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Progress toward Establishing an Open Access Molecular Screening Capability in the Australasian Region

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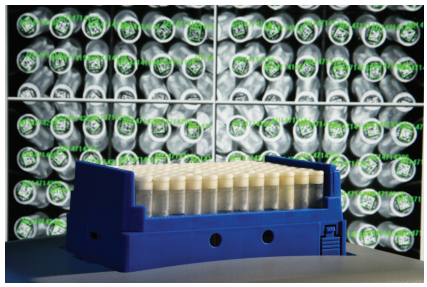
Large pharmaceutical companies have, until relatively recently, been the sole beneficiaries of substantial compound libraries and automated screening to facilitate the identification of small-molecule modulators targeted specifically for the druggable genome (*1*). Over the past five years, however, a growing number of nonindustry organizations, mainly from North America and Europe, have emerged with high-throughput screening (HTS) capabilities to interrogate biology space not typically prosecuted by industry and also to undertake early phase drug discovery. A comparable scheme is poised to unfold in Australasia that, from its inception, pursued a similar vision to that of its northern contemporaries but *via* a somewhat unique model tailored to the specific needs of the region.

An enormous cache of human biology remains to be explored after the completion of the Human Genome Project. The expectation is that selective modulators for new targets will be discovered that, in some cases, will be translated into novel therapeutics. This will most likely be achieved through a combination of chemical biology, typically pursued in a basic research environment, and a concerted drug discovery program that, for the most part, is only possible with the financial backing of industry.

The activities of nonindustry initiatives are broader than those of the pharmaceutical industry. Significant time and effort can be spent on identifying small-molecule modulators for proteins, receptors, DNA, and RNA to further explore the underlying biology—a luxury not readily amenable to commercial reality. Early phase drug discovery is also pursued by some nonindustry centers; several of the more notable programs have the potential to alleviate human suffering from the aptly named neglected diseases that afflict the world's poorest peoples.



Individual microtubes underpin the logistics of the Molecular Screening Collaboration. Each microtube is identified by an exclusive 2D barcode which links to a unique sample deposited by a particular chemist.

The rise in the number of academic and publicly funded initiatives with HTS capabilities has been aided by the advent of more affordable screening equipment and the ready availability of commercial chemistry libraries (*2*). Two of the more high-profile publicly funded schemes are the Molecular Libraries Initiative (MLI) (*3*) component of

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the National Institutes of Health (NIH) Roadmap and ChemBioNet www.chembionet.de from Germany. Recent publications (*4*–*6*) in this burgeoning sector prompt us to report an Australasian initiative that commenced in 2003.

Regional Background. Australia and New Zealand have small populations by world standards (20 million and 4 million, respectively), and this limits the availability of public funds to support infrastructure, functional capability (operating expenses such as staff and equipment maintenance), and project costs (reagents, labware, and other items unique to a screening campaign) for multiple facilities, such as the 10 screening centers in the MLI.

Highly competitive funding models from both national governments have helped to cultivate a quality basic medical research environment (*7*). However, preclinical development is not as strong as its basic research counterpart. For example, Australia's 2.5% of global medical science has not translated into a local industry that accounts for 2.5% of global drug development, because of the relatively small number of drug candidates entering preclinical trials every year (*8*).

Despite capabilities in preclinical lead identification and optimization (ADME/T, absorption, distribution, metabolism, excretion, and toxicity; DMPK, drug metabolism and pharmacokinetics), scale-up, animal models, and clinical trials, Australia and New Zealand currently suffer from a lack of coordinated and affordable access to compound libraries and HTS for biomedical research teams with validated targets. The region would benefit enormously if the discovery of small-molecule modulators was facilitated in an effort to generate potential new therapeutics and act as the starting point for value adding *via* existing centers of expertise, so that a more mature intellectual property position could be obtained before partnering.

The Molecular Screening Collaboration (MSC) in Australasia. The MSC began as a bottom-up process through like-minded individuals that believed amalgamating well-equipped core capabilities into a virtual network run with a common set of business rules would provide the region with an excellent resource to prosecute chemical biology and drug discovery programs. A plan to craft a synergistic network, based on models employed by public–private partnerships such as the Medicines for Malaria Venture, was first discussed in 2003. From its inception, the MSC was a confederated network of resources and facilities that operated under international established best practices.

It was fortuitous that planning for the MSC coincided with a major national effort in Australia to improve acquisition and access to systemic infrastructure. The scheme, known as the National Collaborative Research Infrastructure Strategy (NCRIS) commenced in 2004 with a broad outline of its scope. The research community could participate in the process throughout 2005 prior to the release of an exposure draft of the strategic roadmap. The MSC was based on the same collaborative approach to enable affordable access to high-cost equipment and was submitted as an NCRIS proposal. By 2005 (*9*), grassroots support from 14 universities, 6 medical research institutes, 6 publicly funded research agencies, and 2 major national resource facilities resulted in a proposal for a dedicated compound management and logistics center, the Queensland Compound Library (QCL, www.griffith.edu.au/qcl) (*10*), to collate and curate chemical libraries pooled from individual collections. Two HTS sites, at the Eskitis Institute and Walter and Eliza Hall Institute, also were incorporated to service screening for the biomedical research community. The proposal was included in the NCRIS Roadmap (*11*) for in-principle funding.

An informal road show during 2006 provided feedback from stakeholders that helped refine common business rules that would apply to the MSC and also to potential users. These included, among others:

- Benchmarking of a collaborating facility's performance against key performance indicators.
- Adherence to a unique intellectual property (IP) model that attempted to redress the lack of incentives to progress innovative discoveries to the market. Here, inventors are given 100% ownership of the IP they create. No claim to IP arising out of any discovery by the facility is made in this model. This provides a protected environment for progression of promising commercial ventures in a timely fashion.
- Environmental impacts are taken into consideration wherever possible, for example, a Nanostream μPLC was chosen for compound library quality assurance to minimize solvent waste (Nanostream, www.nanostream.com).
- Any organization, including academia, publicly and/or privately funded research institutes, and industry, can access the MSC to prosecute basic or applied research.
- Project submissions to the MSC must first pass a decision gate that as-

Microtubes can be compiled quickly and reformatted into screen-friendly microplates to meet the specific needs of biomedical researchers. Subsets for retest, secondary assays, or counterscreens are accessed as seaily as the entire set is of a primary screening campaign. Image courtesy of Trine Barfod-Jensen, Griffith University.

sesses the quality of science if full cost recovery is not being considered.

- Specific project costs (reagents, consumables, *etc.*) would typically be borne by the user, whereas other overheads would be assessed on a case-by-case basis. In this model, industry may be charged at full cost recovery, whereas academic groups could bear project-related costs only.

Progress to Date. Compounds are being sourced from the pool of available molecules from Australia and New Zealand in the first instance (*9, 10*). The consolidation of chemistry at a central repository will result in greater coverage of chemistry space (*12–14*) than any single collection across Australasia, public or private, currently achieves. Chemists will be able to store potentially valuable collections under optimal conditions, with vastly increased opportunities to have their compounds tested for biological activity. Biomedical researchers will have access to a unique suite of molecules in screen-ready microplates of their choosing.

A unique IP model that lies somewhere between the proprietary culture of industry and the NIH policy of placing structural and screening data in the public domain (MLSCN Project Team Policy on Data Sharing and IP in the MLSCN Program, www.nimh.nih.gov/dnbbs/datasharing-ip.pdf) was developed for the current Australasian situation. Because MSC facilities do not lay claim to any IP owned or generated by users of the facility, compounds can be deposited with or without full structural details to protect potential downstream patents. Other chemical data such as molecular weight, Rule of 5 compliance (*15*), lead- or drug-like score (*16*), method of production (traditional target-orientated synthesis, natural product isolation, combinatorial library, *etc.*), and any screening restrictions can be specified at the time of sample deposition to facilitate selection of screening sets by biomedical researchers.

In addition to the passive mechanism for deposition of compounds (submission of samples for *potential* access by biologists), chemists are encouraged to proactively seek third-party collaborations with, for example, an industrial or academic partner. In proactive mode, the QCL is able to readily reformat a specific set of samples belonging to the chemist into screen-ready microplates for biological evaluation by the collaborator. This mechanism dramatically increases the likelihood of an individual collection being the starting point of downstream projects.

The QCL will employ microtube technology, rather than a plate-based system, to enable rapid cherry picking of individual samples. All tracking is done through onboard software, with 2D barcodes at the base of each microtube providing additional assurance. Microtube subsets for retest and counterscreens can be accessed as easily as the entire set is for a primary screening campaign.

Biological screening is arguably the strongest mechanism to engage both the biology and chemistry research communities. Confirmed hits following screening are followed up between the biomedical project team owning the target and the chemist(s) owning the best small-molecule modulators. The MSC's formal involvement during the discovery phase ends at this point, and it becomes the remit of the biology and chemistry owners, that is, parties outside of the MSC, to further continue a project in this model. Potential collaborations are negotiated directly between IP owners. Thus, molecules submitted by chemists may be tested further to interrogate biological function or form the basis of a drug discovery program. This model allows synergies to develop and mature into projects that are prosecuted in a way best suited to the collaboration.

Since 1994, the two HTS sites have conducted >300 collective screening campaigns for academia, public–private partnerships, and major pharmaceutical companies. Assays to date have been performed on a diverse array of targets that cover protein–protein interactions, ion channels, enzymes, receptors, nuclear receptors, and whole organisms.

Each HTS site contains readily accessible and affordable detection technologies, whereas more expensive equipment is distributed. The available screening technologies include absorbance, ALPHA (amplified luminescent proximity homogeneous assay) screen, ELISA (enzyme linked immunosorbent assay), FLIPR (fluorescent imaging plate reader), fluorescence, FP (fluorescence polarization), FRET (fluorescence resonance energy transfer), TR-FRET (time-resolved FRET), SPA (scintillation proximity assay), SPR (surface plasmon resonance), HCS (high content screening), and confocal cell imaging.

The present MSC platform includes a fully automated compound management facility and two HTS sites and is well equipped with technology that would not be out of place in an industrial setting. Although a mechanism is in place that allows the core components to jointly prosecute projects, full interoperability and data sharing can be limited on occasion because of legacy informatics at the three sites. This issue is currently being resolved and constitutes the next phase of the MSC's roll out.

The Challenge Ahead. Perhaps the single largest challenge that lies ahead for the MSC is to convert the groundswell of support into affordable access for potential users. Several options are available through different levels of government from Australia and New Zealand to provision operating expenses for limited periods. Savings in this area can be passed on to users of the facility to improve accessibility. In the interim, a competitive cost structure that distinguishes between academia, publicly funded research organizations, and industry has been devised that balances access for users with continued viability of the collaborating centers. This

competitive pricing has already encouraged several members from the chemistry and biomedical research communities to become members of the MSC.

REFERENCES

1. Hopkins, A. L., and Groom, C. R. (2002) The druggable genome, *Nat. Rev. Drug Discovery 1*, 727–730.
2. Lazo, J. S., Brady, L. S., and Dingledine, R. (2007) Building a pharmacological lexicon: small molecule discovery in academia, *Mol. Pharmacol. 72*, 1–7.
3. Austin, C. P., Brady, L. S., Insel, T. R., and Collins, F. S. (2004) NIH molecular libraries initiative, *Science 306*, 1138–1139.
4. Hergenrother, P. J. (2006) Obtaining and screening compound collections: a user's guide and a call to chemists, *Curr. Opin. Chem. Biol. 10*, 213–218.
5. Gordon, E. J. (2007) Small-molecule screening: it takes a village, *ACS Chem. Biol. 2*, 9–16.
6. Lewis, J. D. (2007) The role of the chemical biology core facility at EMBL: a vision for a European roadmap, *ACS Chem. Biol. 2*, 21–23.
7. Department of Education, Science and Training (2003) Mapping Australian Science and Innovation, Australian Government.
8. Department of Industry, Tourism and Resources (2002) Pharmaceutical Industry Action Agenda: Local Priority—Global Partner, Australian Government.
9. Simpson, G. (2005) Drug discovery: a case for national coordination, *Chem. Aust. 72*, 22.
10. Camp, D. (2007) Establishment of an open access compound management facility in Australia to stimulate applied, basic and translational research, *Drug Discovery World,* Spring61–66.
11. Department of Education, Science and Training (2006). National Collaborative Research Infrastructure Strategy Strategic Roadmap, Australian Government.
12. Dobson, C. M. (2004) Chemical space and biology, *Nature 432*, 824–828.
13. Stockwell, B. R. (2004) Exploring biology with small organic molecules, *Nature 432*, 846–854.
14. Lipinski, C., and Hopkins, A. (2004) Navigating chemical space for biology and medicine, *Nature 432*, 855–861.
15. Lipinski, C. A., Lombardo, F., Dominy, B. W., and Feeney, P. J. (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, *Adv. Drug. Delivery Rev. 23*, 3–25.
16. Leeson, P. D., Davis, A. M., and Steele, J. (2004) Drug like properties: guiding principles for chemical design-or chemical prejudice? *Drug Discovery Today: Technol. 1*, 189–195.