SENATE LEGAL AND CONSTITUTIONAL AFFAIRS LEGISLATION COMMITTEE

INQUIRY INTO

PATENT AMENDMENT (HUMAN GENES AND BIOLOGICAL MATERIALS) BILL 2010

SUBMISSION
THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH

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1. Executive summary

The Walter and Eliza Hall Institute of Medical Research (WEHI) understands and shares community concerns with respect to equitable access to leading therapies and diagnostic tests. However, this will not be achieved by banning gene or biological material patent claims. Therefore, WEHI recommends that the Senate Legal and Constitutional Affairs Legislation Committee reject the Patent Amendment (Human Genes and Biological Materials) Bill 2010 based on the following major issues:

Misleading motivation for the amendment – Despite claims to the contrary this amendment introduces broad rather than "*narrow changes*", introduces confusion and not "*clarity*", and presents a major departure from existing patent law rather than applying "*existing law*".

Amendment conflicts with three other review findings - The proposed amendment to the Patents Act is totally contrary to the findings of the Australian Law Reform Commission (2004), the Senate Community Affairs References Committee (2010) and the Australian Council on Intellectual Property (ACIP, 2010) - all reaching the conclusion that gene patents should not be excluded under the Patents Act.

Patents have no significant negative impact on biomedical research – The amendment is not required to enable research in Australia. There are no recent examples of patents hindering research activities and no recent examples in Australia of court cases related to research activities infringing on patent rights. While WEHI supports clarification of a research exemption in law, researchers assume a research exemption in practice.

Dangerously broad scope of the amendment – More than 40% of future therapeutics would be under threat of no patent protection in Australia under this amendment, most likely leading to Australia being marginalised and no longer being a priority market for the clinical development of and access to novel biotherapeutics, vaccines and diagnostics.

Imprecise and confused wording of the amendment - There has been major "scope creep" from the original enquiry that focused on human gene sequences and patents to the current proposal that all biological materials be excluded. Lack of rigour in the wording of the amendment will inevitably lead to unnecessary court challenges and proceedings, and questioning of Australia as a serious intellectual property jurisdiction.

High risk and unforeseen consequences of the proposed amendment - The risks of this amendment are significant and unintended negative economic and social consequences could be considerable. These include loss of image as a major IP territory, reduced investment, reduced return from investment in biomedical research, and strong negative psychoeconomic signals of "dumbing down" Australia's understanding of the value of IP and the need for systems integrity and stability. All at a time when credit is tight, capital is highly mobile and options for investment and return increasingly present in other economies. A unilateral change could also result in *quid pro quo* responses.

Potential major negative impact on WEHI's translational activities - The amendment will negatively impact on our ability to continue to develop new treatments in Australia and keep Australia high on the priority list of our international collaborators. We fear that the innovation intensive companies and investors that we require to develop our inventions will seek alternative more secure environments and have several programs that could be negatively impacted with respect to Australia being a priority development location.

Issues should be addressed through other means - The amendment will fail to address equitable access to therapies and tests and this must be addressed by other means such as Crown use provisions, compulsory license provisions, Commonwealth acquisition and building on the PBS experience

Inventiveness and utility must underpin granted patent claims - We fully support the requirement for patent claims to be inventive and have utility, and a standalone DNA sequence of natural origin without invention and utility should not be patented.

Recommendations:

In summary WEHI makes the following recommendations:

1. Reject the Patent Amendment (Human Genes and Biological Materials) Bill 2010

2. Encourage adoption of the Australian Law Reform Commission (2004), the Senate Community Affairs References Committee (2010) and the Australian Council on Intellectual Property (ACIP, 2010) recommendations

3. Support IP Australia in their clarification of the research exemption and their program to develop Australia's IP system

4. Develop real mechanisms that secure equity of access to therapies and diagnostic tests

2. Introduction

Australia has until now a strong reputation for biomedical research and a patent system that generally functions well. The large number of non-resident patent applications in Australia illustrates the regard foreign innovators place in our system and market. The patent system is important for disclosure, improving innovations and securing investment and nowhere is it more important than in the biomedical sciences.

> *"..it is difficult to believe that the life science industries would have developed as they did in the absence of patents. Patents are probably more important for the fine chemical, pharmaceutical and biotechnological enterprises than for any other industrial sectors*."[1]

In the absence of patents there would be much greater secrecy and in spite of perceived tensions, research activities and intellectual property protection through invention disclosures, patents, trademarks and material transfer agreements beneficially coexist. Importantly, they provide the foundation for translation of Australia's investment in biomedical research into much needed treatments.

The Walter and Eliza Hall Institute of Medical Research (WEHI) understands concerns with respect to equitable access to leading therapies and diagnostic tests and maintains that this will not be achieved by banning gene or biological material patent claims. WEHI previously made a submission to the Senate Community Affairs References Committee concerning "*Gene Patents*" and welcomed the findings of that Committee and the recent recommendations from the Australian Council on Intellectual Property. We also welcome the ongoing program of IP reform being conducted by IP Australia to address many of the issues identified in these reviews.

In this submission, WEHI strongly recommends that the Senate Legal and Constitutional Affairs Legislation Committee reject the Patent Amendment (Human Genes and Biological Materials) Bill 2010 because it is based on false assumptions and representations, no significant evidence that gene patents hinder research, a dangerously broad scope, and imprecise and vague wording. This amendment is in our opinion highly likely to lead to major unforeseen consequences to Australia.

We believe that the proposed amendment makes no contribution to the real issue of equitable access to leading healthcare and in fact is more likely to delay the introduction of innovations in Australia. Even after removal of gene sequence claims a user would require a license to diagnostic and method of use claims – the proposed amendment fails in what it was originally trying to achieve and there are other alternatives that would be more effective and present less risk. Having failed in securing equitable access the amendment will further erode Australia's competitiveness by removing an ability to grant highly valued composition of matter claims for gene sequences and biological materials, such claims being of greater value than method of use claims when attracting the investment required to develop inventions into products.

While we understand that the amendment is not to be retrospective, the following case study provides a clear example of the type of Australian invention that would not be patentable under the proposed amendment. In our opinion future such inventions would be less likely to be introduced into Australia in a timely manner should the amendment be passed.

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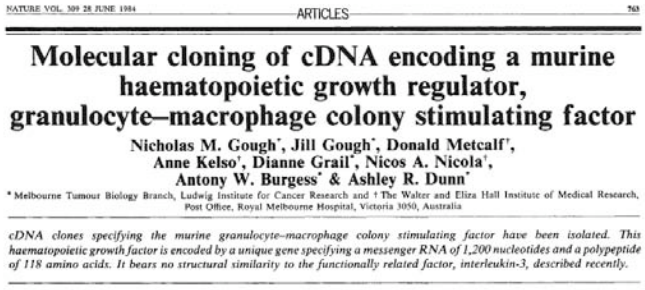
[1] Dutfield G (2009) Intellectual property rights and the life science industries. World Scientific, 2nd edition. (page 328)

Case study: Granulocyte-macrophage colony stimulating factor - understanding the significance of the proposed amendment

The discovery of and subsequent inventions related to granulocyte-macrophage colony stimulating factor (GM-CSF) illustrates the importance to patients of gene sequence and biological material patent claims leading to development of a novel and highly effective treatment. Several million patients have been treated with GM-CSF to increase dangerously low white blood cell levels encountered as a consequence of cancer chemotherapy and organ transplantation interventions[2]. Importantly many families in Australia have benefited directly from this scientific advance that would never have been translated into clinical reality without significant investment by a commercial partner under the protection of granted patent claims. Under the proposed amendment to the Patents Act this advance, a life-saving Australian invention, would not have been allowed. The amendment will seriously impact on similar future inventions.

The scientific findings that were the basis of discoveries in the 1970s resulted in the invention patented by researchers at the Ludwig Institute, Royal Melbourne Hospital and the Walter and Eliza Hall Institute and reported in the leading journal, *Nature* in 1984. The invention was based on many years of research and public investment in science but required patent protection in order to attract a partner to translate this invention into clinical benefit.



NATURE VOL. 309 28 JUNE 1984 ARTICLES 763

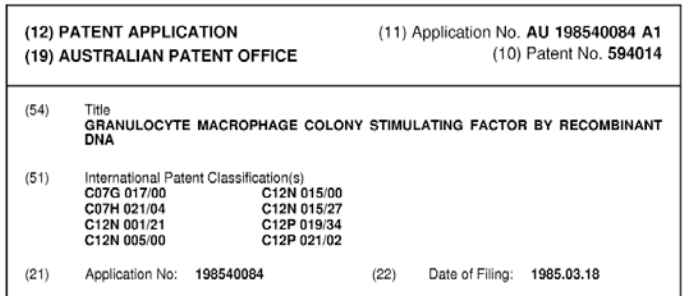
Molecular cloning of cDNA encoding a murine haematopoietic growth regulator, granulocyte–macrophage colony stimulating factor

Nicholas M. Gough*, Jill Gough*, Donald Metcalf†, Anne Kelso†, Dianne Grail†, Nicos A. Nicola†, Antony W. Burgess* & Ashley R. Dunn*

* Melbourne Tumour Biology Branch, Ludwig Institute for Cancer Research and † The Walter and Eliza Hall Institute of Medical Research, Post Office, Royal Melbourne Hospital, Victoria 3050, Australia

cDNA clones specifying the murine granulocyte–macrophage colony stimulating factor have been isolated. This haematopoietic growth factor is encoded by a unique gene specifying a messenger RNA of 1,200 nucleotides and a polypeptide of 118 amino acids. It bears no structural similarity to the functionally related factor, interleukin-3, described recently.

A patent application was filed in Australia, US, Europe and Japan and formed the basis for investment in translation, clinical trials and availability to the community. The development partner was Immunex who required patent protection and specifically, composition of matter claims based on the molecular sequence. The patent application claimed a sequence for a biological molecule.



(12) PATENT APPLICATION (11) Application No. **AU 198540084 A1**
(19) AUSTRALIAN PATENT OFFICE (10) Patent No. **594014**

(54) Title
GRANULOCYTE MACROPHAGE COLONY STIMULATING FACTOR BY RECOMBINANT DNA

(51) International Patent Classification(s)

C07G 017/00	C12N 015/00
C07H 021/04	C12N 015/27
C12N 001/21	C12P 019/34
C12N 005/00	C12P 021/02

(21) Application No: **198540084** (22) Date of Filing: **1985.03.18**

The scientific findings related to GM-CSF have always been published in a timely manner, have not been negatively impacted by third party patent strategies, and have enabled Australia to establish a "first in class position" in both scientific contribution and translation into community benefit with respect to cytokines. Importantly, the history of this case clearly shows how cancer patients can benefit directly to faster access to an invention because it was invented and patented in Australia, with clinical development starting in Melbourne in 1987. The proposed amendment would jeopardise such early access for patients.

Millions of cancer patients have benefited from this invention, marketed as *Leukine*, *Prokine* and now some generics, and global sales still remain more than $400 million, even though the patent has expired in several territories. The famous tenor Senor Jose Carreras was one of the patients treated with GM-CSF, seen here thanking one of the inventors, Professor Don Metcalf, at the Walter and Eliza Hall Institute.

[2] Metcalf D (2010) The colony-stimulating factors and cancer. Nature Rev Cancer 10:425-434

3. Misleading motivation for the proposed amendment

The motivation for the Patent Amendment (Human Genes and Biological Materials) Bill 2010 given to the Australian Parliament in November 2010 is both seriously flawed and misleading, in particular through the representations in presenting the amendment[3]:

a) It is claimed that "*the Bill is very narrow and only seeks to clarify and apply existing patent law*". The proposed changes are far reaching with respect to national and international patent law, have major potential unforeseen consequences, and the proposed wording is legally vague and in no way clarifies any aspects of existing patent law. The unforeseen consequences of such a proposal are simply not warranted by the lack of evidence underpinning the proposed amendment which, in our opinion, fails to address the issues of equitable access that initiated the original gene patent debate. Sections 6 and 7 in this submission expand further to explain why the amendment does exactly the opposite of what is claimed – it introduces broad rather than narrow changes, introduces confusion and not clarity, and presents a major departure from existing patent law rather than applying existing law.

b) It is claimed that the amendment "*will make R&D simpler, less expensive, less risky and less time consuming*". No evidence whatsoever has been presented to substantiate this claim which illustrates a lack of understanding of the genuine interplay between basic research, translational research and the eventual returns to individual or social investors that occurs under the current Patent Act. There is already widespread sharing of materials in our research communities. There is no merit in the argument that the proposed amendment "*will make R&D simpler, less expensive, less risky and less time consuming*" since there is no link between patenting biological materials and the time or cost of research. Section 5 in this submission demonstrates that patents have no significant negative impact on research and researcher fears of legal action are unfounded.

c) It is claimed that "*the bill, if passed, will create more jobs and lead to more R&D in this country*" How will this happen given the clear lack of any evidence that biological material patents hinder research? A serious misunderstanding of how research is actually conducted and the drivers of investment in translation have lead the proponents to a conslusion that by taking away a "barrier" that is not seen in practice will somehow lead to more investment. In our opinion, there is a much greater risk that the amendment would reduce activity in Australia and delay benefits from innovations. Section 8 of this submission outlines some of the unforeseen consequences that could arise from this amendment

d) It is claimed that Prof Ian Frazer will "*benefit with this Bill*" in spite of Professor Frazer being an inventor of many gene sequence patents, including those that underpin *Gardasil* and its returns to Australia. The amendment would do precisely the opposite – not allow gene sequence claims that underpin exploitation of a major innovation. Sections 10 and 11 of this submission expand on other ways of addressing concerns related to gene patents.

[3] Heffernan B (2010) Patent amendment (human genes and biological materials) bill 2010, Second Reading, Australian Senate, November 24, 2010

4. Amendment conflicts with three other review findings

The proposed amendment to the Patents Act is totally contrary to the findings and recommendations of three significant reviews:

- Australian Law Reform Commission (2004)
- Senate Community Affairs References Committee (2010)
- Australian Council on Intellectual Property (ACIP, 2010)

Each of these reviews examined extensive submissions and evidence, and all reached the conclusion that gene patents should not be excluded under the Patents Act.

The Senate Community Affairs References Committee findings are largely in line with the Australian Law Reform Commission findings of 2004. The proposed amendment is totally out of step with the findings of both enquiries that, while areas of Australia's patent system should be improved, there was no case for banning gene patents. Relevant findings from the Senate review include:

> *The lack of evidence regarding the impact of gene patents was also a feature of the Australian Law Reform Commission's (ALRC) inquiry in 2004. The ALRC noted that concerns about the impact of gene patents 'were anecdotal or hypothetical, and evidence of problems in practice – outside that small number of well-known examples – was more difficult to verify.*[4]
>
> *The evidence the Committee received concerned only isolated examples of impacts from gene patents on healthcare.*[5]
>
> *The committee could not therefore conclude that gene patents have caused significant impacts on the provision and costs of healthcare in Australia to date. The Committee also acknowledges that it is possible that patent protection has, at least in some cases, encouraged innovation.*[6]
>
> *There are few instances in Australia where enforcement of a patent has restricted medical research.*[7] *Much of the evidence on adverse impacts was restricted to generalised and/or anecdotal accounts.*[8]
>
> *Committee's inquiry can be more effectively addressed through a range of responses directed not at gene patents per se but at improving the operation of the patent system more generally.*[9]
>
> *The Committee notes that the consequences of an express prohibition on gene patents would be undoubtedly complex.*[10]

The recent ACIP review reached similar conclusions with respect to the specific exclusion of gene patent:

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[4] Senate Community Affairs References Committee (2010) *Gene Patents* (para 3.13, page 30)
[5] Senate Community Affairs References Committee (2010) *Gene Patents* (para 3.142, page 64)
[6] Senate Community Affairs References Committee (2010) *Gene Patents* (para 3.144, page 64)
[7] Senate Community Affairs References Committee (2010) *Gene Patents* (para 3.149, page 65)
[8] Senate Community Affairs References Committee (2010) *Gene Patents* (para 4.113, page 96)
[9] Senate Community Affairs References Committee (2010) *Gene Patents* (para 4.128, page 100)
[10] Senate Community Affairs References Committee (2010) *Gene Patents* (para 4.120, page 98)

> *We have found that no persuasive case has been made to introduce a specific exclusion to prevent the patenting of human genes and genetic products. Accordingly, we do not recommend the introduction of such a specific exclusion.*[11]
>
> *Like us, the Senate Committee found that there was neither the clear case nor the consensus justifying change at this time.*[12]

It is clear that in the face of three consistent independent review conclusions, and in the absence of any new evidence to support a contrary position, the proposed amendment has no justification and should be rejected on the basis of three investigations reaching exactly the same conclusion contrary to the amendment. Furthermore, none of these enquiries anticipated the dramatic expansion of the proposed amendment to ensure exclusion of all biological material as patentable subject matter. This is highly relevant because in the face of no evidence that patents hinder research the expansion to include all biological materials greatly increases exclusions, diminishes patented subject matter and hence increases the economic risk to Australia.

5. Patents have no significant negative impact on biomedical research

5.1 Failure to provide evidence

A serious flaw with the proposed bill is that it confuses the patent system with competitive research behaviour, whether academic or commercial, and erroneously tries to establish a causal link between patents and disruption or hinderance of research activities – in spite of a large amount of evidence to date showing that patents *per se* do not negatively hinder research. This was a conclusion also reached by the Senate Community Affairs Committee and in spite of the lack of evidence of a negative impact of patents on research the proposed bill resurrects the argument and motivates the change based on the same lack of empirical evidence.

It is important to acknowledge that patents do not hinder research and while a research exemption in law should be clarified, the reality is that researchers already assume a research exemption in practice. There are no recent examples of patents hindering research activities and no examples in Australia of court cases related to research activities infringing on patent rights (see Section 5.5). In reality patent holders benefit from the new knowledge created by research activities, and researchers in general benefit from the public disclosure afforded by the patent system. Furthermore, the proponents of the amendment must explain why only gene and biological materials patents hinder research and other patents have no negative impact.

Our own and many other's experience shows that patents have minimal or no negative impact on research and the effects predicted by proponents of the "anti-commons issue" are not borne out in the available data, and fears of blocking the use of upstream discoveries are largely unfounded[13]. Studies show that the vast majority of researchers do not report that patents hinder their activities. Many peer review studies have reached the conclusion that there is only a minor or no negative impact of patents on biomedical innovation and research activities, and that scientists either find ways around patents or

[11] Advisory Council on Intellectual Property (2010) *Patentable subject matter* (www.acip.gov.au) page 60
[12] Advisory Council on Intellectual Property (2010) *Patentable subject matter* (www.acip.gov.au) page 14
[13] Caulfield T, Cook-Deegan RM, Kieff FS, Walsh JP (2006) Evidence and anecdotes; an analysis of human gene patenting controversies. *Nat Biotech* 24(9) 1091 -1094

ignore them [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24]. For example, in a report to the (American) National Academy of Science, Walsh *et al* (2005) found that among academic researchers "*none were stopped by the existence of third-party patents, and even modifications or delays were rare, each affecting around 1% of our sample*' and only 5% of researchers regularly checked for patents on research inputs[25]. In fact the authors concluded that "*a key reason for the negligible impact of patents on the conduct of academic biomedical research is that researchers largely ignore them*."

> *"It appears that academic researchers are becoming more secretive, but that is not shown to be attributable to the patenting process, suggesting that the solution might not reside in modifying patent policy."* ….."*The combination of a lack of empirical evidence of problems and a mismatch between the problems and proposed solutions may explain why there has been little actual policy change.*"(Caulfield et al 2006)

> *"Although theories abound about how patent law encourages or discourages innovation, we actually have little empirical data…"* [26].

> *"Given the state of evidence, no strong conclusion can be drawn for or against the patent system in general."* [27]

> *"There is no evidence that the patent process affected the speed of genetic test development."* [28]

> *"Research … appears to have progressed independently of patenting status. There is no evidence that patents have had any positive or negative impact on hearing loss genetics research."*[29]

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[14] Blumenthal D et al (1997) Withholding research results in academic life science. Evidence from a national survey of faculty. *J Am Med Ass* 277:1224-1228

[15] Walsh, J. P., Arora, A. and Cohen, W. M. 2003, 'Effects of research tool patents and licensing on biomedical innovation', in *Patents in the Knowledge-Based Economy*, eds W. M. Cohen and S. A. Merrill, National Academies Press, Washington, DC

[16] Straus, J. 2002, 'Genetic inventions and patents – A German empirical study', presentation to BMBF and OECD Genetic Inventions, Intellectual Property Rights and Licensing Practices Workshop, Berlin, 24–25 January.

[17] Nicol, D. and Nielsen, J. 2003, '*Patents and* m*edical* b*iotechnology: An* e*mpirical* a*nalysis of* i*ssues* f*acing the Australian* i*ndustry*', Centre for Law and Genetics Occasional Paper no. 6, University of Tasmania, Hobart.

[18] Murdoch, C. J. and Caulfield, T. 2009, 'Commercialization, patenting and genomics: Researcher perspectives', *Genomic Medicine*, vol. 1, article 22.

[19] Walsh, J. P., Cohen, W. M. and Cho, C. 2007, 'Where excludability matters: Material versus intellectual property in academic biomedical research', *Research Policy*, vol. 36, pp. 1184–203.

[20] Jensen, P. H. and Webster, E. 2011, 'The effects of patents on scientific inquiry', *Australian Economic Review*, vol. 44.

[21] Walsh JP, Arora A, Cohen WM (2003) The patenting and licensing of research tools and biomedical innovation. In Patents in the knowledge-based economy, ed Cohen WM, Merrill S. Washington: National Acadamies Press (Page 285 – 340)

[22] Walsh, J. P., Cho, C. and Cohen, W. M. 2005, 'View from the bench: Patents and material transfers', *Science*, vol. 309, pp. 2002–3.

[23] Hong W, Walsh JP (2009) For money or glory? Commercialization, competition, and secrecy in the entrepreneurial university. *Sociological Quarterly* 50: 145 - 171

[24] Murdoch CJ, Caulfield T (2009) Commercialisation, patenting and genomics: researcher perspectives. Genome Medicine 1:22:1- 5

[25] Walsh JP, Cho C, Cohen WM (2005) *Patents, materials transfers and access to research inputs in biomedical research*. Final Report to the National Academy of Science's Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions.

[26] Gold ER, Carbone J (2010) Myriad genetics: In the eye of the policy storm. *Genetics in Medicine*, vol. 12, pp. S39–70 (page 65)

[27] Gold ER, Carbone J (2010) (page 66).

[28] Chandrasekharan S, Heaney C., James T, Conover C, Cook-Deegan R (2010) Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis. *Genetics in Medicine*, vol. 12, pp. S194–211(page 203)

"It is clear that the Tay-Sachs gene patent did not stifle research as it was never enforced. "[30]

"Concerns regarding inhibition of research because of the HFE gene patents do not seem to be supported." [31]

"… we have no evidence that the virtual LQTS monopoly from 2003–8 had a stifling effect on research." [32]

"... the races were driven by wanting priority of scientific discovery, prestige, scientific credit, and the ability to secure funding for additional research based on scientific achievement …. having not found that patents to be a significant impediment to research on Alzheimer's Disease." [33]

Before any amendment is entertained it is critical to understand the dynamics and reality of the global research environment and demand evidence of a significant negative impact. Proponents of the amendment focus on the very old and by now exceptionally rare cases of the Myriad BRCA patents and Chiron's Hepatitis C patents as being exemplars of the inhibition of research by gene patents. No significant new examples have been presented and therefore the proponents of the amendment are putting Australia's standing and patent systems at risk on the basis of few exceptional cases that occurred many years ago.

5.2 Example - BRCA1 gene patents

Myriad's BRCA1 patents[34] are often cited as examples of IP protection that stifles research even though they were granted in Australia and the US more than 10 years ago. There is no significant evidence of these patents hindering research. In the period 1998 – 2010 there have been 5,674 BRCA1 primary sequence publications globally[35] with 1,933 primary sequence publications from the US where the patents are in force (34.1% of total) and 184 primary sequence publications from Australia where the patents are also in force (3.2% of total). Table 1 presents the key global participants in BRCA1 research and highlights the prominence of the Peter MacCallum Cancer Centre and the University of Melbourne in research publication, even in the face of issued patent claims.

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[29] Chandrasekharan S, Fiffer (2010) Impact of gene patents and licensing practices on access to genetic testing for hearing loss. *Genetics in Medicine*, vol. 12, pp. S171–93 (page 173)

[30] Colaianni, A., Chandrasekharan, S. and Cook-Deegan, R. 2010, 'Impact of gene patents and licensing practices on access to genetic testing and carrier screening for Tay-Sachs and Canavan disease', *Genetics in Medicine*, vol. 12, pp. S5–14 (page 11)

[31] Chandrasekharan, S., Pitlick, E., Heaney, C. and Cook-Deegan, R. 2010, 'Impact of gene patents and licensing practices on access to genetic testing for hereditary hemochromatosis', *Genetics in Medicine*, vol. 12, pp. S155–70 (page 156)

[32] Angrist, M., Chandrasekharan, S., Heaney, C. and Cook-Deegan, R. 2010, 'Impact of gene patents and licensing practices on access to genetic testing for long QT syndrome', *Genetics in Medicine,* vol. 12, pp. S111–54 (page 120)

[33] Skeehan, K., Heaney, C. and Cook-Deegan, R. 2010, 'Impact of gene patents and licensing practices on access to genetic testing for Alzheimer disease', *Genetics in Medicine*, vol. 12, pp. S71–82 (page 77)

[34] Filed 1995, published 1996, AU 686004 granted June 1998, AU 691331 granted Nov 1998, AU 691958 granted Nov 1998; expiry 2015

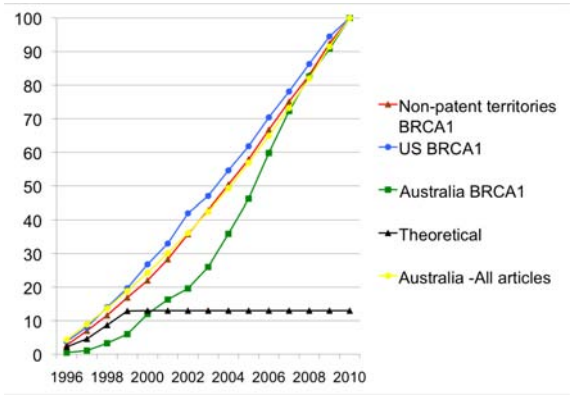
[35] ISI Web of Science and PubMed from January 1998 to end September 2010

Table 1: The origin of primary BRCA1 publications (1998 – 2010)

BRCA1 publications			
Top countries	% total	Top publishers	Publications
1. US	48.7	1. University of Pennsylvannia	187
2. Canada	12.1	2. University of Toronto	141
3. UK	10.6	3. Harvard University	128
4. France	8.8	4. Georgetown University	110
5. Netherlands	6.7	5. University of Utah	95
6. Australia	5.7	6. National Cancer Institute	91
		14. Peter MacCallum Cancer Centre	62
		21. University of Melbourne	52

Contrary to the claims of the proponents of the amendment, a key insight is to understand that patents have not significantly hindered BRCA1 research or its publication. Figure 1 shows the relative publishing trajectory from 1996 to 2010 (normalized to 100%) in global non-patent territories, in the US where patents were granted (1998), and in Australia where patents were also granted (1998) [36]. Australia's initial lagging adoption of the technology, illustrating delays in knowledge diffusion, was replaced by rapid uptake to become the sixth most publishing nation. The theoretical curve illustrates what would be expected if patents prevent research. It is clear from these publication data that the issuance of patents in the US had no significant impact on research publication, that the granting of patents in Australia also had no negative impact on published research activity.

Figure 1: Accummulation of primary BRCA1 research publications



Approximately 12 years after these patents were granted in Australia, 49 research organisations have published research results related to the BRCA1 gene and sequences, including CSIRO, 6 medical research institutes, 13 universities, 18 hospitals, 8 service providers and the Cancer Council. To our knowledge none of these have been taken to court by Myriad or Genetic Technologies Limited for patent infringement and as one of these organisations, WEHI has not experienced any attempt by Myriad or Genetic Technologies to limit BRCA1 research activities.

Much of the debate has focused on the purported negative impact of the Myriad BRCA1 patents on research and the exercising of related rights by Genetic Technologies in Australia. This aspect of the debate is seriously flawed since there are many other holders of BRCA1 patents in Australia and it is illogical to claim that only the Myriad patents hinder BRCA1 research. Examples of BRCA1 patents published in Australia are listed in Appendix 1 and illustrate the wealth of research information that has been published through the patent system. Table 2 illustrates the steady stream of BRCA1

[36] "Myriad" patents filed 1995, published 1996; AU 686004 granted June 1998; AU 691331 granted Nov 1998; AU 691958 granted Nov 1998; expiry 2015

patent applications to publish in Australia to reach a currently identified intellectual property estate of at least 68 patent applications, the majority of which do not involve Myriad[37]. Thus we have a clear example of extensive research being conducted and reported even though there are probably points of potential patent infringement in the absence of a confirmed research exemption. These 68 BRCA1 patent applications in Australia illustrate the vibrant contribution of patents to research dissemination and knowledge and continuing innovation.

Table 2: The number of individual BRCA1 patent applications to publish in Australia

Year	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	Total
No	1	4	5	14	8	3	5	4	5	5	1	1	1	1	9	68

The rich research activity related to BRCA1 both in Australia and globally clearly leads to the conclusions that patents granted to Myriad and to other organisations have not hindered research activities. Myriad maintains it has never enforced its patents against researchers[38] and as Gold and Carbone report:

> *"Myriad fully supported the use of its inventions, without license or payment, by researchers actually carrying out their own research projects*" and
>
> "*Myriad maintains that its position has always been that it welcomed research with the aim of facilitating the discovery of new mutations*."[39]

5.3 Example - Hepatitis C patents

The case of Chiron and its 1992 Hepatitis C patent was used in the Senate hearings as an example of supposed hinderance of research in Australia. To the extent that this occurred it would have had minimal impact on academic research. Since 1992 there have been 68 Hepatitis C gene sequence publications in Australia from 27 organisations, representing 1.4% of the more than 4,800 publications globally[40], the majority of which originate from territories where Chiron's patents granted. The Australian publications came from CSIRO, 11 universities, 7 hospitals, 6 research institutes, and 2 reference laboratories and we are not aware of any action from Chiron in recent years. In our opinion Australia's relatively low share of Hepatitis C publications reflects a relatively low research interest in Hepatitis C rather than researchers being scarred of infringing Chiron's or other's patent claims.

5.4 Example - GM-CSF

Granulocyte macrophage colony stimulating factor (GM-CSF) presents a clear example of intellectual property based on gene sequence claims that has benefited patients and Australia, but would be excluded under the proposed amendment. Several million patients have been treated with GM-CSF to increase dangerously low white blood cell levels encountered as a consequence of cancer chemotherapy and organ transplantation interventions[41].

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[37] Patents identified through PatBase (accessed January 24, 2011) and based on reference to BRCA1 in the title, abstract or claims

[38] Cook-Deegan R et al (2010) Impact of gene patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancer to colon cancers. *Genetics in Medicine* 12:S15-38

[39] Gold ER, Carbone J (2010) Myriad Genetics: In the eye of the policy storm. *Genetics in Medicine* 12:S39-70

[40] Data from ISI Web of Science (Thomson Reuters) and PubMed to October 2010

[41] Metcalf D (2010) The colony-stimulating factors and cancer. Nature Rev Cancer 10:425-434

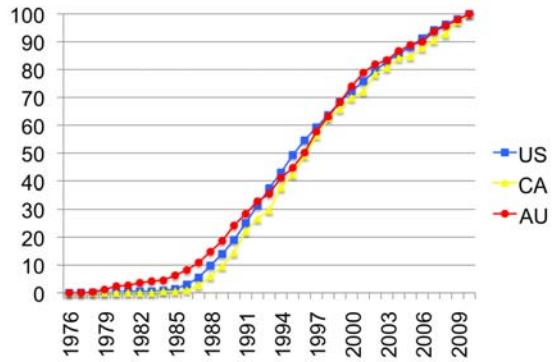
This case is particularly instructive since it involves granted patent gene sequence claims from inventors at the Ludwig Institute of Cancer Research and the Walter and Eliza Hall Institute, clinical development in Melbourne, and effective commercialisation by Research Corporation Technologies in the US with no restriction of research activities for other parties. Between 1976 and 2010 there have been 4,500 primary publications with GM-CSF in the title[42], 317 of which were published by companies. Table 3 illustrates the top publishing countries and organisations, and Australia's relatively high share that reflects the "first mover" advantage. Patents were granted in major territories with the exception of Canada and were essential for the clinical development investment by Immunex.

Table 3: The origin of primary GM-CSF publications (1976 – 2010)

GM CSF publications			
Top countries	% total	Top publishers	Publications
1. US	42.6	1.Harvard University	154
2. Japan	11.4	2. University of Tokyo	106
3. Germany	7.6	3. Royal Melbourne Hospital	102
4. Australia	7.4	4. Immunex	101
5. UK	6.3	5. University of California LA	99
6. Italy	5.6	6. University of Texas	90
7. Canada	4.9	7. National Cancer Institute	89

Figure 2 illustrates the relative publishing trajectory from 1976 to 2010 (normalised to 100%) for primary GM-CSF research publications in the US, Canada and Australia. Patents with gene sequence claims were granted in Australia (1990) and the US (1997) but not in Canada. Apart from the slight lag for Canada there is clearly no difference between these trajectories and the presence or absence of granted gene sequence claims has had no impact on research and its publication.

Figure 2: Accumulation of primary GM-CSF research publications



5.5 The generally unfounded fear of infringement and legal action

The proposed amendment does not address any of the issues related to a research exemption in Australia. Proponents of the amendment have argued that fear of infringing gene patents is hindering research. In the United States, the landmark *Madey v. Duke (2002)* case [43] was meant to be a watershed by ruling that university research was not exempt from liability for patent infringement. In reality, the case was much more complex than simply an academic institution allegedly infringing the law and was driven largely by employer–employee conflicts. The ruling was predicted to spell the end of an assumed

[42] This restriction meant that GM CSF was the main subject of the publications, review articles and other secondary reports were excluded

[43] Madey vs Duke University, Circuit of Appeals of the Federal Court, 307 F.3d 1351, October 3, 2002.

research exemption in the United States, but several years on there have been negligible similar cases in spite of the continuing vibrant growth of the public and commercial research industries in the US. One can only conclude that, if it exists, uncertainty around a research exemption has resulted in very little legal action in the United States.

Review of Figures 1 and 2 shows no impact on publication growth as a consequence of the *Madey v Duke* ruling in 2002.

In the absence of any global impact of the *Madey v. Duke* ruling and returning to the Australian debate, it is essential to question the rigour of the claimed logic that gene patents hinder research. Such assertions raise the question, "*Why specifically gene sequence patents and why not patents in other technology areas?*" If there is to be any validity in the argument that patents hinder research, the proposition must be that 'all patents hinder all research' - evidence to support this proposition remains totally elusive.

It is important to consider the significant scale of activities, for example, in Australia. There are more than 75,000 researchers in Australia publishing more than 25,000 scientific articles per year and filing more than 7,200 provisional patents per year.[44] Currently, more than 26,000 resident and non-resident patents are filed each year in Australia, 1.9 million are filed globally and there are more than 6.7 million patents in force globally. [45] Furthermore, the Australian government invests more than $6 billion per year in research. Given the scale of these activities it is clear that 'freedom to operate' determinations would be burdensome and are not considered by the majority of researchers or their employing organisations. In addition, it is a major undertaking for a patent holder to determine infringement by researchers even if they so desired.

Given this strong research activity in the face of a growing patent estate we should examine whether patent holders are actually enforcing rights against researchers. Examination of Australian patent infringement cases over the last five years [46] provides no evidence of patent holders exercising rights against research infringement. Of a total of 206 patent-related cases in the Federal Court, Full Federal Court and High Court in the last five years, only 17 per cent related to biomedical cases, and of these, approximately two-thirds related to generic substitution issues at the end of patent life. Only 6 per cent of patent cases involved biomedical innovation and only three cases involved academia[47]. In the last five years no case was linked to the fear of patents hindering research, the question of a research exemption and not one gene was mentioned.

Medical research institutes in Australia are increasingly active in IP protection. Review of the *AusPat* database revealed that 27 institutes had 1,282 patent applications in the last 25 years. There are, however to our knowledge, no known examples of any of these institutes taking action against each other to restrict research activities in the light of issued patent claims.

One can only conclude that if the risk and threat of patent infringement through research activities is real, the search for predicted threatening letters and court cases is disappointing. However, the need for clarification of the research exemption in Australia was highlighted by the Australian Law Reform Commission (2004), Senate Community Affairs References Committee (2010) and Australian Council on Intellectual Property

[44] DEST 2005, 'Australian science and innovation system: a statistical snapshot'.
[45] World Intellectual Property Organisation (2010) World intellectual property indicators', WIPO Publication No. 941(E) www.wipo.int/ipstats.
[46] Australian Legal Information Institute-AustLII (2010) www.austlii.edu.au/databases.html. Accessed October 2010.
[47] *Wake Forest University (US) vs Smith and Nephew* (a dispute over license payments for a wound dressing), *University of Sydney vs ResMed* (a dispute over license payments for a nasal mask) and *University of Western Australia vs Gray* (a dispute over IP ownership)

(2010) and is currently being acted upon by IP Australia. WEHI supports this clarification in law.

6. Dangerously broad scope of the amendment

The proposed amendment would diminish Australia's potential domestic position in the discovery, invention and translation of new therapeutics and related diagnostic tests that would potentially impact on every single Australian family. There are two likely consequences of the broad exclusions claimed in the amendment – firstly, development of Australian biological material innovations will increasingly migrate to jurisdictions with a continued integrity of the patent system and secondly, non-resident inventors will increasingly regard Australia as a second priority market for product introduction.

While we understand that the proposed amendment is not retrospective we strongly believe that invention patterns of the past will continue into the future, with in fact an increasing role of biological materials and gene sequences in genetic engineering. A major proportion of past, present and future therapeutics would be disallowed under this amendment and an analysis of approved "new chemical entities" (NCE) provides stark background to the potential ramifications of this amendment.

In the period 1981 – 2006, 1,011 NCEs were approved (in the US with most also being approved in Australia) and these included 124 biologicals, 43 pure natural products, 232 direct derivatives of natural products, 47 synthesised copies of natural products and 39 vaccines containing natural products many of which contained claimed sequences[48]. Only 310 NCEs were purely synthetic molecules not contemplated by the proposed amendment. This means that 17% of all historical NCEs would clearly be ineligible for patent protection under this proposed amendment, and a further 31% would be ineligible subject to court interpretation of the proposed words "*derivative*" and "*substantially similar*". In our opinion, this proportion of 48% of all therapeutics under threat of no patent protection in Australia would likely increase due to the established track record and continued opportunities of natural products, and the increasing role of biological therapeutics such as antibodies, proteins and peptides.

Examples of specific therapeutic areas further illustrates the potential negative impact of this proposed amendment (Table 4) either by direct exclusion or court determined interpretation. Significant examples of drugs that would not be patentable include paclitaxel and its derivative docetaxel, erythromycin and its highly successful derivatives clarithromycin and azithromycin, erythropoietin and the increasing range of leading humanised antibody therapies such as *Herceptin*. *Herceptin* is currently the largest selling oncology drug in Australia, is based on antibody and sequence patent claims, has been listed on the PBS since 2006 and saves the lives of approx. 1,000 women per year in Australia. In our opinion, and in fact through our direct experience of collaborating with Genentech (*Herceptin*'s developer), *Herceptin* would not have been developed in the absence of such patent claims.

The scope of the proposed amendment goes far beyond human gene patents, therapeutics and diagnostics. It relates to all biological material and would impact negatively on many other areas such as the veterinary, agriculture, aquaculture, biofuel, brewing and biomaterials sectors. Most genetically modified organisms rely on natural gene sequences or their derivatives and their application. Novel biopolymers and other biomolecules will most likely be "*derivatives*" or "*substantially similar*" and, based on

[48] Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. *J Nat Prod* 70(3):461 - 477

global trends, their increased use in a wide range of Australian industries is to be expected.

Table 4: Type of approved NCE in the period 1981 – 2006 (see Newman and Cragg)

Therapeutic indication	Total approved	Biological %	Natural %	Natural derivative %	% excluded by amendment
Cancer	100	17	9	25	**51**
Bacterial infection	109	0	9	59	**68**
Diabetes	32	56	3	12	**71**

The biopharmaceuticals market is underpinned by patents related to biological materials and molecular sequence claims. These patents are the fundamental IP drivers of a global market forecast to grow at nearly 7% CAGR through to 2015, with monoclonal antibodies showing higher growth of 9% and continuing to dominate 75% of the market[49]. Growth in global sales of therapeutic proteins is expected to increase from US$61 bn in 2009 to $78 bn in 2015. Similar growth is predicted for the vaccine market that was valued at US$18 bn in 2009 and expected to grow to $28 bn in 2015. Growth of these markets is always driven by those territories affording patent protection where they are given priority attention by the companies responsible for development and marketing. Table 5 illustrates the current top global biotherapeutics having Australian patent applications and which would be disallowed under the proposed amendment. Table 6 outlines just some of the Australian companies with patenting activities related to sequences and biomolecules. In our opinion the proposed amendment will most likely lead to Australia being marginalized and no longer being a priority market for the clinical development of and access to novel biotherapeutics, vaccines and diagnostics

Table 5: Top biotherapeutics[50]

Product	Compound	Company	2010 sales ($ bn)	Class	Main indication
Enbrel	Etanercept	Amgen/Pfizer	7.1	Human TNF R/IgG1 genes	Inflammation
Avastin	Bevacizumab	Genentech	6.8	Humanised MAb	Cancer
Rituxan	Rituximab	Genentech/Biogen	6.6	Mouse/human MAb	Leukemia, autoimmune
Herceptin	Trastuzamab	Genentech	5.7	Humanised MAb	Cancer
Neulasta	Pegfilgrastin	Amgen	3.5	Human G-CSF	Chemotherapy support
Lucentis	Ranibizumab	Genentech	3.0	Humanised Fab	Macular degeneration
Epogen	Epoetin alfa	Amgen	2.6	Human erythropoetin derivative	Anemia
Avonex	Interferon beta-1a	Biogen	2.5	Human interferon	Multiple sclerosis
Aranesp	Darbepoetin alfa	Amgen	2.5	Human erythropoietin derivative	Chemotherapy support
Neupogen	Filgrastim	Amgen	1.3	Human G-CSF derivative	Chemotherapy support
Tysabri	Natalizumab	Biogen	1.2	Humanised MAb	Multiple sclerosis
Xolair	Omalizumab	Genentech	1.0	Humanised MAb	Asthma
Cerezyme	Imiglucerase	Genzyme	0.7	Human enzyme derivative	Gaucher's disease
Soliris	eculizumab	Alexion	0.5	Humanised MAb	Hemoglobulinemia

[49] Business Insights Reports 2010 The Future of the Biologicals Market Market overview, innovations and company profiles
[50] Biocentury Jan 10, 2011 page 4

Table 6: Examples of Australian companies with products based on sequences and biomolecules

Company	IP	Main indication	Stage	Note
Arana Therapeutics	Several humanised MAb	Inflammation, cancer	Market, clinic	Acquired by Cephalon
Bionomics	Gene sequences and MAbs	Neuroscience, cancer	Clinic	
CSL	Gardasil – HPV gene sequences	HPV vaccine	Market	Partnered with Merck
CSL	IL-13 R and MAbs	Asthma	Preclinical	
CSL	G-CSF MAb	Arthritis	Preclinical	Collaboration with WEHI
Evivar	Hepatitis B mutations	Directing Hep B therapy	Market	
G2 Therapies	C5a R humanised MAb	Inflammation	Preclinical	Partnered with Novo Nordisk
Nexpep	Gluten epitopes	Coeliac disease	Clinical	Collaboration with WEHI/MH
Novogen	Clover isoflavone derivatives	Cancer	Clinic	Acquired by Leo
Peplin	Euphorbia ester derivatives	Keratosis, skin cancer	Clinic	Collaboration with Ludwig Institute
Vegenics/Circadian	Human VEGF and MAbs	Cancer	Preclinical	
Xenome	Marine conotoxin derivatives	Pain	Clinical	

7. Imprecise and confused wording of the amendment

The wording of the proposed amendment is extraordinarily imprecise and ambiguous, and has all the hallmarks of "legislation on the run", irrespective of the clearly flawed rationale for such a proposal, and must not be enacted in its current form by the Australian Parliament. We submit that such lack of rigour will inevitably lead to unnecessary court challenges and proceedings, and questioning of Australia as a serious intellectual property jurisdiction. There has been major "scope creep" from the original enquiry that focused on human gene sequences and patents to the current proposal that all biological materials be excluded.

By way of example the proposed substitution in subsection 18(2) of the Patents Act should be examined more closely, the proposed amendment being:

> *(2) The following are not patentable inventions:*
>
> > *(a) human beings, and the biological processes for their generation;*
> >
> > *and*
> >
> > *(b) biological materials including their components and derivatives, whether isolated or purified or not and however made, which are identical or substantially identical to such materials as they exist in nature.*

The interpretation is compounded further by the proposed insertion to Section 18(4) of the Patents Act:

> *(5) In this section:*
>
> > ***biological materials**, in section 18, includes DNA, RNA, proteins, cells and fluids."*

The legal confusion that this proposed amendment will almost certainly cause can be illustrated by the following critical interpretation issues that would arise directly if enacted:

a) The title of the amendment relates to "*human genes and biological materials*". Why specifically "*human genes*" when the exclusion appears to exclude all genes? Are "*biological materials*" only human?

b) Genetically modified crops, including the current cotton and canola variants relying on inserted "natural genes" would not be patentable

c) "*Components and derivatives*" would appear to include all actual and possible metabolites whether actually observed in nature or not. This then means that a claimed innovative metabolic derivative could be declared invalid when it is eventually discovered in nature.

d) "*Substantially identical*" is a significant and major legal drafting error and indicative of the apparent lack of intellectual rigour in the proposed amendment. Clearly, something is identical or it is not. Was the drafting intention "substantially similar"? Does it mean one, two, three substitutions? Does it include a combination of peptide epitopes that are important for a particular treatment? Does it include a protein that lacks a domain to provide better stability? This introduces major uncertainty into Australia's patent jurisdiction and we conclude that the costs of prosecution and litigation will increase in proportion to the level of uncertainty created by such an unclear term.

   Arguably, one of the greatest patents in pharmaceutical history, "*Aspirin",* would probably be disallowed since it could be argued that even with the addition of the "acetyl" group, the "salicylic acid" was "*substantially identical*". The major contribution to diabetes through the invention that the substitution of a single amino acid in pig insulin would create human insulin would be questioned. Is this meant to be the same as the "*essentially biological*" wording that has caused long running lack of clarity in the European Patent Office[51]?

e) The attempt at defining "*biological materials*" is seriously flawed and gives no guidance as to whether the following are intended to be included or excluded from the proposed amendment:

   a. Peptides – there is no mention of peptides in spite of their significance in biology and as therapeutics. When is a peptide a protein? Is an Australian marine conotoxin allowable or to be excluded?

   b. Carbohydrates, lipids and vitamins or their derivatives – there is not a mention in the definition in spite of their critical role in biology, understanding of disease and development of therapeutics and diagnostics.

   c. Does "DNA" specifically include cDNA and antisense sequences?

f) What is a "*fluid*"? Is this meant to cover for example urine, sap, honey, blood, milk, seminal plasma, vitrous humour, synovial fluid, sweat, and tears, but exclude cytoplasm or extracts of cells or homogenised tissues?

g) "Cells" are not defined and this wording does not clearly address prions (arguably only proteins), for example related to "mad cow disease", and whether viruses (arguably combinations of DNA and proteins) are included or excluded under the definition. How would this wording impact on vaccine development where

[51] Dutfield G (2009) Intellectual property rights and the life science industries. World Scientific, 2nd edition. (page 205)

antigens or epitopes are included. A literal interpretation of the proposal would clearly be that *Gardasil* should not be patentable in Australia.

The proposed amendment is unworkable and must be rejected on the basis of unclear definitions, vague language and consequently uncertain legal standing that would inevitably result in unnecessary legal proceedings but make no contribution to equitable access to health care in Australia.

It must be emphasised that the "scope creep" from originally arguing for the exclusion of human genes to now excluding all biological materials raises further serious concerns about the confused motives and goals of the amendment. What was originally a debate about securing equitable access to genetic diagnostic tests has morphed into a vastly different proposition that Australia would somehow benefit from a ban on composition of matter claims for biological materials, their components and derivatives, and material that was substantially similar. It is precisely such claims that have lead to major advances such as GM-CSF (page 6) and the examples presented in Section 6. It is precisely such claims that will help us attract partners and investors to maximise our chance of translating our inventions for the benefit of the community (see Section 9).

8. High risk and unforeseen consequences of the proposed amendment

Patents involving gene sequences and biological material present a complex area that requires rigour in analysis and understanding of how intellectual, social and economic systems and processes interrelate. It is vital to consider all information and aspects before any decisions are made to alter Australia's patent system. It should be emphasised that IP Australia already has significant activities that address recommendations from the ALRC (2004) findings, including a clarified research exemption.

Without balanced, evidence-based, analysis the risks of unintended negative economic and social consequences could be considerable. In reality there are very few examples of things going wrong due to Australia's patent system and the examples used in this debate originate in patents granted more than 10 years ago and shortly due to expire. History must judge the Myriad, BRCA and Genetic Technologies Limited issues to be a point in time of learning for all and not catalysts for changes long after the event in the patent system in Australia – there is too much to risk. By banning patent claims for gene sequences and all biological materials Australia sends a strong signal that will have many direct and indirect consequences – most of which are impossible to quantify.

> "*Without more compelling evidence of an overwhelmingly negative impact in contexts that are critical to the public good, there is no adequate justification for rushing into a radical legislative fix that might have substantial unintended negative consequences*."[52]

> "*The paucity of documented examples in which the fears surrounding gene patents have manifested themselves is striking, particularly when one considers the high level of public concern and the extraordinary nature of the proposed legislative fix*."[53]

[52] Holman CM (2009) The impact of human gene patents on innovation and access: a survey of human gene patent litigation. *UMKC Law Review* 76:295 - 361

[53] Holman CM (2009) The impact of human gene patents on innovation and access: a survey of human gene patent litigation. UMKC Law Rev 76:295 -361 (referring to the US Congress bill proposal "Genomic Research and Accessibility Act")

Image of Australia as a major IP territory - Australia is one of the key major markets for innovator companies and typically represents 2 – 3% of patented product sales. As a consequence of the significant market value and associated skills in translation and rapid adoption, Australia is seen by innovator companies as being a priority, "tier one" market. The Australian Patent Office is 10th in the world with respect to patents granted. Importantly it is 7th in the world for non-residential patents with more than 92% of patents granted in Australia belonging to foreign owners. Approximately 11,000 foreign-owned patents a year being granted in Australia illustrates that we are a highly valued market precisely because of patent protection. Why would we change this image on the basis of no evidence?

Ironically, while our major emerging competitors such as China, India, Russia, Turkey and Brazil are increasingly aligning their IP policies with internationally recognized standards, this amendment would see Australia move in the opposite direction to align itself more closely with Venezuela, considered to be an IP pariah.

Reduced investment in Australia - Patents are an essential component to being able to translate inventions into benefit and return. Patents are vital to attracting investment in invention and developing new therapies and vaccines due to the extremely high cost of their development. Importantly, composition of matter patents (i.e. composition, structure, sequence) are valued more highly than method of use or process patents because they are precise and more easily monitored, enforced and defended. While patent holders must not be allowed to abuse their monopoly, they require a period of exclusivity to justify a highly risky investment. This is especially important given that the failure rate to market approval is well above 90% for both diagnostics and therapeutics.

In concluding that it did not support an express prohibition on gene patents, the ALRC's 2004 report also expressed concerns that this approach could adversely impact on investment in Australia's biotechnology industry:

> *"A prohibition on patenting of genetic materials….would represent a significant and undesirable departure from accepted international practice with respect to genetic inventions, and may adversely affect investment in the Australian biotechnology industry."* [54]

Two examples are the University of Queensland's *Gardasil* which relies on a virus gene sequence and WEHI's GM-CSF which uses a patented gene sequence to produce a protein which has been used to treat millions of cancer patients. *Gardasil* cost more than $300 million to develop and involved more than 20,000 clinical trial subjects – who would fund this without a period of exclusivity? GM-CSF has provided important royalty revenues to the institute that have been reinvested into research into new therapies. Would these two innovations have been available so quickly in Australia in the absence of patent protection?

> *"..it is difficult to believe that the life science industries would have developed as they did in the absence of patents. Patents are probably more important for the fine chemical, pharmaceutical and biotechnological enterprises than for any other industrial sectors*."[55]

The proposed amendment would dangerously erode Australia's position and nudges Australia further down the path of becoming increasingly dependent on other nation's

[54] Australian Law Reform Commission (2004) Genes and ingenuity (page 84)
[55] Dutfield G (2009) Intellectual property rights and the life science industries. World Scientific, 2nd edition. (page 328)

abilities to elaborately transform intellectual property and resources into valued products and treatments.

Reduced return to Australia – Recipients of public research funds are obliged to maximise the chance of IP creation, capture and return to the taxpayer. By creating a disincentive for investment in Australia and increasing the risk of migration of Australian invention offshore, this amendment will reduce the ability to generate returns, for example from NHMRC funded research, and will in no way contribute to the success of such research investment by the Australian taxpayer.

The risk of "dumbing down" - This proposed amendment sends a strong negative signal with respect to Australia's regard for intellectual property and illustrates a "dumbing down" of Australia's understanding of IP and its value. Australia's relative IP standing is already tenuous – ranking 32nd in the world for patents/GDP dollar and 36th in the world for patents/R&D dollar invested. Psychoeconomic signals are enormously important for gaining mindshare of innovation intensive companies and investors. In our opinion the proposed amendment will almost certainly erode Australia's position further as such companies and investors quickly move to alternative more supportive environments.

System integrity and the risk of policy on the run - Australia can hardly claim to have integrity of IP policy and processes when a proposal to ban human gene sequences spontaneously becomes an amendment to ban patent claims related to all biological materials on the basis that they hinder research. Certainly, genetically modified organisms would be banned under the proposed amendment and it would be reasonable for any person to question – what will be next on Australia's agenda? Nanotechnology, clean technology, etc? This amendment creates uncertainty at a time when credit is tight and options for investment and return increasingly present in other economies. A strong, consistent and globally aligned patent jurisdiction is essential to capturing and retaining investment in our biomedical innovations.

Agreement obligations - Australia has obligations under several international agreements (e.g. TRIPS) and while Australia may consider that a unilateral change could be motivated, the realm of international trade is always governed by *quid pro quo*, the price and consequences of which would be totally unknown. While Australia controls its sovereignty, it would be naive to imagine that such a radical unilateral change to our patent law would go without some economic consequences of a negative nature.

9. Potential major negative impact on WEHI's translational activities

As one of Australia's internationally recognised medical research institutes we express deep concerns over the potential negative impact of the proposed amendment and are of the firm view that it will negatively impact on our ability to continue to develop new treatments in Australia. WEHI currently has approximately 470 external collaborations related to 250 projects involving our researchers collaborating with their peers in 43 countries. In addition we have major collaborations with several companies that rely on gene and biological material patent claims – including Abbott Laboratories, Bionomics Limited Cancer Research Technologies, CSL Limited, Genentech/Roche, and Merck Inc. Such a strong international network means we have a good understanding of how Australia is viewed from a research, intellectual property and market perspective.

Table 7 presents key metrics with respect to disclosures, patent applications and commercialisation. Importantly, as for other Australian research organisations our research activities and publications are not hindered by patents. We disseminate our research results through scientific publications and patent applications, and we readily

share our materials with other researchers through Material Transfer Agreements (MTA). These activities support further research by attracting further funding and by promoting collaborations with industry that generally result in additional research support and more importantly, clinical translation for the benefit of the public.

Table 7: Key metrics for WEHI's intellectual property activities

Metric	*2001-2010*	*Annual average 2007-2009*	*2010*
Research expenses ($million)	601	74.1	78.1
Lab operating expenses ($million)	128	15.7	16.3
Full Time Equivalents (FTE)	5620	625	661
Publications	2270	240	249
MTAs	2100	242	245
Invention disclosures	185	23	24
Patent applications	125	16	10
Commercial agreements	400	69	82

WEHI's current and future translational portfolio depends on sequence and biomolecule patent claims. WEHI seeks patent protection for all its inventions and this protection is sought in various jurisdictions, including Australia. Australia is an important jurisdiction for commercial reasons (usually being the 10th largest global market) and development and manufacturing reasons, given Australia's technical capability. Allowing Australia to be a generic territory without patent protection presents a significant risk of erosion of business potential and lack of value capture for the benefit of Australians. We have significant experience and through our role in Cancer Trials Australia in attracting clinical trials from international sponsors and are concerned that the proposed amendment, through the indirect signals discussed above, will lead innovation intensive companies and investors to seek alternative more secure environments.

Approximately 50% of all WEHI's current patent applications (36 patent families at present) involve sequence claims that would not be allowed under the proposed amendment. WEHI is currently lodging a new patent application in Australia and other jurisdictions every 4 weeks, and claims to antibodies and biomolecules dominate our portfolio (see Appendix 2 for examples of our invention claims). There are 300 entries of patent applications from WEHI in the *AusPat* data base and these patent applications are a critical part of our ability to translate our research through investor and industry partnerships. Perhaps the best known example is that of GM-CSF, one of the cytokines jointly discovered with the Ludwig Institute in Melbourne (see page 6), however, there are many more current examples where biomolecules and sequence patent claims underpin a competitive position. Examples include:

> Leukemia Inhibitory Factor (LIF) – Discovered at WEHI, LIF has become a significant research reagent marketed in Australia and worldwide originally through Amrad and then Chemicon, Millipore and now Merck KgA. LIF is a cytokine used for the culture of embryonic stem cells and is protected by patents in several jurisdictions that claim the LIF sequence. This is an example of a widely available patented research tool where a license fee is incorporated into the price and the royalty received by WEHI is reinvested into research and translation activities.
>
> Interleukin 13 (IL-13) – As part of the CRC for Growth Factors, WEHI obtained patent protection for the IL-13 receptor and associated targeting antibody sequences. The intellectual property was licensed to Amrad (subsequently acquired by CSL) which was then able to partner with Merck. Investment in pre-clinical development of an anti-asthma therapeutic

antibody would not have occurred without the patent applications that also included Australia as one of the important exploitation territories.

Malaria antigens – WEHI has a large portfolio of malaria patents that claim sequences to parasites and vaccine antigens. Securing a strong intellectual property position was a condition of funding from the Bill and Melinda Gates Foundation and this set the scene for a Phase 1 clinical trial that has just completed. WEHI has commenced discussions with a partner for the development of a new vaccine based on novel antigens and a strong intellectual property position for developed markets is essential for investment. Given climate change, Australia's vulnerability to mosquito-borne disease and its vaccine development and production capability, a patent position in Australia is a critical part of the investment rationale.

Coeliac disease vaccine - Intellectual property developed at Oxford University and WEHI forms the basis for gluten epitopes that are included in a novel vaccine designed to induce immune tolerance. Sequence claims and a strong patent position in Australia and other jurisdictions were essential to capital raising (more than $4 million) from high net worth individuals and the successful conduct of a Phase 1 clinical trial in Melbourne. We maintain that the investors would not have invested if there was not a strong IP position in Australia, given Australia's leadership position in the research, diagnosis and recognition of coeliac disease, and vaccine technology.

Targeting G-CSF to treat inflammation – A WEHI discovery has lead to the invention of a humanised antibody that targets the G-CSF receptor for the treatment of chronic inflammatory conditions such as rheumatoid arthritis. An initial investment of $5 million by Starfish Ventures in WEHI's spin-out company, MuriGen, was on the basis of a strong IP position that included antibody patent claims in Australia, since Australia is considered to be an important market for development and production of antibody therapies. Subsequently CSL have acquired all rights to the project that is now preparing for Phase 1 clinical trials in Melbourne.

Dendritic cell targeting (Clec-9A) - WEHI has invented a new platform technology for targeting humanised antibodies to Clec9 on dendritic cells. Applications include vaccines against infectious disease, cancer and autoimmune disease and a proof of concept trial is set to shortly commence in Australia. WEHI has cross-licensed and pooled IP with Cancer Research Technologies in London who have also applied for antibody patent claims in Australia. Due to Australia's standing in vaccine development and manufacture a strong IP position in Australia is seen as essential by venture capitalists (under discussion) and a large transnational vaccine company (under discussion).

Apoptosis collaboration with Genentech and Abbott - WEHI's original portfolio of 16 patent families that related to the Bcl-2 family proteins and their role in apoptosis was a major factor in securing a funded collaboration with Genentech (four years) and Abbott (three years). All patent families were lodged in Australia, a jurisdiction that is important for both Genentech and Abbott, and a significant proportion had sequence claims. WEHI is certain that the significant upfront and milestone payments already received depended in part on a rigorous IP strategy that included protection in Australia. This strong IP position has also enabled WEHI clinician researchers to attract Phase 1 clinical trial activity to Australia.

10. Issues should be addressed through other means

The few historical problems that have arisen with gene patents are mainly related to commercialisation strategies and not patent law, and this is particularly true of the small number of cases used to justify the proposed amendment.[56] The proposed radical changes to Australia's patent law are related to a remarkably few historical examples that certainly should have been managed better by all parties.

Governments already have rights under law to intervene when patent rights are inappropriately exercised. Due to the potential unforseen consequences outlined above, issues should be resolved through several potential legal avenues of change to ensure access for patients to medical therapies, diagnosis and prevention rather than changing the patent system. Rather than risk the unforeseen consequence of unnecessary unilateral changes that limit patentable subject matter in Australia, current legal recourse measures should be clarified and given priority.

> Crown use provisions - The Patents Act allows for the government or an authorised representative to exploit a patent without infringement liability if required for provision of government services in Australia[57]. Subject to reasonable negotiations, enactment of this provision would obviate court proceedings and lengthy negotiations.
>
> Compulsory license provisions – Anti-competitive contravention of the Trade Practices Act (1974, Part IV) enables a court to grant a compulsory license under the Intellectual Property Laws Amendments Act 2006.
>
> Commonwealth acquisition – The Patents Act allows for the government to acquire a patent application with compensation to the patent holder[58].

Many other industries have managed to deal with cross-licensing and monopoly issues and there is no reason why the biomedical/biotechnology sector should be any different. There are also additional measures to address patents and monopoly pricing. For example the ALRC (2004) recommended that health departments become more active in challenging the validity of granted patents in much the same way that Myriads BRCA patents in Europe were declared invalid. The PBS, as one of the world's largest monopsonies provides a precedent for setting prices. Because of this, Australian cancer patients have access to *Herceptin* at a cost significantly less than that paid in the US. Global healthcare reform is seeing governments being much more active in access and price setting. This must be the preferred solution rather than unilaterally changing the patent system when such changes will not have a positive impact on access or price in Australia and are likely to lead to unforeseen consequences.

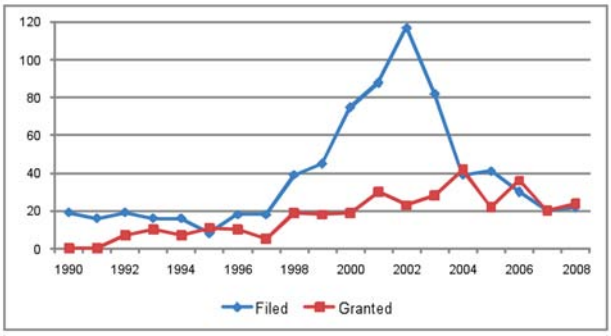
11. Inventiveness and utility must underpin granted patent claims

Finally, we fully support the requirement for patent claims to be inventive and have utility. Patent offices in most major jurisdictions, including the Australian Patent Office, have this view and currently judge patent applications accordingly. Whenever a new technology arises there is a period of adjustment and consideration in the global patent system. With the luxury of hindsight, in our opinion the few examples of patents cited in this case would probably not be granted today (e.g. Chiron's hepatitis C claims and Genetic Technologies'

[56] Myriad, Chiron and Genetic Technologies Limited, their patents and respective corporate strategies
[57] Section 163 Patents Act
[58] Patents Act Section 171

"non-coding DNA" claims). It is also important to note that the majority of human gene patent applications applied for during the "halcyon years" of 1995 – 2002 have been allowed to lapse. Figure 3 illustrates the "bubble" in human gene sequence patents[59] filed in Australia and the major decline since 2002. Importantly, these and fillings in other jurisdictions, and the publication of the human genome set prior art and novelty challenges for new sequence claims. It is also important to be aware that each year in Australia, there are approximately 10-times as many patents granted that claim methods or processes involving nucleic acids as there are patents claiming genes for human or animal proteins.[60] Clearly, the proposed amendment ignores that fact that there will remain substantially more granted patents that would still hinder Australian research if we used the proponents' logic – their proposed solution does not even solve their purported problem.

Figure 3: Human gene sequence patents filed and granted in Australia



[59] IP Australia (c12n 15/12 to 28)

[60] IP Australia (C12Q1/28 and c12n 15/12 to 28)

Appendix 1: BRCA1 patents published in Australia

The following patents have been published in Australia and refer to BRCA1 in the title, abstract or claims.

Application/Patent Number	Patent title	Publication date
AU199518317	Method of detection and diagnosis of preinvasive	19950801
AU199532428	Linked breast and ovarian cancer susceptibility gene	19960307
AU199533212	Linked breast and ovarian cancer susceptibility gene	19960307
AU199533216	Linked breast and ovarian cancer susceptibility gene	19960307
AU199655668	Genetic markers for breast, ovarian, and prostatic cancer	19961107
AU199718414	Protein kinase which specifically phosphorylates BRCA1	19970820
AU199719778	Coding sequences of the human BRCA1 gene	19970828
AU199720653	Characterized BRCA1 and BRCA2 proteins and screening and therapeutic methods based on characterized BRCA1 and BRCA2 proteins	19970902
AU926597	Improved detection method for premature termination mutations	19971009
AU199726873	Method and reagents for testing for mutations in the BRCA1 gene	19971205
AU686004	Linked breast and ovarian cancer susceptibility gene	19980129
AU199736550	BRCA1 compositions and methods for the diagnosis and treatment of cancer	19980202
AU199740514	BRCA1 associated polynucleotide (BAP1)	19980225
AU199740509	Susceptibility mutations for breast and ovarian cancer	19980225
AU199740728	Method of detecting expression of and isolating the protein encoded by the BRCA1 gene	19980319
AU199738293	Modulators of BRCA1 activity	19980326
AU199749769	Beclin, a novel bcl2 interacting gene near BRCA1 on chromosome 17q21 and methods of use	19980402
AU199745866	Differentiation between BRCA1 associated compositions and methods comprising BARD1 and other BRCA1 binding proteins	19980414
AU691331	Linked breast and ovarian cancer susceptibility gene	19980514
AU199850938	Primers for amplification of BRCA1	19980522
AU691958	Linked breast and ovarian cancer susceptibility gene	19980528
AU199864735	Method for determining the presence of mutated BRCA protein	19981020
AU698800	Genetic markers for breast, ovarian, and prostatic cancer	19981105
AU199880398	Diagnostic test kit for determining a predisposition for breast and ovarian cancer, materials and methods for such determination	19981221
AU199881824	Splice variants of BRCA1 and BRCA2	19990208
AU199887768	Coding sequences of the human BRCA1 gene	19990222
AU199892928	Coding sequences of the human BRCA1 gene	19990308
AU199891455	Improved detection method for premature termination mutations	19990405
AU199895865	Genetic panel assay for susceptibility mutations in breast and ovarian cancer	19990412
AU199915952	Carboxyterminal	19990615
AU199935478	Compositions and methods for controlling BRCA1 mediated P53 dependent and independent regulation of transcription	19991018
AU199938388	Tumour Markers	19991129
AU200016713	Cancer Detection Methods and Reagents	20000626
AU200037325	Beclin, a novel bcl2 interacting gene near BRCA1 on chromosome 17q21 and methods of use	20000928
AU200046746	Estrogen signalling pathway regulators and uses thereof	20001117
AU200073646	Mutant of RAD51 gene and its use in the diagnosis of predisposition to breast cancer	20010410
AU200117690	Method of detecting expression of and isolating the protein encoded by the BRCA1 gene	20010530

Application/Patent Number	Patent title	Publication date
AU736210	BRCA1 compositions and methods for the diagnosis and treatment of cancer	20010726
AU200150980	Brca1 regulators and methods of use	20011003
AU200151789	Coding sequences of the human BRCA1 gene	20011025
AU200178952	Compositions and methods for cancer screening	20020205
AU200110470	BRCA1 and hMLH1 gene primer sequences and method for testing	20020515
AU2003203635	Methods of treating a BRCA associated disorder	20020516
AU2002950424	BRCA1 interacting protein	20020912
AU2002316251	Diagnosis and prognosis of breast cancer patients	20030102
AU2002353317	A method for inducing apoptosis	20030630
AU2003225573	Identification of ovarian cancer tumor markers and therapeutic targets	20030904
AU2003203635	Methods of treating a BRCA associated disorder	20031127
AU2003253629	Large deletions in human BRCA1 gene and use thereof	20031222
AU2003281671	BRCA1 interacting protein	20040216
AU2003261366	Methods for regulating BRCA1BRCA2containing	20040223
AU2003282245	Tumour marker proteins and uses thereof	20040603
AU2003283339	Cancer therapy determination	20040607
AU777341	Coding sequences of the human BRCA1 gene	20041014
AU2005247346	Methods and compositions for cancer treatment relating to BRCA1 BRCT domain recognition of phosphorylated BACH1	20051208
AU2005261860	Use of ecteinascidin in treatment of cancer patients with low levels of BRCA1	20060119
AU2007268378	Method for improving neoadjuvant chemotherapy	20071206
AU2007350901	Gene Expression Profiling for Identification, Monitoring and Treatment of Breast Cancer	20081016
AU2008311465	Differentiation between BRCA1 associated and sporadic tumours	20090416
AU2008313634	Prognostic Molecular Markers for ET743 Treatment	20090423
AU2007361302	Gene expression profiling for identification of cancer	20090514
AU2008321128	Treatment of uterine cancer and ovarian cancer with a Parp inhibitor alone or in combination with antitumour agents	20090522
AU2008321382	Treatment of uterine cancer and ovarian cancer with a Parp inhibitor alone or in combination with antitumour agents	20090522
AU2008333786	Treatment of uterine cancer and ovarian cancer with a Parp inhibitor alone or in combination with antitumour agents	20090611
AU2009216728	BRCA1 mRNA expression levels predict survival in breat cancer patients treated with neoadjuvant therapy	20090827
AU2009216723	BRCA1 mRNA expression predicts survival in patients with bladder cancer treated with neoadjuvant cisplatin based chemotherapy	20090827
AU2009246256	Biomarkers for the Identification Monitoring and Treatment of Head and Neck Cancer and uses therefor	20091119

Appendix 2: Examples of PCT claims in selected WEHI patent applications

a) Clec9A PCT/AU2008/001294 "Dendritic cell marker and uses thereof"

Claim 1: A compound that binds a polypeptide which comprises:

i) an amino acid sequence as provided in any one of SEQ ID NO's 1 to 8;
ii) an amino acid sequence which is at least 50% identical to any one or more of SEQ ID NO's 1 to 8; and/or
iii) a biologically active and/or antigenic fragment of i) or ii).

Claim 7: The compound according to any one of claims 4 to 6, wherein the antibody or antigenic binding fragment thereof comprising three CDRs, and wherein
i) CDR1 comprises an amino acid sequence which is at least 90% identical to SEQ ID NO:44

b) Bcl-2 family proteins

BIM PCT/AU98/00772 "Novel therapeutic molecules"

Claim 2: A nucleic acid molecule according to claim 1 wherein said nucleic acid molecule comproses a nicleotide sequence encoding or complementary to a sequence encoding an amino acid sequence substantially as set forth in one of SEQ ID NO:2,4 or 6 or a derivative or homologue thereof or having at least about 45% or greater similarity to one or more of SEQ ID NO: 2, 4 or 6 or derivative or homologue thereof.

BMF PCT/AU02/00693 "Novel therapeutic molecules"

Claim 1: A nucleic acid molecule comprising a nucleotide sequence encoding or complementary to a sequence encoding an amino acid sequence substantially as set forth in one of SEQ ID NO: 2 or SEQ ID NO: 4 or SEQ ID NO: 6 or SEQ ID NO: 8 or a derivative or homolog thereof having at least 45% or greater similarity to one or more of SEQ ID NO:2 or SEQ ID NO: 4 or SEQ ID NO: 6 or SEQ ID NO: 8 or a derivative or homolog thereof

c) Malaria PCT/AU2009/001099 "Methods and compositions for treating and preventing malaria using an invasion ligand directed to a protease-resistant receptor"

Claim 4: An immunogenic molecule according to any one of the claims 1 to 3 wherein the invasion ligand comprises a sequence selected from the group consisting of SEQ ID NOS: 1,2,4,5,6,7,8,9,10,11 and 12, or variants thereof

d) LMO4 antibody for breast cancer PCT/AU02/01246 " A method of diagnosis and treatment and agents useful for same"

Claim 10: An isolated immunointereactive molecule or derivative, analogue or mutant thereof wherein the immunointereactive molecule interacts with LMO4 or *LM04*
Claim 11. The immunointereactive molecule of claim 10 wherein said immunointerreactive molecule is an antibody.
Claim 14: The monoclonal antibody of claim 13 wherein said monoclonal antibody is secreted by hybridoma 16H2 or mutant or variant thereof.
Claim 15: The monoclonal antibody of claim 13 wherein said monoclonal antibody is secreted by hybridoma 20F8 or mutant or variant thereof.

e) IL-13 for asthma PCT/AU97/00591 "Therapeutic molecules"

Claim 3: An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence (sequence) (SEQ ID NO:1) or a derivative, homologue or analogue thereof.
Claim 4: An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence (sequence) (SEQ ID NO:13) or a derivative, homologue or analogue thereof.
Claim 5: An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence (sequence) (SEQ ID NO:21) or a derivative, homologue or analogue thereof.

f) Nasal proinsulin for Type I diabetes PCT/AU00/01299 "A method of prophylaxis and treatment"

Claim 55: An agent for the treatment or prophylaxis of an automimmune disease, said agent comprising an autoantigen giving rise to said autoimmune disease, said autoimmune disease being modified to lack a functional MHC class I restricted epitope.
Claim 60: An agent according to Claim 59 wherein the agent is anti-CD40L antibody

g) Combination vaccine PCT/AU2009/001556 "Compositions and methods for treatment of celiac disease"

Claim 1: An agent comprising
i) a first peptide comprising the amino acid sequence (SEQ ID NO:13) , or a biologically active fragment or variant thereof

h) High affinity LIF mutants PCT/AU2004/001336 "Therapeutic molecules"

Claim 1: An isolated modulator of cytokine signalling via Leukemia Inhibitory Factor (LIF) and gp130 wherein said modualtor comprises a modified LIF molecule having either agonist or antagonist activity to caid cytokine wherein:
i) the agonist LIF variant comprises a LIF molecule or a homolog or chemical analog or functional equivalent thereof…