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RESEARCH PAPER

Governing synthetic biology for global health through responsible research and innovation

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Abstract Synthetic biology (SynBio) is a global endeavour with research and development programs in many countries, and due (in part) to its multi-use characteristics it has potential to improve global health in the area of vaccine development, diagnostics, drug synthesis, and the detection and remediation of environmental toxins. However, SynBio will also concurrently require global governance. Here we present what we have learnt from the articles in this Special Issue, and the workshop we hosted in The Hague in February of 2012 on SynBio, global health, and global governance that generated many of the papers appearing here. Importantly we take the notion of 'responsible research and innovation' as a guiding perspective. In doing so our understanding of governance is one that shifts its focus from preventing risks and other potential negative implications, and instead is concerned with institutions and practices involved in the inclusive steering of science and technology towards socially desirable outcomes. We first provide a brief overview of the notion of global health, and SynBio's relation to global health issues. The core of the paper explores some of the dynamics involved in fostering SynBio's global health pursuits; paying particular attention to of intellectual property, incentives, and commercialization regimes. We then examines how DIYbio, Interactive Learning and Action, and road-mapping activities can be seen as positive and productive forms of governance that can lead to more inclusive SynBio global health research programs.

Keywords Synthetic biology · Global health · Governance · Policy · Responsible research and innovation

Introduction

In this article we will reflect on issues of governance in the field of synthetic biology and global health, building on the papers that we collected in this Special Issue of *Systems and Synthetic Biology*. The majority of these papers have been derived from an international expert workshop on Synthetic Biology for Global Health that we organized as part of the European SYBHEL project (Douglas and Stemerding 2012).[1] As the contributions to this issue clearly show, SynBio has emerged as a global endeavour, it has potential for global health, but it will also concurrently require global governance. This governance challenge is the central theme of Zhang's contribution to this issue, in which she points out that SynBio is in the process of transcending a number of established boundaries that have conventionally facilitated the governance of biotechnological research (i.e. boundaries

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[1] The project Synthetic Biology for Human Health: Ethical and Legal Issues (www.sybhel.org) was funded by the European Commission's 7th Framework Science in Society program. It ran from 2009 to 2012 and included partner institutions from the University of Zurich, the University of Deusto, the Rathenau Instituut, and was coordinated by the Centre of Ethics in Medicine at the University of Bristol. The project examined philosophical and social understandings of life; appropriate methodology for bioethical analysis in SynBio for health; ethical issues arising in utilizing SynBio for health; regulatory and commercial aspects, and public policy over the application of SynBio for health.

vis-à-vis scientific authority and expertise, within and between scientific disciplines, and between geopolitical regions). In this context of fluidity, Zhang argues, governance may not be best framed as a rigid regulatory regime, but as a 'trans-boundary operation' which seeks 'to facilitate effective interactions between a range of current and emerging social actors involved in or affected by scientific and technological developments, to ensure that all parties have the opportunity to express their perspectives and interests at all stages in the pathways of research' (see Zhang 2012).

Zhang's notion of governance nicely concurs with a broader shift that is occurring in European science and technology policy-making towards 'responsible research and innovation' (RRI) (Owen et al. 2012). In a recent discussion of RRI by René von Schomberg, a policy officer at the European Commission, the concept is defined as:

> a transparent, interactive process in which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society) (von Schomberg 2013: 63)

One particular feature of the concept of RRI that gets special emphasis in von Schomberg's description is that it entails a shift from a concern with 'risks' and other potentially negative impacts of new science and technology to the question of the 'right impacts' and how to achieve them. The notions of 'trans-boundary governance' discussed by Zhang and 'right impacts' embodied in the concept of RRI are both highly relevant starting points for our discussion of governance challenges in the field SynBio and global health. To be sure, SynBio is not the only boundary-transgressing technology in the area of health (Vermeulen et al. 2012), and consequently our view of governance stresses the need to approach it in connection with related or converging (bio)technologies that raise similar issues (Metzler and Webster 2011; Hansen and Metzler 2012). With that in mind, the question is how SynBio as a boundary-transgressing endeavor can respond to boundary-transgressing health problems, and how to define and govern the 'right impacts' for SynBio in this global health context? This question has guided us in the formulation of more specific questions that were addressed in the workshop discussions and papers:

1. How can synthetic biology be used to address global health issues, relating for example to vaccine development, drug synthesis, diagnostics and environmental monitoring for human health threats (including pandemics and bio-security threats)?
2. What are the conditions necessary to support the use of synthetic biology for addressing global health issues, such as: social and political conditions for SynBio research and innovation and take-up of its products in different regions of the world; technical and legal conditions relating to the access and availability of SynBio tools and biological parts; policy and regulatory conditions (including transnational collaboration); etc.?
3. How can policy ensure the safe, fair and responsible implementation of synthetic biology on a global level, taking into account: environmental and health related bio-safety and bio-security issues; ethical questions (including questions of global justice); and a diversity of public and cultural perceptions of synthetic biology?

In the following we will discuss important lessons that can be learnt from the articles in this Special Issue and the workshop discussions with regards to the above three questions. In this discussion we not only aim to explore the main governance challenges that arise from these lessons, but also to contribute to the European discussion about RRI by bringing into focus on a more practical level the implications of this vision for policy-making in the field of SynBio and global health. We start in "Global health and how it relates to synthetic biology" section with reviewing the notion of global (public) health as an important context for framing the 'right impacts' of SynBio, and will then discuss the potential of SynBio to achieve these impacts. In "Intellectual property and commercialization regimes" section we will focus on the issue of intellectual property rights and commercialization regimes as other highly important -and contested- framings for the potential impacts of SynBio. In the light of this discussion we will raise, in "More inclusive forms of governance in SynBio for global health" section, the question what mix of (institutional) actors might best support the transnational governance of SynBio in order to facilitate its potential role in the alleviation of global health issues. In the concluding section we will return to RRI as an important perspective for our understanding of the governance challenges in the field of SynBio and global health.

Global health and how it relates to synthetic biology

Notions of global health

The notion of global health is in constant flux. This is due in part to the changing nature of population health, as disease prevalence is an increasing mixture of acute and chronic conditions. What is more our understanding of the world is also changing, which can be partly attributed to the scale and interconnectedness of health problems, and

the inequities within and between nations. Diseases are not confined to 'poor' regions, and health conditions in segments of so called 'developed' countries can often be as bad -or worse- as in their 'under-developed' counterparts. As a result global health can no longer be understood through conventional geo-political boundaries and classes.

Definitions of global health are also closely connected with notions of *public* and *international health*, which together share characteristics of 'population-based and preventive focus; concentration on poorer, vulnerable and underserved populations; multidisciplinary and interdisciplinary approaches; emphasis on health as a public good and the importance of systems and structures; and the participation of several stakeholders' (Koplan et al. 2009: 1993–1994). To differentiate global health from its associated areas of international and public health these authors constructed the below Table 1.

Public health has been defined by the World Health Organization (WHO) as 'the science and art of promoting health, preventing disease, and prolonging life through the organized efforts of society' (World Health Organization 2005: 5). A primary feature of public health is its focus on entire populations rather than individual patients or particular disease. In an attempt to clarify the notion of *global health*, and thereby to set about a series of concerted activities to improve it, the Consortium of Universities for Global Health Executive Board defined global health as:

> an area for study, research and practice that places a priority on improving health and achieving equity in health for all people worldwide. Global health emphasizes transnational health issues, determinants, and solutions; involves many disciplines within and beyond health sciences and promotes interdisciplinary collaboration; and is a synthesis of population-based prevention with individual-level clinical care (Koplan et al. 2009: 1995).

Conventionally global health has addressed challenges relating to infectious diseases like malaria, HIV/AIDS, diarrhoeal and respiratory diseases, and measles. Often these conditions disproportionately affect people in the so called 'developing' or 'under-developed' world, and in particular woman and children there within. In light of that fact maternal and child health is a central concern within global health, focus also extends to issues of nutrition and systematic violence. The 'global' significance of a global health issue is in its scope and scale rather than its geographic location.

Global health requires more than technological fixes

While we found wide-spread acceptance amongst our workshop participants of the *potentialities* of SynBio to contribute to the alleviation of global health issues in diverse ways, it was also emphasized during the workshop discussions that SynBio-based technological fixes will not replace the need for basic infrastructures to prevent, detect and treat diseases of all kinds. This is also pointed out in the literature by global health analyst Laurie Garrett:

> It takes states, health-care systems, and at least passable local infrastructure to improve public health in the developing world. And because decades of neglect there have rendered local hospitals, clinics, laboratories, medical schools, and health talent dangerously deficient, much of the cash now flooding the field is leaking away without result (Garrett 2007: 15).

Obviously, the provision of clean water, safe food, and good sanitation that have been the hallmark of public

Table 1 Comparison of global, international, and public health

	Global health	International health	Public health
Geographical research	Focuses on issues that directly or indirectly affect health but that can transcend national boundaries	Focuses on issues of countries other than one's own, especially those of low-income and middle-income	Focuses on issues that affect the health of the population of a particular community or country
Level of cooperation	Development and implementation of solutions often requires global cooperation	Development and implementation of solutions usually requires binational cooperation	Development and implementation of solutions
Individuals or populations	Embraces both prevention in populations and clinical care of individuals	Embraces both prevention in populations and clinical care of individuals	Mainly focused on prevention programmes for populations
Access to health	Health equity among nations and for all people is a major objective	Seeks to help people of other nations	Health equity within a nation or community is a major objective
Range of disciplines	Highly interdisciplinary and multidisciplinary within and beyond health sciences	Embraces few disciplines but has not emphasised multidisciplinarity	Encourages multidisciplinary approaches, particularly within health sciences and with social sciences

Koplan et al. (2009: 1994)

health interventions need to be rigorously pursued as fundamental bedrocks for health. Without such infrastructural development advanced technological interventions that SynBio is developing are likely to be moot. Pursuant to that are the kinds of organizational developments related to the entire health care system that Garrett describes. Here organization and infrastructure refers not only to the bricks and mortar of hospitals and labs, but also to the intractable problem of training and retaining a diversity of health professionals in the era of globalization. Only with these necessities in place might technological innovations based on research and development in a field like SynBio have the opportunity to make in-roads in the health of all nations. In the same way that we can be sure that global health issues will require more than technological fixes, we are equally sure that they will require more than the provision and deployment of novel health interventions in a top-down or paternalistic manner typical of so many aid and development programs. To this end Koplan et al. (2009: 1994) at the Consortium of Universities for Global Health Executive Board have forwarded a 'shift in philosophy and attitude that emphasises the mutuality of real partnership, a pooling of experience and knowledge, and a two-way flow between developed and developing countries'. In this vein, any attempt to deploy SynBio products or processes for global health will require the 'resources, knowledge, and experience of diverse societies to address challenges throughout the world' (Koplan et al. 2009: 1994). This is a point also well captured in this Special Issue by Betten et al. in their treatment of the Interactive Learning Approach to innovation (see "Incorporating societal stakeholders in the governance of synthetic biology for global health" section below).

Synthetic biology's potential contribution to global health issues

While being sensitive to the fact that challenges pertaining to global health require more than technological fixes, there is a lot to learn from the articles in this Special Issue about the potential contribution of SynBio to alleviating some global health issues. An interesting example is the research described by Vohra and Blakely in this Special Issue, which is targeted at the development of a vaccine that can be used easily on a global scale to prevent diarrhoeal disease. In describing the motivations for their project they point out that 'the infrastructure required to provide basic sanitation, particularly in rural areas, is outwith the financial constraints of many developing countries and will require decades of economic growth, external investment and construction' (Vohra and Blakey 2013). Therefore immunization might offer a more rapid solution to a serious global childhood health issue, especially by using oral vaccines 'which would reduce the need for highly trained staff and could remove the requirement for a cold storage chain' (Vohra and Blakey 2013). In their project the authors are designing and building synthetic gene operons to express antigens for the vaccine in a bacterial host with the ultimate goal to separate and purify the antigens from the bacterial cells and then to administer them orally as a vaccine. In this way they want to prevent potentially adverse pathological side-effects by avoiding the use of live, genetically modified organisms as the vaccine, thus including in their approach 'safety by design' as an important technical precaution.

The work described by Vohra and Blakely is one of the projects being funded by the Grand Challenges Explorations programme (GCE) of the Bill and Melinda Gates Foundation that seeks to apply technologies like SynBio to global health challenges. As explained by Rooke, the GCE funding in this area serves 'to direct the attention and talents of the nascent field of synthetic biology towards global health needs of which it might otherwise not be aware' (Rooke 2013). With a total of thirty $100,000 grants awarded, we can see this funding initiative as an important incentive to steer SynBio research and innovation towards the 'right impacts'. Many of the projects funded use SynBio approaches with the aim to develop novel and low-cost diagnostics and biosensors by engineering whole biological systems, or DNA as nanomaterial that can be added to a sample of blood, urine or water to signal the presence of particular markers or pathogens. Other projects use SynBio for the production of novel classes of engineered large molecules or whole biological systems, like cells and viruses, to be applied as therapeutics or to produce and deliver antigens as oral/ingested vaccines. As Rooke notes, project proposals were also received for applications which could have impacts on global health without being health products per se, including the use of SynBio approaches to engineer safer, stronger and more nutritious crops. This points to 'second order' global health issues, which during our workshop discussions were also mentioned as an important theme for SynBio research and innovation. Richard A. Johnson from the Board of Directors of the BioBricks Foundation provided an illustrative example of these 'second order' health issues at the workshop by pointing out that alternative energy sources could reduce the use of indoor kerosene lamps and stoves, and thereby reducing noxious fumes that they produce and the respiratory disorders that result from them.

In his contribution to the Special Issue James Carothers highlights an alternative innovation strategy that may help SynBio to achieve the 'right impacts'. The starting point in his work are not particular global health challenges, as in the case of the GCE programme discussed by Rooke, but the development of tools and platforms with the potential

to further SynBio research and innovation in a diversity of ways. As Carothers points out 'creating approaches that minimize the time and resources required to engineer novel systems will be essential, particularly for applications targeting diseases and conditions of poverty in low and middle-income countries' (Carothers 2013). With that aim in mind, he proposes a design-driven approach focusing on tools for the modelling and construction of microbial metabolic pathways which may serve as multi-use platforms that can be both 'engineered to produce marketable chemicals and (subsequently) reengineered to produce low cost global health materials' (Carothers 2013). Such platforms might even create, in Carothers' (optimistic) view, opportunities to reengineer devices and systems for a given global health application 'through collaborations between researchers in scientifically advanced countries, scientists in lower-resource settings and members of the Do-It-Yourself bio-community'.

Although there are no engineering 'silver bullets', as Carothers readily admits, the above-mentioned contributions to the Special Issue clearly demonstrate the potential of SynBio in the field of global health. While promising, this potential must be understood in the context of complexities of translating research projects into viable global health interventions. It is important to stress that ideas mentioned above are likely to be deployed in the time span of decades rather than years—if at all. Furthermore, in the interaction with societal actors it will be necessary to specify timeframes for useful applications in global health to avoid raising unrealistic expectations about how and when such health interventions might actually be deployed.

The realization of this potential will arguably require a collective and sustained effort, involving a two-pronged innovation strategy that seeks to achieve the 'right impacts' in global health. Such a strategy could see research and innovation programs targeting both specific diseases, as well as the development of tools and platforms to meet a diversity of global health needs. Ultimately each of these approaches could—and arguably should—be pursued by policies seeking to develop SynBio for global health. What is more, this may be a practicable possibility given the current diversity in SynBio funding streams, which sees the Bill and Melinda Gates Foundation funding research aimed at more direct and immediate applications, while governmental funding schemes in Europe and the US may be more amenable to support the development of multi-purpose platforms described by Carothers. Here achieving the 'right impacts' in global health has much to do with striking a balance between these innovation strategies, as it does with balancing investments in both basic research and futuristic visions or application. Moreover, as we demonstrate in the following sections, other issues besides funding also need to be addressed in order to make SynBio knowledge and technologies more widely accessible in support of broader efforts to solve global health problems.

Intellectual property and commercialization regimes

In their contributions to this Special Issue both van den Belt and Hollis clearly point-out the crucial importance of intellectual property and commercialization regimes in co-determining the impacts of innovation in the field of global health. In this section we will first discuss the role of intellectual property (IP) in pharmaceutical innovation. We then describe how this patent-driven innovation process leads to a mismatch with global health needs, and to hotly debated attempts to reframe current IP regimes. We will then show how the framing of IP issues is debated in SynBio, and finally consider the implications of this debate for SynBio's potential contribution to global health issues. The question driving this section is: how do current IP regimes indeed affect—help or hinder—a quest for the 'right impacts' in the field of SynBio and global health?

The role of intellectual property in pharmaceutical innovation

The conventional means through which medicinal products are developed and delivered to patients are IP-driven commercialization processes. The most common form of IP protection in biotechnology takes the form of patents and patent applications. The patent system is seen as a mechanism to incentivise innovation by offering the patent-holder exclusive rights to license, use, or not use their invention for a fixed period of time—a term of 20 years from the filing date is used in both the European Union (under Article 63(1), European Patent Office 1997) and the Unites States (under Title 35, Part II, Chapter 14, § 154, United States Code 1995). The granting of a patent requires the applicant to demonstrate the novelty of the product or process, their inventive step in the innovation process (i.e., the non-obviousness of the patent), and prospective capability of industrial application (European Patent Office 1997). In the pharmaceutical innovation process patent protection over the production and sale of medicines and diagnostics allows industry players to recuperate investments in the research, development, and deployment pipeline of bringing a product to market, which includes stringent state regulations in the clinical trials process and significant marketing expenditures made to push the sale of their product (Gagnon and Lexchin 2008).

From the late 1950s through to the present day the use of patents in the pharmaceutical industry has come under heavy criticism for being used to 'sustain[ed] predatory prices and excessive margins' because 'costs and prices

were extravagantly increased by large expenditures in marketing' and because the patents themselves protected 'new products [that] were no more effective than established drugs on the market' (Kefauver 1965 in Gagnon and Lexchin 2008: 29). High prices for medicines and diagnostics throughout their patent term can work to limit access to wealthy individuals or those covered by private or state health insurance schemes. While many around the world suffer from a lack of access, these dynamics are particularly pronounced in the so called 'developing' or 'under-developed' world, which has led to various kinds of campaigns for access to essential medicines by organizations like Doctors Without Borders/Médecins Sans Frontières.[2]

How to overcome a mismatch with global health needs?

As Hollis points out in his contribution to this Special Issue, an IP-driven innovation process has at least two implications with regards to global health. One relates to the access to products that are marketed at prices that most people in 'developing' or 'under-developed' countries can't afford. The other relates to the lack of incentives to develop drugs that will principally benefit people in those countries, since the potential users do not constitute an attractive market for pharmaceutical companies (Hollis 2013). Given this twin problem of *access* and *availability*, we may speak of a fundamental mismatch between a patent-driven pharmaceutical innovation processes on the one hand, and global health needs on the other. As a result the dominant IP frame is increasingly challenged by an 'access-to-knowledge' movement which, in the words of van den Belt (2012), 'questions the assumption that exclusive rights are always indispensable for invention and innovation by referring to the contrary experience with free and open-source software in recent decades'. Moreover, the access-to-knowledge frame is defended by a moral point of view, holding that 'human rights (like the right to health …) should never be subordinated to the protection of IP rights' (van den Belt 2012).

Interestingly, tensions between current patent systems and access to common goods have also been acknowledged in a 'Scenarios for the Future' study commissioned by the European Patent Office (2007a). For this study over one-hundred interviews were conducted with key players in the fields of science, business, politics, ethics, economics and law in order to identify key challenges and to develop a series of scenarios reflecting transformations of the European patent system that might result from these challenges over the next 15–20 years. One of the scenarios described sees a drive for access to common goods—like health products—disrupting current IP arrangements:

> In the story told in this scenario, diminishing societal trust and growing criticism of the IP system result in its gradual erosion. The key players are popular movements - often coalitions of civil society, businesses, concerned governments and individuals - seeking to challenge existing norms. This kaleidoscope Society is fragmented yet united - issue by issue, crisis by crisis - against real and perceived threats to human needs: access to health, knowledge, food and entertainment … The main issue is how to ensure that knowledge remains a common good, while acknowledging the legitimacy of reward for innovation (European Patent Office 2007b).

Another interesting response to the mismatch noted above is the proposal for an international Health Impact Fund (HIF) by Hollis (2013) and his colleague Thomas Pogge, see also (Hollis and Pogge 2008; Hollis 2008; Pogge et al. 2010). The scheme proposed does not imply a break with current patent systems, but instead provides pharmaceutical companies with an alternative incentive system for improving global availability and access to medicines. Hollis explains the scheme as follows in this issue:

> The HIF would be established to pay rewards for new, registered drugs. Registration would require the company that owned the rights to the drug … to commit *to supply the drug wholesale at a price that would cover only the costs of manufacturing and distribution*. In exchange, the company would be paid rewards by the HIF, based on the assessed (global) health impact of the drug … Funding for the HIF would come from participating governments, which would, however, save substantially on the cost of new medicines, since registered drugs would be priced much lower than in the absence of the HIF (Hollis 2013).

The HIF thus seeks to reward the 'right impacts' in the field of global health, while remaining within the bounds of a dominant global IP regime. Arguably, adherents of the access-to-knowledge frame may have good reasons to question the scheme for still relying on the assumption of the indispensability of patents as incentives for innovation. As van den Belt (2012) emphasizes in his contribution to this issue, access-to-knowledge is crucially about 'participation in the global networked knowledge-and-information economy', and he refers in this regard to 'the concentration of control over innovative activity in the hands of a limited number of big players' as a major concern of the access-to-knowledge movement.

[2] Médecins Sans Frontières/Doctors Without Borders (MSF) Campaign for Access to Essential Medicines, Accessed February 13, 2013 at http://www.msfaccess.org/.

Intellectual property and synthetic biology: Another mismatch?

The tensions between established IP regimes, access-to-knowledge frames and related concerns about commercialization and monopolization have also struck the emergent field of SynBio. Conflicting views on issues of ownership and sharing in SynBio should be understood against the background of a development in which the IP regime in biotechnology has been gradually extended, to include living organisms, cells and tissues, and synthetic replications of genes and DNA-sequences as patentable subjects. The ambition of synthetic biologists to turn biology into an engineering discipline strongly relies on the use of modular biological parts like genetic sequences with known functions that can be used as building blocks to create new biological systems. If indeed the parts or design methods needed to assemble a new biological device or system would be encumbered with patents, then the established biotechnology IP regime might become a serious roadblock to SynBio's future (van den Belt 2012; Oye and Wellhausen 2009).

In this context too, we may speak of a mismatch between a strongly patent-driven biotech innovation process and a need in SynBio for freedom to operate, based on highly cumulative practices of genetic engineering. As a result of this mismatch SynBio might become highly vulnerable to 'patent sharking' by commercial enterprises whose business model is to conceal their IP rights over a biological part, and to concurrently pursue litigation, license, or settlement fees from other researchers without actually engaging themselves in the development of the patent into further materials or processes (Henkel and Reitzig 2008; Rutz 2009). SynBio on the other hand, might also become a driver for change in IP regimes, a possibility which is explored in one of the scenarios described in the above-mentioned EPO report, in which:

> [c]omplex new technologies based on a highly cumulative innovation process are seen as the key to solving systemic problems such as climate change, and diffusion of technology in these fields is of paramount importance. The IP needs of these new technologies come increasingly into conflict with the needs of classic, discrete technologies… [resulting in a] split in the patent system… by abandoning the one-size-fits-all model: the former patent regime still applies to classic technologies while the new ones use other forms of IP protection, such as the license of rights (European Patent Office 2007a).

Unsurprisingly then, SynBio has become a field in which practices of knowledge sharing have become institutionalized in initiatives like the Registry of Biological Parts associated with the US BioBricks Foundation. Open-access, in this case, is based on the principle of 'get some, give some': 'Registry users benefit from using the parts and information available from the Registry in designing their engineered biological systems. In exchange, the expectation is that Registry users will, in turn, contribute back information and data on existing parts and new parts that they make to grow and improve this community resource' (BioBricks Foundation 2013a).

While the mission of the BioBricks Foundation is to make biology easier to engineer 'so as to benefit all people and the planet', it should be noted that nothing in their Public Agreement prohibits the patenting of novel materials and applications produced using BioBricks Public Agreement-contributed parts (BioBricks Foundation 2013b). Moreover, there is great variation in views among synthetic biologists on precisely where to draw the line between public versus private ownership of parts and design principles (Oye and Wellhausen 2009). A clear illustration is Craig Venter's model of proprietary science as discussed in this issue by van den Belt. This model is not only based on a strategy of aggressive patenting, but also on a close partnership between the non-profit J. Craig Venter Institute (JCVI) and a private company Synthetic Genomics Inc., founded by Venter and his SynBio colleagues Hamilton Smith, Juan Enriquez and David Kiernan, to commercialize the genomic-driven technologies developed by the JCVI. According to the Sponsored Research Agreement between both organizations, Synthetic Genomics Inc. has 'exclusive access to new inventions and discoveries in synthetic genomics research developed by the JCVI' and the company in turn 'sponsors fundamental research at the J. Craig Venter Institute … working on a variety of genomic research and policy fronts' (Synthetic Genomics 2009–2012). In this model of proprietary science the spectre of monopolization is looming again, translating in a morally problematic scenario as described by van den Belt 'in which technological solutions that might be humanity's last hope (as Venter himself suggested…) are locked up in patents that serve to make them inaccessible to any but the most wealthy users' (van den Belt 2012).

Implications for synthetic biology and global health

What are the implications of this complex mixture of open-access and patent protection? How to ensure for SynBio innovation the greatest global value? In his discussion of this question, Hollis first of all agrees that SynBio may have important medical benefits extending to all humanity (Hollis 2013). He also sees it as likely that it will be used chiefly to provide products for wealthy people, with investors and workers in developed countries capturing a

large share of these benefits in selling SynBio products (Hollis 2013). Moreover, as drug regulation might be particularly challenging for novel and complex SynBio products, it may further enhance the costs of applying for market approval and deter companies from small and weak markets. The earlier discussed HIF might be one approach in directing SynBio innovation to important global health needs. However, as Hollis indicates, the problems in global pharmaceutical product innovation are complex and multifaceted, so we should seek for solutions in more than one direction.

Product Development Partnerships (PDPs) are mentioned by Hollis as one of the leading approaches to facilitate disease-focused research and innovation. PDPs seek to bring together technical skills and compound libraries from drug companies with financial support from diverse sources—mostly the Bill and Melinda Gates Foundation and bilateral aid agencies such as the Department for International Development (DFID) and the United States Agency for International Development (USAID). Vohra and Blakely (2013) likewise see this kind of cooperation as a promising route to support product developments that might have global health ramifications, commenting that 'in the current commercially driven world the only way to develop a product is by attracting industrial investment … the moral dilemma is therefore not whether to patent, but rather which company will partner a project and what are their ethical principles'.

A prominent example is the development of a synthetic version of the antimalarial compound artemisinin, the earliest and most often cited demonstration of SynBio's potential in a global health context. In 2004 the Bill and Melinda Gates Foundation awarded $42.6 million to the non-profit Institute for OneWorld Health (IOWH)[3] for development of synthetic artemisinin, which then partnered with the Keasling Lab at UC Berkeley and their spin-off Amyris Biotechnologies 'with the goal of providing unlimited, affordable supplies of first-line antimalarial ingredient using synthetic biology' (OneWorld Health 2012). Although the product had a number of associated patents (Reiling et al. 2006), it was decided by the patent holders to license related technology without royalties so as to facilitate the production and global distribution of the medicine. Amyris granted a royalty-free license to the pharmaceutical Sanofi-Aventis for the commercialization of artemisinin-based drugs. To 'ensure access to affordable malaria treatments in the developing world' the Amyris co-founders established a non-profit organization, Zagaya, responsible for licensing and for raising the money to pay for and apply the technology (Amyris 2012a, b; Zagaya 2012). As Carothers points out in this issue, the example of artemisinin also nicely illustrates the potential of SynBio as a tool-and-parts-based multi-use platform technology, because it is produced on the basis of an isoprenoid metabolic pathway that has been engineered in yeast and can subsequently be re-engineered to serve the production of other isoprenoid-based chemicals with significant commercial value (Carothers 2013).

Schemes like the HIF and PDPs are examples of institutional arrangements that stay within the bounds of current IP regimes, but try to redress them in ways that are conducive to important global health needs. Such schemes are only one possible response to tensions and mismatches that may stand in the way of attempts to achieve the 'right impacts' in global health. Another response emphasizes the importance of institutional arrangements which foster an open-access culture of sharing and participation in research and innovation as a global endeavor. In his discussion of this open-access approach, van den Belt (2012) refers to one of the founders of synthetic biology, Drew Endy, who contrasts current biotechnology practice as dominated by 'hoarding of both materials and property rights' with his dream of SynBio as a practice based on easily accessible tools, sharing and participation. In the following section we will further explore how these more open and inclusive forms of governance might facilitate SynBio's role in the alleviation of global health issues, taking as a starting point Zhang's notion of 'trans-boundary governance' that we already referred to in the Introduction.

More inclusive forms of governance in SynBio for global health

As Zhang (2012) has argued in her contribution to this Special Issue, 'border-transcending characteristics of SynBio urge us to reflect on the conventional remit of governance'. She effectively shows how SynBio tends to disrupt established boundaries between professionals and amateurs, between scientific disciplines, and between geopolitical areas. As a consequence of these fluent configurations, any discussion of governance in this area must take into account a variety of forms through which SynBio is organized, practiced and steered. What is more, this state of flux may actually be conducive to a quest for the 'right impacts' in global health because governance in Zhang's (2012) terms may best be framed as a 'trans-boundary operation that is adaptable to evolving social needs'. In the following we will discuss the (potential) role of a variety of actors in shaping and governing SynBio in a global health context. We will first discuss the role of non-

[3] The IOWH is a non-profit that discovers, develops and delivers safe, effective and affordable new medicines for vulnerable population with infectious diseases in the developing world, with emphasis on diseases that disproportionately affect children (IOWH website, accessed January 11, 2012 www.oneworldhealth.org).

professional SynBio practitioners as described in this issue by Zhang as well as by Landrain et al. Then we will address ways in which wider networks of stakeholders might be incorporated in the governance of SynBio, a topic which has been taken up by Betten et al. in this Special Issue, and which has also been extensively discussed during our Global Health Workshop.

Non-professional synthetic biology communities and global governance

An important aim inspiring SynBio is 'to make biology easy to engineer' which may also facilitate, as Zhang (2012) observes, 'the contribution to scientific innovation from people who are not considered as professional experts in the traditional sense'. Her example are undergraduate students involved in the International Genetic Engineered Machine competition (iGEM), in which hundreds of student teams from all over the globe come together to display their SynBio projects made up of BioBricks freely available from an open-source Registry of Standard Biological Parts. Teams work on a great variety of socially relevant subjects, including a significant number of projects with potential significance for global health. Since the start of the competition in 2004, iGEM has functioned as a global hub for scientific beginners to 'meet and compete' and it plays a crucial role in the '"social" engineering' of the upcoming generation of young scientists (Zhang 2012). As Zhang (2012) argues, the 'get and give' philosophy embraced by iGEM 'is seen to have significantly promoted a global open-access culture', and by integrating so-called 'human practice' work in every project iGEM 'also facilitates global exchange and dissemination of concerns over biosafety, biosecurity, IP regimes, ethics and public engagement'. Thus, the rise of the iGEM community has contributed in significant ways to the global development and governance of SynBio.

Another example of a community that is challenging conventional boundaries between experts and beginners in the field of SynBio is the emerging Do-It-Yourself Biology (DIYbio) movement described by Landrain et al. in this Special Issue. This heterogeneous collection of students, interested amateurs, and/or 'off-duty' scientific researchers constitutes an open science and technology movement that aims to provide an increasing number of people the necessary skills to engineer biology, based on 'de-skilling' approaches of SynBio. DIYbio is becoming—as the authors indicate—a global movement with thousands of people that is spreading both within and outside the US, and is gaining momentum from the presence of a central website and mailing list. What is more, DIYbio is growing through the availability of cheap alternatives to laboratory equipment, the establishment of community labs, and collaborations with enthusiasts from the iGEM community. To be sure the movement is still at a modest and embryonic stage with work tending to concentrate on 'creating and tinkering with scientific hardware, software and experimental protocols' (Landrain et al. 2013). Nonetheless, there are a few examples highlighted by Landrain et al. of DIYbio projects with potential global health significance. These include a widely popularized attempt to engineer a yoghurt biosensor that can detect melamine contamination in milk that was motivated by the recent baby milk disaster in China, and a project which aims to build an open-source PCR diagnostic system tailored for fast and cheap malaria diagnosis.

Not only might DIY projects in biology now be a reachable goal in most places of the world, but cheaper medical diagnostics might also be made with local and easy-to-procure components. Landrain et al. (2013) argue that an emerging DIYbio movement 'can help emerging countries to reduce their dependency on imported, expensive and difficult to maintain machines from developed countries'. Despite the fact that DIYbio may cultivate a garage bio-hackers image, Landrain et al. emphasize its role in actively pursuing forms of responsible research, which can be achieved through the creation of public community labs that foster documented adherence to safety regulations and through initiatives to elaborate a code of ethics for their community. Their account indeed suggests that both the iGEM and the DIYbio communities hold the potential to create more inclusive forms of governance that may also offer new ways to match SynBio to global health needs.

Incorporating societal stakeholders in the governance of synthetic biology for global health

Zhang's notion of 'trans-boundary' governance not only refers to the emerging role of non-professionals in SynBio innovation, but also to attempts to facilitate interactions with social actors who may be affected or addressed by SynBio innovation. The need to incorporate societal stakeholders in an interactive process with innovators is also central to the concept of responsible research and innovation (RRI) that we mentioned in the Introduction. This need may be seen as especially relevant in a global health context where the lack of basic infrastructures may create serious challenges for a proper embedding of new health technologies in society. In "Global health requires more than technological fixes" section we already referred to this in connection to Koplan et al. (2009) who have stressed the importance in global health of real partnership between 'developed' and 'developing' countries. In a similar vein, other authors have emphasized the need for network governance and community based approaches in

order to bridge important translational gaps in the fight against poverty related diseases (Smits et al. 2008).

Another important and complicating question in this discussion is what constitutes—or should be considered as—a global health issue. While our borrowed definition of global health stresses 'the health needs of the people of the whole planet above the concerns of particular nations' (Brown et al. 2006: 62), the discussions in our Global Health Workshop showed that this notion of global needs cannot be taken for granted. Some of our workshop participants felt that individual countries should define for themselves what their main health issues are, and what their desired health outcomes should be. How exactly this priority setting might actually be done was not fully articulated, but what was clear is that it would represent a departure from the health indicators and priority-setting activities undertaken by international organizations like the WHO and philanthropic organizations like the Bill and Melinda Gates Foundation. One alternative to setting priorities in global public health that was explored in the workshop was increasing involvement of stakeholders and 'end-users' on national and local levels. Not only would such partnerships work to strengthen an understanding of the living conditions that lead to public health issues, but it would also help in defining the research agenda for SynBio in public health by appreciating the specific contexts in which technologies would be deployed.

Against this background Betten et al. (2013) describe their experiences with the so-called Interactive Learning and Action (ILA) approach. The ILA approach seeks to open-up technologies like SynBio to a wider range of actors, and do so early on in its development stage (i.e., upstream involvement). Crucial in the ILA process is the mobilisation of the experiential knowledge of participants as a basis for mutual learning and shared understanding, implying that early consultation about the needs of stakeholders and users is of critical importance rather than just end-of-the-line engagement or product evaluation (i.e., downstream involvement). For our purposes here, this could mean bringing patient communities who might benefit from particular SynBio-derived medicines or diagnostics, and/or the health care providers who would be responsible for delivering them, into the research and development process at an early stage.

The ILA approach might thus help to steer SynBio applications towards the 'right impacts' in a global health context, especially applications that are targeted to specific diseases and local conditions. As was forcibly argued, however, by the workshop participant from the BioBricks Foundation, a platform based multi-purpose innovation strategy in SynBio might likewise be geared towards global health needs by engaging a wider network of stakeholders in a roadmapping exercise. Such a collective exercise could be useful for setting short and longer term goals for SynBio, identifying requirements needed for the technology to develop, and coordinating concrete plans of action for the next 10–15 years. In doing so it might integrate technical priorities with research agendas and policy priorities (Johnson 2012).

The idea of a SynBio roadmap for global health would be to stimulate pre-competitive cooperation in the field, and to circumvent some of the challenges relating to the intellectual property protection of biological parts and processes by creating a 'Synthetic Biology Commons' (Johnson 2012). This kind of 'Commons' would be a technical infrastructure that is open, accessible and beneficial for all constructive interests in SynBio (Johnson 2012). Such a comprehensive roadmap would have to be developed in an inclusive process of community engagement, involving researchers, industry, funding agencies, international health and innovation policymaking organisations, NGOs and representatives of end-users in the field of global health (Johnson 2012). While the idea of a SynBio roadmap was broadly supported by the Global Health Workshop participants, it was clearly not accepted naively. Workshop participants noted that for it to have a chance of being successful it would have to be underpinned by principles of transparency, responsibility and diversity. On this basis, it might indeed offer an inclusive and imaginative way of governing the development and practice of SynBio for global health. Interestingly, the Workshop participant from the OECD Working Party on Biotechnology suggested that this organization might play a role in brokering such an activity.

Conclusion

While much of the technological interventions targeting global health challenges are in nascent stages of development, the promise of SynBio to address global health issues is great. Not only are major scientific advances required to bring these interventions to the needed populations, but significant economic, political, social, legal, and ethical factors require consideration for this area of innovation to flourish and be applied globally. Instead of analyzing such factors solely in terms of their risks we have found thinking about them through the perspective of RRI helpful for prioritizing the 'right impacts' of SynBio. In doing so we have sought positive and productive strategies and arrangements for the governance of SynBio rather than exclusively punitive ones.

To be sure, it is not enough to hope and assume that RRI for SynBio and global health will simply come about through market forces; rather, policy actions of various forms are likely to be needed to steer SynBio in this

direction. What we have tried to stress here is that governance—in the area of SynBio as well as others—should not be limited to laws and regulations. Instead what we have forwarded here is that laws and regulations that target important biosafety and biosecurity issues should be coupled with a more positive and productive view of governance that seeks to achieve ameliorations in global health through the recognition and alignment of critical technical, legal, economic, social, and political configurations.

In this context of RRI we have shown how the development of SynBio for global health could involve a two-pronged innovation strategy. Here 'responsible' research could mean a diversity of funders fostering interventions that are targeted at specific global health challenges, as well as developments in design and modeling that could facilitate the multi-purposing of industrial SynBio applications for positive global health outcomes. Furthermore, our examination the pharmaceutical innovation process has suggested a mismatch not only between existing intellectual property arrangements and global health improvements, but also in the role that SynBio might play there within. Here RRI means recognizing the mismatch between SynBio and global health, and developing creative ways (like the HIF) to resolve it. Given the fact that patients in the global health context often lack the financial and/or practical means to access interventions attention must be paid to establishing and maintaining technological infrastructures, as well as facilitating intermediary or translational institutions and organizations (e.g., spin-offs and not-for profits).

Governing SynBio through RRI means the continued promotion of a culture of values (i.e., of openness, sharing, and societal amelioration) through amateur and professional guidelines, education and training. Capitalizing on the grass-roots developments in the iGEM and DIYbio communities will be important in this regard. Achieving real gains in global health will likely require the opening of the SynBio innovation process. Betten et al. have shown in their work on Interactive Learning and Action how producers and consumers can be meaningfully be brought together in SynBio research and development for global health. Like most other health and medical innovations, successful development and deployment of SynBio products in a global health arena will require in-depth local knowledge that includes—but is not limited to—the context of technological use. If a medical innovation is out of step with the morals, values, and everyday practices of a user-community, then up-take of that innovation becomes compromised irrespective of its prospective health benefits. Here creating a dialogue with various publics and end-users about how their values and experiential expertise can be integrated upstream in the development process will be key. Not only might such actions work to facilitate the ultimate uptake of SynBio products, but including more relevant stakeholders and expanding their role in the innovation process is likely to move the entire field in a more responsible direction.

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