Episteme, 10, 4 (2013) 417–439 © Cambridge University Press
doi:10.1017/epi.2013.33

RETHINKING EPISTEMIC INCENTIVES: HOW PATIENT-CENTERED, OPEN SOURCE DRUG DISCOVERY GENERATES MORE VALUABLE KNOWLEDGE SOONER

ALEXANDRA BRADNER
alexandrabradner@gmail.com

ABSTRACT

Drug discovery traditionally has occurred behind closed doors in for-profit corporations hoping to develop best-selling medicines that recoup initial research investment, sustain marketing infrastructures, and pass on healthy returns to shareholders. Only corporate Pharma has the man- and purchasing-power to synthesize the thousands of molecules needed to find a new drug and to conduct the clinical trials that will make the drug legal. Against this view, individual physician-scientists have suggested that the promise of applied genomics work calls for a new form of social organization – the open source sharing of molecular probes – in order to speed the generation and understanding of new therapeutics. Recent successes in open source drug discovery show it is possible to produce valuable, empirically adequate, and sustainable collective beliefs without secrecy, proprietary attitudes, initial cooperation from Pharma, or outsized monetary incentives. After reviewing and differentiating these successes, I diagnose the source of this healthy new epistemic strategy.

INTRODUCTION

> There are, to date, [1,100,000] unique somatic alterations observed in cancers cells, affecting the structure and likely function, then, of 24,000 gene products, which is almost all of them … . Follow-up biology has already identified that up to 479 of these altered gene products contribute to the pathogenesis of this disease. In contrast to this large number of targets needing small molecules, there are just 15 for which there is, currently, a direct-acting therapeutic. And this is all of our challenge. (Bradner 2013).[1]

Cancers produce a great deal of suffering, especially for dying patients and their dependents. It would be valuable to slow, prevent or eliminate cancers with targeted medicines, developed through our growing understanding of regulatory genomics. Yet we have only fifteen direct-acting therapeutics. Why? It could be that the incentives we have in place for drug discovery are quantitatively insufficient. If we were to invest more money in drug discovery and if successful drugs were even more profitable, perhaps we would see more

1 At the time of the original quote, this number was 620,000, and it will continue to increase.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

therapeutics. But this paper argues for something else, namely, that the incentives we have in place are *qualitatively* insufficient. In order for the collective epistemic activity of drug discovery to succeed, we must recognize incentives of a sort more appropriate to the target of drug discovery, patient care.

There are two stages to the arrival of any new clinical therapeutic: drug discovery and drug development. Historically, in drug discovery, researchers have identified a biological process of interest and conducted a phenotypic screen for molecules that accentuate or inhibit that process. In the post-genomic era, it has become commonplace to select a specific protein target of interest and screen for molecules that accentuate or inhibit biochemical function. These molecules serve as starting points for chemical optimizing. Medicinal chemists improve the drug-like properties – the efficacy, tolerability, and toxicity – of the compound by working with laboratory models and non-human animals. From this work, a lead therapeutic candidate emerges, which is then exhaustively characterized in a highly controlled laboratory environment, with the aim of preparing a dataset to provide assurances to the Food and Drug Administration that the molecule is reasonably ready for human clinical investigation. With FDA approval of an Investigational New Drug application, drug discovery ends and drug development begins. This paper focuses on open source activity in drug discovery, that is, on the period during which new therapeutics are discovered, but before they graduate to human trials.[2]

Pharmaceutical industry leaders have argued that the only way to sustain the research required to discover and develop effective therapeutics is to offer huge monetary incentives, adopt proprietary attitudes, work in isolation, and keep data and materials and secret until a drug's first-in-class status has been secured through a successful human trial and the patents publish. Their rationale has three layers: first, it is presupposed (for example, by the business judgment rule) that the directors of a corporation have a fiduciary duty to act in the best interest of the corporation and its shareholders, who are assumed to be the owners of the corporation;[3] second, it is assumed that the best way to maximize profit for shareholders is to pursue blockbuster drugs – drugs that companies can market to wealthy populations suffering from widespread diseases that are chronic, but not deadly, like the flu, diabetes, and high cholesterol. Common diseases that affect lower income populations, especially quickly progressing (deadly) diseases

2 Fewer people advocate for open source drug development, though former Merck & Co. vice president for oncology research Stephen Friend, now of Sage Bionetworks, has done so. One complication is the concern for the privacy of the human subjects. But what stalls this movement and polarizes the various parties, in particular, is the exponential increase in the cost of this kind of experimental work. The human trials required by the FDA before a drug can be marketed cost per trial on the order of US$ 7 million to more than US$ 800 million (in the case of Pfizer's torcetrapib), with an average cost of US$ 86 million (Cutler 2007). Each trial can have hundreds of participants, each of whom requires regular monitoring and multiple procedures – all of which are costly (X-rays, scans, etc.). In 2000, the estimated trial cost per patient was $25,000 before direct care. In 2012, the cost had risen to $100,000 per patient (Kantarjian et al. 2013).

3 This first layer of the rationale is debated in the stakeholder theory literature, which begins with Kenneth Goodpaster's framing of the stakeholder paradox (1991) and lives within the business ethics literature on corporate social responsibility. The 1988 Delaware case *Grobow v. Perot* suggests that the business judgment rule stands as long as the corporate directors have acted in good faith; acted in the company's best interests; were informed when they acted; were not wasteful; and were not acting out of self-interest or self-dealing. If a plaintiff cannot prove that one of these conditions was violated, a plaintiff's case against a corporation's directors for breaching their fiduciary duties cannot go forward.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

and rare diseases, are not as profitable, so these diseases should receive less attention. In particular, companies argue that they have to focus on blockbuster drugs in order to recoup research and development costs. For every successful drug, there are many failures, all of which require substantial investment, but yield nothing in return. The profits generated by blockbuster drugs support ongoing research and sustain the corporation. The third layer of the rationale concludes that the only way to develop first-in-class blockbuster drugs is to insulate project teams from any and all competition by maintaining strict secrecy. Some companies even go so far as to not patent (or wait to patent) their drugs, because patenting is a form of public disclosure. Competitors are free to develop generics after 18 years, so every company is under constant pressure to produce new products. Some of these can be improved versions of older drugs. But because subsequent drugs must gain approval on the basis of improved efficacy and safety – and many drugs, like antacids, for example, are difficult to improve – new versions must be "better than the Beatles," as industry insiders say.

Drug discovery and development is indeed a tough business, and companies that do not take their competition seriously cannot survive. The decision to aim, exclusively, for the maximization of shareholder profit, by focusing on the discovery and development of first-in-class blockbuster therapeutics, can be lucrative and, thus, can attract top scientists to the task. But the decision can have worrisome epistemic consequences. To start, the narrow profit motive can limit project duration and scope. Corporate project horizons usually are capped at three to five years. When the discovery of a drug takes too long to mature or uses up too many resources, when the scientist who has championed the research program retires or leaves, or when the drug company is bought by another company, corporate officers may eliminate entire divisions and start anew. Next, though drug companies have an incentive to ensure that their books and labs remain in compliance with federal and state regulations, on pain of fine or lawsuit, there can be disincentives to taking on the following extra, potentially costly, self-regulatory responsibilities: ensuring the diversity of the human subject population (Stegenga 2013), accurately representing the power of successful human trials (Stegenga 2013), exposing early results to peer review, and reporting negative outcomes.[4] In a worst-case scenario, the exclusive interest in first-in-class status has the potential to lead to the premature approval of a drug for human testing.

There are challenges in academic contexts as well. Academic researchers guard their data and technologies out of concern for priority, because their careers hinge upon the credit and recognition they earn from their peers for novel discoveries (Hull 1988: 290). Academic scientists are under pressure to publish, because they are supposed to be creating new knowledge. At times, this means they must abandon a project, in order to ensure that they can produce more than one article in a particular promotion period. In a paper detailing the use of open source methods to improve an existing drug, an Australian research group warns against viewing academia's drug development prospects through rose-colored glasses:

4 In response to research on www.clinicaltrials.gov suggesting that the site has not been as effective as the FDA might have hoped in encouraging researchers to report negative results (Prayle et al. 2012), Carole Lee (this volume) argues that, in order to improve the publication and trial registration record, and change the norms of author behavior, medical journal editors must do more than merely threaten to block the publication of non-conforming manuscripts.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

> Academia is associated with the free transmission of data and resources, but in many ways this is no longer how it operates. The scientific community generally works towards common goals by competition between closed groups of scientists and communicates research results through publications relying on pre-publication peer-review. Papers frequently omit some experimental information, or ignore negative results. The delays involved in publication of papers, or reviewing of grants are significant. Many of us still publish papers in journals where comments on papers are not permitted, meaning that technical errors can remain uncorrected because rebuttals are usually required to be substantial works in their own right. (Woelfle et al. 2011)

Despite the presumption that information flows freely within academia, there are few professional incentives for professors to share technologies and contribute to open databases – activities that do not generate formal publications. As long as scholarly impact is assessed by multiplying a researcher's number of papers by the impact factor of the journals in which the papers were published, newer forms of scholarly activity will remain invisible and undervalued, and may soon disappear.[5] More seriously, some scholars are concerned about the reproducibility and, thus, the quality of the knowledge that academic medical scientists produce (Prinz et al. 2011; Begley and Ellis 2012). According to a May 2013 study of University of Texas M.D. Anderson Cancer Center scientists' opinions and experiences, half of the scientists surveyed said they had tried to reproduce a published finding and had failed (Mobley et al. 2013). Journalist Sylvia Pagán Westphal reports: "About 30 percent of those surveyed by the M.D. Anderson study said they had felt pressure to publish results to prove their mentor's hypothesis, even if they were not sure of the data. Some 18 percent said they had been pressured to publish findings about which they had doubts" (Westphal 2013).

Pharmaceutical companies have several advantages over academic centers in drug discovery: First and foremost, almost every researcher on the project team is a fully trained scientist, while, in an academic laboratory, most of the scientists are graduate students and postdoctorates. Moreover, in Pharma, teams are specifically recruited for each project. Each scientist on the team contributes a crucial skill set and knowledge domain, with no unnecessary duplication and most gaps filled. Genuine interdisciplinarity replaces the two-discipline collaboration structure often seen in academia. Second, pharmaceutical companies have more resources: bigger budgets, more space, and superior instrumentation. At times, they can leverage other aspects of their companies, for example, by doing their pharmacology in-house. This gives Pharma the ability to conduct studies that are prohibitively expensive, because of their scale. Third, while most academic centers have approximately 10,000–100,000 chemical compounds in their libraries from which to start a screen, pharmaceutical companies often have more than a million compounds. Fourth, drug companies have built up a store of regulatory expertise. After Thalidomide, a German drug often prescribed for morning sickness in the 1950s, was proven to cause birth defects, the industry was left with a legacy of legal barriers and regulations to meet before any drug could be clinically utilized. For-profit drug companies have been working within these regulations for a long time and now have the personnel infrastructure needed to run experiments efficiently, clearly, and legally. Leukemia scientist Hagop Kantarjian writes: "A total of 300 to 600 regulatory steps, half of them judged

5 Because most academic journals will not accept work that already has appeared in the public domain, scientists' donations of time and data to open databases are incompatible with impactful publication.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

unnecessary, are often required to initiate Cancer Therapy Evaluation Program–sponsored or cooperative group trials, with a median time of 400 to 700 days to initiation" (Kantarjian et al. 2013). Finally, as projects move closer to the clinic, they require non-academic expertise in medicinal chemistry, formulation science, and process chemistry. In the face of needs for up-to-date programmers, engineers, and chemists, among other specialists, drug companies have the flexibility, space, and financial resources to hire on demand, using new staff to solve local problems and fill temporary gaps.

Still, academia enjoys some advantages over Pharma. First, though the project teams of Pharma have interdisciplinary breadth, academic researchers often have deep, domain-specific knowledge. These scientists can leverage the interdisciplinary resources of their universities, which have departments of chemical biology, bioinformatics, developmental biology, and medicine in place, all within walking distance of one another. Second, in academia, the tenure system can operate to promote drug discovery. After scientists receive tenure, their research programs are sustained by passion, regardless of market fluctuations. The job security provided by the tenure system enables senior academic scientists to commit to longer project horizons and high-risk, high-reward projects. Academia may be the only context in which certain drugs can be discovered. Third, in some respects, academic scientists can operate quite quickly. Pharma's top-down structure requires that directors sign off on all new initiatives. Corporate bureaucracy can slow the pace of discovery. Moreover, academic scientists are early adopters of disruptive technologies and have immediate access to such technologies, for example, to genome editing and new mouse models. Pharma must wait until these technologies are licensed in order to buy them, a process that usually requires time-consuming legal wrangling.

This might be a dead heat. We may never see therapies for rare diseases, as long as corporate boards strive to maximize shareholder profit. But it is not clear that the solution lies in bankrupting academia. We will have to imagine a plausible, alternative possibility.[6]

OPEN ACTIVITY IN DRUG DEVELOPMENT

There is a history in not-for-profit, medical research of what we might call open activity, which relies on the Linus' Law-like hypothesis that no one scientist or research team is smarter or more capable than a collection of such teams. Open activity in drug discovery can include the open source development of biological software, public websites that organize data and make collaboration possible, crowdsourcing for intellectual assistance or, in drug development, trial participants, and, most importantly, the open source sharing of materials, such as molecular probes and other technologies.[7] This open-activity

6 This paper suggests the open source sharing of molecular probes as a promising avenue. Beyond open source, there are examples of successful collaborations between academia and Pharma that have generated effective medicines, such as the collaborations behind Gleevec and Alimta. Many universities have established High Throughput Screening Laboratories, in order to measure the inhibition of enzyme activity in the presence of compounds. These laboratories can test from 100,000 to 2 million compounds at once and, thus, may help academic scientists identify promising molecular probes and participate in drug discovery. But the follow-up chemistry required to transform promising probes into medications has been a challenge. NIH grant mechanisms RO1 and R21, however, may offer some assistance.

7 Open activities not discussed in this paper include open source biological software development, of which Craig Venter's Celera Assembler is an example (Sourceforge 2013), and web-assisted

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

movement is motivated not by profit, but by the elimination of human suffering, and has prospered thanks to the activist spirit of a small group of individual scientists who are attentive, responsive, and socially engaged.

To call an entity, such as software, "open source," is to say something about its distribution and use, namely, that anyone can access it and decide what to do with it. Open-source material is not secret or private. This general sense follows from the author of the GNU Manifesto, Richard Stallman, who defined and launched the free software movement. Stallman became a champion of free software in the 1970s, as a member of the MIT Artificial Intelligence Lab, where "sharing of software was … as old as computers, just as sharing of recipes is as old as cooking" (Stallman 1999: 53). When the AI Lab hacker community collapsed in the early 1980s, as a result of the Digital PDP-10 computer's obsolescence and the defection of half the Lab to Symbolics, a spin-off company, those who remained found themselves having to sign non-disclosure agreements just to get copies of the operating system that came with the VAX new computer. Stallman writes: "A cooperating community was forbidden. The rule made by the owners of proprietary software was, 'If you share with your neighbor, you are a pirate. If you want any changes, beg us to make them'" (Stallman 1999: 54). He found these policies antisocial and unethical, and devoted the rest of his life to open source activism.

According to Stallman, there is a difference between the free software movement and the open source software movement. In the free software movement, the "free" does not mean gratis, but liberated, like the "free" in free speech (Stallman 2002: 41). This movement aims directly at unfettered exchange among programmers. Anyone should be able to run a program for any purpose, modify it to suit their needs, redistribute copies, either gratis or for a fee, and distribute their modifications, so the community can benefit from the improvements (Stallman 1999: 56). Stallman is not against selling software, but against proprietary restrictions. The open source software movement, in contrast, aims at efficiency, product enhancement, and optimal engineering. This movement is not explicitly committed to any political ideal about how a community should function (Stallman 2002). Open-source drug discovery research, then, would be a movement aimed at increasing the number and efficacy of therapeutics and not a movement about scientists' freedom to create and define their own community. Scientists engaged in open source activity make decisions about their materials, staff, collaborators, research questions, publication schedules, and priorities that aim to improve drugs. The following few examples make it strikingly clear just how effective this new mode of social organization could be, if it were adopted more broadly by the drug discovery industry.

collaboration, such as the plans for the Sage Bionetworks site, a computational framework for chemical biologists, bioinformaticians, doctors, and patients, with a connection to diabetes, obesity, or cancer, who want to collaborate to build models that predict disease responses to drug treatments (Friend and Schadt 2009; Sage Bionetworks 2013)). These examples are less novel and less biology-specific. The first is simply regular, open source software development in the biological domain, while the second is a typical collaboration.

Collaborative projects should be distinguished from coordinated projects, which have a different social organization. Coordinated projects, such as the Human Genome Project (HGP) and ENCODE, have large bureaucracies with a dedicated managers. In collaborative projects, two to four laboratories work on a study with no dedicated manager or hierarchy.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

Sharing material cultures and expertise: Gey's early example

In the 1950s and 60s, George Gey, a scientist at the Tissue Culture Laboratory at Johns Hopkins University in Baltimore, Maryland, shared his HeLa cell line with other scientists. He distributed HeLa cells, derived from a tissue sample now known to have been provided by Henrietta Lacks, to individual scientists, foundations, and private companies. But he also shared his knowledge, by training young scientists and visiting researchers. Rebecca Skloot, a journalist who has chronicled Gey's work in the process of telling Lacks's story, writes of his motives:

> [F]or Gey . . . inventions were only a means to an end. Stopping along the way to publish papers or patent his inventions would have been a waste of precious research time. His goal wasn't to invent equipment; it was to find a cure for cancer. Anything short of that was a technicality. His wife and colleagues nagged, saying, George, if you don't publish this stuff, no one's going to know you did it . . . . He thought that was a bunch of hogwash. If they want to learn what we do, he'd say with a smile, they can just come on down to the Gey lab and we'll show them. And that's exactly what people did. From around the world, students and senior researchers alike came to learn the art of tissue culture. The Geys opened their lab and their home, giving knowledge, and often cells, that researchers would take back to their labs throughout the United States, South America, Russia, and many places between. (Skloot 2001)

Gey packed and shipped his HeLa cells around the world with instructions for feeding and handling. At times, he would deliver the cells personally, carrying them on the plane in his shirt pocket. The National Foundation for Infantile Paralysis set up a facility at the Tuskegee Institute to mass-produce and distribute approximately 600,000 HeLa cultures. And cosmetic companies bought millions of HeLa cells to test their products (Skloot 2001). Experimental pathologist John Masters writes the following about Gey's open attitude and its lasting therapeutic value:

> To cancer research, HeLa is the equivalent of the goose that laid the golden egg – a constant supply of a precious and essential resource. Within a few years, HeLa cells had been distributed worldwide and became the laboratory model of the cancer cell that would be used for much of cancer research. But they are not just used for cancer research – HeLa cells are used throughout biomedical research to study the biochemical pathways of normal and diseased tissue in human cells. Although thousands of continuous cell lines from almost every type of human cancer have since been established – mainly in the 1970s and 1980s (Masters and Palsson 1999) – HeLa is still the most widely used human cancer cell line. (Masters 2002)

Gey's willingness to share his materials, information and expertise, stemming from his physician's desire to relieve the suffering of cancer, exemplifies the open source approach to drug discovery.[8]

8 Thanks to Pittsburgh Center for Philosophy of Science graduate student Julia Bursten for reminding me of Gey's example. There is much more historical work to be done regarding the details of Gey's open source activity through the study of his correspondence, records, and laboratory progress reports, which are held at the Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

Calling for assistance: Open, contributory websites that both facilitate the sharing of promising compounds and compile, organize, and publicize crowd-sourced results

More recently, Michael Woelfle, School of Chemistry, University of Sydney, used open source methods to further develop the drug praziquantel, which treats a parasitic infection – schistosomiasis (also called bilharziasis) – affecting hundreds of millions of people. The researchers modeled their crowdsourcing methodology on the process by which the Linux operating system and Firefox web browser were developed: First, a need or problem was identified; second, a preliminary solution to the problem was posted online; third, an open appeal to the broader community was made, fourth, inputs were received from an unrestricted community; fifth, the cycle was repeated.

Praziquantel already was an effective drug, but needed a few improvements: a smaller size, a less bitter taste, and fewer side effects. Ambitious PhD students were not inclined to select such a humble project for their thesis topic, and there were no incentives for pharmaceutical companies to work on the compound, given the narrow profit margin. So, in 2006, the researchers produced a website about the issue, hoping to attract attention, but the site received little traffic. In mid-2008, they received funding to conduct a study they named the PZQ project, which began in January 2010. In April 2010, they posted a request for suggestions to a closed, 2,500-member, process chemistry networking forum. This prompted eleven people to respond, none of whom were known previously to the researchers. In mid-May, they sent one gram of racemic PZQamine to Syncom, a Dutch contract research organization, which continued work on the problem without pay and posted results to the PZQ project website. This work offered a lead, which was then optimized by the researchers.

Woelfle et al. (2011) conclude that two requirements must be met, in order for an open call to generate results: "[T]here must be a kernel of data or activity with which people can become involved. Without a starting point, people have little to go on and no incentive to contribute. Second, the barrier to entry must be low. Thus it is essential that project summaries are up to date, and that what is required from the community is clear. It is also important that the technology and software people use to contribute is simple." They found that, in order to generate traffic on their site, they had to create publicity for the project, in the form of news articles, popular blogs and online videos. Instead of offering a financial reward to the site's contributors, the researchers decided to conceive of project contributions as gifts. They write: "In a bazaar-type [versus cathedral-type] project, there is a low barrier to entry, and the operation is seemingly chaotic or self-organizing. Leadership is fluid, if it exists at all. The system is effective at what it does, yet requires little investment to start up and relies on the traffic of inherently interested strangers" (Woelfle et al. 2011).

Matthew Todd, also in the School of Chemistry at the University of Sydney, has been working through the website OpenSourceMalaria (OSM) to assemble and publicize medical research on malaria. In operation since August 2011, the site was originally promoted by Tim Wells, now Chief Scientific Officer of the Medicines for Malaria Venture (MMV), a not-for-profit public–private partnership established as a foundation in Switzerland. MMV will ship free to scientists a "Malaria Box" filled with 400 compounds shown to produce antimalarial activity: "200 diverse drug-like compounds as starting points for oral drug discovery and development" and "200 diverse probe-like compounds for use

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

as biological tools in malaria research" (Medicines for Malaria Venture 2013). The compounds were selected by screening approximately four million compounds from the libraries of St. Jude Children's Research Hospital, Novartis-GNF (Genomics Institute of the Novartis Research Foundation), and GlaxoSmithKline. Scientists who receive the box agree to publish their data and make it available to the public. Todd's project investigates promising compounds from the Malaria Box, but the difference is that "everything is open," which means that all of the experimental studies, even flawed studies or studies with negative results, are uploaded to the web, and all of the data is available to everyone:

> Anyone can do anything they wish with the compounds, with the proviso the project is cited .... The main difference is that anyone can take part – people may make molecules, offer guidance and input in other ways that *change the direction of the project as it is happening*, i.e. rather than the release of all data at the end of the project, data are released as the project is happening so that people can become genuinely involved in the research. Thus the iterative cycle of analog synthesis in response to biological data that is normally guided by luck and medchem intuition is now guided by the intuition of the collective. Similarly, since the biological data are all open too, it should be easier to form an objective assessment of a molecule's performance divorced from the judgment of those closest to the compounds. (OSM 2013)

Project leaders believe the science will be better and faster, as it was in the praziquantel case, and that the crowd-source strategy has the potential to wash out error and bias. So far, OpenSourceMalaria scientists have confirmed that the small group of active compounds with which they started are effective, but scientists do not know how the compounds are working to kill the parasite: "it's not known what they are doing in any detail" (OSM 2013). Unfortunately, the OSM website states, "The project has to date had no luck in securing donations of the compounds from commercial suppliers" (OSM 2013). So, in order to access promising compounds that are currently unavailable (either sitting in laboratory refrigerators or too difficult for a particular laboratory to make), Todd has started to plan for a Molecular Craigslist (Todd 2012).

In a final example of crowdsourcing for assistance, we turn to Holger Rohde's efforts to address a dangerous *Escherichia coli* outbreak. In Germany, more than 3000 people were infected in May and June 2011 with a Shiga-toxin-producing *E. coli* O104:H4, a bacterium associated with the hemolytic–uremic syndrome, which often leads to neurologic and myocardial damage. The nationwide outbreak caused more than 40 deaths. Rohde and colleagues, at the University Medical Center Hamburg–Eppendorf, in Hamburg, Germany, responded by posting an isolate from one member of the family and soliciting a genomic analysis through crowd-sourcing:

> To investigate the evolutionary origins and pathogenic potential of the outbreak strain, we set in motion an open-source genomics program of research that incorporated new high-throughput sequencing approaches, public data release, and rapid outsourcing of analyses to bioinformaticians worldwide (crowd-sourcing) ... . Twenty-four hours after the release of the genome, it had been assembled; 2 days after its dissemination, it had been assigned to an existing sequence type. Five days after the release of the sequence data, we had designed and released strain-specific diagnostic primer sequences, and within a week, two dozen reports had been filed on an open-source wiki ... dedicated to analysis of the strain. (Rohde et al. 2011: 721)

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

In less than a week, scientists had determined the lineage of the outbreak strain. The study demonstrates that bench-top sequencing platforms, when exposed to crowd-sourcing strategies, can generate data fast enough to have a clinical and epidemiologic effect. Scientists need not rely on lower resolution phenotypic or molecular analyses (Rohde et al. 2011: 723).

All three of these cases demonstrate the role that open, public websites can play in drawing attention to medical research topics that might otherwise be ignored. In these cases, researchers crowd-sourced for intellectual assistance and created a thriving community of like-minded scientists through a website that enabled them to share material resources and knowledge with impressive results, especially in the cases of Woelfle and Rohde.

The future of open source biology: the free distribution of novel, proven-effective molecular probes

In the cases just discussed, open, crowd-sourcing activity was used (Woelfle) and is being used (Todd) to discover and refine molecular probes. Pharma seems to welcome this kind of work and participates in it by granting bioinformaticians access to massive libraries of potentially promising compounds. But the open source sharing of particular molecules that are novel, fairly well understood, and proven to be effective is the one form of open activity that Pharma continues to resist. This next example represents the fruition of the open source movement in drug discovery, the free distribution of a novel, fairly well-understood probe that has been proven effective. Jay Bradner,[9] associate director of the Center for the Science of Therapeutics (CSofT) at MIT and Harvard's Broad Institute, assistant professor in Harvard Medical School's chemical biology program, investigator at Harvard's Dana-Farber Cancer Institute (DFCI), and stem-cell transplant physician, uses chemical biology to study gene regulatory pathways in cancer. As he often says, he is trying to get cancer cells to forget that they are cancer cells. In 2010, he was a lead scientist on a team that published a paper in *Nature* reporting the synthesis and activity of a small molecule, JQ1, which binds to and inhibits bromodomains (Filippakopoulos et al. 2010). Synthesized chemical compounds such as JQ1 can override the control systems of readers, writers, and erasers that control gene expression by manipulating chromatin structure and function. Writers attach chemical marks (such as methyl groups to DNA and acetyl groups to the histone proteins that DNA wraps around), readers bind to

9 A methodological note: Jay Bradner is my younger brother, whose tri-weekly morning phone calls to me over the past several years (during his commute) generated my philosophical interest in open source biology. To consider the work of one's brother in a professional context might seem to invite bias, but I'm hoping my discussion of his work can be considered in the tradition of David Hull's extended contact with the cladist community (Hull 1988), Barbara McClintock's close relationship with her organism, as conceptualized by Evelyn Fox Keller (Keller 1983), and Carol Gilligan's feminist method of conducting recurring, qualitative, in-depth interviews with a small number of subjects over a multi-year period (Gilligan 1982). These three theorists have different reasons for conducting qualitative research. But all, I believe, would endorse Loraine Code's claim that "aspects of such 'situatedness' often count among the conditions that make knowledge possible" (Code 2010). In this paper, sibling trust enabled me to access information that another researcher might not have been able to access. The epistemic tradeoff between objectivity/fairness and depth of information is an interesting one that, I believe, mirrors ethical tradeoffs between justice and care.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

these marks and regulate gene expression, and erasers remove the marks (Dawson and Kouzarides 2012). NUT Midline Carcinoma is a cancer caused by the fusion of two genes: BRD4, a gene that codes for a reader protein, and NUT (French 2003). When fused into a mutant protein, BRD4-NUT, this protein causes cells to become cancerous. JQ1 slips into a groove in BRD4, preventing it from binding to acetylated histones and activating genes. This creates a chemical smokescreen, which prompts the reader to become so busy that it overlooks the region that causes the cells to become cancerous. Important for the purposes of this paper, JQ1 is a novel probe, an effective probe, and a probe for which there is some understanding of the mechanism according to which the probe operates. As explained in the 2010 paper, "These data establish proof-of-concept for targeting protein–protein interactions of epigenetic 'readers', and provide a versatile chemical scaffold for the development of chemical probes more broadly throughout the bromodomain family" (Filippakopoulos et al. 2010). Since that first paper, the team has published a second paper in *Nature* and four papers in *Cell*, among several others, all inching toward the functional inhibition of the DNA-binding protein c-Myc, which is involved in up to 70% of cancers and was once thought to be undruggable. As it turns out, JQ1 reduces the expression of MYC and its target genes, stopping multiple-myeloma and other cancer cells from dividing in mice (Delmore et al. 2011).

JQ1 is an interesting molecule, but what is also interesting is how and when the team shared the molecule with the broader scientific community. In a paper outlining the features of a good chemical probe, chemical biologist Stephen Frye argues that, among other things, probes should be readily available to the academic community with no restrictions on their use (Frye 2010). Committed to open source drug development and taking Frye's note, Bradner's team offers the new, effective, and promising probe for free, to anyone who makes a request, with a streamlined Material Transfer Agreement (MTA). Material Transfer Agreements, which are notoriously complicated, govern the transfer of research materials, including reagents, cell lines, plasmids, etc. In this case, the MTA is an agreement between the DFCI and the recipient of the JQ1 compound. As opposed to the MTAs written by pharmaceutical companies, with the DFCI MTA, there is:

- No delay in getting the molecule, which arrives with the MTA.
- No restriction on the use of the MTA.
- No obligation to notify the DFCI of research findings.
- No expectation of co-authorship.
- A user's guide that explains the relevant dose, storage conditions, formulations for in vivo use, and recommended starting doses for in vivo use for mouse models.

The Bradner lab will send JQ1 for free, importantly without limitation on quantity. This alone represents a meaningful departure from the usual way in which academic molecules are shared. If the receiving lab would like to remain anonymous, JQ1 is also commercially available for $45/milligram through Cayman Chemical (which set the price). As is typically the case, the DFCI has published the synthesis with a complete annotation of how to make JQ1, as well as the complete NMR spectrum, which other laboratories can use as a reference, to ensure that they have made JQ1 correctly.

Unlike most of the MTAs from pharmaceutical companies, the MTA governing the transfer of JQ1 has never been edited. And the DFCI has never turned down anyone's

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

request for the molecule. Distribution is completely unrestricted – i.e. ungoverned by personal, financial, or competitive interest. So far, 346 samples of JQ1, more than 200 grams, have been sent to scientists around the globe. The DFCI ships JQ1 to small labs, unknown labs, and labs with directly competing research interests.[10] Bradner explains, "We can't be in the position of picking and choosing who gets to study what" (Bradner, personal communication 2013).

Despite this openness, the DFCI's MTA governing the open source distribution of JQ1 does diverge significantly from Stallman's conception of open source software, which specifies that recipients be free to modify, redistribute and sell open source software. The DFCI MTA requires the recipient to agree that: "The Material shall be used exclusively for non-commercial laboratory research by Recipient to study [insert research project]," "The recipient shall not create modifications or derivatives of the material," and that the "Recipient shall not sell or otherwise distribute material to a third party for any purpose" (Dana-Farber Cancer Institute 2010). Concerning this, Bradner explains that these more heavy-handed requirements are vital safety features within a biochemical context: "The application of open source principles to drug discovery has been accompanied by a learning curve. Some requesters have asked to ingest JQ1, or administer the drug to a person or pet. Unlike software code, prototype drugs are accompanied by a non-zero probability of real harm unless education and safeguards are built into the immediate material transfer process" (Bradner, personal communication 2013). It is important to note that these are the terms of the immediate MTA. If recipients have other interests, successful agreements can be crafted around those goals.

Also contrary to what Stallman might have wanted, the DFCI filed a patent on JQ1 and related compounds several years ago. This application is pending review with the United States Patent and Trademark Office. In Bradner's mind, this decision will protect the laboratory's ability to openly distribute JQ1. He explains, "You cannot give something away that you do not own" (Bradner, personal communication 2013).[11]

The DFCI's decision to openly distribute JQ1 has had a pronounced effect on bromodomain research. It usually takes researchers one or two years to access a new molecular

10 Pharmaceutical companies also can get JQ1, but this requires an additional interaction with DFCI's technology transfer office.

11 This offers an interesting shift in emphasis from the recent Association for Molecular Pathology v. Myriad Genetics Supreme Court case, in which the Court concluded unanimously, on June 13, 2013, that one can patent synthetic genes, but not "natural" genes. In that case, Joseph Stiglitz argued, with many academic researchers, that patents on genes inhibit future discoveries by keeping prior knowledge secret (Stiglitz 2013). According to Stiglitz, Myriad argued that patents motivate discovery by serving as important incentives, despite the fact that patents increase healthcare costs disproportionately for lower income people.

Bradner does not think there is any scenario in which patenting *genes* advances science or secures technology. However, he thinks patents are crucial for *therapeutic interventions*, because the development costs are "extraordinary," adding that patents also draw creative people to drug discovery who might not otherwise have chosen the specialty (Bradner, personal communication 2013). Though he writes that the Bradner lab is motivated by intellectual curiosity and the promise of positive results in the clinic for suffering patients, he believes many people are motivated by the promise of patents.

I myself think the existence or non-existence of patents is less important than the commitments of the people who own the patents. Patents are not destructive when the people who own them are consistently willing to license and distribute their probes at an affordable cost. The case of JQ1 demonstrates that it is possible to innovate and share in the same breath.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

probe after publication, because third-party companies cannot sell the probe without a license from the patent holder. But the DFCI began to ship JQ1 before the team's paper was published. Figure 1 shows the number of publications per year on the family of bromodomain proteins inhibited by JQ1: BRD2, 3, 4 and BRDT. Before the DFCI decided to ship its molecule, publications were rising. But once JQ1 was easily available, publications quickly more than doubled (the highlighted bars). Some of the most important work Bradner has done with JQ1 has originated among researchers convening at conferences at which he was not even in attendance. At the annual meeting of the Sarnoff Cardiovascular Foundation, Jonathan Brown (Brigham & Women's Hospital) and Saptarsi Haldar (Case Western Reserve University) discussed the possibility of testing JQ1 in models of heart failure. The scientists approached Bradner to discuss the rationale and experimental strategy, which led to a collaborative, interdisciplinary study demonstrating complete inhibition of heart failure in models of overwhelming stress (Anand et al. 2013). Bradner notes: "In 20 years, my lab could not accomplish all of the research that has unfolded on JQ1 in one year through this open approach" (Maxmen 2012).

The Bradner lab does not require that the researchers who receive JQ1 become collaborators of theirs or note the team as co-authors (though the MTA does require recipients to forward to the DFCI all publications containing experimental results obtained from the use of the material). There is no obligation to reciprocate in any way. JQ1 is a gift from fellow scientists. But Bradner has been gratified to see the studies that other laboratories have conducted with this molecule. Scientists have found that JQ1: contributes to pathogenesis of human papilloma virus, keeps mice alive after septic shock, prevents bleomycin-induced pulmonary fibrosis, and can reactivate latent HIV. Bradner's team has made two significant discoveries beyond its own work on cancer by collaborating closely with scientists from other medical fields. With Haldar, the team has uncovered a new molecular pathway responsible for heart failure and discovered that JQ1 blocks this

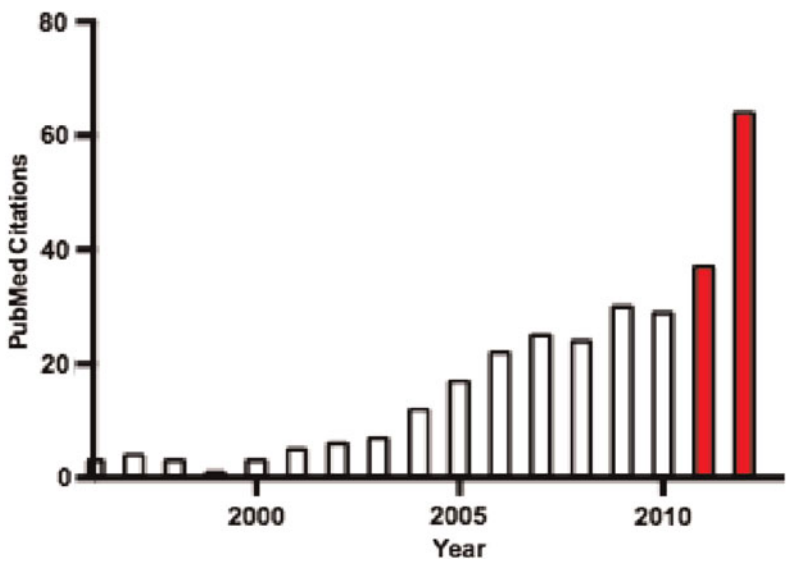


Fig. 1. (colour online) The effect of open source distribution of JQ1 on bromodomain publications.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

pathway to protect the heart (Anand et al. 2013). With Martin Matzuk, from the Baylor College of Medicine, Bradner's team found a potential, reversible, male contraceptive use for JQ1, as the molecule completely inhibits male fertility after a two-month drug exposure. Fertility (sperm count) and phenotypic normality is restored after two months of drug washout (Matzuk et al. 2012). Both discoveries have initiated new research programs – entirely new ways of thinking about contraception and heart disease.

For the Bradner lab, open source drug discovery involves: (1) putting your molecules out there in such a way that everyone can study them – promptly and transparently publishing everything other scientists might need to conduct further research; ensuring that the compound is immediately available and inexpensive to make; and eliminating all nefarious and bogus obstacles to the molecule's dissemination; (2) not interfering with anyone's ideas about how to use the molecule; (3) maintaining responsibility for the molecule by remaining available for questions; keeping the user manual up-to-date; and continuing to study the molecule yourself. Open-source drug discovery here is a lot like conceiving of yourself as the parent of the molecule and the molecule as your gift to the world, one that you had always intended to set free, when the time was right, so the molecule might live a life of its own. You hope to follow its journey, and you wish it a pregnant future. But you no longer exercise your original ownership over it. Beyond the treatment, distribution, and conceptualization of the physical molecule, open source drug discovery involves keeping certain broader observations and experiences foremost in your mind, namely, your face-to-face experiences with the suffering of cancer patients and their families. In Bradner's words: "Open-source biology is transparently publishing all of the data other scientists might need to conduct further research and embracing the research successes of other labs as successes, i.e. as a step closer to a cure" (Bradner, personal communication 2013).

Large-scale, public, open-activity initiatives

Across the globe, a few national scientific organizations are beginning to support openness in drug discovery. India's publicly funded Council of Scientific & Industrial Research (CSIR), in hopes of providing affordable healthcare to the developing world, embraced open source drug discovery in 2008. The CSIR's Open Source Drug Discovery (OSDD) team supports laboratories and projects aiming to discover drugs for tropical infectious diseases, which rarely capture the attention of Pharma. The CSIR's first priority is tuberculosis, which is one of the leading causes of death in developing nations, followed by malaria (OSDD). The European Union has given a €2 billion budget to the Innovative Medicines Initiative (IMI), a public–private health partnership with the mission of building "a more collaborative ecosystem for pharmaceutical research and development" (IMI 2010). European pharmaceutical companies, including Sanofi, AstraZeneca, Bayer, Janssen, Merck KGaA, UCB, and Lundbeck, have agreed to contribute over 300,000 small molecules to the European Lead Factory (ELF), an open library of more than 500,000 compounds accessible to and made available by both public and private organizations. In the United States, part of the rationale for the NIH's Molecular Libraries Probe Production Centers Network (MLPCN) was to put screening data in the public domain. The website PubChem, a repository of data into which users can upload material, is hosted by the NIH's National Center for Biotechnology Information (NCBI) and linked to MLPCN. None of these national agencies, however, are involved yet in the material

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

transfer of novel, proven-effective compounds. Larger, institutional, public–private partnerships are trading only in information and existing libraries of potentially effective molecules. The governmental agencies are simply calling for information to be collected and stored in one place. In the words of CSIR's Open Source Drug Discovery community, their mission is "to collaboratively aggregate the biological, genetic and chemical information available to scientists in order to use it to hasten the discovery of drugs".

A HYPOTHESIS ABOUT THE SOURCE OF OPEN SOURCE

The decision to openly share JQ1 has increased our scientific knowledge of bromodomains and, in making possible the related work on MYC, has brought scientists one step closer to developing powerful, targeted therapeutics that will alleviate the suffering of cancer patients. Moreover, the open source sharing of JQ1 has led to important discoveries in the fields of HIV, fertility, and heart disease research. These are empirical facts, endorsed by the peer reviewers of our best scientific journals. Successful, open source medical research demonstrates that it is possible to produce valuable, empirically adequate, and sustainable collective beliefs without secrecy, proprietary attitudes, initial cooperation from Pharma, or outsized monetary incentives. All it takes to produce valuable beliefs in this way is, first, an institutional structure that permits this form of activity and, second, the kind of training/acculturation into the world of care that physician-scientists undergo during their clinical rotations, as they, sadly, spend their days watching people die and families grieve.

Of the open source researchers discussed here, only Gey and Bradner were trained exclusively as physicians, that is, as M.D.s.[12] Most chemical biologists and even most of the scientists working in drug discovery more broadly have research doctoral degrees. It is extremely rare for a drug discovery scientist to take clinical rounds. The last section of this paper claims that both the form of professional training scientists undergo and the institutional structure in which scientists work play difference-making roles in a scientist's commitment to the open source sharing of valuable biological materials – materials that are novel, fairly well understood, and proven to be effective. For physicians, years of intimate exposure on clinical rounds to dying patients, their families, and more senior physicians gives the science of drug discovery an urgency that carries into the laboratory, an urgency that makes the secrecy and proprietary attitude surrounding such research within the pharmaceutical industry seem anti-intellectual and inhumane.[13] Moreover, the academic context, with its public, not-for-profit orientation, makes possible epistemic strategies that are inconceivable within Pharma's for-profit structure. Bradner explains: "Academic science is a public service, funded by the public and charitable foundations. Illness and science are more connected now than ever. You do not invoke your own priorities when dealing with a patient, and that norm transfers to the lab" (Bradner, personal communication 2013). The concluding hypothesis is that, in regard to therapeutics, we might generate more knowledge and better (more reproducible) knowledge more quickly

12 Matzuk has a M.D./Ph.D., and Rohde has a degree similar to what would be a M.D./Ph.D. in the United States.

13 In the example of drug discovery as practiced by physician-scientists, we may even come across a powerful counterexample to William James's conception of science, i.e., his view that in science we can suspend belief, because our options there are not live, forced, and momentous (James 1897).

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

by habituating all medical researchers into the world of care, the world in which scientists trained as physicians live.[14]

Why the academic context is structurally conducive to drug discoveries made through the open sharing of materials

As not-for-profit institutions, universities routinely look for ways to collaborate with other institutions in order to share costs. Sharing probes lowers costs, as laboratories can request free molecules, instead of producing them *de novo*. The open source strategy – unlike Thomas Pogge's Health Impact Fund (HIF), for example – incentivizes scientific research without extra monetary investment. On the rationale that Pharma can only recoup its investments in research and development by patenting drugs and then charging high prices for them, the HIF offers a reward, based on the medicine's global health impact, for a fixed number of years to companies who register a new medicine with the HIF, as long as the company agrees to forgo monopoly pricing. The company can only charge cost, which is reasonable, Pogge claims, because, once developed, drugs are inexpensive to manufacture. On the HIF track, Pharma would have an opportunity to profit from medicines that would make a big impact, such as medicines for large, underserved populations. During the reward period, the firm can patent their product, but must sell it at the low price. After the reward period, the company must offer free licenses for the technology that is required to manufacture and sell the product.

It is difficult to see how Pogge's fund would be attractive to drug companies, which presently have and would still retain the monopoly option. The risk is that most companies would continue on their present path, while only a few minor players would step up to develop malaria and tuberculosis medications and accept the prize. The HIF website FAQ acknowledges this: "Companies will keep their patent rights and will only choose to register products with the HIF that are not profitable under the current system, but that would be profitable when payment is based on health impact" (HIF 2013). But this statement misconstrues the appropriate comparison class, from Pharma's perspective. The HIF would have to offer a hefty reward to incentivize companies with blockbuster drugs to work on formerly unprofitable drugs. In other words, the HIF reward for the malaria drug would have to be large enough to draw the company's resources away from the blockbuster drug. The appropriate comparison class for the now-profitable-thanks-to-the-HIF malaria drug is not the formerly unprofitable malaria drug, but the super-profitable blockbuster drug.[15] Finally, governments and donors

14 Of course, *n* basically equals 1 here, but I believe my access makes the case epistemically significant. My personal confidence in the connection between Bradner's habituation into the world of care and his decision to share JQ1 comes not through some more general, inductively secured law connecting (a) training in care and sharing and (b) the lack of training in care and not sharing. Rather, my confidence in the connection comes through – what is arguably more reliable than non-monotonic inference from cases – my close observational access to the details. I hope for subsequent research to show that what has occurred in the cases of Bradner and Gey, could also occur for other physician-scientists engaged in drug discovery, and, hopefully, could occur for pharmaceutical scientists with doctoral degrees who seek out clinical experiences with dying patients. "Cases provide the way forward," as Rachel Ankeny has said (Ankeny 2013).

15 The fund basically offers a monetary reward to companies who are not exclusively driven by profit, in that they already invest in the discovery and development of unprofitable malaria drugs. But the fund

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

would have to establish the HIF, and the NIH has lost almost a quarter of its capacity to fund medical research since 2003 (FASEB 2013). In contrast, the open source sharing of compounds cuts R&D costs by gutting competitions, eliminating the duplication of work, and making it possible for scientists in countries with poorer populations to synthesize or order their own molecules to suit their own, specific needs (with assistance from the originating laboratory a short call away), as such material and information is openly available. Because universities share wisdom concerning best practices and resources with one another, in order to save money, and because open source sharing is a practice that saves money by sharing resources, universities are structurally primed for the open source sharing of molecules.

Among academics, within the academic community, there is baseline level trust that exists among fellows who are engaged in and committed to a common form of life, and this trust greases the wheels of open activity. Successful science does not require that collaborating scientists have a pre-existing personal relationship (Shrum et al. 2007: 157). In fact, at times, personal friction and distrust between scientists can be beneficial. The scientists who order JQ1 do not know Bradner personally, but trust his lab will send a functional product on the basis of his professional credentials and institutional backing. They also trust that the DFCI will not restrict their liberty to explore biology and publish in whatever manner they choose. Once the molecule is received and employed, this baseline level of trust is reinforced and enriched, as receiving laboratories conceive the free shipping of JQ1 as a volunteer's act of grace and plan to pass along their own good fortune to other members of the community. Though pharmaceutical scientists go through the very same graduate programs and attend the same conferences as academic scientists, and though there is some movement between the corporate and academic contexts, it is difficult for academic scientists to conceive of pharmaceutical scientists as fellow community members, given Pharma's willingness to accept probes from academic researchers, but Pharma's unwillingness to reciprocate by sharing their own early data, materials, and technologies.

In the pharmaceutical context, money is money. But, in the academic context, credit is money. David Hull argued in *Science as Process* that science consists not of collections of theories, but of traceable lineages of credit: "The form of 'status' that matters in science is the credit that accrues when one scientist makes use of another scientists' work, in particular, its incorporation in his or her own research, preferably with an explicit citation" (Hull 1988: 283). These material traces constitute a theory's survival and, thus, success. He explains: "The chief weapon of the scientific community to new ideas is a conspiracy of silence" (Hull 1988: 287). Scientists with original ideas must be tenacious and clear, in order to protect against extinction (Hull 1988: 288). Thus, it is the social organization of science that is responsible for its success and epistemic power, when compared with other disciplines. Shipping molecular probes far and wide carries the reputation and research of the laboratory far and wide. And laboratories receiving JQ1 are receiving the opportunity to accrue more credit than they would have accrued without JQ1. Finally, though the Bradner lab's techs, graduate students, post docs, and other laboratory members have not received the same level of direct attention as Bradner has received, they

will not encourage companies who are exclusively driven by profit (and, thus, avoid such drugs) to change their tune. The worry here is that there are not very many companies of the first sort and that the health impact fund, as a consequence, won't have much of an impact.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

benefit from their lab's good reputation. The academic context's currency of credit promotes open source sharing, because open source sharing generates credit. Open-source sharing does not generate money. So the for-profit structure of the pharmaceutical industry is less hospitable to open source sharing.

Why medical training – habituation into the world of care – is conducive to drug discoveries made through the open sharing of materials

Physician-scientists involved in drug discovery – of which there are only a handful – come to chemical biology after medical school, a residency, and a fellowship, during which they spend a decade attending to sick patients. This training amounts to an acculturation into a world (Bradner 2012). Within this world, the open source sharing of molecular probes follows as a natural manifestation of the value system, in which those who are suffering have urgent needs, in which the need for relief trumps the need to please shareholders, and in which those who can fulfill needs do so as a matter of course.

A physician's life, much like a teacher's life, is intensely social. Though doctoral students certainly teach and socialize, at least half of their time is spent reading and thinking, which is a solitary activity. Moreover, the time they do spend with people is not as emotionally charged. Physicians work with hundreds of people every week, engaging throughout each day and night with families who are suffering, because their loved ones have fallen ill. Where the most sensitive doctoral students reach out from time to time to help students who lack skills and confidence, there is no way to train as a physician without administering to pain and suffering on an hour-to-hour basis.

Medical students pay upwards of $57,000/year for their training, which makes it very costly for them to abandon the profession once they have started. Most doctoral students, on the other hand, receive some of their training for free and the rest of it in exchange for pedagogical work. Doctoral students are surely determined, passionate people. But the commitment to medicine requires a certainty from which one cannot allow oneself to waiver, on pain of financial ruin. Material considerations may induce students to commit, in an especially forceful way, to the field and its values. Later on, as some M.D.s move on to conduct laboratory research, self-selection may play a role in producing open activity. Academic physician-scientists take a $200,000–400,000 pay cut just to work as professors. For those M.D.s who are willing to accept these cuts, money (for whatever reason) was likely not a priority in the first place. Bradner feels his fallback option gives him a kind of freedom and adventurousness – a Jamesian epistemic boldness – that professors who rise out of the doctoral track don't have the luxury to manifest: "It is true that if I quit science tomorrow, my salary would double. Perhaps it's lucky that my fallback option pays better, has better hours, and has less stress, so I can take more chances" (Bradner, personal communication 2013).[16]

Throughout each day, medical students interact with attending physicians, who mentor their students during clinical rounds. Doctoral students have mentors as well. But the aura is different. Where doctoral students tend to admire their dissertation advisors as brilliant, medical students admire senior physicians as both brilliant and saintly. Medical students

16 The large difference between the salary of a professor and the salary of a physician might explain why there are so few M.D.s in drug discovery – that is, M.D.s who take clinical rounds.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

see first-hand the sacrifices in time, health and energy their advisors make, in order to track course of their patients' illnesses through the night and days that follow the initial diagnosis. Doctors are habituated into a world rich with caregivers, exemplars of caregiving, and a rhetoric that promotes caregiving as finally valuable. Mentors' messages affect the ways in which students handle equipment, schedule their day, talk to patients, think about their personal lives, teach other physicians and students, and work as a team. Bradner explains: "When you're in front of a patient, you're thinking, 'How can I help versus what can I get out of this, what's in it for me?'" (Bradner, personal communication 2013). When medical students make a costly mistake, one that hurts a patient, they are harshly castigated in front of their peers. Of course, doctoral students can be humiliated in an important seminar or at a conference, but the upshot of the criticism is never that the doctoral student is an uncaring person who could have killed someone, someone who has dependents who count on her for love and food.

Finally, medical students must study a serious ethics curriculum, usually with one ethics or sociology of medicine course each term. At the University of Chicago's Pritzker School of Medicine, for example, first-year medical students take "Health care disparities: equity and advocacy" in the summer, "Social context of medicine: the American healthcare system" in the fall, and "Physician-patient-society systems" in the winter and spring, followed by electives in subsequent years, and weekly mortality and morbidity conferences during the residency and fellowship period. This is in stark contrast to the experience of doctoral students in basic science, who take, minimally, a compulsory three-hour laboratory ethics course that focuses primarily on occupational safety, data reporting, and the school's Institutional Review Board procedures for working with human and non-human animal participants, or, maximally, a one-semester course at the undergraduate level on ethics and science, which, for chemists usually focuses on environmental issues.

LOOKING AHEAD

This paper offers a hypothesis. It aims to suggest that scientists, like Gey and Bradner, who have come to drug discovery through medicine, have been habituated into a world of care, in which the open source sharing of biological materials is an automated response to a glaring need: no serious consideration or reflection on the issue is required. Later in their careers, when physician-scientists are spending most of their time in laboratories, deciding which questions to tackle, how to operationalize their hypotheses, whom they should hire, how they should spend their grant money, with whom they should collaborate, and whether they should schedule any leisure time, etc., their visceral experiences with dying patients and suffering families resonate. Bradner explains: "If you make bread dough, you're making a good [i.e. a product to sell]. It's not a selfless activity. When you care for patients, it's a service. When you create knowledge, you can look at it either way. When you take care of people who are running out of oxygen with acute leukemia and then write a grant, it matters. I think of knowledge as a service. People are depending on us" (Bradner, personal communication 2013). In contrast, for most academic scientists and most pharmaceutical scientists, who have come to drug discovery through doctoral programs in basic science, the request to openly share materials must seem like an extra requirement gripping only on those researchers who are especially heroic, but not

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

important enough to trump the more natural aims of originality and priority, in academia, and profit, in Pharma.[17]

As for the later Ludwig Wittgenstein, Norwood Russell Hanson, Thomas Kuhn, and Ian Hacking (albeit in subtly, but importantly, different ways), training does not create a reality, but makes possible a reality *for you*, by calibrating the fine-grained-ness of the lens through which you see the world (Bradner 2012). Consider, for a moment, the training of a fashion designer, a baseball pitcher, a philosopher, and, finally, a physician. These modes of training focus their practitioners on some things and occlude others, making it possible for practitioners to see what others cannot. Habituation is both a lens and a new blindness.

Can Pharma come to see open source sharing as unreflectively natural? There is some reason for hope. Now that academic scientists have begun to create and share data, materials, and technology, there is a question as to whether Pharma's proprietary model will continue to remain competitive. In early drug discovery, time is of the essence. Moreover, open source sharing is not completely at odds with Pharma's financial ambitions, for open source sharing may serve as a way of generating clinical and commercial futures for technologies that have been abandoned. Finally, Pharma is increasingly open, at least, to sharing data. GlaxoSmithKline is a leader in this arena and has recently committed to putting clinical trial data in the public domain, which is quite bold. However, thus far, there is no movement to share novel, fairly well understood, proven-effective molecules with other researchers via streamlined MTAs, as the Bradner lab has done.

Perhaps we could retrain pharmaceutical researchers with doctorates to respond first and foremost to patients' needs. By asking drug discovery researchers without medical training to spend some extended time in the clinic, we could prime them to remain on the lookout for pain and suffering and respond to that pain and suffering whenever possible, even if it were to mean sharing some of their proprietary materials, missing out on an original discovery, or losing a little money. After all, unlike Hacking's contemporary chemists struggling to understand medieval alchemy (Hacking 1993: 297), in this conflict we *can* do "Paracelsian" things, for it is entirely possible to interact with the authentic "Paracelsian" things in their original context. The "things" – the suffering patients – are all around us. They're our colleagues, our friends, our parents, and our children.

This might work, but it would require an extended period of acculturation into the world of care and a mechanism for forgetting the habits of the old world. The more direct way to generate more and better knowledge sooner might be to think carefully about which drug discovery projects are best suited for academia and which projects are best suited for Pharma, based upon estimates of likely project horizons, with Pharma spending three to five years to tweak existing drugs in secret and academia tackling the longer, high-risk-high-reward projects – the "undruggable" targets, such as MYC and KRAS, for instance – in public, with the kind of open source sharing of molecules that comes naturally to physician-scientists who have advanced training in chemical biology. To pursue this last option, we will need many more such people.[18]

17 Of course many individual scientists working within Pharma decide to pursue drug discovery, instead of some other form of chemistry, because they care about the suffering of patients. The point here is not that Pharma scientists are cold-hearted, but that the structural features of pharmaceutical companies and doctoral training ensure that profits and results – rather than patients – are kept in view.

18 For many helpful suggestions, thanks to participants in both the April 2013 conference, "Choosing the Future of Science: The Social Organization of Scientific Inquiry [SOSI]," at the University of

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

REFERENCES

Anand, P., Brown, J. D., Lin, C. Y. et al. 2013. 'BET Bromodomains Mediate Transcriptional Pause Release in Heart Failure.' *Cell*, 150(3): 569–82.

Ankeny, R. 2013. 'Establishing Causes in Medical Practice: The Role of Cases.' Plenary Address. The Society for Philosophy of Science in Practice, Institute for the History and Philosophy of Science and Technology, Victoria College, University of Toronto, Toronto, Canada, June 27, 2013.

Begley, C. G. and Ellis, L. M. 2012. 'Drug Development: Raise Standards for Preclinical Cancer Research.' *Nature*, 483: 531–3. doi: 10.1038/483531a.

Bradner, A. 2012. 'Using *Structure* to Understand Justice and Care as Different Worlds.' *Topoi*, 32: 111–22.

Bradner, J. 2013. 'Epigenetic Targets for Cancer: Bromodomain Inhibition in Cancer.' *American Association for Cancer Research* Annual Meeting 2013, Washington, DC, video, 29:22, April 8, 2013. Accessed April 18, 2013. http://webcast.aacr.org/console/player/20077?mediaType=podiumVideo&.

Code, L. 2010. 'Testimony, Advocacy and Ignorance: Thinking Ecologically about Social Knowledge.' In A. Haddock et al. (eds), *Social Epistemology*. Oxford: Oxford University Press. Accessed 4/16/2013 (Oxford Scholarship Online edition, 2011). doi: 10.1093/acprof:oso/9780199577477.001.0001.

Cutler, D. 2007. 'The Demise of the Blockbuster?' *New England Journal of Medicine*, 356:1292–3.

Dana-Farber Cancer Institute. 2010. 'DFCI Outbound Academic MTA v. 2 2010 Modified for compounds.' Cambridge, MA: Harvard University.

Dawson, M. A. and Kouzarides, T. 2012. 'Cancer Epigenetics: from Mechanism to Therapy.' *Cell*, 150: 12–27.

Delmore, J. E., Issa, G. C., Lemieux, M. E. et al. 2011. 'BET Bromodomain Inhibition as a Therapeutic Strategy to target c-Myc.' *Cell*, 146: 904–17.

DiBona C., Ockman S. and Stone M. (eds). 1999. *Open Sources: Voices from the Open Source Revolution*. Sebastopol, CA: O'Reilly & Associates.

Federation for American Societies for Experimental Biology (FASEB). 2013. 'Sequestration Cuts Biomedical & Biological Research Factsheet.' Accessed May 16, 2013. http://www.faseb.org/Portals/0/PDFs/opa/Sequestration%20factsheet.pdf

Filippakopoulos, P., Qi, J., Picaud, S. et al. 2010. 'Selective inhibition of BET bromodomains.' *Nature* 468: 1067–73.

French, C. A., Miyoshi, I., Kubonishi, I., Grier, H. E., Perez-Atayde, A. R. and Fletcher, J. A. 2003. 'BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma.' *Cancer Research*, 63: 304–7.

Friend, S. and Schadt, E. 2009. 'Something Wiki this way comes. Interview by Bryn Nelson.' *Nature* 458(7234): 13.

Frye, S. V. 2010. 'The Art of the Chemical Probe.' *Nature Chemical Biology*, 6: 159–61. doi: 10.1038/nchembio.296.

Gilligan, C. 1982. *In a Different Voice*. Cambridge, MA: Harvard University Press.

Goodpaster, K. 1991. 'Business Ethics and Stakeholder Analysis.' *Business Ethics Quarterly* 1: 53–73.

Hacking, I. 1993. 'Working in a New World.' In P. Horwich (ed.), *World Changes: Thomas Kuhn and the Nature of Science*. Cambridge, MA: MIT Press.

Health Impact Fund (HIF). 2013. 'Frequently Asked Questions on The Health Impact Fund.' Accessed May 16, 2013. http://healthimpactfund.com/faq/#no18.

Hull, D. 1988. *Science as Process: An Evolutionary Account of the Social and Conceptual Development of Science*. Chicago, IL: University of Chicago Press.

Pittsburgh's Center for the Philosophy of Science, and the June 2013 conference of the Society for the Philosophy of Science in Practice, at the University of Toronto, in particular: Rachel Ankeny, Shahar Avin, Julia Bursten, Elihu Gerson, and Miriam Solomon. Special thanks to Jay Bradner and SOSI organizer Kyle Stanford for reorienting insights.

Innovative Medicines Initiative (IMI). 2010. 'Mission.' Accessed May 14, 2013. http://www.imi.europa.eu/content/mission.

James, W. 1979. *The Will to Believe and Other Essays in Popular Philosophy*. Cambridge, MA: Harvard University Press.

Kantarjian, H., Fojo, T., Mathiesen, M. and Zwelling, L. 2013. 'Cancer Drugs in the United States: *Justum Pretium* – The Just Price.' *Journal of Clinical Oncology*. Published online May 6, 2013. Accessed July 15, 2013. http://jco.ascopubs.org/content/early/2013/05/06/JCO.2013.49.1845.

Keller, E. F. 1983. *A Feeling for the Organism: The Life and Work of Barbara McClintock*. New York: Freeman.

Masters J. R. W. and Palsson B. Ø (eds). 1999. *Human Cell Culture*, Vol. 1–3. Dordrecht: Kluwer Academic.

Masters, J. R. 2002. 'HeLa Cells 50 years on: The Good the Bad and the Ugly.' *Nature Reviews Cancer* 2: 315–319.

Matzuk, M. M., McKeown, M. R., Filippakopoulos, P. et al. 2012. 'Small-molecule Inhibition of BRDT for Male Contraception.' *Cell* 150: 673–84.

Maxmen, A. 2012. 'Cancer Research: Open Ambition.' *Nature* 488(7140): 149–50.

Medicines for Malaria Venture. 2013. 'Open access for malaria box.' Accessed July 25, 2013. http://www.mmv.org/malariabox.

Mobley, A., Linder, S. K., Braeuer, R., Ellis, L. M. and Zwelling, L. 2013. 'A Survey on Data Reproducibility in Cancer Research provides Insights into our Limited Ability to translate Findings from the Laboratory to the Clinic.' *PLoS ONE* 8(5): e63221.

Open Source Drug Discovery (OSDD). 'What is OSDD.' Accessed May 16, 2013. http://www.osdd.net/about-us.

OpenSourceMalaria. 2013. 'Story so far.' Last modified July 10, 2013. Accessed July 25, 2013. http://openwetware.org/wiki/OpenSourceMalaria:Story_so_far.

Prayle, A. P., Hurley, M. N. and Smyth, A. R. 2012. 'Compliance with Mandatory Reporting of Clinical Trial Results on ClinicalTrials.gov: Cross Sectional Study.' *British Medical Journal* 344: d7373.

Prinz, F., Schlange, T. and Asadullah, K. 2011. 'Believe It or Not: How Much can We Rely on Published Data on Potential Drug Targets?' *Nature Reviews Drug Discovery* 10: 712.

Rohde, H., Qin, J., Cui, Y. et al. 2011. 'Open-source Genomic Analysis Of Shiga-toxin-producing *E. coli* O104:H4.' *New England Journal of Medicine* 365(8): 718–24.

Sage Bionetworks. 2013. 'About Us.' Accessed April 19, 2013. http://sagebase.org.

Shrum, W., Genuth, J. and Chompalov, I. 2007. *Structures of Scientific Collaboration*. Boston, MA: MIT Press.

Skloot, R. 2001. 'An Obsession with Culture.' *Pitt Magazine* March 2001. Accessed May 15, 2013. http://www.pittmag.pitt.edu/mar2001/culture.html.

Sourceforge. 2013. 'Main page: celera assembler.' Last modified March 19, 2013. Accessed April 18, 2013. http://sourceforge.net/apps/mediawiki/wgs-assembler/index.php?title=Main_Page.

Stallman, R. 1999. 'The GNU operating system and the free software movement.' In C. DiBona, S. Ockman & M. Stone (eds), *Open Sources: Voices from the Open Source Revolution*, pp. 53–70. Sebastopol, CA: O'Reilly & Associates.

——. 2002. *Free Software, Free Society: Selected Essays of Richard M. Stallman*. Boston, MA: GNU Press.

Stegenga, J. 2013. 'Detecting Harm of Medical Interventions.' In *Science, Policy, Values: Exploring the Nexus. Pre-conference workshop at the Society for Philosophy of Science in Practice, Institute for the History and Philosophy of Science and Technology, Victoria College, University of Toronto, Toronto, Canada, June 26, 2013*.

Stiglitz, J. E. 'How Intellectual Property Reinforces Inequality.' *The New York Times* July 14, 2013. Accessed July 15, 2013. http://opinionator.blogs.nytimes.com/2013/07/14/how-intellectual-property-reinforces-inequality/?emc=eta1.

Todd, M. 2012. 'Molecular craigslist.' Intermolecular blog. April 19, 2012. Accessed July 25, 2013. http://intermolecular.wordpress.com/2012/04/20/molecular-craigslist/

Westphal, S. P. 2013. 'Unverified Science; Studies that can't be Replicated create a Problem with Trust – and Funds.' *The Boston Globe* July 8, 2013. Accessed July 15, 2013. http://www.bostonglobe.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press

com/opinion/2013/07/07/for-research-useful-has-reproducible/MjyEfoq7HDlWvOTmNFfl8L/story.html.

Woelfle, M., Olliaro, P. and Todd, M. 2011. 'Open Science is a Research Accelerator.' *Nature Chemistry* 3: 745–8.

ALEXANDRA BRADNER is an epistemologically minded philosopher of science who currently teaches philosophy of biology and experimental philosophy at Kenyon College in Gambier, Ohio, where she is Visiting Assistant Professor. Meta-philosophically, her work explores the various ways in which naturalists might use empirical results to constrain possibility spaces, for instance, by collaborating with scientists on laboratory experiments, conducting x-phi studies, and getting especially close to qualitative cases. She is particularly interested in the cognitive science of understanding, barriers to understanding, the pragmatics of explanation, and the ethics of care.

https://doi.org/10.1017/epi.2013.33 Published online by Cambridge University Press