Justicia, equidad y eficiencia para el Convenio sobre la Diversidad Biológica y el Protocolo de Nagoya:

*Análisis de un roedor, un caracol, una esponja y un virus**

Fairness, Equity and Efficiency for the Convention on Biological Diversity and the Nagoya Protocol:

Analysis of a Rodent, a Snail, a Sponge and a Virus

Sociedad Peruana de Derecho Ambiental (SPDA) / Peruvian Society for Environmental Law
The ABS Capacity Development Initiative
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Parte 2

Lex

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Appendices

Appendix I

Naked Mole-Rat (*Heterocephalus glaber*)

Anna Deplazes-Zemp

Figure 1. Naked mole-rat

Credits: Josh More / flickr (CC BY-NC-ND 2.0)

Brief history

The naked mole-rat (*Heterocephalus glaber*) is a remarkable species of rodent that is endemic to East Africa (Kenya, Somalia, Ethiopia and Djibouti). The species owes its name to the lack of hair and resemblance to rats yet with a mode of life more like that of moles (Honeycutt, 1992). Naked mole-rats have a social structure more typical of the class Insecta rather than Mammallia. They live in extended underground tunnel systems in colonies, which number on average 75-80 individuals with one reproductive female and a few reproductive males. Other members of the colonies fulfill various worker functions (Honeycutt, 1992; J. Jarvis, U.M. & Sherman, 2002; J. U. M. Jarvis, 1981). Naked mole-rats are exceptional not only for their social organization but also for their physiology. They are the only known cold-blooded mammals. They exhibit longevity, resistance to cancer, hypoxia-tolerance and pain insensitivity (Lagunas-Rangel & Chávez-Valencia, 2017; Mulatu, 2018; Schuhmacher, Husson, & Smith, 2015; Ewan ST. J. Smith, 2019). The combination of outstanding features makes the species a promising object for pharmaceutical research.

Utilization of DSI

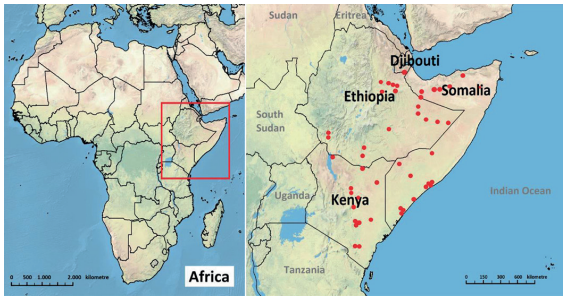
The order Rodentia is well studied. What makes *Heterocephalus glaber* so fascinating is the set of questions regarding the evolution of its exceptional traits. How did mammalian biology and biochemistry evolve such features? Comparison of the genetic sequences of the naked mole-rat – captured under the placeholder "digital sequence information" ("DSI") – with those of other species is a widely used vehicle to answer such questions. Research has been facilitated since publication of the whole genome (Fang et al., 2014; Keane et al., 2014; Kim et al., 2011) which is available on Genebank (https://www.ncbi.nlm.nih. gov/nuccore/AFSB00000000) as well as other databases.

Studies based on genetic sequences span fields from ecology to physiology (Da Silva, Tomasco, Hoffmann & Lessa 2009, Schuhmacher, Callejo, Srivats & Smith 2018). The comparisons of sequences of the whole genome (Kim et al., 2011; MacRae et al., 2015) allow exploration of differences in gene expression, i.e. activated in specific situations (e.g. Bens et al., 2018). The comparisons can also be interesting for the analysis of specific genes and associated proteins that fulfill core functions in mammalian biology. The identification of genetic differences provides crucial insight for understanding of biological processes, including variations that lead to human disease. For example, the introduction of the mole-rat version of a gene into a mouse may throw light on the impact of genetic variants. One analyzes whether the identified naked mole-rat sequence is sufficient to induce the altered biological processes in rat or human cells. Such an approach has enhanced understanding of acid-induced pain, for which naked mole-rats show exceptional insensitivity (Schuhmacher et al., 2018; E. S. J. Smith et al., 2011). The cancer resistance and longevity of the naked mole-rat have also been widely studied using genetic sequences for comparative genomic and gene expression analysis (e.g Hilton et al., 2019; Keane et al., 2014). The cancer resistance is often studied by expressing wild type or mutated versions of naked mole-rat genes in cultured naked mole-rat cells or those of other species (e.g. Seluanov et al., 2009; Tian et al., 2013).

Conservation status and distribution

The naked mole-rat is found in central Ethiopia, northern and eastern Kenya, throughout most of Somalia and in southern Djibouti (Maree & Faulkes, 2016)). They live in arid and hot areas with low or irregular rainfall (Maree & Faulkes, 2016). The Red List of Threatened Species of the International Union for Conservation of Nature (IUCN Red List) classifies the naked mole-rat as a species of "least concern" (Maree & Faulkes, 2016). The species is common and currently not threatened. However, where naked mole-rat territory overlaps with agricultural areas, conflicts arise: the animals eat root vegetables such as cassava and sweet potatoes. In view of the population growth and concomitant agricultural expansion into the habitat of naked mole-rat, pest control measures could threaten the species in the future (Wale, Kassie, & Fekensa, 2016).

Figure 1. Naked mole-rat concentration and general geographic distribution



Distribution of Heterocephalus glaber in the horn of Africa, presence of NMR represent by red dots. https://d3i71xaburhd42.cloudfront.net/46 0625628d0b1411512f50d25027df31bd8435bb/18-Figure5-1.png

Credits: Maree & Faulkes, 2016.

Ex situ status of species

Zoologists became aware of the naked mole-rat in the 1970s; the social organization arose great interest. Jarvis (1981) collected a colony in Mtito Andei, Kenya in 1977 (Jarvis, 1981), which presumably led to the first laboratory lineage of naked mole-rats at the University of Cape Town. Other animals were collected in Kenya in the 1970s and early 1980s. Some collections were to establish laboratory samples at Michigan University and Cornell University (R.D. Alexander, P.W. Sherman), and at the University College London (R.A. Brett) and Harvard University (R.L. Honeycott) (Sherman, Jarvis, & Alexander, 1991). Today ex situ naked mole-rat populations are popular in in zoological gardens. Research with naked mole-rats is usually conducted with the laboratory strains established in the 1970s to 90s rather than capturing new animals from the wild (e.g. Keane et al., 2014; Kim et al., 2011; Hilton et al., 2019; Seluanov et al., 2009, Tian et al., 2013). Research on the molecular biology and biochemistry is performed with immortalized cell cultures in lieu of the live animal. However, some exceptional projects still research animals from the wild, as evidenced by studies on the gut microbiome (Debebe et al., 2017; Debebe et al., 2016). While the authors highlight that the study was authorized by the Ethiopian Wildlife Conservation Authority, ABS was not explicitly mentioned in the associated publications.

Uses

The main user of naked mole-rats remains academia. While the original interest were the social and ecological features, current interest lies more in physiological and genetic traits. Other users are zoos around the world. As discussed below, most patents involving naked mole-rats concern methods of working with the animals rather than with their genetic information. The genome is freely available online at http:// www.naked-mole-rat.org (Keane et al., 2014) and accessible on GenBank under accession number AFSB01000000 https://www.ncbi.nlm.nih.gov/nuccore/AFSB00000000 (Kim et al., 2011).

Type of R&D undertaken and actors involved

Several of the extraordinary properties of the naked mole-rat may hold promise for understanding and treating human diseases. Among the properties of interest are longevity, cancer resistance, insensitivity to agonizing stimuli such as acid and capsaicin, and tolerance for low oxygen (Ewan ST. J. Smith, 2019). A patent search indicates that research is usually conducted at academic institutions for a general understanding of the species rather than for specific components or gene sequences for a potential medical utility. A few exceptions are described in the section on patents below.

The majority of patent documents concerns the “research support sector” dealing

with cultivation methods for naked mole-rat cell cultures. There are also two patents on methods for mating, breeding and pairing naked mole-rats (CN106857386 A, CN106857387 A) or for identifying female mole-rat queens (CN106614276B). Two patents exist on short DNA sequences for biological detection (CN105671040 A, CN105695455 B).

Application of ABS

As of this writing, no monetary benefits obtained from research on naked mole-rat genetic resources are apparent in the literature. Nevertheless, research on this exceptional species generates a non-monetary benefit in the advance of the science of biology. Insights may contribute to a general understanding of biological and biochemical processes, which include deviations that lead to human disease. Nevertheless, discussion on ABS is absent in the context of the use of naked mole-rats in research. As mentioned above, most research is performed with ex situ colonies as laboratory strains, which were established in the 1970s and 1980s. For example, Keana et al. state that the sequenced individual was *"obtained from the colony established by Vera Gorbunova at the University of Rochester, USA. The founder animals originated from the colony of J.U. Jarvis, at the University of Cape Town, South Africa."* (Keane et al., 2014: p3558). Likewise, Kim et al. highlight that *"[t]he sequenced individual male NMR was from a captive breeding colony located at the University of Illinois, Chicago"* (Kim et al., 2011: p226). In the non-systematic literature search performed for this report, no indications for ABS were found in any research paper nor were ABS agreements mentioned in any of the listed patent documents.

Market information

We are not aware of any naked mole-rat products that are commercially available.

Relevant IP involved

A search for patent documents claiming products or processes involving naked mole-rats resulted in 34 hits[1] of which 27 patents[2] were specific for naked mole-rats and 7 patents[3]

1 We would like to thank Prof. Heinz Mueller from the Swiss Federal Institute of Intellectual Property for performing this search. This search covered more than 110 million patent documents (published applications and granted patents) from more than 90 countries. In addition to practically all national patent documents around the world, applications with regional and international organizations (PCT, ARIPO and OAPI patents) are included, as well.

2 WO2019039826 A1, US2014248371, CN107384699 A, CN107142242 A, CN107050045 A, CN107058492 A, CN107034185 A, CN107022520 A, CN106906177 A, CN106834208 A, CN106857386 A, CN106857387 A, CN106754716 A, CN106614276 B, CN106577470 B, CN106520697 A, CN106333761 A, CN105754943 B, CN105671040 A, CN105695410 B, CN105695408 B, CN105695409 B, CN105695455 B,

3 WO2016054032 A1, CN109529054 A, WO2017124086 A1, CN109432129 A, WO2016161973 A1, WO2013149259 A1, US2014023628 A1

concerned a range of animals which includes the naked mole-rat. Most of the patents are registered only in China. Of the 27 naked mole-rat-specific patent documents, only two were applied for jurisdictions outside China, one US patent and one worldwide patent application originating from South Korea. The USPTO reports the status of patent application US20140248371A1 by Carmel-Haifa University of Israel as abandoned as of 23 January 2018. A worldwide application of 2017 has so far only been granted in South Korea. Overall, applicants are mostly academic institutions, indicating that, most applications of naked mole-rats in R&D are concentrated in academia rather than industry. Most of the identified naked mole-rat patent documents concern methods and tools for research with naked mole-rats such as cultivation methods for different types of naked mole-rat cell cultures. A few patent documents exist on short DNA sequences (SNP sequences or primer sequences) for technical detection in molecular biology, for instance, to detect genetic polymorphism in mole-rat colonies (CN105671040 A, CN105695455 B).

Four patent documents relate to potential medical applications. The patent CN107384699A, held by a Hainan Baicaoli Yaotang CO LTD, a Chinese drugstore company, concerns a "naked mole-rat nourishing longevity health wine" to be used in Traditional Chinese medicine, in combination with other ingredients, to inhibit tumors and enhance immunity. The wine contains "naked mole-rat macromolecular hyaluronic acid mixed solution". A second Chinese patent, CN107050045A, held by the Harbin Institute of Technology, covers the use of naked mole-rat hyaluronic acid in "preparation of drugs for treating breast cancer". The patent description mentions that naked mole-rat hyaluronic acid can be gained by over-expression of the naked more rat gene HAS2 in breast cancer cell lines, however, the production of hyaluronic acid or the genetic sequence is not covered by the patent. The third medically relevant patent document is US2014248371 A1, applied for by Carmel-Haifa University in Israel. This patent application concerns a conditioned cell culture medium derived from naked mole-rat cells. The use of this medium was to identify anti-cancer agents as well as active agents selected in this medium and anti-cancer treatments involving these agents. The fourth naked mole-rat patent document with direct pharmaceutical relevance is WO2019039826 A1, held by the Korean Konkuk University Industrial Cooperation Corp. The patent concerns the digital amino acid sequence of a naked mole-rat polypeptide with antimicrobial activity, which could be used for the development of new antibiotics. None of the discussed patent descriptions mentions ABS.

ABS issues

Countries of origin have taken note of the potential value of the naked mole-rat as a genetic resource and ongoing use in R&D without ABS-agreements. On the website describing the CBD Clearing House Mechanism of

Ethiopia, the naked mole-rat has been identified as a potential object for an ABS agreement if access to the organisms occurs in the scope of the national ABS framework (Taye, 2017). Mulatu (2018) discussed the potential for bioprospecting of the rodent but did not explain how benefit sharing would unfold for Ethiopia. Open access to the genome of the naked mole-rat is seen as emblematic of how the object of R&D must be recognized as natural information for any sharing of benefits to be fair and equitable (Peruvian Society of Environmental Law, 2017; Vogel, Ruiz Muller, Angerer and Oduardo-Sierra, 2018). Criticism of ABS lies in the unbounded openness of the genetic resources, despite the potential for medical applications and need for habitat conservation in the countries of origin.

Summary

The naked mole-rat is a treasure trove for academic research. Medically interesting features such as longevity, cancer resistance and insensitivity to pain are being studied at the molecular and biochemical level. The dematerialization of the species, endemic to East Africa, into digital sequences plays an essential role. To date, use of the naked mole-rat as a genetic resource has mainly taken place in academia with the non-monetary benefit being a deeper understanding of biological processes. One may easily imagine R&D on naked mole-rats will result in future medicines and be of monetary benefit to the pharmaceutical industry. Most of the research which utilizes genetic resources from the naked mole-rat, including the open-access genome sequence, used ex situ strains that were established in the 1970s and 1980s. So, the countries *providing* the genetic resources are now those of databases, university laboratories and zoos. Naked mole-rats are generally being used without ABS-agreements with the countries of origin.

Table 1. Details of references to geographic origin of naked mole-rat strains (NMR) mentioned in the literature and discussed for the NMR-case study

Table 1
Details of references to geographic origin of naked mole-rat strains (NMR) mentioned in the literature and discussed for the NMR-case study

References	Materials & Methods section referring to the NMR strain
Honeycutt, 1992	Review article, no country of origin mentioned
J. Jarvis, U.M. & Sherman, 2002	Review article, no country of origin mentioned
J. U. M. Jarvis, 1981	"Mixed colonies or mole-rats have been under laboratory observation for 6 years. In October 1977 an almost complete colony of 40 individuals was collected at Mtito Andei, Kenya" (p. 571)
Lagunas-Rangel & Chávez-Valencia, 2017	Review article
Mulatu, 2018	Review article
Schuhmacher, Husson, & Smith, 2015	Review article
E.S.J. Smith, 2019	Review article
Fang et al., 2014	"A breeding colony of DMRs (Damaraland Mole-rat) (Fukomys damarensis) was housed at the University of Illinois at Chicago. The DMR was known as Cryptomys damarensis prior to a recent subclassification into a new genus, Fukomys"(p. 1361; no origin mentioned)
Keane et al., 2014	"Briefly, high molecular weight DNA was extracted from tissues of a single partially inbred female adult NMR obtained from the colony established by Vera Gorbunova at the University of Rochester, USA. The founder animals originated from the colony of J. U. Jarvis, at the University of Cape Town, South Africa" (p. 3558)
Kim et al., 2011	"The NMR genome was sequenced on the Illumina HiSeq 2000 platform. The sequenced individual male NMR was from a captive breeding colony located at the University of Illinois, Chicago" (p. 226)
Da Silva, Tomasco, Hoffmann, & Lessa, 2009	They analyse Cytochrome b gene sequences in databases
MacRae et al., 2015	Genome analysis (refer to Kim et al. 2011)tochrome b gene sequences in databases
Bens et al., 2018	"NMR colonies were kept inside a climatized box (2×1×1 m) in artificial burrow systems, consisting of eight cylindrical acrylic glass containers (diameter 240 mm, height 285 or 205 mm)..." (p. 9; no origin of NMR is mentioned)
Hilton et al., 2019	"The NM-Rs in this study came from 10 different captive colonies, while the mice were purchased from the Jackson Laboratories (Bar Harbor, ME) and maintained in the vivarium for at least 2 weeks prior to use."(p. 9; no origin or specification of the founder strain mentioned)

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Seluanov et al., 2009	"Naked mole-rats were from the colony of K.C.C. at Vanderbilt University. Mice used for isolation of cell lines were C57BL6"(supplementary material p. 1; no origin mentioned)
Tian et al., 2013	"Naked mole-rats were from the University of Rochester colonies. C57BL/6 mice and NIH III nude mice were purchased from Charles River Labs. Non-albino guinea-pigs were obtained from Elm Hill Labs"(p. 349; no origin mentioned)
Maree & Faulkes, 2016	This is the source of the IUCN red list no empirical data
Wale, Kassie, & Fekensa, 2016	Local research (assessment of naked mole-rat distribution) no export. Study areas in Ethiopia
Sherman, Jarvis, & Alexander, 1991	A book on NMR that mentions some founder strains (as summarized in the case study)
Debebe et al., 2016	The two studies by Debebe et al. are the only studies found in which research was performed with wild animals, without any mention of ABS issues: "Eleven wild naked mole-rats from the Rift Valley of Ethiopia were captured and detained. Intestinal and fecal samples of the animals were obtained from individuals captured in Ethiopia. Permission comprising both, field permit and ethics approval was granted by the Ethiopian Wildlife Conservation Authority (EWCA; ref. No. 31/394/07 dated 27 November 2014)" (p. 2; some of the authors are from the University of Addis Ababa)
Debebe et al., 2017	"Study subjects were captured and detained from the Rift Valley ecosystem in the eastern part of Ethiopia. Briefly, the fecal samples from each animal were collected and immediately frozen in a liquid nitrogen tank and transported to Leipzig, Germany, and stored at −80 °C prior to further analysis. The study was approved and permitted by Ethiopian Wildlife and Agricultural Authorities (reference number 31/25/08 dated 19 November, 2015). Subject collection and sampling were performed in accordance with the Ethiopian Wildlife Law guideline and regulation" (p. 6, some of the authors are from the University of Addis Ababa, but they mention export (as quoted)

Patent applications

CN107384699A	Describes a procedure of producing NMR extracts, but says nothing about the origin or strain of the used animals
CN107050045A	About generating NMR Hyaluronic acid in cell culture with cells that overexpress the NMR gene Has2 → no NMR animals are involved.
US2014/0248371	Mentions "Spalax [NMR] and Acomys [spiny mouse?] were captured in the field and housed under ambient conditions in individual cages in the Animal Facility of the Institute of Evolution, University of Haifa" (Supplementary Information *American Scientist* 80(1) 43-53. Does not mention the country of origin.
WO2019039826A1	Work with sequence data from a protein database UniProtKB/Swiss-Prot → in silico analysis (on the computer) → chemical synthesis of the protein → different tests with bacteria and cultured cells,→ no NMR material

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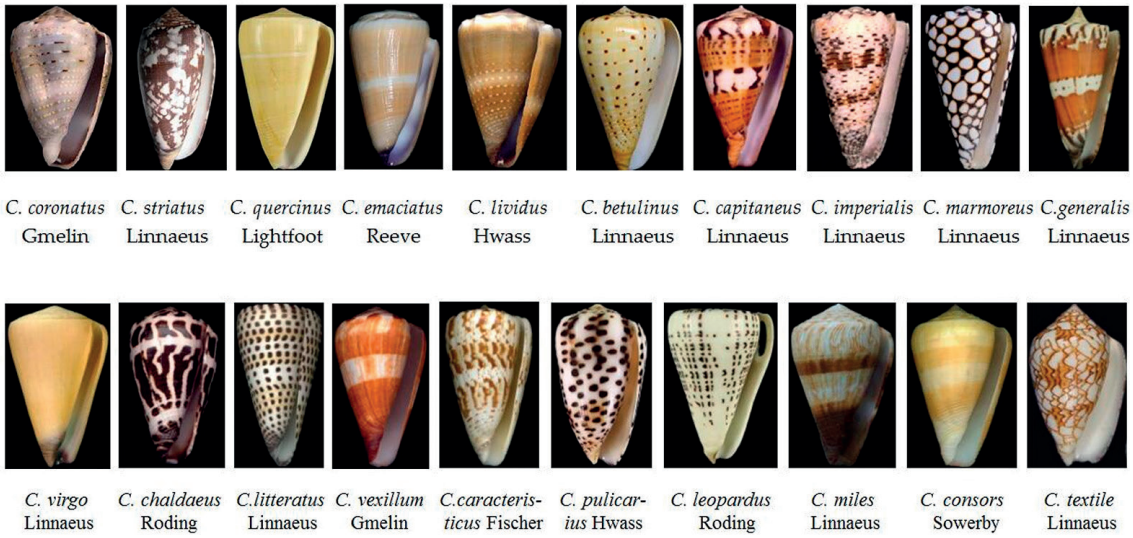
Appendix II

Cone snails (family Conidae and genus Conus)

Nicolas Pauchard

Figure 1. Twenty most abundant Conus species in the South China Sea



Credits: Gao et al. 2017 (CC BY 4.0)

Brief history

Cone snails in the genus Conus from the family Conidae are marine gastropods that take their name from the conic shape of their shells (Figure 1). They are predatory and paralyze their prey through venom injected through a harpoon-like tooth (Baybayon et al. 2017). Cone snails exhibit an extraordinary taxonomic diversity, with more than 830 described species (Uribe, Puillandre and Zardoya 2017), thus making them one of the most diverse genera in the marine environment (Puillandre et al. 2014). The venoms of cone snails, called *conotoxins* or *conopeptides*, are highly diverse neurotoxic peptides. More than 100,000 types are estimated to exist (Lobo-Ruiz et Tulla-Puche 2018). If all variants and fragments are included, the estimate surpasses 700,000 (Puillandre et al. 2014; Dutertre et al. 2013). Numerous post-translational modifications enable chemical diversity (Mansbach et al. 2019). Conotoxins have inspired R&D for over a half century (Olivera and Teichert 2007). Baldomero Olivera and colleagues Lourdes Cruz and Michael McIntosh were among the

pioneers.[1] In the early 1980s, they isolated and characterized a conopeptide (ω-MVIIA) which exhibited powerful analgesic properties (McIntosh et al. 1982). The research would later be developed into analgesic Ziconotide, which goes by the trade name Prialt from Elan Pharmaceuticals. The drug was approved by the FDA in 2004 and is 1,000 times more powerful as morphine. Commercialization of the species lies in the R&D of the medical potential of conopeptides.

Cone snails raise the following ABS issues:

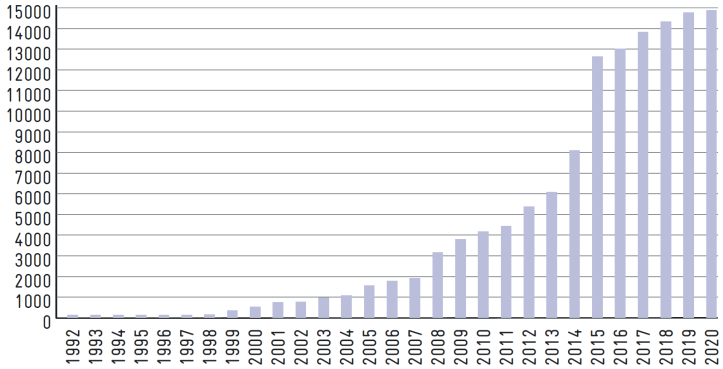
- some species are widely distributed while others, endemic to limited areas;
- specimens can be found within or beyond the exclusive economic zone of coastal countries.
- a high number of genetic sequences, known by the placeholder "digital sequence information" (DSI) by Parties to the CBD, lie in open access through online databases; intense R&D of conotoxins is conducted mainly in university laboratories; one product developed has become a commercially successful drug.

Utilization of "DSI"

The dematerialization of Conidae has been ongoing for almost three decades. Searches on GenBank, as of this writing, generated 25,203 sequences with Conus as the research item and 14,875 results with the family name Conidae. The first entry from 1992 corresponds to a sequence coding for the expression of a conotoxin (Hillyard et al. 1992). To date, the number of conotoxin sequences is 1800 and rapidly rising, with 67 transcriptome data sets available from the NCBI (Gao et al. 2017). Many whole genomes are available. Figure 2 illustrates the upsurge since the beginning of the millennia. As noted by Durek and Craik (2015), the exponential growth in conotoxin sequences and related knowledge from 2010 onward reflect advances in the '-omics' disciplines, viz., improvements in DNA sequencing, bioinformatics, mass spectrometry and high-throughput assays.

The authors determined that more than 50% of the conopeptide sequences described in Uniprot have been publicly released in the last four years preceding their analysis of 2015.

Figure 2. Evolution of the number of sequences from Conidae on GenBank



Source: Generated from search engine on NCBI GenBank using the keyword Conidae, performed on 27.03.2020.

1 Baldomero Olivera is a felipino chemist and distinguisted professor of biological sciences at the University of Utah where he has spent most of his academic career. He is perhaps the leading expert have worked on the cone snail's venom since the late 1960s,

In 2007, David Craik's research team at the Institute for Molecular Bioscience, The University of Queensland, Australia created ConoServer, a database dedicated explicitly to conopeptides.[2] Protein and nucleic acid sequences as well as structural information on conopeptides are available through the platform. Whether they may be classified as DSI depends on how the placeholder is officially defined and then how the definition is interpreted. The sources of the data for ConoServer are peer-reviewed literature and public databases which include UniProt, NCBI GenBank and the World Wide Protein Data Bank. ConoServer enables users, for example, to search a peptide and find the corresponding sequences, pharmacological family and corresponding region and diet of the organism. Some 7,638 conotoxin sequences are now available from the platform.[3]

Regarding the production and utilization of DSI, different fields of research can be distinguished. For example, the remarkable taxonomic diversity of the *Conidae* family is addressed in molecular taxonomy through the identification of molecular markers (Puillandre et al. 2014; Uribe, Puillandre, et Zardoya 2017). Research in genomic, transcriptomic and/or proteomic analysis identifies and explains the molecular processes leading to diverse peptides, i.e., their genes and transcripts (Hu et al. 2011; Lavergne et al. 2013; Gao et al. 2017). Other studies deploy computational techniques to explain conopeptide structures, binding affinity or molecular mechanisms and predict potential molecular targets and applications (Mansbach et al. 2019). Synthetic biology on conopeptides illustrates utilization of DSI. The Chinese patent application for an invention described as a "Method For Biosynthesis Of Conotoxin From Yeast" (CN 110358770 A) describes how the corresponding inventors artificially synthesized an optimized peptide gene from DSI. Bruce et al. (2011) explain how they constructed a recombinant conopeptide coding sequence based on the original sequence P18511 obtained from UniProtKB/Swiss-Prot. The conotoxin of interest is then obtained by transfer of those sequences into engineered yeast strains that ultimately produce the compound.

Conservation status – distribution

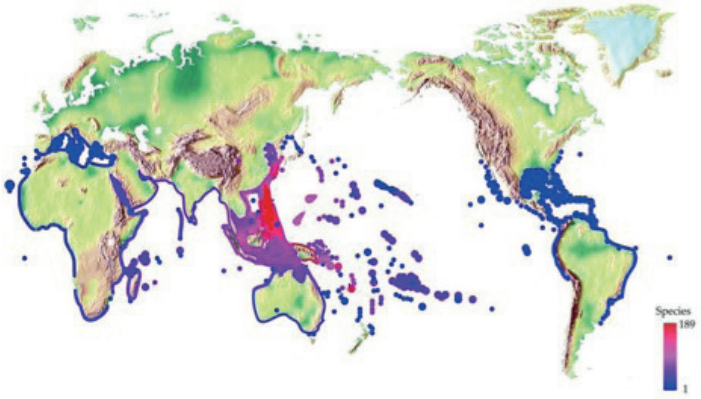
Cone snails are found in the warm waters of tropical and subtropical seas and oceans, with the highest species diversity in the Indo-West Pacific region (Puillandre et al. 2014; Uribe, Puillandre, et Zardoya 2017). The Indo-Pacific region is thought to be the center of evolutionary origin of the family (Puillandre et al. 2014). Some species have radiated and adapted to cooler environments, such as the North American Pacific coast that hosts *C. californicus* (Gao et al. 2017) and the Mediterranean Sea. Some species are cosmopolitan while others have a habitat restricted to a single island or even a bay (Uribe, Puillandre, et Zardoya 2017) (see figure 3).

2 Accessible through the following URL: http://www.conoserver.org/?page=about_conoserver.

3 Using the "search a peptide" tool search and selecting "all" on every proposed research criterion. Search performed through http://www.conoserver.org on 28.03.2020

Figure 3. Worldwide distribution of cone snails.

Credits: Gao et al. 2017 (CC BY 4.0)



Ex situ status of species

The IUCN lists three species as critically endangered (*C. mordeira*, *C. lugubris* and *C. salreiensis*), eleven as endangered, 27 vulnerable and 26 near threatened. The majority (478) are considered as requiring least concern.[4] Despite the IUCN list and classification of conservation status, no cone snail species is listed the appendix of CITES (Convention on International Trade in Endangered Species). The most serious short-term threat to cone snail diversity is the destruction of habitat, which in most cases are fragile reef ecosystems (Dutertre and Lewis 2013). Hundreds of tons of shells (millions of individuals) are also imported each year into the United States and Europe for ornamental purposes (Chivian, Roberts, et Bernstein 2003). The most serious long-term threat is acidification of the ocean (Daniel Karp, 2018, https:// medium.com/student-conservation- corner/ ocean-acidification-becomes-a-big-threat-to-marine- predators-c57905c2722a, Watson, et al, 2017, https:// royalsocietypublishing. org/doi/pdf/10.1098/rsbl.2016.0797, Peters, https://www.york.ac.uk/research/themes/ cone- snails/)

Cone snails have been the subject of international transfers through MTAs and ABS agreements. Liebig et al. (2002) identified an agreement for commercial research that was concluded in 2002 between the Bureau for Fisheries and Aquatic Resources (Department of Agriculture of The Phillipines), the Marine Science Institute of University of the Philippines (UP-MSI), which was the affiliation of the collector and collaborating researcher, Lourdes Cruz, and the University of Utah, which was the affiliation of the principal investigator Baldomero Oliveira. Until 2005, the agreement allowed access to and the transfer of cone snails for research on neurologically and other biologically active compounds. Specimens were sent to the U.S.A under MTAs. The U.S. National Institutes of Health (NIH) funded the research. Information of the number and content of provisions in the MTAs are not publicly available.

Uses

Cone snails are commercialized for their ornamental value in jewelry and, to a lesser

4 These numbers were found by searching for the keyword Conidae on the IUCN red list search engine on 28.03.2020: https://www.iucnredlist.org/search?ta xonomies=100892&searchType=species

degree, for R&D. The lethality of C. geographus envenomation attracted the attention of the toxicology community (Olivera 2002). In 1960, Kohn et al. (1960) conducted the first comprehensive study of the effects of Conus venoms which were followed in the 1970s by Endean et al. who suggested the potential of pharmacological properties (Olivera 2002). By 1990, the complexity of the venom of all cone snails had become clear. One individual species could express some 100-200 different venom peptides (Olivera 2002). Conotoxins have a high specificity and affinity to voltage and ligands-gated channels, which are receptors and neurotransmitter transporters in the central and peripheral nervous systems. The properties render them promising compounds for drug leads (Peng et al. 2016; Sharpe et al. 2001; B. M. Olivera et Cruz 2001). Furthermore, the diversity among and within species makes the diversity of the peptides produced the largest library of natural drug-lead compounds obtained from the marine environment (Gao et al. 2017). Puillandre et al. (2014) argue that the pharmacological diversity of conotoxins has been underestimated. Similarly, Gao et al. (2017) stress that the diverse and selective conopeptides are valuable as research tools, drug leads and drugs. Chivian, Roberts and Bernstein (2003) also remark on the wide-ranging research interest as evidenced by 2600 studies on the subject published since 1980. A quick search on Google Scholar using "conus snail" generated approximately 11,900 results (26.03.2020).

Regarding IP, Gao et al. (2017) conducted an analysis using the largest patent databases (Chinese, US and European patent offices and the World Intellectual Property Organization database). They searched the following keywords: conotoxin, conopeptide, conantokin, contryphan and contulakin. The last three terms belong to families of peptides. The period search ranged from 1998 to 2017.

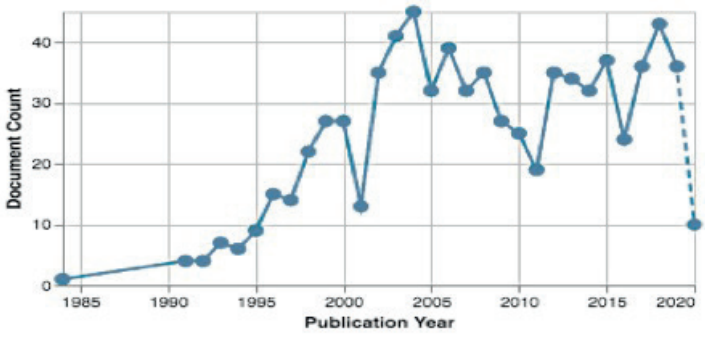
The results comprised 811 patent documents of which 243 were granted. In most cases, property rights were claimed or granted for inventions corresponding to composition of matter (conotoxins) while 360 documents referred to application processes and methods. Some 58% of the patents were claimed or granted in the U.S., 13% in China and 11% in Australia. A similar search using Patent Lens database identified 766 patent documents (251 granted patents and 515 patent applications).[5] The two largest applicants are Utah University, which is home of the laboratory of Baldomero Olivera, and the biotech company Cognetix, for which some 152 and 86 patents have been granted.[6] The next largest are followed the University of Queensland (Australia), Neuraxon (biotech) and the University of California. Regarding inventors, Baldomero Olivera is the most prolific

5 Using the same keywords (conotoxin, conopeptide, conantokin, contryphan and contulakin) in section claims but without any specific time frame (search performed on 29.03.2020). The platform is accessible through the following URL: https://www.lens.org/lens/new-search.

6 Cognetix is a private biotech company located in Salt Lake City (Utah). It was founded by Olivera and the University of Utah, precisely to obtain patents on conopeptides related inventions more efficiently than through the University of Utah technology transfer service (Wells 1998).

first inventor with 174 inventions, followed by Michael McIntosh at 107. Lourdes Cruz, the collaborator of Olivera holds 56 patents.

Figure 4. Evolution of the number of patent documents published per year.



Credits: Patent Lens database using "conotoxin", "conopeptide", "conantokin"," contryphan" or "contulakin" in section "claims" of the patent document, performed on 29.03.2020

Type of R&D undertaken and actors involved

R&D activities on conus snails are concentrated mainly in "red biotechnology", i.e., medical and pharmaceutical fields. Conotoxins are thus used as drug lead compounds for pain, cancer, renal function disorder, gastrointestinal disorder, epilepsy, depression. They are also analytical tools to identify and characterize several ion channels and receptors (Grau et al. 2019). A close look at the patent documents confirms that a majority of the patent documents are classified, according to the Cooperative Patent Classification, into sections, classes and groups corresponding to medical or pharmaceutical fields. For example: group A61K38/00 contains medicinal preparations containing peptides; group 61P29/00, non-central analgesic, antipyretic or anti-inflammatory agents, e.g. anti-rheumatic agents and non-steroidal anti-inflammatory drugs; group A61P25/04, centrally acting analgesics, e.g. opioids. The remaining patent documents are classified into groups corresponding to peptides only (without application domain). For example, group C07K14/435 contains inventions corresponding to peptides having more than 20 amino acids from animals or humans. Group C12N15/12 are genes encoding animal proteins or group C07K7/08, inventions corresponding to peptides having 12 to 20 amino acids. An example of the inventions classified into C07K7/08 is the U.S. application US 2020/0071544 A1 which claims an invention described as *Conotoxin Peptides For Use In Biofouling Deterrence*. In short, the claimed invention is a coating composition, in essence a marine paint, containing conopeptides, which prevents the undesirable accumulation of marine organisms and their remnants on submerged structures. The invention falls within the field of "white biotechnology", also called *industrial biotechnology*, referring to the utilization of microorganisms and, in particular, enzymes of microorganisms to manufacture industrial goods like chemicals, plastics, detergents or energy carriers. The specific geographical origin of the specimens used in R&D is mostly missing, at least in the sources used in this case study.

Application of ABS & ABS issues

Schematically, there are four possible scenarios regarding the application of ABS rules on access and/or utilization of GR from cone snails, where access is

- *in* or *ex situ*, within a national jurisdiction where a legal framework for ABS is in force (for example, in the Philip- pines, after 1995);
- *in* or *ex situ* within a national jurisdiction where no legal framework for ABS is in force (for example in Japan, where no ABS measures for providers are in force).
- *in situ* in areas beyond national jurisdiction (64% of the oceans).[7]
- via a different medium than a tangible specimen (for esample, DSI from cone snails accessed through GenBank or UniProt).

As mentioned above, an ABS agreement was concluded in 2002 between the authorities of The Philippines, a local institution (UP-MSI) and a foreign one (the University of Utah) for commercial research on conopeptides. The cumbersome process took almost four years. The Philippines has had a regulatory framework for bioprospecting of GR in force since 1995 and was the first such framework in the history of ABS (Smagdi 2005). The legal basis under which the agreement was concluded is Executive Order 247 (EO 247), *Prescribing Guidelines and Establishing a Regulatory Framework for the Prospecting of Biological and Genetic Resources, their Byproducts and Derivatives, for Scientific and Commercial Purposes* (entered in force on May 18 1995).[8] Before Executive Order 247, access was as simple as buying specimens from fishermen who sell the colorful shells to tourists (Greer et al. 2004).

Market information

Despite intense R&D and numerous patent applications, submitted and granted, the commercial success of inventions based on cone snails remains limited. To date, only Prialt has reached the market. According to Durek and Craik, "Conotoxins have been, overall, exceptionally valuable as molecular probes in academic research but their transition into the clinical phases has proven to be extremely difficult" (2015, 1169). Several conotoxin drug candidates indeed failed clinical trials (Harvey 2014). The result is not surprising: approximately 90% of drug candidates entering phase 1 clinical trials fail before their eventual approval. Gao et al. (2017) identified 3 conopeptides that have entered the pre-

7 To date, marine GR situated beyond national jurisdiction are not covered by any ABS rule (legal gap). The ABS regime established by the CBD and the Nagoya Protocol only apply to (marine) GR accessed within national jurisdiction. The global legal framework supposed to regulate the marine area beyond national jurisdictions - the United Nations Convention on the Law of the Sea – is currently negotiating ABS rules (Broggiato et al. 2014).

8 EO 247 was further clarified by the Implementing Rules and Regulations on the Prospecting of Biological and Genetic Resources in 1996. The Wildlife Resources Conservation and Protection Act of 2001 (together with its 2004 Implementing Rules and Regulations) and the 2004 Draft Guidelines for Bioprospecting Activities in the Philippines

clinical development phase[9], four are in the clinical phase (I or II)[10] and one (Ziconitide/ Prialt) is in the market. Seven of the eight target ion channels or receptors and act as pain medications; the eighth is for treatment of myocardial infarction and under R&D. In sum, conotoxins present much promise for drug development because of their potent activity, specificity and selectivity as pep-tides toward numerous targets. Natural conotoxins require more medicinal chemistry efforts aimed at optimization to gain acceptable delivery, stability, cost and pharmacokinetic properties to attract investment (Durek et Craik 2015). Durek and Craik also highlight that most large pharmaceutical companies have resumed working on peptide chemistry. This trend is noted by experts who speak about a rediscovery of nature as an efficient provider of drug candidates, in comparison with combinatorial chemistry that ultimately proved to be disappointing (Grabowski, Schneider, 2007; Harvey, 2008 ; Newmann, Cragg, 2012).

Ziconotide is an analgesic for the treatment of chronic pain, which is potent, long-lasting and non-addictive. Nevertheless, the neurological and psychiatric side-effects and the necessary intrathecal administration mode lower its therapeutic value (Durek et Craik 2015). The conotoxin Prialt is based on a peptide (ω-MVIIA) which was first identified and isolated by Olivera and McIntosh in the 1980s. They did not patent the peptide at that time. George Miljanich, working for a biotech start up called Neurex, pursued the research on the peptide and eventually patented the compound as an analgesic (Wells, 1998). Neurex was acquired by Elan Pharmaceuticals in 1998, which brought the product to market in 2004. Ziconotide was then the first new intrathecal analgesic approved in the USA in more than 20 years (Wallace 2006). Regarding its commercial value, in 2006 Elan sold its European-only rights on Prialt to the Japanese Pharma company Eisai for approximately 100 million USD. In 2006, drug sales generated 6.3 million USD in revenues worldwide.[11]

Focusing on the regulation of ABS, the cone snail specimens used by Olivera were accessed in The Philippines well before any ABS regulation was in force.[12] The case typifies the long timeline from R&D to commercial product: three decades lapsed before the FDA approved Prialt (Wynberg 2015). Inasmuch as access to physical samples occurred prior to the CBD, no agreement was necessary. The case also typifies the undefined scope of ABS for dematerialized genetic resources – the controversial issue of DSI – considering the ConoServer and other open-access databases.

9 κ-PVIIA (CGX-1051) for Myocardial infarction, μO-MrVIB (CGX-1002) for Neuropathic pain and Conantokin-G (CGX-1007) for Pain/Neuro protection.

10 α-Vc1.1 (ACV1), Contulakin-G (CGX-1160), ω-CVID (AM336) and χ-MrIA (Xen2174), all for pain treatment.

11 https://www.thepharmaletter.com/article/elan-to-sell-european-prialt-rightsto-eisai (accessed on 30.03.2020).

12 The link between the R&D conducted by foreigners on cone snails from the Philippines and the pressures from Filipino scientists in the early 90s (Greer et al. 2004; Smagdi 2005) for a regulation of bioprospecting activities is not clear.

Almost no provider or user country has any ABS measures that cite DSI. The Philippines is not an exception, although plans exist to introduce measures (Bagley et al. 2020). Additionally, the processes of chemical optimization of GR highlighted by conopeptides complicate the situation. In optimization, the original molecular structure of GR tends to be modified, thereby diminishing the appearance of a 'natural basis' and making monitoring of ABS more difficult. Utilization of the natural information of Conidae through, for example, synthetic biology techniques illustrates just such modification of sequences from cone snail specimens.

Summary

Cone snails are widely used in both basic and applied research. To date, only one product from the R&D of the GR of the cone snail has reached the market. This may change as peptide chemistry once again attracts the interest of pharmaceutical companies. Meanwhile, the ABS regime suffers multiple legal gaps such as the status of DSI, absence of national rules, areas beyond national jurisdiction and cumbersome rules, which enable R&D activities on cone snails to avoid regulation.

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Appendix III

Marine Sponge (*Tectitethya crypta*)

Nikita Kent

Figure 1. *Tectitethya crypta* in Bahamas, San Salvador (2004)

Credits: Sven Zea (2014)

Brief history

Tectitethya crypta is a species of sea sponge found in the shallow waters of the Caribbean Sea.[1] The species is notable for having triggered the discovery of unique nucleic compounds that were developed into several life-prolonging medicines.

Max Walker de Laubenfels named the species *Crypotethya crypta* (1949). He discovered the sponge near the island of Bimini in the Bahamas. Laubenfels noted that this particular species of sponge was amorphous of about 4-7cm per slab, with a color in a spectrum of green, black and a dull, light- brown. Pores on the sponge are small. The visible surface is smooth. The small pores prevent clogging and appear to be an adaptation to burying in the sand. *Cryptotethya crypta* was later officially reclassified as *Tectitethya crypta* by Michele (2002) as belonging to the family *Tethyidae*.

Utilization of (compounds rather than) "DSI"

Compounds isolated from T. crypta's nucleic acids have been developed into three highly popular drugs for antiviral and ant-cancer treatment: Aciclovir (Ara-A), Cytarabine (Ara- C),and Zidovudine (AZT).[2]2 The drugs appear on the List of Essential Medicines by the World Health Organization (2019). As detailed in Table I, Aciclovir is used for herpes simplex via topical cream applied to cold sores or by tablets taken orally. Cytarabine is used globally for severe cases of leukemia and non-Hodgkin's Lymphoma. Zidovudine has also been used to treat HIV and AIDS. Other compounds synthesized from the species have been identified as useful in the treatment of

1 A comprehensive photo guide to Caribbean sponges is available at www.spongeguide.org

2 N.B. The compounds have had many names over the years. Other drugs developed from T. crypta compounds, such as Vidarabine, are no longer in the US market due to displacement by the more effective drug (Trifluridine). For the purposes here, I will be using the nomenclature most common in the literature.

pain and anti-viral treatment (Boué- Grabot, et al. 2020).

The sponge is too complex for a commercial market as a natural product. However, the mechanism of action can be imitated to produce more simple, synthetic analogues which are later useful to chemists, biologists, and pharmacologists alike, as observed in *T. crypta* (Denny, 2010, p.83).

The process of incorporating the nucleoside analogues of *T. Crypta* into modern medicine owes largely to synthetic chemistry. In a paper by Newman and Cragg (2016), a new source category for drug development, labelled "S*", was inspired by the nucleoside analogues found within *T. crypta*. Newmann & Cragg defined the **"S*" category** as "[drugs] made by total synthesis, but the pharmacophore is/ was from a natural product". The respective category is set apart from the 'S' category (i.e., without "*") which applies to "totally synthetic drug[s], often found by random screening/ modification of an existing agent" (p.633; Bergmann & Stempien, 1957; Mayer, 2010).[3]

Historically, specimens or compounds isolated from the sponge, have not been frequently used for research or drug development. The chemical structure obtained at the initial specimen collections or observations, can be used in the laboratory as a starting point for synthetic manufacture and improvement of the compounds or structurally analogue derivatives (Bergmann & Stempien, 1957; Newman & Cragg, 2016). Usually no need exists for specimens as synthetically producing compounds are more cost and time-effective for laboratory work. Only in the new millennium have scientists recognized the value in collecting and studying additional specimens, which have led to the discovery of valuable compounds using modern isolation techniques. Discoveries from the group are described in the subsection *Types of R&D being undertaken and actors involved*.

Conservation status and distribution

T. crypta is associated with the island of Bimini in the Bahamas of the Caribbean, located 80km east of Miami, Florida. Projections based on the IPCC 8.5 protocol, generate predictions that by 2020, the coasts of eastern Brazil, the Caribbean, and northern Australia will also be suitable habitat for *T. crypta* ($p > 0.80$). To date, the overwhelming majority of observations[4] pertains to the Western Central Atlantic Ocean, of the United States of America, the Dominican Republic, West Indies, Bahamas and Cuba (Sara, 2002; Sea Life Base, last edit: 2017, accessed March 2020)

3 Other classifications from this paper include 'B' (Biological source), 'N' (Natural product, unmodified), 'NB (Natural Botanical), 'ND' (Naturally derived, semi synthesized).

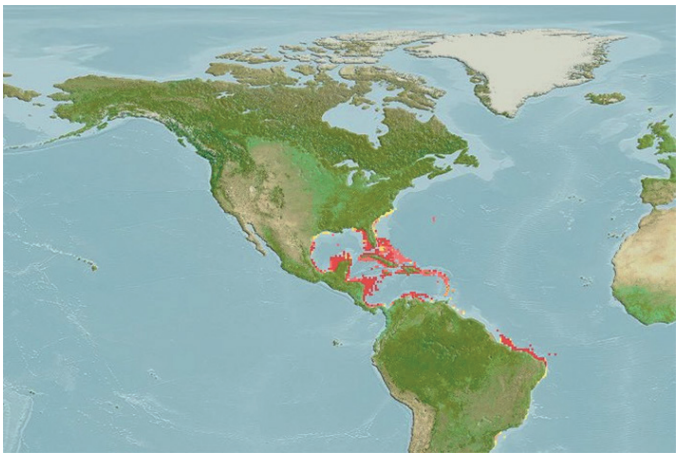
4 The country list of Tectitethya crypta is available at Sea Life Base (online, 2017). Access date March 2020. Information available at: https://www.sealifebase. ca/country/CountryList.php?ID=51717&GenusName=Tectitethya&SpeciesName=crypta

Table 1. Constituents developed from natural information derived from ***Tectitethya crypta*** (Wishart et al., 2017, unless otherwise stated)

Compound Name	Structural Formula	Type of compound	Applied treatments	Know trademark names	Marketed by
Aciclovir (US) Acyclovir (UK)	$C_8H_{11}N_5O_3$	Nucleotide Analogue: *Adenosine Ribose*	Herpes simplex Varicella-zoster Herpes zoster Herpes labialis Acute herpetic keratitis	Ara-A Zovir Aciclovir (ES) Zovirax ® Penciclovir	GlaxoSmithKline (primary). Multiple others, after the patent had expired in the 1990s
Zidovudine 'Ara-T'	$C_{10}H_{13}N_5O_4$	Pyrimidine Nucleoside Analogue: Dideoxynucleoside	HIV/AIDS Anti-Retrovirus	Azidothymidine AZT ZDV Retrovir ®	9 Manufacturers; 38 Labellers GSK/Wellcome (Gupta et al., 2010)
Cytarabine	$C_9H_{13}N_3O_5$	Anti-metabolite (also known as an anti-pyrimidine) (Mathe, et al., 2017)	Non-lymphocytic leukemia Lympho- cytic leukemia Blast phase of chronic myelocytic leukemia.	Cytosine Arabinoside Ara-C Cytosar-U® Depocyt® Udicil® Alexan®	Pfizer (main) 5 manufacturers 8 packagers, including Enzon Inc., marketers of Depocyt® Cytarabine was initially marketed by Upjohn in 1969. Upjohn's product was then acquired by Pfizer in 2003 (Pfizer, 2020).

Given appropriate benefit-sharing mechanisms, the discovery of life-prolonging compounds within marine species could promote protection of coral reefs of tropical and neotropical regions. Kaschner et al., have modeled future distribution patterns of marine species. In Figure II, the native range of *T.crypta* is mapped. Additionally, the University of California researchers Searle and Molinski (1994) successfully isolated 2'- deoxyspongosine from a specimen of T. crypta from Western Australia (Bertin, et al., 2015). De Laubenfels (1949) had noted that the *T. crypta* grew "quite buried" under the sand, indicating that the species may also exist in other neo-tropical ecoregions, other than the Caribbean and await discovery.

Figure 2. Native Range of *T. Crypta* distribution in the Caribbean, Kaschner et al. (2019). Map: Computer generated from SeaLifeBase (2021)



Ex situ status of species

Records or specimens of *T. crypta* are held by predominantly United States institutions, including the United States Smithsonian Museum and the Yale Peabody University of Natural History. Other collections around the world may also hold specimens, without having yet updated their records on Porifera (sponge) information websites such as spongebarcoding.org, marinespecies.org (World Proferia Database). We have confirmed that the Museum of Western Australia, which hosts an extensive Porifera collection, does not have any specimens of this genus or species in their collections, despite Searle and Molinski having reported a specimen obtained from Western Australia in 1994. Specific specimen prototypes examined by marine taxonomist Michele Sarà (2002) are available online in the paper Family *Tehyidae Gray*, 1848.

Uses

Spongonucleosides from *T. crypta* were first isolated by Bergmann and Feeney (1951) at Yale University. The specimen was obtained from the shallow waters of Elliot Key, which is the northernmost of the Florida Keys (p. 981). The two chemists isolated spongothymidine ($C_{10}H_{14}N_2O_6$) from this specimen using a Soxhlet extractor and acetone solution. They discovered spongothymidine bore similarities to thymine deoxyribose, which is one of three pyrimidines that constitute DNA and RNA. Upon identifying a fragment of thymine, spongothymidine was assumed to be a pyrimidine nucleoside, called pentofuranosylthymine, whose composition had not been previously observed (Bergmann & Feeney, 1951, p. 982). Spongothymidine (Ara-T) later became the informational basis for HIV drug Zidovudine via 1-β-D-arabinofuranosyl thymine (Ara-T).

Procedures to isolate a pentose fragment in a nucleoside compound discovered in 1951 from the spongothymidine were unsuccessful. Both scientists found the evidence convincing that the purine nucleoside discovered had not been "encountered in nature... the sponges should prove to be an abundant source of new nucleosides the knowledge of which would be important to the understanding of biochemical evolution." (Bergmann & Feeney, 1951, p. 984-985). Later, in 1955, Bergmann and Burke would later isolate spongouridine which lead to the synthesis of 3-β-D- arabinosyluracil (ARA-U).

The effective activity of these spongonucleo-

sides from the 1950s onward, triggered a worldwide inquiry into the use of nucleoside analogues. The information became the basis for many anti-viral and anti-cancer medicines worldwide[5]5 (De Clercq & Li, 2016, p. 12-13). Although not the first pyrimidine analogue to be synthesized, the compounds based on information obtained from *T. crypta* were different: the spongonucleosides were the informational keystone for the synthesis of 3-β-D-arabinofuranosylcytosine in 1959 (Walwick, Roberts & Dekker) at the University of California, Berkeley. 3-β-D-arabinofuranosylcytosine has been used as the informational basis for drugs cytarabine, vidarabine, and aciclovir, among others (see: Table I). The compound 3-β-D-arabinofuranosylcytosine acts as an antiviral agent by inhibiting reverse transcriptase, which is the genetic information replication process attributed to viruses. However, in anti-cancer cases (non-viral), these nucleoside analogues are similar enough to DNA to be incorporated into the DNA chain but inhibit further DNA chain replication via DNA polymerase. Thus, when cancer patients are treated with pyrimidine nucleoside analogues such as Cytarabine through chemotherapy (cell disruption treatment), the cancerous cells are unable to replicate further. The cytotoxicity of this process often causes adverse symptoms in patients, such as baldness and bone marrow depletion.

Types of R&D undertaken and actors involved

Tectitethya crypta continues to fascinate chemists, microbiologists and the pharmaceutical industry Scientific journals frequently publish new compounds related to the spongonucleosides as well as processes of isolation and synthesis. Although sponge compound R&D is found mostly at academic research institutions, many laboratories also have strong affiliations with anti-cancer or anti-viral institutions and corporations, such as the National Institute for Cancer Research or GSK Corporation in the United States.

Only recently has the Gerwick group (Bertin et al., 2015) reported isolation from a fresh collection of *T. crypta*, which lends support to the hypothesis that a microbe, such as bacterial strain Vibrio harveyi, produced spongosine compounds. An earlier paper published in the journal Molecular Cancer Therapies suggested that microorganisms, living in conjunction with sponges, are the true sources of many bioactive and useful constituents (Simmons et al., 2005, p. 335). Spongosine compounds are currently being used for novel drug development to treat inflammation and pain (Newman, 2018; Bertin et al. 2015).

5 Vidarabine is another medicine used for special cases of herpes simplex and HSV Keratoconjunctivitis (herpes of the eye). Vidaraibine has been discontinued in many countries since another nucleoside analogue, Trifluridine, is more effective and less toxic in HSV cases. However, patients sensitive to the active chemical idoxuridine in trifluridine, are administered vidarabine (Aoki, 2015). In the same manner, patients who are resistant to Ara-A nucleoside analogues (also referred to as pyrimidine nucleosides) are administered alternatives that work in similar ways to Ara A.

This discovery may have been delayed since many compounds found in *T. crypta* from the 1950s have been developed synthetically. For this reason, their presence in the habitat of the sponge has not been studied in depth. These new findings conclude that either T. crypta contains microbes which produce compounds of interest, or sequesters such compounds (Newman, 2018) The answers are as of yet unclear and require further investigation, perhaps utilizing not only samples of the species but also a detailed observation of the habitat.

Application of ABS

ABS rules have been largely ignored in the field of nature- inspired structural formulas based on *T. crypta*. Many scientists and pharmaceutical companies have relied upon the synthetic and biochemical understandings produced by the Bergmann group. They have never worked directly with sponge samples or compounds isolated from sponges but instead rely on information gained by previous investigations into such tangible resources. One exception involves researchers from the Gerwick group,[6] who have recently been involved with the production of a Global Natural Products Social Molecular Networking (GNPS), after having successfully isolated the spongosine compound in 2015 (Wang, et al., 2016).

An example of ABS *unawareness* involves Peter Richardson, who handles the intellectual property of spongosine and adenosine receptors through the company Cambridge Biotechnologies (CBT), whose affiliated subsidiaries are assigned or granted patents related to the spongosine compound, including in China [CN101479268B], South Korea [KR101122495B1] and Japan [JP4836454B2][7]. A majority of the thirty some patents relates to the synthesis of spongosine or its optimisation. The most commercially viable is the "Use of Spongosine for the Treatment of Pain" assigned under CBT Development London [US008252766B2]. CBT raised 6.3 million pounds in 2001 as venture capital and thereafter 18.3 million pounds after three rounds of capital raising (S&P Capital IQ [a], 2021). After numerous restructurings, CBT has finally merged into a private company named BenvolentAI, an artificial intelligence (AI) enhanced, drug-discovery entity valued at one billion USD (S&P Capital IQ [b], 2021). At the time of this writing, Peter Richardson serves as Vice President (Pharmacology) at BenevolentAI (Benevolent AI, 2020; Powell, 2019; CN1910194B).

The sponge *Cryptotethya crypta* is mentioned in Richardson's patent filings regarding spongosine, but little exists regarding the material transfer agreement. In patent publications, Richardson addresses the discovery of Bartlett et al. (J. Med. Chem. (1981) 24, 947-954) who discovered the first biological activity of spongosine. Academic credit appears to be

6 Spongonucleoside MS/MS spectra have been published and annotated at gpns. uscd.edu (Bertin, et al., 2015)

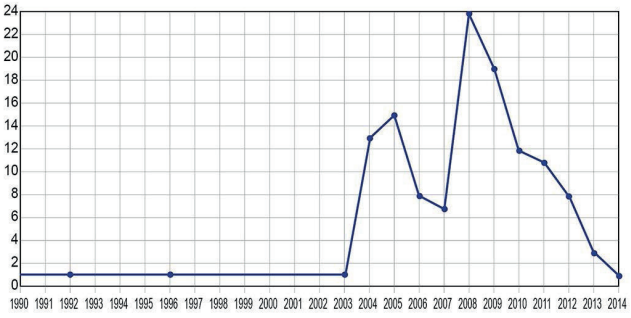
7 Using the keywords ('spongosine') under granted patents. No specific time frame used. The platform is accessible through the following URL: https://www. lens.org/lens/new-search.

the only transaction between the two groups. There are no patents listed under "Robert T. Bartlett", nor any relevant spongosine patents before 1990, which suggests that Richardson was among the first researchers to pursue IP rights aimed at protecting investments based upon biological discoveries performed by academics before him.

The research on spongonucleosides has largely been based in the developed countries of Europe and North America. *T. crypta's* spongonucleosides were first isolated by affiliates of the United States, namely in the US established Lerner Marine Laboratory in the island of Bimini before independence of the Bahamas from Britain in 1973. The chronology and patent searches have pointed to the conclusion that US scientists have led taxonomical and anti-viral/cancer compounds from *T. crypta* compounds, with strong support from the National Cancer Institute (NCI) and affiliated universities. A patent search conducted using keywords of T. crypta's compounds (see: Figure III) has reiterated that 28% of patents filed belong to the jurisdiction of the US, 21% to Australia, and 16% to the World Intellectual Property Organization.[8] The remaining 35% of patents pertains to the EU, New Zealand, Japan, China, South Korea, and Germany.

Based on this search, there has been no evidence of any institution or person originating

Figure 3. A Patent Lens Search of keywords spongosine, spongothymidine, spongouridine, spongonucleosides



from the Bimini Islands, nor the Bahamas, engaging in the chemical, pharmaceutical, or microbiological research of the compounds within *T. crypta* or of benefit-sharing agreements between local institutions and users.

Market Information & Relevant IP Involved

Many chemists and biomedical scientists studying sponge nucleosides either work for large pharmaceutical companies or cooperate with multinational pharmaceutical corporations for more effective R&D of life-prolonging compounds. The chemist Howard J. Schaeffer is one such example, having played a key role in the development of Aciclovir in 1974 while working with Wellcome Research Laboratories in North Carolina and authoring patents of Aciclovir to subsidiaries of GlaxoSmithKline (GSK) [GB2130204A; CA1305138C; US4199574A, among others] (Bouton, 1989). Inasmuch as patents expire after 20 years, a variety of 1990s Aciclovir-containing drugs are now public domain and

8 Patent Lens. Conducted May, 2020. Using key words spongosine, spongouridine, spongonucleosides, sponothymidine. Lens Patent search is available at: https://www.lens.org/

on the world market as generics (Gupta, et al. 2010; The Pharma Letter, 1997). Nevertheless, the most common is Zorivax®, which is still owned and marketed by GSK[9].

In 2000, SmithKline Beecham GlaxoWellcome merged to become GlaxoSmithKline, which co-owns the global specialist HIV company, ViiV Healthcare (2019), along with Pfizer (Moore, Waldholz, Raghavan, 2000). ViiV Healthcare is assigned a majority share of patents for Zidovudine [US9580431B2], and market Retrovir/AZT® (zidovudine), Combivir® (zidovudine and lamivudine), and Trizivir® (zidovudine, abacavir, lamivudine) globally (Wishart, et al. 2017). As a result of numerous mergers and acquisitions, the pharmaceutical giant GlaxoSmithKline controls a large market share of the anti-viral and anti-cancer drugs with compounds which have been inspired by *T. Crypta*.

Cytarabine, the third drug in Table I, has also been marketed by another chemist, John Evans, who discovered anticancer activity in 1961 while working for Upjohn & Co. [Patent US3320132[10]]. In the 1990s, Upjohn was merged with the giant Pharmacia, which later merged with a division of Monsanto in 1999. By 2002, Pharmacia Corp. was acquired by Pfizer (Sorkin, 2002) which now holds title to the widely used Cytarabine Injection product[11] (Pfizer, 2020). However, as the patent for the active ingredient has expired, other companies have also patented their technologies using the active ingredient cytarabine. Examples include: Pharmascience Inc. (Canada) with 'Cytosar®', Pacira Limited (EU), 'Deocyte®', and Novopharm Ltd. (Canada),'Cytarabine-Pws 1gn/vial 'and 'Cytarabine -Pws 2gm/vial', 'Cytarabine - Pws 500mg vial', etc. (Wishart et al. 2017).

Inventors or companies who discover and patent natural products may only enjoy commercial success in the short term, which supports the findings from Gupta et al. (2010). [M]arket exclusivity over the initial patent protection period of 20 years has allowed pharmaceutical entities, in particular GlaxoSmithKline and Pfizer, to enjoy a time-limited monopoly over their invention and thereby recover the costs associated with R&D. Significant benefits have been gained by generics companies upon patent expiry.

ABS issues

Although *T. crypta* is considered a marine "genetic resource", none of the genomes of the sponge is utilized. Rather, research and development based on the unique biochemical compounds found in marine sponges have led to successful results (Vierros et al., 2016). To this end, most researchers and companies

9 GlaxoSmithKline, Consumer Healthcare Products (https://www.gsk.com/en-gb/products/our-consumer-healthcare-products/skin-health/zovirax/)

10 John S. Evans (1963) Composition containing 1-beta-d-arabinofuranosylcytosine useful in treating mice tumors. Patent granted: 1967. Expired: 1984.

11 Pfizer's cytarabine (2020). Available from: https://www.pfizer2.com/sites/default/files/products/uspi_cytarabine_1000mg.pdf)

do not require access to tangible samples of marine sponges, neither in situ nor ex situ. In many cases, published knowledge on structure and bioactivity of the compounds was all that researchers and drug-makers required.

T. crypta has truly produced global benefits. As outlined by Deplazes-Zemp (2018), various benefits are associated with R&D based on genetic resources, including academic credibility and financial gain. Researchers such as Bergmann, Laubenfels and Schaeffer have propelled their careers with findings of nucleosides from the sponge. An example is Gertrude Elion, who spearheaded AZT medication development at Burroughs Wellcome and won a Nobel Prize in 1988 (Bouton, 1989). In addition, pharmaceutical companies have benefited financially. Many patients have prolonged their lives by taking synthetic marine compounds.

Though many people have benefited from T. crypta, the natural habitat of the sponge has not. Anthropogenic damage is greatly diminishing biodiversity in the Caribbean (Jennings, et al., 2016). In 2016, former Environment Minister of the Bahamas, Mr. Kenred Dorsett, was quoted as saying: "For decades, pharmaceutical companies and cosmetic companies have exploited our waters for genetic resources. These resources are used to make medicine and cosmetics and are a part of billion-dollar industries. The Bahamas receives no royalties and no benefit. So, my ministry and this government seeks to change that" (Nassau Guardian, 2016). That same year, Nassau set aside 1.9 million dollars to prepare itself to sign the Nagoya ABS framework but is still not a Party or Signatory as of 2020 (UNSCBD, 2020).

Experience exists where benefits gathered by R&D on sea sponges can be shared with Providers. The University of British Columbia (UBC) shares royalties with the University of Papua New Guinea (UNPG) for the utilization of a sponge akin to *T. crypta* in anti-cancer compounds. Royalties have helped to finance infrastructure and a start- up at the UNPG, thus incentivizing the conservation of the coast of Papua New Guinea as well as enhancing education. As both the UNPG and the UBC own equity in the R&D, both will not be excluded from the mid to long-term benefits arising from the arrangement (Vierros, et al., 2016).

Similar species of marine sponges have been found in highly biodiverse habitats in different parts of the world. Because most countries in the neotropics lack authoritative governing institutions to negotiate and monitor material transfer agreements, patents are usually filed in developed countries. Benefits have not been equally distributed with countries of origin, who are ultimately responsible for conserving coastlines from anthropogenic damage. Furthermore, *T. crypta* lies within the EEZ of countries of the USA, a non-Party to the CBD, thus allowing jurisdiction shopping and an apparent "safe haven for biopiracy" (Vogel, 2007). If the compounds of interest are produced by microorganisms symbiotic with the sponges, the distribution of natural information may be extremely wide. One po-

sitive advancement has been the development of the GNPS software for natural product data, which will support the traceability and accountability of compound usage and development of naturally derived compounds.

Summary:

Discovery of spongosine compounds and drug development based on information about the properties of those compounds constitute a challenge for ABS. Direct links usually do not exist between access to tangible specimens from which the products were inspired by or derived. Any direct connection is further complicated by the fact that spongosine may not be produced by *T. crypta* on its own, but rather by a metabolite of a microbe living in symbiosis with the sponge.

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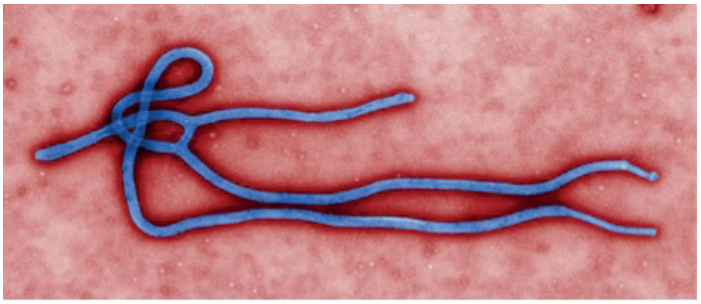
Appendix IV

Ebola

Omar Oduardo-Sierra

Figure 1. Ebola virus virion.



Credits: Health Image Library, #10816 (accessed 2021)

Brief history

Strains from the genus Ebolavirus in the family Filoviridae cause the hemorrhagic fever known as the Ebola Virus Disease (EVD) (WHO, 2020). Only Zaire *ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus and Bundibugyo ebolavirus* are infectious to humans (CDC, 2019). Over the last fifty years, 46 confirmed outbreaks have been reported (CDC, 2019). As of this writing, the confirmed outbreaks occurred in February 2021 (WHO, 2021) and June 2020 (WHO, 2020). As of 19 December 2019, the US Food and Drug Administration (FDA) approved the Ebola vaccine rVSV- ZEBOV, trademarked Ervebo. The vaccine is safe and effective against only the Zaire ebolavirus species (CDC, 2019), which is the deadliest strain (Chowell & Nishiura, 2014).

Ebola originated in Africa. Certain species, such as Reston ebolavirus, have also been observed in non-human mammals in Asia. Various fruit bat species of the Pteropodidae family are natural hosts. Other non-human primates, such as chimpanzees and gorillas, also transmit the virus. Transmission can be transmitted via contact with blood and bodily fluids and in direct contact of contaminated environments (Laupland & Valiquette, 2014). The virus inhibits interferon molecules to hinder the immunological response to the virus. Ebola proteins trigger coagulation by forming blood clots that travel throughout the body, leading to hemorrhaging (Servick, 2014).

Distinguishing features for ABS

Categorized as a Biosafety Level 4 organism by the CDC along with the reconstructed 1918 influenza virus, Smallpox, and SARS CoV, Ebola variants are highly restricted for usage and distribution. Specific guidelines and cold-chain processes must be followed for safety of personnel involved in transportation and care of samples. Research labs collect and sell samples for vaccine development. Several observations are worthy of consideration from what would be the fair and equitable sharing of benefits:

- Samples are collected from individuals with little or no compensation even though resold at a significant price;

- The virus originates in regions where populations have been economically disadvantaged;
- Specimens can be found beyond national and even conti- nental boundaries;
- Impact of research can benefit local populations and potentially prevent future outbreaks;
- Although studied since 1976, the first vaccine was only approved in 2019 and for only one of the known strains affecting humans. R&D continues on other potential vaccines.

Utilization of "DSI"

GenBank uploaded the complete genomes for all Ebolavirus strains (NCBI, 2018) in accord with its policy of open access.1 The ineligibility of patentability of isolated genetic information was established in the landmark 2013 ruling in Association for Molecular Pathology (AMP) v. Myriad Genetics Inc. by the US Supreme Court.2 The information extracted from samples taken from victims of EVD is an essential element in epidemiological research and vaccine development. The question is how to prevent User accessibility from becoming leverage for Provider accessibility to diagnostics, antivirals and vaccines?

In mid-2019, New York-based pharmaceutical Regeneron successfully trialed a treatment for EVD, REGN-EBR, developed using sequence data from the C15 strain of the virus. The strain was sequenced and published on GenBank by the German Nocht Institute, which concluded an MTA over the physical sample. The results of the research were historic as was the method of access to the genetic resource. By citing sequence data rather than physical samples, the issue arose whether sequence data and other interpretations of DSI are under the scope of the NP. Under the current international framework, neither the Guinean woman who supplied the sample or Guinea are entitled to benefits from the estimated $10,000 per dose that Regeneron is posed to collect (Hammond, 2019). It should also be noted that Guinea did not have an ABS regulatory framework at the time of collection.

Conservation status – distribution & *Ex situ* status

When discussing the conservation status of the Ebolavirus, one must consider two routes: the strains themselves and then the organisms that become vectors of the strains. To date, no vector has been identified for the Ebolavirus. The scientific community is in search of eradicating cases. The first was reported in Central and East-Central Africa in what had then been Zaire and Sudan and are now the Democratic Republic of Congo and South Sudan, respectively. Cases have been found throughout the region and also eastward. Cases have also been confirmed in Uganda, Gabon, Congo, Nigeria, Côte d'Ivoire, Liberia, Mali, Sierra Leone, Guinea, and Senegal. The Reston Ebola virus has been observed in The Philippines, indicating that the virus has spread beyond the continent of Africa. On 1

Table 1. Human Pathogenic Ebola Virus Strains

Species	Countries Detected	Genome Publication	Country of Origin	Precedence
Zaire ebolavirus	Congo, DRC, Gabon, Guinea, Italy, Liberia, Mali, Nigeria, Russia, South Africa, Sierra Leone, Senegal, Spain, UK, USA	(Volchkov, *et al*., 1997)	Zaire (DRC)	Articles references samples collected in 1976. Sample received from the Institute Voor Tropische Geeneskunde, Antwerp, Belgium
Sudan ebolavirus	Sudan, UK, Uganda,	(Sanchez & Rollin, 2005)	Uganda	Originated in northern Ugandan city of Gulu
Reston ebolavirus	Italy, Philippines, USA	(Groseth, Ströher, Theriault, & Feldmann, 2002)	Philippines	Originated in Asia among a group of cynomolgus mon-keys (Macaca fascicularis) imported from the Philip-pines into the United States.
Taï Forest ebolavirus	Côte d'Ivoire	(Towner, et al., 2008)	Côte d'Ivoire	Only known case originated in the Taï Forest in the Parc National de Taï.
Bundibugyo ebolavirus	DRC, Uganda		Uganda	

June 2020, the WHO detected new cases in the DRC and dispatched response teams.

The scientific-medical community pursues eradication of Ebolavirus in situ and preservation of only samples ex situ, for further research and development, which concerns the collection, processing, and sharing of Ebola samples.

Uses, R&D undertaken, actors involved & Market information

Samples of Ebolavirus are researched to develop vaccines and diagnostics. Current vaccines in development include replication-deficient adenovirus vectors, replication- competent vesicular stomatitis and human parainfluenza vectors, and virus-like nanoparticle preparations. As of 2020, only one treatment has been approved for sale, Ervebo (rVSV-ZEBOV), developed by the Public Health Agency of Canada and Merck, Inc. The pharmaceutical industry is exploring other options, with GSK, J&J, and Merck leading the race, in collaboration with governments, such as the USA and Russia.

None of the drugs for the treatment of EVD have been approved by the FDA (CDC, 2019). Nevertheless, the above-mentioned REGN-EB3 (US National Library of Medicine, 2018), and MAb114, developed by

NIAID (Gaudinski, et al., 2019) have shown promise (Sabue Mulangu, 2019) and will be distributed to EVD patients (Maxmen, 2019). Other proposed treatments include Remdesivir (GS-5734), which has been repurposed in the fight against COVID-19 (Pardo, Shukla, Chamarthi, & Gupte, 2020).

Vaccine and drug developers are based in Europe or the USA. Crisis first-responders and researchers who collect samples have found that the market price for samples of 0.5mL fetch upwards of €3600 (Evans, Hills, & Levine, 2020). No significant compensation is enjoyed by the victims of the virus or the laboratories in the countries of the victims (McKenna, 2019), nor is the specific provenance of samples disclosed due to patient privacy (Table 1). One may argue that provenance is not relevant, as vaccine development does not require knowledge of the identity of the patient from whom the sample was drawn. However, given the lack of agency of patients with a life-threatening disease in lowest-income countries, prior informed consent seems allusive.

As of the time of this publication, the United States is not a Party to the CBD nor signatory to the Nagoya Protocol and, therefore, is not bound by obligations of ABS when accessed within US jurisdiction. Access is facilitated through reliance on synthetic variations, which are less accurate than genuine Ebolavirus isolates (Branswell, 2019).

Application of ABS and Criticism thereof

ABS does not seem suited to human pathogens as the objectives for public health are not conservation but eradication, and not sustainable use, but containment and vaccine development. Rapid access to samples is key for public health, containment and R&D for vaccines. Hence, ABS should address whether incentives can be created for identification and isolation of strains and their immediate sharing with the international research community.

The use of patents to incentivize R&D on pathogens contrasts with the lack of incentives to provide samples when the resulting technologies lie beyond the purchasing power of lowest-income countries afflicted. The challenge for framework treaties like the CBD and NP are to suggest how modalities of ABS can be adapted for the peculiarities of pathogens.

The American Medical Association (AMA) identifies utility, equity, justice and liberty

Table 2. The Race for more Vaccines

Vaccine	Private Sector	Public Sector
rVSV-ZEBOV	Merck	Public Health Agency of Canada, NIAD, WRAIR
cAd3-EBO	GSK	NIAID, WRAIR
Ad26.ZEBOV MVA-BN Filo	J&J	NIAID

as four justifications in favor of sharing benefits in exchange for improved access to samples. Utility means access to lifesaving interventions or data saves lives. Equity refers to financial gain not coming at the expense of the communities that provide the resource. So, justice would not obtain should samples be collected without providing future benefits. Liberty refers to collection contracts being signed by willing parties, which implies that sampling vulnerable populations during a pandemic is questionable.

Summary

A modality which concentrates a benefit to the Party which first isolates and shares a viral strain would meet the criteria of the AMA and the objectives of the CBD and NP.

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Appendix V

Template for cases

Brief history

Milestones, main features, aspects variant from typical ABS cases.

Utilization of "DSI"

Conservation status – distribution

Range (current) and habitat (potential) / maps

Ex situ status of species

Do regulatory controls exist? Have MTAs been concluded?

Uses

Value added and the chain from access to intellectual prop- erty.

Type of R&D undertaken and actors involved

Technology sectors and research streams (e.g., Pharma, seeds, extracts and so on)? Is utilization by public institutions, universities, share-held or privately held companies and so on?

Application of ABS Market information

Products available, any data on revenue income

Relevant IP involved

Other details of relevance, including, if available, ABS chal- lenges

ABS issues

Grounds by which stakeholders may have criticized ABS (e.g., fairness and equity, transparency, prior informed con- sent and so on). Have countries demonstrated cooperation with Contracting Party in MTAs?

Summary

References

Appendix VI

"Legal Elements for the 'Global Multilateral Benefit- sharing Mechanism' as contemplated in the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization"

Version 3.0

Manuel Ruiz Muller, Joseph Henry Vogel and Klaus Angerer

Preamble:

In recognition of genetic resources being, for the purpose of adding value through intellectual property, natural information disseminated and diffused over taxa and often of a transboundary nature. Recognizing that through the granting of intellectual property rights, especially patents over inventions, many economic sectors, including the biotechnological, pharmaceutical and agroindustrial, have used natural information in varied ways, generating income that is seldom shared as a monetary benefit with the countries from which the natural information is found *in situ*,

Similarly recognizing that Article 10 of the Nagoya Protocol considers the possibility of establishing a Global Multilateral Benefit-sharing Mechanism, in cases where utilized genetic resources for Research and Development (R&D) are found in transboundary situations or where granting or obtaining prior informed consent is not feasible,

Aware of the inefficiency and inequity inherent to one country alone assuming the right to consent access for utilization of natural information, which is of a transboundary or shared nature among several countries,

Also recognizing that with respect to R&D, science has firmly established, since the middle of the 20th Century, that genetic resources are essentially information and that the reductionist perspective allows sound management and practical applications in diverse fields,

Aware of the necessity to better align incentives so that the third objective the Convention on Biological Diversity (CBD) concerning the sharing of benefits, may reinforce the first and second objectives, those being, respectively, conservation and sustainable use of biological diversity,

Suggesting that a fair and equitable sharing of benefits derived from the utilization of genetic resources, together with other measures adopted at the national level, help countervail the tendency to destroy habitats rich in biodiversity, genetic resources and natural information,

Recognizing that the definition established in the CBD of "genetic resources" as "material of real or potential value" has been misinterpreted as only tangible matter, thereby undermining any expectation of fairness and equity in the sharing of benefits,

Also recognizing that the term "natural information" captures cases where research from the biological medium extracts the object of access,

Maintaining that the concept of "information" alone is insufficient and must be qualified with "natural" to be distinguished from "artificial information" that is expressed in innovations of varied sorts, such as computers, software, artistic recordings, literary creations and so on, all of which may be protected through different types of intellectual property,

Also recognizing that the term "natural information", in the context of the Convention on Biological Diversity and the Nagoya Protocol, is understood as only biotic in origin,

Further maintaining that the concept of "natural information" becomes useful for technological applications in diverse industries and areas of human creativity, including biotechnology, biomimicry, pharmacology and pharmacognosy among many others, for which intellectual property-like protection constitutes an homology with the intellectual property rights of artificial information,

Recognizing that economic principles for the efficient regulation of goods and services which are information in character, have been rigorously developed,

Aware that efficiency in a multilateral mechanism for the sharing of benefits and the development of national regulations to facilitate access to natural information, are requisite to generate benefits that derive from utilization and thus guarantee a fair and equitable sharing in said benefit,

Emphasizing that widespread utilization of natural information best assures that benefits rebound effectively on conservation in situ and the sustainable use of biodiversity,

Recognizing that since the ratification of the CBD as international law, the contracts and bilateral agreements concluded for access to genetic resources and the fair and equitable sharing of benefits (ABS) have not proven themselves operative, thereby making necessary a multilateral approach to ABS,

Also concerned by the impossibility of achieving efficiency, fairness and equity in the sharing of benefits derived from the utilization of natural information by means of concluding bilateral contracts among countries and parties, private or public, for information dispersed and diffused among two or more countries in competition for the monetary benefit in exchange of access and utilization of the natural information,

Clarifying that this new approach to ABS by means of the Global Multilateral Benefit-sharing Mechanism is based upon ex post verification of access and successful commercial utilization of the natural information, by means of the intellectual-property system, that allows in turn an efficient sharing that is fair and equitable in monetary benefits,

Likewise recognizing that the multilateral system of sharing benefits for access and utilization of natural information can be implemented for holders of intellectual property in a stepwise fashion, beginning with the economic sectors and types of activities of greatest revenue,

Mindful that, as a general principle, the activities of biocommerce, biobusiness and other uses of biological diversity for which intellectual property rights are not sought over the value added to natural information, are guided by their own rules and principles, which are distinct from those in this Global Multilateral Benefit-sharing Mechanism,

Recognizing, in that regard, that a series of economic principles and legal instruments, already in effect at a national level, regulate production and value chains related to components of biodiversity, such as environmental impact statements, management plans, collection permits and primary processing, sanitary permits, among others,

Aware, moreover, of the intensive and extensive use of natural information extracted and now independent from the biological medium in many industries, with global sales in the hundreds of billions of US dollars annually,

Recognizing that countries, in the exercise of their sovereign rights, have the right to adopt and participate in a Global Multilateral Benefit-sharing Mechanism,

Recognizing that the intensity of drivers are distinct for extinction of marine and terrestrial species,

The Parties to the Nagoya Protocol approve the following Global Multilateral Benefit-sharing Mechanism on the following terms:

Section 1. On definitions

Article 1. The applicable definitions for the mechanism are:

Artificial Information: Any human-made distinction, non- uniformity or difference that is intentional.

Access and Utilization: The process by which one obtains natural information of genetic resources or biological material and adds value.

Bounded openness: The conceptual foundation which allows natural information to flow freely for R&D, until commercial success of an innovation at which time any innovation protected by intellectual property is obligated to share monetary benefits, the percentage of which would be defined according to the category of utilization and other characteristics that correspond to the value added.

Determination of the royalty rate based upon a set of characteristics in the utilization of natural information: Several criteria are to be considered by the Subsidiary Body on Technical and Technological Advice (SBSTTA) which sets the royalty percentage for access and the utilization of natural information. Among them are the type of intellectual property, the economic sector to which the value added corresponds and whether the use is direct or indirect.

Commercial success: The moment in which an obligation to share benefits among country(ies) of origin arises due to having added value to natural information through

an intellectual property right that generated significant economic revenues.

Natural Information (abiotic): Complement of Natural Information (biotic) with respect to that which is not living and was never alive.

Natural information (biotic): Any unintentional distinction, non-uniformity or difference extracted from matter that is living or was once alive.

Country of origin of natural information: Country(ies) in which one finds the biological media of the natural information *in situ.*

Provider of natural information: Country or institution from which one accesses the natural information in conditions in situ or ex situ, as is the case.

Technical mechanism to determine the distribution of natural information: A group of institutions with recognized technical and scientific capacity to contribute toward determining the taxonomic diffusion of natural information and geographic distribution of species of said taxa that convey the natural information, to the extent such determinations are possible.

Biological medium: The vehicle of biological origin that conveys natural information.

Sufficient commercial success: The amount of deposited royalties to justify the expense to determine the diffusion of natural information across taxa and the geographic distribution of terrestrial species that carry said information.

User of natural information: A natural or artificial person who utilizes the natural information for the purpose of adding value through R&D and applies for and maintains an intellectual property right over said value.

Section 2. Objective

Article 2.- The objective of the global multilateral mechanism is to align incentives in a cost-efficient fashion for the conservation and sustainable use of biological diversity, based on a fair and equitable sharing, among countries of origin, of the monetary benefits derived from access and the utilization of natural information.

Section 3. General principles

Article 3.-The multilateral mechanism is based upon the principle of bounded openness for access to and utilization of natural information.

Article 4.- Core to the mechanism are facilitated access, multilateralism, transparency and the timely generation and exchange of information to assure the achievement of the objective.

Article 5.- To assure the generation of significant benefits and the subsequent fair and equitable sharing of benefits among the country(ies) of origin, the Parties will be guided by national legal and regulatory systems that facilitate access of genetic resources for the purposes of utilization of the natural information with the possibility to add value, as foreseen in Article 15(2) of the CDB, which implies that national regimes of access to gene-

tic resources, as biological media or vehicles of this natural information, be simple and clear.

Section 4. On the fair and equitable sharing of benefits

Article 6.- The sharing of monetary benefits derived from access and utilization of natural information among countries of origin will be realized when the innovations or product that contains natural information are protected by intellectual property and achieves commercial success.

Said sharing will be proportional to the habitats conserved of the species from which one could extract the natural information, whenever such determination is possible and when not, proportional to a substantiated proxy made by the technical mechanism of the determination of the natural information.[1]

Article 7.- Access and utilization of natural information can occur in conditions in situ or ex situ. Whichever is the case, benefits will be distributed proportional to habitats, as stipulated in Article 6. In the event of species extinct *in situ*, the benefits will be channeled to the institution(s) which maintain(s) the specimens of said species ex situ for conservation, restoration and other purposes.

Article 8.- The Parties of the multilateral mechanism will adapt policies and regulations about intellectual property to require that an applicant for intellectual property disclose in a simple fashion whether natural information was utilized or not.

Article 9.- If the species for which natural information was accessed is known at the moment of filing an application for an intellectual property, the User will maintain confidential said information until such time of verified commercial success of the innovation which triggers the obligation to disclose said information to the mechanism.

If the species are unknown at the moment of applying for the intellectual property, identification will be performed by the technical mechanism of determination of the distribution of natural information upon commercial success of the protected creation or innovation, sufficient to pay the associated costs of the identification incurred.

Article 10.- The income generated by the fixed royalty established by the SBSTTA and applied to the net revenue of the commercialized good or service, will be deposited at the end of the tax period applicable to the User who commercializes the good or service that contains the natural information, in a fund of sharing benefits according to that established in Article 21 of the system.[2]

Incumbent upon the User of the natural information who has begun to commercialize

1 In cases where the determination of the habitat is not feasible with any acceptable level of confidence, the diffusion may be substituted with the mere presence of the species, weighted by the geographic size of the country, where the substitution is subject to updating in the light of technological improvements and scientific knowledge.

2 This fund may be integrated or separated from already established funds and will have the fiduciary character of escrow.

the good or service that enjoys intellectual-property protection, is to inform the ABS Clearing-House Mechanism of the amount of net sales from the good or service. Non-disclosure entrains penalties and sanctions to be determined by the national competent authority in matters of access to genetic resources.

Article 11. The country(ies) of origin of the natural information will receive a percentage of the monetary benefits generated by the commercialization of the good or service resulting from the process of adding value to said natural information, proportional to the calculation of the habitats in which are found terrestrial species that contain said information, as long as said calculation is cost efficient.

Article 12. Should natural information be endemic to just one country, estimation of the habitat should be periodic. Any percentage diminishment of habitat should be doubled in the percentage diminishment of the royalty rate between periods, thereby avoiding critical depensation of the population and thus aligning incentives for conservation for endemic species.

Article 13.- When significant errors have been detected in the determination of the distribution of natural information made by the technical mechanism, procedures for review and re-calculation of the distribution of benefits will be executed, based upon the date of filing said information.

Article 14- In the case of non-monetary benefits and scientific institutional collaboration, the Parties will be able to maintain their policies and regulations about access and use of the components of biodiversity, including genetic resources, by means of institutional agreements, contracts, memoranda of understanding or other instruments to effects which may be defined internally and which conform to the principles of the CBD and the Nagoya Protocol.

Section 5. On the technical mechanism for determination of the distribution of natural information

Article 15.- The technical mechanism of determination of the distribution of natural information is designed to identify, as precisely as possible, the country(ies) of origin of the species from which said information could have been extracted. Identification includes the geography of the habitats, deploying the technology available at the time of commercial success to calculate said distribution, so that the percentage of benefits will be shared fairly and equitably.

Article 16.- In cases where the expected costs to ascertain the distribution of species is greater than the monetary benefits to be shared, the accumulated benefits up to the expiry of the granted intellectual property, will be used to defray the costs for developing and maintaining the capacities and infrastructure of the technical mechanism for the determination of the distribution of the natural information.

Article 17.- The technical mechanism for the determination of the geographic distribution of natural information comprises those international institutions of recognized standing,

working in activities of taxonomy, monitoring biodiversity, patterns of distribution, developing models of speciation and phylogeny and other activities to understand how biodiversity is distributed.

Article 18. Benefit sharing for marine species will be distributed among Parties which reduce drivers beyond existing commitments. To level the playing field in the decision to utilize marine or terrestrial genetic resources, the conditions and percentages negotiated for terrestrial species will apply to marine species.

Section 6. On the royalties for commercial or industrial suc- cesses

Article 19.- Depending on the commercial or industrial sector corresponding to the innovation or creation and the type of intellectual property solicited, among other relevant considerations, the Ratified Parties of the Global Multilateral Mechanism, by means of the SBSTTA, will fix a royalty percentage for approval by the Conference of the Parties (COP), that will be applied quarterly to the net sales generated for the good or service developed from the natural information and be effective over the lifetime of the right granted. Once the royalty is determined on basis of a set of characteristics, said percentage will be tentatively effective for a period of twenty years.

To encourage timeliness in reaching agreement about the royalty percentage, and only in the case where Parties prolong the negotiations, the percentage will be imposed in a random fashion, between upper and lower limits that are determined by the SBSTTA.

The Parties will review the royalty every five years since its establishment by the COP and can adjust it in conformity with technical and economic considerations that may have arisen.

Article 20.- To avoid stacking of royalties when a good or service has utilized multiple ensembles of natural information, the Ratified Parties will determine a ceiling of summed royalties to be paid, where the countries of origin receive royalty income according to the royalty percentage weighted by the number of distinct ensembles of natural information incorporated in said good or service, as is the case.[3]

Article 21.- The holder of an intellectual-property right will classify his good or service according to the categories established by the COP for determining which royalty is applicable for the value added to the natural information, upon having duly notified and informed the ABS Clearing- house Mechanism of the commercialization.

In the case of imprecise or erroneous classification and any resultant underpayment of royalties, the SBSTTA will calculate a compensatory amount that includes penalties and in the case of overpayment of royalties, a credit with interest.

3 For example, assume that the COP defines a royalty for patents in a sector at 15%; imagine the case of a product which utilizes 5 distinct ensembles of natural information; each ensemble will receive 3% royalty which sums to 15%, thereby avoiding a stacking which would result

Article 22. Natural information utilized in goods or services which are not protected by intellectual property right and lie in the public domain, are not subject to the principles and objectives of this multilateral system, inasmuch as they have not solicited nor obtained intellectual property rights.

Section 7. On the fund for sharing the benefits from the utilization of natural information

Article 23. The Ratified Parties will establish an International Fund of Sharing and Distribution of the Benefits Derived from the Utilization of Natural Information.

Article 24.- The International Fund will be constituted as an escrow, either integrated or annexed to already existing international funds to distribute the monetary benefits in accordance with that established by the technical mechanism for the determination of the distribution of natural information.

Article 25. *Ex situ* collections will participate as a group in the sharing of benefits arising from utilization of accessions. The group will consist of those collections for which the accession pre-dates ratification of the CBD and contain the natural information utilized. The technical mechanism will weigh the group as equivalent to the geographic area sufficient for one "minimum viable population".

Supplementary provisions

First.- The technical mechanism for the determination of the distribution of the natural information will be selected from among scientific international institutions of recognized standing. The mechanism will function with more than one institution to determine the distribution in accordance to specialization and strengths.

Appendix VII

Data for Submission of Views on DSI

Gabriel J. Armador-Cruz

The data were collected from Google-Scholar Search of References in literature on "digital sequence information" conducted 30 October 2019 and from the 2019-2020 inter-sessional period "Submissions of views and information on digital se- quence information on genetic resources", https://www.cbd.int/dsi-gr/2019-2020/submissions/

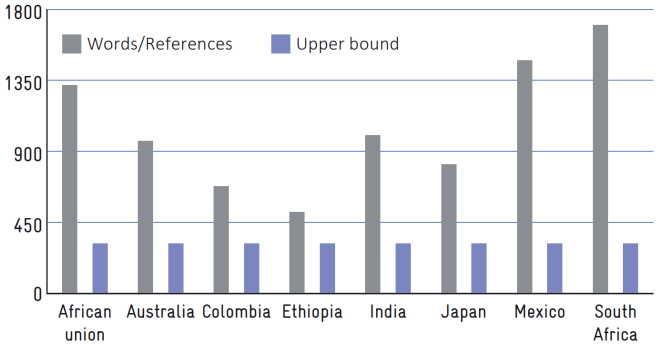
Google scholar page	Number of hits per page	Sample from Published Literature	Words	References	Words/ References	$(X_i-\mu)^2$
1	10	4	8396	49	171.3	4604.1
2	10	6	6548	48	136.4	10564.6
3	9	7	839	5	167.8	5098.1
4	9	10	5969	21	284.2	2028.4
5	10	12	9859	95	103.8	18339.1
6	10	13	24879	53	469.4	52998.7
7	10	14	36805	243	151.5	7698.3
8	10	16	965	1	965.0	526784.6
9	9	20	2676	22	121.6	13821.4
10	10	28	6649	45	147.8	8362.2
11	10	33	3361	8	420.1	32733.6
12	10	43	5441	30	181.4	3344.8
13	9	52	5872	46	127.7	12443.1
14	10	62	15936	195	81.7	24799.2
15	10	64	2313	6	385.5	21403.5
16	10	66	6273	8	784.1	296942.5
17	10	71	4803	13	369.5	16967.9
18	10	77	3279	10	327.9	7867.6
19	10	80	7549	35	215.7	553.0
	186	91	12230	97	126.1	12795.7
		105	8277	55	150.5	7869.4
		118	7274	48	151.5	7684.1
		121	2583	13	198.7	1640.9
		153	1655	6	275.8	1341.9

165	13973	163	85.7	23555.1
169	3787	19	199.3	1590.8
172	29188	281	103.9	18313.9
177	4563	38	120.1	14190.0
178	11808	181	65.2	30263.2
179	30281	349	86.8	23236.6

Average	239.2
S^2	41718.5
S	204.3
95% Confidence Interval	239.2 ± 73.1
	(166.1,312.3)

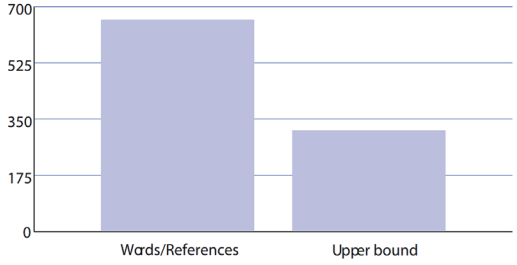
Parties	Words	References	Words/ References	Is it inside the 95% Confidence Interval? (Yes or No)	Upper bound
African Union	3942	3	1314	No	312.3
Argentina	1005	3	335	No	312.3
Australia	962	0	962	No	312.3
Belarus	840	0	840	No	312.3
Brazil	5128	10	512.8	No	312.3
Canada	3335	2	1667.5	No	312.3
Colombia	674	0	674	No	312.3
Costa Rica	1451	0	1451	No	312.3
Ethiopia	511	0	511	No	312.3
European Union	1332	0	1332	No	312.3
India	997	0	997	No	312.3
Iran	389	0	389	No	312.3
Japan	814	0	814	No	312.3
Madagascar	207	0	207	No	312.3
Mexico	1471	0	1471	No	312.3
Republic of Korea	465	0	465	No	312.3
South Africa	1695	0	1695	No	312.3
Switzerland	1356	0	1356	No	312.3

Words/References of Parties

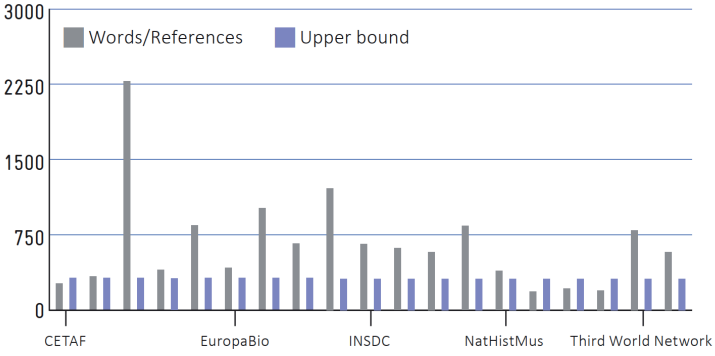


non-Parties	Words	References	Words/ References	Is it inside the 95% Confidence Interval? (Yes or No)	Upper bound
USA	657	0	657	No	312.3

USA



Words/References of Organizations and Stakeholders



Organizations and Stakeholders	Words	References	Words/ References	Within the 95% Confidence Interval? (Yes or No)	Upper bound
CETAF	2868	11	260.7	Yes	312.3
DNFS	3300	10	330	No	312.3
CIPA	2271	0	2271	No	312.3
EcoHealth	394	0	394	No	312.3
EuropaBio	837	0	837	No	312.3
Ibol	1245	3	415	No	312.3
ICC	2020	2	1010	No	312.3
IFRA-IOFI	659	0	659	No	312.3
INSDC	1216	0	1216	No	312.3
JBA	1975	3	658.3	No	312.3
Joint Stakeholder Statement	1855	3	618.3	No	312.3
LERU	1163	2	581.5	No	312.3
NatHistMus	840	0	840	No	312.3
NHM-RGBK- RBGE	3128	8	391	No	312.3
ITPGRFA	1132	6	188.7	Yes	312.3
SPNHC	3072	14	219.4	Yes	312.3
Third World Network	2987	15	199.1	Yes	312.3
BIA	3192	4	798	No	312.3
Wellcome Sanger Institute	2903	5	580.6	No	312.3

Appendix VIII

Filmography

Carolina Sofía Menéndez-Reyes

Scarcity of time is a universal truth. Readers appreciate that scarcity whenever they tackle unfamiliar and difficult subjects. A well executed clip can facilitate understanding. Film can also compress a tremendous amount of information into just a few minutes. Through the Pause button, the viewer can stop and reflect; through the Rewind, repeat and reflect further. Although the temptation may be to substitute the film for the text, the most efficient use of film is as a complement to the text. Below are clips selected for their capacity to engage the viewer effectively. May the links endure.

Section	Fragment from the Report	Title of Clip	URL
2.1	[T]he economic rents, which is the compensation beyond what would be paid in a per- fectly competitive market.	Explaining Economic Rent	https://www.youtube.com/watch?v=2yEC0ncStuM
2.3	The problem of fungibility is highly abstract but no less real. A mundane example would be a subsidy for street arborization when the re-	Fungibility	https://www.investopedia.com/terms/f/fungibility.asp
	[T]he criterion of fairness and equity in the CBD and Nagoya Protocol	Nagoya Protocol and ABS – Simply explained / Swedish EPA / (ABS Capacity Development Initiative)	https://www.youtube.com/watch?v=Bs45B30qmds
		THE NAGOYA PROTOCOL (UICN – ORMACC)	https://www.youtube.com/watch?v=lltjhz6iyoA
2.4	A deadweight loss for con- sumers, also called excess burden, is the value forgone for would-be Users of DSI who desist to use when a sub- scription fee is charged (see Box 3).	Whats Is Deadweight Loss?	https://www.youtube.com/watch?v=-mEn9zxQ0Q0
	[W]hat is the value-in-ex- change of the end-product However, that statistic does not capture the value in use. The paradox identified by Adam Smith...	La paradoja del valor Although the title appears in Spanish, the video is narrated in English.	https://www.youtube.com/watch?v=e7S8jWh6AEs

	Economics can make sense of how the alternative mo- dalities impact utilization. To measure impacts, one must first measure the value of the utilization.	What is VALUE-IN-USE? What does VALUE-IN-USE mean? VALUE-IN- USE meaning, definition & explanation	https://www.youtube.com/watch?v=QLddaZfKcec
	Rather than grapple with consumer surplus, economists quantify a more tractable value, which is nonetheless challenging: the positive ex- ternal effects of life extension. They call it social value.	Econ 120: Two-Minute Economic Lessons (Value)	https://www.youtube.com/watch?v=gYDbLCTHFxM
	Inelasticity means that the quantity demanded adjusts little when prices rise.	What is Elasticity?	https://www.youtube.com/watch?v=d5ayUVV_gKQ
	The abandonment of the patent allows the viewer to shift angles and expose an- other sweeping vista. In the abandonment, the applicants did not commit the fallacy of sunk costs, i.e. they ac- cepted the loss.	The Sunk Cost Fallacy: What is it and why does it happen?	https://www.youtube.com/watch?v=AFPgxIJHxsE
	Price-discrimination seems like the obvious solution. However, different prices for different Users open the doors to arbitrage and leakage, i.e. piracy.	Price discrimination	https://www.youtube.com/watch?v=IZ1iAYhQnwg
5.2.4	The letters represent the order of extinction drivers: H (habitat loss), I (invasive species), P (pollution), P (hu- man population growth) and O (over-harvesting).	E.O. Wilson & Elizabeth Kolbert	https://www.youtube.com/watch?v=GIlvstjsp8I
5.3.1	The potential royalty income, the- refore, depends on the elasticity of demand for the genetic resources as inputs for production. Price elasticity of the final product reflects market con- ditions as well as the quantity currently traded.	Taxes on Producers- Micro Topic 2.8	https://www.youtube.com/watch?v=9gwTH4Yme8I
5.3.2	[P]rofitability of Big Pharma is determined not in the “market” but in the political arena, where compulsory li- censing is a worst-case scenar- io, second only to a scrapping of the entire patent system.	Alexandria Ocasio-Cortez Stands Up to Big Pharma | NowThis	https://www.youtube.com/watch?v=HIQk5B0il-A

	Expenditures on pharma- ceuticals per capita vary from country to country and nowhere are the differences greater than between the USA and the non-OECD countries.	The real reason American health care is so expensive	https://www.youtube.com/watch?v=tNla9nyRMmQ
		Why drugs cost more in America	https://www.youtube.com/watch?v=v7xmkzVU29Q
5.4	The public-good nature of the absence of communicable dis- ease justifies that diagnostics and vaccines be free of charge to the populace, regardless of the economic status of the country.	A Global Vaccine?	https://www.nytimes.com/video/opinion/100000007359483/covax-vaccine-facility-america. html?playlistId=video/opinion
Appendix I	The Naked Mole-Rat (*Heterocephalus glaber*)	True Facts about the Naked Mole-Rat	https://www.youtube.com/watch?v=eHi9FvUPSdQ
Appendix II	Snails of the *Genus Conus*	Baldomero "Toto" Olivera (U. Utah, HHMI): Venomous Cone Snails	https://www.youtube.com/watch?v=L0OiS0a5KFc
Appendix III	Sea Sponge *(Tectitethya crypta)*	Sponges!	https://www.youtube.com/watch?v=m8a0oNsDEx8
Appendix IV	Ebola virus *(Filoviridae)*	Lessons Learned in Sierra Leone: 2014-2016 West Africa Ebola Outbreak	https://www.youtube.com/watch?v=fHnw9W_GdaM

Appendix IX

Lexicon

The fallacy of equivocation is the use of distinct meanings for the same word in an argument. We offer a lexicon to help the reader avoid equivocation. The entries are drawn from biology, economics, law and psychology. For definitions of terms not listed, we defer to the definition of the online *Oxford Learner's Dictionary*. Also included are generally understood terms when they hold special nuance for ABS. Given that the analysis of this report is primarily economic, we draw heavily from two canonical textbooks: the glossaries of *ECONOMICS*, 18th ed. by Paul A. Samuelson and William D. Nordhaus, hereafter, abbreviated (S&N) and *Public Finance*, 3rd ed. by Harvey S. Rosen (HSR). When an economic term appears in one of the textbooks but not in its respective glossary, we include the page number of its appearance after an the initials of the author(s). Sources of other terms may be found in references. Unattributed terms are based on our interpretation of the respective literatures.

Adverse Selection: "A type of market failure in which those people with the highest risk are most likely to buy the insurance. More broadly, adverse selection encompasses situations in which sellers and buyers have different information about a product, such as in the market for used cars" (S&N).

Artificial Information: Any human-made distinction, non- uniformity or difference that is intentional.

Bilateral approach to ABS: One provider negotiates with one user what will be the terms and conditions of the agreement or contract. See also Multilateral approach.

Bounded openness: "Legal enclosures which default to, yet depart, from res nullius to the extent the departures enhance efficiency and equity, which must be balanced when in conflict" (Peruvian Society of Environmental Law / SPDA, 2016).

Cognitive dissonance: Distortion in perceptions to relieve discomfort. With respect to the value of utilization of genetic resources, Providers and Users ignore modalities that would address the distribution of mathematical expectations (probability multiplied by the value of the event). Users may confuse the low probability of an event as if the expectation were also low; Providers may confuse the high value of an event as if the expectation were also high.

Consumer surplus: "The amount by which consumers' willingness to pay for a commodity exceed the price they actually pay" (HSR).

Deadweight loss: See Excess burden.

Digital Sequence Information: A highly controversial and widely rejected placeholder, which emerged at COP13 in response to denunciations of "digital biopiracy". Mindful of the placeholder status and well grounded objections to its usage, no definition is herein provided.

Economics: Common to the many definitions is "resource allocation". The three objectives

of the CBD and the very title of the Nagoya Protocol lend themselves to the abstract reasoning associated with the discipline.

Economics of information: "Analysis of economic situations that involve information as a commodity. Because information is costly to produce but cheap to reproduce, market failures are common in markets for information goods and services as invention, publishing and software" (S&N). Classification of "genetic resources" as natural information triggers application of the economics of information.

Economic rents: Payment in excess of the price that would obtain if markets were perfectly competitive. See Price- equals-marginal cost.

Efficiency: "Absence of waste, or the use of economic resources that produces the maximum level of satisfaction possible with the given inputs and technology" (S&N). The non-discussion of efficiency in the COP may reflect the principal-agent problem.

Elasticity: "A term widely used in economics to denote the responsiveness of one variable to changes in another. Thus, the elasticity of X with respect to Y means that the percentage change in X for every 1 percent change in Y" (S&N).

Excess burden: "A loss of welfare above and beyond taxes collected. Also called welfare cost or deadweight loss" (HSR).

Externality: "An activity of one entity affects the welfare of another entity in a way that is outside the market" (HSR).

Fair and equitable: Equal treatment of economic rents, be they for artificial or natural information.

Fixed cost: "The cost a firm would incur even if its output for the period in question were zero". See also variable costs (S&N).

Free goods: "Those goods that are not economic goods. Like air or seawater, they exist in such large quantities that they need not be rationed out among those wishing to use them" (S&N).

Free riding: "[The] incentive to let other people pay while you enjoy the benefit" (HSR, p. 75).

Fungibility: "Fungibility is a central notion in economics, though often unnoticed and unnamed. It means merely 'substitutable' and is in origin a Latin legal term meaning 'such that any unit is substitutable for another' (from fungor meaning 'do, discharge').
"A debt can be discharged with any money, not merely moneys from a particular account" (italics added, abstract, McCloskey).

Government failure: Because industries successfully shift costs to third parties, markets fail to allocate resources optimally. Intervention is justified. However, the State often does not intervene effectively. The solution to government failure includes election of better administrations, independence of the technocracy from politics or privatization.

Labor theory of value: "The view often associated with Karl Marx, that every commodity should be valued solely according to the quantify of labor required for its production" (S&N).

Marginal cost: "The incremental cost of producing one more unit of output" (HSR) See also fixed cost and variable costs.

Multilateral approach to ABS: Providers and Users negotiate the terms and conditions that will govern any utilization (see Bilateral approach).

Mutually agreed terms (MAT): "[A]n agreement reached between the provider of genetic resources and a user with respect to the conditions of access to genetic resources in the provider country and the benefits to be shared between both parties, further to the commercial or other use of these resources" (UN CBD Secretariat). Under bilateralism, Providers lack agency to extract economic rents. See, Fair and equitable.

Natural Information (abiotic): Complement of "Natural Information (biotic)" with respect to that which is not living and was never alive.

Natural Information (biotic): Any unintentional distinction, non-uniformity or difference extracted from matter that is living or was once alive.

Nested dominance hierarchies: "Societies… are partitioned into units [and] can exhibit dominance both within and between the components...Team play and competition between human tribes, businesses, and institutions are also based upon nested hierarchies, sometimes tightly organized through several more or less autonomous levels…" (Wilson 1975, p. 287). Thirty-seven years after publishing those words, Wilson would double down: "In its power and universality, the tendency to form groups and then favor in-group members has the earmarks of instinct" (Wilson 2012, p. 59).

Opportunity costs: "The value of the next-best use (or opportunity) for an economic good, or the value of the sacrificed alternative" (S&N). Habitat loss has long been identified as the leading cause of terrestrial species extinction. The opportunity costs of conservation are a myriad of land uses.

Principal-agent problem: "In a situation where one person (the principal) wants another person (the agent) to perform a task, the principal may find it difficult to monitor the agent's behavior. The principal-agent problem is to design the agent's incentives so that the principal's expected gain is as high as possible" (HSR).

Price-equals-marginal-cost: The rule derives from the marginalist revolution of the 1860s, associated with Stanley Jevons, Leon Walras and Alfred Marshall. In competitive markets, price is driven down to marginal cost of production, which approaches zero for information goods. See also economics of information.

Price discrimination: "A situation where the same product is sold to different consumers for different prices" (S&N). For intellectual property, the practice is legal and economically justifiable. One price world-wide would be higher than current prices in low-income countries, thereby incurring huge losses of **consumer surplus** and provoking compulsory licensing in pharmaceuticals.

Prior informed consent: "[P]ermission given by the competent national authority of a provider country to a user prior to accessing genetic resources, in line with an appropriate national legal and institutional framework" (UN CBD Secretariat). Like **Mutually agreed** terms (see above), a contradiction exists in the assumption of agency. Under bilateralism, justifiable rents have already been eliminated.

Public Good: "A good which is not rival in consumption; the fact that one person benefits from this good does not prevent another person from doing the same simultaneously" (HSR).

Race-to-the-bottom: A metaphor for fierce competition among Providers, where the bottom is the price paid for genetic resources expressed as a royalty percentage. Because the cost of physically accessing genetic resources may be as low as filling a zip-lock bag with scooped-up soil or gathering a few kilos of dry leaves, the price of genetic resources is largely the transaction costs of MTAs/BSAs.

Ramsey Rule: "To minimize total excess burden, tax rates should be set so that the percentage reduction in the quantity demanded of each commodity induced by the taxes is the same" (HSR).

Rents (economic): The difference between the price paid and that which would have paid in a competitive market in the long run.

Sovereignty: The supreme authority that resides in the people as represented by the State. As a result, the State has certain rights over genetic resources under its jurisdiction and in representation of the people. Contrary to pronouncements from Users and Providers, a Global Multilateral Benefit-Sharing Mechanism is unambiguously an expression of sovereignty.

Stare decisis: Latin for "stand by that which is decided", which obligates courts to follow historical cases when making a ruling on a similar case, often reasoning analogically.

Sunk costs: The situation where future marginal costs exceed future benefits. The rational choice is to abandon the decision previously made. However, **cognitive dissonance** kicks in. People do not lightly abandon costly decisions. Neither do ants. E.O. Wilson observes *"the more elaborate and expensive the nest is in energy and time, the greater the fierceness of the ants that defend it"* (italics in original) (Wilson 2012, p. 130).

Synthetic biology: No generally accepted definition exists. "The COP… acknowledged that the outcome of the work of the AHTEG on the operational definition is 'synthetic biology is a 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'" (UNSCBD Secretariat).

Taboo: Proclivities to assimilate prohibitions remain in modern society, protestations to the contrary notwithstanding. Garrett Hardin's observes: "An element of behavior that is transferred from one culture to another is likely to suffer a sea change. So, it has been with taboo.

Pacific islanders apparently have no hesitancy in explicitly giving taboo as a reason for stopping a discussion. By contrast, Westerners with their cherished tradition of free speech and open discussion, would be embarrassed to say (for instance), 'We will not discuss population because it is under a taboo.' Instead they change the subject" (p. 4).

Theory of Second Best: "In the presence of existing distortions, policies that in isolation would increase efficiency can decrease it, and vice versa" (HSR).

Transaction costs: "The costs that arise beyond the point of production of a good to effect its allocation" (Marneffe). In the context of ABS, think lawyers. MTAs will never be sufficiently standardized to eliminate the need for counsel.

Variable cost: "A cost that varies with the level of output". *See also* **fixed costs** (S&N).

Value in exchange: The price paid for a good or service.

Value in use: Two distinct meanings of the term appear in the economic literature. The meaning for this Report refers to the utility derived from consumption of a good and service, and not to the present net worth of an asset. To complicate matters even more, value in use should not be confused with use value of biodiversity, which is measured by the values-in-exchange in consumption and production.

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SPDA

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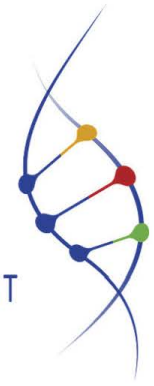
THE ABS CAPACITY DEVELOPMENT INITIATIVE



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