



OPEN LETTER

Ideation and implementation of an open science drug discovery business model – M4K Pharma [version 1; referees: 2 approved, 1 approved with reservations]

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Abstract

M4K Pharma was incorporated to launch an open science drug discovery program that relies on regulatory exclusivity as its primary intellectual property and commercial asset, in lieu of patents. In many cases and in key markets, using regulatory exclusivity can provide equivalent commercial protection to patents, while also being compatible with open science. The model is proving attractive to government, foundation and individual funders, who collectively have different expectations for returns on investment compared with biotech, pharmaceutical companies, or venture capital investors. In the absence of these investor-driven requirements for returns, it should be possible to commercialize therapeutics at affordable prices. M4K is piloting this open science business model in a rare paediatric brain tumour, but there is no reason it should not be more widely applicable.

Keywords

Open science, open drug discovery, rare diseases, regulatory exclusivity

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The drug development business model

The discovery of new medicines is increasingly expensive and risky¹⁻⁵, and the business model has become predicated on the pricing of new medicines at levels barely manageable by even affluent countries⁶⁻⁸. Over the years, and in an effort to improve the situation, the main players in the ecosystem - academia, industry, governments, foundations, and patient groups - have been exploring new models of collaboration, and new schemes for funding and rewarding drug discovery. For example, recent years have seen an explosion of academic drug discovery efforts^{9,10}. However, although the location of drug discovery activities has moved among the players, the fundamentals have not changed. The costs of discovery and the prices of new medicines continue to rise, but there has yet to be a transformative change in the business model. And there are consequences: there are substantially diminished research efforts in riskier or unprofitable areas of drug discovery, such as the neurosciences¹¹, anti-infectives¹², and tropical and paediatric diseases¹³⁻¹⁵. The root causes of the problem are manifold, but include the fact that the current drug discovery system is built on business models that emphasize, even require, proprietary generation and use of knowledge, which in turn leads to secrecy, needless duplication of effort, and ultimately inefficient use of human and financial capital^{3,4}. Open science may provide a solution to this problem, and it is a model that we are piloting at M4K Pharma (M4K, for Meds for Kids).

Open science and the discovery of drug targets

As exemplified by the Structural Genomics Consortium¹⁶, open science – the rapid multilateral sharing of knowledge, results, data, and materials without patent restrictions¹⁷ – has proven to be tremendously successful in pre-competitive research areas related to early-stage drug discovery¹⁸. Open science can: (i) lower transactional barriers to collaboration, (ii) encourage cross-disciplinary contributions of expertise, (iii) distribute project risk, (iii) reduce redundancy, (iv) enable more rapid generation of new hypotheses, (v) enable transparent peer review, and (vi) increase reproducibility^{3,17-19}.

Our hypothesis is that such an open organizational framework can be successfully applied not only to accelerate basic science but also to advance an innovative new drug candidate through discovery, preclinical and clinical development, regulatory approval, and health system uptake. Expanding the scope of open science to include more aspects of drug discovery would amplify its impact by: (i) permitting secondary and meta-analyses to improve decision-making by researchers, funders, health regulators, payers, prescribers, and patients; (ii) providing a mechanism to share failed projects and trials; and (iii) better respecting clinical trial participants by maximizing the scientific benefits of their generous contributions while minimizing their exposure to risk in duplicative studies^{4,19}.

Application of open science to drug discovery and development

Although open science has the potential to create a far more efficient drug discovery ecosystem, it has proven difficult to apply to individual drug discovery and development programs. The greatest concern is that practicing open science makes it more challenging to manage and protect intellectual property: open

science creates prior art in the public domain and also distributes inventorship among scientists in many institutions, potentially without legal agreements in place. The problem is that these properties of open science are inconsistent with creating a patent position, which is the most common intellectual property tool to shield a new drug from generic competition. In fact, it is widely believed that patenting is not only important, but is actually essential to incentivize drug development^{20,21}. This is not the case. As detailed in the next section, sponsors of newly approved medicines in most commercially important jurisdictions are also granted other powerful intellectual property protections in the form of regulatory data and market exclusivities²². These protections are granted whether the drug product is patented or not, as well as provide better, and sometimes longer, barriers to entry from generic competition. In essence, these protections offer a strong alternative to patents for incentivizing drug development and commercialization²³⁻²⁵ and allow for an open science approach to drug discovery and development.

Regulatory exclusivity - a powerful form of intellectual property

Many governments, through their regulatory mechanisms for drug approval, provide an array of non-patent-based incentives to stimulate the discovery of new medicines, and to protect sponsors of new drugs from competition.

The most common form of incentive is regulatory data protection for drugs containing new active ingredients (this is often referred to as *new chemical entity (NCE) exclusivity* for small molecule drugs), in which regulators grant the drug sponsor exclusive rights to the preclinical and clinical data they used to gain regulatory approval for periods of time. This form of “regulatory exclusivity” is valuable because it blocks generic competition: without the ability to reference these data, generic companies are unable to use the abbreviated drug approval mechanisms offered by regulators (e.g. the Abbreviated New Drug Application (ANDA) mechanism in the US). The period of exclusivity varies depending on the product (small molecule or biologic) and among jurisdictions, but the period is significant (for example, 10 years in the EU)²² and constitutes valuable intellectual property. With respect to open science, many major drug product markets (including the US, EU, Switzerland, Canada, Israel, Japan, South Korea, Singapore, and Taiwan) apply new chemical entity exclusivity even if the sponsor’s data are publicly available^{22,26}.

Several governments (US, EU, Singapore, Japan, Australia, Taiwan, and South Korea), through their drug regulators, offer an additional form of regulatory exclusivity (called *orphan drug exclusivity*) for drugs approved for rare diseases, regardless of whether the drugs contain new active ingredients. For these drugs, which must be first granted “orphan status” designation, no competitor may market the same active ingredient in the same rare disease indication, even in the unlikely circumstance that the competitor were to generate its own complete regulatory data package^{27,28}.

There are additional regulatory exclusivity incentives for other special cases, including: data protection for new clinical studies of previously approved active ingredients in the US;

exclusivity extensions for paediatric studies in the US, EU, and Canada; exclusivity extensions for new indications in the EU; and exclusivity extensions for new antimicrobial drugs to treat serious or life-threatening infections through the Generating Antibiotic Incentives Now (GAIN) Act in the US^{29,30}.

Regulators also provide non-exclusivity-based incentives for drug development in specific under-served markets. For example, the US offers “priority review vouchers” to sponsors who achieve new drug registrations for tropical diseases and rare paediatric diseases. These vouchers permit their owners to accelerate regulatory approval of any subsequent drug product. Interestingly, these can be auctioned in the secondary market and have generated as much as USD \$350 million³¹, though prices have fallen to the USD \$110 to \$130 million range in 2017 and 2018³².

Regulatory exclusivity compares favourably with patent protection

A patent grants its owner 20 years of exclusive use of the claimed invention. However, the core “composition of matter” patent of

an innovative drug most often yields only 8–12 years of exclusive marketing rights, even after patent term restoration, due to the length of the discovery, clinical trial, and approval processes³³. To extend their marketing exclusivity and to create further barriers to generic competition, companies often adopt an intellectual property strategy that involves filing additional patents on polymorphs, formulations, and dosage forms. This strategy is very costly and these types of patents are frequently invalidated in litigation^{34,35}. Nevertheless, patents remain the mainstay mechanism through which innovative drug companies attempt to exclude competitors from the market.

The period of market exclusivity granted by the array of regulatory protections compares favourably with the average length of patent protection post-registration (Figure 1). For example, a company that successfully registered an openly developed drug with a new active ingredient in the US, EU, Canada, and Japan would be entitled to: (i) new chemical entity (NCE) exclusivity for periods of 10 years in the EU, 8 years in Canada, and 5 years in the US; and (ii) 8 years of post-marketing surveillance

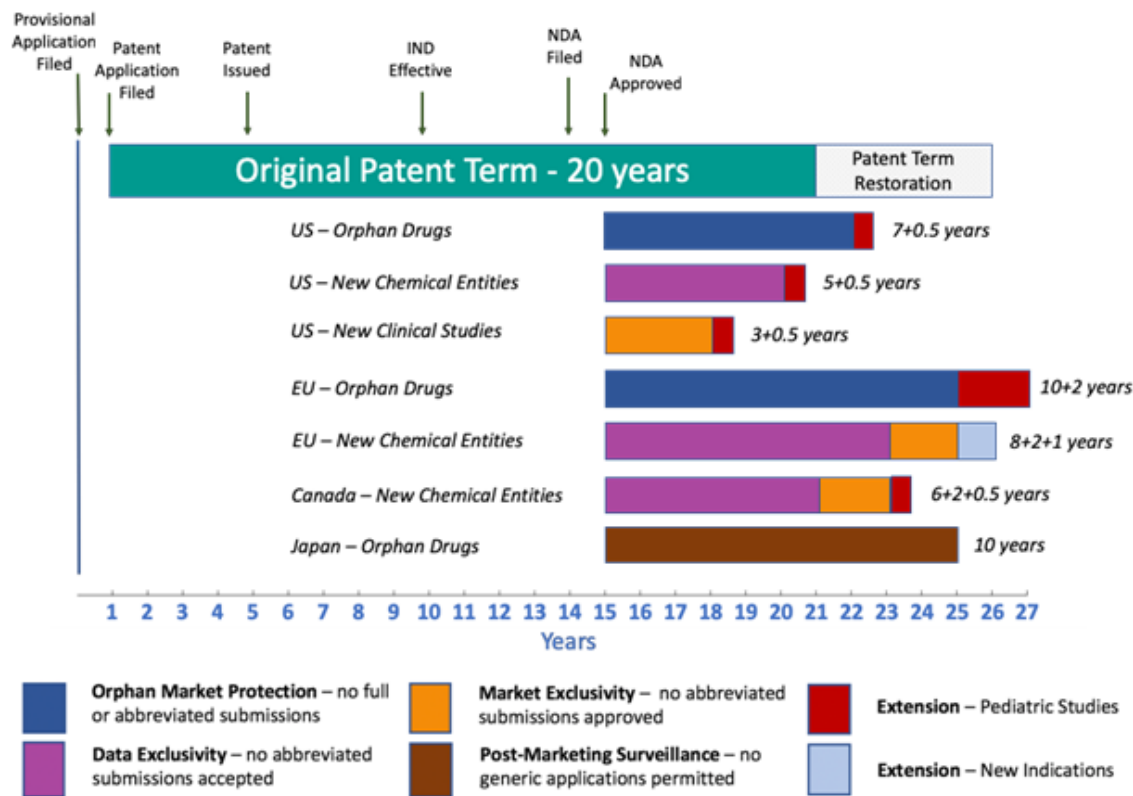


Figure 1. Comparing protection against competition for a new drug sponsor under an average effective patent term in the US with protection against competition under prospective M4K regulatory exclusivity periods in the US, EU, Canada, and Japan, using a new drug targeting DIPG as the exemplar. The average effective composition of matter patent term for a new drug after patent restoration in the US is approximately 11–12 years (source: Cárdenas-Navia, J. Thirty Years of Flawed Incentives: an Empirical and Economic Analysis of Hatch-Waxman Patent-Term Restoration. *Berkeley Technol. Law J.* 29, (2015)). In comparison, irrespective of its patent status, a new drug approved to treat DIPG could be entitled to (i) orphan drug exclusivities of 7.5 years in the US (including a 6-month paediatric extension) and 12 years in the EU (including a 2-year paediatric extension); (ii) new chemical entity exclusivities of 5.5 years in the US (including a 6-month paediatric extension), 10 years in the EU, and 8.5 years in Canada (including a 6-month paediatric extension); and (iii) a period of orphan drug post-marketing surveillance of 10 years in Japan (which acts as an equivalent bar to entry by competitors). Approval of subsequent indications for the same drug could entitle M4K to (i) 3.5 years of new clinical study exclusivity in the US (including a 6-month paediatric extension, if the new indication required further paediatric studies) and (ii) a 1-year extension of new chemical entity exclusivity in the EU (for a total of 11 years).

protection in Japan (an equally effective barrier to generic competition)²². If a company registered a drug for a rare paediatric disease in those markets, it would also be granted (i) concurrent orphan drug exclusivity in the rare disease indication of 7 years in the US and 10 years in the EU, (ii) paediatric extensions of an additional 2 years of orphan drug exclusivity in the EU (for a total of 12 years) and an additional 0.5 years of NCE exclusivity in Canada (for a total of 8.5 years), and (iii) 10 years of orphan drug post-marketing surveillance protection in Japan^{22,27–30}. If a company instead registered a new biologic in the US, the regulatory protections are even more favourable; it would be eligible for 12 years of exclusivity²⁹. If a company registered a new antimicrobial to treat a serious or life-threatening infection, it would gain a 5-year extension of US NCE exclusivity (for a total of 10 years of protection)²⁹.

These regulatory exclusivity incentives provide significant commercial advantages. Regulatory exclusivity periods, unlike patents: (i) are virtually costless to obtain, automatically enforced by regulators, and generally not subject to challenge by would-be competitors; (ii) can be obtained for compositions of matter or potential uses thereof that have been previously disclosed in public literature; and (iii) only begin once a drug receives marketing authorization, thereby providing a sponsor with *ex ante* certainty over the period of market protection^{23–25,36}.

The use of regulatory incentives in the real world

The business case for relying on regulatory exclusivity is also bolstered by real world evidence. After the introduction of NCE protection in the US through the Hatch-Waxman Act, at least 26 drugs containing novel active ingredients were brought to market in the US reliant entirely on NCE exclusivity without listing any patents against the product in the FDA Orange Book (Table 1)^{30,37}. After orphan drug exclusivity was introduced in the US and EU in 1983 and 1999, respectively, there was significantly increased development efforts and product registrations to treat rare diseases in those jurisdictions - even though the laws had no impact whatsoever on available patent protections²⁷. Perhaps the greatest evidence of the commercial importance of regulatory exclusivities lies in the aggressive efforts by industry and trade representatives in the US and EU to negotiate expanded pharmaceutical data protections around the world³⁸.

M4K Pharma – implementing an open science business model

M4K was founded to substantiate the commercial opportunity provided by regulatory data and market exclusivity protections for a new drug developed using open science. M4K aims specifically to discover and develop a precision medicine to treat a genetic subset of diffuse intrinsic pontine glioma (DIPG), an aggressive form of paediatric brain cancer with a small patient population and no effective therapeutic options. One quarter of DIPG tumours have an activating mutation in the ALK2 protein kinase³⁹. This has led to the hypothesis that an inhibitor of the ALK2 kinase will have therapeutic benefit in this subset of patients.

Like all small companies, M4K faces scientific and business challenges. The scientific challenge is to create a potent, selective, safe, and efficacious drug that is brain penetrant. M4K is

tackling this using a traditional structure-guided drug discovery and development scientific path. The business challenges are: to raise the funding to finance drug discovery and development; to create a strong intellectual property position that can be licensed to a drug manufacturer; and ultimately to be able to negotiate affordable pricing. M4K is tackling these using open science, and by adopting the following business strategies.

1. A partnering strategy that encourages publication and data sharing

The aim of the M4K discovery and development strategy is to align independent funding sources and a broad network of scientists towards its drug discovery aims, while both allowing and encouraging each participant to meet their own research objectives. For example, while partners who contribute funding to M4K, such as government and charitable organizations, are helping to invent a new medicine, they are also advancing their own organizational aims, be they knowledge generation or disease cures. While academic scientists and clinicians who collaborate with M4K are helping to contribute to the discovery of a new medicines, they are also advancing their academic careers, as M4K encourages any collaborating scientist to openly communicate or publish their findings.

The M4K partnering strategy also allows industry to participate in M4K's programs to mutual benefit. M4K gains directly from *pro bono* contributions from Contract Research Organizations (CROs), such as from Charles River Laboratories and Reaction Biology Corp, and the CROs in turn benefit by improving employee morale, by being able to openly showcase capabilities to other potential clients, by generating training opportunities, and by advancing corporate social responsibility. Even pharmaceutical companies have shown interest in participating. In addition to their altruistic motivations, M4K could also advance their business interests by helping achieve clinical validation of an interesting therapeutic target and potentially inventing a product to in-license. In summary, the M4K model provides a nexus of shared interests.

2. A partnering strategy that develops an intellectual property position

M4K encourages broad and rapid dissemination of its research results, and its partnership agreements include terms intended to codify open science into the relationship. For example, the agreement terms stipulate that none of the research activity related to M4K will be patented. Collaborators that carry out studies intended for regulatory submission will also need to agree that the exclusive right to use the underlying data for regulatory purposes is allocated to M4K. This restriction will not, however, inhibit public disclosure of the preclinical and clinical datasets, which will be released under a minimally restrictive click-wrap data use agreement that allows for broad follow-on research use but prohibits regulatory use without M4K authorization. M4K documents released in this manner will be clearly watermarked with these terms. The EMA has already begun releasing drug sponsors' clinical data through an analogous mechanism⁴⁰.

These clear up-front positions may deter some scientists and institutions, but in our experience so far with M4K and the SGC, this is rare and the clarity of the commitment to sharing and affordable pricing will attract far more.

Table 1. Examples of FDA new drug approvals from 1986 to 2014 brought to market with new chemical entity exclusivity but either (i) no patents listed in the FDA Orange Book, or (ii) listed patents expiring prior to new chemical entity exclusivity. The priority review eligibility and orphan drug status of each drug are also indicated. Source: Lietzan, E. The Myths of Data Exclusivity. Lewis Clark Law Rev. 20, 91–164 (2016).

| Year of Approval | Drug | Indication | Priority Review Granted ('Significant Improvement' Over Standard of Care) | Concurrent Orphan Drug Exclusivity | Orange Book Listed Patent (Expiry) |
|------------------|---|---|---|------------------------------------|------------------------------------|
| 1986 | Provocholine (methacholine chloride) | Diagnosis of bronchial airway hyper-reactivity in patients who do not have clinically apparent asthma | + | | |
| 1987 | Levatalol (penbutolol sulfate) | Mild to moderate arterial hypertension | | | |
| 1989 | Anafranil (clomipramine hydrochloride) | Obsessive-compulsive disorder | + | | |
| 1989 | Optipranolol (metipranolol hydrochloride) | Open-angle glaucoma and other causes of ocular high pressure | | | |
| 1989 | Lariam (mefloquine hydrochloride) | Mild to moderate acute malaria | + | | |
| 1989 | Clorazil (clozapine) | Severely ill schizophrenic patients | + | | |
| 1990 | Hexalen (altretamine) | Refractory ovarian cancer | + | + | |
| 1993 | Leustatin (cladribine) | Active hairy cell leukemia | + | + | |
| 1993 | Trasylol (aprotinin bovine) | Reduction of bleeding during complex surgery | + | + | |
| 1993 | Flumadine (rimantadine hydrochloride) | Influenza type-A infections | + | | |
| 1995 | Revex (nalmeferene hydrochloride) | Partial reversal of effects of narcotics | | | |
| 1996 | Proamatine (midodrine hydrochloride) | Orthostatic hypotension | | + | |
| 1997 | Normiflo (ardeparin sodium) | Prevention of blood clot formation following certain types of surgery | | | |
| 1997 | Corlopam (fenoldopam mesylate) | Short-term management of hypertension | | | |
| 1998 | Infasurf (calfactant) | Respiratory distress syndrome in premature infants | | | |
| 1999 | Nilandron (nilutamide) | Treatment of prostate cancer in men who have undergone surgical castration | | | |
| 1999 | Curosurf (poractant alfa) | Respiratory distress syndrome in premature infants | | | |
| 2000 | Celexa (citalopram hydrobromide) | Depression | | | |
| 2000 | Innohep (tinzaparin sodium) | Deep vein thrombosis | | | |
| 2003 | Elestat (epinastine hydrochloride) | Prevention of itching associated with allergic conjunctivitis | | | |
| 2004 | Sanctura (trospium chloride) | Overactive bladder | | | |
| 2011 | Potiga (ezogabine) | Epileptic seizures | | | |
| 2011 | Firazyr (icatibant) | Hereditary angioedema | + | + | + (July 2015) |
| 2011 | Ferriprox (deferiprone) | Iron overload in patients with thalassemia receiving blood transfusions | | + | |
| 2012 | Choline C 11 | PET scan imaging agent for detection of recurrent prostate cancer | | | |
| 2013 | Dotarem (gadoterate meglumine) | MRI contrast agent for use in brain and spinal tissues | | | |
| 2014 | Impavido (miltefosine) | Bacterial leishmaniasis | | + | |

3. M4K has a corporate structure inviting for scientists and public and charitable funders

The open science business model depends on contributions from scientists in many institutions and from multiple public and philanthropic funders. In our view, the greatest barrier to attracting these contributions is the perception that one or more of M4K's principals or other contributors would unfairly benefit. To eliminate this perception, and to ensure that all are treated equally, we structured M4K so that no executive, scientist, institution, or funder is entitled to equity or royalty payments. Instead, all equity in M4K is held by an arm's length charity – the Agora Open Science Trust – which is governed by an independent board of directors and whose mandate is to use any proceeds from M4K to support open science and the public good.

4. Licensing strategy

Without profit-driven ownership, M4K can adopt a licensing strategy that prioritizes affordable pricing instead of maximizing returns to the company. Accordingly, once M4K generates a clinical asset that is sufficiently de-risked, it intends to license the rights to its regulatory data package (as well as any marketing authorizations, regulatory exclusivities, and voucher incentives to which it is entitled) to one or more partners capable of bringing the medicine to patients. Because M4K's asset will have been substantially de-risked through public and philanthropic contributions, M4K will seek to negotiate and enforce pricing concessions to ensure affordable access for patients. And if there are any net proceeds from licensing that accrue to M4K, they will be distributed to the Agora charity to further the public good. It is worth highlighting that affordable pricing licensing agreements of clinically de-risked assets to an industry partner have been successfully negotiated by the Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases initiative (DNDi) on several occasions^{41–43}.

This affordable licensing approach can be contrasted with that adopted by the Cystic Fibrosis Foundation (CFF) when it invested USD \$75 million of its charitable funding into the development of ivacaftor, a targeted medicine for cystic fibrosis patients with certain gene variants. CFF sold its right to future royalties in 2014 for US \$3.3 billion but did not seek to constrain pricing. As a result, Vertex Pharmaceuticals, which acquired the rights to ivacaftor, launched it at over USD \$300,000 per patient per year⁷.

Experience after one year of M4K activities

M4K commenced operations in November 2017, and has since progressed its early-stage drug discovery program into lead optimization, with help from significant non-dilutive funding from public and philanthropic sources, as well as generous in-kind contributions of advice, materials, and research efforts from a range of participants. These contributions have reduced direct development costs and accelerated discovery. The progress on the ALK2 drug discovery project as of November 2018 can be viewed [online](#).

1. Funding of M4K activities

M4K was incorporated to be well positioned to obtain financial support from nearly all biomedical research funding sources

(governments, pharma, foundations, individuals, and institutions), with the possible exception of venture capital. Indeed, many governments are creating specific funding opportunities for drug discovery⁴⁴, and although most expect, and sometimes demand, that recipients protect their advances with patents, others are more open to other approaches (see [here](#) and [here](#)).

M4K successfully competed for one such drug discovery grant – part of the Cancer Therapeutics Innovation Pipeline program from the Ontario Institute for Cancer Research (OICR). The funds (CAD\$2M) are being used to support the direct and indirect costs of running M4K and a portion of the research being carried at OICR, the University of Oxford, and partner CROs. Additional funding from the Brain Tumour Charity to M4K's academic collaborators at the University of Oxford is being used to support complementary scientific studies. M4K is well positioned to raise additional grant and philanthropic funding to support future discovery and development efforts.

While the inability to access venture capital in the early discovery phase is a potential drawback of the open science model, it is helpful to note that the annual global research spend for biomedicine and drug discovery is approaching ~\$300B⁴⁵, of which venture capital is only ~\$10B⁴⁶. In one view, while the open science structure of M4K might forsake the opportunity to compete for \$10B of venture funding, in providing wider access to public and philanthropic funding, it positions M4K better to access a far larger pool of capital.

2. In-kind contributions to M4K

It is often challenging for a traditional company to collaborate with academia because of protracted negotiations over the allocation of patent rights and prospective revenue streams. The open science structure of M4K and its affordable pricing positions has provided a solution, and has enabled M4K to rapidly enter into collaborations and access in-kind contributions from multiple organizations, including the Universities of Oxford, Toronto, Pennsylvania, and Houston, Tufts University, and the Children's National Medical Center in Washington, DC. The forms of in-kind contributions from these various partners have included running experiments, providing scientific input, and reviewing both data and documents.

We have also had contributions from the private sector. Senior scientists from three different large pharmaceutical companies (Bayer, AbbVie, Boehringer Ingelheim) have provided advice to M4K, including knowledge gained from terminated internal drug discovery efforts. Contract research organizations and technology providers are contributing resources in-kind on a *pro bono* or reduced costs basis. Charles River Labs, a leading provider of drug discovery services, has an internal program that allows each employee to donate time to a charity of their choice. Its UK chemistry team has decided to allocate a significant amount of staff time to advance M4K's chemistry program, and their pharmacology and biology colleagues have provided drug discovery expertise free of charge. Reaction Biology Corp., a provider of screening services, has donated its services to help M4K test the potency and selectivity of newly synthesized compounds.

3. Knowledge generation for the public good

M4K is also proving attractive to public funders, likely because the company shares its ongoing science, and thus generates freely available knowledge for the community – a core aim of public science funders. The main vehicle for knowledge dissemination is M4K's monthly team meetings, which are live-streamed and then made permanently available on YouTube. These meetings discuss ongoing and prospective science, including chemistry plans. Ancillary consequences of these open drug discovery meetings are that they create prior art and thus freedom to operate for M4K. They also attract new collaborators to its program.

M4K also benefits from collaborations with the [OpenLab Notebooks](#) efforts of the Structural Genomics Consortium. In this project, three collaborating scientists at the SGC at the University of Oxford communicate their progress regularly by publishing their lab notes on the internet. These contributions provide the community up-to-date access to the science that drives M4K, including structural biology of ALK2 and related kinases, cell-based assays and screening methods. These scientists also place their structural datasets into the Protein Data Bank. And while M4K is working diligently to disseminate its pre-clinical drug discovery information, there is room to improve as the information is not standardized nor as findable or accessible as it could be. This is in large part due to the fact that there is no community-accepted data repository for pre-clinical drug discovery information. M4K is working to develop such a repository so that it can be used to openly share all of its drug discovery datasets, as well as datasets from other open science drug discovery companies.

4. The future: open science and clinical development

As M4K moves beyond its early-stage drug discovery efforts, it intends to continue to openly share its science, to crowd-source solutions, and to solicit public scrutiny of its work to improve scientific output in the later stages of drug development. For example, it intends to share clinical trial protocols and analysis plans for public comment, and also release analysable datasets and associated metadata as soon as practicable after clinical study unblinding (while respecting informed consent of trial participants and appropriately de-identifying any personally-identifiable information).

Government can encourage open science companies committed to affordable pricing through policy changes

Although M4K is pursuing a rare disease indication, we believe its open science model does not have to be limited to this area and could be used to discover innovative new medicines for larger markets. And though M4K has identified a viable path forward in the current funding and regulatory environments, a few policy changes could encourage more companies to adopt this promising new business model.

First, government and philanthropic funders could strategically channel more of their translational funding programs into open science drug discovery consortia and companies. Although it is not customary for government to provide support for science carried out within a corporate structure, in open science companies, the objectives are aligned with the public interest:

knowledge generation and affordable pricing. These companies should be eligible to compete for public funds.

Regulators could also create specific infrastructure and incentives for open science drug development, while leaving current proprietary pathways in place. For example, national regulators could collaborate to develop an open drug development data repository to catalyse open projects. This is not unlike the new SPARK program initiated by the Pew Charitable Trust for antibiotic drug discovery⁴⁷. A jointly-developed repository of this nature could ensure ready accessibility of preclinical and clinical data for governments to use in marketing authorization and reimbursement decision-making processes. To incentivize the repository's use, an open developer that deposited a pre-clinical or clinical dataset could be entitled to a reasonable period of protection against competitive use of the dataset during the timeframe *prior to* approval of the open developer's marketing application.

In the interest of encouraging more transparency in the drug discovery and approval process, regulators could also offer an exclusivity period extension for openly developed drugs that gain marketing approval, similar to the paediatric study, new indication, and GAIN Act extensions discussed above. To obtain this 'open science extension', a sponsor could be required to (i) demonstrate that it has diligently made its preclinical and clinical data publicly available via the open drug development data repository, (ii) provide a certification that it has not filed for patents, rendering the sponsor ineligible to list patents for the drug product in the FDA Orange Book or equivalent registries; and (iii) enter into an agreement with the relevant health technology assessment or drug procurement agency to set an affordable price ceiling for the medicine as a *quid pro quo* for the extended exclusivity entitlement.

Finally, while most of the world's major drug product markets provide regulatory data exclusivity regardless of the public availability of a sponsor's data, other countries only adhere to the World Trade Organization Trade-Related Aspects of Intellectual Property ("TRIPS") agreement, which merely requires member states to protect "undisclosed" test data. Formally, competitors in countries that limit protection to "undisclosed" data could seek to register identical drugs based on a sponsor's open data. This creates a perverse incentive for companies to maintain secrecy for as long as possible in all jurisdictions, undermining efforts to encourage more sharing of trial data²⁶. And while it may be good public policy in low- and middle-income countries to limit data exclusivity protections broadly, perhaps there is an argument to consider implementing them exclusively for open science companies committed to affordable local pricing. Specifically, these countries could extend data protection to sponsors of innovative new drugs whose data have been made public, at least where the sponsor has pursued an open, patent-free path to market for a medicine that addresses local needs at a reasonable price.

Perspective

In summary, with M4K, open drug discovery has transitioned from a theoretical notion to a real-world test of the concept. Promising progress on many fronts - scientific, financial, and

community participation - augers well for the success of the model. All players in the system, including governments and regulators, should consider supporting open science drug discovery as a commercially viable business mechanism to invent new, and affordable, medicines.

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Open Peer Review

Current Referee Status:



Version 1

Referee Report 23 January 2019

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For the last two decades, the open-source model has steadily gained acceptance in biomedical research and drug R&D. There is now a large number of initiatives and organizations that have embraced its principles, and are offering it as an alternative to the proprietary research models that have dominated the field for much of its existence. Predictably, its growing popularity has met with challenges and pushbacks. They fall in three categories:

1. Open-source is anti-patents, and patents are essential to entice businesses to engage in drug R&D, and investors to support them. Therefore, open-source is a non-starter.
2. If open-source is so great, where are the drugs that it has produced?
3. Perhaps it fits somewhere in the ecosystem -- and it is unclear where that is -- but certainly not as an alternative to conventional drug R&D

The manuscript addresses these challenges.

On the first item, the authors point out that in areas that make up most of the pharmaceutical market ("US, EU, Singapore, Japan, Australia, Taiwan, and South Korea"), regulators offer alternative ways to protect IP and to provide incentives, such as various types of regulatory exclusivity (Fig 1), and priority review vouchers (PRVs). They go on to show that such non-IP-driven protections and incentives compare favorably with patents with respect to duration. They also enjoy advantages with respect to cost, administrative management, and simplicity, since they preclude the burdensome patenting process with its legal, translation, filing, maintenance, and prosecution fees. If this is true, why the hoopla?

The authors are correct. In fact, industry loves regulatory exclusivities and PRVs for the reasons stated. Yet it remains deeply attached to patents:

- It sees them as an effective bulwark against attempts to water down intellectual property
- It sees litigation costs as offering a degree of additional protection since companies can outspend challengers
- It also see them as the currency that enables the transaction of assets during drug development, by giving them value

Some of these objections, especially the first one, tend to be generational. They disregard the benefits from widespread knowledge-sharing because companies, which historically have had little exposure to it have tended to be dismissive of its value. Yet, as this value is documented by big science initiatives (e.g., HGP and derivatives); the output of open-source models (e.g., SGC, Critical Path Initiative); and the now routine requirement of many funders that the results of the research they support be made immediately available to the scientific community, opposition to open-source has eroded.

The third objection, however, that IP enables an innovation market that matches assets with the

companies most motivated to develop them, deserves more attention from the authors. Some scholars, such as CIP@Gothenburg and its many followers, have argued that IP is just a device to create value, and the holders of that IP can do whatever they want with it -- hold it, sell it, donate it, or put it in the public domain). So, it is not incompatible with open-source. Perhaps, the resolution of that debate hinges on regulators offering additional ways to recognize value earlier. The FDA's Breakthrough Therapy Designation has been a step in that direction, and companies and investors have been quick to embrace it. It is most often granted based on phase 2 data, but could conceivably be awarded sooner if drug developers can show evidence of superior treatment response along with safety.

The authors then describe their experience with M4K, a startup designed to show that open-source can deliver novel therapies as well as or better than conventional R&D. M4K is owned by the Agora Open Science Trust, and seeks a treatment for DIPG, a rare and fatal pediatric brain cancer with no treatment. It claims no patent, puts immediately all its data in the public domain, but restricts the right to use it for regulatory purposes (to thwart misappropriation by potential competitors). It is funded by grants from government, foundations, and donors who adhere to its open-source commitment. It conducts its works through scientists and organizations that share the same ethos (e.g., Charles River Labs, Ontario Institute for Cancer Research). Some pharma companies have also shown interest in participating. Any drug that it produces will be licensed to a partner who will receive the right to use the data package for securing approval upon the condition that it will make the drug affordable. After one year of operation, M4K has ALK inhibitors in lead optimization. Most of its support has come from non-profit sources, but several large pharma companies (Bayer, AbbVie, Boehringer Ingelheim) have made in-kind contributions. These results are interesting and encouraging, but fall short of a full validation of the model, which will only happen when a drug has been approved. Yet, one can make several comments about challenges that the model might experience:

- How scalable is it? Can we rely on non-profit sources and benevolent scientists to produce dozens of drugs annually? How far can we go before we dry up the pool of such talent. Perhaps surprisingly, there is ground for optimism that the authors should explore. The rare disease community has experimented with many low-cost models of drug development -- some of which have yielded drugs -- that are not radically different from M4K. There is also lots of talent trained by industry but now idled or retired, which would love to work on meaningful projects. And there is a venture philanthropic community which does not always find the outlets it seeks for its generosity. What's missing is a clearinghouse that can match needs with resources -- perhaps an endeavor whose time has come.
- M4K's drug candidates are small molecules. This is maybe inevitable since they must penetrate the brain. But small molecules is a tough domain to demonstrate superiority over pharma because of the vast store of tacit knowledge that the industry has accumulated when it comes to things like improving ADME or mitigating toxicity. It would have been easier to "compete" with different drug candidates (e.g., biologicals) where pharma does not have as much of a translational research advantage. But this may not have been an option for DIPG.

This brings us to the last question, which is the role of open-source in the drug R&D ecosystem. Is it a replacement, an alternative, or a partner to pharma? It would be interesting to get the authors' views on this. Clearly some data about costs and timeline would help understand how M4K compares with traditional pharma, but the early stage of M4K's research may make this premature. Still, as uninformed opinions are being floated that we can, for instance, fix the drug pricing problem by getting the government into drug manufacture, or other dubious schemes, It would be interesting to hear from the authors how they see open-source fitting in the ecosystem, and contributing to making drug innovation affordable, in view of their experience with M4K.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.


Referee Expertise: pharmaceutical innovation; economics of drugs R&D; R&D productivity; open-source drug R&D

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 23 January 2019

<https://doi.org/10.21956/wellcomeopenres.16301.r34396>



Matthew H. Todd 

University College London, London, UK

This paper by Morgan, Roberts and Edwards is a clear, important contribution on many levels that is suitable for publication with a few minor modifications. It deserves to be widely read and its implications understood.

It is refreshing to see this specific subject matter so squarely addressed, and with an evolving example. Many of the technological barriers to working openly are quickly being solved. Alleviating the psychological worries of working openly is more of a challenge. This article correctly passes quickly over many of these issues, however, and instead focuses on the key economic objection that is often heard. As a practitioner of open source drug discovery, I have experience in receiving the question "how can you square openness with a sustainable economic model?" There is no one answer, just as there is no one medicine, or disease. Many interested and well-qualified people working to solve problems with the way we discover and develop new medicines (including my colleague Mariana Mazzucato, who I see has also written a review of this paper) warn against exclusivities as not being in the spirit of a necessary change of culture, and bundle them with patents as monopolies that interfere with equitable pricing (e.g. Section 4.2 of the [People's Prescription report](#)). Whether one agrees with this position or not, the value of this paper in the ongoing discussion is the thesis that exclusivities can conversely be seen as enabling of open research, in this case of providing an economic model for drug discovery that is independent of the patent

system, meaning, crucially, that the R&D can be freely shared. This is a radical change in culture, if it can be made to work. As the authors note, it may in fact be worth enforcing exclusivity arrangements *more* aggressively for open science projects (with the realistic assumption that such projects are wedded to affordability) as a means to help them flourish. A missing citation here is Marden's relevant (but seldom-cited) [paper¹](#) which includes the paragraph "For example one could introduce a new form of data exclusivity... This would allow the drug developer a fixed term to recoup some of its investment." (Minn. J. L. Sci. Tech. 2010, 11, 217)

The paper makes an excellent general argument, and it is exciting that a currently-operating private-sector initiative, M4K, is used as an example. The authors make no claim that this is *the* example, which is appropriate. For example, the authors lay out the future strategy as one relying on a licensing strategy "to one or more partners capable of bringing the medicine to patients" and there are other options here (it might be appropriate to point the reader to the general discussion of this from my, and others', [open source pharma roadmap paper²](#)). It is interesting that the authors are not optimistic about the value of venture capital investment as part of the investment portfolio (something I have argued for) and I would be interested in 1-2 sentences to account for this pessimism. Is there a structural problem, or is it distaste at the likely terms? There are (currently nebulous but nevertheless interesting) arguments, for example, that [Blockchain technology could permit a series of locked-in contracts that would enable easier mixed investment](#), with individual terms for individual investors. If contracts can be bespoke, why limit the source of money?

The comments made about the quality inputs received from the community in an open source research project ("A Partnering Strategy...") are interesting - others, including me, have witnessed the same effect and a reference to these examples would not be inappropriate to illustrate that these are not accidents, e.g. [the substantial and counter-intuitive involvement of the private sector](#), [the involvement of federated student groups and the value of live-online strategy meetings³](#). Similarly the comment about open notebooks as the bedrock of the technical platform could usefully cite other experiences in this area (e.g. [Labtrove](#) or [Chemotion](#)), and the mention of databases could cite existing ways of sharing related data that precede the new SPARK initiative, such as [ChEMBL](#) (even though ChEMBL does not currently prioritize clinical data).

The paper is arguing the case, via a specific example, for an "alternative" to the more traditional patent-based pharma model. The most valuable feature of the article is a reminder of the distinctness of the patent system from the various forms of data and market exclusivity. It is surprising how little-known this is in the general drug discovery community. What is particularly valuable in this article is the Table of examples of medicines either without patents or where patents expired before NCE exclusivity. The authors are to be congratulated on this valuable, citable resource that will help move the community discussion forward.

The sentence "Finally, while most of the world's major drug product markets provide regulatory data exclusivity regardless of the public availability of a sponsor's data" for me is crucial. It would be helpful to know if the corollary could be stated explicitly - that the real-time public availability of clinical data will be no impediment to the granting of exclusivity in certain jurisdictions, or whether this statement is not yet completely clear. Have there ever been examples of exclusivities being granted where the relevant data were all public domain? Does e.g. the FDA have a stated position? The uncertainty over this issue (arising from the language used in TRIPS around "protecting" undisclosed data) may be sufficient to deter future investors and it would be helpful to be shot of it.

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Is the rationale for the Open Letter provided in sufficient detail?

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Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: I have a grant application under review, and others in development, that include members of the Structural Genomics Consortium as co-applicants.

Referee Expertise: Drug discovery (including open source initiatives such as Open Source Malaria and MycetOS), organic chemistry.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 17 January 2019

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Overview

In this open letter, the authors describe the experience of M4K pharma, which operates with an open science model for drug discovery.

It opens with an explanation of the problem faced by the current drug discovery system, especially the lack of productivity. Highlighting the “proprietary generation and use of knowledge” as a key cause of the inefficiency in the collaborative innovation process, the authors argue that an open science model without patent restrictions is the necessary way forward. They further explain that regulatory exclusivity, which compares favourably to patents (in terms of length of protection, cost and the provision of regulatory certainty) and has already been widely applied in the real-world setting, can be used as the mechanism to protect intellectual property and incentivise innovation in lieu of patents. Then, the authors focus on M4K pharma as an example of a viable open science business model that uses regulatory exclusivity to protect intellectual property without hindering knowledge dissemination, and one that is structured to prioritise access over profit for its organisational goals. The authors report that M4K has demonstrated feasibility and success in attracting public and private resources to support open science, and propose that given stronger support from governments and regulators, the M4K model can be scaled up and replicated in other disease areas outside M4K’s expertise.

Overall, the content of the article receives a favourable review from the reviewer. Appropriate to the Open Letter format, the article introduces the important and exciting work of M4K, a very laudable effort that shows the world 1) pharma innovation can be done differently and at the same time done well, and 2) open science is an achievable and practical idea, and it is high time to drop both nay-saying and paying lip-service to the idea and just put it in practice. The language of the article is accessible for the lay reader.

However, the article has insufficiencies in parts in its current form that weaken its emphasis, flow and strength of arguments.

Specific recommendations

1. The article needs an introduction to explicitly set out its purpose and rationale. Crucially, it needs to explain what M4K Pharma does and the rationale for the choice of its disease speciality right at the beginning. It should also briefly explain why M4K can be a good example of the open science business model.
2. The article has too many sections, which interrupts the flow of the piece. For example, sections that explain the context of drug discovery and establish need for an open science business model, including “The drug development business model” and “Open science and the discovery of drug targets”, can be combined under one single heading of, for instance, ‘The need for an open science drug development model’. Similarly, sections that explain the use of regulatory exclusivity can be grouped together and made more succinct.
3. The relevance of applying regulatory exclusivity to the M4K model has to be explicitly established. The article convincingly argues that the protection of intellectual property is the key concern for any open science model. From a legal-economic perspective this is true, but there are other factors at work too, such as technological infrastructure, organisation, politics and culture. The encouraging progress made by M4K described in the article in a way shows that having an alternative mechanism to protect intellectual property and at the same time permits open science is a necessary but insufficient condition for an open science business model to work. Is the chosen emphasis of this article on regulatory exclusivity simply a general assessment, or is it to do with the fact that this is fundamental to M4K’s business model? Either way, recognising that there are other factors that

can make open science difficult (doesn't have to be long – perhaps an extra sentence or two just to outline other factors) will give the reader a better sense of the field. Moreover, having dedicated a significant proportion of content to explaining the context and key concepts, the article needs to explicitly address why the foregoing is important to the experience of M4K (because the article is about M4K after all).

4. The description of how regulatory exclusivity works as a non-patent approach to protecting intellectual property is somewhat partial, and slightly biased towards its advantages. First, the relationship between regulatory exclusivity and patent is not clearly explained. Regulatory exclusivity is a statutory provision and is often used in parallel with patents; the two are not mutually exclusive. The article can be clearer on that, especially when in the abstract it describes regulatory exclusivity is used “in lieu of” patents, which may seem to hint at mutual exclusivity to the lay reader. This leads to the second point, that the comparison between regulatory exclusivity and patents misses the point why patents are preferred. The comparison here mainly concerns the time span of the term of protection granted by patents vis-à-vis regulatory exclusivity, which is useful, but it does not represent the full picture. On the one hand, there's a question of generalisability of the analysis. Regulatory exclusivity tends to be longer in developed economies such as the US and the EU, and it tends to be stronger for special indications exemplified by orphan diseases (presumably part of the reason why M4K chose rare disease to test its business model--rare indications can play to the advantages of regulatory exclusivity more than others). On the other hand, while both mechanisms are used to delay entry of generics, patents – as rightly noted in the article – allow for a greater scope of secrecy and flexibility (though this comes with a higher cost and introduces a higher degree of uncertainty); but this is exactly the reason why they are a key tool for pharmaceutical company to maintain and prolong monopoly (this aspect is discussed in detail in, for example, "[The people's prescription: Re-imagining health innovation to deliver public value](#)"). Therefore, third, the article can benefit from better situating the non-patent-based approach described here in an innovation system that overridingly favours the use of patent as a tool for rent-seeking. The article has done a good job in highlighting the merits of only using regulatory exclusivity, but for the reader to appreciate the wholistic picture, it needs to acknowledge its drawback vis-à-vis patents in terms of profit generation – the life and blood of the pharmaceutical industry – and thus the potential resistance an alternative, non-patent business model is likely to encounter.
5. The limitations of the M4K model is not sufficiently discussed. While positive experiences of collaborating with the private sector highlighted in the article are highly positive and encouraging, the implicit limitations and challenging aspects for this model to disrupt the status quo are reflected in the type of inputs from the private industry partners at this stage, which are limited to in-kind contributions under the corporate social responsibility framing. But the ability to bring in private actors' cash to the game is absolutely crucial if the open science model proposed here is to access the ~\$300bn potential in the global research spend for biomedicine noted in the article, as much of the cash will concentrate in the private sector. In light of the analysis made in point 4 of this review, there will certainly be challenges going forward in order to broaden the application of M4K's experience to areas outside rare disease indication and outside developed economies. Based on M4K's experience and future plans, what are the possible measures to overcome its limitations?
6. Given the above, the article can draw a more nuanced conclusion than the existing one, namely “Although M4K is pursuing a rare disease indication, we believe its open science model does not have to be limited to this area and could be used to discover innovative new medicines for larger markets”. Before covering broader policy recommendations that can encourage open science

overall, it can first draw direct lessons and implications that are more pertinent to M4K's example.

7. The article needs a proper conclusion section to summarise a balanced perspective on the experience of M4K and open science models in general.

Is the rationale for the Open Letter provided in sufficient detail?

Partly

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

Referee Expertise: Economics of innovation and public value

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
