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A New Pharmaceutical Commons: Transforming Drug Discovery

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The Oxford Martin Programme on Affordable Medicines was established in 2017 to address the challenge that, while humanity's need for new medicines continues to grow unabated, the traditional systems for discovering new drugs are inefficient, costly and have high failure rates. In order to drive change, proof is needed of the benefits of new drug discovery models; the aim of the programme is to generate solid, data-backed and non-biased evidence upon which to base recommendations for policymaking and with which to stimulate innovation and collaboration. Its interdisciplinary team draws on wide-ranging academic and industry expertise.

The Institute for Science, Innovation and Society (InSIS) is a member of the Oxford Martin School, researching and informing key contemporary debates on the social implications of scientific and technological change. It currently hosts research programmes on climate change technologies, pharmaceutical markets, global health governance, and natural resource stewardship. InSIS is based at the University of Oxford's School of Anthropology and Museum Ethnography, one of the world's largest and most vibrant centres for teaching and research in the field.

The Structural Genomics Consortium (SGC) is a global public-private partnership created in 2004 to catalyse research in new areas of human biology and drug discovery by focusing explicitly on less well-studied areas of the human genome. The SGC accelerates research in these new areas by making all its research output available to the scientific community with complete freedom to operate (without any patents or restrictions), and by creating an open collaborative network of hundreds of scientists in universities around the world and in nine global pharmaceutical companies. Together, this network of academic and industry scientists is driving a new scientific and drug discovery ecosystem whose primary aim is to advance science and is less influenced by personal, institutional or commercial gain.

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Executive Summary

The demand for affordable pioneer drugs is growing: ageing and expanding populations throughout the world require more effective and safer medicines in all therapeutic areas, including neurology, psychiatry, cancer, cardiovascular, metabolic, and infectious diseases. High rates of failure and extended research timelines demonstrate the need for substantial innovations in the way we organise drug discovery.

The traditional model for the discovery and development of new medicines is predicated on secrecy and the maximum use of Intellectual Property (IP) rights. Today's situation requires bold new approaches to the organisation of pharmaceutical research and development (R&D). In particular, it calls for infusing drug discovery with the ethos of open science through adoption of a less restrictive approach to the sharing of pharmaceutical tools and data, and redefinition of the role that IP plays in the drug discovery process. Recent experimentation of varied open models by organisations around the world suggests that a radical reconstruction of the drug discovery ecosystem is not only urgently needed but also possible.

In this paper we argue that open science models represent the most promising and most tractable path forward for a pharmaceutical R&D sector in need of profound reinvention. We review the current state of open science initiatives and examine their potential to increase the productivity of pharmaceutical R&D.

The paper calls on governments and research funding bodies to increase their investment in open science initiatives, to facilitate the extension of the principles of open science to the clinical evaluation of drug candidates, and to create a system of incentives that would encourage pre-competitive, IP-free research. The paper further advises pharmaceutical companies to consider new mechanisms for the management of open science work conducted in-house or in collaboration with other R&D organisations, and to develop new metrics for the evaluation of their impact.

Finally, the paper recommends that academic institutions develop technology transfer policies that do not rely primarily on IP as the foremost measure of productivity, and that they incorporate the culture and principles of open science into their research training curriculum.

Immense ingenuity and unprecedented levels of funding are available in the drug discovery ecosystem, yet it is failing to produce the medicines that will tackle the devastating diseases of the 21st century. In order to capitalise on the enormous reserves of talent and resources at society's disposal we need to reconstruct the drug discovery ecosystem and facilitate greater exchange amongst its actors. This policy paper provides insights into how this restructuring might begin.

1. Introduction

Pharmaceutical research and development (R&D) is one of the best examples of human ingenuity at work. It concentrates some of the most brilliant minds in the world, employs highly advanced technological platforms, and attracts vast amounts of funding and investment. Over the last century, this engine of innovation has greatly enhanced the quality and length of human life.

Yet this engine is sputtering. Despite significant advances in our understanding of the biological basis of disease, pharmaceutical R&D is struggling to sustain the levels of productivity and efficiency it reached in the second half of the 20th century. The conventional way of organising drug discovery consistently fails to provide the required therapeutic solutions in crucial medical areas such as Alzheimer's disease or novel antibiotics.

New organisational models are clearly needed. At its heart, this requires a deep rethink of how we use, or do not use, Intellectual Property (IP) rights to stimulate drug discovery efforts.

This policy paper highlights the proven potential of open science models in early-stage drug discovery. The paper goes on to present a number of recommendations that would strengthen and extend this promising new component of the drug discovery ecosystem. There is no magic bullet that will solve the structural difficulties of drug discovery, and new ideas will always need to be tailored to the specific scientific and organisational challenges of each therapeutic area. Yet strengthening the open component of the ecosystem has the potential to radically transform how we tackle the medical challenges of our century in a way that is beneficial to patients and producers alike.

2. The challenge

The pharmaceutical industry has encountered significant difficulties in its efforts to sustain the productivity and profitability of drug discovery. Measured by the number of new drugs approved by unit of R&D investment, the productivity of pharmaceutical R&D is suffering a long and slow decline (Figure One).[1] Even when we adopt an expansive definition of innovation and consider a more diverse range of therapeutic products, pharmaceutical R&D appears to be stuck in a protracted period of stagnation.[2]

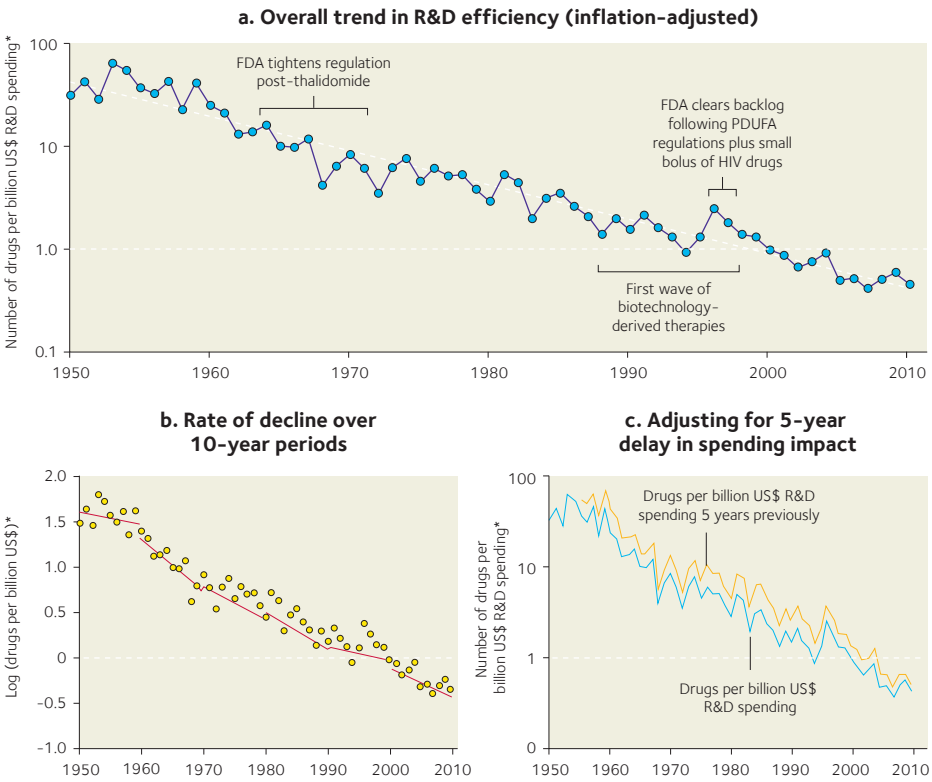
This trajectory is particularly striking if we consider that the last two decades have witnessed dramatic advances in our understanding of molecular biology, and that new technologies of automation have radically accelerated compound screening and other elements of the R&D process.

It is also remarkable that multiple waves of consolidation in the pharmaceutical sector have not resulted in any discernible increase in overall output. The arrival of new and seemingly disruptive innovators, such as the biotechnology companies of the 1990s, does not appear to have significantly changed the levels of productivity of the drug discovery ecosystem as a whole.[3]

Several factors are at work in this scenario. Many of the diseases that remain to be effectively tackled are still poorly understood: the underlying human biology is vastly complex and presents very significant challenges for pharmacological and clinical approaches. The regulatory environment has also changed significantly over the last few decades, and new drugs have to demonstrate their safety and efficacy in wider-scale and longer studies. Yet research on the impact of regulatory requirements on the productivity of pharmaceutical R&D suggests that this is not the most critical variable in explaining low levels of productivity.[4]

Examining *when* in the drug discovery pathway projects are likely to fail sheds some light on the structural weaknesses in the ecosystem. Close to 90% of the candidate drugs that enter Phase I trials fail. In fact, most of those drugs will not even progress to a Phase II trial, the point at which the efficacy of a candidate drug is evaluated for the first time in humans.[5] The high failure rate at this early stage suggests not only a patchy understanding of pathophysiology, but also a skewed process of pre-clinical target and candidate drug selection. Studies of decision-making processes in major pharmaceutical companies show organisational cultures oriented towards volume-based criteria of evaluation, leading to a progression-seeking bias that partly accounts for the high failure rates in early trials.[6]

Figure One: The decline in pharmaceutical R&D efficiency.



Source: Scannell, J. W., Blanckley, A., Boldon, H., & Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery*, 11(3), 191-200. Adapted by permission from Macmillan Publishers Ltd: [NATURE REVIEWS DRUG DISCOVERY] (11(3), 191-200) copyright (2012).

a | *The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on R&D has halved roughly every 9 years.* **b |** *The rate of decline in the approval of new drugs per billion US dollars spent is fairly similar over different 10-year periods.* **c |** *The pattern is robust to different assumptions about average delay between R&D spending and drug approval. R&D costs are based on the Pharmaceutical Research and Manufacturers of America (PhRMA) Annual Survey 2011. PhRMA is a trade association that does not include all drug and biotechnology companies, so the PhRMA figure understates R&D spending at an industry level. The total industry expenditure since 2004 has been 30–40% higher than the PhRMA members' total expenditure, which formed the basis of this figure. The new drug count, however, is the total number of new molecular entities and new biologics (approved by the FDA from all sources, not just PhRMA members). *Adjusted for inflation. PDUFA (the Prescription Drug User Fee Act) is a 1992 United States law that injected new resources into the drug review process and eliminated part of the backlog of products due for evaluation by the FDA.*

The high attrition rate for candidate drugs is at the heart of the dramatic increase in the cost of drug discovery. In 2014, the Tuft Center for the Study of Drug Development calculated an average cost of $2.6 billion per new drug approved in the United States.[7] By the estimates of that organisation, this represents a 145% increase in inflation-adjusted terms over the previous decade. A recent assessment by Deloitte of the returns obtained by 12 leading biopharma companies puts the average cost of development, from initial discovery work to regulatory licensure, at $1,539 million.[8]

Less visible but equally important are the costs incurred by the patients enrolled in clinical trials, who are exposed to drug candidates with a high probability of failure. This direct human impact is never accounted for in conventional measures of "productivity", yet it represents a crucial dimension of the social harm caused by the closed model of drug discovery.

This is a system beset by duplication of effort and wastage of resources. In any given disease, pharmaceutical R&D generally focuses on a narrow range of targets, with many organisations – in academia and industry - often pursuing the same underlying hypotheses. The case of human protein kinases is a good example. These are proteins that regulate key aspects of cellular signalling and whose modulation has provided the mechanism of action for a multitude of drugs across therapeutic areas. Yet only a small proportion of kinases have been explored so far: pharmaceutical research in both academia and industry has concentrated on fewer than 50 of the more than 500 known human kinases. Barriers to sharing information about which targets have already been evaluated, and a generalised unwillingness to explore riskier areas of the kinome, explain this concentration of effort on a very limited set of targets. As a result, large sections of the human kinome remain effectively unexplored.[9]

These systemic weaknesses in the pharmaceutical R&D ecosystem will not be solved by simply doubling down on traditional economic incentives. The history of drug discovery over the last two decades indicates that increasing the volume of research funding or extending IP protections fails to enhance the overall efficiency of pharmaceutical R&D. This is an inelastic system, unable to extract the full benefit from new economic or scientific inputs, and a system that cannot be re-energised simply by intensifying conventional financial or proprietary incentives.

In fact, we confront two broad categories of productivity failure, neither of which can be successfully tackled by simply reinforcing conventional funding models or IP instruments.

2.1 Disease areas deemed highly profitable

In disease areas deemed highly profitable, the existing incentives lock drug discovery organisations into proprietary and secretive courses of action that lead to massive duplication of effort and high failure rates in the development of new therapeutics. Alzheimer's disease is a case in point, with most pharmaceutical companies following parallel strategies that address the same or very similar drug targets. In this context, IP-intensive R&D models severely restrict the sharing of data and know-how, resulting in an enormous wastage of resources. This is an area where novel coordinating mechanisms and better ways of connecting basic research and drug discovery are badly needed.

2.1.1 Alzheimer's disease

More than 45 million people live with Alzheimer's disease worldwide, and the number is expected to increase rapidly over the next decade.[10] Cost of care for these patients, in the United States alone, is estimated to be in the range of $225 billion per year (including 17.9 billion hours of unpaid care by family and friends of Alzheimer's disease patients). In the absence of more effective therapies, this cost could increase to $1.2 trillion a year by 2050.

Against this challenge, the pharmaceutical record is disappointing, to say the least. In fact, the success rate against the disease is zero: there is no drug currently on the market that reverses the progression of the disease or treats its underlying causes. Between 2002 and 2012, 413 clinical trials were conducted to assess a total of 244 potential drug candidates against Alzheimer's disease. The failure rate of these trials was 99.6% (with 72% of agents failing in Phase I, and a further 20% failing in Phase II).[11]

Late-stage failures of once promising compounds have become the norm, for example bapineuzumab (a beta amyloid antibody), semagacestat (a gamma-secretase inhibitor), or solanezumab (a humanised monoclonal antibody), a compound that has failed in three differently designed Phase III trials. The future prospects are not much brighter, despite the fact that the potential market for Alzheimer's disease therapies represents a gigantic economic incentive for innovation.[12]

2.2 Disease areas that lack clear market incentives

In disease areas that lack clear market incentives, such as neglected tropical diseases or new-generation antibiotics, there is insufficient expenditure of resources. Even when the political will exists to redirect pharmaceutical R&D to tackle these diseases, existing IP rights limit the capacity of actors to collaborate effectively. Greater innovation in these areas depends on new ways of bringing together public and private stakeholders, and the success of these partnerships in turn requires innovative ways of organising IP and data sharing.

2.2.1 New-generation antibiotics

The World Health Organization (WHO) has declared antibiotic resistance "a threat to global health security." According to Keiji Fukuda, former WHO Assistant Director-General for Health Security, we may be entering "a post antibiotic era, in which common infections and minor injuries can kill." The discovery of new antibiotics capable of reversing this scenario presents distinct scientific, economic and organisational challenges.[13] A novel antibiotic able to target multidrug-resistant pathogens is a very particular kind of public good, one that is likely to require massive R&D investment but should be used as sparingly as possible.

In the last three years, the UK and US governments have launched initiatives to reinvigorate drug discovery in this area. These programmes seek to create new incentives along the drug development cycle, including increased funding for early-stage discovery activities, experimentation with new reimbursement models, and, in some cases, new taxation schemes.[14] The European Union's Innovative Medicines Initiative has recently launched the DRIVE-AB project to explore alternative funding mechanisms to increase private R&D spending on a new generation of antibiotics. Some of these mechanisms explore the possibility of de-coupling revenues from volume of sales, for instance by providing innovation prizes.[15]

3. A way forward

Drug discovery is best seen as an ecosystem; it is made up of a complex array of actors, each possessing different capacities and operating under specific constraints. Perhaps the most remarkable change in this ecosystem over the last two decades is the degree of inter-dependence among its actors.

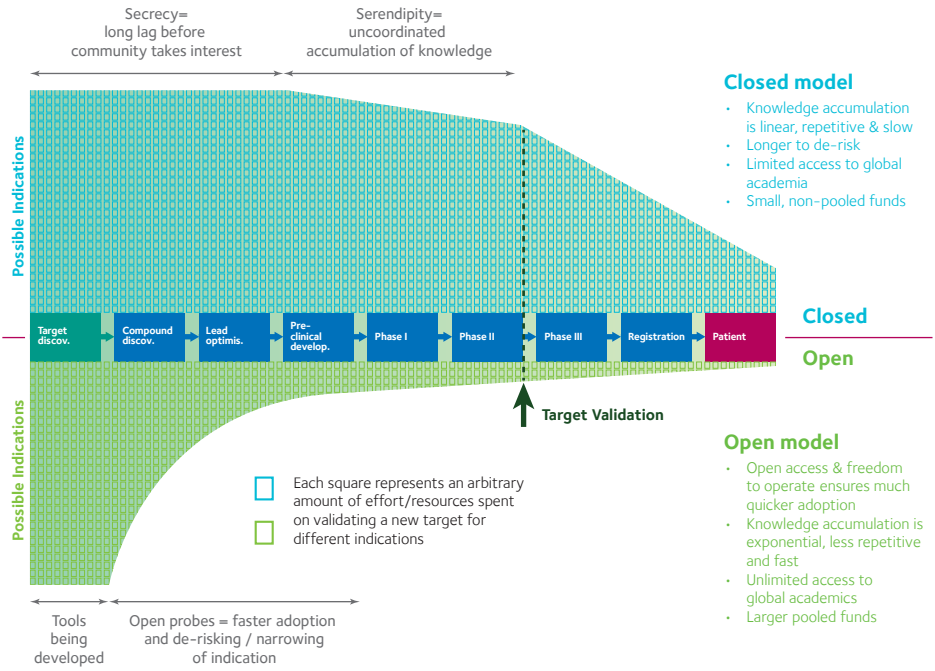
Fifty years ago a typical drug was discovered and developed by a single organisation, able to encompass all the different steps in the process, from target identification to the registration of a new therapeutic. Increasingly, however, key elements in the drug discovery process, including essential scientific inputs, are developed outside traditional Big Pharma, typically in academic or small start-up laboratories, and are internalised at some point along the R&D process. This means that the quality of the relationships between actors in the system determines its overall productivity.

The fundamental value of open science drug discovery is precisely that it fosters greater connectivity and in so doing enhances long-term productivity. A critical contribution of open science approaches is to facilitate the sharing of data and know-how in the earliest and riskiest stages of the drug discovery process, when biological targets for therapeutic interventions are selected or the range of relevant chemical matter is being evaluated.[16] Eliminating barriers to collaboration and knowledge exchange in this phase of pharmaceutical R&D can dramatically reduce duplication of effort and expand the range of pharmacological strategies under consideration.

This in turn can lead to significant changes in the organisational culture of pharmaceutical firms. Sharing creates a counterbalance to the emphasis in most organisations on creating and exploiting an ever-expanding IP portfolio. The prioritisation of IP as the output of R&D activities is at the root of the culture of secrecy and the massive duplication of effort. The adoption of open science approaches allows organisations to experiment with new forms of collaboration. In the process, they become more discriminating about their real competitive advantages.

Open science thus disrupts the entrenched patterns that lead to these rigidities (Figure Two). It removes the incentive of defensive IP, and encourages actors to explore less well-known and riskier areas of biomedicine. It facilitates the sort of collaboration across the academia-industry divide that is essential to putting drug discovery on an even stronger scientific basis. It helps create further transparency across the system and thus removes some of the informational asymmetries that explain why huge amounts of resources are invested in projects that are doomed to fail. It expands and nourishes the drug discovery ecosystem by creating a playing field where for-profit and non-profit actors can join efforts while pursuing different strategies. Before we offer specific suggestions for improving the system along the lines suggested above, let us briefly review some of the most significant experiences in this area.

Figure Two. Open science accelerates identification of the best targets and drug indications, in the correct patient population.



The closed (upper half) model is compared to the open (lower half) model; the availability of open access chemical tools for novel proteins and the resulting freedom to operate enable a global community of researchers to explore different indications and diseases in parallel and quickly share their results through publications. The breadth and depth of the studies in the open model lower the risks of failure in subsequent stages in a typical drug discovery programme, allowing the scientists to focus on the most promising indications, whilst reducing the level of effort (open squares), wastage, and duplication engendered by the secrecy that characterises the closed models. Each square represents an arbitrary amount of effort and resources spent on validating a new target for different indications. Source: Lee, W.H. (2015). Open access target validation Is a more efficient way to accelerate drug discovery. PLoS Biol, 13(6): e1002164.

4. Selected case studies of open science drug discovery initiatives

In this paper we use the term 'open science drug discovery' broadly. For us the concept encompasses initiatives that make raw materials, data and the outputs of scientific research freely available in an effort to avoid duplication of effort and/or re-direct resources to neglected or high-risk areas of pharmaceutical R&D. In our definition, open science drug discovery includes at least two distinct models: pre-competitive R&D consortia, in which a defined number of parties agree to pool resources amongst themselves, and open-source pharma, when those resources are made available to anyone within the drug discovery ecosystem. The boundary between these two categories is fluid, however. In some cases, as we will see below, pre-competitive consortia generate outputs that are freely available to any actor in the drug discovery ecosystem. In those cases, what starts as a 'commons' – a set of actors agreeing to share a resource while excluding non-members from its use – morphs into a free-access platform. Below we describe in more detail some of the most significant experiences.

4.1 Pre-competitive R&D consortia

Pre-competitive consortia are agreements between research organisations to pool together resources, including IP, to facilitate drug discovery. They are compatible with a full protection of the parties' pre-existing IP positions. For instance, since 2010 AstraZeneca and Bayer have had an agreement to grant each other access to their respective compound libraries and screening platforms, yet in all other respects the two companies pursue fully independent, IP-protected strategies.[17]

In some cases, pre-competitive consortia are committed not to develop any IP around the work conducted collaboratively. This greatly simplifies the IP architecture of the consortium, and offers greater clarity and certainty to all of the parties involved. In this model, nothing prevents any group (academic or industrial, participating in the consortium or not) from further developing collective outputs, adding innovative steps that might lead to a new, proprietary molecule protected by patents. The race for the commercial exploitation of consortium output starts at a later phase in the drug development process, however, and once the target and/or the molecule(s) have been significantly de-risked. This radically reduces duplication of effort and wastage of resources at the ecosystem level.

4.1.1 The Structural Genomics Consortium[18]

For the past decade the Structural Genomics Consortium (SGC) has experimented with new approaches to pharmaceutical R&D, by pooling together resources and expertise from pharmaceutical companies, philanthropies and patient organisations in order to accelerate the discovery of new drug targets and chemical probes. It then places its full scientific output – knowledge and reagents (as tangible, physical entities, e.g. chemical compounds) - in the public domain, without any restriction on its use and in the absence of patents. By sharing both data and physical reagents, the SGC's open science approach has already accelerated drug discovery processes in significant areas. For instance, its work on the role of bromodomains in NUT midline carcinoma (an incurable form of cancer) led to the registration by GSK of the first clinical trial aimed at this class of proteins merely 16 months after the initial publication.[19] To date (June 2017) the newly validated bromodomains family of targets has already attracted in excess of $1 billion in private investment for development of new medicines.[20] The SGC's commitment to openness also allows it to pioneer new ways of involving patient organisations in the R&D

process, re-designing pre-clinical and clinical research programmes in collaboration with these stakeholders.[21]

4.1.2 Eli Lilly's Open Innovation Drug Discovery Program

In 2009 the US-based pharmaceutical company Eli Lilly launched the Phenotypic Drug Discovery Initiative (PD2), an open innovation platform to search for new, promising pharmaceutical compounds. In this model, Eli Lilly agrees to evaluate for free any structure submitted to PD2 that meets a series of basic criteria, conducting a series of phenotypic screens to assess the activity of the compound against some key indications. The results of these evaluations are given to the provider of the original compound, who can then decide whether to take the project forward in collaboration with Lilly.

The company has since extended this programme through the Lilly Open Innovation Drug Discovery Program (OIDD), which grants external researchers access to Lilly's proprietary drug discovery resources. So far OIDD has evaluated more than 30,000 compounds of interest to the global R&D community. In a recent initiative, OIDD evaluated the pharmaceutical collection of the National Institute of Health's National Center for Advancing Translational Sciences (NCATS), characterising more than 2,000 clinical phase approved drugs and releasing the results into the public domain.[22] The openness of the OIDD platform is compatible with the protection of intellectual property of the parties who submit chemical structures for evaluation.[23]

4.1.3 European Lead Factory: Joint European Compound Library

Sponsored by the Innovative Medicines Initiative (IMI), the European Lead Factory is a public-private partnership aiming to enhance the productivity of pharmaceutical R&D by identifying new drug discovery starting points. It has established a Joint European Compound Library (JECL), a collection of chemical compounds initially drawn from the libraries of seven pharmaceutical companies (AstraZeneca, Bayer, Janssen Pharmaceuticals, H. Lundbeck, Merck, Sanofi-Aventis Deutschland and UCB Pharma). To the 300,000 compounds provided by its initial pharmaceutical partners, the library has since added more than 100,000 novel molecules designed by academic partners and the small and medium-sized enterprises that participate in the consortium. This collection is freely accessible to academic laboratories and small companies around the world. Participating institutions retain IP rights over the chemical compounds they place in the shared facility, and the JECL ensures that those compounds can be compared and characterised while preserving the confidentiality of their chemical structures. In the meantime, a vast amount of proprietary chemical matter and follow-up medicinal chemistry data is made available to researchers around the world.[24]

Since its establishment in 2013, JECL has handed over to European universities and businesses more than 1,000 hit compounds and 1,300 bespoke compounds, allowing them to launch new drug development programmes. A critical contribution of the partnership has been to expand the range of chemical space explored in drug discovery efforts.[25] On the basis of the work conducted at the European Lead Factory, researchers at the University of Oxford have recently filed a patent application for a novel series of chemical structures with the potential to assist in combating multidrug resistance.[26]

4.1.4 Drugs for Neglected Diseases initiative's Neglected Tropical Diseases Drug Discovery Booster

The Drugs for Neglected Diseases initiative (DNDi) is a non-profit organisation dedicated to finding cures for the most neglected diseases in the world. In 2015 DNDi launched the Neglected Tropical Diseases Drug Discovery Booster to develop new treatments against leishmaniasis and Chagas disease. The Booster currently includes six pharmaceutical companies: Eisai, Shionogi, Takeda, AstraZeneca, Celgene, and Merck. DNDi shares with these companies a 'seed' compound that has shown activity against one of these diseases. The companies, in turn, search their compound libraries for similar and potentially better molecules, and share their most promising candidates with DNDi. DNDi conducts a blind evaluation of the resulting set, and sends the most promising compound

back to the partners for further rounds of screening. There are no IP barriers to the further development of the compounds that result from this process of collective evaluation.

The initiatives described above share two characteristics: they are experimental, and thus involve actors doing things in new and untested ways; and they are focused on the early stages of the drug discovery process. Their success has to be measured by their ability to energise pharmaceutical R&D, particularly in areas that previously failed to attract sufficient investment (e.g. neglected tropical disease) or have been marked by prohibitive rates of failure (e.g. antibiotics). Whilst early-stage initiatives have yet to translate fully into more and/or better therapies, our contention is that these efforts demonstrate the potential of open science collaborations to shake pharmaceutical R&D from its defensive and unproductive ways. Extending this approach downstream and bringing it to bear on the clinical phase of pharmaceutical R&D will be critical to maximise its benefits and impact.

4.2 Open Source Pharma

Open Source Pharma extends to pharmaceutical development the principles and experiences of the free software movement.[27] Open-source drug discovery initiatives overlap to some extent with pre-competitive models, but they are more radical in pursuing the goal of discovering and developing new medicines in the absence of IP protection.[28]

The attraction of Open Source Pharma projects is that they have the potential to transform the process of drug discovery – traditionally conducted in-house and shrouded in secrecy – into a collective, crowdsourced, and transparent effort, independent of organisational biases and attractive to any scientist in the world with relevant expertise. The challenge, on the other hand, is to extend the principles of open source work along the drug discovery pathway, from the more speculative (and cheaper) early-stage work through to clinical development. This will require innovations in funding arrangements, either by establishing a system of prizes to reward investments in the development of the candidate, or possibly by construing a form of IP (and licensing) compatible with the open science goals of the initiative. It will also demand ingenuity in terms of meeting the evaluation criteria of regulatory agencies. For these reasons, open-source initiatives are best seen at the present time as accelerators of drug discovery efforts, in complex interaction with organisations that simultaneously pursue more conventional, even IP-centric models.

4.2.1 The Pathogen Box

Many of the most radical innovations in open science drug discovery are taking place in the context of efforts to discover new drugs against neglected tropical diseases.[29] The Pathogen Box is a recent example. Created and distributed by the Medicines for Malaria Venture, a public-private product development partnership, the Pathogen Box is a collection of four hundred drug-like molecules with proven activity against pathogens responsible for several neglected diseases. Most of these compounds have been made available by pharmaceutical companies after screenings of their proprietary compound libraries. The Pathogen Box is available, free of charge, to any interested researcher around the world. The only constraint on the use of the compounds is that researchers publish any resulting data and place it in the public domain within two years.

4.2.2 Open Source Malaria

Open Source Malaria (OSM) is a community of researchers, drawn from both academic and commercial organisations, applying open source principles to the discovery of new antimalarials. The molecules OSM works with include those drawn from the compound collection of GSK, which was made publicly available in 2010, and include compounds with demonstrated *in vivo* activity against malaria parasites. OSM conducts its medicinal chemistry work in an open fashion, publishing all of its data online in close to real time. Anyone can participate in the work of OSM, or pursue work on these structures independently. The only condition is that the contribution of the OSM community is acknowledged in any further development of that work (OSM uses a Creative Commons Attribution 3.0 License). OSM has so far evaluated four chemical subseries.[30]

4.2.3 The Community for Open Antimicrobial Drug Discovery

Funded by the Wellcome Trust and the University of Queensland, the Community for Open Antimicrobial Drug Discovery (CO-ADD) is an open-access facility allowing any chemist in the world to test compounds for antimicrobial activity. The providers of the compound have 18 months to patent and develop the compound before they are asked to make structures and information publicly available. As with other initiatives discussed in this paper, the primary purpose of CO-ADD is to expand the global collection of compounds with proven activity against the most dangerous, multidrug-resistant pathogens, and in particular to explore regions of chemical space that have not been traditional hunting grounds for pharmaceutical companies. Since its launch in 2015, CO-ADD has screened more than 25,000 compounds, submitted by more than 80 different organisations around the world.[31]

5. Risks and opportunities

There is a healthy debate over the potential advantages and disadvantages of open science approaches to drug discovery. The main argument of critics is that open initiatives jeopardise future commercial exploitation routes, and in so doing might pre-empt the investments from commercial R&D organisations that are necessary to ensure the clinical evaluation of promising drug candidates. Academics worry about the effects of open science activities in the context of a reward system that prioritises first-past-the-post publishing. Industry and venture capitalists overlook open assets as these don't bring enough exclusivity to fend off potential competitors. Our contention is that these concerns are often based on a polarised, black-and-white understanding of how open science relates to proprietary models, an understanding that ignores the more nuanced variations of openness that are being developed on the ground.

Nevertheless, it is true that we lack good metrics to assess with precision the economic benefits of open science models in drug discovery. There is evidence, from some of the experiments discussed above, that open science leads to significant increases in R&D productivity, as measured for instance by the number of compounds screened, collaborative scientific articles published, or even patents filed.[32] These are, however, proxies for more significant metrics of success: improvements in the overall efficiency of the drug discovery ecosystem, and, ultimately, a greater ability to deliver better drugs at more affordable prices.

Recent in-depth analyses of open science initiatives have begun to quantify the increments in efficiency this approach brings to the drug discovery process, and elucidate the factors that explain their success and failure.[33]

Yet we still lack robust models of how changes in the organisation of R&D processes affect the productivity of organisations and the ecosystem in which they are embedded. It is critical that we gather more and better quantitative and qualitative data on the impact of pre-competitive and open source initiatives, and that we establish a clearer understanding of how open science initiatives might be translated into more, and more affordable, medicines. We need better evidence to inform policymaking as well as strategic decisions by all relevant stakeholders.

In particular, we need comparative analyses that contrast traditional IP-centric R&D approaches with those premised on the free availability of scientific outputs. It is furthermore critical to involve multiple stakeholders in these assessments, in order to make sure that the evidence generated can inform their decisions. These analyses will help anticipate potential risks as well as benefits, and they will enable greater calibration of the degrees and modes of openness most useful in specific contexts (e.g. pre-clinical or clinical research, as well as areas with different levels of challenge such as neuro-psychiatry or anti-microbial infections). This is indeed the framework of a new research programme launched by the Oxford Martin School in 2017, addressing the topic of affordable medicines.

6. Transforming the policy context

Public policy plays an active and crucial role in shaping the drug discovery ecosystem, and it is critical to the strengthening of open science initiatives. As public and charitable organisations fund a very significant portion of pharmaceutical R&D activities in the UK, the criteria they use to guide their funding decisions are key to the evolution of this ecosystem. Over the last few years we have witnessed changes in the award conditions of many research funding organisations. For instance, there has been a visible shift towards mandating that the data generated by any funded research be made publicly available and accessible to researchers around the world. The UK government's 100,000 Genomes Project, for instance, seeks to sequence the genomes of 100,000 National Health Service (NHS) patients, and will make the resulting data available to commercial firms to kick-start biomedical innovation.[34] UK Research Councils have adopted a set of criteria on the public availability of research data, including a commitment to making publicly funded research data generated with their support freely available with as few restrictions as possible. Key philanthropic actors, including the Wellcome Trust and the Bill and Melinda Gates Foundation, have developed increasingly strong stances on the obligation to make the data whose production they sponsor publicly available.

These changes go well beyond the UK. The Amsterdam Call for Action on Open Science, for instance, sponsored by the Netherlands' 2016 EU Presidency, outlined a vigorous EU-wide drive towards a speedy transition to open models of R&D.[35] In the United States, the Federal Government and executive agencies have launched numerous programmes in this area, including the 2015 White House initiative "Open Science and Innovation: Of the People, By the People, For the People," with the purpose of expanding and scaling citizen science and crowdsourcing efforts. As the life sciences become increasingly data-centric, a policy environment that encourages and incentivises data-sharing can have a transformative effect in the drug discovery ecosystem.[36]

Another public policy mechanism with the potential to steer the drug discovery ecosystem towards open science solutions is the re-formulation of IP policies. In the UK, the state currently supports both proprietary and open science strategies, but the emphasis of legislation tends to be on the protection and promotion of IP monopolies. The 2013 'Patent Box' initiative, for instance, applies a lower tax rate on income generated by patent licenses, and thus encourages R&D organisations to develop an ever-larger portfolio of patents. There is no open science equivalent in tax policy to the 'Patent Box'. As a result, the government effectively reinforces the default case for patents and monopolies in drug discovery and elsewhere.

All in all, public policy continues to be organised around a central dogma that equates higher levels of IP protection with higher levels of innovation. That central dogma is in need of serious revision, and nowhere is this need more evident than in the case of pharmaceutical innovation.[37] The desire to experiment with new research funding models needs to be complemented by changes in IP law and taxation, the areas where the power of the state bears most directly on the constitution of the R&D ecosystem.

The open science initiatives described above focus on the early stages of drug discovery, including target elucidation, compound screening, and lead optimisation. If these initiatives are to be effective in the delivery of new, affordable medicines, it will be necessary to extend the guiding principles of open science drug discovery to the clinical evaluation of new drug candidates, all the way to regulatory authorisation and licensure. Here, the state can leverage its considerable resources to push the threshold of pre-competitive and open source drug discovery down the development pathway.[38] This can include supporting the trend within the pharmaceutical sector towards greater transparency of clinical evaluation data, in particular the commitment to make clinical trial data available to researchers worldwide.[39]

A complementary action is the strengthening of brokering organisations, along the lines demonstrated by the SGC, which can play a crucial role in coordinating the interests and resources of the multiple actors interested in conducting pre-clinical and clinical studies in an open science manner.

The infrastructures that support open science drug discovery require greater and more sustained financial backing. The cost and complexity of the work necessary to maintain a public resource – a free-access chemoinformatics database, for example, or an open collection of compounds or strains – is not negligible. These infrastructures need to be put on a sustainable financial basis, yet grants rarely extend long enough to guarantee effective returns to the initial investments required to create and curate open-access resources. Furthermore, whenever possible these infrastructures should be built with open-source tools (i.e. software), so as not to give any particular provider control over the architecture of these public resources. This is an area where greater experimentation by government and research-funding agencies is needed.

As things stand, we currently have a patchwork of open science efforts and initiatives. Public, philanthropic and corporate actors have spent considerable resources funding a plethora of initiatives. These have enriched pharmaceutical research in their respective areas, and have demonstrated that creative alternatives to the traditional, closed model of drug discovery are possible and indeed profitable to individual participants and to society as a whole. For these efforts to add up and contribute to a structural transition in the drug discovery ecosystem, however, we need to connect the dots and create a more sustainable framework for open science pharmaceutical R&D. Only then will current investments fully pay off. The final section of this paper provides recommendations to key actors in pharmaceutical R&D aimed at strengthening this component in the drug discovery ecosystem.

7. Recommendations

As we have asserted, there is no simple, one-size-fits-all solution to the challenges and structural weaknesses of the drug discovery process. Yet supporting open science R&D has the potential to have a significant impact across the board. The following recommendations are aimed at strengthening and extending this component of the drug discovery ecosystem.

Recommendations for UK legislators and government departments:

- Provide tax incentives for pre-competitive research. The UK government currently incentivises the prosecution of IP rights by pharmaceutical research organisations. The Patent Box, for instance, allows companies to apply for a lower rate of corporation tax for profits earned from patented inventions. We recommend an open science equivalent to the Patent Box to encourage drug discovery strategies that do not revolve around the hoarding of IP assets. This could consist of a 'Patent Box +' provision for patented innovations that are placed in free-access platforms.
- Use regulatory designations to encourage collaborative drug discovery. Special regulatory designations are a direct and relatively cheap way of re-orienting drug discovery efforts towards socially beneficial goals (e.g. orphan diseases and breakthrough therapies). The European Medicines Agency and the US Food and Drug Administration (FDA) use designations, such as orphan medicine or breakthrough therapy, to facilitate the review process for candidate drugs, thus potentially saving applicants significant amounts of time and money. A specific designation could be introduced for products developed through open science collaborations. This designation could lead to fee reductions, enhanced scientific advice and protocol assistance to drug developers (particularly in the design of clinical trials), or fast-tracked review of technical data.
- Introduce time-limited tax incentive schemes to stimulate novel IP-creation from assets produced from patent-free, open science efforts. This will incentivise first-movers to take up patent-free assets, and to develop these all the way to market. Once those routes are laid (e.g. new business models, new funding structures and new customer bases), new initiatives can follow and reproduce the model for other assets.

Recommendations for drug discovery organisations:

- Establish a specific management portfolio for projects that adopt a pre-competitive or open science philosophy. These projects should be subjected to the same scientific criteria of quality control as any other drug discovery effort within the organisation, but the overall evaluation can integrate an additional set of metrics that capture the specific value proposition of open science research. In particular, it is essential to assess the strength of the networks created through open science approaches. This additional level of review is currently performed informally, and often by top-level internal managers. This review function could be strengthened and made more explicit with the help of panels of external stakeholders and scientific advisors.
- Create schemes that allow research staff to contribute a percentage of their time to open science drug discovery initiatives. Several companies already allow their research staff to participate in not-for-profit activities, but this pro-bono work should be further encouraged and properly acknowledged within drug discovery organisations.

Recommendations for academic research institutions:

- Encourage the shift towards open science publishing in areas critical to pharmaceutical development.
- Avoid IP-centric measures of performance in the evaluation of technology transfer offices (TTOs), and enhance their role as brokers of multi-party, multi-stakeholder collaborations. The adoption of responsible licensing by university TTOs, which is meant to facilitate access to innovation in cases of pressing global need, provides an example of how to diversify the metrics of good performance in this area.
- Bring the open science ethos into the classroom by extending these principles to the training of postgraduate students. This is increasingly done in several of the UK Research Council-funded Centres for Doctoral Training, which often pool the resources provided by their industrial partners. This is an opportunity to train a new generation of biomedical scientists in the ethos of open R&D.

Recommendations for research funding bodies:

- Increase investment in open science drug discovery initiatives. Open-source initiatives often required an externally-funded 'kernel' of activity around which they can create a self-sustaining collective effort. Develop specific funding programmes to sponsor such 'kernels' to catalyse collective drug discovery efforts.
- Develop new metrics of research productivity that capture the strength of collaborative activities in early-stage drug discovery, as well as the value created through the dissemination and curation of open-access resources. Build greater expertise in the socio-economic and legal aspects of pre-competitive and open-source pharmaceutical R&D.
- Increase support for the open access infrastructures that enable pre-competitive R&D and open data sharing. In particular, support long-term data standardisation and dissemination initiatives that assist pre-competitive or IP-free drug discovery endeavours.

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Immense ingenuity and unprecedented levels of funding are available in the drug discovery ecosystem, yet pharmaceutical research and development (R&D) is failing to produce the medicines that can tackle the challenging diseases of today and tomorrow, many with devastating consequences for our society. New organisational models of drug discovery are clearly needed, and this policy paper argues that open science approaches represent the most promising path forward by addressing both scientific and organisational bottlenecks. It reviews open science based initiatives at the University of Oxford and beyond, and examines their potential to increase the productivity of pharmaceutical R&D. The paper concludes by presenting a series of recommendations that would nurture and grow the open science component of the drug discovery ecosystem, potentially transforming how the medical challenges of this century are tackled in a way that is beneficial to patients and producers alike.

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