Asian Biotechnology and Development Review (ABDR) is a peer reviewed, international journal on socio-economic development, public policy, ethical and regulatory aspects of biotechnology, with a focus on developing countries. ABDR is published three times a year with support of Department of Biotechnology, Government of India and UNESCO by Research and Information System for Developing Countries (RIS), a New Delhi based autonomous think-tank, envisioned as a forum for fostering effective policy dialogue among developing countries on international economic issues.

This special issue is on regulation, innovation and intellectual property rights and has five papers. The first paper discusses recent ideas in regulatory theory and practice and contextualises them for agri-biotech. The second paper gives an over view of emerging scenario in intellectual property rights and biosafety in many countries while the third paper describes the technological options and choices in the age of anthropocene and climate change. The fourth paper discusses stakeholders perception on gene editing and identifies the issues to be addressed for effective regulation. The last paper by comparing experiences in China and India in Bt cotton draws key lessons for policy making in innovation, intellectual property rights and access to technology. It applies the principle of Responsible Research and Innovation (RRI) to agri-biotechnology, to suggest how the key elements of RRI can be applied in agri-biotechnology innovations.

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4. Use figures (rather than word) for quantities and exact measurements including percentages (2 per cent, 3 km, 36 years old, etc.). In general descriptions, numbers below 10 should be spelt out in words. Use thousands, millions, billions, not lakhs and crores. Use fuller forms for numbers and dates— for example 1980-88, pp. 200-202 and pp. 178-84.
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Special Issue on Regulation, Intellectual Property and Innovation

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Editorial Introduction

K. Ravi Srinivas*

We have great pleasure in publishing this special issue on the occasion of FAO International Symposium 'The Role of Agricultural Biotechnologies in Sustainable Food Systems and Nutrition' to be held at Rome from 15th to 17th February 2016. We have chosen 'Regulation, Intellectual Property and Innovation' as the theme for this issue.

While it takes time to develop regulations and laws, the technology advances and the increasing gap between technological developments and the regulatory frameworks is a matter of concern. In case of agricultural biotechnology the differences in regulatory frameworks in USA and Europe, based on different principles has been at the core of the dispute at WTO between USA and Europe. But both precautionary principle and substantial equivalence may not be sufficient to meet the emerging technologies. The USA is now working on revising its biotechnology regulatory framework. GM mosquitoes, plants developed using genome editing technology and non-GM biotech crops open up many technical possibilities and the current frameworks may not be adequate to regulate them. But as technology is global, national level regulation is necessary but not sufficient for effective global regulation. Added to this is the link between trade and diffusion of technology and the emerging picture become complex. There are convention and protocols like Cartagena Protocol and also trade rules like SPS and TBT Agreements. Are these adequate to effectively govern the new technologies and outputs of these technologies? For example, Cartagena Protocol specifies Living Modified Organisms (LMOs) but today the products from genome editing can be of a different category than LMOs. Given the potential for diffusion of technology among countries with

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different capacities to regulate, global regulation of technology becomes a major challenge. The article by Michael Howlett and Ishani Mukherjee examines recent developments in regulation theory and experiences in regulation of agri-biotechnology. Although talking of capacity building has become a cliché this paper goes beyond clichés to emphasis on key factors in regulatory capacity and developing this. We hope that this article will be of interest to regulators and policy makers.

The role of intellectual property rights in agricultural biotechnology has been much discussed and in this topic also recent developments indicate that new opportunities are opened up on account of expiry of patents over GM technologies. Similarly, the relevance of sharing of intellectual property rights and mechanisms like patent pools, open source biotechnology and clearing houses is getting increasingly explored. The paper by David Jefferson and Meenu Padmabhan describes the emerging scenario in intellectual property in agricultural biotechnology and biosafety in many countries.

While anthropocene has become a buzz word, very few understand the implications of anthropocene and link that with developments in life sciences. William Hoffman elaborately describes the challenges and the technological options in his paper. He is not suggesting that technology will solve all problems in the age of Anthropocene. Instead he highlights the technological possibilities and underscores the importance of thinking beyond technology as panacea.

Of late, genome editing and gene drives are in the news and they raise many questions including that of governance and regulation. While the national level governance norms are slowly taking shape, the importance of understanding the perceptions of stakeholders and their views on regulation are important to develop a credible regulatory regime. Jennifer Kuzma, Adam Kokotovich and Aliya Kuzhabekova discuss the findings of a survey on gene editing and situate that in a larger context of gene editing technology regulation. Their findings interestingly indicate that although the technology is new, not all stakeholders want a totally new regulatory regime.

Comparing the Bt Cotton experience in China and India, Sachin Chaturvedi, K. Ravi Srinivas and Amit Kumar explore how these two

countries handled issues on innovation and intellectual property rights in Bt cotton and the impacts of these on diffusion, affordability and biosafety at the field level. Using the emerging concept of Responsible Research and Innovation (RRI) they examine how agricultural biotechnology can incorporate the key elements in RRI resulting in better acceptance and socially acceptable products.

These five papers provide us many ideas on emerging themes in innovation, intellectual property and regulation. We hope that these are of interest and relevance to the readers, particularly policymakers and regulators.

I thank Prof. Sachin Chaturvedi, DG, RIS for his support to bring out the special issue. The contributors of this special issue adhered to a tight time schedule that enabled us to publish this just when the Symposium is taking place. The publication unit at RIS rose to the occasion and ensured that the issue is out in time.

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Achieving Regulatory Excellence in the Agri-Food Biotechnology Sector: Building Policy Capacity

Michael Howlett
Ishani Mukherjee

Abstract: What capacities are needed on the part of policymakers in areas such as the agri-food biotechnology sector in order to attain excellence at the individual, organisational and systemic levels of regulatory operation? To address this question, this paper draws upon work recently carried out on regulatory excellence by the Penn Programme on Regulation and couples it with recent studies on how to build policy capacity. Derived from a multi-jurisdiction, multi-sector review of regulation, the Penn programme identified three core areas or 'pillars' of regulatory excellence – namely, stellar competence, empathic engagement and utmost integrity –which reflect the kinds of individual actions of a regulator, the traits of the regulator as an organisation, and the broad systemic outcomes of regulation which are needed for excellent performance. This work does not examine what is needed on the part of public organisations to achieve these goals, however, and to this end, the paper draws upon a second set of recent studies into the various types of policy capacities that affect policy-making to illustrate what regulators must do in order to achieve excellence. Examples from agri-food biotechnology regulation are used to illustrate the concepts of, and prerequisites for, achieving regulatory capacity and excellence in this sector, although the lessons and implications are also valid in many others.

Keywords: regulatory capacity, precautionary principle, regulatory excellence, integrity, engagement

Introduction: The Concept of Regulatory Excellence

Questions regarding how to improve regulatory processes and bring about better outcomes of regulations have occupied the attention of many academics and regulatory practitioners over the last three decades (Hood 1995; Graham

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2005; Coglianese and Nash 2006; Moynihan 2008; Finkel, Walters and Corbett 2015). Regulatory 'best practices' identified in these studies have included suggestions for enhancing participation in the formulation process of regulations (Ansell and Gash 2007); applying standard and transparent performance and progress management mechanisms for attaining public value (Moynihan 2008; Radin 2009), and engaging strategically with stakeholders in the regulated industry or activity (Hutter 1997). These indicators of regulatory excellence echo those identified by national and multilateral agencies alike (World Bank 2006; UK Environment Agency 2013; Gardener *et al.* 2013).

Recently a systematic analysis of regulatory strategic plans from around the world, including Canada and the United States, examined many instances of regulatory activity in order to identify the structure and behaviour needed to achieve exceptional performance. Like those identified earlier, these related to analytical know-how, instrumental aptitude and high standards of performance; purposeful, even-handed engagement with stakeholders and civil society members; and the attainment of the highest level of integrity among regulators with respect to fidelity to the law, commitment to the public interest and dedication to democratic principles and practices (Coglianese 2015). This multi-jurisdiction, multi-sector review of regulation, identified three core 'pillars' of regulatory excellence behind these practices: *stellar competence, empathic engagement* and *utmost integrity,* each of which can be reflected in the individual actions of a regulator, the traits of the regulator as an organisation, and the broad systemic outcomes of regulation related to public value (Coglianese 2015).

While clear in its explanation of what defines regulatory excellence, however, the Penn work and those others cited above do not examine in detail what is needed on the part of public organisations to achieve these goals. That is, what capacities, competences and capabilities at individual, organisational and systemic levels of regulatory operation are needed on the part of policymakers to attain regulatory excellence?

To address this question, this paper draws on ongoing research work on policy capacity in the field of public policy (Wu *et al.* 2015) and couples the insights of this work to the synthesis on regulatory excellence established bythe Penn Programme. The findings from this work are illustrated and

applied to the agri-food biotechnology sector although many of these conclusions and insights apply to many other policy sectors as well.

Policy Capacity at the Individual, Organisational and Systemic Levels

Adopting a multi-level perspective on the capacities needed for regulatory excellence is necessary in order to analyse exactly how and at what levels of regulatory activities distinction can be achieved.

Studies of the formulation and implementation of policy in general have concluded that success in these activities rests on the interplay of analytical, managerial and political capacities on the part of individual policy actors, regulatory organisations and the general policy system (Wu *et al.* 2015; Gleeson *et al.* 2011). These policy capacities span a variety of analytical resources that are needed to help effectively generate policies, including regulations, and also include the managerial capabilities that let state resources be allocated effectively to different policy priorities and the political endowments that delineate the policy making space that policymakers and administrators have to coordinate, create and implement their plans (Tiernan and Wanna 2006; Gleeson *et al.* 2011; Wu *et al.* 2010; Rotberg 2014; Howlett and Ramesh 2015).

The combination of resources and skills available at different levels of policymaking yield nine distinguishable types of policy capacity (Table 1).

Table 1: Dimensions and Levels of Policy Capacity

Level Dimension	Individual Level	Organisational Level	System Level
Analytical Skills	**1. Policy Analytical Capacity** Knowledge of policy substance and analytical techniques and communication skills	**2. Organisational Information Capacities** Information and e-services architecture; budgeting and human resource management systems	**3. Knowledge System Capacity** Institutions and opportunities for knowledge generation, mobilisation, and use

Table 1 continued...

Table 1 continued...

Operational Skills	**4. Managerial Expertise Capacity** Leadership; strategic management; negotiation and conflict resolution	**5. Administrative Resource Capacity** Funding; staffing; levels of intra-agency and inter-agency coordination	**6. Accountability and Responsibility System Capacity** Rule of law; transparent adjudicative system
Political Skills	**7. Political Acumen Capacity** Understanding of the needs and positions of different stakeholders; Judgment of political feasibility	**8. Organisational Political Capacity** Politicians' support for the agency; levels of inter-organisational trust and communication	**9. Political economic system capacity** Public legitimacy and trust; adequate fiscal resources

Source: Howlett and Ramesh (2015).

At the individual level, analytical capacity entails various substantive skills, while managerial capacities surround effective individual leadership and management strategies, and political competences are embodied by the individual acumen of regulatory actors to assess the needs and interests of different stakeholders. For organisations, pertinent analytical skills are centred on information dissemination and creating an information sharing architecture for the effective transfer of knowledge within and across administrative agencies, while managerial competences surround successful coordination of resources and staffing between agencies, and political aptitude has to do with gaining political support and trust for the agency and its efforts. At the systemic level the wealth of a society, the extent of accountability of its administrative system and the quality of its knowledge system are all key components, and indicators, of policy capacity.

Each of the Penn Programme pillars of regulatory excellence set out above can be seen to draw on each of these capacities. Excellence requires informed individual regulator actions, organisational-level agency traits which promote evidence-based and technical competences and system level traits which confer legitimacy or governments and their actions.

Coupling each of the nine indicators of capacity with the tenets of excellence identified by the Penn programme results in the situation set out in Table 2. That is, each of the principle 'tenets' of regulatory excellence set out in the Penn programme can be seen to require high levels of capacity in terms

of individual level efficiency, education and information; multiplicative agency relationships, proportionality of regulatory response to perceived public risks, and agency vitality based on skill and resource endowments, as well as equity in the distribution of regulatory cost, benefits and public engagement; honesty and the upholding of regulatory integrity (Finkel et al. 2015; Coglianese 2015).

Table 2: Capacity Requisites of Regulatory Excellence

Level of Regulatory Excellence **Core Regulatory Qualities and Defining Capacities**	**Individual Actions**	**Organisational-level traits**	**Systemic Outcomes**
Analytical Capacity **Stellar Competence**	**Analytical Know-How** • Scoping of data reliability and synthesis of quality evidence • Technically consistent analysis • Smart management of risks	**Instrumental Aptitude** • Sufficiently funded and highly trained staff • Organisational culture supportive of adopting high quality, innovative tools and technologies • Regular performance evaluation and management	**High Performance Standards** • Consistent and quality delivery of public value
Managerial Capacity **Emphatic Engagement**	**Even handedness** • Fair and egalitarian engagement with regulation targets • Outreach to ensure participation and equal opportunity to communicate interests	**Attentiveness** • Awareness of regulator and policy target interests and incentives	**Responsiveness** • Timely engagement and response to concerns • Providing full and open explanations of regulatory decisions and decision making processes

Table 1 continued...

Table 1 continued...

Political Capacity **Utmost Integrity**	**Fidelity to Law** • Regulator compliance with all laws and legal procedures	**Commitment to public interest** • Primary and unbiased focus of regulatory body to serve public interests	**Upholding democracy** • Clear delineation of responsibilities of elected officials, administrators and regulators. • Initiating and contributing to public dialogue on policy issues relevant to regulatory action.

The Agri-Food Case

These basic principles and the need for high levels of policy capacity in order to achieve regulatory excellence are well illustrated by the agri-food biotechnology case. In this rapidly progressing field of regulation, several questions regarding lessons for the achievement of excellent policy and governance outcomes and processes have been raised and continue to be made as governments balance their support of biotechnology research and trade implications with regulatory oversight and civil society concerns.

Efforts towards the improved regulation of agricultural biotechnology have taken place in a variety of different jurisdictions and through a variety of different policy processes over the last four decades. This regulation has evolved beyond a 'first generation' focus on genetic engineering technologies and the development of genetically modified organisms (GMOs), towards a 'next generation' emphasis on innovations in technologies related to genomics, proteomics, metabolomics and transcriptomics (collectively labelled as 'omics' technologies) and has moved from the realm of scientific expert to the public realm of concern for individual and public health as well as that of crops and agricultural bio-systems in general (Laycock and Howlett 2013).

Aiming for policy effectiveness and striving for excellence in a complex area such as agri-food biotechnology regulation requires sound analytical, operational and political capacities on the part of those tasked with designing and delivering policy. These competences are important across the board even if the organisational structure of agricultural biotechnology regulation may vary by jurisdiction, especially so since most governments are now

"moving to establish flexible biosafety systems on the basis of internationally accepted guidelines and linked to existing national legislation" (Komen and Persley1993, p. 48).

Critical Capacities for Achieving Excellence in Agri-Food Biotechnology Regulation

There is no doubt that all the nine different capacities identified in Table 1 are important for the effective generation of biotechnology regulations in the agri-food sector. That is, in general, at the broadest systemic level, analytical abilities are needed for the creation of institutions and opportunities for knowledge generation, managerial capabilities are needed to design and implement a transparent adjudicative system and systemic capacities are required to uphold the rule of law and gain widespread public legitimacy (Howlett and Ramesh 2015; Woo *et al.* 2015). However, a specific focus on regulatory capacity can go a step beyondthis to define the key or *critical attributes* of the analytical, managerial and political skills and resources that are necessary to achieve regulatory *excellence* (Coglianese 2015; Finkel *et al.* 2015).

Firstly, achieving the exceptional regulatory competence identified in the Penn scheme depends on having the *analytical capacities* needed to develop effective technical knowledge and skills, "risk-informed priority setting" and achieve high performance delivery of intended regulatory outcomes (Coglianese 2015; Finkel *et al.* 2015). At the level of regulatory action, having well-resourced and sound analytical competence and skills leads to the generation of reliable data and the quality evidence which makes available technically consistent analysis to efficiently manage risks. Similarly, having sound instrumental aptitude depends on the establishment and operation of high level organisational information capacities, including budgeting and management systems that allow regulatory organisations to have sufficiently funded and highly trained personnel and an organisational environment that is conducive to innovation and regular performance evaluation. At the systemic level, capacities for knowledge generation, mobilisation and use determine high performance standards for delivering public value through regulation. For example, annual reports such as those made available through the USDA Foreign Agricultural Service (FAS) make available information on field tests conducted on GMO crops, coexistence

laws and monitoring of agronomic performance which is essential for effective regulation.

Secondly, having high level managerial capacities on the part of regulators is essential to engaging effectively with the public as well as with the subjects or targets of regulation. Leadership, strategic management and arbitration skills are necessary to ensure an egalitarian approach to regulation targets, allowing for even-handed opportunities for communicating various public interests. Many European nations with a long history of public debates on the merits and hazards of agricultural biotechnology, for example, have designed a variety of mechanisms for enhancing public participation in the deliberation process which has added to the legitimacy and perceptions of the efficiency and effectiveness of European regulators (Howlett and Laycock 2013). These include a variety of means for stakeholder consultations as well as participatory technological assessments (TA)involving either ordinary citizens or expert representatives in order to bring forward "marginalised alternative problem-definitions that would suggest different evaluation criteria and alternative innovation trajectories", for products such as genetically modified crops in France and the UK, and herbicide-tolerant crops in Germany (Levidow 2007).

At the organisational level, administrative capacities allowing effective inter- and intra-agency communication are vital assessing and designing incentives aimed at policy targets as well as clarifying the regulator's own interests in regulatory activity. For example, the US agricultural biotechnology regulation, as governed by its 1986 Coordinated Framework for Regulation of Biotechnology Products (51 Fed. Reg. 23302), relied, and continues to rely, on the concerted regulatory action of three existing federal agencies – the United States Department of Agriculture (USDA), the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) – rather than creating a separate new agency for agricultural biotechnology regulation. This was only possible as it was judged that all the federal departments have "reflected a position that biotechnology could be adequately regulated through the existing federal infrastructure and by adapting existing laws to new technologies" (Belson 2000, p. 268) given their high levels of capacity in this area.

Similarly, at the level of regulatory outcomes, high levels of individual, organizational and systemic capacities for accountability and transparent

adjudicative procedures ensure that regulators are able to engage and respond to concerns in a timely manner while providing full explanations of regulatory decisions and processes. Modern regulatory regimes for agri-food biotechnology in Asian countries such as Japan, Korea and China, for example, have been strongly responsive to civil society and non-governmental groups who have been able to raise concerns on the government agenda to influence the rigorous regulation of genetically modified agricultural products, enhancing the legitimacy of both products and regulators in so doing. All three countries have now adopted mandatory labelling (unlike the US or Canada). And all three have ratified the Cartagena Protocol: Japan in 2002, China in 2005 and Korea in 2008(Tiberghien 2012, p. 125).

Lastly, for a regulator to aspire for utmost integrity in "its commitment to serving the public interest, to respecting the law and duly elected representatives" (Coglianese 2015, p. 23) high level political capacities are needed to realize and garner widespread policy and social support for existing and proposed regulations. At the individual level the political acumen of regulators for "understanding the political trade-offs necessary for an agreement among contending actors and interests" is key (Wu *et al.* 2015, p. 169; Pal and Clarke 2015). Organisational level political capacity, on the other hand, goes beyond individual-level capacities for assessing feasibilities and compliance with laws, to ensure broader inter and intra-agency learning and political support (Dunlop 2015).Exceptional integrity at the organisational level is defined by an unbiased commitment to serving public interests (Coglianese 2015). The European Commission's regulatory regime surrounding biotechnology is strongly embedded in the precautionary principle in direct response to public concerns regarding the possible negative effects of GMOs (European Commission 2000) and is a good example of this. Directive 2001/18 adopted by the Commission in 2001 had an explicit goal to inspire public trust in GMO regulatory processes (Johansson 2013), as it stated that "member states, in accordance with the precautionary principle, shall ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the deliberate release or the placing on the market of GMOs" (European Council 2001). Similarly, gaining public trust was the cornerstone emphasis of the agricultural biotechnology regulatory guideline

report published by the Australian Department of Agriculture, Fisheries and Forestry. According to the report, "four strategic imperatives are identified: a national path to market for biotechnology products and services; necessity to build consumer knowledge of biotechnology sciences and their applications (risks and benefits) and also consumer confidence in regulation; a refocus of the current regulation of genetic modification from an input-based process to an output-based process to ensure consistency across emerging technologies; and an engagement in international biotechnology science and research" (Staffas *et al.* 2013, pp. 2768).

Conclusion

Derived from a multi-jurisdiction, multi-sector review of regulation, the Penn programme identified three core areas or 'pillars' of regulatory excellence: stellar competence, empathic engagement and utmost integrity. As set out above, achieving each of these goals relates to the capabilities and competences of individual regulators, of the regulator as an organisation, and the broad systemic capabilities of regulation related to public value, legitimacy and trust.

Opinion on the excellence and effectiveness of existing regulation and regulatory efforts in the agri-food biotechnology sector has raised many concerns including "inattention to food safety, insufficient accountability to citizens via product labelling, threats to biodiversity and the environment, placing scientific progress ahead of the public interest and enhancing the power of large global corporations vis-à-vis poorer countries and consumers" (Laycock and Howlett 2013, p 5).

While enhancing the first two capacities set out above can address many of these concerns and can be relatively easily achieved through the dedication of additional resources to recruitment and training of qualified staff, and the provision of adequate informational and other resources to regulatory agencies, ultimately, the legitimation capacity of the political-administrative system must also be high in order to garner social and political trust on the part of stakeholders and the public (Wu *et al.* 2015; Woo *et al.* 2015).

Gaining public legitimacy has been a particular concern of regulators in the agri-food biotechnology sector and enhancing the legitimacy and public trust in regulators of new and future agricultural biotechnologies has been the subject of many efforts in this area. However, it is the most

difficult the three Penn indicators of regulatory excellence to achieve. That is, from the 'first generation' experience with GMOs, this issue continues to remain critical to effective regulation of 'second' and 'third' generation agricultural biotechnologies and efforts to bolster this capacity on the part of governments and regulators continue to remain a crucial barrier to achieving regulatory excellence in this sector (Rehmann-Sutter 2013).

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Recent Evolutions in Intellectual Property Frameworks for Agricultural Biotechnology: A Worldwide Survey

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Abstract: The present paper focuses broadly on changes to legal and regulatory frameworks relevant to intellectual property (IP) and agricultural biotechnology in multiple territories across the world. Specific evolutions of interest include changes to patentability requirements surrounding genetic material, the expanded availability of IP mechanisms to protect new varieties of plants, and implementations of and reforms to regulatory regimes governing biosafety for genetically modified organisms. The overall purpose of the paper is to provide a general overview of global trends, so that the reader may better navigate a shifting landscape of IP laws and regulatory requirements related to agricultural biotechnology innovation.

Keywords: Intellectual Property, Biotechnology, Agriculture, Gene Patenting, Plant Variety Protections, Biosafety Regulations.

Introduction

The emergence of biotechnologies for agricultural applications and the expansion of private intellectual property ('IP') rights have developed inextricably from one another over the course of the past several decades. Especially since the 1980s, new approaches to plant breeding, that employ molecular markers, genetic engineering, and most recently genome editing, have unfolded along with the worldwide strengthening of IP rights regimes.

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Many observers have remarked that the bolstering of IP protections in many ways facilitated the rapid development of agricultural biotechnologies ('agbiotech'), and that such scientific advances would not have occurred but for the ability to recoup investments in research afforded by exclusive rights (*e.g.*, Lesser 1998). Whether or not this is truly the case, it is certain that in order to fully appreciate the landscape of agbiotech research, one must understand the role that intellectual property plays in this scenario, both at local and global levels.

In the past, scientific advancement in agricultural technologies was a public goods issue. Public sector institutions and universities acted as the primary drivers of research and development ('R&D'), and their resulting products (e.g., new crop varieties) were transferred directly to farmers through extension services (Conway and Toenniessen 1999). While this model persists in many world regions, changes to IP laws, that broadened the ambit of protectable subject matter, have resulted in a substantially greater role played by private sector entities in agricultural R&D (Kowalski *et al.* 2002).

This shift from public to private action has been especially true in the realm of agbiotech, given the significant financial and temporal investments required to develop new biotechnologies and steward them through complicated regulatory frameworks (Alandete-Saez *et al.* in press). Furthermore, the fact that regulatory approvals for transgenic technologies are territorial in nature effectively aligns them with national systems for intellectual property protections, thereby further consolidating what some have termed an 'IP-regulatory complex' for agricultural biotechnology (Graff and Zilberman 2016; Jefferson *et al.* 2015). As such, it is now impossible to consider the relationship between IP rights and agbiotech R&D without comprehending the impact of regulatory regimes on this sector.

Notwithstanding the high costs associated with the effective commercialisation of agricultural biotechnologies, the contemporary innovation system requires a balance of exclusive and non-exclusive access to proprietary technologies to effectively support new crop development (Alandete-Saez, *et al.* in press). An equilibrium between public and private is also critical to provide commercial growers and subsistence farmers alike the best genetic technology possible to cultivate productive, nutritious,

and marketable crops. Yet in many parts of the world, this balance has not been achieved, and farmers, researchers, and consumers face formidable challenges in obtaining rights to use the proprietary products of agbiotech innovation.

It should be noted that this review is not intended to serve as a practical guide to IP protection nor regulatory approval of agricultural biotechnologies. Furthermore, a thorough discussion of several issues is outside of the scope of the present paper, which focuses on presenting certain recent evolutions in legal and regulatory frameworks related to IP protections for agricultural biotechnologies. Nevertheless, it merits mention that the way in which relevant laws and regulations are written can have tremendous impact on stakeholders across the agricultural value chain.

For instance, failing to properly account for the role that smallholder – and frequently indigenous – farmers have historically played in crop genetic improvement can deprive these communities of the recognition and material benefits associated with new varieties developed through landrace germplasm (*e.g.*, Adi 2006). Conversely, overly stringent restrictions on access to plant genetic resources can stymie the efforts of scientific researchers attempting to develop future improved varieties (*e.g.*, Jinnah and Jungcurt 2002). For these and other reasons, it is critical that new legal frameworks encompass the perspectives of all stakeholders, with a proportional balance of representation of all interested parties.

With these considerations in mind, recent worldwide evolutions in laws governing agbiotech products are reviewed below. While the information presented may enable the readers to draw conclusions about global trends, the purpose of this paper is primarily to present specific instances of legal change. The discussion begins with a brief review of the intersecting history of intellectual property rights and agricultural biotechnology, and then delves more deeply into recent shifts that have occurred across Africa, Asia, Australia, Europe, and North America.

History of Intellectual Property for Agricultural Biotechnology

Over the past several decades, the global agricultural production chain has experienced a paradigm shift. Historically, research efforts in many countries were led by universities and other public sector institutions, and the resulting

innovations were distributed to farmers for free as public goods (Bennett *et al*. 2013). In contrast, the contemporary R&D system for agricultural innovations – especially biotechnologies – is increasingly dominated by private companies who liberally utilise regimes for intellectual property protections, and regard their products as private assets.

Whether this new paradigm can be understood as a positive development is hotly contested. Some have claimed that stronger IP protections over agricultural innovations have resulted in enhanced breeding activity, and that a greater number of farmers have access to a greater quantity of new crop varieties with desirable traits such as increased yield, or disease, pest, or drought resistance (*e.g.,* Louwaars *et al.* 2005). Conversely, others argue that stronger IP rights for agricultural products may unduly restrict access to these technologies, a proposition that could imply negative consequences for global food security, nutrition, economic development, and other issues of fundamental importance (see Wong and Dutfield 2010).

Since the late 1960s, the visibility of IP rights claiming agricultural biotechnologies has inspired scholars to develop two inverse hypotheses related to the under- or over-utilisation of resources (Alandete *et al.* in press). According to one hypothesis, a 'tragedy of the commons' results when individuals overuse shared resources, such as common pastures, because they have no incentive to conserve or extend the life of the resource (Hardin 1968). By analogy, Heller and Eisenberg (1998), described a 'tragedy of the anti-commons', which as the result of the proliferation and fragmentation of intellectual properties across multiple owners, prevents any single institution or company from assembling all of the necessary rights to produce a product, resulting in the under-use (or non-use) of resources. In contrast to the idea that patents and other forms of IP function as mechanisms to encourage investment in R&D, the existence of anti-commons has the opposite effect, blocking future innovation.

The complexity resulting from fragmented IP ownership and the potential for anti-commons to arise are exemplified in the case of 'Golden Rice,' which involved the development of β-carotene-enriched rice to combat vitamin A deficiency in South and Southeast Asia. To create Golden Rice, public-sector researchers used at least 40 patented or proprietary methods and materials belonging to a dozen or more owners in the gene

transfer process (Kryder *et al.* 2000). In multiple instances, the researchers' infringement was discovered after substantial research had already been conducted. Thus, the commercialisation of Golden Rice – a product intended to have broad public benefit – was initially constrained by private sector IP rights.

Since the anti-commons surrounding the Golden Rice case was first made visible in the early 2000s, the international legal and regulatory landscapes relevant to intellectual property rights in agricultural technologies have evolved substantially. For instance, the International Treaty on Plant Genetic Resources for Food and Agriculture[1], administered by the Food and Agriculture Organisation of the United Nations, was implemented in 2007. Additionally, the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation to the Convention on Biological Diversity[2] entered into force in 2014. Together, these agreements have significant implications for the sourcing and transfer of the plant genetic resources which form the basis of agbiotech research, the full extent of which remains to be understood as countries continue to implement national frameworks based on the treaties.

Finally, an increasing number of developing countries are in the process of implementing national-level frameworks to offer forms of IP specifically designed to protect new plant varieties, as well as acceding to bilateral and multilateral treaties to achieve the same end. For example, in 2014 multiple sub-Saharan African nations joined the International Union for the Protection of New Varieties of Plants[3] ('UPOV'), and it is likely that many other countries from this region will join UPOV in the near future (Jefferson *et al.* 2014). In addition to these broad shifts, many localised evolutions are concurrently unfolding across the world.

Recent International Evolutions in Legal Frameworks for Agbiotech-Related IP

Multiple legal regimes are relevant to research, development, and commercialisation surroundingagbiotech innovations. These include mechanisms for intellectual property protections – principally utility patents and plant breeders rights ('PBR') – as well as 'biosafety' laws, which establish regulatory frames under which transgenic technologies may be

effectively tested and commercialised. Changes to these various types of legal regimes have occurred over the past several decades concomitant with the maturation of the field of agricultural biotechnology. Examples of important juridical evolutions are discussed below, with a focus on territories in which a substantial amount of agbiotech activity occurs.

Genetic Material as Patentable Subject Matter

Ever since patents were first granted for living organisms in the 1980s, debate has flaredover the appropriate scope of these protections, not to mention whether life forms should be considered patentable subject matter at all (*e.g.* Kass 1981). In the past decade controversy has especially centered on whether isolated genomic DNA sequences should be eligible for patent protection. This question has been the subject of litigation in certain countries in recent years, including the United States, Canada, and Australia, while 'gene patenting' has been challenged through administrative means in territories such as Europe.

In the United States, for many years the Patent and Trademark Office (USPTO) granted patents for isolated and purified DNA molecules having the same sequence as a naturally occurring gene, based on the logic that this gene would not exist in its isolated form in nature. However, on 13 June 2013the Supreme Court of the United States reversed years of USPTO precedent by issuing an opinion with enormous implications for biological research and its resulting innovations. In Association for Molecular Pathology v. Myriad Genetics ('Myriad') (2013), the Court determined that isolated DNA is not patentable subject matter under United States law, and that such isolated nucleotide sequences are barred by the 'product of nature' exclusion to patentability.

A major implication of *Myriad* was the immediate invalidation in the United States of thousands of 'gene patents,' which had claimed isolated nucleotide sequences of genomic DNA. The court in *Myriad* also held that complimentary cDNA sequences could still be patent-eligible. Nevertheless, the impact of the decision on agricultural biotechnology research is substantial, given the extent to which such work relies on isolating particular genomic regions for the purposes of subsequent genetic transformation in host organisms, and the volume of such research that occurs in the USA.

In Australia the issue of patentability of genetic material has also

been the subject of recent litigation. In September 2014, the Federal Court of Australia, which hears appeals, upheld a claim for isolated DNA – essentially the same patent that was at issue in the USA *Myriad* decision. The case – *D'Arcy v. Myriad Genetics Inc. & Anor* – was appealed to the High Court, and oral arguments began in June 2015. In contrast to the United States doctrine, under which laws of nature, natural phenomena, and abstract ideas act as de facto statutory exceptions to patentability, in Australia an invention is prima facie patentable if it is a 'manner of manufacture'(Sherman 2015).

In fact, the outcome of the Australian case turned on the determination by a majority of the High Court judges that the operative characteristic of DNA is not its physical structure, but rather the information contained therein. In October 2015, the High Court held that a gene's 'substance is information embodied in arrangements of nucleotides. The information is not 'made' by human action. It is discerned.' (D'Arcy v. Myriad Genetics 2015).Thus, the key element of isolated DNA – the genetic information itself – cannot be classified under Australian patent law as a manner of manufacture.

While the *Myriad* cases in the United States and Australia have significant implications in their own right, they also have the potential to influence the outcome of debates over 'gene patenting' in other major agbiotech jurisdictions. For instance, although the Patents Act of India (1970) expressly prohibits the patenting of naturally occurring substances as well as mere discovery of living organisms, the Indian Patent Office ('IPO') has granted multiple patents claiming isolated genetic material and nucleotide sequences (Ravi 2013).

Augmenting the confusion in India is the fact that the IPO published new Guidelines for Examination of Biotechnology Applications for Patent in 2013. This document explicitly states that 'products such as micro-organisms, nucleic acid sequences, proteins, enzymes, compounds, etc., which are directly isolated from nature, are not patentable subject-matter' (IPO Guidelines 2013). However, these Guidelines do not have the force of law, and would be superseded by the Patents Act, 1970 and the Patents Rules, 2003 in the event of any discrepancy. Finally, it remains unknown whether the IPO still considers the patents claiming isolated nucleotide sequences that were granted before the passage of the 2013 Guidelines to be valid (Ravi 2013).

While in territories such as the United States and Australia patents over isolated DNA sequences are no longer valid and the situation appears muddled in India, in other countries in which substantial agbiotech R&D occur, gene patents technically remain available. For instance, in China, if a gene or DNA fragment with an unrecorded base sequence is first isolated and extracted from its natural state, can be precisely characterised, and has commercial value, then that gene or DNA fragment constitutes patentable subject matter (Li and Cai 2014).For its part, Canada remains steeped in controversy over the patentability of isolated nucleotide sequences. Inspired by the *Myriad* cases in the USA and Australia, in November 2014 the Children's Hospital of Eastern Ontario (CHEO) filed a lawsuit against the University of Utah Research Foundation, Genzyme Genetics and Yale University. The claim asked the Canadian Federal Court to find that the defendants' patents claiming isolated nucleic acids from human DNA are invalid under the Patent Act of 1985 (CHEO 2014). At present, the Canadian Federal Court has yet to issue an opinion in the CHEO case.

Due to the fragmentation of the global landscape of patent eligibility of isolated DNA sequences, proposals have been launched in recent years to harmonise the field of gene patenting worldwide. Solutions could involve top-down intervention such as amending the TRIPS agreement or more dispersed strategies like voluntary independent licensing agreements or patent pools formed between biotechnology patent holders (Jamison 2015).Indeed, the ambiguous language of TRIPS surrounding exclusions from patentability for biological processes leaves gene patenting open to interpretation among signatory countries (Kumar and Mishra 2015). Therefore, to date, the question whether isolated nueclotide sequences are patentable remains localised and highly splintered.

Protectability of New Plant Varieties

In addition to questions concerning the patentability of isolated nucleotide sequences, the availability of intellectual property protections for new plant varieties holds significant implications for agbiotech research. New varieties of plants constitute patentable subject matter in a very small number of countries worldwide. In the USA, patent protection has been explicitly available for plants produced by either sexual or asexual reproduction and for plant parts including seeds and tissue cultures since the 1980s (*Ex parte Hibberd* 1985).

Likewise, Australia has allowed for standard patents (*i.e.*, not 'innovation patents') to be granted for new plant varieties since the passage of its 1990 Patents Act, provided that there is an 'invention' claimed, defined as 'an innovative idea which provides a practical solution to a technological problem' (Australia Patents Act 2015).In Japan, new plant varieties became patentable in 1985 following the deletion of exclusions related to patentability of plants in the Japanese patent examination guidelines that year (Parvin 2009). Notwithstanding these rare cases, in the vast majority of countries in the world it is still impossible to obtain patent protection for new varieties of plants.

In the specific case of transgenic plants, patent protection is available in Europe if the technical feasibility of the invention (e.g., a genetic modification) is not confined to a particular plant variety (EPO 2016). Additionally, in early 2015, the highest court of the European Patent Office (EPO) considered two cases arising out of patent applications for tomato and broccoli varieties and declared that plant products, including fruits, seeds, and parts of plants, are patentable, even if they are obtained through essentially biological breeding methods involving crossing and selection (Enlarged Board of Appeal of the European Patent Office, Case No. G 0002/12; Case No. G 0002/13). It is still possible that the European Union Commission could take measures to overturn the EPO's decision; however, it appears that all new plant varieties are now presumptively patentable in Europe.

While patents for new plant varieties – whether transgenically or conventionally obtained – remain limited to a handful of countries, protection is available in many other jurisdictions via Plant Breeders Rights ('PBR') (a/k/a 'Plant Variety Protection' ('PVP')) regimes. A thorough review of frameworks for PBR is beyond the scope of this paper. However, it is worth noting that a worldwide ratcheting-up of IP protections through PBR mechanisms has been underway for several decades (Jefferson 2014). This trend is most obviously noticeable in the burgeoning membership in the UPOV convention. As recently as 1990, the treaty had only 27 signatories. As of 2015, UPOV had 74 members, including two intergovernmental organisations (the European Union and the African Intellectual Property Organisation, 'OAPI') (UPOV 2015).

Of further significance is the fact that increasingly, developing countries are either joining UPOV or otherwise establishing national-level frameworks for PBR. As mentioned above, OAPI, a bloc of 17 West African nations, adhered to the UPOV convention in 2014. Even more recently, Tanzania joined UPOV in November 2015. Another African intergovernmental organisation – the African Regional Intellectual Property Organization ('ARIPO') – is currently in dialogue with the UPOV Council, and will likely sign onto the treaty in the near future.

Developing countries in other regions are likewise attempting to implement *sui generis* national legislative frameworks for the protection of new plant varieties. One of the pre-eminent examples of a national, *sui generis* regime for PBR is contained in India's Protection of Plant Varieties and Farmers' Rights Act, established in 2001 (PPVFR Act). The PPVFR Act of India conforms to the requirements of the 1978 version of the UPOV convention, but it endeavours to provide additional safeguards to protect the interests of public sector agricultural breeding institutions and farmers.

Malaysia and Thailand[4]also provide examples of frameworks for PBR outside of the UPOV system. Finally, in some other countries – such as Zimbabwe, Ethiopia, and Zambia – PBR legislation contains certain *sui generis* elements, even while these laws generally follow the UPOV model (Correa *et al.* 2015). One advantage of implementing a country-specific form of IP protection for new plant varieties is that particular countries may enshrine important national priorities in law, such as the recognition of farmers' rights and limitations on the breeder's right based on specified public interest considerations, while still remaining compliant with TRIPS obligations (Correa *et al.* 2015).

Recently, in November 2015 Pakistan's government introduced in the National Assembly a proposal for its own *sui generis* system, via the Plant Breeders Rights Bill. The legislative Standing Committee is currently discussing the bill and has invited comments from relevant stakeholders (Muhammad 2015). Similarly, in Bangladesh the Plant Variety and Farmers' Right Protection Act of 2015 is currently undergoing an apparently final stage of review before the national Cabinet (Siddique 2015).

In general, the evolving and expanding landscape of intellectual property protections worldwide demonstrates that IP mechanisms will continue to be

highly relevant for agbiotech R&D. Yet as an increasing number of countries implement laws governing both IP protections for transgenic plants and biosafety protocols for biotechnology products, the interaction between these two types of legal frameworks is becoming increasingly complex. In addition to recent evolutions in IP protections relevant to agbiotech, the past twenty years have witnessed substantial shifts in the regulation of genetically engineered crops.

Intertwining of IP Rights and "Biosafety" Regulations for Biotech Crops

Recent Changes to National Biosafety Frameworks

In addition to the recent legal evolutions in IP protections discussed above, the past twenty years have witnessed substantial shifts in the regulation of genetically engineered crops. Much like regimes granting IP rights, transgenic plants are administered on a jurisdiction-by-jurisdiction basis, at either regional or national levels. Currently, GM traits (known as 'events') have been approved in 40 countries worldwide, though in some jurisdictions transgenic crops are permitted to be imported but not grown (ISAAA 2015). Furthermore, several territories are currently in the process of approving research field trials of transgenic events. Seven of these countries are located in Sub-Saharan Africa, an indicator that this region will likely represent a sizable new market for GM crops in the near future (James 2014).

Indeed, there appears to be a trend in much of the developing world towards an increasing number of regulatory approvals for biotech crops, even while 'anti-GMO' sentiment continues to be expressed in certain countries. For instance, in 2014 developing countries planted more GM crops than industrial countries for the third consecutive year (James 2014). Of the 28 states that planted biotech crops that year, 20 were developing nations. Also in 2014, Bangladesh initiated the commercialisation of its first approved biotech event, which it accomplished in less than one year. Vietnam and Indonesia began commercialisation of GM crops in 2015. Finally, Kenya, Uganda, Mozambique, and Tanzania are all expected to release their first approved GM varieties in 2017(James 2014).

Yet civil society debate surrounding the cultivation and sale of biotech crops is ongoing in many regions of the world, which in some instances

has resulted in legislative action disfavouring the commercialisation of agbiotech products. In 2015, the European parliament approved a new directive that permits European Union member states to restrict or ban the cultivation of GM crops at the national level, even if EU regulators have declared the particular events in question to be safe for cultivation (Directive (EU) 2015/412). However, this law does not apply to the free circulation or import of GM seeds and plant propagating material. Another recent proposal by the European Commission would allow EU member states to entirely ban the use of GMOs in food and feed (EC Press Release 2015). Unlike the former initiative, this latter proposal has not yet been approved by the European Parliament and has been met with substantial criticism and resistance (Teffer 2015). Currently, Monsanto's MON810 maize is the only GM crop grown anywhere in Europe, and its cultivation has already been banned in eight EU countries (James 2014).

Cultivation of GM crops continues at a massive scale in countries with industrialised or semi-industrialised agricultural sectors such as Argentina, Brazil, Canada, China, India, Pakistan, and the United States. However, even in these territories burdensome regulatory requirements for biosafety assessment may impede the commercialisation of new transgenic events. For instance, in the USA regulatory criteria are not evidence based, in that these criteria have not incorporated the results of experience from decades of research on and commercialisation of transgenic crops, nor expanding knowledge of plant genome structure and dynamics (Bradford *et al.* 2005). This has led to a system that critics believe simultaneously over-regulates crops and technologies that have proven track records of safety, and fails to provide oversight of crops that should be considered as genetically engineered, yet prematurely attain "deregulated" (*i.e.*, deemed safe) status (Camacho *et al.* 2014).

In other countries, regulatory regimes for transgenic crops are similarly convoluted. For instance, over the course of the past decade Pakistan's framework for oversight of GM plants has changed substantially, providing scant stability for biotech researchers. The national regulatory structure in Pakistan was initially established in 2005, primarily as a response to the informal introduction of Bt cotton into the country in 2002 (Gabol *et al.* 2012). At that point, a National Biosafety Committee (NBC) was also created

to review and approve laboratory procedures, monitor field trials, regulate trade, and facilitate the commercialization of biotech crops and products.

However, only five years later, in 2010, the 18th Amendment to Pakistan's Constitution was passed, which devolved many federal powers to the provinces, including the regulation of transgenic crops. Since then, the Punjab Seed Council, the organisation responsible for regulating GM plants in the Punjab province, has approved 18 new Bt cotton varieties for cultivation within its borders (James 2014). Many additional GM cotton varieties as well as other crops are currently undergoing laboratory or field testing in the Punjab. Yet simultaneously – and paradoxically – other Pakistani provinces are actively opposing the development and commercialisation of transgenic plants.

In any event, the framework for biotechnology regulation is far from settled in Pakistan. Indeed, the issue is currently being litigated in the High Court of Lahore. Meanwhile, at the time of writing the national legislature the 2015 Biosafety Act was still being reviewed. If approved, this bill would reassert the federal regulatory structure that was in effect prior to the devolution of powers under the 18th Amendment. The turbulent situation in Pakistan has been criticised as providing little certainty to researchers and breeders, and for the associated limitations in promoting the safe and effective use of Bt cotton (Spielman *et al.* 2015).

Similarly, in recent years India's biosafety regulatory system, through which GM crops are approved and commercially released, has come under increased social and political pressure. In 2010 following a public outcry expressing safety concerns over transgenic eggplant varieties that were set for commercial release, the Indian government issued an indefinite moratorium, halting the release of the crop, and granted state governments the power to ban GM field trials(Gupta *et al*. 2015). Meanwhile, neighbouring Bangladesh showed strong political will in favour of GM crop commercialisation by expediting the release of Bt Eggplant, a process that took only one year (ISAAA 2015).

Ultimately, the federal government in India has relaxed its stance, and the national Genetic Engineering Appraisal Committee (GEAC) has approved 80 field trials in the past several years for multiple new traits. However, following the 2010 devolution of power, only eight states have permitted

these trials and as many as 20 states continue to exercise their right to ban the trials (Gupta *et al*. 2015).

It is difficult to draw overarching conclusions from the recent experiences surrounding biosafety regulation in various countries across multiple regions. These regulatory frameworks are often cumbersome, and consistently face the challenge of reconciling scientific, commercial, economic, and civil society interests. Yet it is undoubtable that GM crops will continue to occupy a significant space in the global agricultural production chain. For this reason, it will be especially important to monitor legal and regulatory developments as intellectual property protections increasingly intermingle with proprietary regulatory data.

The Danger of IP-Regulatory Rights Complexes

While legal frameworks granting intellectual property protections and governing the commercialisation of genetically modified organisms separately pose acute challenges for the commercialisation of agbiotech products, the interaction of these two types of regimes is even more contentious. The specific worry is that 'IP-regulatory complexes' will emerge as patents over key agricultural technologies expire (Graff and Zilberman 2016; Jefferson *et al*. 2015).

For instance, the last United States patent granting rights over one of the first major agricultural biotechnology products – the original glyphosate herbicide tolerance trait marketed as Monsanto's 'Roundup Ready' in soybeans – expired in April 2015. Thus, Monsanto can no longer bring patent infringement lawsuits against scientists, farmers, or competitors for the unauthorised use, manufacture, or commercialisation of this trait. However, the question of if, and if so how, previously-granted regulatory approvals apply to generic versions of the glyphosate herbicide tolerance trait remains unresolved (Jefferson *et al.* 2015).

The uncertainty over how these so-called 'agbiogenerics' will be regulated is further complicated by the fact that the timing of regulatory re-approvals for GM crops varies significantly in different countries. In the United States, once a transgene that has been inserted into a crop is approved for commercialisation ('deregulated'), that crop may be used indefinitely. In contrast, most other countries require regulatory approvals for transgenic

traits to be renewed periodically, the timing of which is variable. For instance, in China applications must be resubmitted every three years, in Korea every five, and in Japan and Europe every ten (Grushkin 2013).

Market considerations convolute this already complicated situation even further. Entities that formerly enjoyed IP rights over GM products have an incentive to remain in control of regulatory filings, even once the relevant patents have expired. Regulatory approvals can frequently provide a source of market exclusivity, since the more costly and complex the process is the greater the barrier to entry it poses for competing products (Chi-Ham *et al*. 2014).

For instance, in Argentina the Roundup Ready soybean trait was never patented, and therefore has effectively always been generic. Yet Nidera, an Argentinian seed company, was the first entity to obtain regulatory approval to commercialise the glyphosate tolerance trait in Argentina, in 1996. This early entry to market gave Nidera a lasting commercial advantage, and five years later the company continued to enjoy a 70 percent market share in Argentina for certified soybean seed (Qaim and Traxler 2005).

Similarly, in India, transgenic insect-resistant cotton (Bollgard I cotton) containing the *cry1ac* gene from *Bacillus thuringiensis* (Bt) was never patented. However, Mahyco, an Indian seed company that had partnered with Monsanto, was the first entity to gain the approval of a Bt cotton line, and for several years it remained the only approved Bt cotton product in the Indian market (Chi-Ham *et al*. 2014). Competitors who wanted to introduce competing Bt varieties faced significant costs of generating new data and documentation to submit to regulators for the approval of their lines. Therefore, many competitors found it cheaper to simply breed in the Monsanto/Mahyco *cry1ac* trait, for which data and documentation were accessible via a license.

Given obvious commercial advantages, former patent holders of transgenic technologies, who still own the proprietary data that is required to attain regulatory approvals, may wish to extend their exclusive control of regulated articles, even after their patent rights have expired. Despite this possibility of monopolisation of agbiotech innovations, virtually no governmental action has been taken in any country that would endeavour to steward the transition of formerly proprietary products into a generic market.

Instead, many of the largest companies conducting agbiotech R&D have crafted a proposal for self-regulation, embodied in the 'AgAccord' (ASTA and Bio 2012).The framework that the AgAccord proposes for the management of proprietary regulatory data following patent expiration is intriguing. However, the agreement is notably bereft of any public sector participation or oversight, instead embodying an industry-centric solution (Schonenberg 2014). In future, it may be desirable for the national governments of countries with large agbiotech sectors to negotiate an international instrument to regulate the emergence of agbiogeneric products (Jefferson *et al.* 2015). Additionally, measures could be taken through national-level legislation in countries that require periodic maintenance of regulatory approvals, which would provide for exceptions to renewals for previously approved, generic events.

Conclusion

Historically, agricultural innovations were typically conceived as public goods in most parts of the world. In contrast, over the past several decades converging trends – especially in countries with industrialised farming sectors – have led to the privatisation of many key technologies utilised as agricultural inputs, including crop genetics. Thus, scientific advances in molecular biology and genetics, combined with increasingly complex protocols for the regulation of biotechnologies, and coupled with the availability of expanded protections for intellectual property, have together conspired to reconfigure the landscape of agricultural research and development.

Throughout the present paper, specific instances of legal and regulatory change across multiple world regions have been reviewed. By considering these various reforms together, it is possible to draw a few general conclusions. First, patentability of isolated nucleotide sequences remains fragmented, with some territories expressly barring 'gene patents' while others continue to grant them. However, it is also notable that in several of the major agbiotech countries, gene patents have either recently been invalidated or likely could be in the near future.

Additionally, it is evident that notwithstanding the restrictions on gene patents recently installed in certain jurisdictions, the ambit of agricultural

intellectual property continues to expand worldwide. This trend is witnessed in the number of countries implementing national frameworks for plant variety protections, as well as those signing onto international treaties intended to grant these or other forms of protection. For instance, many territories are joining the Nagoya Protocol for the purpose of establishing a framework to protect the plant genetic resources located within their borders. Likewise, negotiations are currently underway in the Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore of the World Intellectual Property Organisation (WIPO), with the intention of developing an international legal instrument to protect traditional knowledge and to address the IP aspects of access to and benefit sharing in genetic resources.

Beyond the ever-increasing importance of intellectual property rights to agbiotech research and development, regulatory 'biosafety' regimes merit scrutiny. This is especially the case as patents over first-generation agbiotech products expire, and the public and private sectors alike attempt to maintain approvals of transgenic events. In the future, regulating the interaction between IP rights and proprietary regulatory data may require some governmental intervention, although the form that such a framework would take remains uncertain. Ultimately, policymakers along with industry representatives, academic scientists, and consumers should endeavour to attain a balance between proprietary and open access agricultural biotechnologies, to continue to advance goals of fundamental public importance.

Endnotes

1 The International Treaty on Plant Genetic Resources for Food and Agriculture is a treaty that seeks to "recogniz[e] the enormous contribution of farmers to the diversity of crops that feed the world; establish[] a global system to provide farmers, plant breeders and scientists with access to plant genetic materials; [and] ensur[e] that recipients share benefits they derive from the use of these genetic materials." http://www.planttreaty.org/content/texts-treaty-official-versions.

2 The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation to the Convention on Biological Diversity has the objective of "the fair and equitable sharing of benefits arising from the utilization of genetic resources, thereby contributing to the conservation and sustainable use of biodiversity." https://www.cbd.int/abs/about/.

3 The International Union for the Protection of New Varieties of Plants (UPOV) is an intergovernmental organisation headquartered in Geneva. Its stated mission is "to provide and promote an effective system of plant variety protection, with the aim of encouraging the development of new varieties of plants, for the benefit of society." http://www.upov.int/portal/index.html.en.

4 Malaysia's sui generis PBR law is known as the Protection of New Plant Varieties Act 2004; Thailand's system is administered through the Thai Plant Variety Protection Act.

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Ecosystems, Food Crops, and Bioscience: A Symbiosis for the Anthropocene

William Hoffman

Abstract: Changes in Earth's climate at the end of the last ice age brought about seasonal conditions that favoured the cultivation of annual plants like wild cereals, helping to launch the agricultural revolution. Earth's climate is changing again, mainly through the effects of human actions on the biosphere. To feed a projected population of 9.6 billion people by 2050 while reducing agriculture's carbon, nitrogen, and environmental footprints requires a revolution in food crop productivity and a deeper understanding of the interplay between sustainable food production and natural ecosystems. These goals cannot be achieved without making appropriate use of advanced technologies. Genome-wide association studies, marker-assisted selection, and genomic selection of orphan crops in developing countries can help enhance yields, nutrition, disease resistance, and crop resilience in the face of climate change. With major cereal crop yields stagnating or in decline, successful C4 photosynthesis engineering of rice and wheat and nitrogen fixation engineering of rice, wheat, and maize would have enormous consequences for crop productivity, environmental remediation, and land, soil, and water conservation. Next-generation DNA sequencing, genome editing, synthetic biology, and molecular modeling provide the tools needed for these ambitious efforts to succeed. Innovative food crop bioscience and healthy ecosystems constitute a symbiosis for the Anthropocene.

Keywords: Climate, Crops, Ecosystems, Genomics, Genome editing, Synthetic Biology

So Gilgamesh felled the trees of the forests and Enkidu cleared their roots as far as the bank of the Euphrates. – The *Epic of Gilgamesh*

The ability of human societies to modify and transform biological systems will increase more in this century than it has in the hundred centuries since the dawn of agriculture. -- *Nature*

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Introduction

Crops and climate have a long kinship. The systematic cultivation of plants for food occurred independently in various parts of the world during the early Holocene, a period of global warming that followed the end of the last ice age (Ferrio, Voltas and Araus 2011). The adoption and spread of plant and animal domestication constituted the first large-scale human inroad into natural ecosystems and laid the groundwork for the rise of complex human societies. At the regional level, Near East farming communities cleared forests for crops to take advantage of more bountiful rainfall associated with changes in atmospheric circulation (Araus *et al.* 2014; Black, Brayshaw and Rambeau 2010). In so doing, they unwittingly initiated a process that now is reaching critical mass and disrupting the only realm where life is known to exist, Earth's biosphere (Ruddiman 2003; Barnosky *et al.* 2012; Williams, M. *et al.* 2015, Waters *et al.* 2016). Yet microbial life helped to shape Earth long before *Homo sapiens* began remodeling the planet (Gross 2015). Even as we contend with biophysical disruptions of our own making, powerful new molecular tools derived from microbial life are poised to assist us in restoring Earth's natural cycles and enhancing the food plants we grow (Science 2016; Nature 2015; Doudna and Charpentier 2014; Sternberg and Doudna 2015; Voytas and Gao 2014).

Energy, Ecosystems, and Agriculture

The total amount of energy in the biosphere sets the overall conditions for life. The role of energy in ecosystem food webs was first described in the mid-twentieth century, thereby linking living things with their physical surroundings (Lindeman 1942, Odum 1953; Hoffman 2016). Since then Earth has experienced a "Great Acceleration" marked among other things by rapid growth in the human population, surging energy production and consumption and resulting greenhouse gas emissions, ocean acidification, environmental degradation, habitat fragmentation and dissolution, and the mass extinction of species (Rockström *et al.* 2009; Lewis and Maslin 2015, Steffen *et al.* 2015a). A new human-dominated geological epoch, the Anthropocene, has been proposed (Crutzen and Stoermer 2000; Crutzen 2002).[1]

The energy demand for life – for metabolism, respiration and reproduction – has not changed. The energy demand for human life, as humans prefer to live it, has changed exponentially, running up against constraints posed by ecology and thermodynamics (Brown *et al.* 2011; Barnosky *et al.* 2012; Schramski, Gattie and Brown 2015). These constraints have yet to be reflected in standard neoclassical macroeconomic growth models, delaying wider appreciation of economics as a life science as well as a social science in the Anthropocene (Arrow *et al.* 1995; Mayumi and Gowdy 1999; Brown and Timmerman 2015). The view that entropy law "is of no immediate practical importance for modeling what is, after all, a brief instant of time in a small corner of the universe" (Solow 1997)[2] is increasingly untenable. The "small corner of the universe" is undergoing a profound biophysical transformation, and economies are embedded in the biosphere (Victor and Jackson 2015). The long-term social and economic productivity costs of fossil fuel energy production and consumption are projected to mount (Rozenberg and Hallegatte 2015; Burke, Hsiang and Miguel 2015) as are environmental costs associated with the "Great Acceleration.[3] With respect to fossil fuels exploration and climate, U.S. courts are just beginning to require calculation of carbon costs for leasing of federal lands.[4]

Foods systems, which are heavily dependent on fossil fuels, consume nearly one-third of global energy supplies (FAO 2014). A framework of "planetary boundaries" has been proposed to create a "safe operating space" for humanity and prevent potentially catastrophic biophysical thresholds from being crossed (Steffen *et al.* 2004; Rockström *et al.* 2009; Steffen *et al.* 2015b). With respect to agriculture, they include climate change, biodiversity loss, disruption of the nitrogen and phosphorous cycles, and changes in land use. Climate change, biodiversity loss, and the nitrogen cycle have already crossed their proposed boundaries. A boundary of 15 percent is proposed for the percentage of global land cover converted to cropland (Rockström *et al.* 2009). It is estimated that cropland currently covers 11-12 per cent of Earth's land surface (Rockström *et al.* 2009; Foley *et al.* 2011). The total amount of cropland *per se* is less of a factor in the land-systems change boundary than the amount of forest cover sacrificed for cropland because forests, especially tropical forests, have a strong influence on climate regulation (Steffen *et al.* 2015b). In the tradeoff between

carbon stocks and crop yield or "trading carbon for food," increasing yield on existing tropical croplands including through genetic innovation is preferable to clearing new land (West *et al.* 2010). Agriculture, forests, and greenhouse gas emissions are inextricably linked. The linkage offers opportunities for "climate-smart" local agricultural practises in tropical regions (FAO 2013; Carter *et al.* 2015) where deforestation for crops and pasture as well as timber proceeds apace (Kim, Sexton, and Townshend 2015) and where the human population is expected to grow faster than anywhere else in the world.[5]

Crop Yields, Climate, and Bioscience

Global food crop production grew approximately 160 per cent from 1960 to 2005, mostly by improved production on existing farmlands. The 45-year span of yield improvements largely associated with efficient management as opposed to expanding croplands at the expense of forests also served to mitigate greenhouse gas emissions (Burney, Davis and Lobell 2010).[6] But the era of unbound crop productivity growth using current technology and management practises may be drawing to a close. Today global yields of the world's major cereal crops (maize, rice, wheat) have stagnated in one-third of producing regions (Ray *et al.* 2012). Overall growth in yields of these crops plus soybean will be inadequate to double their production by 2050 to meet projected demands mainly from human population growth and diets with more meat and dairy products (Ray *et al.* 2013; Tilman and Clark 2014). Indeed, the crops needed to feed the poultry, beef and other livestock to meet projected demands for meat would require every acre of the planet's cropland, leaving no room for human plant food production (Elam 2015; Bunge 2015).

Regional climate variability (temperature and precipitation and their interaction) may explain as much as one-third of global crop yield variability for maize, rice, wheat, and soybean, which together account for about two-thirds of current harvested global crop calories (Ray *et al.* 2015). About half of global maize production is concentrated in high yielding maize belts primarily in two regions—the American Midwest and the Chinese Maize Belt (Ray *et al.* 2015). In these two regions nearly half of corresponding yield variability can be explained by variability in temperature and rainfall and the interaction between the two. Cropland is much more sensitive to

extreme climatic conditions such as drought than are natural ecosystems, as measured by vegetation productivity (Ma *et al.* 2015). The 2012 drought in the American Midwest, which reduced overall maize yields to 1995 levels, was estimated to have cost the U.S. economy between $20-$77 billion.[7]

In their highly cited seminal article "Solutions for a Cultivated Planet," Foley *et al.* (2011) observe that to meet the world's future food security and sustainability needs food production must grow substantially at the same time that agriculture's environmental footprint must shrink dramatically. Agricultural expansion should be halted,consumers should shift away from meat-based diets and reduce food waste, and farmers should strive to improve the yield and resilience of cropping systems including on underperforming lands. Multiple paths exist for improving the production, food security and environmental performance of agriculture. In searching for solutions we should remain "technology-neutral" with respect to conventional agriculture, genetic modification, and organic farming (Foley *et al.* 2011). Both demand-side and supply-side emissions mitigation measures need to be implemented in agriculture, with the latter focusing on the production of more agricultural product per unit of input (Smith *et al.* 2013).

Genetic research a century ago prepared the soil for the wave of hybrid seed varieties that swept over American cropland in the 1930s. It was, in many ways, the first genetic revolution, bringing together Mendel's field research on heredity with experimental laboratory science like Morgan's fruit fly studies in the broader context of industrial growth (Allen 1979). Hybrid seed development and the Green Revolution that followed together with steady advances in agricultural mechanisation resulted in remarkable increases in food crop productivity. In recent decades, advances in molecular biology enabled plant transgenesis or the genetic modification (GM) of plant genomes through the introduction of foreign DNA to improve food crop productivity and management. In 2014, 82 per cent of soybeans growing on 111 million hectares and 30 per cent of maize growing on 184 million hectares contained one or more transgenes that provided traits such as resistance to insects or herbicides (James 2014). Worldwide, of the 1.5 billion hectares of arable land, about 12 percent were planted with GM seed in 2012. Nearly all were planted with GM soybeans, maize, cotton, and canola in five countries: the U.S., Brazil, Argentina, Canada, and India (Hoffman and Furcht 2014a).

The complex, costly, and time-intensive regulatory system in the United States discourages public-sector researchers from using molecular methods to improve crops for farmers. Thus transgenic or GM crops have been limited largely to those for which there is a large seed market such as soybeans, maize, and cotton. "Without broader research programmes outside the seed industry," editorialised *Nature*, "developments will continue to be profit-driven, limiting the chance for many of the advances that were promised 30 years ago," among them feeding the planet's growing human population in a sustainable way and reducing agriculture's environmental footprint (Nature 2013; Hoffman and Furcht, 2014a). Transgenic or GM crops have other limitations. Rather than harnessing a plant's native genetic endowment to create desired traits as in selective breeding, GM adds genetic material from another species through recombinant DNA technology. Two decades of scientific study have shown no greater risk posed by genetic modification through recombinant DNA than that posed by other forms of genetic modification (Sanchez 2015). Still, public concerns over the cultivation of crops with foreign DNA, particularly those generated by the introduction of genes from distantly related organisms, have contributed to their limited use (Voytas and Gao 2014; Wolt, Wang and Yang 2015), in the view of some to the benefit of wealthier countries and at the expense of poorer ones. Farmers in poor countries rely almost entirely on food crops that could benefit from GM, not on GM crops for animal feed or industrial use that benefit a handful of farmers in countries like the U.S. (Paarlberg 2014). Yet campaigns to connect biosafety to public concern for the vulnerability of farmers and food with the operations of ag-bio corporate monopolies have been highly successful.

Bridging the Gap Between New Science and Smallholder Farming

Five hundred years ago the Columbian Exchange linked continental ecosystems together, facilitating the global dispersion of animal, plant, microbial and human genes (Crosby 1973). The term "Homogenocene" is sometimes used to describe the ensuing era marked by the homogenisation of biosystems and ecosystems (Samways 1999).Today the genomes of most of the major domesticated animals and plants and infectious disease pathogens in the Columbian Exchange have been fully (or nearly) sequenced (Hoffman

2014). In our Genomic Exchange era, animal, plant and microbial as well as human genetic and regulatory sequences travel around the world over high-speed data networks, a profound and disruptive advance for human and animal health and future food production.

Among the plant foods exchanged between the Old World and the New World were cassava (manioc), which was domesticated in Brazil, and today is a food staple in Africa and Asia, and yams, which are native to Africa and Asia and are widely cultivated there today as well as in Oceania and the Americas. The genomes of cassava and yam have been sequenced (Wang, L. *et al.* 2014; Oli *et al.* 2016). Genomic sequencing provides valuable insights for advancing basic research, gene discovery and genomic selection-assisted breeding to introduce improved traits. Cassava and yams are examples of "orphan crops," that typically are not traded in international markets but that may be vitally important for regional food security. Small-scale farmers or smallholders in developing countries grow many orphan crops, often on marginal land. These crops receive comparatively little attention from crop breeders and research institutions. For that reason, public-sector investment is considered indispensable to orphan crop research given the limited commercial potential of these crops in global markets. As Foley *et al.* (2011) contend, significant opportunities may exist to improve yield, the resilience of cropping systems, and preserving crop diversity by improving orphan crops because by and large they have not been genetically improved (Foley *et al.* 2011).

Private philanthropy has stepped forward and is laying the groundwork for the application of agriculture biotechnology to orphan crops, which number more than 12,000 species. The African Orphan Crops Consortium (AOCC), with financial and materials support from Mars, Inc., the sequencing powerhouse BGI, the sequencing instrument powerhouse Illumina, and a host of private and non-profit partners plans to sequence, assemble and annotate the genomes of 100 traditional African food crops.[8] AOCC's long-term goal is to use the information to develop more productive, nutritious and robust varieties that can better adapt to climate change. To help reach its goal the AOCC will train several hundred plant breeders in genomics and marker-assisted selection for crop improvement. The McKnight Foundation's Collaborative Crop Research Program (CCRP) funds collaborative research between smallholder farmers, encouraging

local researchers, and development practitioners to explore solutions for sustainable, local food systems.[9] Long-term CCRP funding has allowed Ethiopian and Cornell University scientists to develop the resources necessary for tef, a nutritious orphan cereal crop that is vital for feeding some 50 million people in the Horn of Africa, to benefit from the revolution in biotechnology (CALS 2007-2010). Genomic studies of tef currently underway are designed to identify molecular markers and breeding targets for enhanced productivity, climate adaptability, and abiotic stress tolerance, and to gain a better understanding of the proteins that are responsible for the human immune response to gluten (Girma *et al.* 2014; Cannarozzi *et al.* 2014). The Bill and Melinda Gates Foundation helped to fund the Global Seed Vault on the arctic Norwegian archipelago of Svalbard, which includes the genomes of some orphan crops, though a number of species important for tropical countries are not represented (Westengen, Jeppson and Guarino 2013). The International Center for Tropical Agriculture (CIAT) and the Global Crop Diversity Trust are working to remedy the problems; the CIAT genebank stores thousands of varieties of beans, cassava, and tropical forages (CIAT 2016).

Can genomics boost the productivity of orphan crops? The question constitutes the title of correspondence by scientists from India, Mexico, Australia, the U.S., and Italy published in *Nature Biotechnology* (Varshney *et al.* 2012). The authors provide an overview and appraisal of the application of association mapping or genome-wide association studies, marker-assisted recurrent selection, and genomic selection in improving yields of orphan crops in developing countries. They conclude that the impact of genomics-assisted breeding on crop development programmes in these countries remains very limited. A number of steps need to be taken to incorporate genomic science into agricultural practise with respect to orphan crops:

- Train local scientists in modern breeding technologies;
- Improve local infrastructure for accurate and relevant crop plant phenotyping;
- Provide local access to centralisedhigh-throughput genotyping and sequencing; and
- Implement appropriate phenotypic and genotypic data management systems.

Taking these steps would help to realise the potential of converting orphan crops into "genomic resource-rich crops" and could serve to separate these crops from the term "orphan" altogether (Varshney, *et al.* 2012).

Tracking Traits in the Genomic Exchange Era

When the hybrid seed revolution swept across the American Midwest in the 1930s the idea that the code of life could be extracted, read, rewritten, and edited with uncanny accuracy was still many decades away. The best geneticists could do in the laboratory was to bombard life forms with radiation and then select a desirable mutation from the resulting mutational mess. But help was on the way. As corn with hybrid vigor shot up around Ames, Iowa, a physicist – John Vincent Atanasoff at the state college there created the first of what today is an indispensable tool for genetic research all over the world – the electronic digital computer. Life may not be a genetic algorithm, but genetic algorithms and machine learning will have a lot to say about life, ecosystems, natural cycles, and food security in coming decades as the digital world ineluctably expands.

Dramatic advances in biological methods and instrumentation during the second half of the twentieth century owe much to Moore's law. In 1965, Intel's Gordon Moore made a prediction from his careful observation of an emerging trend. Moore postulated that computing would dramatically increase in power, and decrease in relative cost, at an exponential pace. Soon computer hardware and software were put to the task of deciphering the A's, T's, G's, and C's of life code in automated machines. By the turn of the century, computer-driven DNA synthesis and sequencing instruments and amplifiers together with DNA microarrays were standard equipment in basic biological and agricultural research laboratories. The power of Moore's law pushed the life sciences in new directions.

Today biology in many ways resembles an information science based on codes, signals, systems, and networks. Next-generation DNA sequencing (NGS) of whole genomes is considered a key tool for characterising crop plant genomes and connecting plant genetic resources around the world. NGS technology enables high-resolution exploration of the relationship between genotype and phenotype at the whole genome level. It accelerates discovery of genes and quantitative gene loci (QTLs), regions of the

genome encompassing multiple genes that account for a significant part of the variation of a complex phenotypic trait, say a trait for yield, nutrition, seed quality, seed dormancy, plant architecture, root system pattern, pod shattering and seed dispersal pattern, disease resistance, drought or salt tolerance, or high-temperature tolerance. QTLs are typically mapped by a number of methods including linkage analysis and genome-wide association studies. QTL mapping and marker-assisted selection (MAS), which allow gene and QTL pyramiding (stacking) in both inbred and hybrid lines, are key tools for precision plant breeding (Guimarães*et al.*2007). NGS complements these approaches and may in time replace them as the cost of whole genome sequencing declines and capabilities for analysing the vast amounts of resulting genomic data are improved. NGS technologies provide genome-wide marker coverage at a very low cost per data point, enabling practitioners to assess the inheritance of the entire genome with nucleotide-level precision (Varshney, Terauchi and McCouch 2014).

The data-sharing Genomic Exchange era is applying a suite of "omics" technologies – genomics, proteomics, transcriptomics, metabolomics, microbiomics, and others – to food crop science (Benkeblia 2014). Findings are exchanged with scientists, practitioners, and gene banks and seed banks around the world. Data from agricultural research must be widely shared to have maximum impact.[10] In addition, it is critical to connect genomics and agronomic research to individuals and communities engaged in creating new crop varieties, especially locally adapted varieties. In the view of Varshney, Terauchi, and McCouch (2014), this will require a massive reorganisation of the way plant scientists are trained. Training will have to be integrated across the scientific fields of genetics, plant breeding, computer science, mathematics,engineering, biometrics and bioinformatics. Breeding programmes will have to be reorganised and cultivars as well as data will have to be widely shared. New forms of communication will need to be developed so that farmers are well informed about the availability of improved varieties, innovative crop management systems, and market trends.

The value of online information and mobile communications devices in this context cannot be exaggerated (Sylvester 2013). "Enabling smallholder farmers to grow more food and sell it in formal markets for a fair price would change life for almost every poor person in Africa," wrote former

UN Secretary General Kofi Annan and a colleague. "The keys to fixing this problem are supplying smallholders with appropriate seeds and fertiliser, providing education and training, and ensuring easy access to markets and larger economic networks. Mobile technology can help on all these fronts" (Annan and Dryden 2015). Like cassava, yams, tef and other orphan crop plants raised in rural Africa, the mobile phones of smallholders are more likely than ever to be powered by energy from the sun. Solar-powered phone chargers and charging stations are experiencing an entrepreneurial surge across the continent.

Disruptive Tools Make Their Debut

Like all endeavours involving the manipulation of life code, plant agricultural today is poised at a "technological inflection point" (Voytas and Gao 2014). Not since the birth of molecular biology has the power of technology been brought to bear on life so precisely as with genome editing. As "Solutions for a Cultivated Planet" with its action plan for food production in the Anthropocene was being written and published (Foley *et al.* 2011), scientists were investigating and assembling these powerful genomic technologies. They include zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), meganucleases, and the leader among them, the extraordinarily efficient and comparatively easy to use CRISPR/Cas9 nuclease system (Jinek *et al.* 2012). CRISPR/Cas9 has an additional advantage over the others in that it requires only a guide RNA rather than a complex protein assembly to target the nuclease to the gene of interest.

These natural and engineered nucleases allow double-stranded DNA sequences in living cells to be cut and edited precisely, letter by letter. Because the mutation created by genome editing is difficult to distinguish from one that may occur naturally, plus the fact that foreign DNA is generally not incorporated into the DNA of the cell, the US Department of Agriculture (USDA) has thus far waived regulations that apply to genetically modified organisms. Genome editing that involves DNA base and gene insertions and deletions, which are accomplished through the natural DNA repair mechanisms of homologous repair or non-homologous end joining of double-strand DNA breaks, are under USDA review. Regulatory agencies in the U.S., Europe, Canada, and other countries are wrestling with the

question of whether and, if so how, to regulate a set of technologies whose effects on living cells are increasingly indistinguishable from what occurs in traditional crop plant breeding and within plant communities in the natural world (Wolt, Wang and Yang 2015; Huang *et al.* 2016).

Genome editing or genome engineering technologies are set to transform basic biological research and plant breeding. With them it is possible to first determine the DNA sequence changes that are desired in a cultivated variety and then introduce the genetic variation within plant cells precisely and rapidly. The ability to control genetic variation within crop plants precisely and efficiently without the cost and controversy surrounding transgenic or foreign DNA will overturn the way new varieties are generated (Voytas and Gao 2014). "This technology promises to change the pace and course of agricultural research," write Jennifer Doudna and Emmanuelle Charpentier, inventors of the CRISPR/Cas9 genome editing system (Doudna and Charpentier 2014). In experiments they cite, genetic edits made by the system were passed to the next generation of plants without new mutations or off-target editing, leading Doudna and Charpentier to conclude that such findings suggest internal modification of plant genomes to provide protection from disease and resistance to pests "may be much easier than has been the case with other technologies."

Heritable targeted mutations created through genome editing have been demonstrated in a number of food crop plants, among them rice, wheat, maize, barley, sorghum, potato, tomato, and Brassica (Bortesi and Fischer 2015; Wang *et al.* 2015; Lawrenson *et al.* 2015). Sweet orange is the first fruit crop to be genetically edited (Jia and Wong 2014), potentially opening the way for the development of fruit crops with superior characteristics in countries where GM crops are poorly accepted (Kanchiswamy *et al.* 2015). Already genome editing is being used in crop production in the developed world, and this technology can also be used to improve the crops that feed the burgeoning populations of developing countries (Voytas and Gao 2014).

Agri-food systems influence the nutritional quality of foods and the availability of critical nutrients to local populations (Kaput *et al.* 2015). Genome editing could facilitate the generation of food crops with higher levels of bio-available micronutrients that are frequently lacking in the diets of people in the developing world, though some are likely to remain

wary of genetically bio-fortified food crops no matter what technologies are employed (Hefferon 2015). A number of food crops have been experimentally fortified using genetic modification: rice with beta-carotene, iron, and folate; maize with ascorbate; soybean with oleic acid; canola with omega-3 fatty acid; wheat with amylose; and tomato with anthocyanin. Genome editing technologies enable researchers to expand and accelerate these advances without incorporating DNA or protein from other species in the final product (Chen and Lin 2013) while eliminating detectable off-target mutations (Kleinstiver *et al.* 2016), both of which can be verified through whole genome sequencing.

Such unprecedented control over gene sequences, activation, and expression also opens the door for the development of future crops that can better withstand pests, stress, flooding, drought, higher temperatures, and that are able to grow on marginal lands. Crop plants with such traits could be created in some cases by "knocking out"(deleting) just a few nucleotides of the billions their chromosomes carry or "knocking in" (inserting) sequences that amplify certain traits. Genome editing makes it much easier to create crop plant gene knockouts, which are key to revealing gene functionand crop plant phenotype as well as potentially controlling the loci involved in complex traits. The generation of targeted, heritable gene knockouts with nucleases like ZFNs, TALENS, CRISPR/Casand superior systems almost certain to follow will greatly facilitate genetic analysis of orphan crop species as well as crops that trade in international markets (Voytas and Gao 2014). Orphan species have lagged behind in genetic research (consistent with their "orphan" designation) due in part to the complexity and cost of creating knockout individuals for study. Together with NGS genomics and other exponentially efficient technologies, genome editing may well hasten the retirement of the term "orphan crop" if allowed to do so.

Biosynthesis and Photosynthesis for the Human Age

Genome editing is the most spectacular tool in the toolbox of the emerging field of synthetic biology, a nascent discipline founded around the turn of the millennium. Synthetic biology is based on the idea that purposeful design and engineering can be employed to study cellular systems and re-create them using biological component parts to achieve improved function (Carlson 2011; Hoffman and Furcht 2014a). In brief, synthetic biology

joins science and engineering to design and construct new biological parts, devices, and systems. Artificial biosystems are modeled, constructed, and iteratively tested until their performance is optimised. Unlike the "top down" reductionist approach that characterises molecular biology, pioneers of the synthetic biology envisioned "bottom up" approach that, in some manifestations, has a lot in common with the computer hacking culture.

Although they are the most important source of the primary metabolites that feed the world and their biology is relatively well understood, plants are just beginning to draw the interest of synthetic biologists (Baltes and Voytas 2015). New biological systems involving plant cells, plant physiology and reproduction, and ecology are now in their sights. Plants use the readily available nutrients, carbon dioxide and sunlight to generate an annual photosynthetic biomass production estimated to be on the order of 2o0 billion tonnes (Baltes and Voytas 2015). Engineered plant-based biosystems hold the potential not only to improve food crop productivity and reduce crop losses but also, on a larger scale, to alter photosynthesis and natural cycles in ways that benefit ecosystems and the environment. Two such projects are well underway: the effort to equip rice, which uses C3 photosynthesis, with much more efficient C4 photosynthesis found in maize, thus increasing rice biomass and reducing its water and land area needs; and the effort to equip cereal crops with nitrogen fixation capability. If cereals like rice, wheat, and maize could have the nitrogen fixation capability of soybean and other legumes, it would relieve the enormous environmental burden of nitrogen-based fertilisers, help restore the natural balance in the nitrogen cycle, and alleviate nitrogen's contribution to greenhouse gas emissions and climate change.

In their perspective "Redesigning photosynthesis to sustainably meet global food and bioenergy demand," an international team of 25 plant scientists assert that increasing the efficiency and productivity of photosynthesis in crop plants is key to meeting future food demand (Ort *et al.* 2015). Photosynthesis functions far below its biological potential, limiting crop yields. The investigators propose several targets: increasing the ability of plants to capture light and convert light energy more efficiently; increasing the ability of plants to capture and convert carbon to plant biomass; and engineering a "smart canopy" that would enable plants that interact cooperatively to maximise the potential for light harvesting and biomass production per unit of land area.

Although C4 plants comprise less than 4 per cent of global terrestrial plant species, they contribute approximately 20 per cent to global primary productivity (Ehleringer, Cerling and Helliker 1997), a profound agricultural, ecological, and atmospheric advantage. The main obstacle to reengineering C3 to C4 photosynthesis is the carboxylation enzyme RuBisCO (ribulose-1, 5-bisphosphate carboxylase/oxygenase), the planet's most abundant protein responsible for fixing nearly all the carbon in the biosphere. But evolution has structured RuBisCO to be a relatively slow-acting enzyme, limiting the ability of plant leaves to absorb direct midday sunlight. Attempts to bolster RuBisCO through protein engineering have fallen short owing to the complexity of the molecule. Alternative strategies for increasing photosynthetic efficiency based on synthetic biology and genome engineering are now feasible. Many of the key components of RuBisCO and the photosynthetic electron transport chain are encoded in the plastid genome, which can now be engineered precisely (Bock 2014). Proof-of-concept evidence exists for how targeted alterations of the nuclear and chloroplast genomes could be made, how they would serve to redesign regulatory circuits, and how these changes would scale to a whole canopy (Ort *et al.* 2015).

The leading project for reengineering photosynthesis is the international effort to transform C3 photosynthesis in rice into much more efficient C4 photosynthesis. Investigators at the International Rice Research Institute (IRRI) in the Philippines are identifying genes associated with C4 photosynthesis and related traits. They are using the CRISPR/Cas system to knock out and knock in genes to validate their function (NCBP 2015). Genome engineering and synthetic biology equip researchers with the tools to model and control DNA from the *in silico* design and *in vitro* synthesis of standardised genetic elements to the *in vivo* manipulation of host DNA and gene expression (Baltes and Voytas 2015). Establishing a C4photosynthesis pathway in rice will require not only the insertion and activation of genes and promoters critical for C4 conversion and suppression of genes that inhibit the process but the fine tuning of gene expression to optimise protein levels in keymetabolic pathways. Analysis of transcriptomic and metabolic data from rice and maize leaves is revealing molecular components of the anatomical innovations associated with C4 photosynthesis, providing a rational systems approach to the engineering of C4 photosynthesis in rice (Wang, W. *et al.* 2014).

Another ambitious international project is also aimed at improving upon evolution, not by energising a sluggish enzyme but by outfitting certain plants that lack the ability to fix atmospheric nitrogen, namely rice, wheat, and maize which together provide 60 per cent of the world's food energy intake. Besides ameliorating the environmental damage done by the large-scale production and use of nitrogen fertilisers, even a small increase in available nitrogen through engineered fixation would be beneficial for many smallholder farmers in the developing world who have limited access to nitrogen fertilisers and tend to grow crops in low nutrient conditions (Oldroyd and Dixon 2014). Two approaches are being pursued. A number of plant species including legumes depend on bacteria such as rhizobia to convert atmospheric nitrogen into compounds that plants can use to make their essential proteins. Rhizobia produce signalling molecules called nodulation (Nod) factors during the initiation of nodules on the root of legumes. A mutually beneficial relationship or symbiosis is formed when legumes take up the bacteria. The challenge is to transfer the Nod factor signalling pathway from legumes to cereals (Oldroyd and Dixon 2014; Lau *et al.* 2014; Baltes and Voytas 2015). Signalling pathways downstream of a bacterial disease-resistance receptor that were transferred from *Arabidopsis*to wheatwere functional in responding to target bacterial pathogens (Schoonbeek *et al.* 2015), suggesting that signalling pathways are conserved across distant plant phyla and can be transferred. Alternatively, rice already possesses a mycorrhizal symbiosis signalling pathway. Because this pathway has many parallels to the rhizobial signalling pathway important in nodulation, it may be possible to engineer it to perform rhizobium Nod factor signalling in rice and possibly other cereals (Sun *et al.* 2015).

A second approach to engineering nitrogen fixation relies on the fact that some bacteria carry out their own version of the Haber-Bosch industrial process for producing ammonia from nitrogen and hydrogen. They use the enzyme nitrogenase to reduce atmospheric N_2 into NH_3, a more bio-available form. By expressing nitrogenase, plants would be able to fix their own nitrogen, a more direct approach to nitrogen fixation than that by Nod factor signalling pathway transfer. The challenge is to transfer the nitrogenase enzyme from nitrogen-fixing bacteria to plant cells (Oldroyd and Dixon 2014; Lau *et al.* 2014; Baltes and Voytas 2015). Numerous nitrogenase fixation (*nif*) genes would need to be transferred into a host plant and then

properly regulated for this approach to work. Using sequence-specific gene editing nucleases, these genetic elements together with their desired regulatory elements could be integrated into "safe harbor" loci within plant genomes. Or they could be integrated downstream of endogenous cereal promoters that have the desired expression characteristics (Baltes and Voytas 2015). Both Nod factor signalling transfer and *nif* genes transfer to cereals will require microbial and plant metabolic systems analysis and engineering to be optimised (Lau *et al.* 2014). Even a limited crop plant capability to fix nitrogen would be beneficial, especially for smallholder farmers in the developing world (Oldroyd and Dixon 2014).

Conclusion: A Symbiosis for the Anthropocene

Photosynthesis and nitrogen-fixation engineering are arguably the boldest molecular endeavours ever undertaken by plant scientists, with potentially the greatest consequences for food crop productivity, environmental remediation, and land, soil, and water conservation. Rice and wheat, which together feed 40 per cent of humanity, would yield an estimated 50 per cent more using less water and nitrogen if they were successfully reprogrammed with C4 pathway photosynthesis. This would enable them to fix carbon as efficiently as the C4 crop maize, the most important cereal crop in the world measured by annual metric tonnes of production (1 billion tonnes in 2013 compared to 740 million tonnes of rice and 711 million tonnes of wheat, FAOSTAT, 2016). Other C4 crops such as sorghum and millet can tolerate hotter, drier regional conditions, which are expected to become more prevalent as the planet warms. C3 crops like rice, wheat, barley, rye, and oat are generally more sensitive to heat and drought. More than three billion people worldwide depend on rice as a dietary staple; wheat is the most widely grown crop in the world and the second most important crop after rice in the developing world. Equipping these crops with the productive efficiency even approaching that of maize would be a global game-changer for food production and ecosystems health.

Cereal crops that are capable of meeting their own nitrogen needs in whole or part could significantly reduce the application and environmental impact of inorganic fertilisers. Nitrogen fertiliser application surplus and post-harvest loss also need to be brought into balance for cereal crops (Mueller *et al.* 2014). Both strategies – engineered nitrogen fixation and

nitrogen fertiliser conservation enabled by information technology –should be harnessed to reduce the amount of new reactive nitrogen in the biosphere by as much as 75 percent to maintain a safe planetary boundary (Rockström *et al.* 2009). Many of the nearly 200 signatories of the 2015 United Nations Framework Convention on Climate Change (UNFCCC) Paris agreement (COP21) include nitrous oxide emissions reduction in their Intended National Determined Contributions (INDCs) to mitigate greenhouse gas emissions (UNFCCC 2015b). Agriculture is responsible for an estimated two-thirds of anthropogenic nitrous oxide emissions, which are projected to double by 2050 under a business-as-usual scenario (Davidson and Kanter 2014). Only China has specifically committed "[t]o develop technologies on biological nitrogen fixation" (China's INDC 2015). China's use of nitrogen fertilisers has surged, making agriculture the country's leading industrial polluter and persuading its leadership to accept agricultural biotechnology as a means of ameliorating the problem despite public misgivings (Hoffman and Furcht 2014b).

As Earth warms perhaps 2 degrees Celsius by 2050 compared to pre-industrial temperatures, yields of cereal crops and other food staples are projected to stagnate exactly when they need to be growing to feed an expanding human population. That is why population biologist Paul Ehrlich and ecologist John Harte contend that to feed the world in 2050"will require a global revolution" (Ehrlich and Harte, 2015). Humanity now faces severe biophysical constraints on food production. Arguments about "insufficient food" versus "inequitably distributed food," hamper efforts to achieve sustainable food security. They doubt that technological fixes will address the likely threat to future food supplies – climate disruption and call for "a revolutionary change in human society."

If technological advances can indeed make a major contribution to sustainable food production in the Anthropocene, it will be in part because of advances in mapping, sequencing, and editing the code of life. It will be because early life forms have evolved intricate and efficient tools of self-protection that humans can now access and implement to enhance food crop biomass, yield, nutrition, resistance to pests and drought, and a crop plant's ability to thrive when grown in higher temperatures and on marginal and saline soils. It will be because landrace seeds stored in gene banks harbour valuable genes for climate adaptation, genes that can inform and guide the

development of climate adaptive and genetically diverse crop varieties. It will be because seemingly intractable challenges like engineering C4 photosynthesis and nitrogen fixation are within reach as the new genomic, molecular synthesis, and modeling tools are now available. And perhaps most important, if technological advances can make a major contribution to meeting sustainable food production by 2050, it will be because both the knowledge and the tools to make it possible are widely disseminated around the world.

The new agricultural biotechnologies have little recourse but to become more transparent and democratically available than those that preceded them. The initial large-scale application of molecular biology to agriculture has been tightly controlled by large corporations, limiting access by entrepreneurs and farmers alike and serving to fuel the potent anti-GMO movement. Agricultural biotechnology's first decades have hampered regulatory approval of grains, legumes, vegetables, and fruits with superior traits but smaller markets than maize, wheat, rice, and soybean. Regulatory and intellectual property regimes, both of which are under scrutiny, will be obligated to take into account the rise of the sharing economy as biology evolves as an information science – a realm of massive data, open-source software, facile genome editing, and incipient biohacking as well as proprietary biomolecular products and methods.

In the era of "trading carbon for food," familiar ways of perceiving problems and how to solve them no longer suffice. No economic sector is more susceptible to changes in climate patterns than agriculture because no other economic sector depends so much on the biophysical environment. To meet the requirements of expanded food production in concert with shrinking agriculture's environmental footprint, federal regulatory frameworks like the Coordinated Framework for the Regulation of Biotechnology, now under review in the U.S., need to be structured within larger frameworks, encompassing the planet and its boundaries for safe operating space. The UNFCCC Paris agreement recognises "the fundamental priority of safeguarding food security and ending hunger, and the particular vulnerabilities of food production systems to the adverse impacts of climate change" (UNFCCC 2015a). The practise of "climate-smart agriculture" through increased efficiencies, adaptation, and mitigation in the food-producing sector figures in the strategies of many countries to

meet their INDC targets to reduce their greenhouse gas emissions.[11]

The "global revolution to feed the world" must occur in accordance with the global revolution to reduce environmental degradation. This monumental challenge cannot be met without deeper understanding of the interplay between natural ecosystems and food production. The chances that it will be met are diminished without due attention to ecosystem services that regenerate soil, purify water, and regulate climate through carbon storage in woody biomass, forest floor litter, grassland root systems, sediments and soils. The chances this challenge will be met are also diminished without making appropriate use of advanced technologies including in food plant genetics and bioengineering.

Healthy ecosystems, climate-smart agriculture, and innovative food crop bioscience in the hands of practitioners in fields, orchards, greenhouses, and gardens, constitute asymbiosis for the Anthropocene. We may imagine that in 2050 the planet will be powered largely by renewable energy and will also be capable of feeding its human inhabitants, half of them living in the tropics. What we can imagine is more important than what we know right now. Imagination is more important than knowledge, as Albert Einstein saw it. Knowledge is limited. Imagination, like a membrane with vast potential awaiting an impulse, envelops the earth.

Endnotes

1 For a description of geological evidence of human-induced environmental change to help define the Anthropocene as a potential geological time unit, see Waters *et al.* 2014 and Waters *et al.* (2016). See also the website for the Working Group on the 'Anthropocene' of the Subcommission on Quarternary Stratigraphy at http://quaternary.stratigraphy.org/workinggroups/anthropocene/.

2 The writings of Nobel economist Robert W. Solow represent perhaps one the most illuminating treatments of natural resource and environmental sustainability from the standpoint of mainstream macroeconomics and economic growth. In his lecture "The Economics of Resources or the Resources of Economics" (Solow 1974), Solow emphasises that the fundamental principle of the economics of exhaustible resources is "a condition of competitive equilibrium in the sequence of futures markets for deliveries of the natural resource," a sequence that "extends to infinity." The resource-exhaustion problem must depend on two aspects of technology: first, the likelihood of technical progress, especially progress that saves natural resources, and second, the ease with which other factors of production, labour and capital in particular, can be substituted for natural resources in production. Technical progress and substitutability will offset natural resource depletion. In his paper "Sustainability: An Economist's Perspective" (Solow 1993), Solow considers sustainability (in his view a "vague

concept") as "a matter of distributional equity between the present and the future" and therefore a problem about saving and investment, "a choice between current consumption and providing for the future." It would help if governments made "a comprehensive accounting of rents on non-renewable resources." A scarcity rent isthe marginal opportunity cost imposed on future generations by extracting one more unit of a resource today. Solow's comment that entropy law "is of no immediate practical importance for modeling what is, after all, a brief instant of time in a small corner of the universe" (Solow 1997) is from a collection of articles written as a tribute to the pioneering ecological economist Nicholas Georgescu-Roegen, author of *The Entropy Law and the Economic Process* (Mayumi and Gowdy 1999). Georgescu-Roegen and his successors contend that entropy law is increasingly coming into play with human population growth and the resulting "Great Acceleration" of environmental and biophysical consequences (see for example, Brown *et al.* 2011; Barnosky *et al.* 2012). Much of the debate turns on whether energy is just an input like other [economic] inputs (Krugman 2014) or whether standard economic equilibrium conditions fail to account adequately for the thermodynamic constraints of energy conversion (Kümmel and Lindenberger 2014). Energy production and consumption at present scale endanger critical complex ecosystem services whose substitutability by technical advances may not be feasible, a factor Solow does not take into account in his analysis (Sá Earp and Romeiro 2015).

[3] The costs of environmental management, decline and degradation should be taken into account in measuring national wealth. In 2012, the UN University's International Human Dimensions Programme on Global Environmental Change (UNU-IHDP) and the UN Environment Programme (UNEP) jointly launched the Inclusive Wealth Index (IWI), a sustainability index that goes beyond traditional economic and development indices such as gross domestic product (GDP). Economic growth should mean growth in wealth, which is the social worth of economy's entire stock of capital assets including the typically underestimated value of natural capital embodied in natural resources and ecosystem goods and services (Dasgupta 2014). Two IWI reports have been issued (UNU-IHDP and UNEP 2012; UNU-IHDP and UNEP 2014). The 2014 IWI report, which covers 140 countries from 1990 to 2010, describes its goal as an effort to cement the role of the IWI as "the leading comprehensive indicator for measuring nations' progress on building and maintaining inclusive wealth – a central pillar of the sustainability agenda – and gauging global sustainability as part of the post-2015 development agenda as outlined in the [UN's] Sustainable Development Goals."

[4] In 2014 Judge R. Brook Jackson of the U.S. District Court for the District of Colorado faulted federal agencies for failing to calculate the social cost of greenhouse gas (GHG) emissions on the basis that such a calculation was not feasible (*High Country Conservation Advocates v. U.S. Forest Service* 2014). High Country is the first case to set aside an agency's decision for its failure to consider appropriately its effect on climate. Jackson ruled that it was arbitrary and capricious for agencies to proclaim the benefits of mineral leasing that involved expansion of coal mining exploration on federal land while ignoring the costs, which in his view could be calculated using the federal government's social costs of carbon (SCS) protocol (see Executive Order 12866, 2010). The White House Council on Environmental Quality (CEQ), which coordinates federal environmental efforts, regards the SCS estimate as a tool to monetize costs and benefits and that available quantitative GHG estimation tools should help guide federal

agency analysis and decisions (CEQ 2014; Ore 2013).

5 Stateofthetropics.org

6 Burney, Davis and Lobell (2010) suggest that the climatic impacts of historical agricultural intensification were preferable to those of a system with lower inputs that instead expanded cropland to meet global food demand and that "enhancing crop yields is not incompatible with a reduction of agricultural inputs in many circumstances." They acknowledge that yield gains alone do not necessarily preclude expansion of cropland and that agricultural intensification must be coupled with conservation and development efforts. Phelps *et al.* (2013) argue that agricultural intensification, which has become central to Reducing Emissions from Deforestation and forest Degradation (REDD+) policies across the tropics, actually escalates future conservation costs and may serve to accelerate deforestation in tropical regions. The UNFCC Paris Agreement (UNFCCC, 2015a) "[r]ecognises the importance of adequate and predictable financial resources, including for results-based payments, as appropriate, for the implementation of policy approaches and positive incentives for reducing emissions from deforestation and forest degradation, and the role of conservation, sustainable management of forests and enhancement of forest carbon stocks…." [I. Adoption, no. 55] The agreement also calls for "[i]ncreasing the ability to adapt to the adverse impacts of climate change and foster climate resilience and low greenhouse gas emissions development, in a manner that does not threaten food production…." [ANNEX, Article 2: 1b]

7. The 2012 drought in the American Midwest was the most severe and extensive drought in at least the previous quarter century, affecting three-quarters of U.S. maize and soybean production and reducing maize yields 13 per cent to 1995 levels (USDA 2012; USDA 2013). The drought was estimated to have cost the U.S. economy between $20-$77 billion (Munich Re = $20 billion, Aon Benfield = $35 billion, Morgan Stanley = $50 billion, Purdue economist = $77), which would rank it among the costliest natural disasters in U.S. history (Svoboda 2013; Keen 2012; Larsen 2015). Crop indemnities alone were estimated to be $20 billion (Svoboda 2013). Although natural climate fluctuations are thought to be primarily responsible for the 2012 drought (Mallya *et al.*2013), anthropogenic warming tends to exacerbate these natural variations (Williams, A. P. *et al*. 2015) and may reduce average annual maize yields 15 per cent in the U.S. by 2050 (Burke and Emerick 2016). Globally, drought reduced maize, rice, wheat production an estimated 9-10 percent during the period 1964-2007, with developed countries experiencing disproportionate damage (Lesk, Rowhani and Ramankutty 2016).

8 Africanorphancrops.org

9 CCRP.org

10 See, for example, DivSeek at Divseek.org and the GODAN Initiative at Godan.info

11 See McArthur (2015) and the UNFCCC's Intended Nationally Determined Contributions (INDC) database at http://unfccc.int/focus/indc_portal/items/8766.php. Emissions reductions for agriculture are not specified for large advanced producers like Australia, Canada, and the United States. In contrast, the European Union does specify areas within agriculture for emissions reduction, though how those emissions will be measured is not clear. India, which produces the world's second-largest volume of agricultural emissions, after China, is alone with China in proposing agricultural biotechnology as a tool to achieve its emission reduction goals. Its National Mission on Sustainable Agriculture strategy aims at enhancing food security and protection of resources including biodiversity and genetic resources. The mission "focuses on

new technologies and practices in cultivation, genotypes of crops that have enhanced CO_2 fixation potential, which are less water consuming and more climate resilient."In the private sector, large seed companies are beginning to respond to the international consensus. Monsanto announced its commitment to a carbon-neutral footprint across its operations by 2021 (Salter 2015).

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Attitudes towards Governance of Gene Editing

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Abstract: Gene editing technologies are revolutionising plant biotechnology. They allow for the rapid editing of multiple genes with either mutational, cisgenic, or transgenic approaches. They are also challenging regulations in several countries, as definitions and processes are based upon first generation methods for genetic engineering. In this paper, we describe results from a U.S. study investigating the attitudes of subject matter experts (SMEs) towards the governance of genome editing. We find some areas where SMEs seem to agree, including the need for pre-market oversight and stakeholder engagement. However, the SMEs had different visions as to the novelty of the technology, primary issues of concern, hopes for the technology, and what specifically should be done in a regulatory context. Key narratives arose including the view that gene editing provides an new opportunity to rethink the oversight of agricultural biotechnology to improve existing systems (adapter view), that gene editing although revolutionary should undergo less regulation than 1st generation biotechnology (technohype-hyporeg view), and that gene editing makes the engineering process so easy that risk analysis and the regulatory system might not be able to accommodate the speed of development and thus greater caution is warranted (systems view). Current policy debates are revealing these differing perspectives,and formal decisions about how to govern this next generation of agricultural biotechnology are pending.

Keywords: Biotechnology, Gene Editing, Regulation, Oversight, Governance

Introduction

Recently the field of biotechnology has been revolutionised with the introduction of promising new technologies, which can be collectively

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called "gene editing". Unlike traditional genetic engineering technologies, which introduced changes in genomes randomly, these new methods allow scientists to modify DNA sequences at precise locations. These techniques include the use of protein-nucelotide complexes, such as engineered zinc-finger nucleases (ZFN), meganucleases, transcription activator–like effector nucleases (TALENs), or more recently CRISPR-Cas 9, to create DNA double-stranded breaks at specific genomic locations and mutate, replace, or add new genes at those locations (Gao *et al.* 2010; Shukla *et al.* 2009; Townsend *et al.* 2009; Bogdanove and Voytas 2011; Pennisi 2012; Wang and Church 2011; Esvelt and Wang 2013). After cutting the DNA with these site-directed nucleases (SDN), genetic engineers can make the cell to mutate itself with small point changes to the gene (SDN-1), can provide a template to make larger insertions or deletions to the gene sequence (SDN-2), or provide a template for insertion of a different gene altogether, perhaps even from a distant species (SDN-3).

These new technologies are changing biotechnology by making the engineering process for plants and animals easier and allowing multiple site-directed modifications to organisms in a short period of time (Porteus 2009; Bogdanove and Voytas 2011; Esvelt and Wang 2013). Recently, the CRISPR-Cas9 system was used to edit 62 genes in order to make pig organs free of viruses for human transplantation (Yang *et al.* 2015). Gene editing is revolutionising our abilities to manipulate living organisms and represent a transition between old recombinant DNA (rDNA) genetic engineering and synthetic biology.

Gene-editing is also posing significant oversight challenges. While the technologies are speeding up, formal oversight for products of gene editing seems to be lagging behind (Kuzma and Kokotovich 2011; Waltz 2012). Several gene-edited product developers are arguing for relaxed authorities especially for crops that are edited to result in point mutations (SDN-1). Scientifically, some argue that cisgenic gene-edited plants should be considered to be like chemically mutagenised varieties and should not be subjected to regulations developed for first generation genetic engineering (Schouten *et al.* 2006), while others disagree (Russell and Sparrow 2008). Recently, international discussions have focused on which SDN categories fall under regulatory definitions and systems across different national oversight regimes (Wolt *et al.* 2015).

In the United States, gene-edited plants are falling outside existing regulatory systems that used to govern genetically engineered organisms (GEOs) (Lusser and Davies 2013). For example, the US Department of Agriculture (USDA) has regulated the first-generation of GE crops as "plant pests" under the Federal Plant Pest Act of 1957 (PPA) (which was consolidated into the Plant Protection Act of 2000), as directed by the US Coordinated Framework for the Regulation of Biotechnology (CFRB) (OSTP 1986). In the beginning of crop engineering, the vast majority of GE crops were made with DNA sequences from plant-pests, like Cauliflower Mosaic Virus and Agrobacterium, which were inserted along with the desired genes as part of the engineering process in order to get the foreign DNA inserted and expressed into the host genome. Regulations under the PPA (USDA 1987, 1997) state that a plant should be regulated if it is engineered using rDNA from a listed "plant pest" organism or if the USDA Animal Plant Health Inspective Service (USDA-APHIS) administrator has reason to believe the resulting genetically engineered plant is a plant pest. USDA's initial policy under the CFRB was to capture all GE crops under the PPA regardless of the engineering process (NRC 2000, 2002).

However, recently the USDA has excluded several gene-edited plants from regulatory scrutiny claiming that they do not contain plant-pest sequences and do not pose a plant pest risk (USDA 2011; Waltz 2012). For example, a ZFN-modified corn designed to have lower phytate content and produced by Dow Agrosciences will not be regulated by the USDA. The USDA stated that "no plant pest was used to create the ZFN-12 maize plants, which contain deletions at the IPKI gene. There is no reason to believe that Zea mays containing an IPKI deletion is a plant pest or is likely to pose a plant pest risk. Therefore, the ZFN-12 maize plants with induced deletions due to the use of zinc finger nuclease technology are not considered regulated article" (USDA 2011). In this case, the USDA-APHIS administrator chose not to exert authority to regulate under a broad conception of potential plant-pest risk. As a result, these plants will be allowed onto the market without the pre-market field review typically given to GE plants.

Basic understandings of what gene editing is, of its likely future, and how it should be governed are still being established. As such, in this study we interviewed people involved in biotechnology, gene editing research, and biotechnology policy to ask questions about their conceptions of gene editing technology and governance. In a previous article, we summarised attitudes

towards plant gene-editing governance into three general, theoretical views: optimistic, pragmatic, and critical depending on how they would like to change or adjust the regulatory system (Kokotovich and Kuzma 2014), but we did not detail or quantify specific concerns about and hopes for gene-editing raised by the interviewees. In this paper, we extend our analysis to include the following questions: Do gene editing technologies evoke the similar or different concerns from the precursor technology? How does our current governance response compared to different stakeholder understandings of the technology, its implications, and governance? What are the similar or conflicting desires for governance among stakeholders? and How can these understandings inform the design, development, and implementation of governance systems?

Methods

The data for the project was collected with qualitative interviews and online surveys. The goal of the interviews was to determine the various views that subject matter experts (SMEs) hold about the gene editing technology and its regulation as compared to traditional biotechnology. Specifically, the questions assessed SMEs' views about: (1) the extent to which and ways in which gene editing is different or similar to traditional biotechnology from a technical, environmental, and societal points of view; (2) the benefits of gene editing as compared to the benefits of traditional biotechnology; (3) the concerns and issuessurrounding gene editingin comparison with traditional biotechnology; and (4) the extent to which the perceived strengths, benefits, and limitations of the existing regulatory system for biotechnology apply to gene editing. In addition to that, a set of demographic questions was asked at the end to determine the SMEs' affiliation, specialisation, educational background and experience with targeted genetic modification.

The target population for the interviews included academe- and industry-based SMEs in biotechnology and gene editing technology, representatives of regulatory agencies overseeing biotechnology, of NGOs and consumer groups concerned with the health and environmental effects of biotechnology, as well as members of academe specialising in biotechnology policy and science and technology studies. A database of potential interviewees was generated from the lists of attendees of conferences on biotechnology and gene editing, from the bibliographic information in publications and policy reports on the technology, as well as from the contacts of the authors and of a faculty member specializing in gene editing at the University of Minnesota.

Thirty-one SMEs from the United States were recruited for the interviews. Disciplinary expertise and potential bias were considered to balance the group. Out of these 31 respondents, 28 participated in the online surveys. 65 per cent of participants were affiliated with academia, 16% with the government, 3 interviewees represented NGOs, 2 interviewees came from the industry. The interviewees' expertise represented a broad spectrum of disciplines, including policy studies, molecular biology, plant science, agronomy, ecology, law, philosophy, social science, business, and history.

Prior to the interviews, given the diverse background of the participants, some of whom had experience only in traditional biotechnology and not necessarily in gene editing,the participants were supplied with an article that provided an overview of the technical aspects of one method of gene editing. This was intended to help facilitate the discussion. Interviewees were also provided a document that outlined the definition of gene editing we used (based on Figure 1 from Kuzma and Kokotovich 2011).

The data collected during the interviews was analysed using thematic coding and code frequency counting. Two coders implemented the analysis using NVIVO and Atlas Ti. Coding was implemented by themes within each question. Interviewers were classified by affiliation, specialisation, and experience with gene editing; and frequency counts were implemented for individual themes and for various types of interviewees by theme.

As a follow-up to the interview, the interviewees were invited to complete an online survey. The goal of the survey was to obtain a more detailed understanding of the SMEs' opinions about the desired features of gene-editing regulation, as well as of the variation in the views in terms ofgene-editing's risk and benefits, and goals of regulation that serve as a basis for particular views on the future of gene-editing oversight.

Results

Technology Views

When assessing the views of SMEs on technology our main goal was to reveal the extent to which SMEs view gene editing as revolutionary or

incremental, as well as to determine which aspects of the technology are viewed by SMEs as revolutionary. The participants were asked in what ways they view gene-editing technology to be the same as or different from the first generation biotechnology. As a result of this analysis we identified different views on gene editing technology, which are described below.

Some SMEs viewed gene editing as being very different from first generation biotechnology. The main distinctive feature that made gene editing revolutionary, in their view, is the ability of the technology to provide greater control and precision of integration site in the genome (23 references by 19 SMEs). As a result of greater precision, gene editing has several other important features:(a) greater technological and cost effectiveness (19 references by 14 SMEs), (b) fewer off-target effects (15 references by 12 SMEs), and (c) better predictive ability concerning what an organism will do (6 references by 6 SMEs). Table 1 summarises the expert views on similarities between the technologies and provides some illustrative quotations.

Some SMEs were very skeptical about the revolutionary nature of gene editing when it comes to precision and risk. They believed that gene editing does not really have greater precision compared with conventional biotechnology (4 references by 3 individuals). They also thought that, since there is no real increase in precision, (a) off-target effects still occur (17 references by 12 individuals) and (b) generated traits are the same in gene editing as in conventional biotechnology (5 references by 4 individuals). Table 2 provides sample quotations demonstrating expert views on differences between technologies.

The third group of SMEs thought that the importance of precision is over-estimated and that it does not really matter. They argued that the erroneous perception of the qualitative difference between the technologies can be explained by some technical misconceptions. First, some confusion is caused by the faulty assumption of the one-to-one correspondence between a trait and DNA (5 references by 4 individuals). Second, the overly-optimistic view of gene editing fails to account for evolution of traits and DNA (4 references by 4 individuals) and for the contextual effects (4 references by 3 individuals). Table 3 contains quotes that demonstrate expert views on the technical misconceptions.

Table 1: Expert Opinions about Technical Differences between Gene Editing and First Generation Biotechnology

Technical difference between technologies	Number of references	Number of quoting individuals	Example of a quotation
Greater control and precision of integration site in the genome	23	19	In traditional trans genesis it's a lot more of a shot in the dark; when you're trying to introduce a gene you have no control over where a gene may be inserted, how many copies, so on and so forth. And with targeted approaches the idea is to introduce it at a specific location in the genome and then perhaps in some of these other instances that you've highlighted here, it could be further besides introducing DNA to modifying DNA or replacing DNA and so the targeted versions are more precise and controlled.
Greater technological and cost effectiveness	19	14	I'd really be interested to see how the whole process will change based on this idea of being able to reproducibly insert into a single location to make the whole process more efficient and specific. It drives the cost down tremendously and at a certain point, if these things come to be, that you have reduced regulatory processes results, reduced cost from that perspective, you have screen a fewer number of plants.
Fewer off-target effects	15	12	Well certainly the immediate thing that comes to mind is that the more targeted you can be when you make a modification of any kind better from previous, from the point of view of, number one, you know decreasing the likelihood that something unintended is going to occur. That is probably the most important thing
Better prediction of what an organism will do	6	6	The technique is really very powerful and the advantage of that is because you are doing everything at the original locus, you don't have the problem of expression, so a lot of transgenes, if introduced in a normal GMO way, they are just fused to a plant promoter, and they integrate randomly in the genome and you can never be sure whether the expression pattern which you then get of that transgene actually reflects the original expression pattern of the gene.

Table 2: Expert Opinions about Similarities of Gene Editing and Conventional biotechnology

Technical similarity between technologies	Number of references	Number of quoting individuals	Example of a quotation
Off-target effects still occur	17	12	There's still the potential for a lot of unintended effects that people are concerned withthat are in - besides the insertion effects. I think people have concerns also about pleiotropic effects and epistatic effects and gene interactions that, you know, if you're putting something new in there, how is it going to interact with the genes that are already there or how might it affect other phenotypes in the plant besides the one that it's intended to affect.
Generated traits are the same	5	4	The targeting technology is not really involved in trait production. You got to have the trait first. So you got to know what you want to do. The targeting technology just enables you to get it done. So at the end of the day, you've made the same product that you were going to make anyway, but you've made it, certainly at least in terms of the overall qualities of the plant, you've just made it more efficiently and potentially made it a little bit better in the sense that you don't have quite as much baggage that you had to stick into the genome to get it made.
Precision is not really greater	4	3	There is a perceived difference between this targeted genetic modification that would allow people to place a piece of DNA in at least one predetermined location in the genome and conventional biotechology. Depending on how it works it could mean a big difference if we assume that you get a single insertion. But I don't think that is a given. The fact that you can get an insertion in the place that you wanted doesn't mean that other insertions do not happen, or that you cannot have fragmentation and re-assemblage. In which case, the transformation in my mind is really equivalent.

The total number of references to characteristics of gene editing, which were viewed as different from conventional biotechnology was 63, compared with 26 references to similarities, which implies that the dominant view is that the new technology is revolutionary. We also found differing opinions about the complexities of the gene editing at the genetic level among SMEs.

Table 3. Expert Opinion about Technical Misconceptions that lead to perception of Difference

Technical misconceptions that lead to perception of difference	Number of references	Number of quoting individuals	Example of a quotation
Both technologies are based on the faulty assumption of one-to-one correspondence between a trait and DNA	5	4	Normally people talk about these things as if a piece of DNA was always unequivocally and unavoidably related to one specific function, a trait ….And the way to establish whether that particular insertion of a piece of DNA in a given genomic context is active or not is by measuring the expression of that one trait. And that has always been a very serious failure of concept in the whole transgenic modification, because a piece of DNA … might be related to a whole bunch of other things that because we are not looking for them, nobody is actually detecting it. So when people are saying this piece of DNA is inactive, they might well be right that it is inactive in regards to the trait that they're talking about, but it could be very active in other activities within the cell or within the whole organism, that because we're not looking for them, we're simply not seeing.

Table 3 continued...

Table 3 continued...

Both technologies fail to account for evolution of traits and DNA	4	4	The future development, evolution if you will, of the piece of DNA that we might be talking about is also something that's not different between your standard and your targeted genetic modification. These pieces of DNA are not static and they are not closed to evolution like any other piece of DNA, and thus they are really open to change, even within a generation, but certainly across generations. And how we follow the function, the transformation of that function over time is something that is completely missing, completely lacking in terms of research let alone application, and it's a complete field of uncertainty that doesn't get changed by the targeted transformation.
Both technologies do not account for contextual effects	4	3	The same thing, can be said about the introduction of new pieces of DNA into the ecological context of the genome. That we really don't know what the whole set of relationships with other parts of the genome as well as other parts of the cell and so on will be in the context, you know? That to me has always been the failure of the model of transgenic manipulations. That there is really no conceptual model of what the context is and how the context plays into the expression of this one piece of DNA and its descendants and its relationships. So that continues to be the Achilles heel of the proposal, which is a proposal that has been with us for a very long time, and I do not see it changing very dramatically through targeted transformation.

Concerns

A set of questions was designed to determine what kind of concerns SMEs have about biotechnology governance and whether gene editing lessens or increases these concerns. Our analysis showed that to a great extent, SMEs viewed gene editing as presenting the same regulatory concerns as traditional biotechnology. The most frequently mentioned concerns

shared by traditional biotechnology and gene editing included international harmonisation of regulation (17 references by 13 individuals), intellectual property-related (IPR) impact on competition (9 references by 7 individuals), IPR -related impact on public research (8 references by 8 individuals), fair distribution of benefits (8 references by 5 individuals), and public understanding and acceptance (8 references by 5 individuals).

A number of SMEs, who generally viewed gene editing as being more precise, believed that some of the regulatory concerns for gene editing would lessen compared with concerns about traditional biotechnology. Two SMEs mentioned that greater control over technology would lessen concerns about animal welfare. As one of these SMEs explained "… for some people, the fact that you might [not] have to kill off a lot of animals to get the one animal that has mutation or whatever it is working the way you wanted would make it more acceptable...." Environmental safety was also sometimes viewed as presenting less concern for gene editing due to its greater precision (2 references by 2 individuals). Some SMEs thought that greater precision of and control allowed by gene editing would lower concerns about toxicity:

> …some safety concerns can be addressed in the planning process; that is, if one could say yes, we understand you were concerned about toxicity because of the Brazil nut gene problem of introducing a particular toxin or allergen, and we can now be more precise about that, or we can engineer it so that the ability to spread or to interbreed can be controlled better or something like that.

Twelve out of the 31 individuals identified governance concerns that are stronger for gene editing than for traditional biotechnology (15 references). The most prominent of these was concern about communication and public understanding (5 references by 3 people):

> The only thing that I saw that struck me as more complex was actually the explaining of it. It's been hard enough for non-scientists to understand what GM crops are. And if you now have to say, well, okay, we're actually talking about two different kinds: one that's sort of the sledge hammer approach, and one of them is the dentist drill, I'm not sure how successful that's going to be.

Some other regulatory concerns, which were believed to be more prominent for gene editing, included greater public distrust due to negative prior experiences with genetic modification (3 references by 3 people) and security concerns, including potential use of the technology for terrorist purposes (2 by 2) especially given the ease and speed of the technology. Table 4 summarises expert views about regulatory concerns.

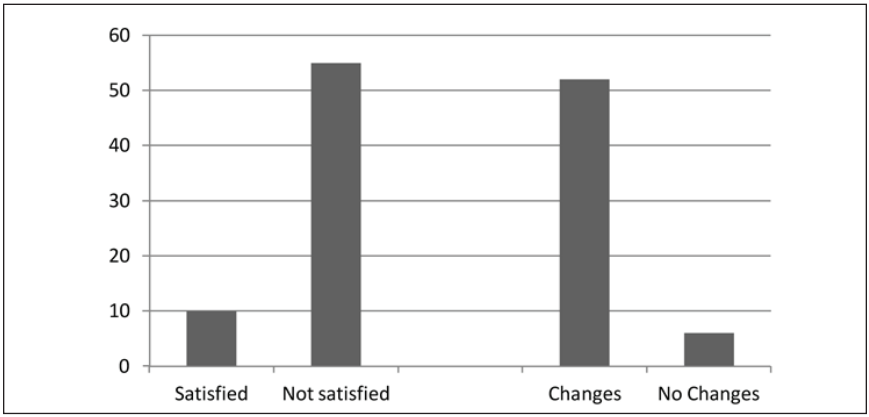
Table 4; Expert Concerns about Targeted Genetic Modification as Compared to their Concerns about Traditional Biotechnology

Comparison of impacts	Number of references	Number of quoting individuals
More problematic concerns	15	12
-communication and public understanding	5	3
-greater public distrust due to negative experiences with GM	3	3
-security issues may become more problematic	2	2
-ethical oversight	2	1
-fair distribution of benefits	1	1
-fascination with gene editing may overshadow safety concerns	1	1
Less problematic concerns	6	6
-Animal welfare concerns	2	2
-environmental safety	2	2
-toxicity	2	2
Same concerns	68	32
-international harmonisation of regulation	17	13
-fair distribution of benefits	8	5
-public understanding and acceptance	8	5
-regulatory capacity building in developing countries	5	4
-maintaining crop variety	3	3
-ownership of germplasm banks	2	2
-IPR-related impact on competition	9	7
-IPR-related impact on public research	8	8
-impact on access in developing countries	4	3
-impact on research relevant to the needs of developing countries	4	3

Oversight Change

SMEs were asked a set of questions to assess their views about the existing biotechnology oversight and the changes in oversight that they anticipate as a result of development of gene editing. The overwhelming majority of SMEs were dissatisfied with the existing system and expected the system to change. Figure 1 summarises total counts of references to comments about (dis)satisfaction with current oversight and whether the system should change or not. We compared the themes that the SMEs raised to their affiliation and specialisation. We found no systematic difference in the types of issues raised based on specialisation or affiliation.

Figure 1: Counts of references to comments regarding (dis) satisfaction with current biotechnology oversight and whether the system should change or not as a result of gene editing development.



When asked why they were dissatisfied with current biotechnology oversight, SMEs indicated that the system was very confusing (8 references by 7 individuals), piecemeal (7 references by 5 individuals), unable to adequately address safety (6 references by 5 individuals), creating competition and conflict among agencies (5 references by 5 individuals), having loop holes (5 references by 5 individuals), and favouring big companies (5 references by 5 individuals). Other limitations includes slow approval process, lack of scientific rigor, poor enforcement, lack of transparency and public participation, and lack of post-market monitoring.

When asked what changes in oversight would be needed as a result of development of gene editing, many SMEs indicated that the greater speed of development, production, and adoption may overwhelm the regulatory system (14 references by 7 individuals). Several SMEs expected the approval process to become faster (11 references by 5 individuals). Some SMEs expressed a concern that a greater variability in traits and in products may not be successfully handled by the oversight system (11 references by 6 individuals). Other anticipated changes included the need for a new definition of genetic modification or engineering, the failure of the old process-based approach, the emergence of new ethical concerns, the requirement of greater scientific capacity for regulators, and the decreased need for testing. Table 5 summarises expert opinions about anticipated changes in the system.

However, in the data, we did find different narratives that emerged on desired pathways for regulation. Figure 2 provides a visual representation of the three dominant views on governance in relation to views about gene editing technology. The first opinion was shared by individuals who perceived gene editing as an incremental technology. They believed that while gene editing will not change technology concerns dramatically, and will not force a government change, it will provide an opportunity to re-examine and change governance. In other words, gene editing as an extension of genetic editing, will challenge regulatory definitions and open the policy window so that the oversight system can be improved. Generally, the improvements suggested were more modest in nature than other narratives, and we call this viewpoint "adapters".

Figure 2: Narratives about Governance Given Perceptions about Gene Editing

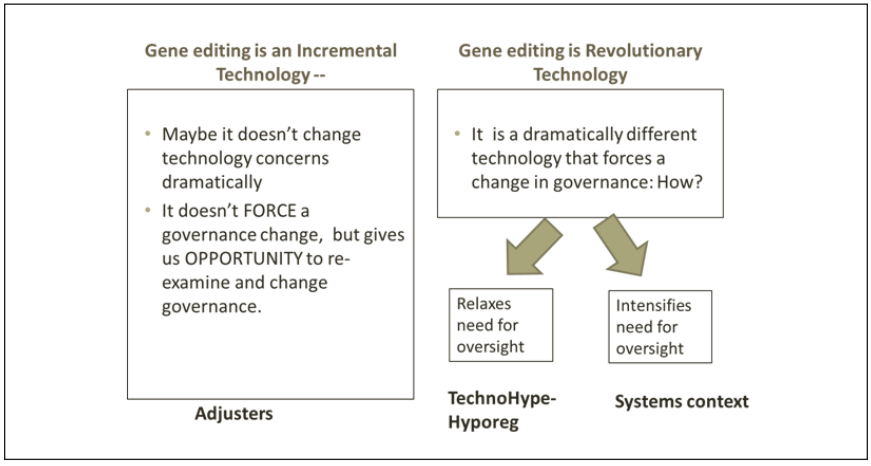


Table 5: Expert Opinions about Anticipated Changes in Oversight that Gene Editing may Cause

How will gene editing affect oversight	Number of references	Number of quoting individuals
There will be changes	52	30
Greater speed of development, adoption, production may overwhelm the regulatory system	14	7
Faster approval process	11	5
Greater variability in traits and products may not be successfully handled by the oversight system	11	6
New definition of GM will be necessary	5	3
Greater access to technology will present issues for regulatory regimes and their coordination	3	3
Will fail the old process approach	3	2
Regulators will start to encourage the technique	2	1
New ethical concerns	1	1
New scientific capacity will be required from regulators	1	1
Less testing will be necessary	1	1

Two additional narratives were identified that represented opposing views on governance, yet with the same understanding of the technology. Polar views were identified among those who believed that gene editing is a revolutionary technology. One group hyped the power of the technology but downplayed the need to regulate it (technohype-hyporeg). SMEs in this group believed that the dramatic changes in genetic modification introduced by gene editing should relax the need for oversight. Another group, on the contrary, shared the view that the dramatic changes in the technology intensify the need for strict oversight. They tended to think more about the capacity of the oversight policy system to deal with the large volume of gene edited products given that they are easier to make. They also tended to take a systems view on organism biology and ecology, believing that the sometimes even small genetic changes caused by gene editing could cause unintended shifts in biochemistry or ecosystems. We call this group a "systems view".

In general, we noticed complex attitudes towards technology and governance arising out of the interviews. The following quote by one of the SMEs clearly demonstrates the complexity in which the technology is simultaneously described as powerful ("changing physiology") and not so

powerful ("All you've done"), and regulation is viewed as wanting to be raised for business purposes.

All you've done is taken a few bases out, which fundamentally changed the physiology, but there's no clear regulatory pathway by which that plant would or would not be considered genetically modified. So I think we'll probably see significantly streamlined approval processes. And actually, one thing that we're hoping for as a business is that the regulatory hurdles will actually be raised for GM plants that are not made using technologies like ours.

Table 7: Survey Responses Regarding Concerns about Gene Editing

18. With regards to targeted genetically modified plant products, how concerned are you about:					
	Not at all	**Somewhat**	**Moderately**	**Very**	**Extremely**
Environmental risks	22.2% (6)	**33.3% (9)**	**33.3% (9)**	7.4% (2)	3.7% (1)
Human health safety	22.2% (6)	**44.4% (12)**	22.2% (6)	11.1% (3)	0.0% (0)
Intellectual property rights issues	7.4% (2)	**29.6% (8)**	25.9% (7)	**29.6% (8)**	7.4% (2)
The ability of farmers to afford products	11.1% (3)	**40.7% (11)**	25.9% (7)	18.5% (5)	3.7% (1)
The adequacy of public funding for basic research	14.8% (4)	25.9% (7)	**33.3% (9)**	18.5% (5)	7.4% (2)
The adequacy of public funding for product development	25.9% (7)	22.2% (6)	11.1% (3)	**29.6% (8)**	11.1% (3)
The adequacy of public funding for environmental and human health studies	14.8% (4)	14.8% (4)	14.8% (4)	**33.3% (9)**	22.2% (6)
The control exerted by industry	14.8% (4)	22.2% (6)	14.8% (4)	22.2% (6)	**25.9% (7)**
The technical performance of the products	19.2% (5)	**42.3% (11)**	23.1% (6)	15.4% (4)	0.0% (0)

In addition to assessing differences in views about governance, we asked questions about how to improve governance. Many SMEs recommended development of novel IPR regimes (22 references by 16 individuals). Two other popular recommendations were to ensure broader public participation (17 by 17) and better communication about the technology (4 by 4). Table 6 summarises all recommendations suggested by the SMEs.

Table 6: Expert Suggestions on How To Improve Gene Editing Oversight

How to improve oversight	Number of references	Number of quoting individuals
Broader public participation	17	17
Novel IPR regimes	22	16
Better communication of technology	4	4
Upfront international discussion	2	2
New model of oversight	2	2
Anticipatory governance as co-production	1	1
Additional foresight agency	2	1
New labeling approaches	1	1

Agreement and Disagreement on Oversight

In addition to the interviews, we were able to get a sense of the diversity of viewpoints of the group from a quantitative survey that asked a variety of questions about oversight of gene editing. For the questions about the technology and concerns, the group was split according to their rating of the type and magnitude of concern about environment and health risks, industry concentration and ownership, and public versus private funding (Table 7). They were also divided as to whether there should be more or less regulation for gene editing (Figure 3) and whether advancing the technology is more important than studying the risks, confirming that we had a group of SMEs with diverse biases (Figure 4). However, three questions stood out for which there was significant agreement: the importance of stakeholder involvement in decision making (Figure 5), pre-market timing of regulatory action (Figure 6), and the need for something more than voluntary or self-regulation (Figure 7).

We conclude in the following section by discussing current regulatory policy efforts for gene editing in the context of the views of the SMEs who we interviewed and surveyed.

Figure 3: Survey responses on whether regulation for gene editing should be the same intensity as for 1st generation genetic engineering

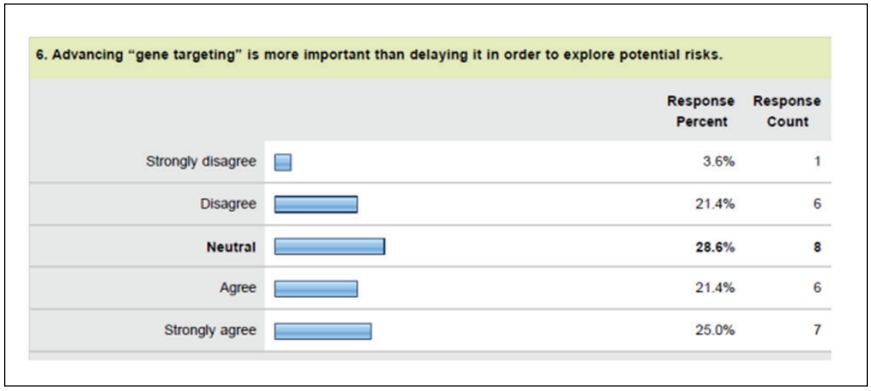


Figure 4: Survey responses regarding thebalance between gene editing and exploring risks.

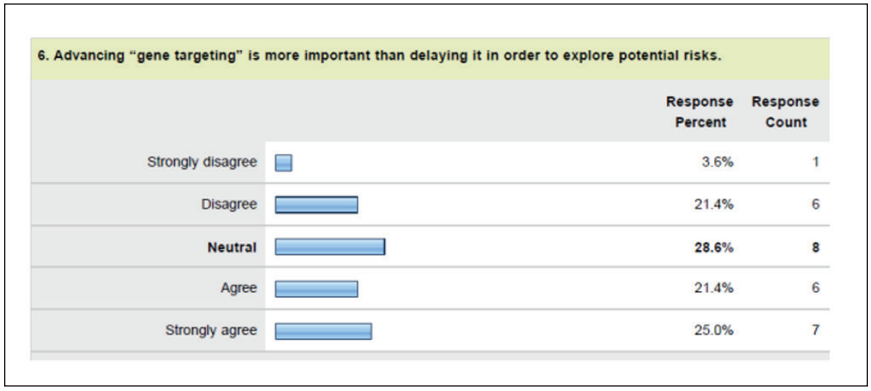


Figure 5: Survey responses on stakeholder involvement in decision making

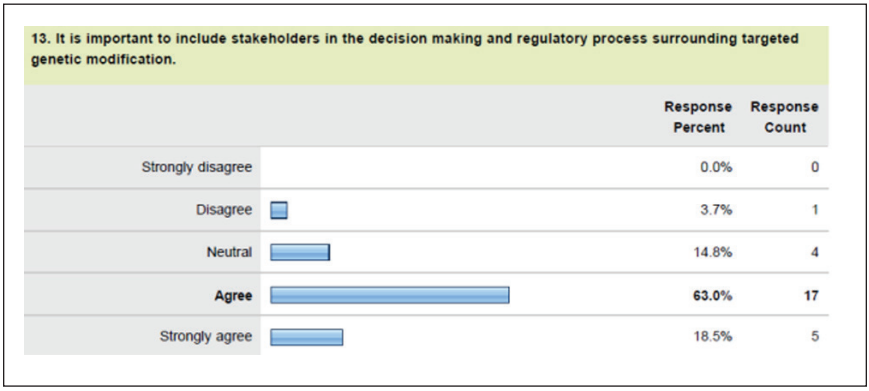


Figure 6: Survey responses on when regulatory action should take place

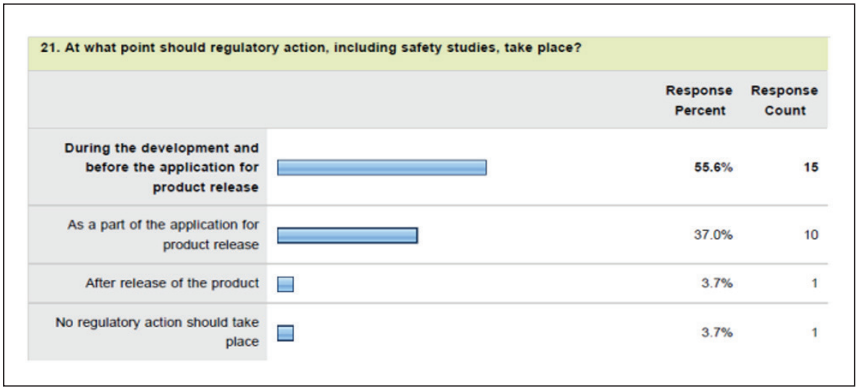
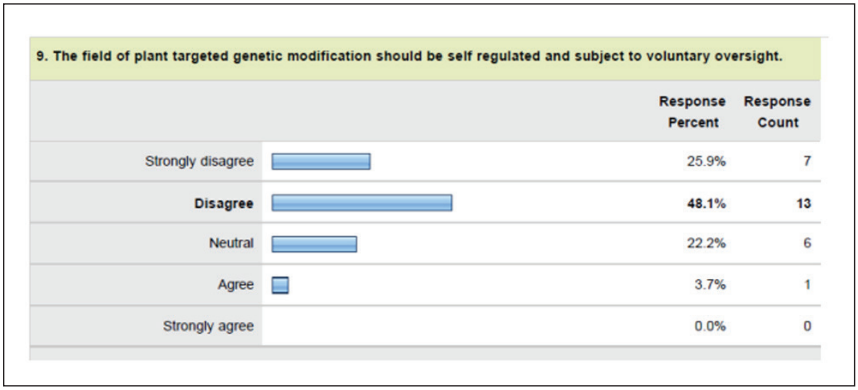


Figure 7: Survey responses on whether gene editing should be subject to self-regulationand voluntary oversight



Discussion

The SMEs in our study had different visions as to the novelty of the technology, concerns about risks, and what specifically should be done in a regulatory context. However, most agreed that stakeholder involvement is important in decision making, and most did not endorse self- or voluntary regulation. Key narratives arose including the view that gene editing provides a new opportunity to rethink the oversight of agricultural biotechnology to improve existing systems (adapters), that gene editing, although revolutionary, should undergo less regulation than first generation biotechnology (technohype-hyporeg), and that gene editing makes the engineering process so easy that the regulatory system might not be able to accommodate the speed of development and thus greater caution is warranted (systems view). Current national policy debates are revealing these differing perspectives about how to govern this next generation of agricultural biotechnology, as several countries are in the process of making decisions about whether and how gene editing fits into existing regulatory schemes.

For example, in the United States, decisions about gene-edited crops have been taking place on a case-by-case basis between developers of the product and regulatory agencies. As individual letters of inquiry are submitted for gene-edited crops, the US Department of Agriculture has agency staff review the applications and decide whether it fits the statutory definition of plant pest (Waltz 2012; Wolt *et al.* 2015). Several products have passed through this review without being captured by the U.S. regulatory system (Wolt *et al.* 2015). This approach lies in contrast to the desires of pre-market, mandatory oversight expressed by most SMEs in our study. Furthermore, these decisions have not been made openly in consultation with an advisory committee or stakeholders and are left to be discovered through Freedom of Information Act (FOIA) requests (Waltz 2012), and are also in contrast to the view of our SMEs that stakeholders should be consulted in decision making. The USDA's choices are proving to be controversial, and some SMEs and stakeholders are questioning the behind-the-scenes approach to setting policy especially given previous controversies with GE crops (Waltz 2012; Ledford 2015).

In part due to this attention and other controversies over GMOs and GM foods, the Office of Science and Technology Policy has recently started to convene US regulatory agencies to review the Coordinated Framework for the Regulation of Biotechnology (CFRB) (OSTP 2015). OSTP also hosted a public meeting on the topic. During this meeting, it was stated that the review would not be likely to result in the revision or creation of new authorities, but rather that it would clarify CFRB existing authorities in the context of new technologies (Waltz 2015). How gene editing is treated in a US regulatory context might change as the CFRB is re-considered in this process.

Meanwhile, in the media, gene editing is being portrayed as the next revolution, especially the subset involving CRISPR systems. Recent media descriptions include "CRISPR: The Disruptor A powerful gene-editing technology is the biggest game changer to hit biology since PCR" (Ledford 2015) and it has been covered by popular press as "biotech's most promising breakthrough" (Johnson 2016). The public narrative is that gene editing is revolutionary, and this narrative has been fueled by interviews with SMEs in the media. Yet, the experts interviewed often also complain about regulatory delays and too much regulation (e.g. Abbott 2015). This "technohype-hyporeg" approach could potentially cause public confusion and a loss of public confidence as it might be hard to see how a technology can be so new and powerful and yet not require any formal government oversight. The different kinds of gene editing (SDN-1, SDN-2, and SDN-3), layered over the novelty of the technology, risk issues, and regulatory options seems extremely difficult to convey in popular press.

In contrast to the US, the European Union has taken a slower, expert-advised approach to making decisions about gene editing, although this has caused some frustration among product developers and some are suspending their work as a result (Abbott 2015). The EU has spent a few years interpreting its 2001 directive on releasing GMOs into the environment in the context of gene editing. Meanwhile, individual EU countries are making their own decisions to allow for certain gene edited crops in field trials, such as those without foreign DNA in the final product (Abbott 2015). The narratives of regulation hindering product development play prominent in media reports of the EU situation. Interestingly, genetic engineers are also now using *process* based arguments to exclude certain crops from regulation

when in the past they have argued that the *product* should be the focus of risk assessment and regulatory review. We noticed the same arguments about *process* in our expert interviews in cases where gene editing was argued to have more precision of insertion and lesser risk. These arguments are not likely to stop opposition to gene edited products, however, as NGOs have argued that genetic engineering is still involved, products can still be harmful to health, and call for these crops to be treated the same as first generation transgenic products (Abbott 2015). Some SMEs in our interviews acknowledged that the phenotype of the crop is what matters for risk, and that even in a few cases nucleotide changes can add to the hazard potential of a crop (systems view).

In this study, we examined the early and diverse views of SMEs towards gene editing. Our data was collected a few years prior to the media and regulatory buzz around gene editing, yet by conversing with diverse SMEs and stakeholders early in the process of technology development, the narratives that we found seem relevant to and predictive of the contemporary discourse. It seems that the viewpoints of SMEs could be useful in "anticipatory governance" approaches designed to prepare for societal decisions about emerging technologies' by revealing salient issues that could guide research and development further upstream (Karinen and Guston 2010; Kokotovich and Kuzma 2014).

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Agriculture Technology Choices and the Responsible Research and Innovation (RRI) Framework: Emerging Experiences from China and India

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Abstract: Drawing on the lessons from India and China in Bt cotton, this paper argues that emerging linkages between regulation, promoting innovation and access to innovation call for a new approach. Intellectual property rights and regulatory regimes may constrain diffusion and usage of technology. In the new approach, state's intervention through appropriate policies for promoting innovation is important and Socio-Economic assessment of technologies should also play a role in policy formulation. The emerging concept of Responsible Research and Innovation (RRI) can be useful in framing the new approach. The paper points out that understanding of access to and availability of innovations can be linked with the RRI framework, and a coherent policy framework that promotes both access and responsible innovation can be developed. It also points out that this framework will facilitate development of socially relevant innovations and will also be useful in addressing controversies in development and use of innovations.

Keywords: Agricultural Biotechnology, India, China, Responsible Research and Innovation (RRI), Intellectual Property Rights

Introduction

Cotton is an important fiber crop which has a long history of domestication and improvement. It is cultivated in more than 70 countries with an estimated 180 million people associated with cotton cultivation and industry (Zhang

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2015). Since the 1990s, Bt (*Bacillus thuringiensis*) cotton has emerged as an important option in cotton cultivation, and transgenic cotton is now one of the most widely used transgenic crops in the world (Baffes 2011).

In this paper we examine the experiences of China and India in introducing Bt cotton and analyse how the two countries have handled issues relating to biosafety, intellectual property rights, seed prices and access to technology. A technological option like Bt cotton confers new opportunities for farmers although issues like biosafety, pest resistance and gene flow remain important concerns. The diffusion of Bt cotton since 2000 in China and 2002 in India has been phenomenal, with Bt cotton replacing hybrids and earlier varieties and now account for about 90 per cent of the area cultivated under cotton in both countries. But critics point out Bt cotton is more suited for irrigated areas, and in rain-fed areas farmers tend to get trapped in a vicious circle of biotechnology and insecticides (Gutierrez *et al.* 2015). Such issues, together with environmental concerns, stress the need for comprehensive socio-economic impact assessments of Bt cotton. Intellectual Property Rights (IPRs) are an important factor in determining access to technology, but regulation and biosafety norms also impact access. IPRs are an important incentive for innovation, and both national governments are committed to protecting IPR under the Trade Related Intellectual Property Rights (TRIPS) Agreement. However, the policy framework in each country has dealt with IPR and competition differently, resulting in different outcomes for both seed prices and the affordability of Bt cotton for farmers.

Responsible Research and Innovation (RRI) is an emerging concept that can be used to assess Bt cotton.[1] In this paper, we examine Bt cotton using RRI as a bench mark. It underlinesthat linking the RRI framework with a policy framework that meaningfully balances access, incentives for innovation and regulation can result in a coherent framework that can influence the development of innovations that are socially desirable, environmentally sound and affordable. The outlines the elements of such a framework based on case studies of Bt cotton in India and China, and debates on RRI.

Modern Biotechnology in Agriculture

Biotechnological applications in agriculture relate to different products and services. Among them the most widely adopted and the most controversial are the Genetically Modified Organisms (GMOs). While conventional plant breeding resulted in better yielding varieties and varieties with different traits, the introduction of biotechnology enabled plant breeders to insert genes to confer the desired characteristics. These genetically modified plants have novel traits such as herbicide tolerance, insect resistance and pest resistance, and future applications include development of drought tolerant varieties.

IPRs have played an important role in the commercialisation of agribiotechnology (Kloppenburg 2005). GMOs can be protected by patents in many countries, while most countries in the world have introduced IPR for plants and plant varieties on account of the TRIPS Agreement coming into force. The availability of IPR has acted not only as an incentive for innovation, but has also raised concerns about the impacts on seed availability and food security (Schutter 2009). IPRs are central to any discussion on access to germplasm and seeds, innovation in plant variety development and food security (Srinivas 2015).

Following the development of hybridisation technology in the 1930s plant breeders and seed companies were able to develop hybrids which provide excellent yields. But for farmers, who use first generation hybrids and replant the seeds, the yields decrease significantly in the next generation. In order to maintain or increase the yield from hybrid varieties, farmers have to buy seeds, resulting in extra cost. Cultivation of Open Pollinated varieties (OPV) could solve the problem but they may not be available for all crops and crop varieties. In the case of varieties that contain patented genes or technologies, replanting the seeds can be construed as infringement of patents, if the laws so provide, as is the case in the USA. The increasing use of hybrids and IPR in agriculture thus restricts farmers' choices regarding seeds, and their options to reuse farmer-saved seed or exchange of seeds among farmers.

An important feature of modern agricultural biotechnology is that in its development and expansion the private sector has played an important role, and the private sector uses IPR to protect its innovation and commercial

interests. Globally there has been a consolidation in the seeds and agri-inputs industry with the top six firms holding more than 50 per cent of the market share between them. Cross licensing and strategic partnerships among these firms have ensured that new entrants face significant barriers in market penetration (Howard 2009).

Development and testing of new varieties with novel traits developed through biotechnology take about a decade, and as there are significant costs in obtaining regulatory approvals, only firms, that have expertise in these areas and access to financial and technological expertise, can succeed in the market. While the Green Revolution was spearheaded by public sector research centers, the agribiotechnology revolution is led by the private sector. Bt technology has been applied in many crops, including cotton. There are advantages in using crop varieties with the Bt gene inserted as the farmers need not spray pesticides. As the resistance to protection is inbuilt, both the number of sprays and quantum of pesticides used can be reduced significantly. The second generation biotech crops have more than one trait inbuilt and by stacking genes traits can be combined and conferred upon. This could result in advantages like reduction in use of insecticides and pesticides, reduction in labour cost and time, and can also boost yields.

Bt Cotton in China

To boost productivity and gain from agricultural biotechnology, China embarked upon an ambitious programme on biotechnology, and has invested in agribiotechnology since the early 1980s. The government has undertaken a 12 year National GM Variety Development Programme (GM programme 2008-2020) with about US$ 3.8 billion investment (Huang *et al*. 2012). In 1997 a variety of Bt cotton owned by the Chinese Academy of Agricultural Sciences (CAAS) and a variety owned by Monsanto were permitted for cultivation. In subsequent years many more varieties owned by CAAS and Monsanto were granted approval for cultivation. China has approved only Bt cotton, virus resistant papaya, and insect resistant poplar for wider cultivation. Bt cotton is cultivated in about 4.2 million hectares, virus resistant papaya in about 5800 hectares, and insect resistant poplar in 600 hectares, respectively. The adoption rate of Bt cotton was estimated to be 90 per cent in 2013 and most of the farmers who cultivate it are small, resource poor farmers (ISAAA 2014).

A review of 15 years of Chinese experience with Bt cotton indicates that Bt cotton has been successful across all regions in China. Total economic benefit gained on account of Bt cotton cultivation is estimated to be more than 33 billion yuan (Qiao 2015). The economic benefits have remained stable and continue to accrue to farmers. Pesticide use decreased significantly in terms of use of labor in cotton cultivation, and the introduction of Bt cotton resulted in significant reductions of factors such as reduction in time spent for pesticide spraying, and picking up bollworms. Bt cotton has also resulted in an increase in seed cost, but this increase has been more than offset by yield increase which is more than one-third. Studies have corroborated the claim that Bt cotton has resulted in economic benefits and reduction of pesticide use in China (Wang *et al.* 2013).

Although China has approved only three GMOs, it is investing heavily in agricultural biotechnology. Bt rice, transgenic wheat and transgenic corn are among the GM crops that are being developed and tested in China (Talbot 2014). This is not surprising, given the potential of agribiotechnology to develop varieties that are better adapted to climate change and to increase productivity. Even if the approval for wider cultivation is restricted to a few crops and varieties, this could make a difference, as is evident from the case of Bt cotton.

The Chinese government did not liberalise Foreign Direct Investment (FDI) in the seed sector and has placed restrictions on investment firms from abroad holding a controlling interest. As a result, Monsanto had to reduce its controlling interest in the cotton joint venture. While foreign firms have been permitted to undertake activities like development, breeding and production of new varieties, they have to contend with being minority shareholders in joint ventures with Chinese firms. Despite these restrictions, seed Multi-National Corporations (MNCs) like Monsanto and Syngenta have invested in Chinese joint ventures, as well as undertaking joint developments with CAAS. For such firms, access to a market like China and the available opportunities are too important to be ignored on account of these restrictions. Nevertheless seeds from these joint ventures account for less than 20 per cent share of the market.

After becoming a member of the World Trade Organisation (WTO) China had to comply with the TRIPS Agreement, and brought in changes to

IPR laws. China's Plant Variety Protection Act was enacted in 1997. While Chinese law permits farmers to reuse saved seed and informally exchange seeds, it prohibits commercial sales of seeds by farmers. The Chinese law is less liberal than the Indian law regarding farmers' rights over seeds, but is more liberal than the law in the USA. The Plant Variety Protection conferred is thus weaker than the protection offered by patents.

The Chinese domestic seed market is the second largest in the world, next to that of the USA. The market is fragmented and there are thousands of seed companies. Most of them cater to a region or a province. After the reforms undertaken in the seed markets, the seed system was decentralised. While MNCs are active in the Chinese seed market, the government is planning to promote consolidation in the domestic seed industry. The government expects that the largest 50 companies will double their share of the market to 60 per cent by 2020 (Yap 2015). The number of seed companies declined to 5,200 in 2014 from 8700 in 2011. Even the large Chinese seed companies do not invest much in R&D. They do not have the capacity to compete with Syngenta and Monsanto, nor do they have such a diversified portfolio in technologies, processes and products.

The consolidation and integration in the global seed industry has resulted in a few companies having strategic access to important technologies, and patented technologies are crucial for product development. MNCs hold significant numbers of patents in agribiotechnology in China. Monsanto and Delta and Pine Land established a joint venture, Jidai, with Hebei Provincial Seed Group Company for developing and distributing biotech seeds. In 1997, Jidai was permitted to market Bt cotton in a single province. In 1996 two varieties of Bt cotton developed by CAAS were approved for commercialisation in nine provinces. As seed companies were slow in adopting these varieties CAAS set up Biocentury Transgenic Corporation for licensing and seed sales. Biocentury received funding from government programmes on biotechnology. In 2002, varieties developed by CAAS were approved for marketing in Yangtze River Region. Due to decentralisation and other factors, the seed market is dominated by small seed companies and seed dealers (Huang *et al*. 2015).

The government's policy on FDI and denial of permission to market varieties developed by Monsanto in many provinces enabled CAAS to

succeed in Bt cotton. Interestingly patent protection was not available for biotechnology products when the initial varieties released by CAAS and Monsanto were approved. In granting plant variety protection, cotton was excluded until 2005 (Linton and Torsekar 2009).

As a result, initially most of the Bt cotton events were in Open Pollinated Varieties (OPVs) rather than in hybrids. This resulted in proliferation of unapproved seeds and varieties. Although Monsanto and CAAS later applied for and received patents on Bt cotton events, Monsanto was unable to attain a dominant position in China in patenting or in technology, as CAAS had developed equally good varieties, received earlier approval for wider cultivation and had the benefit of state investment in the company promoting it.

Thus, through strategic decisions and by strengthening public sector research and commercialisation activities the Chinese government ensured that Monsanto faced strong competition from the public sector. This resulted in a competitive market for Bt cotton seeds. Hence, there was no need for the state to intervene in the market through fixing the prices for seeds. However, it should be pointed out that most of the Chinese seed companies were dependent on technology from CAAS or Monsanto.

China, like many other countries, has a regulatory framework for testing and approval of GMOs. The regulatory framework encompasses laboratory development to approval/rejection for cultivation. Completing the stages and the biosafety may take up to 10 years. The National Biosafety Committee was established in 1997 and evaluates biosafety assessments on experimental research. The Office of the Agricultural Genetic Engineering Biosafety Administration (OGEBA) is the final authority for deciding on applications for approval. If OGEBA approves commercialisation, then a Biosafety Certificate (BC) is issued. At the provincial and county levels there are biosafety regulation institutions for monitoring and reporting on GM crop cultivation and production (USDA 2014). The strict regulation and high costs associated with developing and testing make it difficult for small seed companies to conduct tests and apply for a BC (Huang *et al*. 2015).

In China's fragmented and decentralised seed market there are many seed companies with different capacities and resources. There are many varieties without a valid BC. These can be classified into two groups. The

first group consists of unapproved varieties in which the approved gene (Bt gene) is incorporated. The seed companies and dealers produce and sell these varieties, and often give them new names or rename the varieties to avoid payment of royalties. The other group consists of varieties that have not undergone the regulatory process, or else they are unapproved varieties without the approved gene. China has an elaborate procedure for import of GMOs for processing and permits such imports. It is taking steps to strengthen biosafety regulation and post-approval monitoring mechanisms (USDA 2014).

The widespread use and availability of unapproved varieties indicate that the biosafety regulatory and monitoring regime needs to be improved. It is possible that the Chinese seed market was liberalised too soon, and this has resulted in the proliferation of 'illegal' and 'unapproved' seeds which undermined the trust among farmers in the regulatory regime (Ho *et al.* 2009). It has also been suggested that China should opt for regulating the events rather than varieties as this would reduce the regulatory cost and the time taken for approval. This may enable smaller companies to apply for BC and enable faster adoption of new GM varieties (Huang *et al*. 2015).

The case study on Bt cotton indicates that the Chinese state has played a key role in promoting and regulating this technology. Its handling of IPR issues and the farsighted policy of promoting the public sector to develop events and varieties as well as recent efforts in seed sector reform are worthy of emulation by other countries.

Bt Cotton in India

Bt cotton is the first agricultural transgenic crop to be commercialised in India since 2002, following the approval of GEAC (Genetic Engineering Approval Committee) for the release of 3 Bt cotton hybrids by Mahyco Monsanto Biotech (MMB).[2] From 2002 to 2014, the area under cultivation increased from 50,000 hectares to 11.6 million hectares, i.e. about 230-fold increase in thirteen years (ISAAA 2014).

From 2002 until 2006, MMB owned the only Bt gene that could be legally sold in India. The domestic companies that licensed Bt technology from MMB were required to pay a one-time license fee as well as a royalty fee for availing the gene. This led to a large price difference between Bt and

non-Bt hybrids. The price for official Bt cotton seeds in India in 2006 was around INR 1600 per packet of 450 grams, which was around four times the price for the non-Bt hybrid. Out of this seed price of INR 1600, INR 1250 was charged by MMB as the 'trait value'. In late 2005, South India Cotton Association raised the issue of high prices with seed companies and wanted them to lower their prices. This idea gained currency and many farmers' organizations joined the protest.

Taking cognizance of the seriousness of the matter following complaints from farmers and peoples' representatives, the Andhra Pradesh (AP) government filed a case with the Monopolies and Restrictive Trade Practices Commission (MRTPC) against MMB, on 2 January 2006, for 'exorbitant pricing of Bt cotton seeds'. The MRTPC directed the US-biotech major, Monsanto, not to charge the trait value of INR 900 per packet of 450 gm Bt cotton seeds in an interim order pronounced in the court on 11 May 2006. Stating that the company had indulged in restrictive trade practices, the MRTPC wanted Monsanto to fix a reasonable trait value, considering the trait value that was being charged by its parent company in China (INR 45) and in the US (INR 108), as against INR 900 in India. On 29 May 2006, AP government instructed all seed companies in the state not to sell Bt cotton seed beyond INR 750 per packet of 450 grams. The Supreme Court declined to stay the orders of the state government and MRTPC.

Commentators have pointed out that this comparison is inappropriate because apart from the different agro-ecological conditions across these regions, Bt cotton technology has been commercialised in OPVs. In both China and India, it has been incorporated into hybrids, for which seed production is more costly. They further argued that in China, Monsanto faced competition through public sector Bt cotton technology, which was developed by the CAAS and commercialised in some of the states where Monsanto varieties were also sold (Sadashivappa and Qaim 2009). The AP state government enacted an Act to regulate the supply, distribution, sale and fixation of the sale price of cotton seeds in the state. Similar Ordinances/ Acts were enacted by other states, such as Gujarat in 2008 and Maharashtra in 2009 , which led them to bring down the prices of Bt cotton seeds.

ABLE (Association of Biotech Led Enterprises) has argued that cotton prices should be determined by market dynamics. Similar concerns have

been raised by the NSAI (National Seed Association of India) in their petition to hike the selling price fixed by the government for Bt cotton seeds. Regarding the price control mechanism, it has been argued that an alternative policy measure to increase the benefits for farmers as well as seed providers would be to allow competition among alternative gene providers, which could reduce the seed prices on its own (Arora and Bansal 2012).

The Technical Experts Committee (TEC), constituted by the Supreme Court, in its final report was of the view that the concentration of IP and resources for GM crops in the private sector is resulting in perverse and exploitative relationships of public institutions with the private sector in developing countries and that these are not successful in meeting development and sustainability goals (TEC 2013). While many studies have confirmed that Bt cotton, has yielded significant benefits to farmers, economists who support the cultivation of Bt cotton point out that this technology is scale neutral and can benefit all groups of farmers. They express concern that most research in agribiotechnology is done by a few multinationals that might not develop varieties with traits desired by or suitable for use by resource-poor farmers (Rao and Dev 2009). In India the Bt gene was inserted in hybrids and as farmers preferred the varieties with the Bt gene, many varieties that were popular earlier were subsequently not preferred for cultivation (Ramasundaram *et al*. 2011).

Pricing of Bt cotton seeds is still an issue, and recently the Maharashtra government requested seed producers to reduce the prices of seeds (Bhosale 2015). However, the Central Institute of Cotton Research (CICR) has proposed to develop an alternative to the Bt cotton technology of Monsanto by using the technologies developed at Delhi University, the National Botanical Research Center and Tamil Nadu Agricultural University, for developing an event with three genes stacked in, which would confer significant advantages to farmers (Fernandes 2015).

Regarding biosafety concerns, although there were illegal or unauthorised varieties in the earlier years, most, if not all, Bt cotton varieties planted in India are based on approved events. But due to high regulatory costs and IPRs being held by one or a few companies, the competition is limited, resulting in higher seed prices and limited options for farmers.. It has been argued that India's current regulatory framework for approval of

$$Y_1 = \beta_0 + \beta_1 Y_2 + \beta_2 X + U$$

Bt hybrids is very complex and time consuming and has acted as an entry barrier for new genes (Lalitha *et al.* 2008).

While Monsanto had the first mover advantage, it also had access to the technology developed by its parent company and could afford to meet the regulatory costs. JK Agri Genetics Ltd. (JKAL) obtained the cry1Ac gene from the Indian Institute of Technology (IIT), Kharagpur, and its event (Event-I) was approved in 2006. But JKAL could not succeed in the market as Monsanto, having obtained approval in 2002, had an early mover advantage. By 2006 Monsanto had obtained approval for its event (Bollgard II- MON-15985) with two genes (cry1Ac and cry2Ab2) stacked. This ensured that Monsanto could offer better varieties to farmers. The sheer absence of competition ensured that Monsanto could have a virtual monopoly in the market. India has a Competition Law and a Competition Commission to regulate market distorting behaviour. But in the absence of effective competition and availability of alternative technological options to farmers and seed companies, legislation alone would not be effective.

Lessons from China's and India's Experience with Bt Cotton

In both countries the role played by the respective governments was crucial for the success of the introduction of Bt cotton. But there are significant differences in the roles played by the governments, the responses of the governments and the impacts of this on farmers. As discussed above, in India IPR issues played an important role in pricing and access issues. The near monopoly position enjoyed by Monsanto and MMB ensured that they could extract a premium from the farmers. Although the public sector had been undertaking R&D in Bt cotton it did not develop varieties that could be commercialised successfully. The only exception is the utilisation of the gene provided by IIT Kharagpur by JK Agri Genetics, but, the company did not succeed in the market which was dominated by Monsanto.

Public sector institutions like the Indian Council for Agricultural Research (ICAR), and state agricultural universities did obtain patents on Bt cotton technology (Sastri *et al*. 2011). But they could not develop a product that could compete in the market. As a result state governments had to intervene to reduce the prices. Such moves have not been successful,

and in the long run these are not viable solutions. Invoking competition law also offers a solution, but this is unlikely to work well, as this in no way impacts on the near monopoly power enjoyed by Monsanto.

China handled the issue differently. The public sector CAAS had developed events that could be commercialised and also had patents over the technology. Its varieties were approved for use in more regions than that of Monsanto and thereby it had an advantage. CAAS established a company to handle seed sales and licensing, and government supported that through investment. Although Monsanto had the technology and patents, it could not dominate the market, as CAAS was equally well equipped to challenge the competition. Both India and China invested in and supported R&D in agribiotechnology in the public sector, but unlike in India, Chinese public sector R&D resulted in events and varieties that could be commercialised.

India liberalised the seed sector and allowed FDI in the sector in the late 1980s. China modernised its seed laws but placed restrictions on FDI in the seed sector and prevented MNCs from holding a dominant position in joint ventures. While foreign MNCs took advantage of liberalisation in the seed sector in India, the public sector seed industry did not enhance its own capacity, nor did it expand and diversify its outputs in agricultural biotechnology. It has been observed that the technological edge is with private sector in India (Spielman *et al*. 2011)

This resulted in the private sector dominating in hybrids for cash crops and vegetables. At least in the initial years in China, Bt cotton varieties were sold as OPVs, and the absence of plant variety protection for cotton till 2005 ensured that seeds could be exchanged and used for replanting.

Both countries have a credible biosafety regulation regime. But the problem of unauthorised seeds and unapproved varieties is a bigger problem in China than in India. India too faced the same issue in the initial years and governments ensured that the problem was contained. In China, unapproved varieties and varieties without BC are easily available. Better monitoring and strong enforcement can solve this problem. In India the regulatory process seems to be functioning well, but the comments by the TEC and similar analyses could be considered in order to improve the system. In both countries smaller companies could be provided with assistance in meeting the regulatory norms, which would enhance competition and may increase the number of available varieties and traits.

Socio-economic assessment remains weak in both countries. In India this was pointed out by the TEC appointed by the Supreme Court. Socio-economic assessment is a comprehensive process to be undertaken at different stages (Chaturvedi *et al*. 2012). It has been put into practice in many countries and has linkages with sustainable development. However, the major benefit is that socio-economic assessment goes beyond cost-benefit analysis and can provide a comprehensive assessment of an innovation and its impacts on various stakeholders. The key lessons from the experiences of these two countries can be summed up as below:

IPR can adversely impact access to GMO technology and thereby impede faster diffusion and wider adoption. The state should strive to promote competition in the market and ensure that the monopoly power conferred through IPR is not abused. States should ensure that biosafety and regulatory regimes are based on sound science and are trustworthy. To enable participation of public sector and small seed developers/companies, states can help by building their capacity to meet the requirements under biosafety and regulatory regimes.

Socio-economic assessment should be made an integral part of the regulatory framework. Findings from socio-economic assessment can be used to assess the impacts and estimate whether the stakeholders are adversely affected or not. Seed sectors should be modernised and innovation should be promoted. Restrictions on FDI in this sector are desirable and gradual opening up is a better option than a one-time, no-holds barred liberalisation. Given the importance of the public sector in the seed sector, government should strengthen it and enhance its capacity. A new approach based on the above points and emerging linkages between regulation, innovation and access can be developed. This is important as new actors emerge in the context of new technologies and the regulatory framework should be dynamic enough to meet the new challenges (Chaturvedi 2010).

In developing our suggestions for this approach we draw upon the emerging concept of Responsible Research and Innovation (RRI).

Responsible Research and Innovation and Agricultural Biotechnology

Responsible Research and Innovation (RRI) has emerged as an important concept in academic studies on science, technology and innovation and in

science policy and funding. While it is primarily put into practice in Europe, its relevance elsewhere is not yet visible.

RRI can be conceptualised as a process, or as an outcome, or as an idea that espouses some values and identifiable criteria to measure whether an activity/process/product conforms to RRI. Contextualising this in China or India would mean that RRI could be an idea that is framed globally but adopted to local needs and values. So in different societies, based on the lessons from science-society relations in the past, the versions of responsibility may be different; different actors may give emphasis to these different versions and may lay stress upon different objectives, and assess responsibility on the basis of innovation's contribution to meeting that objective. While RRI may be primarily a European idea, it could be interpreted and applied differently in different contexts.

The diffusion of technology could result in unanticipated benefits and risks. Often potential implications are difficult to understand or anticipate beforehand and only guesses can be made. But regulator and innovator may differ in their criteria to assess how responsible an innovation is. A responsible innovation from the perspective of the innovator may not meet the criteria set by the regulator. So addressing this issue may call for more regulation and stricter assessment criteria which may not reduce the utility of the innovation per se, but can make it more expensive or act as a barrier in deployment and diffusion. Striking a balance between these two views on responsible innovation is necessary.

Comparing RRI with 'broader impact' criteria, Davis and Lass (2014) point out that the US National Science Foundation has used 'broader impacts' criteria in assessing projects and is moving in the direction of RRI. Goujon, Gianni and Pearson (2014) identify the following as key elements of RRI: Responsibility, Transparency, Interactivity, Ethical Acceptability, Sustainability, Social Desirability, and Embedding of Scientific and Technological Advances in Society. Reflecting on the concept of RRI, Rip (2014) points out that RRI is a social innovation that is being articulated, and the novelty is in the roles and responsibilities of actors and stakeholders in research and innovation. Stilgoe, Owen and Macnaghten (2013) have identified anticipation, reflexivity, inclusion and responsiveness as dimensions of RRI. In our view, these dimensions capture the key features

of RRI, and at the same time reflect its spirit. Using the four dimensions of anticipation, reflexivity, inclusion and responsiveness, we outline the elements of a framework that can be used in agricultural biotechnology policy making.

Anticipation and Agricultural Biotechnology

Although scientists and policy makers argue that GM agriculture is necessary to address various problems in agriculture, such arguments are hotly contested. Chaturvedi and Arora (2014), drawing on the examples from India on conventional breeding, GM crops and organic agriculture, point out that each of these have some merits and disadvantages and governments cannot afford to choose one at the cost of others.

There is a strong case for holding inclusive debates on technological choices and policy options in agriculture and an informed assessment of the technological choices should be made. We should assess the socio-economic costs and benefits of each technological option and examine how they can be used without affecting long-term sustainability. Addressing questions through debates and public engagement will be necessary for ensuring that agribiotechnology R&D complies with the norms of RRI. In this context, a recent publication from the USA points out that public engagement is not the same as persuasion, and people have different perceptions about science and hence often arrive at different decisions when it comes to science (NAP 2015).

Inclusion and Agricultural Biotechnology

Although many studies indicate that Bt cotton technology is scale neutral, the picture is more complex. While technology per se may be scale neutral, often small and marginal farmers are not able to derive the best benefits from it on account of reasons such as non-appropriateness of the variety for that agro-climatic region, lack of access to quality seeds at affordable prices, lack of awareness of refugia and inexperience in handling the technology. While better extension services and capacity building can address some of these issues, we need to take into account the users' needs and perceptions right from the R&D stage.

Scientists should study the needs of such farmers and try to develop varieties that are more suited to them. Given the wider impacts of

GM agriculture, the interests of and impacts on different stakeholders should be taken into account. There is a need to address gender issues in agribiotechnology (Srinivas *et al.* 2015). Stakeholder engagement should go beyond farmers and labourers, but for the sake of brevity we are not elaborating this here. Engaging with diverse stakeholders will be necessary to address the inclusion dimension of RRI.

Reflexivity and Agricultural Biotechnology

Reflexivity means going beyond the cherished assumptions about one's work and its outcomes. In the case of agribiotechnology the reflexivity should be applicable for institutions and funders. For example, reflexivity would call for closer introspection on the values, objectives and norms that drive the innovation process and examine whether hubris underlies some of the claims of research and development. This also calls for engaging with insights from other disciplines and other perspectives. In the case of agribiotechnology such reflexivity can result in better consideration of other technological options in agriculture and addressing the limitations of technocratic problem solving.

Responsiveness and agricultural biotechnology

Often decision making in agribiotechnology is driven by technocratic understandings of governance and regulation and is not transparent enough to inspire confidence. In China information about field trials is not available in the public domain, while in India the regulatory regime is viewed with suspicion by some sections of civil society. Enhancing transparency and building a culture of deliberative policy making can be a solution.

Towards a New Framework

Enhancing access is an important part of the proposed RRI framework. Access could be hampered by many factors and in the case studies that we discussed IPR is an important factor. We have pointed out how China has addressed the IPR issue and how through promoting competition it has allowed the market to resolve the price issue. In many countries this may not be feasible due to lack of capacity in public sector. In such cases the state could use the options available under TRIPS including compulsory licensing, invoking competition law, and other mechanisms such as allowing

parallel trade. States can encourage open source agribiotechnology and promote OPVs over hybrids.

A policy framework that includes the four dimensions of RRI, as discussed above, and takes into account sustainability and societal desirability can be developed. This framework would evaluate R&D proposals on the basis of the societal desirability of the innovation and its 'broader impacts'. It would also include socio-economic assessment as part of the regulatory regime. The framework would promote responsible innovation and responsible regulation, taking into account the sustainability of the innovation.

Linking RRI with innovation and regulatory policy in agribiotechnology through a comprehensive framework would help in developing innovations that are well suited for society, and this framework would gain credibility and trust as it addresses the concerns of stakeholders, and goes beyond the technocratic mode of decision making and governance. While controversies and backlash from some sections of society may be inevitable, such a framework is better equipped to handle them than a technocratic framework, and can still fulfill the objective of promoting innovation and economic growth.

Endnotes

1 "Responsible Innovation means taking care of the future through collective stewardship of science and innovation at present" (Stilgoe et al. 2013).

2 A joint venture between an Indian seed company, Mahyco, and US multinational seed company, Monsanto.

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