217 (2002) (discussing programmers' motivations).

13. See Dennis Normile, *Monsanto Donates Its Share of Golden Rice*, 289 SCIENCE 843, 845 (2000) (describing Monsanto providing "royalty-free licenses to speed up work on a genetically modified rice that could alleviate vitamin A deficiency around the world); Dennis Normile, *Syngenta Agrees to Wider Release*, 296 SCIENCE 1785, 1785, 1787 (2002) (stating that the Syngenta group releasing its rice genome sequence on its web site and on CD-ROM); Personal Communication with V. Holt, CEO of One World Health.

14. Arti Rai, *Open and Collaborative Research: A New Model for Biomedicine*, in INTELLECTUAL PROPERTY RIGHTS IN FRONTIER INDUSTRIES: BIOTECHNOLOGY AND SOFTWARE (Robert Hahn, ed., forthcoming 2005).

15. See JANE S. SMITH, PATENTING THE SUN 220-23, 338 (William Morrow and Co., Inc. 1990) (chronicling the development of the polio vaccine).

The arrangement was good business. While contract profits may have been small compared to patents, the risk was also small. Fifty years later, contract research still makes sense. Generic drug companies, developing world drug manufacturers, contract research organizations, and biotechnology firms have all said that they would consider contracts to develop open source drug candidates.<sup>16</sup>

### C. COST CONTAINMENT

Since the operation would exist mainly on the Web, budgets would be more or less the same as existing software collaborations. The exception to this rule, computing time, would be expensive but manageable. Furthermore, today's biologists routinely scrounge resources from university machines or borrow time on home computers.<sup>17</sup> Open source's most obvious cost saving is that sponsors do not have to pay for labor. But open source's cost advantage does not end when the volunteers go home. Traditional subsidies create cost containment problems.<sup>18</sup> Open source would escape this trap by making discoveries freely available. This would allow governments and charities to invite companies to bid against each other for the right to perform further development under contract. Competitive bidding is a powerful mechanism for containing costs. It is also a good way to develop drugs. Virtual Pharma has extensive experience supervising contract research.<sup>19</sup> Finally, the absence of patents would keep prices low once drugs reached the market. Patents, after all, are designed to keep prices high. U.S. drugs frequently fall to about one-fourth of the original price once patents expire.

---

16. Personal Communication with Michael Spino, Vice President for Scientific Affairs, Apotex Inc.; Personal Communication with S. Sharma, Chief Scientific Officer, Nicolas Piramel India Ltd.; Personal Communication with Frank Hijek, Director, Therapeutic Development, Duke Clinical Research Institute; Personal Communication with Donald P. Francis, Genentech, Inc.

17. See, e.g., Stanford University, GENOME@HOME, at <http://www.stanford.edu/group/pandegroup/genome> (last visited Sept. 17, 2004); University of Oxford, SCREENSAVER LIFESAVER, at <http://www.chem.ox.ac.uk/curecancer.html> (last visited Sept. 17, 2004).

18. See Ganslandt, *supra* note 4, at 792.

19. Personal Communication with Solomon Nwaka, Scientific Officer, Medicines for Malaria Venture; Personal Communication with V. Holt, CEO, OneWorld Health.

#### D. GETTING PHYSICAL

This Web-centric, low-budget computational approach is probably enough to generate new science and ideas for follow-up experiments. Although this is a good start, it is not a complete solution. Computational biology works best when it can interact with wet chemistry and biology experiments. Thus, in practice, an open source drug discovery effort is likely to include modest physical experiments.

To support physical experiments, academic scientists could use discretionary resources and, in some cases, tropical disease grants. Furthermore, good science generates its own funding. We expect experimentalists to turn the collaboration's web pages into grant proposals. A truly balanced research program would also require sponsors. Charities could support open source drug discovery by making wet chemistry and biology experiments a top priority. Corporations could also help by donating funds, laboratory time, or previously unpublished results. One low cost/high value option would be to reveal pre-existing data whenever the collaboration was about to explore a "dry hole."<sup>20</sup>

### III. CONCLUSIONS

So far, we have argued that open source is feasible, but what are the risks? Experience with software collaborations highlights the main social and economic challenges. First, the project will have to find and motivate volunteers. Based on existing software collaborations, we estimate a required minimum "critical mass" of a few dozen active members. Second, modest chemistry and biology experiments can increase the chances for success. Resources of several hundred thousand dollars per year – most in the form of in-kind donations such as databases, laboratory access, and computing time – would make open source drug discovery much more powerful. By most standards, such risks are real but acceptable.

The largest uncertainties are scientific. Can a volunteer effort based on computational biology and modest experiments produce leads that are promising enough to catch Virtual Pharma's attention? We have argued that a successful

---

20. Personal Communication with Russ Altman, Stanford University.

program must (a) make a significant contribution toward supplying the genomic insights that Virtual Pharma needs, and (b) make useful drug candidates freely available. Ten years ago, these goals would have been unrealistic. Today, however, researchers frequently use computation to find promising protein targets and lead compounds.<sup>21</sup> Open source drug discovery looks feasible. The only way to be sure is to perform the experiment.

---

21. See Marcin von Grotthus, Lucjan S. Wyrwicz, & Leszek Rychlewski, *MRNA Cap-1 Methyltransferase in the SARS Genome*, 113 *CELL* 701, 701-02 (2003) (using computing to identify a protein of the SARS virus); Brian K. Shoichet et al., *Lead Discovery Using Molecular Docking*, 6 *CURRENT OPINION IN CHEM. BIOLOGY* 439 (2002). See generally Christine S. Ring et al., *Structure-Based Inhibitor Design by Using Protein Models for the Development of Antiparasitic Agents*, 90 *PNAS*. 3583 (1993).