Capstone Advisory Committee Final Capstone Project Signature Form

Can the Sustainable Collection and Research of Marine Natural Products for Biomedical Uses Contribute to Conservation in Curaçao?

Mikki Dochez

MAS Marine Biodiversity and Conservation

Capstone Project

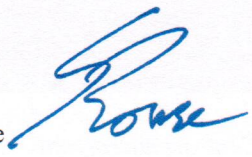
Capstone Advisory Committee

Signature _____ Print Name Tamara Mayer, MAS Date _____

Affiliation Sirenas Email tamara.mayer@sirenasmd.com Phone 858-909-5105

Signature _____ Print Name Dr. Stuart Sandin Date _____

Affiliation SIO Email ssandin@ucsd.edu Phone 858-534-4150

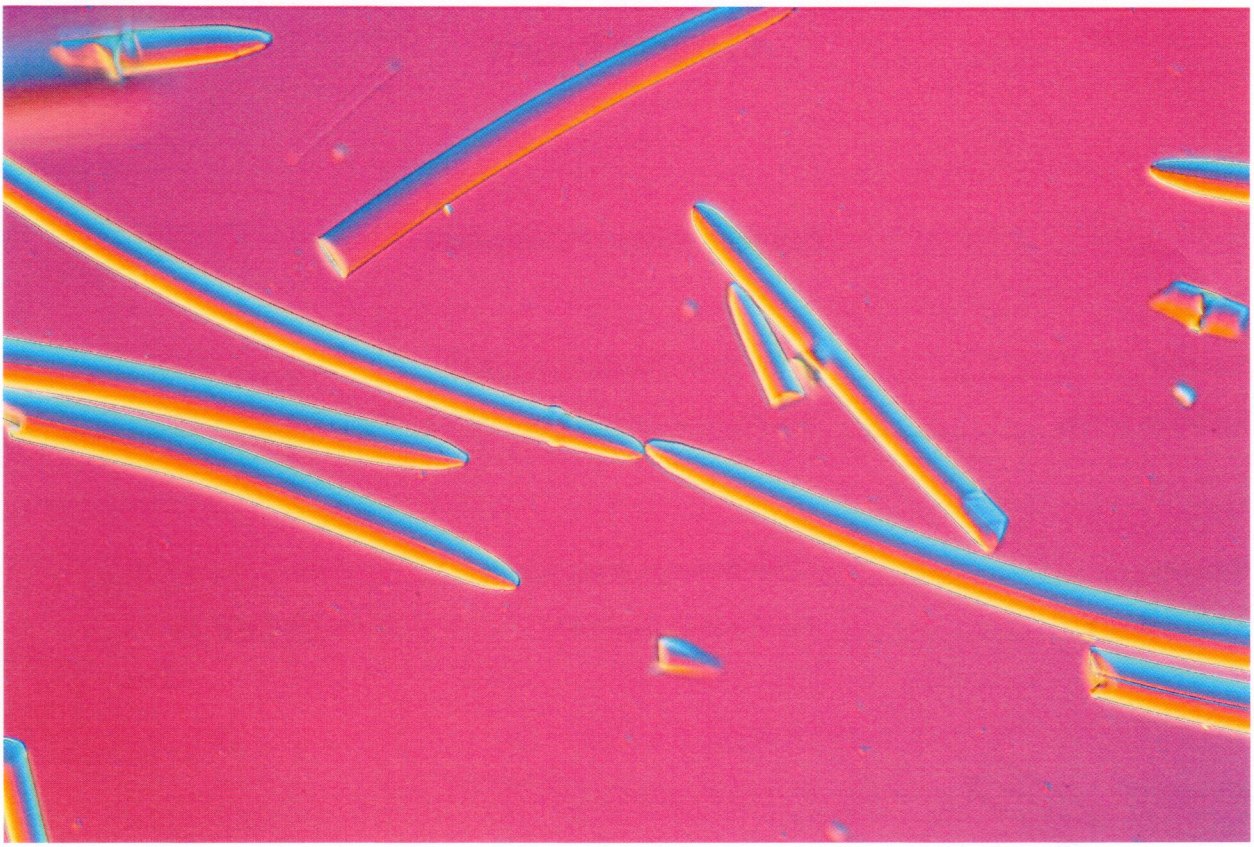
Signature  Print Name Dr. Greg Rouse Date 5-31-16

Affiliation SIO Email grouse@ucsd.edu Phone 858-534-7973

MBC 296 Capstone Final Report -- Spring 2016

Can the Collection and Research of Marine Natural Products for Biomedical Uses Contribute to Conservation in Curaçao?

Mikki Dochez



Spicules from Xestospongia sponge collected in Curaçao, Differential Interference Contract microscopy

Introduction

While studying Biology as an undergraduate at George Mason University, I became interested in Conservation Biology and took two 6-credit courses on the subject during my Senior year. After I graduated, I volunteered at the Airlie Center for Environmental Studies, helping with a project that aimed to teach endangered Trumpeter Swans their natural migration route so they could be reintroduced to the wild without becoming a nuisance species, like the Canada Goose after it was reintroduced in the 1900s. It was an incredible experience, which was supposed to lead to a Masters Degree, but after six months with no return to school on the horizon, the realization set in that I needed a paying job. I landed in Clinical Research, a field that pays well and has lots of jobs. It felt rewarding to make a small contribution to improving the health of patients with autoimmune disorders and organ transplants. However, my heart was always calling me back to nature and the ocean.

In late 2009, I moved to Palau, where I worked as a dive guide for five years. I loved being in the water every day, swimming along breathtaking walls of hard and soft coral, with sharks, manta rays, ribbon eels, nudibranchs, and, occasionally, massive spawning aggregations of snapper and parrot fish. I saw and learned something new on almost every dive. I fell in love with Palau and wanted to do more to help conserve the place that had given me so much. I decided the best way to do that was to go back to school, like I planned to do so many years ago. When I discovered the Center for Marine Biodiversity and Conservation at Scripps Institution of Oceanography, it felt like the perfect fit. Through connections I made at Scripps, I began to see that I could marry my experience in clinical research within the pharmaceutical industry and my desire to

contribute to marine conservation. I believe that as more people understand the potential marine organisms have to produce drugs that treat areas of unmet medical need, they will be motivated to protect the marine environment, because, unfortunately, everyone is affected by disease.

What are Natural Products?

A natural product is defined most simply as "a small molecule that is produced by a biological source.[1]" Although the term "natural products" is relatively new, there is evidence that humans have been using them since before recorded history. Paleoanthropologists found pollen deposits in a grave at Shanidar Cave, Iraq, suggesting that Neanderthals may have used plants as medicines more than 60,000 years ago[2],[3]. Many discoveries borne out of natural products have greatly contributed to our ability to survive and thrive throughout history -- curing diseases, improving food crops, and increasing our overall quality of life. People in many developing countries still depend on traditional healing practices derived directly from nature. Even the most developed countries continue to rely on medications and treatments derived from natural products[4]. In fact, the modern pharmaceutical industry has its roots in natural

---

[1] "All Natural." *Nature.com*. Nature Publishing Group, 2016. Web. 09 June 2016. http://www.nature.com/nchembio/journal/v3/n7/full/nchembio0707-351.html.
[2] Solecki, R. S. "Shanidar IV, a Neanderthal Flower Burial in Northern Iraq."*Science* 190.4217 (1975): 880-81.
[3]Ji, Hong-Fang, Xue-Juan Li, and Hong-Yu Zhang. "Natural Products and Drug Discovery. Can Thousands of Years of Ancient Medical Knowledge Lead Us to New and Powerful Drug Combinations in the Fight against Cancer and Dementia?" *EMBO Rep EMBO Reports*10.3 (2009): 194-200.
[4] Scott, Preston. "Bioprospecting as a Conservation Tool: History and Background." *Crossing Boundaries in Park Management: Procceedings of the 11th Conference on Research and Resource Management in Parks and on Public Lands* (2001): 228-32. The George Wright Society. 17 May 2016. http://www.georgewright.org/38scott.pdf.

products derived from actinomycetes, isolated from soil. The "Golden Age of Antibiotics" in the 1950s and 1960s marked the major period of growth for the pharmaceutical industry[5]. Earlier this year, a Yale Center for Molecular Discovery analysis of the history of FDA-approved drugs revealed that "natural products and their derivatives represent over one-third of all [FDA-approved] NMEs [New Molecular Entities, or innovative new medicines]"[6]. These new molecular entities -- from animal, plant and microbial sources -- are developed into therapeutics that treat a wide range of disease areas, including many types of cancers, neurological disorders, chronic pain, and infectious diseases. Over time, the percentage of natural products from microbial sources has increased and now represents "a significant portion of approved antibiotics, including more than two-thirds of all antibacterial NMEs"[7]. "It is notable that 69% of all antibacterial agents originate from natural products, with 97% isolated or derived from microbes ... [and] since the year 2000, 77% of approved antibiotics are natural products, 100% of which were derived from microbes"[8]. Unfortunately, "the holy grail of antibiotic progress—a new class of antibiotics—has not been seen since 1987 … which is troubling given the increasing trend of antibiotic resistance"[9]. A 2012 review on antimicrobial resistance states that "a continued rise in resistance by 2050 would lead to 10 million people dying every year and a reduction of 2% to 3.5% in Gross Domestic Product (GDP). It would cost the world up to 100 trillion USD"[10]. Even worse, in recent years, there has been a

---

[5] Baker, B. J. *Marine Biomedicine: From Beach to Bedside*. CRC, 2015.
[6] Eric Patridge, Peter Gareiss, Michael S. Kinch, and Denton Hoyer. "An Analysis of FDA-approved Drugs: Natural Products and Their Derivatives." *Drug Discovery Today* 21.2 (2016): 204-07.
[7] Patridge et al., 2016.
[8] Patridge et al., 2016.
[9] Theuretzbacher, Ursula. "Center for Disease Dynamics, Economics & Policy (CDDEP)." *Recent FDA Antibiotic Approvals: Good News and Bad News*. The Center for Disease Dynamics, Economics & Policy, 12 Mar. 2015. 22 May 2016. http://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news#sthash.4QYBpDMh.dpbs.

declining focus on natural products, which has negatively affected the pipeline of NMEs and, thus, new drugs, from specific classes. New drugs in the pipeline will likely continue to slow down unless there is increased investment in natural products[11].

Of course, getting natural products from "beach to bedside"[12] has traditionally been a long and complicated process filled with legitimate concerns and obstacles. Some worry that collections of organisms from natural products research may not be sustainable, or that the source country from which an organism is collected won't be fairly compensated, which has happened in the past. Since the 1990s, a number of high profile cases of biopiracy have been the subject of intense controversies[13]. The recently ratified Nagoya Protocol of the Convention on Biological Diversity was designed to address this issue; it provides the legal framework for access and benefit-sharing rights related to natural products. In practice, it has actually created some confusion and roadblocks since each signatory country must create its own specific regulations.

There is also a lack of funding for natural products research from the pharmaceutical industry, also known as Big Pharma because of its annual US$300 billion market value[14], which has severely clogged the discovery pipeline of new compounds for novel medications[15]. This is a huge disadvantage to the industry and, more importantly,

---

[10] O'Neill, Jim. *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations.* The Review on Antimicrobial Resistance, Dec. 2012.

[11] Patridge et al., 2016.
[12] Baker, 2015.
[13] Rabitz, Florian. "Biopiracy after the Nagoya Protocol: Problem Structure, Regime Design and Implementation Challenges." *Bras. Political Sci. Rev. Brazilian Political Science Review* 9.2 (2015): 30-53.
[14] "Pharmaceutical Industry." *WHO*. 26 May 2016. http://www.who.int/trade/glossary/story073/en/.

humanity. Cancer remains one of the leading causes of death worldwide, with 14 million new cases and 8.2 million cancer-related deaths in 2012[16]. The rise of antibiotic resistant bacterial infections also pose a huge public health risk[17]. Additionally, Neglected Tropical Diseases (NTDs) affect over 1 billion people in developing countries around the world[18]. These areas of unmet medical need require the discovery and development of novel drugs. Fortunately, despite the pharmaceutical industry's shift away from natural products research, scientists in academia and smaller research labs around the world have made significant advances and new discoveries in the field[19]. Therefore, it makes sense that the spotlight of innovation in drug discovery has fallen on academia and these small startup companies[20],[21].

Novel Medicines: Inspiration from the Ocean

One extremely vast, and largely unexplored, resource of natural products is our world's oceans. The oceans cover two-thirds of the earth and several branches of life are exclusively marine, housing biodiversity that can't be found anywhere else on the planet[22]. Marine natural products discovery started to take off as a scientific discipline within academia in the 1970s, fueled by very unique chemistry found in marine

---

[15] Patridge et al., 2016.
[16] "Cancer Statistics." *National Cancer Institute*. Web. 09 June 2016. http://www.cancer.gov/about-cancer/understanding/statistics.
[17] Theuretzbacher, 2015.
[18] "World Health Organization." *World Health Organization*. Web. 09 June 2016. http://www.who.int/gho/neglected_diseases/en/.
[19] Marris, Emma. "Marine Natural Products: Drugs from the Deep." *Nature*443.7114 (2006): 904-05.
[20] Gerwick, William H., and Bradley S. Moore. "Lessons from the Past and Charting the Future of Marine Natural Products Drug Discovery and Chemical Biology." *Chemistry & Biology* 19.12 (2012): 1631.
[21] Kaitin, K. I. "Deconstructing the Drug Development Process: The New Face of Innovation." *Clinical Pharmacology & Therapeutics* 87.3 (2010): 356-61.
[22] Marris, Emma. "Marine Natural Products: Drugs from the Deep." *Nature* 443.7114 (2006): 904-05.

organisms, including a variety of organohalogen compounds[23], like "highly halogenated terpenes and acetogenins from Rhodophytes such as, the highly toxic polyketide "tedanolide" from the fire sponge *Tedania ignis*, and prostaglandins from the gorgonian coral *Plexaura homomalla*"[24]. Initially, research focused on the origins and ecological significance of the unique chemistry, but funding from the National Cancer Institute (NCI) refocused the research on drugs from the sea, specifically compounds that are cytotoxic against cancer cell lines[25]. As more cryptic organisms were studied, the list of unique molecular species continued to grow. By 2000, the study of marine natural products was a well-established subdiscipline of natural products chemistry, having described several thousand compounds. Attention is now being shifted to ever smaller marine microorganisms, like cyanobacteria, fungi, and eubacteria, which has led to many new discoveries in marine natural products chemistry. In addition, research on marine microorganisms has led to "the realization that many compounds previously isolated from macroorganisms, such as sponges and tunicates, are actually metabolic products of associated microbes (Piel, 2009)"[26]. While huge advances have been made through this research, scientists have only scratched the surface of the "phylogenetic richness present within microbial groups in the sea. From seawater alone, it is estimated that only 1% of bacteria present have been cultured"[27].

Marine natural products research has been very effective at "defining major trends in the secondary metabolism of diverse classes of marine organisms"[28]. In fact, Dr.

---

[23] Baker, 2015.
[24] Gerwick et al., 2012.
[25] Baker, 2015.
[26] Gerwick et al., 2012.
[27] Gerwick et al., 2012.

William Gerwick, distinguished professor at the Center for Marine Biotechnology and Biomedicine at Scripps Institution of Oceanography, explains the rate of discovery for marine natural products has "a better track record" than that of other types of discovery platforms. The NCI estimates that, in general, 15,000-20,000 compounds need to go through the screening pipeline for every single drug that's approved; there are only 23,000 known compounds derived from marine natural products and, as of 2015, 13 of them have entered the clinic as approved drugs. They are mostly cancer therapies, but also include hyperlipidemia treatments, therapeutic macromolecules that treat heparin overdose, cyclic peptide pain treatments, and antiviral medications[29].

The recent increase in "omic" approaches in marine natural products discovery – metabolomics and genomics, for example – has connected natural products chemistry with modern molecular biology, enabling researchers "to address fundamental questions about the biosynthetic capacity of marine organisms, the synthetic role of microbes in marine invertebrate natural product chemistry, and the bioengineering potential of marine drugs. Without a doubt, marine organisms synthesize a plethora of small molecules with fascinating chemical structures and potent biological properties[30]." Knowledge of biosynthesis began from isotope tracer experiments with marine microbes, algae, and invertebrates that showed many differences in biosynthetic strategies between marine and terrestrial organisms[31,32,33].

---

[28] Gerwick et al., 2012.
[29] UC Television. "Groundbreaking Innovations at UCSD: Marine Drug Discovery with William Gerwick and Paul Jensen." YouTube. YouTube, 23 June 2015. https://youtube.com/watch?v=MN_dttB9LnA.
[30] Gerwick et al., 2012.
[31] Gerwick et al., 2012.

The Pharmaceutical Industry Abandons Natural Products

The most widely recognized reason that leading pharmaceutical companies shifted their focus away from natural products was to explore combinatorial chemistry and hit-to-lead, or high throughput screening (HTS), approaches[34]. In the mid-1980s, companies wanted a more scalable approach to drug discovery using technologies like synthetic chemistry libraries, combinatorial libraries, and high-throughput and ultra-high-throughput screening, a trend that continued through the 1990s. During that time, there was concern among pharmaceutical companies that natural products were not compatible with drug discovery platforms that used such high-throughput screening, directed at molecular targets[35,36]. Natural products simply didn't fit the new technology. A single natural product sample contains many thousands of compounds and, even when chemists fractionate a sample, breaking it down into crude extracts, they still end up with hundreds of compounds in each of their 1,536 test wells. "This is where the wheels fell off of this thing," said Paul Armond, a plant cell biologist who spent 30 years in drug development at Pfizer. "High-throughput screeners hated these samples. They didn't want to have anything to do with them because even if you got a hit in one of these fractionated samples, you didn't know which of the hundred compounds in the test well

---

[32] Moore, Bradley S. "Biosynthesis of Marine Natural Products: Microorganism (Part A)." *ChemInform* 36.52 (2005).
[33] Moore, Bradley S. "Biosynthesis of Marine Natural Products: Macroorganisms (Part B)." *ChemInform* 37.42 (2006).
[34] Baker, 2015.
[35] Harvey, Alan L., Ruangelie Edrada-Ebel, and Ronald J. Quinn. "The Re-emergence of Natural Products for Drug Discovery in the Genomics Era." *Nature Reviews Drug* Discovery 14.2 (2015): 111-29.
[36] Rishton, Gilbert M. "Natural Products as a Robust Source of New Drugs and Drug Leads: Past Successes and Present Day Issues." *The American Journal of* Cardiology 101.10 (2008).

was the active one." High-throughput screening is designed to test as many compounds and get as many hits as possible, and natural compounds clogged the pipeline. Even if an interesting biologically active compound was isolated, Armond says, "it would be, from the organic chemist's point of view, some ugly compound, this big, giant molecule that no chemist could ever possibly synthesize. They'd say, 'What am I supposed to do with this?'"[37] When a compound seems promising, it is typical for medicinal chemists to "add things to it, take things away, rearrange things, and find where the important parts of the molecule are and where the not-so-important parts are"[38]. Through combinatorial chemistry, researchers are able to target the molecule more accurately and diminish unwanted side effects. However, if a compound from a natural product is too complex to synthesize, "then you can't do any of those things"[39].

Companies also feared that there weren't reliable natural sources for repeated isolation of known compounds. "Getting enough of the desired compound can be difficult because living things normally vary by season or site—and sometimes disappear completely. It happened to another NCI research team in the late 1980s. When they got a promising hit for an anti-HIV compound from a tree in Sarawak, Malaysia, researchers hurried back to collect more samples. But someone had cut down the only known tree. After a frantic search, the only other evidence of the species they could find was a 100-year-old specimen in the Singapore Botanical Garden. Chemists eventually figured out how to synthesize the compound, and Calanolide A is now an experimental treatment for HIV patients"[40].

---

[37] Conniff, Richard. "A Bitter Pill - Conservation." *Conservation RSS*. University of Washington Conservation Magazine, 09 Mar. 2012. http://conservationmagazine.org/2012/03/a-bitter-pill/.
[38] Conniff, 2012.
[39] Conniff, 2012.

Big Pharma's Big Disappointment

In practice, large combinatorial library collections turned out to be very disappointing drug discovery platforms, as it became understood "that diversity within biologically relevant 'chemical space' is more important than library size"[41]. In fact, "a retrospective analysis of one company's HTS campaigns indicated that the selection of plates containing natural products would have significantly improved hit rates"[42]. "The combinatorial compound libraries researchers worked with in the early years were so badly flawed, according to Christopher Lipinski, a drug development guru who spent most of his career at Pfizer, that the industry would have been more productive if it had 'stored them in giant dumpsters.' Even now, after tens of billions of dollars and 25 years of research, combinatorial chemistry and high-throughput screening have put only a single completely new FDA-approved compound into the marketplace. The new methodologies can thus seem a bit like the drunk who searches for his keys under a lamp post, not because that's where he dropped them, but because the light is better there"[43].

The disappointment surrounding the drug discovery platforms of the 1980s and 1990s has created "an increasingly powerful case for revisiting natural products for drug discovery"[44]. Now, automated fractionation can rapidly break down samples, parsing

---

[40] Conniff, 2012.
[41] Harvey et al., 2015.
[42] Harvey et al., 2015.
[43] Conniff, 2012.

their natural complexity down to just three compounds per test well for high-throughput screening[45]. "The use of simplified fractions, together with sensitive NMR [nuclear magnetic resonance] techniques, has addressed the isolation and structure-elucidation bottleneck. Additionally, as fractions are prepared by a chromatographic method, subsequent chromatography on existing fractions is more likely to be achievable, avoiding the previous danger of not finding the responsible constituent in active crude extracts"[46].

Additionally, the rapidly shrinking drug product pipeline has prompted some companies, especially smaller startups, in the pharmaceutical industry to begin reexamining compounds derived from natural sources, including marine organisms[47]. "The lack of development of early-stage leads has been a major issue in natural products drug discovery research for some time, and was part of the rationale for formulating Drug Discovery Groups (DDGs) through the National Cancer Institute's (NCI) very successful National Cooperative DDG program. In this program, groups of academic investigators teamed together with partner pharmaceutical companies and the NCI so as to improve the focus of the cancer drug discovery process as well as to have development capacity inherently built into the endeavor. During the 23-year period of the NCDDG program (1984–2007), there were 21 New Investigational Drugs that went into clinical trial (12 small molecules and 9 biologics) that derived from substantial input from this program. Indeed, this is widely perceived as the single most effective granting mechanism by

---

[44] Harvey et al., 2015.
[45] Conniff, 2012.
[46] Harvey et al., 2015.
[47] McGee, Patrick. "Natural Products Re-emerge." *Drug Discovery & Development*. 09 June 2007. 22 May 2016. http://www.dddmag.com/articles/2007/09/natural-products-re-emerge.

which to bring fundamentally new cancer treatments into existence, and with its disappearance, we have taken a giant step backward"[48]. Now academic investigators have been left to forge these critical connections with industry on an individual basis. In some cases, large pharmaceutical companies have licensed compounds from startups or purchased entire companies after they have successfully brought an innovative new therapy to clinical trial. Unfortunately, small startups usually face financial constraints and, ironically, advancing a successful new therapeutic often requires cutbacks and layoffs in the research departments that discovered them to begin with. Therefore, the way the industry is currently structured generally slows down the process of early stage leads becoming clinical candidates[49]. However, "combined with a greater sensitivity to druggable targets, broad knowledge of disease biology, and the capacity of meaningful development of leads across the valley of death and into the clinic, large Pharma is an invaluable partner to the highly innovative yet risky approaches of academic natural products laboratories. Indeed, the NCDDG structure is an inspired concept that needs to be renewed in some form"[50],[51].

Bioprospecting and Biopiracy

---

[48] Gerwick et al., 2012.
[49] Gerwick et al., 2012.
[50] Gerwick et al., 2012.
[51] Crews, Phillip, William Gerwick, Francis Schmitz, Dennis France, Kenneth Bair, Amy Wright, and Yali Hallock. "Molecular Approaches to Discover Marine Natural Product Anticancer Leads – An Update from a Drug Discovery Group Collaboration." *Pharmaceutical Biology* 41.Sup1 (2003): 39-52.

"Biodiversity prospecting" or "bioprospecting" has been defined as "the purposeful evaluation of wild biological material in search of valuable new products"[52]. In other words, bioprospecting involves the discovery of biodiversity for potential commercial use. "Biodiversity" is defined by the United Nations Convention on Biological Diversity as "the variability among living organisms from all sources including, *inter alia*, terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are part; this includes diversity within species, between species and of ecosystems"[53].

The term bioprospecting, coined by proponents of sustainable development in the 1980's[54], can be inferred differently, depending on the audience. For some, "bioprospecting" has an innate association with technology, which is generally beneficial to humankind, and has a mostly positive connotation. For others, however, "prospecting" conjures images of the gold rush days of the Wild West, where lawless activities were commonplace. This may cast a negative shadow over the term "bioprospecting" – alluding to the notion that lawless practices may also be used to plunder biological resources. The similar sounding term "biopiracy" may also contribute to a negative view of bioprospecting[55]. Those who view bioprospecting as biopiracy believe it is a political, economic, and cultural oppression perpetrated by the money-

---

[52] Artuso, Anthony. "Bioprospecting, Benefit Sharing, and Biotechnological Capacity Building." *World Development* 30.8 (2002): 1355-368.
[53] "CBD Handbook." *CBD Home*. 18 May 2016. https://www.cbd.int/doc/handbook/cbd-hb-01-en.pdf.
[54] Hayden, Cori. "Bioprospecting: The 'Promise' and Threat of the Market" *The North American Congress on Latin America*. 17 May 2016. https://nacla.org/article/bioprospecting-promise-and-threat-market.
[55] Pan, Peter G. "Bioprospecting: Issues and Policy Considerations" *Legislative Reference Bureau* 1 (2006).

rich, resource-poor against the money-poor, resource-rich, where benefit-sharing agreements are not worth the harm caused by bioprospecting[56].

Access and Benefit-Sharing Regulations

A less discussed reason the pharmaceutical industry stopped using natural products for drug discovery during the 1990's was concern about access to resources, spurred, in part, by the United Nations Convention on Biological Diversity (CBD). The CBD is the product of the Rio Earth Summit in Brazil in 1992. It sets guidelines pertaining to access to, and use of, biodiversity, or "genetic resources," across international boundaries. The CBD states that countries have sovereign rights over genetic resources in their territories and that access to those genetic resources by foreign entities requires prior informed consent (PIC) from the appropriate authority in the source country. Furthermore, access, on mutually agreed terms, should be facilitated by the source country, and benefits from the use of genetic resources should be shared in a fair and equitable way with the source country. The source country should be involved in relevant research on genetic resources, if possible, and should also benefit from the technology transfer. The CBD was signed by most countries in the world (194 to date), and has been ratified by most of those, with the notable exception of the United States. The impact of the CBD has varied widely by country, since it requires that each individual country adopt its own laws and regulations to implement the principles of the CBD.

---

[56] Vandana Shiva, Biopiracy: The Plunder of Nature and Knowledge, Cambridge, MA: South End Press, 1997, referring to the Convention on Biological Diversity.

Subsequently, the Nagoya Protocol on Access and Benefit-Sharing (the ABS Protocol), adopted in October 2010, was created to address one of the three objectives of the CBD -- the fair and equitable sharing of benefits arising from the utilization of genetic resources[57]. Previously, the CBD's Bonn Guidelines were created to tackle access and benefit-sharing challenges, but they were relatively ineffective because they were strictly voluntary[58]. The Nagoya Protocol provides a detailed legal framework for Access and Benefit-Sharing related to natural products and traditional knowledge[59]. However, the Protocol was not passed easily; anxiety ran high during the negotiations over the acceptance of this new multilateral agreement, and it remained uncertain until the last hours of the overnight plenary session if it would pass the consensus-based COP approval. "Negotiations resembled an emotional roller-coaster, as positions between the biodiversity rich Global South and the financially rich Global North over the Protocol's scope, genetic derivatives, and compliance mechanisms remained wide apart. Besides the Protocol, the approval of the plenary session was needed for two other crucially important documents, each contingent upon one another for acceptance — a new Strategic Plan containing conservation targets for 2020 and a new Resource Mobilization Strategy for meeting these targets. It appeared that developing countries, collectively owning more than 80 percent of the world's biological diversity, had a bargaining leverage over the industrially developed world and therefore were unwilling

---

[57] *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization*. Montreal: Secretariat of the Convention on Biological Diversity, 2011. *Nagoya Protocol Fact Sheet*. Convention on Biological Diversity. 21 May 2016. https://www.cbd.int/abs/infokit/revised/web/factsheet-nagoya-en.pdf.

[58] Kuruk, Paul. "Regulating Access to Traditional Knowledge and Genetic Resources: The Disclosure Requirement as a Strategy to Combat Biopiracy." *San Diego International Law Journal* 17th ser. 1.Fall (2015).

[59] Harvey et al., 2015.

to accept new conservation targets unless the ABS Protocol was also accepted and more finances were made available"[60].

The Nagoya Protocol has been signed by 92 countries, and ratified by 75; it entered into force on 12 October 2014, but it is only legally binding for those countries which have ratified it[61]. The core elements of the Nagoya protocol are access obligations, benefit-sharing obligations, and compliance obligations. *Access obligations* are domestic-level measures designed to promote legal "clarity and transparency[,] ... establish clear rules and procedures for prior informed consent and mutually agreed terms, provide for issuance of a permit or its equivalent when access is granted, and create conditions to promote and encourage research contributing to biodiversity conservation and sustainable use"[62]. *Benefit-sharing obligations* are also domestic-level benefit-sharing measures that "should provide for the fair and equitable sharing of benefits arising from the utilization of genetic resources, as well as subsequent applications and commercialization, with the contracting party providing the genetic resources. Utilization includes research and development on the genetic and/or biochemical composition of genetic resources. Sharing of benefits is subject to mutually agreed terms. Benefits may be monetary (such as royalties) or non-monetary (such as sharing research results or technology transfer). The Nagoya Protocol also proposes the creation of a global multilateral benefit-sharing mechanism in order to address benefit-sharing with respect to genetic resources occurring in trans boundary areas or situations where prior

---

[60] Feditchkina, Elena. "The Last Call for the Minerva's Owl: The Politics of the 11th Hour in Negotiating the Nagoya Protocol at the CBD COP 10 Meeting." *Leadership in Global Institution Building* (2013): 232-49.
[61] "Parties to the Nagoya Protocol." *Parties to the Nagoya Protocol*. 18 May 2016. https://www.cbd.int/abs/nagoya-protocol/signatories/.
[62] Montreal: Secretariat of the Convention on Biological Diversity, 2011.

informed consent cannot be obtained. The nature of this mechanism is to be defined. Benefits from the mechanism are to be used to support the conservation and sustainable use of biodiversity globally"[63]. *Compliance obligations* "support compliance with the domestic legislation or regulatory requirements of the contracting party providing genetic resources, and contractual obligations reflected in mutually agreed terms, are a significant innovation of the Nagoya Protocol"[64]. User and provider parties to the Nagoya Protocol Parties should ensure that genetic resources are only accessed with prior informed consent, and after the terms have been mutually agreed upon. The Protocol also established an Access and Benefit-Sharing Clearing House to provide a way to share information and provide access via National Focal Points to the Intergovernmental Committee for the Nagoya Protocol on Access and Benefit-Sharing[65]. The Swiss ABS Clearing House is the information node and aims to facilitate the exchange of scientific, technical and legal information on ABS between parties and the general public[66]. Each party should cooperate in cases of alleged violation against the other party's requirements and encourage dispute resolution in mutually agreed terms. Parties should provide an opportunity to seek legal recourse when disputes arise from mutually agreed terms, and take measures to monitor the use of genetic resources during various stages of research, development, innovation, pre-commercialization or commercialization[67]. "The Nagoya Protocol also provides for the development, update

---

[63] Montreal: Secretariat of the Convention on Biological Diversity, 2011.
[64] Montreal: Secretariat of the Convention on Biological Diversity, 2011.
[65] Montreal: Secretariat of the Convention on Biological Diversity, 2011.
[66] "Eidgenössische Ethikkommission Für Die Biotechnologie Im Ausserhumanbereich EKAH." *SIB*. 22 May 2016. http://www.sib.admin.ch/en/nagoya-protocol/.
[67] Montreal: Secretariat of the Convention on Biological Diversity, 2011.

and use of model contractual clauses for mutually agreed terms, as well as codes of conduct, guidelines and best practices and/or standards for different sectors"[68].

Less than a year before the Earth Summit in Rio gave rise to the CBD, an unprecedented deal was made between multinational pharmaceutical giant, Merck, and Costa Rica's National Biodiversity Institute, INBio in October 1991. Merck agreed to pay $1.1 million for bioprospecting rights, in addition to a royalty from any drugs that were commercialized from the venture. Before this landmark deal, pharmaceutical companies commonly practiced biopiracy, collecting samples wherever they wanted and shipping them home to study. With a lot of luck, they might develop one or two of them into a commercialized drug without the providing country even knowing.

Environmentalists lauded the agreement between Merck and INBio, since a share of all payments were designated to protect the habitat from which the samples were taken. While short-term cash crops like soybeans, cattle, and shrimp were destroying rainforests and wetlands around the world, this Fortune 500 company placed a higher value on nature intact. One economic analysis claimed that bioprospecting for drugs would increase the value of some habitats by more than $3,600 an acre. Others warned that estimate was much too high -- the added value was probably less than $25 an acre. Still, when the CBD was created in June 1992, many hoped it would be the beginning of a new era in drug discovery, international development, and habitat preservation[69].

---

[68] Montreal: Secretariat of the Convention on Biological Diversity, 2011.
[69] Conniff, 2012.

However, in 2008, Merck quietly halted its natural products discovery, shifting to synthetic compounds and vaccines. In 2011, the pharmaceutical giant gave away its entire library of natural compounds—100,000 extracts representing 60 percent of all known plant genera. Pfizer, Eli Lilly, Bristol-Myers Squibb, and most other pharmaceutical companies followed suit and also abandoned their natural product discovery platforms[70].

After the CBD was introduced, government agencies, including the U.S. National Park Service, became more serious about negotiating access and benefit-sharing terms with researchers. These negotiations were frequently framed by resentment over past biopiracy, especially in the developing world, and by uncertainty about fair market value for access to genetic resources. Since each country is responsible for creating its own ABS regulations, each new negotiation starts from scratch and often requires long periods of "significant legal and travel expense, all before a single collection is made," according to James Miller, vice president for science at the New York Botanical Garden. The uncertainty surrounding these negotiations "may be more of an impediment to pharmaceutical companies," he suggests, "than the actual commitment to share potential profits"[71]. Miller explains that in the late 1980s, a U.S. National Cancer Institute (NCI) team in the West African nation of Cameroon was working on a compound that appeared to be a cure for AIDS. "This was a plant that was still eating research dollars at an enormous rate, it wasn't making any money, and, man, the Cameroonians were all wanting to buy themselves new Mercedes." The researchers had an access agreement

[70] Conniff, 2012.
[71] Conniff, 2012.

with one government agency but "about five other ministries stood up and said, 'Oh you should have signed that with us.'" The compound proved to be too toxic to be a viable treatment option, but even if it had great potential, Miller said "I'm not sure we would have been able to work on it because the Cameroonians put such tight clamps on it"[72].

Capstone

My Capstone Project explores whether the sustainable collection and research of marine natural products can contribute to marine conservation, using the small island nation of Curaçao as a case study. I traveled to Curaçao for two weeks in April 2016, where I joined the collection team from Sirenas, a small marine natural products discovery startup here in San Diego, and the Sandin lab from SIO.

I worked closely with Tamara Mayer, an MAS MBC alumna now working for Sirenas, and with Dr. Stuart Sandin and Dr. Greg Rouse, at SIO, to develop an innovative benefits-sharing platform that was launched with CARMABI (Caribbean Research and Management of Biodiversity) Institute in Curaçao.

I researched various perspectives on natural products discovery, also known as "bioprospecting," and explored what has caused both positive and negative perceptions. I also examined ways that Sirenas has positively contributed to the perception of bioprospecting for biomedical research. The Sirenas collection model is to make

[72] Conniff, 2012.

sustainable collections, by hand, to mimic natural predation on collection organisms, and sensitive or threatened organisms are always excluded from collections. Because the founders and scientific advisors at Sirenas are leaders in the fields of marine drug discovery, informatics, organic synthetic chemistry, and early stage drug development, a small, one-time collection is all that is required. This expertise also allows Sirenas to overcome common obstacles in the drug discovery and development process to produce high value therapeutics inspired by marine organisms on a shortened timeline, often connecting chemical and biological applications with the click of a button[73]. Previous collaborations between Sirenas and the ocean communities in which they have made collections culminated in the Sirenas "Explorer Network," which has membership benefits designed to promote marine conservation. Membership benefits include annual grants for educational opportunities, community or research projects, and a share of the "Discovery Pool," which is 1% of Sirenas' annual net profits distributed evenly between members.

Part of my project involved expanding the benefits of the Explorer Network to include access to an interactive oceanographic database where members may access, provide, and utilize ocean data. A beta version of the database, which I named "Kalymnos," is currently under construction and I plan to get feedback about it from the scientific community at the International Coral Reef Symposium in June 2016. The beta version will contain real data from the 9 samples we collected at our two photomosaic sites in

[73] "Sirenas | Marine Inspired Therapeutics." *Sirenas*. 27 May 2016. http://sirenasmd.com.

Curaçao. Each Explorer Network member will be given access to Kalymnos and will have an active part in developing new features of the database to suit their research needs. I developed the concept of this database to improve technology transfer between collaborators and Sirenas, and to provide information about the ecology, organisms, and oceanographic data at each collection site, as well as a tracking feature that will allow users to follow the work flow of each collected biomass. One unique feature I was able to include through collaboration with Dr. Sandin are three dimensional photomosaics of each collection site, which provide an interactive view that allows users to see changes at sites over time, observe a sample's association with other marine organisms, and improve the biomass accessioning process. Dr. Sandin's lab took images to process into 3D photomosaics right before samples were collected in Curaçao. Unique identifiers were placed on each sample before the images were taken, which enables us to see what impact, if any, the collections have on the site over time, when the same sites are re-imaged. Another important feature developed with Dr. Rouse is a phylogenetic tree, created from the DNA barcodes of the samples we collected in Curaçao, which will provide information about the evolutionary history of a sample and how closely it's related to other collected samples, or other organisms that are known to contain biologically active compounds.

Sirenas formed several collaborations as a result of this trip, which will contribute positively to conservation efforts in Curaçao. The collaboration with the Sandin lab has leveraged the photomosaic technology for Kalymnos, and the lab's connections to island nations around the world could potentially expand the Explorer Network, and

Sirenas' collection footprint. A collaboration with Chapman Expeditions, which owns and operates a submersible capable of diving to over 300 meters, and has access to a research vessel for longer, offshore expeditions, will support deep sea exploration, while providing Sirenas with a way to reach previously inaccessible samples. Finally, CARMABI is an excellent model for how well collaborations can work and benefit both parties, as well as the local community. CARMABI was instrumental in walking Sirenas through the permitting process and provided extremely useful local knowledge about potentially interesting collection sites and how to access them. Sirenas was asked to create an education module for CARMABI on drugs from the sea, which I am spearheading. On average, 11,000 Curaçaoan students take a field trip to CARMABI every year. The interactive program is aimed at high school students who have completed Biology and Chemistry. The program will take them on a virtual collection dive to one of our collection sites, using the 3D photomosaics, where they can choose an organism to collect and study. Dr. Rouse showed me how to prepare slides of sponge spicules or spongin, tunicate spicules, and cyanobacteria filaments. He also took micrographs of the prepared slides. The students can use the micrographs and slides to identify interesting structures and features of the organism they choose. For each organism, I will provide information about its biology, ecology, evolutionary history, symbiotic relationships with microbes and other organisms, and potential to treat certain diseases based on its extracted compounds, and how they compare with known compounds. At the end of the activity, there will be an essay contest and the prize will be a dive in the submersible. It's a great opportunity to reach young members of this ocean community and get them engaged in learning more about the organisms that live

in their backyard and how important their coral reef ecosystem is, not only to their island, but to the world. My observations and experiences in Curaçao proved that collections for natural products research and scientific research can benefit each other and the ocean community.