CASE STUDY 1:

GRIFFITH UNIVERSITY, QUEENSLAND-ASTRAZENECA: THE NATURAL PRODUCT DISCOVERY UNIT (NPD) PARTNERSHIP[1]

Introduction

In 1993, the State of Queensland's Griffith University and Astra Zeneca established the Natural Product Discovery Unit (NPD) within the Eskitis Institute for Cell and Molecular Therapies at Griffith University. Now in its 14th year, the NPD screens extracts of flora and fauna - including plants from Queensland's rainforest and marine invertebrates (including sponges, octocorals, lace corals and sea squirts) of the Great Barrier Reef - to identify bioactive molecules as potential leads for pharmaceutical discovery and development. More than 45,000 samples have been collected to date. Terrestrial collections are made by the Queensland Herbarium, and have included more than 100 plant species new to science; marine collections are made by the Queensland Museum, with several thousands of new species discovered – for example, of the more than 3,000 sponge species collected, around 70% are new to science (Camp and Quinn, 2007; Hooper, 2007). Collections have also been made under sub-contract in Tasmania, China, India, and Papua New Guinea. NPD has discovered over 700 new bioactive compounds from its approximately 45,000 specimens. In addition to collections of marine and terrestrial organisms that identified new species and populations of endangered species, the NPD provided critical information on biodiversity 'hot spots', and was used not only in drafting the Queensland Biodiversity Act 2004, but in environmental planning and management throughout the region.

Astra Zeneca has invested more than $100 million USD in the collaboration, which has created a state of the art natural product discovery unit. The NPD has served, in effect, as an arm of the Astra Zeneca R&D network, and as such had an exclusive partnership with Astra Zeneca. This exclusive relationship concluded in 2007, although collaboration on specific projects will continue. The end of the exclusive partnership with Astra Zeneca will allow Griffith University to use its facilities, know-how, and staff to build collaborations with other research and commercial groups. No commercial products from the partnership have as yet reached the market, but this is not unusual given the long timelines for drug-discovery and development, particularly for natural products, and the low odds of developing commercial products in this sector. The collaborative agreement and consequent investment in Queensland has resulted in significant technology transfer and plays an important role in the development of the state's Brisbane biotechnology hub. It stands as one of the few 'developed to developed country' natural product discovery models for technology transfer.

Legal frameworks

The Griffith University and Astra Zeneca partnership spanned a critical time in the development of policy guiding access to "genetic resources" and sharing of benefits

[1] This case study is excerpted from a longer study published by UNU-IAS, Queensland Biodiscovery Collaboration: A Case Study of the Griffith University Eskitis Institute and Astra Zeneca Partnership for Natural Product Discovery, by SA Laird, C Monagle, and S Johnston (in press).

from their use, beginning in the same year – 1993 - that the Convention on Biological Diversity entered into force (Box 1). The CBD established that States have sovereign rights over their genetic resources. It also confirmed the authority of States to determine access to genetic resources, and sets out that Parties should facilitate access to genetic resources by instituting legislative, administrative or policy measures that also ensure fair and equitable sharing of benefits arising from the commercial use of these resources.

These international access and benefit-sharing obligations were provided for by the Government of Australia in the Environment Protection and Biodiversity Conservation Act (1999) and later detailed in Part 8A of the Environment Protection and Biodiversity Conservation Regulations. In 2002 and consequent to the adoption of the Bonn Guidelines all Australian states and territories agreed to a nationally consistent approach to access to genetic resources and to apply the Guidelines. In Queensland and the Northern Territory this has resulted in specific legislative measures, the Queensland Biodiscovery Act 2004 and the Northern Territory Biological Resources Act 2006 (DEWHA, 2007). In other states and territories no dedicated legislation yet exists, though in some jurisdictions there are limited access and benefit sharing measures implemented pursuant to more general legislative and policy instruments. All states remain committed to the implementation of the Bonn Guidelines, with most having already initiated legislative development processes. For example, in Tasmania a comprehensive access and benefit sharing approach is currently being developed in a process led by the Tasmanian Department of Primary Industries (K.Kent, pers.comm.2007). Western Australia has also indicated in its Biotechnology Industry Development Strategy that dedicated legislation will be developed in that jurisdiction by the end of 2008 (http://www.doir.wa.gov.au/documents/businessandindustry/WABiotechnologyDevelopmentStrategy.pdf, page 22).

The Partners

Astra Zeneca

Based in the UK, Astra Zeneca is one of the largest pharmaceutical companies in the world, ranked number six in 2006 with global sales of $26.7 billion USD (IMS Health, 2007). Astra Zeneca employs over 12,000 people in R&D, around 4500 of which are part of Global Discovery. There are 6 major Discovery and Development facilities in the UK, US and Sweden, and 4 Discovery sites in the US, Canada and France. In Japan, the company runs a facility for clinical development. R&D investment in 2006 was $3.9 billion USD, and 21 candidate drugs were added to the early development portfolio in 2006 (Astra Zeneca annual report, 2006; Astra Zeneca, 2007). More than 1,700 external R&D collaborations and agreements have been formed to complement in-house capabilities, reflecting an industry-wide trend towards such external partnerships in the industry. In 2006 alone 325 new collaborations were formed (Astra Zeneca, 2007). In Australia, Astra Zeneca employs more than 1,000 people as part of export, sales and marketing to the region, through research collaborations at major teaching hospitals and universities, and as part of its collaboration with Griffith University (Denerley, 2006). The major research areas for Astra Zeneca are respiratory (asthma, COPD), inflammation (osteo-arthritis), CNS (Alzheimer's, depression, anxiety, psychosis), pain (neuropathic, and chronic nociceptive), infection (antibacterials), cancer (anti-invasives, anti-angiogenics), and cardiovascular (thrombosis, metabolism, arrhythmia) (Astra Zeneca, 2007).

Eskitis Institute for Cell and Molecular Therapies, Griffith University

The Eskitis Institute is a research centre of Griffith University, founded in 1975 and located in Brisbane, the capital of Queensland (Griffith University, 2007). The Eskitis Institute undertakes research on the molecular and cellular mechanisms of human diseases, specifically cancer, infection and immunity, neglected diseases, neurological diseases, and stem cell biology. Specific research programs include bioactive molecule synthesis, cancer biology, chemical biology, clinical neurosciences, drug discovery and design, molecular libraries, stem cells, structural chemistry and systems biology (Eskitis, 2007). The Eskitis Institute incorporates five key facilities – the Queensland Compound Library, the National Centre for Adult Stem Cell Research, Cancer Therapeutics CRC, Nature Bank and Eskitis Molecular Screening (Eskitis Institute, 2007).

The Queensland Herbarium

The Queensland Herbarium was established in 1855, and is located on the grounds of the Queensland Botanic Garden in Brisbane. Administratively, the Herbarium falls within the Queensland Environment Protection Authority, an authority of the Queensland Government. The Herbarium undertakes a range of activities including maintaining historical specimens and reference collections, surveys and mapping of Queensland vegetation, and research into plant diversity (Environment Protection Authority Queensland, 2007), The Herbarium in 2003 employed 68 staff, including 33 botanists (Queensland Herbarium, 2003).

The Queensland Museum

The Queensland Museum, established in 1862, is a Statutory Authority of the Queensland Government, situated in Brisbane with regional services delivered through the Museum Resource Centre Network in six regional sites across the State of Queensland (Queensland Museum, 2007). The Museum provides museological services in science, natural environment and cultural heritage, and employs over 215 people and many volunteers (P.Riley, pers.comm 2007). The museum's organisational structure reflects its focus on the themes of knowledge generation, knowledge management and knowledge dissemination. Falling within the Knowledge Generation theme are the substantive divisions of Biodiversity and Geosciences, Cultures and Histories, and Science and Technology in Society (Queensland Museum, 2006). Within the knowledge management theme falls the museum collections maintenance and accession activities. In recent years, these accessions to Museum collections have been from a range of activities including but not limited to the AZ/Griffith collaboration. Other collection programs include a monumental seabed mapping of invertebrate marine life and fish throughout the Great Barrier Reef inter-reed region (GBR Seabed Marine Biodiversity Project), and the Torres Strait Seabed Mapping Project, undertaken by a consortium of agencies including the Museum, Australian Institute of Marine Sciences (AIMS), Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO), Marine & Atmospheric Research and Queensland Department of Primary Industries and Fisheries (DPI&F), funded by Commonwealth agencies and industry. The Museum, like most public institutions in Australia, is funded through a combination of government funding, research grants, consultancies, corporate sponsorships for particular activities, and business endeavours, such as retail shops (Queensland Museum, 2006).

The Natural Product Discovery Partnership

The NPD partnership was launched in 1993, renewed in 1998 and again in 2002, and is due to conclude in 2007.As part of the NPD partnership, Astra Zeneca provides funding to Griffith University to participate in their biodiscovery and commercialization efforts. Griffith University in turn partners with domestic and overseas collecting institutions to undertake biota collections (see below), make extracts of samples, and then run these samples through high throughput screens (HTS). Active compounds are then identified and isolated at Griffith University via bioassay guided fractionation, and structures are elucidated (Quinn et al, 2002; Camp and Quinn, 2007; Denerley, 2006; Chart 1.). The role of Griffith University evolved during the course of the partnership – originally, the HTS and lead discovery were to be done at Griffith and the leads sent to collaborators at Astra Zeneca, but over the years Griffith also assumed lead-optimization and medicinal chemistry components because they had the expertise in-house, and the interest in pursuing this research. (Quinn, pers. comm.. 2007).

The high level of involvement of Griffith University researchers in the discovery process is unusual for ABS partnerships, most of which involve collections in high biodiversity regions and higher level discovery within the company. However, NPD was viewed within Astra Zeneca as an extension of the R&D programme, researchers within NPD were in almost daily contact with those at Astra Zeneca, and Griffith University provided expertise on HTS and natural products to Astra Zeneca during the course of the partnership. Griffith University staff sat on the Global Chemistry Forum of Astra Zeneca, headed up the Natural Product Competence Centre, and worked closely with the other research programmes within the company. Integration of Griffith University's work into the company to this extent meant that NPD was not able to work with other parties, whether academic, government or commercial, and Astra Zeneca had exclusive rights to the samples collected during the lifetime of the agreement. Griffith University staff were also required to seek permission prior to publication of any articles reporting on the research, the same as staff of Astra Zeneca. During the lifetime of the project, Griffith University staff published many articles on the NPD research. This high level of collaboration with Astra Zeneca, and the attached conditions, however, also account for the unusually extensive benefits that accrued to the institution and the country (see discussion below). Today, with the exclusive partnership concluding, Griffith University can leverage the fruits of the collaboration – in expertise, capacity, infrastructure, and collections – to strike new partnerships with government research institutions, industry, and academic researchers, and the samples collected are the property of Griffith University and are housed in the Queensland Compound Library.

The activities of NPD are subject to the laws of Queensland and the Commonwealth of Australia. When accessing materials outside Queensland (whether in other states and territories of Australia or internationally) the University is also subject to any applicable laws in the jurisdiction in which collections take place, as well as the Convention on Biological Diversity, which Australia has ratified. To meet its access and benefit sharing obligations under the Queensland Biodiscovery Act 2004, the Astra-Zeneca and Griffith University collaboration has an approved Biodiscovery Plan lodged with the Queensland Department of Tourism, Regional Development and Industry. When collecting on Commonwealth Lands or waters collection is subject to obtaining the appropriate permits under Part 8A of the Environment Protection and Biodiversity Conservation Regulations 2000. When research is for commercial purposes, as it is in the case of the NPD process, a benefit sharing agreement with the access provider must also be lodged with the Department of the Environment, Water, Heritage and the Arts. Permits for access to genetic resources from

Commonwealth controlled lands and waters only came into effect for samples collected after December 2005, however.

Collection of samples

The first step in the discovery process is the collection of samples. Griffith University subcontracted collections to the Queensland Herbarium for terrestrial samples, and The Queensland Museum for marine samples. Most collections were made in Queensland, but others came from Tasmania, China, India and Papua New Guinea. In 2007, the NPD Biota Library, containing collections from the lifetime of the NPD partnership, has in excess of 45,000 biota samples, including vascular plants, algae and macro fungi from Queensland (>20,000), PNG (5,743), and China (6,545). Marine invertebrate samples number more than 9,500 biota from tropical and temperate Australian waters. The Library also includes more than 2,000 soil and aquatic microbial extracts from India and Australia (Camp and Quinn, 2007). The plant collection represents more than 9% of the world's species diversity of higher plants, with representation from 73% of the world's plant families. The marine collection contains more than 10% of global diversity of sponges and ascidians, and 5% of soft corals and gorgonians (Griffith University, 2007; See Table 1). The 2004 Queensland Biodiscovery Act requires samples of all specimens collected to be lodged with the Queensland Museum or Herbarium, something which has been done since the beginning of the partnership in 1993.

The Queensland Museum

The sea is considered by NPD a greater potential source of genetic diversity than the land, having a much larger variety of life forms (phyla). Of the 28 marine phyla less than a third of the total number of species living in Australian waters – which are in turn estimated to comprise about 30% of the world's marine fauna – were known to science at the start of the NPD (Quinn et al, 2002). Over the course of the NPD, the Queensland Museum has collected more than 12,000 specimens of around 5,000 species of marine invertebrates and algae. 8,000 specimens have been extracted and subjected to HTS. Target phyla were predominantly sessile invertebrates - animals fixed to the seabed - including soft corals and gorgonians (cnidarians), lace corals (bryzoans), sea squirts (ascidians) and sponges (Porifera). Of particular interest to NPD are sponges, which show the greatest bioactivity at low "tissue" concentration, highest diversity, and span a greater range of marine habitats (Hooper, 2007). Sponges have extraordinary chemical diversity compared to other phyla, and along with ascidians have yielded the majority of novel compounds and new bioactive natural products. Sponges show such proportionally high chemical bioactivity compared to other marine phyla because: toxins are produced to repel predators, 'free-loaders', and provide a competitive advantage in crowded encrusting communities; many sponges excavate the substratum, breaking down and recycling calcium carbonate back to the reef system; they have a chemical mechanism to facilitate mutualistic associations in the reef; and they form symbiotic relationships with microorganisms (Hooper, 2007).

Examples of sponge species from the Great Barrier Reef demonstrating significant bioactivity include: *Stylissa flabellata*, with a new compound showing significant activity as an anti-inflammatory agent; *Aplysinella rhax*, showing bioactivity against cardiovascular and metabolic assays; *Haliclona ('Adocia') aculeata*, with several new compound analogues showing potential efficacy against osteoporosis; and *Citronia*

astra, a new genus and species of sponge, showing significant bioactivity against anti-thrombosis screens (Hooper, 2007)

For both the Queensland Museum and the Queensland Herbarium, agreements were made with Griffith University that guided the collections and provided up front payments to the institutions to complete the work, including hiring professional staff to manage the project, undertake collections and identify specimens, and to purchase equipment and other materials. A percentage of the royalty received by Griffith University from any commercial product developed was also negotiated, to be shared with the State of Queensland, because both institutions are part of the government.

The Queensland Herbarium

The Queensland Herbarium began a scientific partnership with Griffith University in 1990, and in 1992 entered into a contractual agreement with Griffith to supply plant samples for the Astra Zeneca biodiscovery program. During the first 10 years of the agreement, The Herbarium supplied plant samples for the growing collection, and in the last five years focused only on re-collection of species of interest. The collection of plant samples and herbarium vouchers were initially to include all species occurring in Queensland, but as the collaboration progressed families without intebioactivity were eliminated (eg Poaceae, Cyperaceae and later Eucalypts). Collections for the NPD were undertaken only in Queensland, and by staff of the Herbarium. Collections were comprised of plant material of either flowers, fruits, leaves, stems, and sometimes roots, up to a maximum of 100g dry weight for each taxon (species, subspecies variety), plus a herbarium voucher specimen. During the course of the collections, more than 16,000 plant specimens were added to the Herbarium collection, and at least 100 species new to science were discovered (G. Guymer, pers. comm., 2007).

Unlike the Museum, which provides taxonomic and location details with samples, the Herbarium initially supplied plant samples without these details, and instead provided a bar code to trace specimens within the Herbarium collection. This was done in part to require a return to the Herbarium for re-collection, and also to protect the identity and location of rare and endangered species. In 2001, after many years of collaboration and building of trust between the partners, the Herbarium provided Griffith University with family and genus level taxonomic information on all species in the collection. This assists with literature and database searches on promising leads, and clustering plants for further analysis and de-replication. Griffith University can also obtain species-level detail upon request. Locations for collections remain sensitive, and are not necessary for the NPD on a regular basis in any case, although these too are provided if there is a specific request.

TABLE 1: THE ESKITIS BIOTA COLLECTION, 1993-2007

Regions/countries of collection and type of collection	Number of samples	Number of species (or Operational Taxonomic Units, OTUs)	Number of families	Collecting institution
Queensland	>20,000	>8,000	276	Queensland

vascular plants, algae and macro fungi				Herbarium
Queensland marine invertebrates	>8,000	>3,500		Queensland Museum
Tasmanian marine invertebrates	>1,200	>700		Queensland Museum
China plants (ZiYuan county, Guangxi Province)	6,545	>2,000	183	ZiYuan Medical Company
Papua New Guinea plants	5,743	>1,500	163	Biodiversity Limited

Source: Griffith University, 2007

China

Terrestrial collections in China are made in Zi Yuan county, of Guangxi Province in the southwest of the country. It is a mountainous region with interesting biological niches, and one of the five most biologically-diverse areas of China. Collections are undertaken by the Zi Yuan Medicine Company, which is a major supplier of Traditional Chinese Medicine (TCM). Collections include plants used in TCM, as well as those of taxonomic interest (ie from families showing interesting biological activity). However, traditional knowledge about species use within TCM is not supplied with samples – their use in TCM is used instead as a general screen for activity of any kind (A Carroll, pers.comm., 2007). Voucher specimens for the collection are retained within the company. A taxonomist from the Department of Biology at Guangxi University coordinates collection programs for the Zi Yuan Medicine Company, of which he is a director. Zi Yuan Medicine Company was a state-owned company in the early years of the partnership, which began in 1997, but has since become a privately run company.

Collections of new samples in China concluded in 2003, although re-collection of larger volumes of species already in the collection continues. These recollected samples are now provided in extract form, with Zi Yuan Medicine Company subcontracting extraction to an industrial facility that specializes in TCM extracts (A. Carroll, pers.comm., 2007). It proved difficult to get large quantities of "unknown" bulk plant material into Australia, due to strict quarantine requirements given government concerns about pests and diseases and invasive species, and China has high levels of capacity in extraction that are utilized by botanical medicine and other companies around the world.

The original agreement between Griffith University and Zi Yuan Medical Company was signed in China in 1997, after a few years of discussions between partners, and with a range of government institutions. The Zi Yuan Medicine Company facilitated the dialogue with government, hiring a lawyer from the region to negotiate with the

central government in Beijing for the first agreement, and subsequently, for approval of the second agreement, with the Zi Yuan County Peoples Government of the Zi Yuan Autonomous Region, which granted the collecting permits, and signed off on the collaboration between Zi Yuan Medicine Company and Griffith University. The Trade, Development, and Food and Drug bureaus within the County government reviewed and approved the permits. For the second agreement, the central government said that only county government approval was necessary, and that they, rather than the provincial or central governments, should review and grant such permits. China did not have a central body dealing with ABS, or a national ABS focal point, through which the agreement passed during the negotiation of these agreements (A. Carroll, pers. comm., 2007) (see Box 5).

The agreement between Griffith University and Zi Yuan Medical Company is similar in content to those signed with the Herbarium and Museum, guiding sample quality (eg specifying moisture content, mesh size for grinding), quantity of samples supplied per year, information supplied with samples (eg identified to species level, GPS location of samples), and detailing benefits to be received by the company. The latter include payments for the agreed-upon work plan and samples, provision of a vehicle and the equipment necessary to do this, and royalties (of the same percentage received by the Herbarium and Museum) should a commercial product be developed (A. Carroll, pers.comm., 2007).

Papua New Guinea

Terrestrial collections in Papua New Guinea were undertaken by Biodiversity Limited, a small company run by a natural products researcher who is also based at the Department of Chemistry of the University of Papua New Guinea in Port Moresby. Collections began in 1997. Voucher specimens were lodged with the Papua New Guinea National Herbarium, Lae. As in the case with China, NPD staff felt they had large and representative enough collections for the library and the Astra Zeneca partnership, and so concluded collections in 2003. Collections were made throughout the country, and of the more than 1500 species collected, many were new or previously unknown to science. The collections did not include traditional knowledge, and were random or taxonomically-driven (A. Carroll, pers. comm.., 2007).

Negotiation of an agreement with Papua New Guinea took a few years to conclude. This process included discussions between Biodiversity Ltd and Griffith University, and subsequent approval for collections from the PNG Department of Environment. At the time, the government of PNG did not have an ABS measure in place, nor a national focal point to deal with these issues, so permission was sought through the traditional agency within government for plant collections, the Department of Environment. The elements of the agreement are the same as those described above for China, although in this case royalties go to the government of PNG, as well as the company.

Tasmania

Marine collections in Tasmania were undertaken by Aquenal Pty Ltd., a marine environmental consultancy company. The focus of the collection was temperate marine invertebrates and algae. Around 1600 samples were provided to NPD through this partnership. Aquenal has expertise in collecting and cataloguing samples, and do some in-house taxonomic identifications, particularly for bryozoan, ascidian and

algae, but they also partner with the Tasmania Museum on identifications. The Queensland Museum does all the sponge identifications and is paid separately for this by NPD. Voucher specimens are held at Aquenal, the Tasmanian Museum, and the Queensland Museum. Aquenal use the collection data for their surveying purposes and to assist with recommendations for coastal management in the region (A. Carroll, pers.comm., 2007).

Two, three year agreements have been signed between Aquenal and Griffith University since 2002. Tasmania does not have biodiscovery legislation, so government approval for collections was obtained by Aquenal through collection permits. The agreement between NPD and Aquenal is similar in content to those used for the Queensland Museum and the Queensland Herbarium, in terms of samples received, payments, and royalty sharing.

India

Between 1996 – 2000 a collection of approximately 1800 strains of soil fungi were provided by Biocon Ltd, a private company based in Banglalore India. The agreement between NPD and Biocon is similar in content to those used for the other international collections (A.Carroll, pers.comm, 2007).

The Role of Traditional Knowledge

Traditional knowledge was not collected as part of the Astra Zeneca- Griffith University partnership. This is primarily because for the disease categories of interest to Astra Zeneca – in particular those afflicting older and more affluent populations – traditional knowledge is not considered an important lead for drug discovery efforts (Ron Quinn, pers. comm.., 2007). In some cases, species that show promise in the NPD discovery process have also been used in traditional medicine, but traditional knowledge, given the broad, systematic screening process of the NPD, did not lead researchers to these species. Indirectly, traditional knowledge informed collections in China, in that species, genera, and families used in TCM were requested as part of collections made by the ZiYuan Medical Company, but this was as a way of selecting broadly for activity, and information on how species are used traditionally was not supplied with the samples.

Concerns associated with traditional knowledge and indigenous peoples' rights to control the use of their knowledge and resources have also been raised about collections, especially those made on Aboriginal lands, and the need to develop side agreements with the Aboriginal people whose land and resources are accessed (eg Tooth, 2001). It is clearly critical that the role of indigenous stewardship and ownership over resources found on their lands is recognized and respected, even if traditional knowledge is not used in the research process (eg see Article 8j of the Convention on Biological Diversity). However, the Queensland Herbarium did not collect on Aboriginal lands as part of this partnership, and most collections were made in national parks like the Daintree Forest or otherwise on crown lands (P.Forster, pers.comm 2007; G.Guymer, pers.comm., 2007)

Benefits from the Partnership

Astra Zeneca invested more than $100 million USD over the 14 year lifetime of the NPD, and Australian institutions contributed expertise, infrastructure, and financial

incentives. Queensland, and to a lesser extent China, India, PNG, and Tasmania, provided access to their remarkable biological diversity. Of the Astra Zeneca investment, $45 million USD went to build the research unit at Griffith University, annual costs of running the collaboration came to roughly $9 million/year USD, and $9 million USD went towards collection of samples by partner institutions. Benefits accrued to the range of collaborators in the NPD – Astra Zeneca, Griffith University, The Queensland Herbarium, The Queensland Museum, and companies and institutions in China, India, Papua New Guinea, and Tasmania. At the same time, broader benefits were achieved or may still emerge for the State of Queensland, the Australian research community, the Australian public, and the international community. Benefits that accrue to a cross-section of stakeholders include those that helped build scientific and technological capacity within the State and country, and contributed to the management and conservation of biodiversity.

Benefits included monetary benefits like fees for samples (or to cover the costs of an agreed-upon workplan) and royalties. Non-monetary benefits included the provision of vehicles, equipment, technology, training, building of a state-of-the-art natural product discovery unit, and increased knowledge of biodiversity. Royalties may or may not materialize, since they are dependent upon a drug reaching the market. However, immediate monetary benefits in the form of funds to support the work of collaborators - eg collecting samples, undertaking extractions, HTS, and optimizing leads - and non-monetary benefits like facilities, equipment, training, and capacity-building were shared throughout the partnership. Following is a discussion of the benefits that accrued to various partners and groups during the course of the partnership.

The Eskitis Institute, Griffith University

The Eskitis Institute received the bulk of monetary and non-monetary benefits over the course of the NPD. Monetary benefits include royalties, at a rate standard to the industry but not publicly available (as is standard practice in bioprospecting agreements with pharmaceutical companies). Financial support for agreed workplans, including hiring staff, purchase of equipment and support of infrastructure were also significant, with annual payments to Griffith University averaging $9 million/year.

The most significant benefit for Griffith University is the combination of enhanced expertise, biota collections and compound libraries, scientific and technological capacity and know-how, and infrastructure, in the form of a new state-of-the art facility, acquired during the course of the partnership which – together – have created a leading natural product discovery unit. Now that the exclusive partnership with Astra Zeneca has ceased, Griffith University can leverage these assets into new partnerships with academia, government, and most significantly with other companies.

The NPD was extremely unusual for bioprospecting partnerships, which generally involve little more than the collection of samples sent to companies for screening. The high level of involvement of Griffith University staff in the R&D process, and their close and regular contact with researchers at Astra Zeneca, resulted in enormous benefits for science and technology in the region. It allowed staff to develop skills in working with industry and to their requirements, as well as in the science and technology of HTS, robotics, separation of molecules, and medicinal chemistry, and to become a leader in those areas within the country. Griffith

University is now able to convert a natural product into a normal medicinal chemistry product, which removes much of the complexity and cost traditionally associated with natural products. At a time when in-house natural product discovery programs in the large pharmaceutical companies is in decline (Koehn and Carter, 2005), and natural product discovery is increasingly done by smaller companies, and academic and government research institutes, which then license compounds to large pharmaceutical companies for development, Griffith University is well-situated to play an important role in this field in the coming years.

Specific benefits to the Eskitis Institute that combined to create this state-of-the-art natural product discovery unit over the last 14 years, include:

Building Expertise

Roughly 50 graduate and post graduate staff received training and worked for the NPD at Griffith University over the course of 14 years; many of these have gone on to other institutions and companies (eg MerLion in Singapore, a leader in natural product discovery). Given the shortage of training opportunities in natural product research, this building of expertise is a significant benefit not only for the University, but for the country and the field of natural product research.

Students were not actively involved in the NPD, given their need to publish and constraints placed on publications resulting from the research partnership, but they will be involved in new partnerships growing from the NPD, such as that on neglected diseases (see below). A stream of students were, however, hired over the years as research assistants by the NPD, and after their work with advanced technologies and equipment went on to do PhDs.

Biota collections and compound libraries

Griffith University retains ownership over the samples collected as part of the NPD. The result today is the NatureBank, the Queensland Compound Library, and the Lead-Like Peaks Library. These collections include:

- 45,000 samples reside in the Eskitis Institute natural product collection from biologically diverse terrestrial and marine sites in Queensland, Tasmania, China, India, and Papua New Guinea. These represent "unparalleled taxonomic breadth containing almost 60% of global plant diversity at the family level, including all major plant families containing more than one genus… and 9,5000 biota of marine invertebrates, including 10% of global diversity of the world's sponges and ascidians and 5% of global diversity of soft corals and gorgonians" (Eskitis Institute, 2007).

- 300,000 pre-fractionated natural products are in the Lead-Like Peaks Library, which is part of the wider Queensland Compound Library;

- Advanced systems for chemical isolation and structure identification led to the discovery of more than 1500 bioactive compounds.

Scientific and technological capacity and know-how

The NPD exposed Australian scientists to natural product discovery in an industry setting, and access to the latest scientific and technological advances. HTS was first performed at Griffith University in the early 1990s, some ten years before any other group in the country. The NPD, by incorporating the most advanced and 'cutting

edge' equipment and technologies, also allowed Australian science to stay abreast of new developments in imaging and separation technologies (Camp and Quinn, 2007).

Intellectual Property Rights

Griffith University retains ownership over the biota samples and compound libraries that resulted from the NPD. Intellectual property rights to commercial products developed from the partnership remain with Astra Zeneca..

Publications

Publications are a measure by which individual scientists, scientific institutions and universities are judged. Past publication records are often directly linked to recruitment criteria, and to institutional funding allocations. The ability to publish is also a feature that helps to attract the best students and staff to a project, and ensures research results reach a wider audience with the associated benefits that the free flow of information generate. Despite restrictions placed on their ability to publish scientific articles from the NPD research, staff of Eskitis Institute published many articles and papers over the course of the partnership,[2].

Griffith University

Beyond the Eskitis Institute, Griffith University benefited from the partnership with Astra Zeneca through the contribution of the NPD to its overall funding base and enhanced research reputation, and as a result its being significantly more competitive in university league tables. The University also benefits from the resulting facility and assets of the Eskitis Institute, which are now available to other research scientists within the University, and other Australian and international research institutions, as well as new public/private partnerships.

The Collecting Institutions

The NPD benefit-sharing package for collecting institutions is standard across institutions and includes up front fees per sample that cover costs of collection including staff, equipment (eg compound microscopes, computers, field equipment), and vehicles, as well as identification of species, and royalties should a commercial product be developed. Roughly $9 million was spent on collections over the course of the 14 years of the NPD. Royalties accrue to the State of Queensland for collections made by the Queensland Herbarium and Queensland Museum, to the government for collections in Papua New Guinea, and to companies collecting under contract in China, India, and Tasmania. The royalty received by collecting agencies is a percentage of that received by Griffith University, and is set at 15% .

[2] A selection of these are listed on the Eskitis web page of the director Ron Quinn at http://www.griffith.edu.au/professional-page/professor-ron-quinn/publications, for example, A. R. Carroll et al., Dysinosin a: A novel inhibitor of factor Vila and thrombin from a new genus and species of Australian sponge of the family dysideidae, Journal Of The American Chemical Society 124, 13340 (Nov 13, 2002); Davis, R. A.; Carroll, A. R.; Watters, D.; Quinn, R. J. The absolute stereochemistry and cytotoxicity of the ascidian-derived metabolite, longithorone J. *Natural Product Research* 2006, 20, 1277-1282

Staff and training

The Queensland Herbarium was able to employ a botanist and technical officer for the duration of the program, which required an experienced botanist who knew what to collect, how to collect, and with good field knowledge and good knowledge of the flora (G. Guymer, pers comm., 2007). Graduate students associated with the Queensland Herbarium used collections to discover new compounds, and these were published in the scientific literature with Herbarium staff as joint authors (G. Guymer, pers comm., 2007).

The Queensland Museum supported 4 full-time parataxonomic positions at the Museum each year, some individuals remaining for many years, and receiving more in-depth training in taxonomy, curation, and marine collection skills. A total of 20 individuals received training over the 14 years of the NPD, and 5 of these have gone on to become taxonomists, and a few to also study molecular biology and chemistry, one of whom now heads-up the Sponge Barcoding Project (Hooper, 2007; J Hooper, pers comm., 2007; www.spongebarcoding.org). Taxonomic research on newly acquired collections was also supported through postdoctoral research fellowships partially funded by the NPD collaboration and partially by other traditional sources of funding (Hooper, 2007).

The value of support for staff, and training in collection, curation and taxonomy cannot be overstated. Although the government promotes academic and commercial partnerships based on the country's unique flora and fauna, and there is increasing demand for taxonomic skills to assist with environmental planning, management and conservation, funds for taxonomy remain limited. The Australian Marine Sciences Association reports a steady decline in the number of taxonomists over the last decades, with the latest count showing 23 marine taxonomists in Australia's museums and research agencies. Nine have retired in the past five years and have not been replaced (Leung, 2007). State governments are the main employers of taxonomists through their herbaria and museums, but are unable to maintain the taxonomic work force in the face of competing claims on State budgets. The Federation of Australian Scientific and Technological Sciences has initiated a research project looking into the taxonomy skills shortage in marine, plant, insect and parasite science (Leung, 2007).

"There are potentially millions of species that remain undocumented and yet fewer and fewer people are employed in this area, or have the necessary taxonomic expertise. Commercial partnerships are currently a major source of employment and support for the development of taxonomic capabilities in research institutions in this country, especially long term collaborations such as that with NPD for which a few key staff were employed for over a decade …" said John Hooper of the Queensland Museum, "Some people, particularly those with political and managerial agendas, feel naming things is futile without a direct economic outcome – this is another reason why biodiscovery has been good in Australia. Not only does the partnership have immediate non-monetary benefits (data for management decisions, conservation planning, and so on), and potential downstream monetary outcomes (royalties), but it also has the knock-on effect of making government more interested in supporting these kinds of jobs." (J Hooper, pers comm., 2007).

Biodiversity information

The most common and significant benefit cited by collecting institution staff from the NPD is the support for collections that would otherwise not be possible within

institutions dependent upon limited government support, and the biodiversity information with important scientific and conservation applications that resulted. Marine invertebrate biodiversity, in particular, is poorly known, expensive to collect, and the expertise to document it is grossly inadequate (Hooper, 2007). Taxonomic identification is expensive and time-consuming, and most research institutions have backlogs which cannot be covered with government support; commercial partnerships are seen as an important way to get this work, central to the Herbarium and Museum's mission, done. "Without knowledge about what species exist, their distribution and their interaction, no informed and sensible environmental management decisions can be taken. Without a comprehensive taxonomy governments cannot safely allocate resources and set priorities for conservation and natural resources utilisation" (Geoff Burton, pers. comm., 2007)

The Queensland Herbarium "always viewed the increase in the knowledge about the State's flora as its [the NPD's] major benefit and the funding from the program delivered this outcome" (G. Guymer, pers comm., 2007). The NPD supported collections and research by the Herbarium that resulted in the discovery of more than 100 species new to science, many of conservation concern, together with hundreds of new records for the distribution of species (eg the extension of range), and collections in parts of Queensland that had never before been systematically surveyed (G. Guymer, pers. comm., 2007).

Expansion of collecting institution collections are a significant benefit of the NPD. More than 16,000 plant specimens were added to the herbarium collection (G. Guymer, pes comm., 2007), and the Queensland Museum incorporated 12,000 specimens of roughly 5,000 species of marine invertebrates and algae into its permanent collection (Hooper, 2007).

These marine specimens yielded more than 200 bioactive compounds, most with novel bioactivity, and 23 new structural classes discovered. Sponges (Porifera), in particular, were most productive, both in terms of new chemical compounds and species diversity (Hooper, 2007). In 1994, there were 1385 species of sponges described for the entire Australian fauna (including its external territories), with less than half of these known to live in tropical waters; this knowledge took 200 years to acquire (Quinn et al, 2002). In contrast, over the past 15 years, 3,000 sponge species were discovered, about 70% new to science, providing a three-fold revision of previous estimates of sponge diversity in Australia and worldwide (5,000 and 15,000 respectively). (Hooper, 2007). The conservation benefits linked to the biodiversity information yielded by the NPD is further discussed below.

Benefits for Conservation of Biodiversity

Although "access and benefit-sharing" (ABS) arrangements are linked to the conservation of biodiversity within the Convention on Biological Diversity and national ABS measures, in practice many ABS partnerships manifest few concrete benefits for conservation . When samples are provided but specimens are not lodged with national research institutions engaged in this process, and these institutions are not supported through collections, the benefits for conservation are limited or none. In a very few cases, bioprospecting partnerships include payments to protected areas and support local conservation activities, such as the case of InBio and Merck in Costa Rica. But even in that case, and overall, the most significant benefits for biodiversity conservation resulting from this type of research have generally been found in the

biodiversity information they provide that is critical for setting conservation priorities, conservation planning, and for management.

The NPD is an extraordinary example of this type of benefit for conservation, providing support for collections of marine and terrestrial organisms, particularly in Queensland, that identified new species and populations of endangered species, provided critical information on biodiversity 'hot spots', and was used not only in drafting the Queensland Biodiversity Act 2004, but in environmental planning and management throughout the region.

In addition to collecting and identifying 100 species new to science, and new records on the distribution of species as described above, the Queensland Herbarium also found new populations of threatened species in remote areas, providing genetic resources to propagate the species, and documented weed encroachment in native forests that has helped inform forest management (Camp and Quinn, 2007). Increased knowledge of species distribution has also been used in environmental planning for Queensland.

The Queensland Museum made astounding taxonomic discoveries as a result of their work for the NPD, and has also made some major advances in the knowledge of spatial distribution of marine organisms across northern Australia, which in turn has contributed to marine conservation and planning processes. This has included the delineation of Marine Protected Areas (MPAs) based on faunal characteristics. It also provided data to undertake biodiversity "hot spot" analysis across northern Australia, identifying areas of comparative species richness, high endemism, and phylogenetic relationships amongst these regional faunas (Hooper, 2007). The material collected from the NPD and other projects also allowed the study of population genetics of some species, and an analysis of "beta diversity" trends (spatial patterns where there are major species turnover points across an environmental gradient) at medium and large spatial scales. As a result, it was possible to delineate a number of biogeographic transition zones across northern Australia and compare these data to traditional marine biogeographic models for Australia. These sorts of data were useful to national bioregional planning processes in both State and Commonwealth waters such as the Great Barrier Reef Marine Park Authority and the Representative Areas Program (Hooper, 2007).

Astra Zeneca

Astra Zeneca benefited from the NPD partnership through access to the remarkable marine and terrestrial biological diversity of Queensland, and to a lesser extent Tasmania, China, India and Papua New Guinea. They also benefited from collaboration with an increasingly sophisticated natural products discovery unit that worked closely with Astra Zeneca researchers, from the existing high levels of scientific expertise within Griffith University and the country, and from working in a country with a robust legal system, and an increasingly clear ABS regulatory environment that grants them legal certainty over the material they study. The Commonwealth and Queensland State governments also provided financial incentives to Astra Zeneca in the form of pricing incentives through the Commonwealth's Factor F scheme, and provision of the research building and other support through the Government of Queensland.

Queensland, Australia and the International Community

The State of Queensland and Australia at large benefited from the investment of $100 million by Astra Zeneca in the NPD, the employment and building of expertise it provided, as well as increased scientific and technological capacity, including the first natural product HTS facility in Australia, and the Queensland Compound Library and Molecular Screening Collaboration that resulted in part from the NPD. Opportunities for private/public partnerships and investment in Australia are also enhanced, as is the potential to employ Australian scientists and so alleviate the scientific brain drain which has afflicted the country. Australia will also benefit from innovative business partnerships that build upon the unique biological and cultural diversity of the country.

The range of benefits for biodiversity conservation described above serve the public in Queensland, Australia, and worldwide, as do the contributions to scientific knowledge and the potential development of new medicines. For example, the Eskitis Institute is working with a range of international organisations in the search for new therapies to combat neglected diseases. These include the Seattle Biomedical Research Institute (SBR) on the biology of disease-causing parasites, the Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi). These groups are supporting HTS campaigns at Eskitis Institute to identify natural products that show promise against malaria and sleeping sickness (Quinn, pers comm, 2007; Eskitis 2007).

Conclusions

The NPD provides a valuable opportunity to examine the ways bioprospecting partnerships can yield benefits for provider countries, and for biodiversity conservation, over time. Running for 14 years – much longer than most other such ABS partnerships – it offers a window onto the extent of scientific and technological capacity that can be built, the enormous wealth of biodiversity information that might be collected and analysed, and the ways that the many benefits regularly articulated in ABS policy documents can come together over time to add up to more than the sum of the parts.

Monetary and non-monetary benefits in this case fall within the standard package for "best practice", but it is in the accumulated and multi-faceted nature of the benefits that the real gain for the State and country are to be found. These include the collections and compound libraries, the advanced natural product discovery unit, and the enormous gains in taxonomic and ecological understanding that resulted from the collections. This case demonstrates that these benefits can be of equal, or greater, importance to potential monetary benefits from royalties should a product be commercialized.

The pre-conditions that attracted Astra Zeneca are also the very things that make this a difficult model to reproduce in many other countries – eg existing high levels of scientific and technological capacity, unique biodiversity, a legal system that provides legal certainty, and government incentives for investment. However, the NPD is instructive in terms of providing an example of what ABS "best practice' in partnerships generally seeks to achieve. This includes a wide range of benefits in the short, medium and long term, undertaking high levels of research within provider countries, building scientific and technological capacity, and significant benefits for biodiversity conservation. The building of capacity within the NPD collaborators in ABS policy under the CBD, and working with new state and federal ABS regulations, is also a significant benefit of the partnership.

Conclusion of the exclusive Astra Zeneca-Griffith University partnership provides an excellent opportunity to view in the coming years how the significant accumulated benefits of such a "best practice" partnership can be leveraged to form new collaborations with a range of partners, serve a wider range of public needs (e.g. research on neglected diseases, innovative partnerships based on the country's biological and cultural diversity, support for Indigenous peoples' priorities), and generate benefits for science, medicine, and biodiversity conservation over time.

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