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Potential implications of new synthetic biology and genomic research trajectories on the International Treaty for Plant Genetic Resources for Food and Agriculture

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Scoping Report

Potential implications of new synthetic biology and genomic research trajectories on the International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA or ‘Treaty’)

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Executive summary

Introduction

This scoping report focuses on the potential implications of new synthetic biology and genomic research trajectories on the International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA or ‘Treaty’). Specifically, it provides an introductory examination of how the evolving technological, legal and institutional context surrounding the exchange and use of digital sequence information (DSI) for synthetic biology and genomic research affects the principles of the Treaty, and specifically its access and benefit-sharing (ABS) framework. Seen broadly, the report addresses the phenomenon of dematerialization, which suggests that “the information and knowledge content of genetic material [could increasingly be] extracted, processed and exchanged in its own right, detached from the physical exchange of the plant genetic material” (FAO, IT/GB-5/13/4).

The analysis in the scoping study is organized into five main components: 1) key principles and structural dimensions of the Treaty that focus the inquiry; 2) scientific and technological changes; 3) legal considerations; 4) potential opportunities for benefit-sharing; and 5) synthesis of findings and possible next steps. Based substantially on a review of documents, academic literature and analysis of expert interviews, the scoping study aims to provide a useful resource for the Treaty community, as it seeks to determine how it should address technological changes in genomics and genetic research.

Key principles and structural dimensions

DSI and dematerialization have the potential to affect at least three key ABS principles – identification, monitoring and value generation – and three structural features of the Treaty’s ABS framework – pooling, decoupling of benefits from individual provider, and diversity of benefits. *This study considers the impact of DSI/dematerialization on all six.*

1. Identification logic. ABS policies are based on the principle that control over access to resources enables the identification of users and the establishment of agreements on use.
2. Monitoring of usage. In ABS policies, the transmission of the rights associated with the resources through subsequent exchanges is conditional upon the capacity to identify such exchanges, notwithstanding the lack of any obligation in the Treaty framework, to track individual germplasm samples.
3. Value generation. ABS is based on the principle that value is extracted from the use of resources; value can be either of a monetary or non-monetary nature.
4. Pooling/standardization to facilitate access. The Multilateral System of Access and Benefit-sharing (MLS) pools resources across member countries, which collectively agree to standardized terms and conditions for exchange.

5. Decoupled monetary benefit-sharing from individual providers. The MLS pools benefits in a common fund to rationalize the administrative costs of organizing the sharing of benefits and decreasing the need to attribute benefits into a number of shares.
6. Diversity of benefits. In addition to monetary benefits, the Treaty foresees four different benefits: i) facilitated access to plant genetic resources for food and agriculture (PGRFA) within the MLS; ii) exchange of information; iii) capacity-building, and iv) access to and transfer of technology.

Key findings

Science and technology dimensions

Scientific and technological changes have a significant impact on how research is conducted, and how materials are sourced and used. Several summary findings are evident.

There are three main ways in which new synthetic biology and genomic technologies are being used that may have implications for the Treaty: 1) mining plant genomic information for gene editing purposes in agriculture; 2) mining for use outside of agriculture; and 3) using the plant as a ‘workhorse’ to produce other products. The first of these is the most common, but new policies should broadly recognize the constantly evolving scientific and technological context.

The new digitization era is producing a large amount of sequence data that is widely available and easily exchanged. The high number of decentralized data libraries and organizations raises significant challenges to the ABS logic of identification, and the different expectations of monitoring that are currently in the Treaty framework.

Technological changes have accelerated the dematerialization revolution. Even though many researchers still require or prefer to have the physical material for their work, there is an increasing separation between material and data in the research enterprise. As a result, it is less and less likely that the ABS system can rely on the link between material and data to identify ownership and location.

For many reasons noted in this section, monitoring DSI exchange is a challenging prospect. But even if a robust tracking system were possible, other factors including partial sequence combinations, and the fact that the same sequence may occur in multiple organisms, further challenge the ABS principles.

Legal dimensions

The development and use of DSI in synthetic biology projects may pose a challenge to the ABS structure of the Treaty. Article 12.3(a) of the Treaty specifies that access to material under the MLS is solely for purposes of “utilization and conservation for research, breeding and training for food and agriculture”, and excludes “chemical, pharmaceutical and/or other non-food/feed industrial uses.” Researchers can effectively use DSI from MLS material (e.g. obtained through

DSI in publicly accessible databases) in any kind of research, including chemical and/or pharmaceutical, without such usage being easily monitored.

Moreover, even though scientists working on DSI may be using sequence information from identifiable published material, the chain of transmission is often neither transparent nor easily documented, and there are no indications that legal innovations such as open material transfer agreements (MTAs) will improve monitoring of downstream uses of Treaty genetic material or DSI. As such, it may be difficult to assess benefits from uses of Treaty genetic material or DSI. While some patents obtained for inventions incorporating DSI may provide geographic origin information, others may not, or the information may be hidden if a particular sequence could be obtained from more than one kind of organism. In addition, patents may not always be necessary to extract value from DSI, as trade secret protection can be a viable alternative under certain conditions. Finally, if the Treaty chooses to generate DSI for MLS crops and adopt a fee (e.g., subscription) model for access, it is to be considered how downstream uses of the DSI from the MLS are identified effectively.

Opportunities for benefit-sharing

The Treaty recognizes the fact that “facilitated access to PGRFA which are included in the Multilateral System constitutes itself a major benefit of the Multilateral System”. It also acknowledges the importance of three other mechanisms for the fair and equitable sharing of the benefits arising from the use of PGRFA, namely the exchange of information, access to and transfer of technology, and capacity-building.

To better understand opportunities for benefit-sharing, interviewees were asked to assess where the primary value lies in the synthetic biology and genomic work. Four conceptualizations of value emerged: innovation, sequence and part functionality, plant system understanding and education and exploration. Additionally, interviewees were asked about the requisite infrastructure for undertaking synthetic biology research. Through interview data, three general perspectives were identified: high-cost infrastructure, low-cost infrastructure and flexible infrastructure. Recognition of the diverse sources of value and different approaches to infrastructure helps to inform study findings on opportunities for non-monetary benefit-sharing.

A review of background materials and interviews undertaken for this scoping report led to the identification of five different strategies employed by researchers that are currently in place: 1) *ex ante* investment to facilitate access; 2) grant-based funding for hard infrastructure investment; 3) facilitated access for research community building; 4) structured research collaboration; and 5) education and training. These different strategies can be linked to the values framework and investment approaches above, and could be considered by the Treaty community as it addresses benefit-sharing and DSI.

Synthesis and implications

A final step in this scoping study is to connect findings from the interviews to the initial framework on ABS for the Treaty, and reflect on the implications of the analysis.

1. Identification logic. To what extent does DSI/dematerialization affect the ABS principle of control over access to resources, including assumptions about the ability to identify users, provenance, and owners for the purposes of establishing agreements on use, use restrictions, dissemination and benefit-sharing derived from use?

In general, findings indicate that the underlying *ABS logic of identification* will be subject to erosion over time, given the proliferation of data, multiplication of users, varied importance of information about provenance and other factors. As researchers may be less likely to return to the original material over time, it will become more difficult to identify the source of the gene sequence. Additionally, database owners, sequencing companies and others are neither keeping nor requesting information about the material source of the DSI.

2. Monitoring of usage. To what extent does DSI/dematerialization affect the ability to monitor PGRFA over time and the transmission rights associated with them through subsequent exchange?

Although researchers may use sequence information from identifiable published material, the chain of transmission is often not transparent or easily documented, and there is evidence of resistance from at least some database operators to facilitating ABS-based monitoring. While some patents obtained on inventions incorporating DSI may provide geographic and/or species origin information, others may not, or the information may be hidden if a particular sequence could be obtained from more than one kind of organism. In addition, patents may not always be necessary to extract value from DSI, as trade secret protection can be a viable alternative under certain conditions. Overall, the ability to monitor appears to be eroding and, without some mechanism or incentive to build norms of exchange across multiple users and uses, it will probably continue to do so.

3. Value generation. To what extent does DSI/dematerialization affect the value generated from DSI, either monetary or non-monetary?

A significant portion of the value of DSI is in its aggregation (along with characterizing information) in accessible libraries/databases. An individual sequence may have value as part of a group of sequences from diverse sources combined to provide an organism, such as a plant or bacterium, with new functionality to produce high-value products. However, such value is diffuse, and spread across all the individual conjoined sequences necessary for the modified organism to function. Additionally, the value of an individual sequence from a species may be very difficult to quantify. This raises three overarching issues that the Treaty constituency may consider.

- a. Mining of genomic information from the plant genomes that could be used to edit plant genetic materials, including those inside the pool of the Treaty.

- b. Mining of genomic information from plant genomes that could be used outside the agricultural sector.
- c. New approaches to using the plant as the ‘workhorse’ to build/understand certain components or traits of the plant in order to produce an output.

DSI/dematerialization/synbio has led to a multiplication of innovation trajectories, diffuse uses and means of combining sequences and parts. This evolution makes articulation of a specific monetary value of a sequence within an entire new product or process challenging. Nevertheless, the potential for generating high-value products, and thus monetary and non-monetary benefits, will probably grow with the increasing use of synbio technologies in the future.

4. Pooling/standardization to facilitate access. To what extent does DSI/dematerialization impact the aggregation and standardization approach promoted by the MLS?

The multiplication of holders of DSI collections distributed in a number of media and the diversity of standards, norms and behaviours will make it difficult to establish an aggregated and standardized system at a desirable scale, as it would require a central authority to adopt and manage collective rights, which would probably lower flexibility for adaptation to specific contexts.

The development of new synbio technologies for education, tool provision and low-cost investment (challenges, kits and curricula development), while still early in their development, create potential for new forms of pooled resources. The various innovators of these technologies and practices represent potential partners for investment in pooled resources for the Treaty.

5. Decoupled monetary benefit-sharing from individual GR provider. To what extent does DSI/dematerialization impact the MLS approach of decoupling benefit sharing from individual provider?

As many synbio products are developed with the contribution of sequences from multiple species, the average value of individual contributions remains rather low in most cases, and the benefits to be shared would be diluted among a wide range of stakeholders. Benefit-sharing by the Treaty would have to consider the multiplication of sources, pathways and producers of DSI and DSI-based innovation. Within the synbio research context, frontiers between organisms and species are increasingly blurred, and pathways are more and more diversified and complex. There is a shift in perceived value of the collection of DSI and recognition of the value of particular entries within DSI databases. This could potentially result in different willingness to pay ‘fees’ on access.

6. Diversity of benefits. To what extent does DSI/dematerialization affect the realization and relative weights of the different benefits foreseen under the MLS?

The scoping study identified a wide range of benefits, most of which can be categorized as one of the four types of non-monetary benefits: facilitated access to PGRFA within the MLS; exchange of information; capacity-building; and access to and transfer of technology. For any potential for meaningful monetary benefit-sharing to be realized, the monitoring complexities that dematerialization brings forward should be addressed.

New mechanisms are being developed to facilitate public access to synthetic biology technologies and tools that operate as building blocks for a range of research-related activities, from education to advanced science. Different approaches to infrastructure investment have made technologies and innovation available to both entry-level and advanced users. Differentiation of services has increased access points for investment and participation in the various components of the design-build-test (DBT) system. Importantly, the synbio research community is attempting social and institutional innovations that could be recognized by the Treaty as mechanisms for identifying and capturing collective benefits.

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I. Introduction: Scoping study objectives and structure

This scoping report focuses on the potential implications of new synthetic biology and genomic research trajectories on the International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA or ‘Treaty’). Specifically, it provides an introductory examination of how the evolving technological, legal and institutional context surrounding the exchange and use of digital sequence information (DSI) for synthetic biology and genomic research affect the principles and framework of the Treaty. Seen broadly, the report addresses the phenomenon of dematerialization, which suggest that ‘the information and knowledge content of genetic material [could increasingly be] extracted, processed and exchanged in its own right, detached from the physical exchange of the plant genetic material’ (FAO, IT/GB-5/13/4).

The report, based substantially on a review of documents, academic literature, and analysis of expert interviews, aims to provide a useful resource for the Treaty community as it seeks to determine how it should address technological changes in genomics research. As such, it tries to avoid value-laden judgments, preferring to focus on uncovered evidence about the relevance of socio-technological changes and new modes of organization for the Treaty. The report does not discuss what constitutes a genetic resource, what legal definition of DSI, genomic/genetic data/information may conventionally be adopted, whether DSI falls under the Treaty, or ethical or safety dimensions of genetic engineering in the food and agricultural sectors. A description of the methodology for this study is presented in the Appendix.

The report is presented in seven main sections, including the introduction. The next section identifies the key principles and structural dimensions of the Treaty and outlines the objectives of the inquiry. Each of the three sections that follow examines technological changes, legal issues, and opportunities for benefit-sharing. Questions investigated in the three sections include:

- Technological dimension: What are the characteristics of the technological change? How are data different from material? How are sequence data stored, exchanged and shared? What are the documentation practices? Can DSI be traced to material?
- Legal dimension. How are actors addressing ownership, property rights, and tracking for DSI? What are the emerging intellectual property (IP) practices? To what extent have researchers experienced IP constraints?
- Benefit-sharing dimension: What are the different ways that actors assign value to DSI? How accessible is DSI to individuals, institutions and countries with different levels of scientific and technical capacity? What investment options exist for developing scientific and technical capacity in synthetic biology and genomics?

The sixth section of the report synthesizes study findings, and identifies potential ways in which the technological changes could affect the principles and ABS structural dimension of the Treaty. The final section identifies limitations of the study and potential next steps for further investigation. The report does not provide recommendations, but rather sets out possible implications and potential points of consideration for the Treaty community.

II. Implications of DSI/dematerialization for the Treaty

The Treaty provides an international framework for the conservation, use and exchange of plant genetic resources for food and agriculture (PGRFA). It recognizes “that plant genetic resources for food and agriculture are a common concern of all countries, in that all countries depend very largely on plant genetic resources for food and agriculture that originated elsewhere”. The recognized high degree of interdependence across countries for plant germplasm is the main justification for the establishment of the Multilateral System of Access and Benefit-sharing of the Treaty (MLS), the objective of which is “to facilitate access to plant genetic resources for food and agriculture, and to share, in a fair and equitable way, the benefits arising from the utilization of these resources, on a complementary and mutually reinforcing basis”.

The Treaty was designed in a context in which informational components, such as passport or phenotypic data, were always considered in relation to the physical material.¹ This may no longer be the case, given the phenomenon of dematerialization arising from the significant technological changes in genomics research. Scientific and technological changes are transforming the research and innovation system designed around material genetic resources (and associated information), to one that is more dependent upon DSI. The new socio-technological paradigm that emerges has the potential to affect ABS under the Treaty: cheaper and faster DNA sequencing and synthesis capabilities, along with more accessible and improved genome editing and assembly tools could affect the principles and ABS structural dimensions of the Treaty. This report focuses specifically on six dimensions of ABS – three general principles and three specific features of ABS under the Treaty – to provide focus for the analysis to come.

Potential impact of DSI/dematerialization on general ABS principles

DSI and dematerialization have the potential to affect at least three key ABS principles: identification, monitoring and value generation. Although the Treaty follows a specific approach that adjusts these general principles, considering ABS constituents helps to address some specific features of the Treaty framework in the subsequent section.

- i* Identification logic. ABS policies are based on the principle that control over access to resources enables identification of users and establishment of agreements on use. The principle is dependent on the ability, albeit not absolute, to identify the source, and on the assumption that the characteristics of the resources are linked specifically to the source from where they have been accessed. *This study considers the extent to which DSI/dematerialization may affect this logic.*

¹ Article 12.3 of the Treaty related to the MLS, states that “all available passport data and, subject to applicable law, any other associated available non-confidential descriptive information, shall be made available with the plant genetic resources for food and agriculture”.

- ii. Monitoring of usage. For ABS policies, the ability to transmit the rights associated with particular resources to subsequent exchanges is conditional upon the ability to recognize such exchanges. *This study addresses the ability to monitor exchanges of DSI.*
- iii. Value generation. ABS is based on the principle that value is extracted from the use of resources; value can be either of a monetary or non-monetary nature. *This study examines how DSI/dematerialization may relate to value generation.*

Framework: ABS principles and structure of the Treaty

The Treaty's ABS mechanisms are designed to reduce transaction costs associated with the exchange and use of PGRFA. This objective manifests itself in three structural features of the Treaty's ABS framework: pooling, decoupling of benefits from individual provisions, and diversity of benefits.

- iv. Pooling/standardization to facilitate access. The MLS is built around the recognition that: i) material has long been exchanged across borders; ii) is available *ex situ*, including in places outside of the centre of origin; and iii) is widely exchanged internationally, as all countries depend significantly on PGRFA that originated elsewhere; and iv) products that incorporate contributions of PGRFA from multiple providers obtained at different points of the R&D process require management of different legal conditions contributing to the same product. To reduce transaction costs involved in the international exchange of material, the MLS moves away from a case-by-case, bilateral ABS approach. Instead, it pools resources across member countries, which collectively agree to standardized terms and conditions for exchange. *This study examines how DSI/dematerialization may impact the aggregation/standardization approach of the MLS.*
- v. Decoupled monetary benefit-sharing from individual PGRFA providers. The Treaty's MLS recognizes that identifying the individual benefit shares and respective beneficiaries is difficult because: i) the process of genetic improvement is usually incremental and continuous, occurring over many successive generations; ii) innovation is non-linear, in that a product is never the end point, but always an intermediate step in a chain of improvement and recombination. The MLS pools benefits in a common fund to rationalize administrative costs of sharing of benefits, and reducing the need to attribute benefits into shares. *This study investigates whether and how DSI/dematerialization may impact the MLS approach to decouple benefit-sharing from provision.*
- vi. Diversity of benefits. In addition to monetary benefits, the Treaty foresees four other benefits: i) facilitated access to PGRFA within the MLS; ii) exchange of information; iii) capacity-building; and iv) access to and transfer of technology. The pooling and decoupling of benefits within the MLS enable the realization of collective benefits. The use of PGRFA is intended to generate non-monetary benefits and external spillover effects that have a collective or public value. *This study examines how DSI/dematerialization may affect the realization and relative weights of the different benefits foreseen under the MLS.*

III. Technological issues

Scientific and technological changes are transforming the research and innovation system designed around material genetic resources (and associated information), to one that is more dependent upon DSI. The transformation has led to the production of large quantities of data, the creation of new organizations designed to house data, the development of new technologies such as CRISPR Cas-9, and the advent of new fields, such as synthetic biology. At the same time there has been a significant and persistent push toward open data and open exchange of data across the world. This section of the study presents key dimensions of such technological change, and reflects on how those changes affect key ABS principles and components of the MLS.

Synthetic biology

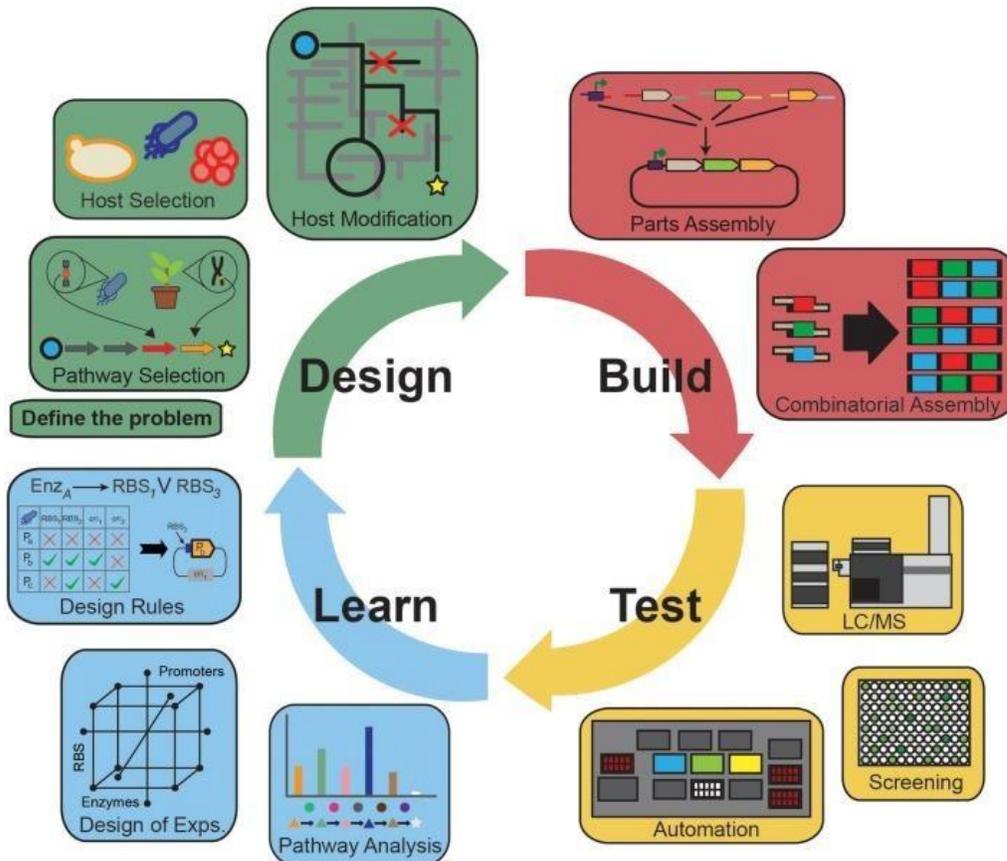
Synthetic biology is a concept, based on engineering disciplines, that incorporates many different genetic/genomic technologies and techniques. Synthetic biology has been defined in multiple ways (highlighted in Box 1). While there is no agreed upon definition and no definition will be able to incorporate the rapidly changing technology landscape most definitions include similar elements of the engineering disciplines based upon applied science, technology and incorporating different types of applications.

Box 1. Example definitions of synthetic biology

- ❖ Synthetic biology is the further development and new dimension of modern biotechnology that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems (U. N. Biology 2015).
- ❖ Synthetic biology is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms (SCENIHR 2014).
- ❖ The deliberate design or biological systems and living organisms using engineering principles (Martin 2008).
- ❖ The design and construction of novel artificial biological pathways, organisms and devices or the redesign of existing natural biological systems (Society 2017).
- ❖ The use of computer-assisted, biological engineering to design and construct new synthetic biological parts, devices and systems that do not exist in nature and the redesign of existing biological organisms, particularly from modular parts. (I. C. Biology 2011).
- ❖ A new research field with in which scientists and engineers seek to modify existing organisms by designing and synthesizing artificial genes or proteins, metabolic or developmental pathways and complete biological systems in order to understand the basic molecular mechanisms of biological organisms and to perform new and useful functions (Commission 2009).

Synthetic biology is typically described inside the engineering concept of the design-build-test cycle (DBT). The cycle is illustrated in Figure 1 (Petzold, et al. 2016; Petzold et al., 2015). The technologies making up each part of the DBT may change, be replaced, or evolve over time (National Academies of Sciences 2017).

Figure 1. Design, build, test cycle for DSI



Synthetic biology and associated technologies represent a significant shift towards dematerialization and the use of DSI. One of synthetic biology’s major advancements is its ability to “enable researchers to envision and plan the engineering of biological components including DNA base pairs, codons, amino acids, genes, gene segments, regulatory elements, and the environmental context in which they may operate (National Academies of Sciences 2017)”.

The automation of this design component through computer algorithms, computer software and machine learning (National Academies of Sciences 2017) has reduced substantially the time it takes to design new biological components. One important aspect of this automation is that researchers can use “collections of realizable DNA constructs” (National Academies of Sciences 2017) to not just design new genetic functions or traits, but also to predict how those genetic functions will operate in a particular living organism or system (i.e. gene expressions). Ultimately,

advances in computer and design programmes, along with access to more DNA constructs, are enabling researchers to design more complex biological systems.

New technologies and plant breeding

As noted above, researchers are increasingly able to use computer-assisted approaches to scan DSI and identify traits of interest across multiple species. In agriculture, these traits can then be introduced into plant species, utilizing genetic engineering and/or synthetic biology techniques. Examples of agriculture-related technologies associated with genetic engineering and synthetic biology include (UWE 2016):

- **Transgenesis**: the transfer of genes between two species that could not naturally breed with one another. This is typically how genetically modified organisms (GMOs) have been developed in the past.
- **Cisgenesis**: the transfer of genes between the same species of plant or between species that can breed naturally. This is usually associated with a gene that confers resistance to a particular disease, which is ‘cut and pasted’ from one individual to another, creating a hybrid of the two.
- **Intragenesis**: the transfer of a series of genes between individuals of the same species, or between a species that can naturally breed with one another. This can be associated with a gene that inhibits certain detrimental effects, but is unable to be adequately expressed. That particular gene is isolated and combined with other pieces of DNA that can increase its expression rate, and then inserted into the genome of the plant.
- **Targeted gene editing**: the targeted editing of a plant’s genome using enzymes such as CRISPR – Cas9. These have the ability to cut and paste specific regions inside a plant’s genome.

Advances in genomic technologies and digital libraries of DNA sequence information now enable a researcher to screen large collections of biological material with computer software, identifying the trait of interest, without necessarily handling the original physical material. Many researchers we interviewed suggested that, despite these advances, they would still need/prefer to go back to the original physical material in which the traits of interest were identified. Genomic mining and design tools can “facilitate the pursuit of more complex protein engineering, such as designing a new protein or enzyme capable of functioning with a level of specificity similar to that of natural proteins” (National Academies of Sciences 2017).

“Using computer software researchers can screen large libraries of DNA sequence information to identify genes or proteins that encode for specific desirable traits or functionality (National Academies of Sciences 2017). Once identified, these genes can be synthesized and tested in vitro or in vivo.” This type of manipulation of the biochemical pathway of a cell to produce a desired trait, typically to produce a chemical, is referred to as ‘metabolic engineering’. Recent advances in technology are also allowing phenotype engineering, or the result and interactions of the particular trait that was engineered as it relates to the organisms or plant.

The “explosion of sequence information and accompanying systems biology characterization of multiple organisms have provided a cornucopia of possibilities for engineering phenotypes that involve much more complex networks of genetic components” (National Academies of Sciences 2017). Simultaneously, “the rise of DNA construction and genome editing technologies could facilitate the construction of multiple variants that involve alterations to multiple genes across an organism” (National Academies of Sciences 2017).

The incredible complexity of plant chemistry, and the difficulty of extracting isolated active compounds of interest, led to the view that even if genomic sequence information were available, they would not be very helpful. However, breakthrough advances in many areas of plant research are increasing the feasibility of wider use of plant genome sequence information and plant chassis for vaccine, therapeutic, and speciality chemical production.

It was believed that relevant genes for important pathways would probably be scattered far and wide, thereby necessitating a needle-in-a-haystack type of search. However, scientists have learned that important biosynthesis pathways are actually clustered together in the genome, and with new scanning algorithms, candidate pathways and chemistries are easier to identify in genome sequence information. In addition, while much synthetic biology work has focused on coaxing yeast or *E. coli* to produce drugs and high value chemicals, synthetic biology advances show that plants could be vastly more efficient and productive producers of vaccines, therapeutics, and customizable chemicals, compared with microorganisms or traditional chemical synthesis.²

Taken together, these technologies are used in three main ways that have implications for the Treaty. First and currently most frequently practised, they are used to mine plant genomic information to identify sequences and genes to be used in editing materials for agriculture, including crops included in the MLS. Second, it is possible to mine plant genomic information within the Treaty for use outside agriculture. Finally, the technologies can be applied in ways that harness the plant as a ‘toolbox’, using it to produce other types of outputs, such as vaccines. More detail on DSI and plant breeding is presented in Box 2.

² See, e.g., James Reed, *et al.*, A Translational Synthetic Biology Platform for Rapid Access to Gram-scale Quantities of Novel Drug-like Molecules, *METABOLIC ENGINEERING* 42 (2017) 185–193 (“Plants have many inherent advantages over microbes for expression of genes, enzymes and pathways of plant origin. However, they have historically been overlooked as efficient heterologous hosts for small molecule production”); John Innes Center, “CPMV-HT Protein Expression System,” available at http://www.pbltechnology.com/assets/technologies/07.439_CPMV-HT_Tech_Sheet_2.pdf (describing the HyperTrans system for expression of foreign proteins (e.g. flu vaccines) in plants in high quantities); Melissa Salmon *et. al.*, “A conserved amino acid residue critical for product and substrate specificity in plant triterpene synthases,” vol. 113 no. 30, *PNAS* (July 26, 2016) (discussing synthetic biology-based methods of developing and accelerating production of novel and diverse triterpenes (plant products with a myriad of medicinal applications)).

Box 2. DSI and plant breeding

Humans have been modifying/engineering plants and animals ever since we began selecting plants and animals for specific traits more than 10,000 years ago. In the early to mid-20th century, breeders began to seek new ways to introduce genetic traits into plants, and the term genetic engineering emerged. Over the past 70 years, plant breeder understanding and discovery about how physical and chemical manipulations introduce mutations in the DNA of a plant has led to thousands of new plant varieties in hundreds of plant species (Nogue, *et al.*, 2016). Many of the new varieties can be accessed through the FAO/IAEA Mutant Variety Database (FAO/IAEA 207). More recent genome engineering techniques affecting plant breeding, broadly characterized as site-directed nuclease (SDNs), are based on the introduction of double-stranded breaks at specific locations within the plant genome. These techniques include: meganucleases (MNs), zinc-finger nucleases (ZFNs), transcription-activator like (TAL) effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeat (CRISPR) (Podevin, *et al.* 2013). How broadly applicable these new techniques will be for plant breeding is an open question, as they have only been attempted on a few species of plants, focusing on a few specific traits.

Breeders and researchers have characterized numerous alleles (or mutations) associated with plant domestication and improvement, and have identified the genes and phenotypic differences between crops and their wild relatives. According to some researchers, these mutations are the “raw material on which selection can operate making species adaptation and long-term evolution possible” (Nogue *et al.*, 2016). This ‘raw material’ is equivalent to computer codes that can be analysed, reprogrammed and theoretically used either within the plant it was obtained from, or within a different species of plant. This type of description or abstraction of the plant’s genetic make-up is part of the scientific/engineering philosophy surrounding synthetic biology

Synthetic biology, as it relates to plant breeding, has been enabled in part by advancements in quantitative traits loci mapping (QTLs) (Olsen, 2013) (Nogue, Mara, Collonnier, & Casacuberta, 2016). With advances in high-throughput genotyping and phenotyping technologies, QTL tools enable researchers to identify regions in a plant’s genome that are associated with agronomic traits (Nogue, Mara, Collonnier, & Casacuberta, 2016). Combining the advances in SDNs, genome mapping and the increasing characterization and cataloguing of alleles (mutations), plant breeders are better able to identify, understand and deliver specific traits into a particular species of plant. If sequencing technologies become more accessible, it is possible that new alleles can be identified in plant varieties from a more diverse set of geographic locations with different environmental variables. According to the hypothesis of synthetic biology, these alleles do not need to be naturally occurring. Aided by computer aided design, synthetic biology proposes developing alleles “otherwise not present in the available genetic diversity” (Nogue, Mara, Collonnier, & Casacuberta, 2016), building on the genetic information of naturally occurring alleles and designing “synthetic alleles” with new or improved functionality.

Advances in SDN technologies and machine learning, combined with the growing size and complexity of plant genetic sequence databases, could affect plant breeding programmes more broadly. The science behind these recent advances is still in its infancy (relatively speaking), and will depend on our understanding of the biology of the plant species (i.e. self-pollinated v. cross pollinated, perennial v. annual, haploid v. polyploid etc.), the complexity of the traits of interest (i.e. whether it depends or not on multiple locus), and how they interrelate. There does not appear to be a consensus among plant breeders on how effective these new technologies may or may not be. Access will be a limiting factor for plant breeders – access to the tools in order to search for new naturally occurring alleles (bioprospecting), access to databases containing the genetic information of plants and subsequent alleles, access to the knowledge needed to understand that genetic information, and access to SDN technologies, in order to use that genetic information for plant breeding.

The proliferation and decentralization of data

Scientific and technological advancements are enabling researchers to “create larger libraries of combinatorial variants”, or genomic parts, and use machine learning to choose the best result (National Academies of Sciences 2017). Machine learning approaches can continuously create new variants, generate new design rules and could “ultimately remove human designers from the design process, allowing DNA design, assembly, and verification equipment to explore” large sets of DNA data automatically (National Academies of Sciences 2017). The results of these programmes can be stored, shared and validated electronically (National Academies of Sciences 2017).

In the past, the physical material was accessed through collections held in gene banks, botanical gardens, or private/public collections. As the technologies have developed, there has been a rise in digital collections that include complete genomes as well as ‘parts’ registries. Digital collections are diverse in terms of structure, as well as in terms of who operates them, and who has access to them. Some are public databases (e.g. the iGEM registry, university collections and botanical gardens), some are public/private partnerships (e.g. foundries), and others are individual researcher collections. Many of these collections also include the physical materials that make up the ‘parts’ (DNA), along with the digital file. As costs have dropped, the field seems to be moving towards a highly distributed service oriented model in which foundries³ and DNA synthesis companies (producers of DNA/organism) build their own collections of sequence data (or entities send them their own sequence data), and then they produce physical constructs based on those digital files.

The technologies associated with synthetic biology and the shift towards DSI have been accompanied by an increasingly differentiated research organizational structure. The evolving structure is highly decentralized, and based increasingly on a service model in which sequencing, synthesis, storage, assembly, screening and other activities are conducted by numerous different actors.

Whereas the sources of physical material are distributed across countries, making access complex and enabling many different avenues for exchange, with varying practices regarding MTAs, in this new era, the distribution of data resources as DSI is even more decentralized, dynamic and rapid. For the Treaty, this suggests that reliance on the logic of identification and expectations of monitoring the exchange of DSI may be tenuous. But as science and technology shifts towards DSI, a key question concerns who has access to these digital collections, and who has the ability to analyse and/or take advantage of DSI.

³ According to interviewees, foundries employ the latest technology to make the process of engineering biology easier, faster and scalable. The integration of advanced software, automation and analytics allows the rapid design, build and testing of engineered organisms. See: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4900743/>

Moving from data to material

Prior to DSI-related technologies, a researcher interested in an organism's genetic information would need to obtain the organism and then have its DNA sequenced. Today it is possible to simply download the genetic code or information from a database (or academic journal) and have it synthesized by one of the many DNA synthesis companies. However, a number of factors determine whether it is possible to 'build' living material from collections of DNA sequences, and whether such material will function in a living system. These include: cost, time available, ease of access to DNA synthesis and construction, quality of the DNA libraries and digital sequence data in them, quality of the DNA parts (if in a physical format), and the ease and/or quality of the synthesis capabilities (National Academies of Sciences 2017). The trend seems to suggest that lower costs are providing researchers with the option to contract large-scale foundries or synthesis firms for sequencing and synthesis services.

Recent technological advances may enable researchers to synthesize their own DNA without having to use a commercial company: "SGI-DNA, a Synthetic Genomics company, has introduced the world's first DNA printer, a machine which will allow any biotechnology company or academic laboratory to create genes, genetic elements and molecular tools on their benchtop hands-free, starting with electronically transmitted sequence data" (SGI-DNA n.d.).

While technology is making it easier to create genetic elements from digital information, interviews demonstrated that many researchers still need the physical material in order to understand the phenotypic characteristics (e.g. an organism's physical characteristics, and how it interacts with its environment) of that organism's genotype (genetic information). Nevertheless, as digital libraries of genetic information grow, the ability to screen for variations in phenotypic information will also increase. As this occurs, an understanding of how genotype relates to phenotype will guide a designer's ability to achieve a desired phenotypic outcome (National Academies of Sciences 2017), and may reduce the need for the physical material.

High-throughput screening is further enabling the abstraction of physical material from digital genomic information. As technologies have improved, along with the growing libraries of genetic data, automation of screening enables researchers to "screen thousands to billions of individual variants of an organism for function or phenotype (National Academies of Sciences 2017)". Demand for screening technologies is increasing and moving towards "-omics approaches that are agnostic to the type of organism being tested (National Academies of Sciences 2017)", moving further away from the need for the physical or 'origin' material. For example, "a researcher could conduct a high-throughput screen of variants using a technology or technique (e.g. CRISPR/Cas9 library, MAGE, or DNA shuffling), whereby a set of related genes or genomes is broken down into smaller pieces that are re-assembled. The variants selected could then be selected for growth on a novel substrate, potentially identifying both a gene and an organism whose sequence was not fully included in any of the original precursor genes (National Academies of Sciences 2017)."

Acquisition, use and sharing of data (and material)

The process of acquiring physical genetic material by synthetic biology researchers appears broadly similar to that of other researchers, and generally involves use of a material transfer agreement. However, this is not always the case. A recent report notes that “many labs use materials either without going through an MTA process or not strictly adhering to the agreement.”⁴

Moreover, the response of synthetic biology researchers to actual or perceived difficulties in obtaining genetic material is often to simply bypass formal and institutional barriers and construct the material by themselves. As one interviewee explained:

“[B]efore we had to ask for the material...if we wanted to repeat or to continue the work . . . that had been done in other labs. But now because of synthetic biology, it’s quite easy to standardize some very complex construct and it’s easy to do CRISPR. So for instance, if we want to do something and say nothing to anybody – let’s say someone published something interesting and I want to reproduce or do some specific work on it – I could just use the data that was published to reproduce [it] myself or to do my own construct and do it very quickly...almost as quickly as to use the seeds...[T]en years ago it was quite complicated. It was easier to ask . . . people [to send the seeds]. But now...if I have the name of the gene and an idea of the construct, I could standardize the construct myself and do the transformation. ...[I]f you want to do something very complex, you just do it on your computer and [send it to a foundry]...the company will do it for you for – it’s very cheap.”

This ability to bypass the use of physical material is expected to increase over time and, with the proliferation of easily accessible DSI, may pose a challenge to the Treaty’s material-based ABS regime. In addition, some researchers noted that while they might like to use material from the MLS, they choose not to because of royalties. Interviewees claimed that if they use multiple traits in a single product, it would necessitate paying the royalty percentage for each trait, which would arguably eliminate the already low (as opposed to pharmaceutical) agricultural profit margin in a licensing scenario.

The uses of DSI of plant and non-plant origin are diverse, and seemingly limited only by the human imagination. For some researchers, having access to a published sequence is all they need in order to identify traits of interest encoded in that sequence, bypassing difficulties in obtaining tangible material. At this digital prospecting stage, researchers do not really need the physical material, unless it has not been sequenced, or the sequence is not of high or trusted quality. For other researchers, having access to DSI along with a physical sample is necessary or at least desirable, in order to understand the linkages between genomic and phenotypic interactions. Based on research being conducted, it may not be enough to simply identify a particular trait encoded in a genome, but will require understanding how those traits operate within the genome, and its

⁴ OpenPlant Intellectual Property Working Group Meeting Report, p. 8 (2015), available at <https://static1.squarespace.com/static/54a6bdb7e4b08424e69c93a1/t/58a2ee88a5790a100dcb8ff9/1487072905283/Preport.pdf>

interaction with its environment. Nevertheless, the use of DSI, in combination with other technical advances, can dramatically reduce the amount of time necessary to observe phenotypic changes in an organism.

Some researchers noted that the quality of the sequence information, or the synthetic reconstitution of the DSI by a synthesis company or foundry, varied and could impact their ability to effectively use DSI. As a result, some researchers prefer to obtain the physical material in order to ensure better control over the sequencing process. Conducting their own sequencing increases their trust in the data and information generated.

For researchers using DSI in plants, any traits identified would generally need to be reinserted into a plant to confirm whether expected changes have actually materialized. This is true even if that sequence information is used to create a synthetic, modified sequence. Hence, while the original research may not have utilized any physical material, eventually physical material will be utilized.

However, DSI used to identify valuable traits, and the subsequent modified or synthetically created sequences, may not be introduced into the plant species from which they originated. This creates a complex situation in which the source of the original resource is not easily identified, thereby contributing to a breakdown in the ABS identification logic.

Monitoring of DSI

Use of material from the MLS requires compliance with the Standard Material Transfer Agreement (SMTA), which attaches to and is conveyed with any future transfers of the material to third parties. This allows for linking MLS material usage and provenance. However, the proliferation of DSI is likely to diversify this system. Vast amounts of DSI are being made publicly available at an accelerating rate in databases and repositories such as GENBANK, Addgene, NCBI and others. While some researchers still prefer to obtain high quality sequence information from the tangible material, as noted above, others are using only sequences obtained from databases or published academic papers, and reproducing the material themselves or with the help of foundries. In such cases, there may be no material transferred and no monitoring of access to and use of the data in relation to the material or *per se*.

While some interviewees mentioned data sharing and use agreements, there were no indications that such agreements are widespread or imposed by database operators for DSI, although large databases managed by the US National Institutes of Health do request data users to submit data use agreements. In theory, database access could be tracked; however, some interviewees noted that database operators have been and will probably continue to be resistant to implementing such tracking. Moreover, even with such tracking, identifying uses of accessed data would not be intuitive due to (1) the myriad ways that partial sequence information can be combined, and (2) the fact that the same sequence or portion of a sequence may be present in multiple organisms. For example, Evolva's patent on steviol glycosides (synthetic biology-derived substitutes for stevia) describes diverse sources of nucleotide sequences for use in the claimed invention, including maize (an MLS crop), a grapevine, a fungal plant pathogen, and a species of poplar. In

addition, the patent notes that sequence information is available in the publicly accessible GENBANK database and other patent applications.⁵

Some researchers mentioned the ability to use the NCBI BLAST tool to find an identical sequence in a different organism as a way to avoid tracking, if a researcher were so inclined.⁶ Moreover, multiple researchers noted that foundries, by and large, do not ask about the origin of sequences sent to be synthesized. They only conduct a biosecurity screen to ensure, for example, that the requested product is not for a dangerous pathogen.

Summary

In summary, scientific and technological changes are having a significant impact on how research is conducted and how materials are sourced and used. Several summary findings are evident.

There are three main ways in which new synthetic biology and genomic technologies are being used that may have implications for the Treaty: (1) mining plant genomic information for gene editing purposes in crops; (2) mining for use outside of agriculture; and (3) using the plant as a ‘workhorse’ to produce other products. The first of these is most common, but new policies should broadly recognize the constantly evolving scientific and technological context.

The new technological era is producing a large amount of sequence data that is widely available and easily exchanged. The high number of decentralized data libraries and organizations collecting

⁵ Language from the patent (U.S. Patent No. 9,562,251) is illuminating:

It has been discovered that expression of certain genes in a host such as a microorganism confers the ability to synthesize steviol upon that host. As discussed in more detail below, one or more of such genes may be present naturally in a host. Typically, however, one or more of such genes are recombinant genes that have been transformed into a host that does not naturally possess them. . . . [C]onversion of geranylgeranyl diphosphate to steviol in a recombinant microorganism involves the expression of a gene encoding a kaurene synthase (KS), a gene encoding a kaurene oxidase (KO), and a gene encoding a steviol synthetase (KAH). Steviol synthetase also is known as kaurenoic acid β -hydroxylase. . . . Suitable KS polypeptides are known. For example, suitable KS enzymes include those made by *Stevia rebaudiana*, *Zea mays* and *Populus trichocarpa*. See, SEQ ID NOs: 132-135. Nucleotide sequences encoding these polypeptides are described in detail below. See, for example, Table 3 and SEQ ID NOs: 40-47. . . .

Suitable KO polypeptides are known. For example, suitable KO enzymes include those made by *Stevia rebaudiana*, *Arabidopsis thaliana*, *Gibberella fujikuroi* and *Trametes versicolor*. See, SEQ ID NOs: 138-141. Nucleotide sequences encoding these polypeptides are described in more detail below. See, for example, Table 5 and SEQ ID NOs: 52-59. . . . Suitable KAH polypeptides are known. For example, suitable KAH enzymes include those made by *Stevia rebaudiana*, *Arabidopsis thaliana*, *Vitis vinifera* and *Medicago trunculata*. See, e.g., SEQ ID NOs: 142-146; U.S. Patent Publication No. 2008-0271205; U.S. Patent Publication No. 2008-0064063 and **Genbank Accession No.** gi 189098312. . . .

In particular, the activity of a KO and/or a KAH polypeptide of plant origin can be significantly increased by the inclusion of a recombinant gene encoding an exogenous CPR polypeptide. Suitable CPR polypeptides are known. For example, suitable CPR enzymes include those made by *Stevia rebaudiana*, *Arabidopsis thaliana*, and *Giberella fujikuroi*. See, e.g., SEQ ID NOs: 147-149.

U.S. Patent No. 9,562,251, col. 12, lines 8-57. Emphasis added.

⁶ See <https://blast.ncbi.nlm.nih.gov/Blast.cgi>

these libraries raises significant challenges to the Treaty ABS logic of source identification and benefit generation.

Technological changes have accelerated the dematerialization revolution. Even though many researchers still require or prefer to have the physical material for their work, there is an increasing separation between material and data in the research enterprise. As a result, it may become less and less likely that the ABS system can rely on the link between material and data to identify the MLS source.

For many reasons noted in this section, monitoring exchange of DSI is a challenging prospect. But even if a robust tracking system were possible, other factors including partial sequence combinations, and the fact that the same sequence may occur in multiple organisms, further challenges the ABS principles identified in Section II.

IV. Legal considerations

Intellectual property protection issues are, not surprisingly, quite pertinent to DSI developments. Plant regulatory oversight issues, however, have been excluded from analysis as not relevant for the Treaty.

Intellectual property and DSI

Intellectual property protection poses a conundrum for many synthetic biology researchers. On the one hand, there is a strong open source sharing ethos among many scientists, evident in open access ‘parts’ registries and projects such as the Twist Biosciences and BioBricks Foundation’s 10,000 public-benefit gene donation initiative.⁷ Moreover, the Bermuda, Ft. Lauderdale, and Toronto Agreements and more recent accords, all encourage the rapid, pre-publication release of genomic, proteomic and other datasets for the public good.

On the other hand, patents hold the same appeal to synthetic biology researchers and companies seeking opportunities to commercialize their developments as to other inventors. As a result, there is a tendency among some researchers to strategically patent research tools (e.g. CRISPR-Cas) that facilitate genetic modification/construction,⁸ and products, such as protein-encoding synthetic nucleic acids,⁹ with clear commercial applications,¹⁰ while publishing and making accessible other ‘parts’ or information whose money making potential is more theoretical. Such thinking lies behind the OpenPlant initiative, which encourages the collection and free exchange of DNA parts that researchers can combine in different, novel ways to develop more complex products that could be protected by patent and commercialized.¹¹ However, it can be difficult for a researcher to know with certainty whether or not a synthetic gene sequence or ‘part’ made available in an open access database is, in fact, free from patent protection.

⁷ <http://www.prnewswire.com/news-releases/twist-bioscience-and-the-biobricks-foundation-announce-first-of-its-kind-partnership-to-provide-10000-public-benefit-genes-to-the-synthetic-biology-community-300474391.html>

⁸ Patented tools may also be made available with an MTA, a process facilitated by entities such as the Addgene repository (www.addgene.org). As noted on the Broad Institute’s website: “We make CRISPR tools, knowledge, methods and other IP for genome-editing freely available to the academic and non-profit community. Since February 2013, Addgene has shared [more than 40,000 plasmids](#) and reagents with more than 2,000 institutions across 59 countries[.]” The Broad Institute, “Information about Licensing CRISPR Genome Editing Systems,” available at <https://www.broadinstitute.org/partnerships/office-strategic-alliances-and-partnering/information-about-licensing-crispr-genome-edition>

⁹ See U.S. Patent No. 9,376,669.

¹⁰ See, e.g., “Recent Patents in Synthetic Biology,” *Nature Biotechnology* 34:8, p. 822 (Aug. 2016) (describing patents covering tools and products such as synthetic sRNA for optimizing metabolite production, synthetic “mimics of cell-penetrating peptides,” “kits and devices for transfecting, gene editing and reprogramming cells,” synthetic peptide amine ligands for use in pharmaceutical compositions for treating pain and inflammation, etc.).

¹¹ See www.openplant.org (“The next generation of DNA tools for “smart” breeding of crop systems should be shared - to promote global innovation and equitable access to sustainable bioeconomies”).

Patents have long been sought and obtained on material derived from Treaty crops,¹² and in some countries, patents are also being obtained on DNA sequences from such crops.¹³ This has led to a variety of concerns, including the possibility that synthetic sequences which, perhaps through gene editing, correct detrimental mutations or introduce beneficial ones,¹⁴ may be patented and asserted against farmers who later grow crops in which the genetic change occurs naturally, or through traditional breeding methods.

Patents have been, and likely will continue to be, the primary form of IP protection for synthetic biology innovations, more broadly, and DSI in particular.¹⁵ However, recent judicial decisions on gene patent subject matter eligibility in the United States and Australia have eliminated patent protection for some synthetic biology inventions. In particular, the United States Supreme Court's decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.* (2013) eliminated patent protection for isolated genomic DNA (gDNA) and other claimed inventions that do not satisfy the requirements for patent eligibility articulated by the Court.¹⁶

The Supreme Court did distinguish between gDNA and synthesized complementary DNA (cDNA), such as generally would be involved in synthetic biology research, holding that most cDNA claims would pass the patent eligibility hurdle. Thus, while the decision did eliminate protection for some low-hanging fruit that might have had relevance for traditional biotech and agricultural inventions using Treaty material, its significant for synthetic biology based inventions appears more attenuated (Brinckerhoff 2015). However, the Court cautioned that short cDNA sequences might be unpatentable if indistinguishable from "natural" DNA (McFarlane, Sharp, and Aquino 2014). Moreover, even longer synthetic sequences could face problems if they are not

¹² See Paul Oldham *et. al.*, (2013) Biological Diversity in the Patent System. PLoS ONE 8(11): e78737. doi:10.1371/journal.pone.0078737 (noting that "[t]he top species for genetic engineering and agriculture are *Zea mays* (maize), *Oryza sativa* (rice), *Brassica napus* . . . , *Triticum sp.* (wheat), *Hordeum vulgare* (barley), *Helianthus annuus* . . . followed by *Solanum tuberosum* (potato), *Brassica oleracea* . . . , *Sorghum sp.* (sorghum) and *Pisum sativum* (pea). Patent activity for food crops is concentrated in a small number of companies led by Du Pont (including Pioneer Hi-Bred), Monsanto, Bayer, BASF and Syngenta").

¹³ However, because not all countries are party to the Treaty, the actual patented inventions may not involve material or information from the MLS. Also, not all countries allow patents on DNA sequences, and some that do, only allow patents on synthetic sequences. See, e.g., *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013); *D'Arcy v. Myriad Genetics, Inc.* (2015) HCA 35, Council Directive 98/44/EC, 1998 O.J. (L 213) 13 (OC), Art. 8-9.

¹⁴ See, e.g., Application No. PCT/US2014/028445 for "Engineering plant genomes using crispr/cas systems" (describing methods of modifying the genomes of plants including wheat, maize, rice, and cassava), and Application No. US14898208 "Methods for non-transgenic genome editing in plants" (same).

¹⁵ This section incorporates and modifies material from Margo A. Bagley, *The De-Materialization of Genetic Resources: Synthetic Biology, Intellectual Property, and the ABS Bypass*, in *Routledge Handbook of Biodiversity and the Law*, (Charles McManis and Burton Ong Eds. Forthcoming 2017) and Margo A. Bagley, *Digital DNA: Synthetic Biology, Intellectual Property Treaties, and The Nagoya Protocol* (2015) (Woodrow Wilson International Center for Scholars).

¹⁶ In addition, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012) ("Mayo") in conjunction with *CLS Bank v. Alice*, 134 S. Ct. 2347 (2014) imposed an "inventive concept" requirement for claimed inventions involving a law of nature or abstract idea; thus both cases are particularly relevant to biotech diagnostic or therapeutic method claims.

“markedly different” from what exists in nature (Diamond v. Chakrabarty 1980). Claims already have been rejected for cDNA sequences on that basis in at least one synthetic biology-based patent application (Parida et al. 2014). In addition, the United States Patent and Trademark Office’s initial interpretation of *Myriad* and other Supreme Court patent eligibility decisions drew severe criticism and consternation from the biotech industry and patent attorneys, as it appeared to go significantly beyond the Court’s decisions in restricting patentability. However, more recent guidance from the Office indicates a less stringent approach to inventions based on products of nature (United States Patent & Trademark Office 2014a & b; 2015).

Patent law is territorial in nature and patents only take effect within the national/regional borders of the countries that grant them. Thus, the U.S. *Myriad* decision only has effect in the United States; researchers still may be able to obtain patent protection on gDNA in other countries, such as EU member states, as the European Union Biotechnology Directive explicitly allows for patents on gene sequences that would fail U.S. patent eligibility requirements (Council Directive 1998; Sherkow 2017, Liddicoat, Whitton and Nicol 2015).¹⁷

On October 7, 2015, Australia’s highest court deemed invalid several of Myriad’s Australian patent claims covering BRCA1 gDNA and cDNA sequences (D’Arcy v. Myriad Genetics 2015).¹⁸ The High Court ruled that such claims cover information which is “discerned” not made, and thus do not come within the statutory requirement of a man-made “manner of manufacture.” As the decision is relatively new, it is unclear what its implications will be for the patenting of synthetic DNA sequences, or how different from naturally occurring sequences they will need to be in order to be considered made by man and thus patent eligible.

Scientific and technological advances in synthetic biology are creating new interest in the collection and use of plant genome DSI, and the protection, via patents, of the fruits of such use. While foundational developments often are being published, patents are also being sought on downstream commercial applications. Moreover, while early success in using plants to produce commercial compounds has been achieved in the tobacco family of plants,¹⁹ it certainly is possible that the genomes and suitability of other plants, including Treaty crops, will be investigated for similar beneficial applications as well.

¹⁷ Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, Article 5(2), states: “An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.”

¹⁸ The Court noted that the isolated nucleic acid claims “[embrace] a nucleic acid sequence or protein removed from its naturally occurring environment and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.”

¹⁹ See James Reed *et. al.*, A Translational Synthetic Biology Platform for Rapid Access to Gram-scale Quantities of Novel Drug-like Molecules, *Metabolic Engineering* 42 (2017) 185–193, 186 (“*Nicotiana benthamiana*, a wild relative of tobacco, is particularly amenable to agro-infiltration-mediated transient expression and is currently being used for commercial production of flu vaccines”).

The highly publicized patent battles between academic entities – the Broad Institute/MIT, the University of California, and Dr. Emmanuelle Charpentier of the University of Vienna, surrounding the CRISPR-Cas9 technology²⁰ – have had a perceptible effect on some synthetic biology researchers. Some researchers noted that they have chosen to steer clear of using the technology in their work due to the litigious actions of the various patent owners and contenders, while some others seek to develop alternative gene editing techniques or to defensively patent CRISPR-Cas-related developments for leverage, and to make such improvements available freely to other researchers in the field. Still others in plant research are finding the tool incredibly useful in generating and deleting mutations and accelerating the speed of discovery and understanding of valuable traits, but not for commercializable research that would necessitate costly (and possibly indeterminate) patent licensing negotiations. It is possible that the formation of a recently announced CRISPR patent pool may help to reduce or eliminate some of these transaction costs, as in the U.S. alone, 18 different entities are reported to own 60 different CRISPR patents (A. Mika 2017).

In the plant arena, such licensing negotiations would most likely include DuPont Pioneer, as the company has amassed a broad portfolio of CRISPR-Cas patents and licenses covering agricultural uses of the gene editing technology.²¹ DuPont Pioneer has plans to use CRISPR-Cas in crops such as soybeans, canola, wheat and rice, beginning with commercializing waxy corn hybrids by the end of the decade. However, some CRISPR-Cas users have expressed concern regarding their inability to commercialize, even for developing countries, their CRISPR-Cas-based inventions, without negotiating what may be a very expensive license under the various relevant patents.

Some researchers mentioned that it may be impossible to detect which of several gene editing technologies such as zinc finger proteins (ZNFs), transcription activator-like effector nucleases

²⁰ These are the primary entities quarreling over the foundational U.S. patent rights. In Europe (and likely other jurisdictions) the situation is more complicated, as at least six entities are battling over CRISPR rights. See Jon Cohen, “CRISPR patent battle in Europe takes a ‘wild’ twist with surprising player,” Aug. 4, 2017 available at <http://www.sciencemag.org/news/2017/08/crispr-patent-battle-europe-takes-wild-twist-surprising-player> (cite the interference, patent battles abroad, CRISPR related patents).

²¹ See “DuPont Pioneer Secures Exclusive Rights to ERS Genomics’ CRISPR-Cas Patent Portfolio for Agriculture,” June 27 2017, available at <http://www.prweb.com/releases/dupont-pioneer-seed/crispr-ers-genomics/prweb14463659.htm>; “DuPont and Caribou Biosciences Announce Strategic Alliance,” Oct. 8 2015, available at <http://www.dupont.com/corporate-functions/media-center/press-releases/dupont-and-caribou-biosciences-announce-strategic-alliance.html>

”According to the DuPont Pioneer website:

Based on a natural system, CRISPR-Cas can be applied to precisely improve a seed without incorporating DNA from another species. It’s a continuation of what people have been doing since plants were first domesticated – selecting for desired characteristics, such as higher yields, disease resistance, longer shelf life or better nutrition. “Abundant Potential for Agriculture,” available at <http://crisprcas.pioneer.com/crispr-cas/> The Monsanto Company has also licensed the Broad Institutes’ CRISPR-Cas9 patents for certain agricultural uses. See “Monsanto licenses CRISPR technology to modify crops — with key restrictions,” Sept. 22 2016, available at <https://www.statnews.com/2016/09/22/monsanto-licenses-crispr/>

(TALENs) or CRISPR-Cas variants is used to develop a product, implying that it might not be possible for owners of CRISPR-Cas9 patents to establish infringement of their process patent.

However, the laws of most countries provide a process patent presumption in line with the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property (TRIPS) Article 34.22 While the burden is normally on the patent proprietor to establish infringement, this provision shifts that burden in the case of process patents, and creates a presumption that the product is made by the patented process. Thus, it would be for the defendant to establish, by providing evidence such as laboratory records, that it actually uses a different process. In addition, since gene-editing does not need to involve insertion of a gene from a foreign species into a plant, but rather manipulation of the genes present in the plant itself, the fairly standard distinction between GMO and non-GMO plants (due to the presence or absence of foreign genes) can no longer be relied on by breeders for avoiding infringement liability.

Patents and the Open MTA

Freedom to operate concerns relating to potential patent thickets were a major impetus for the creation of the path-breaking Open Plant project and the related Open MTA.²³ OpenPlant and the BioBricks Foundation are both working towards the launch of a new ‘open’ material transfer agreement (Open MTA) that will facilitate the development and sharing of DSI-based discoveries. Many existing MTAs, such as the widely used Uniform Biological Material Transfer Agreement (UBMTA), are ‘closed’, in the sense that a party receiving material under such an agreement generally cannot redistribute it to others without a separate time-consuming negotiation process, and may not be able to patent discoveries made using the material. The transaction costs associated with conventional MTA negotiations can be significant, sometimes resulting in no agreement

²² TRIPS Article 34 provides in pertinent part:

Process Patents: Burden of Proof

- (1) For the purposes of civil proceedings in respect of the infringement of the rights of the [process patent] owner . . . , if the subject matter of a patent is a process for obtaining a product, the judicial authorities shall have the authority to order the defendant to prove that the process to obtain an identical product is different from the patented process. Therefore, Members shall provide, in at least one of the following circumstances, that any identical product when produced without the consent of the patent owner shall, in the absence of proof to the contrary, be deemed to have been obtained by the patented process:
 1. if the product obtained by the patented process is new;
 2. if there is a substantial likelihood that the identical product was made by the process and the owner of the patent has been unable through reasonable efforts to determine the process actually used.

Article 34(1), Marrakesh Agreement Establishing the World Trade Organization, Annex 1C: Agreement on Trade-Related Aspects of Intellectual Property Rights, 15 April 1994, 1869 U.N.T.S. 299, 33 I.L.M. 81 (1994).

²³ See OpenPlant Intellectual Property Working Group Meeting Report, p. 4 (2015), available at <https://static1.squarespace.com/static/54a6bdb7e4b08424e69c93a1/t/58a2ee88a5790a100dcb8ff9/1487072905283/Preport.pdf> (“patent “thickets” and proliferating cross-licensing arrangements are becoming problematic, even for large pharma and agrochemical companies, and can be crippling for small companies. Innovation in a young field like synthetic biology requires freedom to operate. We believe steps to facilitate free exchange of DNA parts and tools will substantially speed the take-up of new technologies in plant synthetic biology”).

being reached. In such cases, the UBMTA is often a default and deemed to apply, possibly imposing more onerous obligations than the parties would have negotiated.

The goal of the Open MTA is thus to facilitate low-transaction cost access to genetic material/information globally for scientific progress. The rounds of negotiation required for conventional MTAs were seen as infeasible and detrimental to the speed at which developments are advancing in the synthetic biology arena. Taking the UBMTA as a starting point for the new agreement, the drafters removed limitations that did not fit the design goals of the project.

The Open MTA will allow for royalty-free access and free redistribution of material, the potential (but not the obligation) of attribution of source of origin, and non-discrimination between kinds of users, commercial and non-commercial. Importantly, there are no limitations on the obtaining of patents on developments made with material or information shared under the Agreement.²⁴ In fact, such patenting is arguably encouraged, with the hope that it will lead to commercial applications and improved products for society.

Some researchers noted that making foundational tools available through the Open MTA would offer good opportunities for training researchers and accelerating advancements in the field. However, the Open MTA might not be appropriate for developments with commercial potential, particularly where, for example, the research was funded by government entities interested in local or regional job creation, and in seeing clear economic benefits returning to taxpayers.

The Open MTA logic may not be in full harmony with the Treaty, because although it has been designed to address intellectual property concerns, it is completely silent regarding ABS obligations. This omission may simply be due to the drafters' lack of familiarity with the Treaty, the Convention on Biological Diversity (CBD) and the Nagoya Protocol, or it may have been a conscious decision to leave the complexities of meeting ABS obligations to users. Even though the Open MTA notes the possibility of attribution, a concept relevant to the Treaty, there are no indications that the source to be attributed is that of the original material, as opposed to the researcher presently transferring the (possibly) value-added matter.

Individuals involved in the development of the Open MTA approach considered alternative models of addressing IP-related freedom to operate concerns. Three options received marked consideration: (1) developing non-legal, "technical solutions to remove barriers to reuse of

²⁴ Open Plant is explicit regarding the role of patent protection for plant synthetic biology:

The intention of OpenPlant is to promote innovation using a two-tier system for IP management. While freedom to operate is necessary for foundational technologies, the commercial applications and products that will be built upon these foundational technologies require investment in development, production and distribution for which IP protection is usually necessary. This two-tier model for IP management involves a decision about which route is most appropriate for a given technology to achieve its desired impact. Low-level technologies with little commercial value in isolation, or with high potential to spur innovation, are made available openly, while high-value applications may be patented or otherwise protected.

OpenPlant Intellectual Property Working Group Meeting Report, p. 5 (2015), available at <https://static1.squarespace.com/static/54a6bdb7e4b08424e69c93a1/t/58a2ee88a5790a100dcb8ff9/1487072905283/1/Preport.pdf>

materials”, such as an improved infrastructure for DNA parts repositories; (2) creating a “system of bio-engineers’ rights akin to plant breeder’s rights”, allowing academics to work freely with material, but developers to have certain proprietary and commercialization rights; and (3) giving away all IP rights by dedicating developed materials to the public domain.²⁵ While the Open MTA was viewed as superior to these approaches (due in part to the need for certainty around freedom to operate), some of these ideas may gain greater traction over time within the synthetic biology community as worthy of further study. Nevertheless, as with the Open MTA itself, these three alternatives would not fully recognize the ownership rights and user obligations inherent in the Treaty and its multilateral system.

The BioBricks Foundation recently launched a new initiative called the ‘Public Domain Chronicle’ to further openness in synthetic biology research. The Chronicle is a simple tool for inventors to contribute findings of their choice to the public domain in a way that immediately creates verifiable, time-stamped published prior art. It combines a ‘mercifully short’ disclosure form with a public declaration of the inventor’s intent to claim the discovery for the commons, and a license ensuring that the information can be freely redistributed and utilized.²⁶ To the extent the Chronicle is employed, by users of the Treaty MLS, to dedicate more discoveries to the public domain as an alternative to patent protection, it theoretically could reduce the potential of funds for the Treaty.

Copyright and DSI²⁷

Some researchers and scholars see copyright protection as a preferable alternative to patents, as it may produce a more “socially desirable balance” of permitted vs. restricted uses of DNA sequences (Torrance 2011). Copyright protection lasts longer than patents – life of the author plus 50 or 70 years, depending on the jurisdiction vs. 20 years from filing for patents—but the protection is not as strong. Unlike for patents, independent creation is a defense to copyright infringement, there are limits on damages for innocent infringement, and the copyright fair use defense might reasonably allow many uses of protected sequences, such as for experimentation and instruction, not allowed by the strict liability patent law system (Torrance 2011). Moreover, copyright protection is seen by some as better able than patents, to foster an open source biology regime (Torrance 2011).

²⁵ See OpenPlant Intellectual Property Working Group Meeting Report, pp. 7-9 (2015), available at <https://static1.squarespace.com/static/54a6bdb7e4b08424e69c93a1/t/58a2ee88a5790a100dcb8ff9/1487072905283/IPreport.pdf>

²⁶ See BioBricks Foundation, ‘Public Domain Chronicle,’ Oct. 9, 2017, available at <https://biobricks.org/pdc/>.

²⁷ This section incorporates and modifies material from Margo A. Bagley, *The De-Materialization of Genetic Resources: Synthetic Biology, Intellectual Property, and the ABS Bypass*, in Routledge Handbook of Biodiversity and the Law, (Charles McManis and Burton Ong Eds. Forthcoming 2017) and Margo A. Bagley, *Digital DNA: Synthetic Biology, Intellectual Property Treaties, and The Nagoya Protocol* (2015) (Woodrow Wilson International Center for Scholars).

Copyright protects original works of authorship fixed in tangible mediums of expression such as literary works, musical works, architectural designs, and even computer programs. Several commentators, making an analogy to computer software, have suggested that copyright may be appropriate for synthetic biology, noting that synthetic DNA sequences meet the originality and fixation requirements and may require expressive choices (Holman 2011; Karjala 2011; Torrance & Kahl 2014; Murray 2014; Torrance 2010; Torrance 2011). Moreover, for open source proponents, the exclusivity provided by copyright law possibly could be used to impose sharing requirements on users, an approach that some in the free/open software movement have used effectively with “copyleft” licenses (Rai & Boyle 2007).

However, the possibility of copyright protection for DSI is far less certain than that for patents. Detractors argue that copyright is a poor fit for DSI, as sequences generally are dictated by the desired function they are to perform, leaving little room for an author’s expressive choices. In India, the Delhi High Court in *Emergent Genetics India Pvt. Ltd. v. Shailendra Shivam and Ors.* denied the copyrightability of hybrid seed DNA sequences. Although the seeds were not produced using gene editing or other synthetic biology techniques, the bases of the decision appear broadly to deny copyright protection to any gene sequences. The court noted that even if the selection of which sequences to combine was original, it still would violate the merger doctrine because the idea of combining various gene components or constituents, is expressible in limited ways.²⁸

In the United States, where the lion’s share of synthetic biology research is performed, the copyright office has indicated that DNA sequences are not copyright-eligible subject matter. Consequently, copyright protection does not appear to be a viable option for DNA sequences there at this time (Holman, Gustafsson, & Torrance 2016; Ledford 2013). However, as with computer software, which the copyright office originally rejected as ineligible for copyright protection, that position may change over time (Holman 2011). Interestingly, the public license used with the BioBricks Public Domain Chronicle, discussed above, allows inventors to claim copyright for findings, which can include DSI, published via the Chronicle.²⁹ In view of the challenges posed by patent and copyright law, some commentators have suggested that a sui generis IP regime for DSI might be most appropriate (Samuelson 2013 & Rai & Boyle 2007). If countries ever actually develop such systems or extend copyright protection to DSI, the additional forms of protection may provide additional benefit-sharing avenues for DSI from Treaty material.

Trade secrets and DSI

Some commercial providers of DNA design and synthesis services use both trade secret and patent protection for their developments. Trade secret law generally protects information that provides a competitive advantage to its owner from not being general known to, or readily ascertainable by,

²⁸ *Emergent Genetics India Pvt. Ltd. v. Shailendra Shivam and Ors.* on 2 August 2011, I.A. Nos. 388/2004, p. 12, available at <http://indiankanoon.org/doc/183763759/>.

²⁹ See <https://publicdomainchronicle.org/server/legal-tool>.

those who could effectively use the information.³⁰ Not surprisingly, such providers must maintain the confidentiality of any sequences or parts that they develop for clients, and such products appear to be less likely to be patented, compared with sequences and products that a synthetic biology client might develop in-house and choose to strategically patent.³¹ However, commercial DNA service providers are also developing significant and valuable secret databases of DSI that can give them a competitive advantage *vis a vis* other industry players.

Moreover, individual researchers may choose not to publish sequence information, but instead to keep it as a trade secret, sharing data only with trusted researchers on a confidential basis. Some researchers also noted that they do not publish all their sequence data due to the voluminous amount of data that they produce, and the time and other costs associated with assessing and documenting its value and importance for scientific competitiveness. This may be another consequence of the ‘youthfulness’ of the synthetic biology field, with many early career researchers highly concerned both about being ‘scooped’, and about having limited time to publish and make available data not directly included in a scientific publication.

The likelihood of commercial viability, as well as the feasibility of maintaining trade secret protection, the difficulty, uncertainty and expense surrounding the seeking of patent protection, and other strategic considerations which normally inform the patent vs. trade secret calculus, may all further influence disclosure or secrecy in relation to DSI. To the extent that trade secret protection is adopted, the ability to track uses of MLS material or information becomes virtually non-existent, except perhaps in cases where truly unique sequences are identified as being present in commercial crop products.

Summary

The development and use of DSI in synthetic biology projects may pose a challenge to the ABS structure of the Treaty. Article 12.3(a) of the Treaty specifies that access to material under the MLS is solely for purposes of “utilization and conservation for research, breeding and training for food and agriculture”, and excludes “chemical, pharmaceutical and/or other non-food/feed industrial uses.” Researchers can effectively use DSI from MLS material (e.g. obtained through DSI in publicly accessible databases) in any kind of research, including chemical and/or pharmaceutical, without such usage being easily monitored.

Moreover, even though scientists working on DSI may be using sequence information from identifiable published material, the chain of transmission is often not transparent, nor easily documented, and there are no indications that legal innovations such as open MTAs will improve the monitoring of downstream uses of Treaty genetic material or DSI. As such, it may be difficult to assess benefits from uses of Treaty genetic material or DSI. Patent protection for DSI remains available in many countries despite judicial decisions eliminating protection for certain kinds of

³⁰ See Defend Trade Secrets Act

³¹ See, e.g., Evolva’s patents on steviol glycosides and synbio vanillin.

sequences in the United States and Australia. While some patents obtained for inventions incorporating DSI may provide geographic origin information, others may not, or the information may be hidden if a particular sequence could be obtained from more than one kind of organism. In addition, patents may not always be necessary to extract value from DSI, as trade secret protection can be a viable alternative under certain conditions, although copyright protection currently is not. Finally, if the Treaty chooses to generate DSI for MLS crops and adopt a fee (e.g. subscription) model for access, it is to be considered how downstream uses of the DSI from the MLS are to be identified effectively.

V. Benefit-sharing

Introduction

The principle of benefit-sharing aims to link, directly or indirectly, the value produced from use of PGRFA to compensation. Benefit-sharing is typically outcome-based and temporally structured, such that fair monetary or non-monetary returns accrue as compensation only after value is demonstrated. In the case of the Treaty, monetary benefits are typically triggered when new products using material from the MLS accrue revenue. In ongoing negotiations by the Treaty constituency, an alternative benefit-sharing scheme (‘subscription system’) is being considered. The scheme would entail upfront payments based on the overall revenue generated by crop(s) sales. Benefits are contributed to a global common pool in which accumulated funds support select projects aimed at increasing capacity in member countries, and achieving the Treaty’s overall objectives of food security and sustainable agriculture.

Beyond sharing monetary benefits, the Treaty recognizes that “facilitated access to PGRFA which are included in the Multilateral System constitutes itself a major benefit of the Multilateral System”. It also acknowledges the importance of three other mechanisms that could help fair and equitable sharing of the benefits arising from the use of PGRFA, namely exchange of information, access to and transfer of technology, and capacity-building. These mechanisms are usually qualified as non-monetary, in the sense that they can be generated even independently of whether or not any product reaches the marketplace. In the functioning of the Treaty ABS framework, these mechanisms contribute to increasing the ability to take advantage of the facilitated mechanisms to PGRFA, as established under the common pool.

Some interviewees were knowledgeable about the genetic resources policy discussions surrounding genetic sequence data, but many were unfamiliar, or only vaguely familiar. Those who were knowledgeable about the Treaty recognized that the common pool MLS of the Treaty could provide some advantages (over the Nagoya Protocol prevalently bilateral system) for developing a viable benefit-sharing system. Mainly, this was related to the significant difficulty of full tracking and monitoring, identifying and linking provenance of sequence data and parts to innovation outputs, and the highly distributed nature of potential beneficiaries (see Section III above). Interviewees generally considered the pooling of benefits to be more feasible and more in line with common research practice.

Opportunities for value generation

Developing a viable benefit-sharing system first requires gaining a better sense of where the value lies in synbio, and a better understanding of the cost of entry required in order to generate benefits from it. Based on interviews, the following sections provide initial information on these subjects.

Perceived value

The shift toward use of sequence data and DNA parts as key components of research has affected a range of actors, organizations and technologies that use genetic resources for education, research and innovation purposes. The primary perceived value of synthetic biology and genomic research varies by actor – universities and institutes, non-profit organizations, academic journals, repositories (Addgene) – in ways that have implications for benefit-sharing. To better understand opportunities for benefit-sharing, interviewees were asked to assess where the primary value lies in the synthetic biology and genomic work.

Four conceptualizations of value emerged. Several researchers noted that the value would ultimately be an innovation, such as a new product or a new process. For example, synthetic biology researchers could integrate multiple genetic sequences or DNA parts from different organisms to produce a synthetic compound that mimics a natural one. The synthetic biology process could make use of sequences and synthesized parts using PGRFA governed under the Treaty. Value from innovation is also due to the accelerated rate of the breeding process by synthetically integrating different genes that code for traits of interest in one plant in one generation, compared with conventional breeding, where this is a lengthy process. Other interviewees consider the primary value to be knowledge about the sequence and part functionality by which sequence or parts operate in cells. Fundamental knowledge about the mechanisms by which sequences or parts operate is substantially upstream from, or prior to innovation. This set would include identification of gene sequences that could be edited in or out of agricultural plants that are governed under the Treaty. A third set of interviewees discussed the potential for plant systems to rapidly produce high value products such as medicines and chemicals. Plant system understanding is fundamental in nature, and considered to be at an early stage of development. Education and exploration comprises a fourth value perceived to emanate from the new scientific and technological trajectory. This group of interviewees identified the potential to make synthetic biology globally accessible to students and early career researchers. The group considers the technology to offer flexible approaches to localized investigation, education and exploration though the use of kits and team-based competitions. In sum, interviewees identified a range of sources of value of synthetic biology and genomic research, from education, knowledge development and application.

It should be noted that none of the interviewees reported that monetary benefits had already been shared with providers. This is probably normal considering that many of the applications are still at an early stage, and have not yet reached the marketplace. Nevertheless, as this report stated earlier, some synthetic biology companies are being established with the expectation of profits.

Although it is difficult to identify precisely where the value is generated, the recognition of the diverse sources of value helps to frame and inform study findings on opportunities for non-monetary benefit-sharing. Before addressing non-monetary benefits directly, it is important to get a better sense of the infrastructures perceived to be needed for conducting synbio research and development with material available within the MLS and DSI.

Structure of required investment

What are the entry costs for doing synbio research? To what extent could synbio potentially lower or increase the technological divide among countries? As part of the scoping study, experts were asked about the requisite infrastructure for undertaking synthetic biology research. Three general perspectives were identified: high-cost infrastructure, low-cost infrastructure and flexible infrastructure.

High-cost infrastructure: Some interviewees were convinced that synthetic biology requires significant investment of hard infrastructure – buildings, microbiology laboratories and other fixed equipment. This group recognized that needs for capacity to conduct DSI-related research varied, depending on the type of research activity. Sequencing and storing of sequence data seems to have the lowest barriers, although there are basic issues of capacity in some areas, such as access to stable server space and human informatics skills. These researchers generally indicated that concomitant investment in and existence of scientific and technical human capital is necessary to foster the development of synthetic biology across countries. We heard from multiple interviewees that simply being able to sequence a sample, or have access to sequence data, is not enough to produce significant value. A researcher needs the ability to analyse the data and to produce or synthesize long stretches of DNA. Education systems that include advanced studies in microbiology and genetics are best placed to take advantage of revolution in sequence-based research and innovation.

These researchers perceived a wide gap in capacity between high- and low-income countries. Interviewees identified several mechanisms to close this gap. First, many high-income countries have a grant-based system to fund investment in hard-infrastructure in lower-income countries. Most of these investments target middle-income countries rather than the low-income countries, eg. in Africa. Curriculum development is a second mechanism for closing the gap. Some interviewees had developed new higher education curricula specifically designed to create the scientific and technical knowledge base in developing country universities for synthetic biology and genomic research. Other researchers discussed short-term training initiatives or higher education programmes in the US and Europe, which host students from lower-income countries. These initiatives generally rely on strong linkages between researchers and research institutions in both high- middle- and low-income countries. Strong linkages are often fostered through initial seminars and workshops, but are frequently enabled by identification of a small set of researchers who arrange exploratory scholarly visits, develop initial research strategies and identify sources of funding. Proponents of high-cost infrastructure are more likely to value research that builds fundamental knowledge about sequence and part functionality and plant system understanding.

Low-cost infrastructure: By contrast, other interviewees believe synthetic biology to be a relatively low-barrier, accessible field for researchers and students with more limited scientific background and training. This group considered the infrastructure needs to be low and relatively non-reliant

on hard infrastructure, such as buildings, laboratories and fixed equipment. This low-cost infrastructure approach is best characterized as ‘bottom-up’, in which local ideas and interests drive engagement in exploratory research and innovation.

To foster this exploratory research, organized programmes match the investigation interests of research teams with kits that include relevant sequence data, DNA plasmids and other components. Such programmes are often structured as two-tiered competitions in which groups of researchers propose synthetic biology research ideas to a selection committee and, if selected, use programme-provided kits to undertake the research. Panels of judges evaluate research outputs and determine awards. Reportedly, research teams from lower-income countries in South America and Africa have successfully participated in these types of research competitions. Interviewees who identify with low-cost infrastructure recognize the value of synthetic biology and genomic research to reside in exploration, education and innovation.

Flexible infrastructure. A final perspective integrates both low- and high-cost infrastructure perspectives: some researchers recognize that infrastructure needs are flexible, and depend on the research objectives and existing hard infrastructure and scientific and technical capacity. This perspective considers synthetic biology and genomic research to be multidimensional, such that different investigative trajectories are possible. In some cases, bottom-up approaches that incentivize students and researchers with little access to formal training are preferred, because they engage in exploration, teamwork and innovation. In other cases, high-cost investment in infrastructure – hard infrastructure and higher education – are necessary to foster fundamental work and sustain scientific advance. The first approach may require greater relative dependence on local networks, while the second may require stronger and more formal international ties among established researchers and research institutions.

The flexible infrastructure approach recognizes that the determinant of engagement and success in research using DSI is less a function of the ‘infrastructure approach’, and more a function of the ‘research and education approach’. It recognizes that low-cost and high-cost infrastructure are two ends of a continuum. A broader approach to capacity development should ask: What different capacity modalities can be established and sustained to maximize research engagement?

Opportunities for sharing non-monetary benefits linked to DSI

This scoping report considers a variety of non-monetary benefit-sharing opportunities that are simultaneously relevant for the Treaty and linked to DSI. Each of the benefit-sharing opportunities is relevant to one or more of the four types of non-monetary benefits that are core to the Treaty: facilitated access, exchange of information, access to and transfer of technology, and capacity-building. Review of background materials and interviews undertaken for this scoping report identified five different strategies employed by researchers that are currently in place: 1) *ex ante* investment to facilitate access; 2) grant-based funding for hard infrastructure investment; 3) facilitated access for research community building; 4) structured research collaboration; and 5) education and training. These different strategies can be linked to the values framework and

investment approaches above, and could be considered by the Treaty community as it addresses benefit-sharing and DSI.

1) Linking access to sequence data to *ex ante* investment in technical and analytical capacity. As noted above, monetary benefit-sharing represents a system in which some form of payment is provided to the Multilateral Benefit-sharing system of the Treaty. Payment of monetary benefits is typically *ex post*, occurring after revenues have been generated from the use of materials in the MLS. But *ex ante* payments are also possible, whereby member countries could contribute some form of upfront payment to secure access to sequence data. The PIP framework (Box 3) provides one example of an *ex ante* monetary benefit system that has potential relevance for the Treaty.

Such a benefit-sharing system may be easier to develop in the area of health, where viruses are easily identified, the pathway from the GR to the product is clear, and the producers (pharma) are visible. Such a context does not exist in agriculture, where there are multiple sources, pathway and producers. This trend is even exacerbated within the synbio research context, where frontiers between organisms and species are increasingly blurred and pathways are more and more diversified and complex. This could make incentives for *ex ante* payment lower, as multiple options exist for accessing DSI (or for synthesizing them).

Box 3. Pandemic influenza preparedness (PIP) Framework

The objective of the Pandemic Influenza Preparedness (PIP) Framework is to improve pandemic influenza preparedness and response, and strengthen protection against the pandemic influenza by improving and strengthening the World Health Organization (WHO) global influenza surveillance and response system (WHO GISRS), with the objective of a fair, transparent, equitable, efficient, effective system for, on an equal footing: the sharing of H5N1 and other influenza viruses with human pandemic potential; and access to vaccines and sharing of other benefits (quoted from http://www.who.int/influenza/resources/pip_framework/en/). In part, the framework aims to facilitate the sharing of genetic sequence data for disease prevention. Articulated ABS principles are available here:

http://apps.who.int/iris/bitstream/10665/44796/1/9789241503082_eng.pdf

Discussions are currently under way between WHO, pharmaceutical companies and different country and CSO representatives to develop a benefit-sharing plan for the sharing of influenza viruses, which goes beyond the current plan of making vaccines available to provider countries. The benefit-sharing plan currently under negotiation concerns an *ex ante* monetary benefit, provided by pharmaceutical companies, used to pay for clinics in countries with limited capacity to analyse and process samples. In this way, monetary payments are directly connected to clear capacity development objectives, related to sample collection and analysis for disease recognition and control.

2) Grant-based funding for hard infrastructure investment. Some interviewees identified grant programmes offered by national funding agencies to invest in research facilities in developing countries. Award success generally depends upon demonstration of established research

collaborations, specification of research questions and trajectories, linkage to education and training in developing countries, interest by key institutional partners and potential for sustained funding once the infrastructure is operating.

Investment in hard research infrastructure falls within the high-cost category, but integrates values for education with efforts to build fundamental knowledge about genomic research. Interviewees contrasted this type of public-led grant-based investment in research infrastructure with private sector infrastructure investments, which mainly employ individuals who are already highly trained. Interviews identified a grants programme model that undertakes this type of investment for synthetic biology and genomics.

So far, to our knowledge, such infrastructure investment strategy has not been considered as a priority within the Treaty context. However, should this grant-based funding for infrastructure investment be seen as a relevant strategy within the context of the Treaty, there may be two possible (not mutually exclusive) trajectories worth considering in the Treaty context. The first would consist of including such a funding scheme in one window of the call for proposals under the Benefit-sharing Fund. The second would consist of partnering with national funding agencies to ensure funding in their scheme for synbio/agriculture in connection with Treaty's general objectives (food security and sustainable agriculture development).

3) Facilitated access for capacity development. Two types of access to DSI for capacity development were evident in the study: open access and formalized access.

Open access is a traditional open-sharing approach in which researchers publicly release sequence data, as well as the associated information and knowledge from research. Once released, uptake and use of the sequence data is unencumbered. Open access is perceived to enable replication and confirmation of research findings, as well as building scientific and technical knowledge over time. Academic journals increasingly require publication of the sequence data as evidence, and universities also encourage researchers to make sequence data available. Nevertheless, according to interviewees, the provenance of the sequence and its associated material are identified in publications only when they provide critical information for the research.

Importantly, availability of DSI is not equivalent to accessibility, as not all countries have the same ability to make use of the resources. Beneficiaries of open access to DSI tend to be those entities (nations, researchers, companies) that have the requisite infrastructure and knowledge. However, low-cost infrastructure approaches and education may also benefit from open access. Additionally, access to data is necessary for the development of collaboration networks, fostering new investigations, and the development of scientific and technical capacity.

Formalized access includes such efforts as OpenPlant and Open MTA, which are formal mechanisms to build an open repository of sequences, 'parts' and related information. OpenPlant, described above, aims to build a data and information foundation for the synthetic biology community of plant scientists. Formalized access to sequences, parts and associated

information is considered necessary, given the perceived need to attract and engage plant scientists and stimulate the development of a community of plant researchers in synthetic biology.

By creating a resource that depends upon community use and development, OpenPlant aims to increase the overall capacity of the plant synthetic biology community. Interviewees noted that the establishment of Open MTA, which formalizes the availability of sequence data and parts for further research, establishes transparent processes and creates more formalized practices for openness among scientists. It is important to note that OpenPlant and Open MTA are in the early stages of development, and have not yet been proven to work as intended. Additionally, these initiatives do not attempt to systematically identify the provenance of the sequences or associated genetic material.

Certainly the importance of unencumbered access has long been emphasized by most researchers. But new initiatives aiming to make information and tools available to a community of plant researchers represents a pooled approach to technology transfer. Though this pooled approach is not currently recognized as a non-monetary benefit for either the Treaty or for actors such as OpenPlant, it could be. There may be opportunity for the Treaty to consider efforts such as OpenPlant and Open MTA as partners or facilitators of technology transfer and capacity development. Further work would need to be done to determine the feasibility of such an approach.

4) Research collaboration. *Traditional research* collaboration structures tend to occur in two forms. One comprises a network of trained scientists interested in producing fundamental research. Within the context of capacity development, these collaboration networks can be characterized as a mixture of scientists from low- and medium-income countries with scientists from high-income countries. Capacity development will depend upon the mixture of graduate students and technical staff from both sets of countries. These projects may focus on local research interests, but more often they are driven by research priorities of the industrialized countries that fund them.

A second form of collaboration emerges from *research challenges*. These generally aim to encourage exploratory and innovation-oriented research requiring low-cost infrastructure, often in the form of kits. Challenges depend on the engagement of clusters of individuals who receive kits holding sequence data and DNA. Kits can be designed for students with low to moderate levels of formal training in microbiology, genetics and genomics, or for trained scientists. The competition approach encourages engagement and community development. To date, it does not appear to be strategically used as a means of capacity development.

Collaboration in research contributes to facilitated access to DSI, information exchange, capacity development and technology transfer. Yet collaboration is difficult to establish, and when capacities of researchers on teams are highly variable, it is often symbolic. Scientists interviewed, particularly synbio plant scientists, tended to agree that the best way to develop collaboration (of either type, traditional or challenge) is to identify research questions in

developing countries that are locally relevant. It is often the case that locally relevant research questions are also of interest to the broader community, making them opportunities for collaboration. Such collaboration would not only leverage facilitated access to genetic resources through the Treaty, but would also produce and share the DSI and the tools needed for investigation. These types of collaboration would probably require a flexible infrastructure approach, as discussed above.

5) Education and training. Education and training aims to enhance scientific and technical human capital through workshops, short courses or training programmes, longer-term education programmes, and curriculum development. This approach involves both in-country and foreign training. With *in-country training*, one or more synbio experts visits a research or education facility in a low or middle income country (LMIC) for a short, intensive stint (e.g. two weeks) to engage in on-the-ground training and education of teams or groups of researchers. With *foreign training*, individual researchers from LMICs travel to labs in higher-income countries for one to two years. They are expected to return home being able to provide a higher level of sustained training and capacity-building to local researchers. Each form of training has benefits and drawbacks. The primary tradeoff is the investment of time in one individual and the concomitant delay in reaching a critical mass of expertise embedded in the foreign training, compared with a lower level of competence potentially being gained by a larger group of individuals with short-term in-country training.

iGEM – one example of an education-focused challenge programme requiring low infrastructure investment – is presented in Box 4. The global geographic distribution of iGEM research teams is presented in Figure 2. The iGEM competition has expanded rapidly since 2010. At the same time, so has access to gene editing tools, materials and equipment. As gene editing techniques become more accessible and democratized, the Treaty will need to keep pace with the rapidly expanding ecosystem of actors as they access digital sequence data, or begin to sequence materials themselves with portable DNA sequencers (Technologies 2017).

As the Treaty constituency may consider the ways in which it could address DSI, it should evaluate the range of different synbio initiatives that are global and dedicated to bottom-up exploration, education and innovation. iGEM and other initiatives may provide opportunities for partnership in which, for example, the Treaty sponsors one or more teams in agriculture from member developing countries to enter the iGEM synbio competition.

Box 4. iGEM global competition for undergraduate and graduate students

The International Genetically Engineered Machines competition (iGEM) is an annual synthetic biology event where undergraduate, graduate university and high school students and community biotech labs (DIYbio) compete to build genetically engineered systems using standard biological parts called BioBricks. According to the Registry of Standard Biological Parts, which is maintained by the iGEM Foundation, a BioBrick or a biological part “is a sequence of DNA that encodes for a biological function, for example a promoters or protein coding sequences. At its simplest, a basic part is a single functional unit that cannot be divided further into smaller functional units. Basic parts can be assembled together to make longer, more complex composite parts, which in turn can be assembled together to make devices that will operate in living cells.” (Competition 2017)

The iGEM Registry of Standard Biological Parts is a collection of genetic parts that can be “mixed and matched to build synthetic biology devices and systems” (iGEM, Registry of Standard Biological Parts 2017). Teams are provided with an initial kit that contains about 1,700 parts, and throughout the competition, they create new parts and improve other parts contained in the registry. All these parts are available for anyone to access, use and share. There are over 20,000 documented genetic parts in the Registry and “teams and other researchers are encouraged to submit their own biological parts to the Registry to help this resource stay current and grow year to year” (iGEM, Registry of Standard Biological Parts 2017). Recently, the Registry has begun collating a library of parts associated with plants (iGEM, iGEM Registry of Standardized Parts - Plants Collection 2017).

While iGEM currently supplies physical material, in the parts format, and teams submit parts (physical material) back into the registry, iGEM teams are now also provided with a “budget of 20,000 bases of DNA synthesis” by Integrated DNA Technologies. This suggests that as costs continue to fall, the physical parts of the iGEM registry may be easier to have synthesized further moving the competition towards dematerialization and DSI.. In 2016, nearly 5,600 students (mostly under the age of 25) from 42 countries participated in the International Genetically Engineered Machines competition. Since 2003, over 20,000 students have participated in iGEM from across the globe (Figure 2: iGEM map).

Figure 2. Teams participating in iGEM 2004-2016



Note: Colours represent the year in which a particular team participated in iGEM; circle=college team; square=high school team; diamond=community labs. Details available at: <http://igem.org/About>

Summary

The Treaty recognizes that “facilitated access to PGRFA which are included in the Multilateral System constitutes itself a major benefit of the Multilateral System”. It also acknowledges the importance of three other mechanisms that could help to ensure fair and equitable sharing of the benefits arising from the use of PGRFA, namely exchange of information, access to and transfer of technology, and capacity-building.

To better understand opportunities for benefit-sharing, interviewees were asked to assess where the primary value lies in the synthetic biology and genomic work. Four conceptualizations of value emerged: innovation, sequence and part functionality, plant system understanding and education and exploration. Additionally, interviewees were asked about the requisite infrastructure for undertaking synthetic biology research. Three general perspectives were identified: high-cost infrastructure, low-cost infrastructure and flexible infrastructure. Recognition of the diverse sources of value and different approaches to infrastructure helps to inform study findings on opportunities for non-monetary benefit-sharing.

A review of background materials and interviews undertaken for this scoping report identified five different strategies employed by researchers that are currently in place: 1) *ex ante* investment to facilitate access; 2) grant-based funding for hard infrastructure investment; 3) facilitated access for research community building; 4) structured research collaboration; and 5) education and training. These different strategies can be linked to the values framework and investment approaches above, and could be considered by the Treaty community as it addresses benefit-sharing and DSI.

VI. Implications of DSI/dematerialization/synbio for the Treaty

A final step in this scoping study is to connect findings from the interviews to the initial framework on ABS and reflect on the possible implications of the analysis for the Treaty community. This section provides an initial analysis of such implications.

1. Identification logic. To what extent does DSI/dematerialization affect the ABS principle of control over access to resources, including assumptions about the ability to identify users, provenance, and owners for the purposes of establishing agreements on use, use restrictions, dissemination and benefit-sharing derived from use?

The study found substantial variation in researcher needs for physical material. While all researchers interviewed use DSI, they differ on whether they return to the original material at some point or not. Several reasons explain these differences. Some researchers want the original material in order to conduct their own sequencing and synthesis, as they do not trust the validity and quality of the DSI provided by companies or other actors. Others take the opposite approach, and aim to obtain sequence data in the easiest way possible. Some other researchers want the original material in order to better understand the phenotypic data and relationships or, more generally, to better understand the context in which that original genomic data was developed. Overall, since most believe that researchers will be less likely to return to the original material over time, it becomes more difficult to identify the source of the gene sequence. Additionally, database owners, sequencing companies and others are not keeping or requesting information on the material-data linkage to DSI.

In addition, because of the different ways in which synbio researchers use DSI, assumptions that users, provenance, and owners of such information will be identifiable appear difficult to sustain. This may point to the need for greater consideration of downstream (e.g., finished product) as opposed to upstream (e.g. access limitations) benefit-sharing models. These findings, in combination with others about the proliferation of data, multiplication of users and varied importance of information about provenance, may imply that the underlying *ABS logic of identification* will increasingly be subject to erosion.

2. Monitoring of usage. To what extent does DSI/dematerialization affect the ability to monitor PGRFA over time and the transmission rights associated with them through subsequent exchange?

The study provides some evidence that the highest quality and most trusted sequence data has some origin information with it, especially because most people want to go back to the original material at some point, or they need to understand the context of the studies that generated the data. However, ‘origin’ may not mean geographic or MLS origin in this context, but rather may refer to the original researcher from whom the data was obtained. Moreover, it is also evident that the changing S&T trajectory is enabling a multiplication of possible uses and modes of transmission. Additionally, the multitude of different actors operating within the DBT context and

the lack of norms, standards or even desire to include origin information, are likely to work against accurate monitoring.

Even though scientists working on DSI may be using sequence information from identifiable published material, the chain of transmission is often not transparent or easily documented, and there is evidence of resistance from at least some database operators to facilitating ABS-based monitoring. While some patents obtained on inventions incorporating DSI may provide geographic and/or species origin information, others may not, or the information may be hidden if a particular sequence could be obtained from more than one kind of organism. In addition, patents may not always be necessary to extract value from DSI, as trade secret protection can be a viable alternative under certain conditions. Overall, the ability to track appears to be eroding and, without some mechanism to build norms of exchange across multiple users and uses, will most likely continue to do so.

3. Value generation. To what extent does DSI/dematerialization affect the value generated from DSI, either monetary or non-monetary?

A significant portion of the value of DSI lies in its aggregation (along with characterizing information) in accessible libraries/databases. An individual sequence may have value as part of a group of sequences from diverse sources combined to provide an organism, such as a plant or bacterium, with new functionality to produce high-value products. However, such value is diffuse, and spread across all the individual conjoined sequences necessary for the modified organism to function. In addition, an individual sequence or ‘part’ has more value in a library where it can be screened with other sequences to find the connections between a particular trait and its function and use in other things. The ‘screen’ is becoming more ‘abstract’ in relation to the physical material, as more sequences are collected and deposited into databases. As a result, the value of an individual sequence from a species may be very difficult to quantify. This raises three overarching issues that the Treaty may have to address:

- a. Mining of genomic information from the plant genomes that could be used to edit materials within the Treaty.
- b. Mining of genomic information from plant genomes that could be used in other places (e.g. outside the agricultural sector).
- c. Open access technology model which is about opening up the ‘plant’ toolbox in order to use the plant as the ‘workhorse’ to build/understand certain components or traits of the plant in order to produce some output. Currently, researchers do not seem to be working with MLS materials for this purpose (though this scoping report is not exhaustive in that regard). But in the future, crops and materials within the Treaty could be used either for direct agricultural purposes, or by enabling crops to produce other products.

In addition to these sources of value, DSI/dematerialization/synbio has led to a multiplication of innovation trajectories, diffuse uses and means of combining sequences and parts. This evolution

is making the articulation of a specific monetary value of a sequence within an entire new product or process challenging. However, the potential for generating high-value products, and thus monetary and non-monetary benefits, appears set to grow with the increasing use of synbio technologies and the rapid pace of development that they may enable.

4. Pooling/standardization to facilitate access. To what extent does DSI/dematerialization impact the aggregation and standardization approach promoted by the MLS?

The multiplication of holders of DSI collections distributed in a number of media and the diversity of standards, norms and behaviours will make it difficult to establish an aggregated and standardized system at a desirable scale, as it would require a central authority to adopt and manage collective rights, which would probably lower flexibility for adaptation to specific contexts. Additionally, the proliferation of data repositories includes several that are fee-based. If a fee-for-service sequence database trend develops, it should be modulated, so as not to create barriers to entry for students and researchers. Moreover, even if the Treaty chose to generate DSI for MLS crops and adopt a fee model for access, it would have to be determined how further uses of the MLS DSI could be monitored.

The development of new synbio technologies for education, tool provision and low-cost investment (challenges, kits, and curricula development), while still early in their development, create potential for new forms of pooled resources. The various innovators of these technologies and practices represent potential partners for investment in pooled resources for the Treaty.

5. Decoupled monetary benefit-sharing from individual GR provider. To what extent does DSI/dematerialization impact the MLS approach of decoupling benefit-sharing from individual provider?

As many synbio products are developed with the contribution of sequences from multiple species, the average value of individual contributions may remain rather low in most cases, and the benefits to be shared would be diluted among a wide range of beneficiaries. Additionally, the study identified several opportunities for pooled non-monetary benefit-sharing that could be considered by the Treaty. Such a benefit-sharing system would have to consider multiple sources, pathways and producers of DSI and DSI-based innovation. Within the synbio research context, frontiers between organisms and species are increasingly blurred, and pathways are more and more diversified and complex. Finally, there is a shift in perceived value of the collection of DSI and recognition of the value of particular entries within DSI databases. This could potentially result in different willingness to pay ‘fees’ on access.

6. Diversity of benefits. To what extent does DSI/dematerialization affect the realization and relative weights of the different benefits foreseen under the MLS?

The scoping study has identified a wide range of benefits, most of which can be categorized as one of the four types of non-monetary benefits: facilitated access to PGRFA within the MLS; exchange of information; capacity-building; and access to and transfer of technology. For any potential for

meaningful monetary benefit-sharing to be realized, the monitoring complexities that dematerialization brings forward should be addressed.

Nevertheless, new mechanisms are being developed to facilitate public access to synthetic biology technologies and tools that operate as building blocks for a range of research-related activities, from education to advanced science. Different approaches to infrastructure investment have made technologies and innovation available to both entry-level and advanced users. Differentiation of services has increased access points for investment and participation in the various components of the DBT system. Importantly, the synbio research community is attempting social and institutional innovations that could be recognized by the Treaty as mechanisms for identifying and capturing collective benefits.

VII. Limitations and next steps

As with any research, there are limitations to its ability to generalize. This report is primarily based on interviews with researchers working on synthetic biology and genomics, as well as with administrators and representatives of civil society organizations. Given time and resource constraints, the interviews were limited to six locations on three continents. Not all interviewees contacted were able to meet, nor did all individuals respond to requests for interviews. Therefore, the data that forms the basis of this scoping study are likely to be incomplete, and may not be representative of the entire population of relevant individuals. Finally, although the team of researchers consists of four individuals with different disciplinary approaches and backgrounds, researchers from other disciplines or representatives of other organizations or countries may have identified different constraints and opportunities for the Treaty in the findings. Despite these limitations, this report provides an initial step towards a better understanding of how new technological trajectories might affect the Treaty.

Given these limitations and the scope of the study, there are several areas that deserve additional investigation. Further work should examine the potential rules and procedures that different organizations in the research infrastructure – DSI repositories, major research institutions such as universities, national granting agencies, academic journals and others – use for the exchange and use of DSI. This distributed network of institutions actually represents the current administrative complex of DSI. Additionally, the synbio trajectory can be characterized as bottom up, whereby various actors are attempting to build a new research community (and possibly research approach) that goes beyond the usual disciplinary divides and the crop-specific silos that exist in plant genetic resources sciences. Further investigation of the opportunities to access the community for developing countries is probably needed at this early juncture. This includes an assessment of participation by developing country teams and other collaboration ventures in the areas of synthetic biology and genomics. Also, more work should be conducted to understand and possibly quantify the economic implications of these new technological and innovation trajectories for plant sciences. Finally, there is significant opportunity for investigating approaches to making DSI available (open, quasi-open, closed dissemination approaches) and the behaviours, attitudes and incentives surrounding sharing and use of DSI for research. More micro-level research that

examines how different types of actors share and use DSI would help to inform the Treaty as to how it can construct policies that increase its impact.

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Appendix. Research methodology

The study collects and analyses data from two main sources: background literature and document review, and interviews of researchers and administrators working with sequence data in several institutions in different countries.

1 Literature and document review

The project collects and synthesizes academic publications and grey literature, such as policy reports and documents from organizations and associations. The literature review has served three purposes. First, it provided an initial background for the development of the interview protocol. The research team has used results from the literature review to highlight potential areas of conflicts, sensible topics, and areas of interest to be addressed within the interviews. Second, results from the literature have been used as a secondary source of information to support findings from interviews. Triangulation of information sources is important to increase the validity of findings in qualitative studies. Moreover, this has allowed the research team to assess areas of divergence and communality between literature and interview findings. Finally, the literature review will provide an additional resource for the Treaty Secretariat to further increase knowledge about the topics addressed by this research.

2 Interviews.

Sampling. The research team has conducted interviews with scientists, legal experts and other knowledgeable individuals who have been identified based on their expertise on synthetic biology issues. The project adopted a simple design in which the members of the research team identified a purposive list of people representing different perspectives, yet involved in some way with the exchange and use of genomic data, particularly as it relates to the use of sequence data for synthetic biology in plant sciences and agriculture. A purposive sampling strategy is appropriate for this research as it is not possible to interview all individuals involved in the area of interest (i.e. synthetic biology), and a random sampling is likely to miss important sources of information. The selected interviewees provide a variety of perspectives due to their academic background (biologists, lawyers, engineers), country of origin (developing and developed countries), and diversity of employment sector (academia, industry, government).

Data collection. The interviews focused on the interviewees' perceptions of and experiences with gene sequence use and exchange. The research team conducted semi-structured interviews with all selected individuals. A set of general questions was developed into a flexible interview protocol, which was adapted according to the interviewee. The protocol is structured into four main questions, followed by a number of probes that helped the research team to maintain focus on the interview goals and collected relevant information from the interviewee. The protocol includes questions about the interviewees' research activities and background; experiences and perceptions of collaboration forms in synthetic biology; data exchange and use practices in synthetic biology projects; perceptions of value of data exchanged and used in synthetic biology

projects; and regulations and rules encountered when using and exchanging gene sequences. The full protocol is available below.

During May and July, the team conducted 21 interviews with scientists and administrators in more than 15 organizations. Interviews were conducted either in-person or (in only a few cases) via Skype, by at least two or, usually, three members of the team. In-person interviews were conducted in three US cities – Phoenix, Boston, and San Francisco – as well as in the United Kingdom and South Africa. While the research team preferred interviewing one single individual per time, in three cases the research team conducted an interview with more than one individual – two group interviews and an interview with two individuals. Group interviews were either proposed by the interviewees themselves, or scheduled to facilitate data collection when the research team faced significant time constraints (i.e. trip to UK). Interviews lasted from 45 minutes to over 2 hours. All interviews were digitally recorded and transcribed. Once transcribed, they were distributed to the research team. All interview data and notes are confidential. Interview transcripts have been de-identified before analysis, and the key file is currently stored on a secure server at CSTEPS, ASU.

Data analysis. Throughout the project, the research team regularly discussed key findings from the interviews. Regular meetings ensured that the research team identified areas to be further investigated; explored common themes and divergences across interviews; and adapted the interview protocol according to new topics emerging as important for the study.

As part of the analysis, the research teams compared notes across interviews to identify common trends and differences, and therefore assess areas of consensus and disagreement among individuals involved in synthetic biology projects and research. Results from this first part of the analysis were assessed against participant backgrounds, research areas, institutions, and country, to seek explanatory patterns between responses and interviewee characteristics. The research teams also assessed differences and commonalities between interview findings and themes emerging from the literature review.

Results from the analysis of interview data are presented in this report. Findings are reported only in aggregate, so as to ensure interviewee anonymity.

Interview protocol

Synthetic Biology Scoping Study for the International Treaty for Plant Genetic Resources for Food and Agriculture

1. INTRODUCTION - Have you always been involved in synthetic biology research? Would you categorize all of your research activities under the domain of synthetic biology? (*Objective to gain conversational tone, familiarity, build rapport*).
 - a. Briefly, could you tell us what your main research area is?
 - b. What would you consider to be the biggest differences between synthetic biology research and other types of research, for instance genetics or genomics research?
 - c. We are particularly interested in the interplay between materials and data in synthetic biology, where new technologies have led to the digitalization of gene sequences, allowing researchers to bypass accessing tangible material.
 - i. Do you mainly work with data only or begin with material from which you extract data for your research?
 - ii. Do you go back and forth from material to data and vice versa? For example, do you develop sequences and then embed them in material?
 - iii. Can you talk about how much of a sequence you use?
2. COLLABORATION – Can you tell us a bit about the forms of collaboration in synthetic biology research? For example, which types of people or groups are typically involved; what technology infrastructures are needed; how centrally located or dispersed are they; do you have well defined team boundaries or are they rather fluid, etc.?
 - a. For example, are collaborations large; do they typically include private sector actors; are there people from multiple disciplines; are they geographically distributed; etc.?
 - b. In general, what are the main sources of data and material? Are there individuals who exclusively work with data or material?
 - c. Do you have technology infrastructures that help you collaborate and share? For instance, do you generally use an open repository or bank to store data or publish your gene sequences?
3. DATA PRACTICES –We would like to know more about data exchange and use practices in synthetic biology. Thinking about your projects, how are data managed?
 - a. If you work with other scientists on a research project, are data generally open and easily accessible to all collaborators? Is there someone who is responsible to control data use and access among collaborators / research team members / lab members?
 - i. Are rules different for access to stored data and materials by individuals outside your team / lab / not collaborating with you?

- b. Do you have particular expectations when you exchange data with your collaborators? For instance, sharing results, or returning the data?
 - i. Are there different expectations in the research community about proper and fair use and exchange of data? If so, what are the main approaches that you encounter?
 - c. Do you usually have any exchange protocols or record-keeping system that help you to track data exchange and use?
 - i. Do you know where data come from? Are you able to track the origin of material from which a gene sequence you used was generated?
 - ii. Are you required (either by your institution, your own lab protocols or other rules) to identify/document ownership or proprietary rights associated with the data?
 - d. Are you familiar with the Bermuda rules, Fort Lauderdale agreement and Toronto agreement for data release?
 - i. If so, in your experience, to what extent do researchers use such instruments for regulating data release and exchange?
 - ii. Are there other agreements that are used by the community? Is there a publishing standard when it comes to sequence data?
4. VALUE DIMENSION – As last questions, we would like to talk about the perceptions of value associated with data you exchange and use. As a researcher, how do you assign value to the data you use or exchange? Do you view such data as the same as or different to (in terms of value) tangible material you use in your research?
- a. When you exchange or use data, do you take into consideration their potential market value? If so, at what stage of the research process?
 - b. Is the way you think about the value of data different than your research collaborators or the way non-scientists think about it – for example, regulators, policy-makers, lawyers, etc. If so, in what way(s)?
 - c. Do you ever have to deal with intellectual property rights? For instance, have you sought patent rights over synthetic biology inventions? Could you give us an example of IP you dealt with (trade secrets, patents, copyrights, trademarks)?
 - i. [If encountered IP] At what point of the research process does IP come into play?
 - ii. [If have inventions] For your inventions, did you use data from private (shared) or from publicly accessible sources (e.g., databases) or both?
 - iii. [If never experienced IP] When you think about IP what are your thoughts on the DNA parts/sequences? In other words, should the sequence that is developed be patented or IP protected?

- d. Have you experienced other types of regulation on the exchange and use of sequence data or materials?
- i. For instance, are you familiar with the Nagoya Protocol, the International Treaty on Plant Genetic Resources for Food and Agriculture or Access and Benefit-Sharing regulations in general?
 - ii. *If so*, what impact have these treaties or rules had on the way you access research data or material, or you share the benefits of your research, monetary or non-monetary, with providers of genetic material or data? And what are the obstacles to your complying with such treaty requirements for material? For data?
 - iii. *If not*, would you be surprised to know that these treaties require researchers to obtain permission to use genetic material from provider countries and share benefits (monetary or non-monetary) with those countries? Would you be surprised to know that these treaties may be interpreted to impose these same requirements for genetic information?

Research team

Four primary members – Eric Welch (Lead), Margo Bagley, Todd Kuiken and Selim Louafi – collaborated on this scoping report, each providing a different disciplinary perspective. Each of these members contributed equally to the conduct of the research and the production of the draft. A fifth member, Federica Fusi, provided assistance with the research planning, interviews and document review.

Eric Welch, Ph.D. CSTEPS, Arizona State University

Dr. Eric W. Welch is a Professor in the School of Public Affairs at Arizona State University where he teaches courses in innovation and science and technology policy. He earned his Ph.D. in public administration in 1997 at Syracuse University's Maxwell School of Citizenship and Public Affairs, where he specialized in science and environment policy. His research interests include genetic resources policy, information technology in government and public management, among others.

Eric currently directs the Center for Science, Technology and Environment Policy Studies (C-STEPS) at ASU, where he is the primary investigator on several nationally and internationally funded projects on the global exchange and use of genetic resources. Currently, he is the primary investigator on a multi-year NSF-funded project entitled *Contested Resource Inputs to Science: How Institutional Provisions on the Access and Use of Materials and Data Affect Research Collaboration Structures and Outcomes*. Dr. Welch has received several fellowships to conduct research in genetic resources, including an OECD Biological Resource Management for Sustainable Agriculture fellowship, an Agropolis Foundation Research fellowship, and a Japan Science and Technology Agency fellowship. He has published over 100 articles, reviews and book chapters.

Todd Kuiken, Ph.D., Genetic Engineering and Society Center, NCSU

Dr. Todd Kuiken is a Senior Research Scholar with the Genetic Engineering and Society Center at NC State University, where he explores the scientific and technological frontier, stimulating discovery and bringing new tools to bear on public policy challenges that emerge as science advances. He has numerous projects evaluating and designing new research and governance strategies to proactively address the biosafety, biosecurity and environmental opportunities/risks associated with emerging genetic technologies. He was previously the principal investigator on the Woodrow Wilson Center's Synthetic Biology Project.

Dr. Kuiken is a member of the United Nations Convention on Biological Diversity Ad-Hoc Technical Expert Group on Synthetic Biology. He is also a member of the human practices committee of the International Genetically Engineered Machines competition, and a founding member of its biosafety/biosecurity committee. Dr. Kuiken has provided expert testimony in front of the U.S. National Security Agency Advisory Board, the U.S. National Academies of Science, the United Nations Bioweapons Convention, the Organization for Economic Co-operation and Development, has been featured on NPR's Science Friday, and is a regular speaker on public policy issues related to nanotechnology and synthetic biology.

After completing his B.S. in Environmental Management and Technology at Rochester Institute of Technology he worked directly with renowned scientists on the biogeochemical cycling of mercury at the Oak Ridge National Laboratory. He earned an M.A. in Environmental and Resource Policy from The George Washington University concentrating on the scientific, economic and community development aspects of environmental issues. While there, he worked at various environmental non-profits including the National Wildlife Federation, where he worked within the Clean the Rain campaign that dealt with the environmental and public health threats associated with mercury pollution. Dr. Kuiken earned his Ph.D. from Tennessee Tech University, where his research focused on the air/surface exchange of mercury associated with forest ecosystems. As part of his dissertation, he synthesized these results with other studies associated with mercury cycling, public health threats and policy alternatives, to bring attention to the threats and the need for improved public policy dealing with mercury pollution.

Margo Bagley, J.D., Emory University School of Law

Margo A. Bagley is an Asa Griggs Candler Professor of Law at Emory University School of Law. She rejoined the Emory faculty in 2016 after ten years at the University of Virginia School of Law, where she was most recently the Hardy Cross Dillard Professor of Law and the Joseph C. Carter, Jr. Research Professor of Law. Her scholarship focuses on comparative issues relating to patents and biotechnology, access to medicines, genetic resource appropriation, and technology transfer. Professor Bagley served on the National Academy of Sciences Committee on University Management of Intellectual Property: Lessons from a Generation of Experience, Research, and Dialogue, is a technical expert and advisor to the Government of Mozambique in World Intellectual Property Organization (WIPO) matters and consults with companies, governments, and intergovernmental organizations, and other entities on a variety of patent-related matters. She is currently Lead Facilitator and Friend of the Chair in the WIPO Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge, and Folklore and a Consultant to the UN Food and Agriculture Organization Secretariat for the International Treaty on Plant Genetic Resources for Food and Agriculture. Professor Bagley has published numerous articles, book chapters, and monographs, as well as two books with co-authors: Bagley, Okediji and Erstling, *International Patent Law & Policy* (West Publishing 2013) and *Patent Law in Global Perspective* (Okediji and Bagley eds. Oxford University Press 2014). A chemical engineer by training, Professor Bagley worked in industry for several years before attending law school and is a co-inventor on a patent for reduced fat peanut butter. She is a frequent speaker and writer on patent related topics in the U.S. and abroad and has taught in law schools in China, Cuba, Germany, Israel, and Singapore.

Selim Louafi, Ph.D., CIRAD

Sélim Louafi is a Senior Research Fellow at the Centre International de Recherche Agronomique pour le Développement (Cirad, Montpellier, France). He is an agronomist by training and has a PhD in Agricultural Economics. He worked at the Centre of Philosophy of Law in Louvain la Neuve in Belgium on Global Governance of Genetic Resources. He then worked at the Institute of Sustainable Development and International Relations (Iddri) in Paris, where he was in charge of the Biodiversity Programme. From 2007 to 2009, he served as Senior Officer at the Secretariat of the International Treaty on Plant Genetic Resources for Food and Agriculture (FAO), where he was in charge, among other things, of implementation of the Multilateral System of Access and Benefit-sharing. Since 2010, he has been part of a team of biologists and geneticists at Cirad (Montpellier) working on science and global policy interactions in the field of agricultural biodiversity. He was recently awarded a Marie Curie Outgoing Fellowship Grant to study institutional structures, constraints and incentives of Bio-based Research in Agriculture (2014-16). Sélim Louafi has also been appointed for five years (2014-2019) as a member of the Capacity Building Task Force of the International Platform on Biodiversity and Ecosystem Services (IPBES). He is a member of the Comité Economique, Ethique et Social of the Haut Conseil des Biotechnologies (France).

Federica Fusi, Doctoral Candidate, CSTEPS, Arizona State University

Federica Fusi is a PhD candidate at Arizona State University. She works at the Center for Science, Technology and Environmental Policy Studies (C-STEPS), where she has been involved in several projects on the impact of regulation on genetic resource exchange, use and access, scientific collaboration networks, and the design of new organizations and institutions for data sharing in science. Her other research interests include technology in public organizations, open government and data sharing in city governments.