Submission to the

INQUIRY INTO THE DEVELOPMENT OF HIGH TECHNOLOGY INDUSTRIES IN REGIONAL AUSTRALIA BASED ON BIOPROSPECTING AND BIOPROCESSING

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Firstly, allow me to present my credentials.

I obtained my PhD in chemistry at the University of Western Australia in 1984, being among the first to explore the chemistry of Western Australian marine algae and porifera (sponges). Indeed, even after almost 20 years my PhD research represents one of the more significant studies to emerge from Western Australia on marine natural products chemistry. Following a 2 year appointment as a Postdoctoral Fellow at Scripps Institution of Oceanography, California, I returned to Australia to take up a 4 year appointment as a Research Fellow at the Research School of Chemistry, ANU. During my time at ANU I pioneered a very productive research program targeting novel bioactive metabolites from southern Australian (and Antarctic) marine sponges. In 1988 I accepted an appointment as a lecturer in chemistry at The University of Melbourne, moving through the ranks of senior lecturer to my current position of associate professor, all the time advancing my research interests in marine natural products chemistry. Over my career I have established a reputation as a leading Australian and international figure in the field of marine bioprospecting, with >120 published articles in peer reviewed journals, the discovery of many hundreds of novel bioactive natural products to my credit, and having personally trained >40 postgraduate research students. Many of these postgraduates have since assumed positions of note in bioprospecting – both in academia and industry, within Australia and overseas. My research has consistently attracted funding from the Australian Research Council, and considerable support from industry, and is a leading source of published research in the field of bioprospecting Australian marine ecosystems. I have successfully negotiated research collaborations with industry that have seen millions of dollars in sponsorship flow to the University of Melbourne over the last few years, with even more committed into the future. This practical experience both as a scientist, educator and manager of basic and applied research has instilled an acute awareness of the challenges faced in discovering new generation pharmaceuticals and agrochemicals from Australian biodiversity. I believe this knowledge allows me to speak with some authority on the topic of bioprospecting. In my submission I will confine my comments to bioprospecting.

Some Observations on the Submission Invitation.

Media reports on "bioprospecting discoveries" are typically couched in terms that overly emphasize the potential for commercial returns, both to the inventors, sponsors of the research, and the host region, state or nation. People like to believe in the "clever country" and in a climate of economic rationalism what better way to be clever than to "make money from science"! It is a sad reflection on the current Australian psyche that for an important scientific discovery to be newsworthy it must be reduced to dollar earning potential. Unfortunately, this practice is not limited to the media, but is increasingly employed by scientists and academics who in writing applications for government grants all to often chant the mantra …*give me money for my research and I will cure x, y & z, draw international praise on Australia, and most importantly* <u>*make a mint in the process*</u>. This strategy does not come naturally to most scientists who by their very profession tend to be conservative, but is forced on them by the dire shortage of research funding and the need present their research as "commercial" in order to win even a modest measure of support. This is not to say that bioprospecting cannot yield amazing scientific discoveries with enormous commercial potential, but more that overuse of this expectation grossly distorts the likelihood of success, and diminishes the significance of non-commercial discoveries. The challenge is separating the reality of bioprospecting from the "hype", in order that discussions leading to policy decisions can be based on facts and not popular perceptions or third party reinterpretations of "media grabs".

The invitation to make a submission to this inquiry was accompanied by a document,

"BIOPROSPECTING AND REGIONAL INDUSTRY DEVELOPMENT IN AUSTRALIA - SOME ISSUES FOR THE COMMITTEE'S INQUIRY"

This supporting document not unreasonably attempts to identify some noteworthy scientific achievements (refs 3-5) in order to put into context the value of pursuing bioprospecting. Disappointingly, the citations in support of the <u>selected</u> discoveries are limited to "media reports". Such "newsworthy breakfast bites" are frequently chosen by the media for their novelty rather than scientific value, and surely any serious invitation to review these important issues deserves a more detailed analysis of the existing literature, and <u>considered choice</u> of exemplars. To select "noteworthy" discoveries based on lay media coverage is dismissive of the breadth of solid science carried out across Australia, and to those with some expert knowledge reveals a casual attention to detail that calls into question the sincerity of the inquiry process. As if to reinforce this view, the aforementioned document highlights the unsubstantiated claim,

"…that within as little as five years all Australia's biota could be screened with the resulting intellectual property and knowledge sold off…"

Such a statement smacks of the… *I met someone who knew someone who said …* approach to defining a discussion topic, and its lazy acceptance lends it more merit than it deserves. In this instance an indefensible claim is deliberately elevated to a discussion point! Even modest researching of the issues would reveal the problems with such a statement.

What is meant by,

- **Australia's biota** — *Does it include marine as well as terrestrial? What about microbes?*
- **Screening** — *What screens, at what cost, and by who? And what of genomics which offers the potential of a vast number of new screening targets that have yet to come online.*
- **Intellectual Property** — *The process of detecting, isolating, characterizing and identifying new drugs takes time, resources and skilled personnel – all of which are in short supply in Australia. You cannot sell IP until you have it.*

I am concerned that if the mediocre standard of research that underpins the supporting document is a measure of the depth with which this inquiry wishes to explore the issues, then such a shallow inquiry will achieve little more than generate a few short lived media grabs. Nonetheless, as a passionate advocate for the merits of bioprospecting, and as someone who has dedicated his scientific career to this field, I trust you will accept my misgivings in good faith, and indulge my observations outlined below.

WHAT IS BIOPROSPECTING?

Bioprospecting is the search for valuable metabolites from natural sources.

To properly grasp the meaning of this statement it is necessary to expand on the meaning of (a) metabolites, (b) valuable, (c) natural source, and (d) bioprospecting.

(a) Metabolites

Metabolites, also called natural products or secondary metabolites, are substances produced by a living organism. These substances are organic molecules, and are assembled from the biosynthetic pathways in operation within the source organism, whether the source be a tree, bacteria or whatever. The biosynthetic pathways themselves are a complex interplay of proteins (also called enzymes or peptides), that are themselves constructed following the blueprints laid down in the DNA of the organism. In summary, every living organism is defined by its DNA, which codes for the creation of a range (many thousands) of proteins, which in turn act as molecular factories, constructing the vast array of different molecules required for the particular organism to survive, prosper and reproduce. Among these molecules a very small number will elicit biological properties that can be defined as valuable (for example the ability to kill invading bacteria – which we might employ as an antibiotic). It is these metabolites that typically (but not always – see below) attract the attention of bioprospectors.

(b) Valuable

What constitutes ***valuable*** will vary and might broadly be classified into applied and basic science.

- **applied science** — *Defines value by a positive response to one or more biological screens – antibiotic, anticancer, antiviral, specific enzyme inhibitors etc… with an eye towards a new drug.*
- **basic science** — *Defines value on the basis of molecular, functional and/or biosynthetic novelty, with no particular regard to commercial use… the goal being to advance our understanding of the natural world.*

Of course a valuable metabolite could have commercial potential and be biosynthetically unusual, thereby attracting the attention of both applied and basic scientists. In recent years government research funding has been directed in such a way as to bias the more applied approach to bioprospecting. Support from industry (and government) has of course always been easier for those who would promise a new billion dollar product. While it is easy to appreciate the dollar value of applied science, one should not forget that applied science only succeeds because of the wealth of basic science that underpins it. Both strong basic and applied research programs are critical to success. For example, a study into the taxonomic classification of temperate marine tunicates has no obvious intrinsic applied value, that is until perhaps a subsequent research program discovers a potent anti-viral agent from a tunicate and seeks to explore this niche of biodiversity. At that time any and all marine ecology (basic science) on tunicates becomes invaluable. Much as governments would like to anticipate such relationships ahead of time, and use the knowledge to direct limited funding resources, the fact that research is infused with the unpredictable defies such narrow planning.

(c) Natural Sources

Likewise the definition of ***natural sources*** is very broad, embracing desert, temperate and tropical plants, insects, animals and microbes – or put simply, virtually any living system that engages in biosynthesis. Through trial and error certain natural sources have proved more productive. Terrestrial microbes have been a mainstay of the pharmaceutical and agrochemical industry for decades, in part because they produce exotic bioactive metabolites, but also because large scale fermentation in factories allows us to harness this biosynthetic capacity and have the bugs make their wonder drugs at low cost and on large scale. The popular perception of rainforests as pools of natural medicines has basis in fact, with many developing countries dispensing plant extracts as over the counter medications. In a marine setting sponges are well known for their ability to produce structurally novel bioactive metabolites, some of which will undoubtedly lead to new drugs. When we talk of biodiversity in the Australian context it is necessary to not only include our unusual terrestrial fauna and flora, but also the impressive marine biodiversity that inhabit ecosystems across our marine economic exclusion zone, which is itself far larger than the land area of mainland

Australia – and extends from the tropics to temperate to antarctic waters, from intertidal to shallow to deep waters, from coral reefs, to mangroves to estuaries to seagrass beds and to beaches. Furthermore, Australian biodiversity should be seen to extend to microbes, bacteria and fungi, as well as cyanobacteria and phytoplanktons. These culturable organisms hold the promise of renewable resources, supplying valuable substances to industry either as feed stocks or drugs in their own right.

(d) Bioprospecting

To the uninitiated the term bioprospecting is all too easily equated with mineral prospecting and the inevitable wholesale mining (or harvesting) that follows raises the specter of environmental damage and concerns about conservation, as well as claims for compensation and prior resource ownership. As sincere and well placed as these concerns may be, bioprospecting is less about identifying harvestable ecosystems, but rather a knowledge trawling exercise. It is typically the resulting *discovered knowledge* that has value, not the rights to harvest and exploit the source organism. While all activities that impact on the health and character of Australian ecosystems warrant close attention, when performed appropriately bioprospecting poses no risk. It is necessary to qualify this with "appropriate" because, as in any activity, one must guard against cowboys who would operate outside accepted standards. Bioprospecting typically involves the collection of a single or at most a small number of samples of any given species, in a fashion that does not impact on the environment in any serious fashion. Depending on the nature of the biodiversity being sampled (microbes, plants, marine invertebrates etc.) this process can involve the collection of a few grams of soil, to ~1 kgm of plant material, or a single sponge. As the main objective with "sampling" is to explore as wide a selection of biodiversity as possible, individual samples are usually kept to a modest size. This collection of biodiversity is then subjected to an array of biological screens, in order to identify those specimens that display "valuable" characteristics (see above). Such specimens are then subjected to detailed chemical analysis in order discover the identity of the valuable metabolite. Depending on the skill of the bioprospectors, and the yield of the active metabolite, it may be necessary to return to the collection site to secure a larger sample size for a given species (assuming this is feasible and environmentally acceptable), but even this resupply is a one off modest collection and will not by itself constitute a new industry.

When **bioprospecting** is defined as shown above, the magnitude of the challenge we face in bioprospecting all Australian biodiversity begins to emerge. If this were not enough, the biology, ecology and zoology of many of the ecosystems we would "prospect" have yet to be fully explored. This leads to other questions.

- *How unique are the valuable metabolites locked away in Australian biodiversity?*
- *Can we explore Australian biodiversity at our leisure, or will others discover the same or related valuable metabolites from alternate sources obtained outside Australia, possibly before we get around to doing it ourselves? In the pharmaceutical industry there are no prizes for second place – the economic reality is patent or perish!*

- *Can we afford the resources (cash, infrastructure, human and intellectual) needed to go it alone?*

- *Should we share the challenge, including the cost, risk and return, with those outside Australia, and if so on whose terms?*

- *If we do impose restrictions and guidelines for bioprospecting how will they differentiate basic from applied research?*

- *Can policies apply nationally, or must they be on a state by state, or even regional basis, keeping in mind that biodiversity does not respect geopolitical boundaries?*

- *If "government" elects to claim royalty share in advance of any discovery, perhaps as a condition for sampling selected pools of biodiversity, how will this impact on our capacity to engage industry sponsors?*

- *Will bioprospectors simply shift there attention to less encumbered pools of biodiversity?*

- *Rather than discourage, should we entice industry sponsors to explore our biodiversity by becoming partners in the process, and if so can we limit our contribution to access to the biodiversity or do we have to put up more (cash, infrastructure, personnel)?*

WHAT TO EXPECT FROM BIOPROSPECTING.

There is no doubt that bioprospecting has and will continue to discover valuable metabolites, and that some of these will lead to commercial products. What returns can Australia expect from investing in bioprospecting.

Scientific Skill Base

As forecast by most informed commentators the next century will see the dominance of knowledge based industries, with information science (IT) and biosciences (genomics, proteomics) appearing to have something of a lead at this time. For Australia to have any hope of maintaining 1st world status it is imperative that we be among those nations that herald in this future, rather than those consigned to follow and pay-for-use. This requires a dynamic, innovative and scientifically literate workforce, equipped with all the skills needed to be receptive to rapid technological change. It also demands a willingness by Australian business to move beyond the *office block* investment strategies of yesteryear, and invest in Australia's future by under righting R&D initiatives that draw on our unique biodiversity and proven intellectual capacity. The involvement of some of our brightest young Australians in bioprospecting at a postgraduate level not only contributes to the success of such research, but also provides invaluable training and experience that will carry forward into future careers. As a nation we need to ensure that these most skilled individuals turn their talents towards discoveries in Australia, rather than move offshore as is all too often the case now. With the right investment support strong Australian science will foster startup companies which will take new discoveries from the laboratory to commercial production.

New Industries

Bioprospecting as defined above is less about harvesting (ie a primary industry) and more about searching for knowledge. Having detected and identified a valuable metabolite it may very well be that there is no necessity to ever return to the collection site.

The metabolite may have;

- *been derived from a microbe, which can be cultured in laboratories and/or factories (anywhere in the world), or*
- *been successfully synthesized at high yield for low cost in a factory, or*
- *served as the entry into a class of bioactive substances, with the end drug being a purely synthetic substance that is not produced by the source organism at all.*

In all these cases the prospect of a new regional industry and associated local financial return is negligible. On the other hand, the valuable metabolite;

- *may prove impossible to secure in sufficient quantities from anything but the natural source.*

In this case a new high value regional industry may emerge almost overnight. Such industries may initially rely on wild harvesting, but will no doubt need to evolve into renewable cropping. The anti cancer agent taxol is an excellent example of this latter model. The Pacific Yew Tree, once disposed of as lacking in any value, is now the source of the extremely valuable and useful drug taxol, leading to plantation farming. Having acknowledged the potential for harvest it is worth noting that reliance on crops for high value added drugs may not be attractive to industry in the long run. Tissue culture, and gene transfer, offer more scope for manipulating and controlling yield and metabolite variations, without reliance on seasons, crop failure due to weather extremes and/or pests. Should factory based supply opportunities arise it is likely that industry will avail themselves of these. The challenge for Australia is to ensure that such developments occur in Australia. The *take home message* here is that even if a particular bioprospecting discovery offers the option of a new primary industry (for example harvesting a native plant), this is an industry of last century and, while we may capitalize on the opportunity in the short term, we should be looking beyond the paddock to knowledge based supply solutions.

In order that Australia retains a measure of influence over where in the world such valuable metabolites are eventually manufactured/harvested it is absolutely critical that we contribute to the intellectual discovery process – even if this is done in collaboration with overseas partners. One attractive model could be that while samples sufficient for screening can be exported from Australia under licence, to facilities equipped with specialist screening infrastructure and expertise, the larger scale samples required to identify the valuable metabolite could be confined to Australia. While retaining such samples in Australia will ensure the involvement of Australian scientists, it does bring with it the obligation that we carry through on such

research – a challenge that given the appropriate resources we are more than capable of meeting. After all, many Australian postgraduates are currently employed overseas carrying out just such research – to the ultimate benefit of host nations. Having carried the cost of training these individuals surely we can find the means to gain a return on their intellectual output during their most productive years.

Obviously there are many models that could be put forward, but I would urge the committee to give serious consideration to using Australian biodiversity as leverage with which to establish and retain serious research collaborations. This approach has the potential to build and maintain our R&D base, train young Australians, and ensure Australian involvement in new industries.

Conclusions

I encourage the committee to address the reality of bioprospecting, and not be swayed by emotive media coverage, the wishful expectations of potential regional beneficiaries, or popular myths that appear to promise windfall profits for little on no investment other than *digging it up and selling it*.

Bioprospecting must be viewed as an investment, with a variety of returns, some guaranteed (training, science), others with no guarantee (billion dollar drugs). The popular stereotype of the Australian character is not that of an individual averse to risk taking, on the contrary, the *larrikin image* is endearing because of a willingness to gamble the present for a better future. Surely its time to take a few risks at the national level in order to secure a place among the successful knowledge based economies of the next century. To do any less is far more of a gamble, with very little prospects of an economically attractive outcome.

I encourage the committee to appreciate that bioprospecting embraces both basic and applied sciences, and that any policies must reflect Australia's need to train and employ a talented and receptive workforce.

Outcomes that this inquiry might aspire to should include enhancing Australia's ability to;

- *conserve and derive economic prosperity from Australian biodiversity.*
- *establish guidelines for access to biodiversity that encourage (or even require) Australian involvement in the science and intellectual discovery process.*
- *encourage and support bioprospecting science (basic and applied) in Australia.*
- *maintain high standards for scientific training in Australia.*
- *establish mechanisms to capitalize and develop new industries based on IP arising from bioprospecting discoveries derived from Australian biodiversity.*

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