The Open Therapeutics* Mission Paper

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Introduction

The pharmaceutical industry faces a host of worsening problems: Multibillion-dollar expenses and decade-long development times to bring new drugs to market, high failure rates for new drug candidates, and a patent system that is both expensive and uncertain. Demanding regulatory requirements and governmental pressures on prescription costs add yet more pressure on drug development. Although the situation does not yet constitute a crisis, its current trajectory is becoming increasingly untenable.[1] While the industry itself has been resourceful in introducing technological advances and operating reforms such as increased collaboration through patent pooling,[2] these efforts do not exhaust the possibilities for improvement. In particular, there has been an emerging, more agile and responsive alternative model in pharmaceutical research and development, namely open source synthetic biology – a rapidly developing and highly collaborative effort based on engineering principles involving the design and construction of biological systems using standardized modules of DNA. Synthetic biology began entirely open to those who wished to participate, provided that they agreed to share their results without restrictions. In its current and more mature state, it retains much of its open source character and is consequently less dependent on secrecy and patent protection than the pharmaceutical industry's largely proprietary approach.

The success of open source synthetic biology has inspired us to further develop that approach for research and development in microbiology and its pharmaceutical applications. What we have accomplished and how we intend to proceed is the subject of this mission statement. We begin, however, with a review of the history and progress of open source science and technology.

I. Open Source Predecessors in Programming and Synthetic Biology

A. Open Source Computer Programming. Open source developments in computer programming provided the model for later open source developments in synthetic biology. The Linux operating system, as eventually commercialized by Red Hat® is, by all accounts, the "poster child" for successful open source programming.[3]

It had, however, a rather inauspicious beginning. In 1991, Linus Torvalds, a computer science student at the University of Helsinki, developed a Unix-like operating system that he called Minix and later renamed Linux. He then published a post announcing that "I'm doing a (free) operating system (just a hobby, won't be big and professional like GNU [a free software project started in 1983]) . . . I'd like any feedback on things people like/dislike in Minix . . . I'd like to know what features most people would want."[4] Enthusiasts and disgruntled systems programmers joined in, and soon there were a number of iterations of Linux up and running.

Red Hat was eventually able to commercialize a version successfully around 1994. Initially, Red Hat made its money through the sale of software support for what was still essentially an open source, free product, subject only to what became known as "copyleft" agreements. In short, while the initial version of the software is copyrighted (thereby creating a property right to the literal coding but not to its functionality), it is "left" to those who agree to the "copyleft" restrictions to further develop that version, provided they allow subsequent access to their work subject only to a similar copyleft agreement.[5]

Later in 2003, Red Hat created and offered the more proprietary Red Hat Enterprise Linux®, which is sold through a subscription including updates, patches, and bug fixes. A wide range of coordinated proprietary software is also offered.[6] Despite this commercialization, Red Hat continues to keep its open-source roots alive with the Fedora Project, whereby Linux (*sans* the support of Enterprise Linux) is freely provided to those willing and able to develop the software. Fedora thus serves the purpose of facilitating the continued existence of a hot-house, open source community for creating and showcasing leading-edge Linux developments.[7] The end result is that versions of Linux, Red Hat and otherwise, now "power 98% of the world's super computers, most of the servers powering the Internet, the majority of financial trades worldwide and tens of millions of Android mobile phones and consumer devices."[8]

How successful has this been for Red Hat *as a business venture*? Open source presumably comes at a price. The straightforward answer is that Red Hat now has a market capitalization of more than $13 billion with a 2016 fiscal year revenue of over $2 billion.[9] Those values, however, are just a fraction of the size of its strictly proprietary competition. So the point is not that open source ventures such as Red Hat will replace or dominate large-corporation development, but rather that they can occupy an *economically secure and*

significant niche – a niche that provides an extra and *creatively efficient* level of competition for the closed high-stakes corporate players. That Red Hat's creative efficiency – due to its open, crowd-sourcing business model – is a significant business asset is confirmed by its recent invitation to join in a partnership with Microsoft for the further development of Microsoft's Azure cloud services.[10] In a similar vein, Mark Russinovich, CTO of Microsoft Azure, explained at a recent All Things Open conference, that Microsoft is now supporting dozens of open-source projects precisely because it is a "practical business decision."[11]

B. Synthetic Biology. It was not by accident that the next major development in open source science and technology was in synthetic biology.[12] One of the founding fathers of the approach was MIT computer scientist, Tom Knight, who understood perfectly well that DNA is a form of coding – not plain and simple, but in essence a coding of process. In addition, there was another commonality with computer coding, namely, modularity. This is an important element of real-world programming. While efficiency and its close cousin elegance, are obvious desiderata, so too are ease of debugging, maintenance, and further development. Unfortunately, these two sets of criteria are often in conflict. It is here that modularity comes into play: discrete and independent sub-sections of code with specific purposes form modules which can then be connected together to form coherent code that satisfies the practical criteria. Modularity, however, is a feature not only of successful computer programming, but also of electrical and other types of engineering. And most importantly, it is also a central feature of evolutionary biology! Insofar as evolutionary pressures select and help propagate changes in genetic coding, nature has responded with modular structures.[13]

It was thus a short, but prescient effort *to take nature a step further* and create, in the laboratory, biological modules – synthetic instruction sets of DNA known as "Biobricks" – with discrete functions whereby those modules could be combined with emergent functional effects once inserted into a host or "chassis" cell, typically E. coli or yeast. Knight's initial problem was to develop a standardized biological container, where these containers could be used to house different sub-sets of DNA, and where these containers could be connected together and installed in a receptive chassis with the desired functional effect. As explained by Knight, the motivation underlying this modular approach was to replace existing non-standardized and "ad hoc" DNA assembly techniques "with a set of standard and reliable engineering mechanisms to remove much of the

tedium and surprise during assembly of genetic components into larger systems."[14] In short, these containers and their specific DNA coding contents were to be analogous to (1) modular computer coding routines that can be combined efficiently and predictably, and (2) the use of standardized components in electrical engineering.

It was fortunate that the above innovations were created in an academic and thus open source environment. In order to retain the open character of these innovations, the effort was made to develop openly as many basic synthetic modules as possible and make them freely available, subject only to what is known as a "click-wrap" license which grants access subject to certain conditions. In this way, a "commons" of synthetic modules was made freely available. Here the strategy was one of "defensive publication," *i.e*., by making inventions public, subsequent patent applications would be unable to satisfy the novelty requirement. The BioBricks Foundation, for example, serves as a repository for module specifications where contributors agree not to assert property rights and recipients promise to provide attribution to the contributor and include the BioBrick trademark logo in uses, commercial or otherwise, of the module.[15] But, because there is not an underlying property right, such licenses bind only those who are parties to the agreement. This leads to the problem of leakage: non-party free riders who gain access to a module specification and make unrestricted use of that information. Such leakage can be mitigated by making use of trade secrets law, though this has the disadvantage of compromising the openness of the process.[16] More significant, however, is the fact that BioBrick licensees are free to patent assemblages they create from the modules.[17] Knight himself has further commercialized the creation of bio-parts with the creation of Ginko Bioworks, the world's first organism-engineering "foundry."[18] The company has adopted both proprietary – with patent protection – and open source activities, including a publically available engineered DNA promoter. It has been rewarded for its efforts with $54 million dollars in recent funding.[19]

An alternative, purely open-source albeit patent protected approach has been adopted by the Biological Innovation for an Open Society (BiOS). The initial elements of the commons are certain patent protected gene transfer technologies. With a property right thus established, BiOS can insist that licensees put any improvements they develop into the BiOS commons and, moreover, can legally enforce its established property rights against infringement.[20]

While the initial stages of the development of synthetic biology were decidedly open source, in its more mature state the trend with respect to patent applications appears to be no different from those in other areas of biology.[21] There is thus an emerging *hybrid* system of discovery and development in synthetic biology that combines open source beginnings with more traditional forms of intellectual property at later stages of research and development. *The question then is: what are the optimal contours of such a hybrid system*? To even begin to answer such a question, we need to take a deeper look at patents and the protection of intellectual property that they provide.

II. Patents and the Protection of Intellectual Property.

A. Computer Software. Computer software cannot be readily patented. Patent law requires functionality but excludes formulas and algorithms. Ergo, software *per se* cannot be patented. Unless, as recently held by the Supreme Court in *Alice v. CLS Bank*, it serves as a sufficiently "inventive concept" in the implementation of some independently patent-eligible "abstract idea." Applying this test, the Court held that an otherwise ineligible abstract idea is not transformed into a patent eligible invention by the use of a generic computer implementation.[22] But other than holding that the abstract idea in question – intermediated financial risk settlement – was ineligible, the Court determined that it did not need to "labor to delimit the precise contours" of what constitutes an abstract idea, eligible or otherwise. It was thus left for the lower courts to wrestle with such determinations in future cases.[23] In any event, the Court's decision continues to allow for inventive implementations designed to improve the functioning of a computer or other types of technology, *i.e*., where there is an underlying patent eligible abstract idea.[24]

B. Synthetic Biology. The difficulty and consequent uncertainty of obtaining a software patent was a good thing for the uninterrupted development of open source software. The situation is quite different though when it comes to synthetic biology, since in this field patent protection was and continues to be more readily available. Moreover, the conventional wisdom is that an extensive and robust suite of patents is essential for a genuinely viable venture in the research and development of pharmaceuticals.[25] If so, doesn't it follow that there's something counterproductive about open source synthetic biology? The conventional wisdom, however, must be tempered by the fact that, in actual practice, patents are very much a mixed blessing. There is, of course, the

initial expense of patent preparation and filing, often followed by the very high expense of defending litigation challenges, currently estimated in major cases to average around $7 million.[26] But putting aside these transactional costs, there are the following well-documented shortcomings.

1. Uncertainty About Patent Eligibility: Section 101 of the Patent Act specifies that patentable subject matter is "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." In its explication of this provision, the Supreme Court has long held that "laws of nature, natural phenomena, and abstract ideas" are exceptions and thus not patent eligible. Once a patent application passes this §101 threshold test of eligibility, it is then subjected to the requirements of being novel, non-obvious, and useful. Thus in *Association for Molecular Pathology et al. v Myriad Genetics, Inc. et al*., the US Supreme Court held that "[a] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring."[27] This was a serious defeat for Myriad Genetics, because it had hoped to be able to patent two genes useful in the detection of cancer susceptibility and treatment on the grounds that it had successfully developed techniques sufficient to locate and isolate these genes and their mutations. The *Myriad* decision was seen as good news for synthetic biology, since it deals with the creation of DNA that does not occur naturally.[28] But, while favorable for synthetic biology, the decision raises considerable doubts on the viability of patents previously granted for naturally occurring bacterial proteins.[29]

On the other hand, the Court expressly noted that its decision in *Myriad* did not deal with *method* claims or *application* of knowledge claims. In fact there were "no method claims" before the Court, because the methods used by Myriad used to isolate the genes in question were "well understood" and "widely used" and thus not patentable.[30] What then can be said about the patent eligibility of a "method," *i.e.*, what in terms of §101 is an invented or discovered "process." To begin, such eligibility has very often been problematic. In short, this is because every process is in essence a specific instance of more general laws or phenomena applied to a restricted set of conditions, and because of this is itself a law of nature or natural phenomena. Thus the "laws of nature" and "natural phenomena" exceptions to §101, if taken to their logical limit, would deny eligibility to all process claims. This problem has most recently been highlighted by Judge Alan D. Lourie of

the Federal Circuit, who noted that "all physical steps of human ingenuity utilize natural laws or involve natural phenomena. Thus, those steps cannot be patent-ineligible solely on that basis because, under that reasoning, nothing in the physical universe would be patent-eligible."[31]

The challenge, therefore, is where to draw the line between patent ineligible natural laws and patentable applications of those laws. And, even assuming such a line, there is the closely associated problem of determining the range of similar applications that are to be understood as being within the ambit of the patent grant. The Supreme Court undertook to tackle these issues in *Mayo Collaborative Services v. Prometheus Laboratories, Inc*.[32] The patent claims in question dealt with a set of multiple-step procedures for determining the appropriate dosage of thiopurine drugs, and as such were an application of known results regarding the correlation between the blood concentration of thiopurine metabolites and the effectiveness of thiopurine dosage.

The starting point of the Court's analysis was its determination that a patent application cannot "simply recite a law of nature and then add the instruction 'apply the law.'" Accordingly, the question then is whether "the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?" The Court's answer, based to some degree on earlier cases, is that what is required *for purposes of the §101 eligibility requirement* is an "inventive" component that elevates the patent claim above and beyond a simple application of a law of nature. The Court's concern was that without such an "inventive" requirement, a patent grant could tie up the application of natural laws and thereby "inhibit future innovation premised upon them." Thus, the requirement of sufficient invention serves two purposes: (1) to separate non-eligible natural laws from their patent eligible applications, and most importantly (2) to restrict the application of the underlying natural laws to the particular inventiveness required to satisfy the §101 threshold.

Applying its newly minted requirement, the Court held that the patent claims at issue did not satisfy the threshold conditions imposed by §101 because "the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field."[33] But beyond this ruling the Court offered little clarification. The result, at least in the opinion of many

commentators, is that "the confusion generated by *Mayo* has produced an arbitrary, standardless patent regime."[34] Excessively harsh perhaps, but the Court did have the opportunity to reconsider when Sequenom, Inc. applied for review after its patent claim was held to have failed the *Mayo* requirement of inventiveness in *Ariosa Diagnostics, Inc. v. Sequenom Inc*. Despite the fact that there were twenty-two amicus briefs urging review and further clarification, the Court nevertheless denied review.[35] The contours of the inventive requirement thus remain highly uncertain – much to the detriment of those in the pharmaceutical industry who rely on patent protection.

2. Increased Risk from Post-Patent Review: The uncertainty of continuing patent viability has been further exacerbated because of the recent reforms and simplifications of the post-patent review procedure: the *Inter Partes* Review (IPR).[36] While the intended purpose of the IPR was primarily to facilitate more efficient adjudication of competing patent claims, its success in that regard has had the largely unforeseen consequence that seventy-seven percent of all U.S. patent claims so adjudicated have been invalidated. And, according to one estimate, existing patent claims have consequently lost two-thirds of their value. Moreover – and not surprisingly – the IPR is typically used against economically successful patents.[37]

3. Broad Foundational Patents. Patents that cover claimed inventions that have extremely broad and disparate application pose a problem for researchers unaware of their existence or what will be asserted by the patent owners to be their extended range of application. A closely related issue is caused by the ownership of large sets of narrow but related patents which affect a great range of technology because of the collective foundational nature of the individual patents. Such patent "thickets" increase the possibility of "hold up" by a previously unknown patent holder who emerges only after large investments have been made.[38]

4. Patent Trolling and Innovation. While patents are supposed to further innovation, their track record in this regard is not always positive. The principal villains are so-called *patent trolls*, *i.e.*, entities that buy patents in order to obtain licensing fees from those who make products. The justification for such trolls is that they act as efficient middlemen by bringing new technology from inventors to those who can implement it. A recent empirical study, however, found that few such licensing demands actually led to new innovation. In fact, in most cases such demands "simply involve payment for the freedom of doing what the licensee was

already doing."[39] Surprisingly, this result essentially held true when licensing demands came not from patent trolls but rather from universities and product-producing companies. In short, patent trolling serves mainly to add additional expense to an already very expensive activity. Exactly how much, however, is a topic of some dispute.[40]

5. Global Limitations. U.S. patents do not guarantee global market exclusivity. This disconnect is especially so in countries where there is a pressing public health need for the pharmaceutical product. For example, patent applications by Gilead in India and China were denied for its Sovaldi® and Harvoni® hepatitis drugs.[41] The same was true for patent applications by Abbott Laboratories for Humira™.[42] The situation has become such that GlaxoSmithKline recently announced it will stop seeking patent protections in developing and low-income nations.[43]

C. Initial Open Source Development and Minimized Patent Protection. Given the many problems with patents and the success of open source programming and synthetic biology, the furtherance of open source research and development – with *minimized* patent protection – is a project well worth considering. In particular, there should be an emphasis on *initial open source, collaborative efforts that are unencumbered by unnecessary and premature forms of intellectual property protection*. Encouragingly, there are a number of such hybrid efforts currently underway. Especially notable is the open source methodology adopted by the Structural Genomics Consortium (SGC). Here the idea was to develop inhibitor probes that could be used to identify and determine the role played by the more than 400 proteins known to be involved in epigenetic regulation. Support was obtained from GlaxoSmithKline, as well as a private trust and the Ontario government, and the probes were provided to the research community without restriction and with great results.[44] SGC subsequently entered into a research collaboration with the CDHI Foundation in which the parties agreed not to file for patents on the collaborative research and to make all research results and reagents available without restriction.[45] Open source methods of pharmaceutical research and development have also been announced by firms such as Boehringer Ingelheim,[46] AstraZeneca,[47] Sanofi,[48] Merck, and Novo.[49] In the following sections we explain what we at Open Therapeutics have done and intend to do in the furtherance of such open source pharmaceutical research and development.

III. Open Therapeutics: Products and Technology

A. Genetically Modified Organisms. Having been inspired by the open source successes in programming and synthetic biology, Open Therapeutics has from its inception in 2009 sought to develop open source micro-organic products and technologies. As described below, we have created a suite of genetically modified organisms that include bacteria and viruses that can be used to produce, build, sense, and perform functions for the water, energy, chemical, and pharmaceutical industries. In short, these are highly miniaturized sensing and manufacturing biological robots. We have also recently added to our offerings a novel class of amphiphilic amines that have demonstrated promise for anti-cancer therapy.

Our approach is open-source because we have, in essence, utilized the licensing and contractual arrangements already successfully used in open source programming and synthetic biology. Genetically modified organisms and associated technology are thus made freely available on condition that users agree to abide by similarly open source licenses and contracts if and when they enter into agreements with outside third parties. Similarly, we have also adopted a range of variations on this theme of open source license and contract that allow for corresponding forms of intellectual property protection. So, for example, open source contributors ("innovators") can license rights to their discoveries to Open Therapeutics which in term publicizes these contributions and grants access to interested parties ("adopters") on condition that patent rights to and trade secrets protection for further developments by adopters be shared with Open Therapeutics and innovators. In addition, the parties may and have entered into equitable compensation agreements. Open Therapeutics has also negotiated arrangements with innovators whereby products and services are exchanged between the parties with corresponding agreements as to shared rights with respect to further developments.

The company is financed by fees collected for technological support and related products, as well as shared rights in any patents or other forms of intellectual property protection that arise as the result of open-source collaboration. Financial support also comes in the form of governmental grants awarded to us and our collaborators. In more detail, we currently offer the following products and related technology.

1. BactoBots™ SSU1. These are genetically engineered bacteria that can perform many activities that assist in the detection and killing of cancer cells. Our in-house researchers[50] are currently developing the

associated technologies needed to harness the potential of BactoBots. Also under development is the AuriBot™ project, which shows promise for being an adjunctive or standalone surgical therapeutic opportunity for lytically killing cranium-based neoplasm tumors known as cholesteatoma. Cholesteatoma are notorious for destroying the inner ear anatomy, causing deafness. This open therapeutic technology has *in vitro* results of selectively attaching to cholesteatoma cells. The National Science Foundation and Open Therapeutics funded this effort with collaborative assistance from Bacmine SL, a synthetic biology company based in Madrid.

2. ViruBots™ TPC1, TPC2, and TPC3. These are genetically engineered viruses that can be used to target cancer cells in unique ways, as well as to stimulate the immune system to act against cancer cells. We have entered into what have become mutually beneficial open source agreements with Nationwide Children's Hospital regarding the production and use of ViruBots. In particular, Timothy P. Cripe, MD, PhD, of Nationwide Children's Hospital[51] has authenticated and provided a suite of potential cancer discovery and cancer killing immunotherapy ViruBot platform technologies to Open Therapeutics for global scientific collaboration.[52] Also under development, the AurēBot™ project utilizes the ViruBot TPC3 technology platform, and like AuriBot, is aimed at providing a surgical procedure for lytically killing cranium-cholesteatoma neoplasma.[53]

3. Proteome Bio™. This is an open source effort to identify the proteins that pathogens require to survive. The effort, led by Drs. Pablo Pomposiello[54] and Victor de Lorenzo,[55] employs a heavy chain, single polypeptide mini-antibody platform provided by Bacmine SL. Open Therapeutics has and will continue to provide financial and technical support for the discovery of these proteins and will freely provide their identification to the global community. The global community can then collaboratively develop novel antibiotics to target the pathogens in question, including antibiotic resistant pathogens which pose an increasingly serious threat to global health. To date, the identification of *E. coli* essential proteins has been made public, and further efforts are underway with respect to additional pathogenic essential proteins, including those essential for *P. aeruginosa* and MRSA.

With regard to the economic feasibility of Open Therapeutics as an open source provider of microorganisms, we should note that our BactoBots and ViruBots products, collectively *MicrobialBots,* are

protected against theft and misuse, or accidental release, by a consumable genetics rights management GeRM™ system. When the *MicrobialBots* are separated from the commodity priced additive molecular keys, the *MicrobialBots* cease reproduction and eventually die. This technology will be openly made available by Open Therapeutics in late fall 2016.

4. Amphiphilic Amine RC16. This is a specific instance of novel class of amphiphilic amines (RCn) that shows great promise with respect to antitumor effects, as well as targeted delivery of chemotherapy drugs. In particular, the lead compound RC16 has been shown to have significant antitumor effects *in vivo* using human xenografts and a metastatic model of murine neuroblastoma. The research and development of this amine class was conducted in an extensive collaborative effort involving Dr. Cripe and scientists at the University of Bologna and the Ohio State University Comprehensive Cancer Center.[56] The underlying therapeutic technology has been licensed to Open Therapeutics and will be made freely available for open-source development. The original licensees, however, will be able to leverage their contributions by means of independent consulting agreements for further development of the technology.

B. Further Development of An Open Source Approach. The success of our open source projects clearly demonstrates the feasibility of further expansion of the open source business model pioneered in programming and synthetic biology. Even so, from a practical perspective, there remains this nagging question: Isn't it still the case that open-source pharmaceuticals can at best be no more than a niche player? A more compelling question is not one of being just a niche player, but rather *how big a niche* can be carved out by open-source methods. Answer: As big as it takes to meet the smaller and specialized research and product needs not satisfied by the large pharmaceuticals. But there is a *greater potential* and more than just this because, as convincingly demonstrated in a recent analysis by Deloitte, there is "a higher success rate for open innovation pursuits than for closed-model product development."[57] This result is not surprising given the *creative efficiency* inherent in open source methods as exemplified in the success of Red Hat and the Linux operating systems. And it is this greater potential because of creative efficiency that we intent to harness at Open Therapeutics.

There is an important and certain corollary here, namely, that creative efficiency requires an *efficiency of interaction*. Accordingly, we have developed an interactive open-source web portal that will not only facilitate peer-to-peer commentary and evaluation but also the efficient submission of this commentary and evaluation to journal editors for publication as well as to other interested parties such as granting agencies.

IV. The Open Therapeutics Web Portal Platform

Peer reviewed publications provide two essential ingredients for scientific progress: validation and dissemination. With the advent of the Internet, access to scientific publications has been greatly expanded and facilitated. Academic and research libraries can now purchase online institutional subscriptions that researchers can access from their desks or at home, avoiding the need to search among dusty stacks with primitive catalogue systems. In addition, sophisticated search engines seek out and provide relevant citations. Even the most committed Luddite would find it hard to complain about such progress. However, there are further noteworthy developments.

A. The Advent of Open Distribution Preprints. Particularly important for current purposes is the transformation of the role preprints play in research and collaboration. Preprints have always been with us. Before the Internet, hard copies were distributed among friends and colleagues. The Internet, along with word processing, however, made such interaction more convenient and affordable to the point where viable systems have developed for open access preprint distribution. The first, dating from 1991, is arXiv which is currently operated by Cornell University Library. Originally created for the high energy physics community, it is now widely used in physics, mathematics, computer science, and quantitative biology. Crucial for its success was arXiv's incorporation of the TeX formatting system which at the time was the only available way to accurately compose complex mathematical formulas. arXiv also includes an active network of moderators (who filter initial applications) and endorsers (who are necessary for submission).[58] Economics has a similar initiative called RePEc (Research Papers in Economics).[59] With the exception of the use of arXiv by quantitative biologists, biological preprint publishing surprisingly has been essentially stillborn.

Why should this be? Especially since the benefits of a robust and open preprint system are evident. To begin, there is the increased speed and extent of dissemination, as well as the associated benefit of rapid

feedback. And here we note that these benefits have elevated importance for those early in their scientific careers. Then there is the important – often critical – matter of establishing priority. Getting your work out in the public is far better way to avoid intellectual theft than having your manuscript languish during the drawn out review process involved with traditional publication. Finally, because so much of biological research is publically funded, there should be a corresponding obligation to get the results out as quickly and extensively as possible.

But, as has been noted, despite these evident benefits, "the field of biology has effectively no preprint culture, with the exception of small pockets of primarily highly quantitative research (e.g., epidemiology, population genetics)."[60] The reasons for this are not entirely clear. Partly to blame are the many prestigious journals that until recently refused to accept submissions that had already been available in preprint form. There is also the perception that preprints make it easier to steal ideas.[61] On its face this doesn't make much sense, but what is likely motivating such a perception is the underlying notion that restricting access until final publication is more important than establishing priority with early preprint publishing. This appraisal is likely reinforced by the elevated importance of profitable patents in biological research. Thus, the benefits of feedback from prepublication are seen as not worth the bother given that the ultimate goal is publication in an elite journal and possibly a corresponding patent application filed before publication.[62]

There is an additional, and we think, compelling reason for biologists to become more involved in open source prepublication. Ronald D. Vale has recently isolated a publication problem that had not previously received attention, namely, the increasing amount of data and consequently time required to publish a paper in a conventional journal.[63] Vale used a set of sophisticated methods to ascertain the nature of this increase and the deleterious effects that the increase has had on the time and effort needed for publication and, very importantly, on Ph.D. education and the careers of newly minted practitioners. What is clearly needed is an open preprint *system* that publishes *initial and less data intense* versions of the research, especially of young practitioners. Vale makes two specific recommendations that merit serious attention:

> Future innovations and experiments in peer-to-peer commentary and evaluation could be built around an open preprint server. Indeed, such communications might *provide additional information* and *thus aid journal-based peer review*.

> In addition, one could imagine an option of *incorporating author-initiated peer evaluations* as part of a preprint ….[64]

Such a system would encapsulate collaboration, dissemination, and validation of both the research *and* the scientist – all in a single package, thus creating a *virtual research community*. In fact, as described in the following section, Open Therapeutics has already developed and made available an open source prepublication system that incorporates exactly these features.

B. Therapoid™: The Open Therapeutics Web Portal Platform. The Therapoid web portal platform has been deliberately designed not only to facilitate peer-to-peer commentary and evaluation but also to enable the efficient submission of this commentary and evaluation for external review by journal editors, granting entities, and other interested parties. In a nutshell, Therapoid creates a virtual research community because it includes:

- A list of all ongoing projects.
- The underlying hypothesis and purpose of each project.
- The names and affiliations of those involved in each of the projects.
- The authors' description and data associated with their projects.
- A dynamic history and record of such document flow and commentary, including revisions of the underlying research.
- Transmission and reception capabilities for the retained dynamic history of the ongoing projects.

So, for example, such information and feedback capability will be available on our preprint server not just to the research participants but also to journal editors when participants decide their work is ready for submission to a journal – traditional or otherwise. The point of all this is not to replace the referee processes already in place at the journals but rather to assist in an approval process that is, by all accounts, under serious stress. Moreover, this material can also be made available for funding, employment, and other informational purposes, thereby further facilitating those activities.

Conclusion

For the reasons given above, we believe that our efforts at Open Therapeutics fall squarely in the tradition of the open source science and technology pioneered in computer programming and synthetic biology. Just as in those endeavors, Open Therapeutics exemplifies what we have identified as an emerging hybrid system of discovery and development that combines open source beginnings with more traditional forms of

intellectual property at later stages of research and development. To maximize the *creative efficiency* inherent in open source collaboration, we are proud to say that our efforts have been unencumbered by unnecessary and premature forms of intellectual property protection.

In particular, as shown above, we offer in an open source form a wide range of engineered viruses and bacteria – as well as more recently RC16 – that are currently being used world-wide in research and development. And not just products, but so too has our collective expertise – scientific and legal – been incorporated into all our contractual agreements. Finally, our commitment to the ideals of open source scientific discovery and development is made even more comprehensive by our creation of an open source web portal that acts both as a nurturing arena for initial research and interaction, as well as an engine of refinement for ultimate publication in traditional peer reviewed publications.

REFERENCES

* Open Therapeutics is a global biotechnology firm based in Cincinnati, Ohio, with a presence in China, Europe, and India. For more information on the Open Therapeutics products and programs described in this Mission Statement, please contact us at http://OpenTherapeutics.org, or Jason@OpenTherapeutics.org.

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