Nature Bank and the Queensland Compound Library: Unique International Resources at the Eskitis Institute for Drug Discovery

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ABSTRACT

The Eskitis Institute for Drug Discovery is home to two unique resources, Nature Bank and the Queensland Compound Library (QCL), that differentiate it from many other academic institutes pursuing chemical biology or early phase drug discovery. Nature Bank is a comprehensive collection of plants and marine invertebrates that have been subjected to a process which aligns downstream extracts and fractions with lead- and drug-like physicochemical properties. Considerable expertise in screening natural product extracts/fractions was developed at Eskitis over the last two decades. Importantly, biodiscovery activities have been conducted from the beginning in accordance with the UN Convention on Biological Diversity (CBD) to ensure compliance with all international and national legislative requirements. The QCL is a compound management and logistics facility that was established from public funds to augment previous investments in high-throughput and phenotypic screening in the region. A unique intellectual property (IP) model has been developed in the case of the QCL to stimulate applied, basic and translational research in the chemical and life sciences by industry, non-profit, and academic organizations.

KEY WORDS

compound management, drug discovery, Eskitis Institute, lead-like enhanced extracts, natural products, Nature Bank, Queensland Compound Library

INTRODUCTION

An enormous cache of human biology remains to be explored following completion of the Human Genome Project (HGP). The expectation is that selective modulators for new targets will be discovered that, in some cases, will be translated into novel therapeutics. Small molecules (organic compounds with a molecular mass < 500 Daltons comprised mainly of carbon, hydrogen, nitrogen and oxygen atoms, but typically also sulfur and fluorine, and less often chlorine, bromine and phosphorus) that can reversibly modulate new targets are important tools in this quest. Such modulation may require new chemical scaffolds. Indeed, the identification of new structural classes is one of the many drivers *en route* to understanding biological systems and developing innovative, safer therapeutics with novel modes of action. The incredible number of molecules, estimated to between $10^{20} – 10^{200}$ compounds, depending on the variables used to calculate this figure, effectively ensures a vast reserve of structural diversity can be mined to achieve this goal [1]. To date, approximately 2.7×10^{7} molecules have been reported which equates roughly to the mass of a proton to the sun if the Bohecek number (6×10^{62}) [2] is used to represent the set of small molecules with drug-like properties. Clearly, it would be impossible to produce one molecule of each from this set with the Earth's resources (estimated to contain 10^{51} atoms) [3]. The real challenge lies in the selection of small molecules that can actually probe or otherwise modulate human biology in a therapeutically useful manner. In this respect, biologically relevant small molecules that interact with biology space (e.g. the surface of a protein) have become critical tools for understanding important cellular events and biological pathways involved in health and disease.

Until the completion of the HGP, only a few hundred human proteins had been studied in detail via small molecules [4]. Because many of these compounds were often natural product derivatives, prepared one at a time, following testing in animals [5], more modern approaches had to be developed to keep abreast of the massive amount of data emanating from the HGP and millions of compounds that could be produced by combinatorial chemistry techniques. The resulting paradigm shift was driven by advances in molecular biology and robust automation so that it is now possible to undertake high-throughput screening (HTS) of 100,000s of compounds per day against an isolated biomolecular target or cell line to facilitate the efficient discovery of many more useful compounds. The screening of megalibraries that impede the function of specific proteins is now commonplace in industrial drug discovery programs [6]. The same tools (compounds) and techniques (automated screening) are also being used by academia in the interdisciplinary field of chemical biology to identify new proteins and map biochemical pathways [7-9].

Current wisdom suggests that the discovery phases of drug development (i.e. hit identification and lead identification) will be facilitated via a combination of chemical biology and phenotypic screening, typically pursued in a basic research environment, while the latter phases (lead optimization, clinical trials) would only be possible with the financial backing of industry. Significant time and effort can be dedicated in academia to identifying small molecule modulators for proteins, receptors, DNA and RNA that further explore the underlying biology of a specific system; a luxury not readily amenable to commercial reality. However, while the activities of academia are broader than those of industry, both sectors are inextricably linked as the industrial pipeline of candidate drugs comes to rely progressively more upon knowledge generated by academic researchers. This trend is expected to continue given the many and complex issues currently facing the pharmaceutical industry. Hence, academic research that aims to comprehend the underlying biology of a disease state, validate drug targets, engage in lead discovery, or otherwise add value to basic research will become increasingly more important.

Early phase drug discovery is also undertaken by many academic screening centers in addition to curiosity-driven research as the underlying infrastructure, skill sets and procedures required to unearth a new modulator for further chemical biology is very similar to the identification of a lead molecule for potential development into a pharmaceutical. The possible development of a marketable product in the form of a therapeutic following screening of a target that was identified in a basic research environment makes the acquisition of infrastructure for screening molecular libraries extremely attractive. In this scenario, a hit is usually taken as far down the value added chain as possible before partnering with industry.

The following overview focuses on points of difference between the Eskitis Institute for Drug Discovery at Griffith University compared with many other national and international research institutes pursuing chemical biology and drug discovery programs. The two major features of Eskitis are: Nature Bank a substantial collection of biota and natural product extracts aligned with lead- and drug-like physicochemical profiles; and the Queensland Compound Library (QCL), a national resource for compound management and logistics. The relationship between these two resources is shown in Fig. (**1**) by way of a workstream.

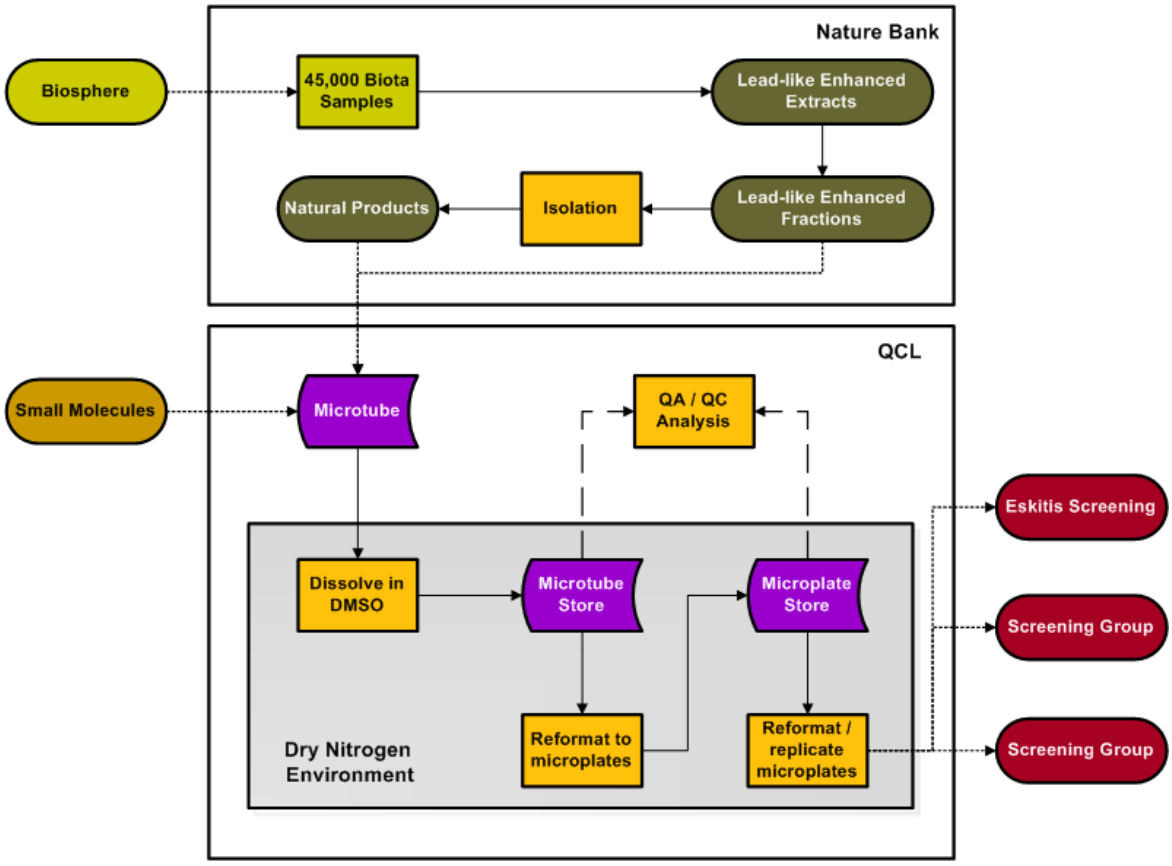


Fig. (1). Workstream depicting the flow of samples from the biosphere into the QCL via Nature Bank and, ultimately, to screening centres, including the Eskitis Institute's own platforms. Small molecules from third parties are also submitted to the QCL for solubilization and reformatting into labware compatible with various screening platforms/technologies. Adapted with permission from *Structural Chemistry* **2010**, *21*(5), 1117-1129, © 2010 Springer [10].

NATURE BANK

A recent review by Newman and Cragg has shown that natural products and their derivatives continue to make a significant contribution to the pharmaceutical industry [11]. Indeed, the real value of natural products becomes self-evident when they are analyzed as a percentage of all new drug approvals. This peaked in 2010 when natural products, their derivatives, or synthetically inspired analogues accounted for 50% of all new drug approvals. Clearly, natural products are still furnishing leads to the pharmaceutical industry [12]. The challenge, as we see it, is to better integrate natural products into contemporary chemical biology and drug discovery so that both the total number and percentage contributions can increase.

To help achieve this goal, over the last two decades the Eskitis Institute has acquired a significant biota collection of predominately terrestrial plants from Queensland, China and Papua New Guinea, and marine

invertebrates from the Great Barrier Reef and Tasmania. Value adding to the biota samples was achieved via a generic procedure that aligned extracts and subsequent fractions within lead- and drug-like physicochemical space based on log *P* [13-15], the so-called 'Lord of the Rules'[16]. The current methodology relies on initially preparing crude extracts that are then passed through an SPE cartridge containing a copolymer of divinylbenzene and *N*-vinylpyrolidone to afford a lead-like enhanced extract [13-14]. Subsequent chromatography provides simplified fractions for screening [13-14]. Both the lead-like enhanced extracts and fraction are curated in labware that facilitates rapid reformatting for prosecution by automated screening.

This methodology permits molecular weight (MW), structural data and retest of active pure compounds to be acquired in a highly efficient manner directly following primary screening. Supplemented with analytical and spectroscopic information from liquid chromatography, ultraviolet spectroscopy and evaporative light scattering detection (LC-UV-ELSD) and taxonomy to the species level, active fractions are quickly analyzed and prioritized. A confirmation is obtained by a combination of liquid chromatography and mass spectrometry (LC-MS) analysis of the active fraction to further resolve the individual constituents and obtain retention time, UV spectra and, importantly, MW information for each component and preliminary structural data via nuclear magnetic resonance (NMR) spectroscopy. The MS and NMR data can be used for dereplication and also as a trigger to pursue an isolation project. This allows natural product drugs that satisfy the log *P* criteria, but have one or more Rule of Five violations such as paclitaxel, rapamycin and trabectedin, to be isolated.

The combined MW, LC and other spectroscopic data also facilitate scale-up isolation of the active components without recourse to bioassay-guided fractionation. Here, isolation of the actives from the original biota is guided by the chromatographic retention time of the active in the prefractionated library. Ultimately, mass-directed or NMR directed isolation can be used to home in on the desired molecule(s) in a highly efficient manner [14-15].

A large-scale process of extraction is conducted in an equivalent method as the fractionation procedure (Fig. **2**). The extract is also passed through a series of chromatographic steps to remove tannins/highly non-polar products, and also to reduce the loading of the next purification step. At this point, with the knowledge of the polarity of the active fractions, a certain LC program in a set of standardized protocols is applied. Knowledge about UV, MS and NMR of the active fraction is used as a checkpoint for every purification step. A standardized procedure facilitates scale-up and, ultimately, isolation of active components from fractions in shortened timeframes. This effort is made possible via a suite of systemic infrastructure that includes: high performance liquid chromatography (HPLC); analytical and preparative LC-UV-ELSD-MS; high throughput

direct infusion MS; and high-field NMR. In addition, the amount of biota held in Nature Bank enables identification of active components down to 0.001% dry yield (Fig. **3**).

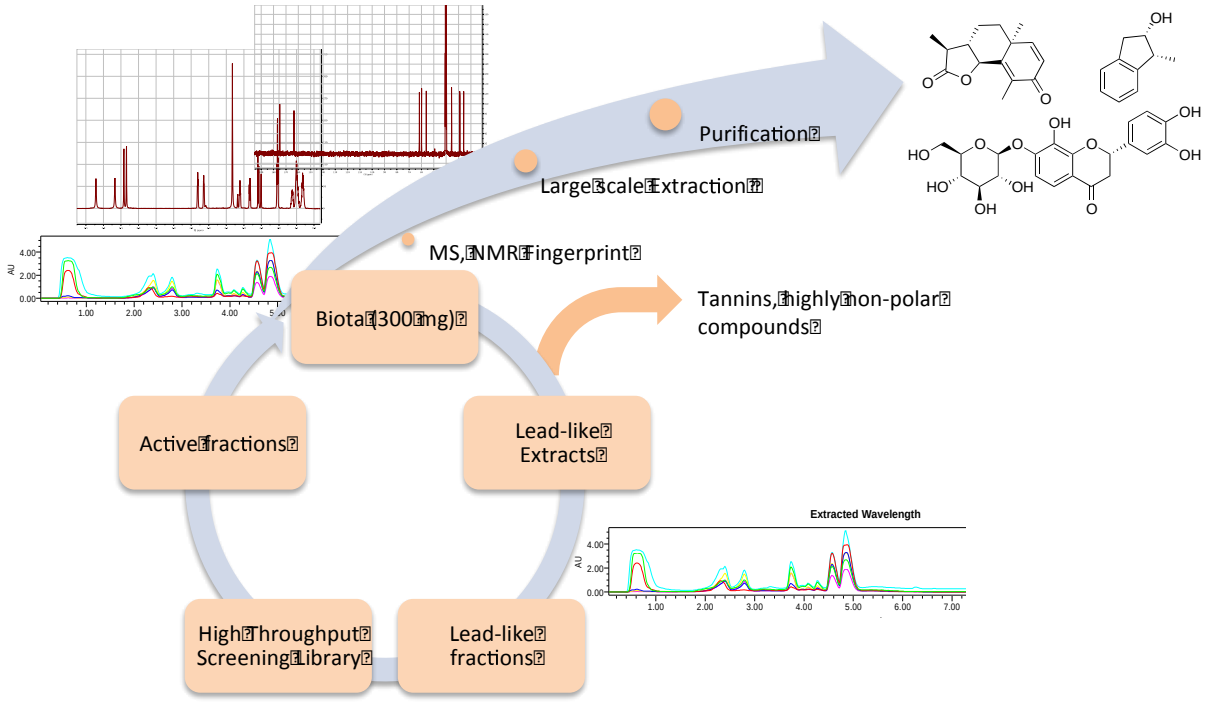
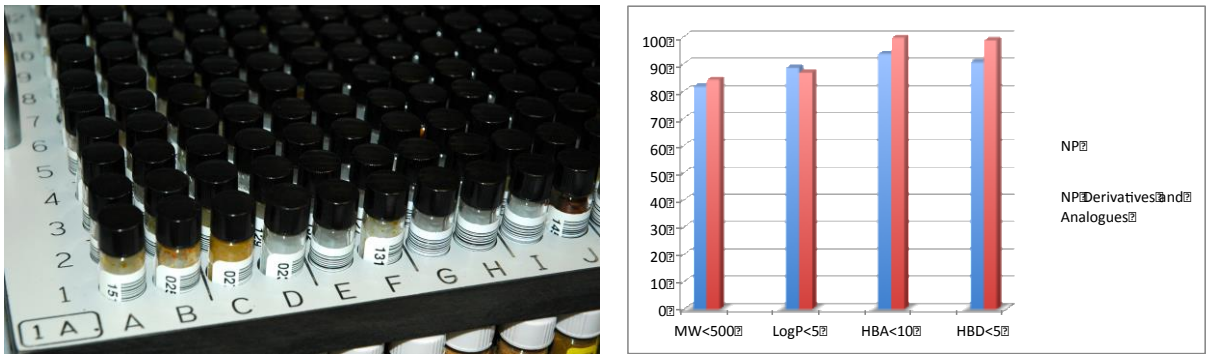


Fig. (2). A continuation from small-scale screening library preparation to large-scale isolation for pure compounds – a key feature for success in natural product drug discovery via HTS.

Besides the 45,000 plant and marine invertebrates, Nature Bank also incorporates with 5,000 pure compounds of which 2,000 are purified natural products and 3,000 are natural product analogues and derivatives. An in-house analysis showed that over 80% of the compound library complied with Lipinski's Rule of Five, i.e. MW $\leq$ 500, log *P* $\leq$ 5, hydrogen bond acceptor (HBA) $\leq$ 10, and hydrogen bond donor (HBD) $\leq$ 5 (Fig. **4**) [17]. Pure compounds are stored in vials (Fig. **3**) and as liquid samples are solubilized in dimethyl sulfoxide (DMSO) in microtubes and 384-well plates to facilitate rapid reformatting for biological assays [18-19].

Fig. (3). The Eskitis Institute's Biota Library. All samples are sorted by taxonomy and individually barcoded.

Nature Bank has extensive experience working with pharmaceutical companies, non-profit organizations and academia. The complete library, or any subset, can be sent to collaborators or screened at Eskitis. The HTS-friendly format of the fraction and compound libraries is one of the key features that facilitate collaborations. The fraction library (200,000 wells), and subsequent cherry-picked lists for retest, have been sent worldwide in a via the QCL (*vide infra*) with a 2-3 week lead-time.



(A) **(B)**

Fig. (4). (**A**) Small molecule natural product library in vials. (**B**) Analyses of Nature Bank's pure natural products and natural product derivatives/analogues indicate that over 80% pass Lipinski's Rule of Five.

Nature Bank and the UN Convention for Biological Diversity

When undertaking research involving biodiscovery it is critical to consider the United Nation's Convention for Biological Diversity (CBD). The CBD entered into force in December 1993 and includes as a supplementary agreement, i.e. the *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS)*. In summary, the Nagoya Protocol aims to provide greater legal certainty to biodiscovery, including the predictable and consistent access to genetic resources, and ensuring that proper benefit-sharing arrangements are put in place with the appropriate stakeholders that represent the owners of the genetic resources. These stakeholders may be a national, state or regional government, a private landowner, or a traditional owner.

Nature Bank has been designed and created from the ground up to abide by the CBD since before the Convention came into force in 1993. Benefit-sharing agreements are in place with state governments in the Australian states of Queensland and Tasmania, the Guangxi county government in China and the national government of Papua New Guinea. These benefit-sharing agreements ensure that a proportion of any financial benefit coming to the University is paid to the relevant organization. The Nature Bank resource has been studied and presented as a "best practice" research partnership undertaking biodiscovery, in its earlier guise of the Griffith University-AstraZeneca Natural Product Discovery Partnership [20].

Although the relevant provisions of the CBD have not yet been implemented in Australia, Nature Bank is expected to be declared a "trusted collection". Such collections, examples of which include seed banks and botanical gardens, will serve as established, identifying collections that are fully and properly documented. Those researchers and companies that access trusted collections will be considered to have already complied with their obligations to undertake due diligence in terms of access and benefit sharing. This framework is expected to significantly streamline access to genetic resources and both facilitate and accelerate biodiscovery research.

Nature Bank IP Model

Eskitis researchers recognize that maximum scientific value can be extracted from Nature Bank by collaborating with biology research groups worldwide. These groups provide expertise in target disease biology. In most cases, academic collaborations take the form of Nature Bank fractions being sent to a research partner (a University or publicly funded research institute) for screening again a specific drug target. Eskitis expertise in isolation and structure elucidation is used to follow-up the identified Hit fractions. Each partner bears their own costs to undertake the research. The resulting intellectual property (IP), that is, the knowledge

of the interaction between an identified small molecule from Nature Bank and an assay or protein provided by the partner, is shared between the collaborators 50:50, or in legal terms, as tenants in common in equal shares. This shared IP is then used as a basis for joint grant applications to advance the project further, for example to identify or create analogues for structure activity relationships (SAR), or to undertake lead optimization.

By contrast, commercial screening of Nature Bank can take place under a variety of frameworks depending on the needs and business model of a commercial partner. This can range from fee-for-service screening of a target for a big pharma, to risk-sharing projects where upfront or milestone payments are foregone in return for an increased product royalty. In all cases, however, ownership of Nature Bank compounds remains with Griffith University with licenses granted to commercial partners; this is a requirement of the Australian state of Queensland's Biodiversity legislation, i.e. Biodiscovery Act (Qld) 2004.

THE QUEENSLAND COMPOUND LIBRARY

By the mid-2000s, several Australian groups had invested in HTS platforms and it became necessary to consider the creation of a compound management and logistics facility from a national perspective [18]. A centralized repository that met the national need would clearly benefit from economies of scale that smaller facilities scattered throughout the country could never achieve. The Eskitis Institute at Griffith University took the lead in acquiring this infrastructure, partly because there was already a clear need to automate the then 70,000 lead-like enhanced extracts from Nature Bank (*vide supra*) and partly because a considerable knowledge base had already been acquired during a 15 year exclusive arrangement with AstraZeneca that expired in 2007. Ultimately, a national facility known as the Queensland Compound Library (QCL) was established through funding provided by Griffith University and the Queensland State Government [19]. The Commonwealth Government contributed additional funds to expand the capacity, and utility via purchase of a 30,000 strong small molecule library for screening.

QCL Infrastructure

The QCL design principle was governed by modularity and scalability. This permitted the facility to meet the immediate need and also address future proofing. The current configuration would not be out of place in a small biotech firm, and comprises capacity for up to 600,000 samples in microtubes and in excess of 1,500,000 samples in 384 well microtiter plates. The infrastructure to submit, curate and retrieve samples is provided by 5 × TTP Labtech comPOUND® microtube stores (one of which can curate up to 200,000 tubes; Fig **5**); 2 × Hamilton Storage Technologies (HST) asmStore (each holding 2,160 standard microtiter plates fitted with SealTite™ lids); an asmPlateServerST, and 3 × Agilent BioCel® sample processing units.

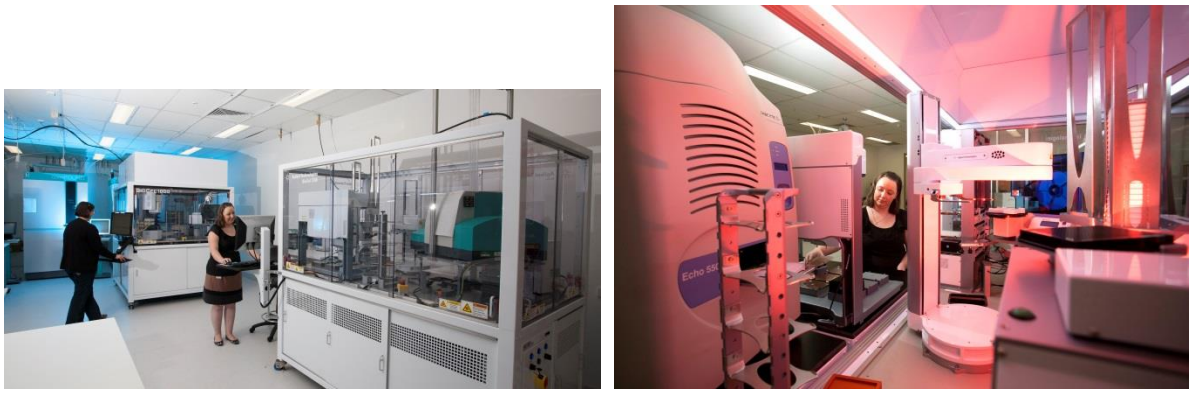
Fig. (5). Liquid sample storage at the QCL. All samples are held individually barcoded microtubes.

Compounds are initially transferred to a microtube and then dissolved in dry dimethyl sulfoxide (DMSO) (Fig. **1**). The microtubes are then deposited into the store for curation under a dry nitrogen atmosphere for up to 5-6 years. The format free environment facilitates cherry picking of individual microtubes for reformatting into microtiter plates. Microtube subsets for retest or counter screens are accessed as easily as the entire set is for a primary screening campaign. It is imperative to maintain a low humidity environment because of the potential for precipitation and degradation of samples due to ingress of adventitious water. At best, the presence of water can precipitate compounds but, in the worst case scenario, promote degradation, especially if a strong acid like trifluoroacetic acid was used to cleave a molecule from a solid support and/or purify the compound prior to curation [21]. Precipitated compounds may be rescued by forcing them back into solution, typically through ultrasonic techniques [22-23]. Degraded compounds, on the other hand are discarded.

A BioCel® 1200 is connected to the asmStores/PlateServer. This unit is equipped with a Labcyte Echo® 550 to enable nanolitre dispensing which is becoming increasingly more popular as assays are miniaturized ever further into low volume 384-well plates and 1536-well plates. Some cell based assays like those run using FLIPR® technology also benefit from acoustic droplet ejection by reducing the volume of DMSO used to solubilize samples, which can be a causative agent for cell death. The Echo® 550 can deliver miniscule volumes of concentrated solution (up to 10 mM) rather than larger volumes of more dilute solutions typically used to probe molecular targets with other technologies. Additionally, the Echo® 550 is used to determine the amount of hydration in microtiter plate wells as part of regular QC checks [24].

A BioCel® 900 permits collation of reformatting of microtubes into working plates while the preparation of assay ready plates is generally carried out on BioCel® 1800 (Fig. **6**). Importantly, the 3 × BioCel® units have a high degree of redundancy such that replication of working plates into assay ready plates, for example, can be undertaken on all three platforms. Reformatting is where an aliquot is taken from a particular storage format,

such as microtubes, and transferred to another format, like a 384-well microtiter plate. Microtitre plates can also be reformatted in a process known as quadranting. Here, 96- or 384-well plates may be reformatted into higher density 384- (4 × 96) or 1536- (4 × 384) well plates respectively. Replication, as the name suggests, is a direct transfer of an aliquot held in one format to a destination in the same format, e.g. the preparation of daughter plates from working plates where both would be the same plate density and layout.



(A) **(B)**

Fig. (6). (A) The QCL's BioCel 1800 (back) and 900 platforms (front) for plate making and microtube operations; **(B)** BioCel 1200 robot incorporating the acoustic dispensing technology for delivery of nL volumes of compounds into a microtiter plate.

QCL IP Model

Australia is strong in terms of the quality of its basic science funded by the Australian Research Council and National Health and Medical Research Council. Its major weaknesses are the lack of mechanisms and strong incentive for translating the innovative discoveries through to commercial outcomes, and the paucity of a culture of entrepreneurial and risk-taking activity which can promote translational research. To help promote a culture of innovation, users of the facility retain all IP. This provides a protected IP environment to facilitate progression of promising commercial ventures in a timely fashion.

This model is ideal for any organizations that are most active in the early discovery phases of the drug development pipeline, and represents the space where the majority of Australian industry and academia currently reside. Some chemists have taken advantage of the proactive storage mechanism (*vide infra*) to pursue collaborations of their chemistry with large pharmaceutical companies and biotechs. The QCL is not part of any negotiations and contracts are a matter between the user and a potential collaborator. The fact the QCL does not impinge any IP rights can bring additional surety to negotiations. This model allows synergies to develop and mature into projects that are prosecuted in a way best suited to the partners. As a result, molecules submitted by

chemists may be tested further to interrogate biological function as part of a chemical biology project or form the basis of a drug discovery program.

Because the facility was established as an inclusive national resource that aimed to synergize interactions, not only between chemists and biologists, but also a variety of organizational types, the model had to strike a balance between access to compounds deposited by chemists and how they could be used by biologists. The model also had to be sensitive to the needs of all users from academia to industry. In this respect, a flexible framework that allows the user to decide the level of comfort associated with submission or posting of data was employed. Thus, chemists from industry would be permitted to submit molecules with a limited amount of detail (typically only a compound identification number) while those from academia were free to divulge structures.

However, while some organizations were not in a position to divulge structures, their comfort level was much higher for submitting fingerprints and physicochemical profiles (clog *P*, MW, number of H-bond donors and acceptors, etc.). Fingerprints are an abstract form of the structure that allow substructure and similarity searching, but not exact matching. All fingerprints are held by the facility and searching for similar structures or common substructures is undertaken by facility staff. Physicochemical profiles, on the other hand, are provided to users that have an interest in selecting lead- or drug-like molecules [25-27].

Because the QCL is dedicated to the delivery of a compound management and logistics service, it does not undertake any screening and all biological data resides with the group that screened the compounds. The right to access compounds is only possible after an agreement is signed that prohibits any attempts at structural elucidation of compounds or passing the compounds onto a third party.

Given structures of compounds are not always divulged, there is a strong possibility that all, or part of, the selection will be screened blind. In this scenario, the screening group will hold biological data associated with a compound (even if just an identification and/or batch number) and would initiate discussions with chemistry groups that deposited molecules which most effectively modulated the biological system. This is not unlike the pursuit of a bride by many suitors. Several suitors (chemists) can woo the intended bride (biologist) with good modulators. However, the biologist is at liberty to choose the chemistry group which they would prefer to enter collaborative partnerships. This is particularly relevant for academic groups where collaborations with research leaders having strong track records can enhance proposals to the two leading grant agencies in Australia.

IP considerations must also account for global conventions like the CBD (*vide supra*) and IP rights of indigenous peoples. Policies for both circumstances are posted on the QCL's website for additional clarity,

while specific mention is made in all agreements with chemistry depositors regarding their obligations under the CBD should they submit samples derived from the biosphere.

Deposits may be made via one of three categories: open, restricted or closed. Chemists depositing molecules in the open category have not encumbered the sample in any way and it is free to be used in all assays. Restricted compounds are essentially the same except the chemistry owner may have ongoing collaborations with, for example, an agrochemical company. In this instance, the owner can still make the compounds available for screening but restrict usage to non-agrochemical targets/assays. The closed mechanism, as the name suggests, means that the chemistry owner does not permit access directly via the QCL so that the samples are essentially invisible. Closed samples may still be accessed following written permission being received from the owner.

To allay concerns related to IP, there is no requirement to submit structural details. This would ideally suit chemists that deposited samples into the closed and possibly restricted categories. Storage can be via one of two modes for chemists in the QCL model, i.e. passive or proactive. Passive storage occurs when the chemist submits samples for *potential* access by biologists. Here the biologists drive the selection of compounds. This may be based on physicochemical profiles or structures known to be active in specific target classes. Proactive storage, on the other hand, is where the chemist pursues third party collaborations with, for example, an industrial partner. In proactive mode, the QCL is able to readily reformat the chemist's samples into microtiter plates for biological evaluation by the collaborator. The latter mechanism dramatically increases the likelihood of an individual collection becoming the starting point of downstream projects.

Biologists, for their part, may access all open and restricted category compounds (provided their screen does not impinge on any restrictions in the latter case). The benefit is that potentially novel compounds may be found following screening as the samples have been sourced from academia for the most part. The novelty stems from the fact that academic chemists work in niche areas that give their group a point of difference and therefore, in the best case scenario, produce novel structures or, more generally, molecules that are not normally available through commercial vendors [28]. Importantly, biologists are not able to loan or give the samples they accessed from the QCL to any other party. Neither are they permitted to reverse engineer sample structures.

HOW THE QCL AND NATURE BANK CAN ASSIST COLLABORATIVE PARTNERSHIPS

Nature Bank and QCL were established to synergize interactions between Australian chemists, life scientists, and their international colleagues. No distinction is made between Australian and international academics so far as costs to access the facility are concerned. By promoting collaborations, value can be added to the already

excellent basic medical research, synthetic organic chemistry and natural product expertise in the region. In the case of the QCL, screening the combined collection has enormous potential to negate missed opportunities for both chemists producing novel molecules and biologists in quest of chemical starting points for validated targets. Lead compounds identified following HTS or phenotype screening may be progressed as an academic investigation [10] or prosecuted via a different route to deliver a therapeutic, agrochemical or other marketable product.

Several groups have utilized the services of Nature Bank and the QCL to prosecute international collaborations. By way of example, the natural product screening set which is part of Nature Bank contains extracts and fractions enhanced with lead- and drug-like components formatted in over 600 × 384-well plates. Copies have been sent to various industry partners, non-profit organizations and universities for screening. Similarly, the Commonwealth Scientific and Industrial Research Organisation (CSIRO) has opened its unique library for biomedical and agrochemical research to industry and non-industry partners alike through the QCL. In all situations, the QCL can provide cherry-picked subsets for further evaluation in an efficient manner.

Industry affiliates haves utilized the QCL in a number of ways. By way of example, several organizations have deposited compounds for screening against biological targets. This strategy exposes the corporate collection to selected targets that can potentially lead to fruitful new avenues of research with a strong IP position and, ultimately, a marketable product. Other industry organizations have acquired commercial libraries that are screened against in-house targets. As part of their business model, these organizations will sell a copy of their library to selected partners in exchange for the first right of refusal if a promising hit is discovered. In these examples, all compound management activities are effectively outsourced to the QCL. This strategy allows small-to-medium enterprises to access a high quality facility without having to invest in expensive infrastructure worth several millions of dollars, employ dedicated staff, or pay preventative maintenance contracts/repair costs. Moreover, corporate compound collections can be deposited as closed sets where no structural details are provided. Being closed to the outside world effectively ensures that the molecules are invisible to other users and places the onus of screening onto the depositor.

The QCL's collection of open-access compounds, including the 30,000 compounds recently purchased using commonwealth funds and Nature Bank, can be evaluated against a propriety target that has been identified in-house to further probe biological function or identify chemical starting points for a drug development program. Additionally, access to unique molecules submitted by academia has the potential to identify an innovative lead molecule for downstream optimization.

The metrics that drive academia are vastly different to those that drive industry. Success is measured, *inter alia*, by the number and quality of peer-reviewed publications, typically in journals, the ensuing number of citations contributing to the 'H-index' [29], and funding awarded through competitive grants. As is the case for industry, however, the screening of a unique set of compounds sourced from academic laboratories opens up the possibility for serendipitous discovery of new modulators for biological targets and pathways. Novel structures (and structural classes) with new modes of action can be published in high impact journals that, in turn, can lead to increased citations with concomitant boosting of the researcher's H-index and, ultimately, success with nationally competitive grants.

CONCLUSION

Nature Bank and the QCL provide a point of difference for the Eskitis Institute in the chemical biology and drug discovery landscape of Australian research. The combination of a flexible IP model for both international resources creates an environment that encourages collaborations between different groups of scientists.

For natural products in particular, many of the impediments that hindered uptake since emergence of the high-throughput paradigm in the 1990s have largely been resolved by way of 'smart' lead-like extraction and fractionation process that are supported by automated screening and a fully integrated compound management system. The stage is now set for a renaissance of natural products to impact positively on drug discovery and chemical biology.

ACKNOWLEDGEMENTS

David Camp, former Associate Director of Biota and Compound Management and Foundation Director of the QCL, contributed to the development of lead-like enhanced extracts, management of Nature Bank and establishment of the QCL. Stuart Newman is the Strategic Business Development Manager and has made a significant contribution to ensuring the Institute is compliant with all international and national legislation associated with access and benefit sharing under the auspices of the UN CBD. Ngoc Pham is the current Manager of Nature Bank and contributed to enhancements of the natural product workflow and internationalized Nature Bank uptake. Ron Quinn is the Director of the Eskitis Institute for Drug Discovery, founder of Nature Bank and initiated the application of pharmaceutical industry principles to natural product research.

CONFLICT OF INTEREST

The authors and the Eskitis Institute have been major advocates for natural product drug discovery.

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