1. Introduction

The Walter and Eliza Hall Institute of Medical Research submitted a written response to the proposed Patent Amendment (Human Gene and Biological Materials) Bill 2010 (registered as Submission No 59). On April 28, 2001, Professor Doug Hilton and Dr Julian Clark provided verbal evidence to the Senate Legal and Constitutional Affairs Legislation Committee to the effect that the Walter and Eliza Hall Institute does not support the proposed amendment and recommends that the "Raising the Bar" changes currently proposed by IP Australia will adequately address the issues raised, and that findings of previous enquiries with respect to gene patents provide a sound basis for these changes.

During the testimony two questions to the Walter and Eliza Hall Institute were put on notice:-

> **Question 1 - Senator XENOPHON:** Maybe you could take this on notice, but there was a patent granted on 8 January 2009 for the prostate stem cell antigen and back on 8 September 2008 there was a patent granted over the flea head. ……It is the genetic material of a flea head? ……How will that not restrict others' research? (Hansard page 8)
>
> **Question 2 - Senator SIEWERT:** During our discussions on this whole issue, we have heard of numerous decisions made by IP Australia over patenting genes. We were told, 'No, you can't do that,' and then there was example upon example of where it had occurred and not been overturned. So I am just wondering how often it has happened, to your knowledge, and who has triggered it……How many times are you aware of a grant by IP Australia being overturned? (Hansard page 12)

2. Question 1 – Prostate stem cell antigen and flea heads

No references or details were provided about the patents being referred to in the question on notice nor were any details provided as to why these two patents were exceptional when compared to the many thousands that have been granted in recent years. We were also not aware of these specific patents at the time of questioning. Therefore we have used our best endeavours with limited resources to identify what we believe are the patents and to provide comment in the context of our submission and direct experience of biological material patents.

It is our understanding that Senator Xenophon referred to:

1. Australian Patent No. 2004263823 entitled "Prostate stem cell antigen (PSCA) variants and subsequences thereof" (filed May 28, 2004) with Agensys, Inc as the applicant and FB Rice as the Australian attorney

   and

2. Australian Patent No. 2004216672 entitled "Flea head, nerve cord, hindgut and malphighian tubule nucleic acid molecules, proteins and uses thereof " (application date October 1, 2004) with Heska Corporation as the applicant and Allens Arthur Robinson as the Australian attorney

2.1 Prostate stem cell antigen

Upon a preliminary examination of this patent family we observe that it is an example of how the patent system captures an invention that has isolated biological sequence claims, and

that could be of major significance in the development of therapeutics for the treatment of cancer. Importantly, it is an example of how an initial intellectual property position results in investment, new resources being applied to translation and commercialisation and the retention of employment in the US.

The applicant, Agensys, was a research intensive small US biotechnology company founded in 1997 and based in Santa Monica. Agensys was acquired by Astellas in December 2007 for an upfront payment of US$386 m and further potential milestone payments of US$150 m. At the time of acquisition Agensys had approximately 100 employees, no sales revenue and an intellectual property portfolio of more than 100 allowed patents and approximately 300 pending applications. Also at the time of acquisition, Agensys had approximately 30 proprietary target antigens with 10 of these in preclinical and early clinical development (including AGS-16M18 and AGS-8M4 in Phase 1 trails at the time). Agensys is currently managed as an independent business unit within Astellas focusing on antibody based therapeutics with Sef Kurstjens as CEO, however, detailed disclosures are no longer made.

In 2005, Agensys entered into a collaborative development agreement with Merck, an agreement based on the intellectual property described in the questioned patent and related to a human antibody targeting PSCA as described in the claims. In that agreement there was an upfront payment of $17.5 m to Agensys[1].

In a move typical for the global market, Agensys was acquired by Astellas on the basis of its substantial intellectual property position, including prostate stem cell antigen (PSCA). Astellas is in the top 20 global pharmaceutical companies and was formed in 2005 through the merger of Yamanouchi and Fujisawa in Japan. Sales in 2009 were approximately US$10.5 bn with an R&D investment of US$2.1 bn per year, including investment in developing the Agensys prostate stem cell antigen as a therapeutic target.

This acquisition of American Agensys by Japanese Astellas is in stark contrast to the acquisition of Bergamo Ltda in Brazil by Amgen that was highlighted by Senator Xenophon and suggested as evidence for the vibrancy of the Brazilian market and Amgen's foresight . Bergamo is a minor generics and over-the-counter manufacturer in Brazil with sales of approx. $80 million in a market with a value of $26 bn (i.e 0.3% market share) and no innovator track record. Amgen paid US$215 m for the acquisition which is immaterial when compared with Amgen's global revenue of US$15 bn (i.e. Bergamo accounts for 0.5% of total Amgen revenue from. In our opinion, Amgen's acquisition of Bergamo had nothing to do with Brazil's intellectual property environment and certainly not Bergamo's position as a major intellectual player in the therapeutic or biotechnology sectors in Brazil or any other jurisdiction. We maintain the argument that Amgen's move into Brazil is for volume growth, largely through generics, and was delayed by about two decades[2]. Also it is important to understand that Brazil has little or no position or track record in therapeutic innovations in pharmaceuticals and biotechnology.

On the other hand, Astellas' acquisition of Agensys is in many ways a parallel of a "dream scenario" for an Australian biotechnology company – a strong intellectual property position and know-how that leads to acquisition by a global player with the resources required to translate an invention into clinical reality. This is the journey that the Walter and Eliza Hall Institute and Ludwig Institute required for GM-CSF to be developed and commercialised for the treatment of millions of cancer patients – an intellectual property position based on an isolated sequence, expression and novel use that was an invention strong enough to motivate Immunex to invest more than $100 m in clinical development (much of which was done in Australia).

[1] http://www.biotech-intelligence.com/html/html/6f9c7d0452df5a89f423b3016dd619e7.html

[2] This view is supported by Ken Rapoza of Forbes Magazine (April 12, 2011) referring to Amgen's entry into Brazil as "better late than never" to exploit the rapidly growing generics market (http://blogs.forbes.com/kenrapoza/2011/04/12/what-amgen-faces-in-brazil/?partner=yahootix)

We have not conducted an exhaustive search but Table 1 illustrates Agensys' view of the potential patent jurisdictions. It is important to note that the patent has been granted in Australia, New Zealand, US and South Africa with an intention to grant being notified in Europe. We are not aware of any oppositions. Also the fact that applications have been made by Agensys in China, Mexico, Russia and Brazil illustrates the perceived importance of these emerging markets with respect to intellectual property protection.

Table 1: Patent prosecution status of WO/2005/014780 "Prostate Stem Cell Antigen (PSCA) Variants and Subsequences Thereof"

Country	**Patent/Application Number**	**Status**
AU	2004263823	Granted
CA	2526274	
CN	200480021931.4	
EP	1629088	Intention to Grant
IL	171966	
JP	2006515056	
KR	1020057022987	
MX	PA/a/2005/012957	
NZ	543840	Granted
RU	2005141341	
US	7622564	Granted
ZA	200509606	Granted
BR	PI0410842	

The claims of AU 2004263823 define an isolated polynucleotide that encodes a PSCA protein, wherein the polynucleotide comprises SEQ ID No. 6537 or 6545. The residue numbers are further defined and in addition, specific residues are defined.

The claims further define isolated PSCA protein having specific sequences, an antibody, an *in vitro* method of detecting the proteins and polynucleotides defined, an *in vitro* method of inhibiting growth of a cell expressing a PSCA protein as defined, an *in vitro* method of delivering a cytotoxic agent to a cell expressing the PSCA protein and a method of inducing an immune response to the defined PSCA proteins.

The claims of this patent application, while differing in detail, between jurisdictions, define *isolated* nucleic acid molecules, proteins and antibodies and are therefore, a manner of manufacture as required under the Patents Act. The specifications also describe a use for the inventions and in our opinion, if Astellas succeeds, this intellectual property would be a major breakthrough for many cancer sufferers. The patent claims are typical of those that attract the major investment required to develop a therapeutic. On the basis of a strong intellectual property position as defined in the patent, Astellas has progressed a drug candidate from Agensys, AGS—1C4D4, to Phase 2 clinical trials for treating pancreatic cancer, one of the most deadly forms of cancer that has enormous unmet therapeutic needs.

On the basis of our brief examination we are not aware of any material opposition to this patent in any jurisdiction. Furthermore, we are not aware of any action that has threatened or stopped research into PSCA. We could find no history of significant litigation of intellectual property rights by Agensys against research organisations. Importantly, a review of *PubMed* identified more than 290 research publications related to PSCA since 2004[3].

2.2 Flea head molecules

The relevance of this specific example presented by the committee seems to be unclear. In our opinion and upon initial investigation, this intellectual property appears to be based on a

[3] 2011 -25 articles, 2010 – 64, 2009 – 49, 2008 – 54, 2007 – 40, 2006 – 25, 2005 – 24, 2004 - 10

significant unmet market need, i.e. relevance, novelty, utility and method of manufacture. Fleas are major causes of allergy and disease through companion animals and livestock. The role of companion animal health and related allergy is increasing in importance in our societies as they age and there is a trend towards singleness. Again, we emphasise that we do not follow intellectual property decisions as they relate to fleas and at the time of the question did not have knowledge of the relevant patent applications.

Upon a preliminary examination of this patent family we observe that it is also an example of how the patent system captures an invention that has isolated biological sequence claims, and that could be of major commercial and social significance. The rationale for focusing on the flea head, as well as the gut and malpighian tubules as control targets is to our understanding novel and we know of no others who have thought of this inventive approach.

We understand that this patent application is sponsored by Heska Corporation, a relatively small specialty allergy and veterinary products company based in Colorado with an international sales operation based in Fribourg, Switzerland. Heska employs approximately 280 people and has sales revenues of US$65.5 m, an operating income of only $0.4 m with an investment of approximately $1.6 m in R&D (2010). The organisation has 88% of sales in the US, 5% in Europe and 7% in other territories including Australia (under agreement with Gribbles/Healthscope).

As of December 2010, Heska owned, co-owned or had rights to 193 issued US patents and 127 issued foreign patents with a focus on novel allergans and antigens, disease detection, vaccines, flea control and related pharmaceuticals. Heska competes directly against major transnational companies such as Pfizer, Bayer, Merck, and Novartis.

We examined Heska's reports to the SEC and found no evidence of any material legal proceedings as at December 2010, and importantly did not find any history of litigation against other research organisations. As for the previous example raised by the Committee we do not have the resources for an exhaustive examination of this example. However, initial searches revealed that the patent application has granted in Australia, Europe and the US, albeit with different specific claims but with the same overall structure to the claims (see Table 2). The limited number of territories for which protection has been applied represents in all likelihood the limited resources and sales reach for a small vertically integrated company.

Table 2: Patent prosecution status of (WO/2000/061621) Flea Head, Nerve Cord, Hindgut and Malpighian Tubule Nucleic Acid Molecules, Proteins and Uses Thereof

Country	**Patent/Application Number**	**Status**
AU	2004216672	Granted
CA	2372028	
EP	1169343	Granted
JP	2000611562	
US	7348410	Granted

The claims of AU 2004216672 define isolated nucleic acid molecules from the head, nerve cord, hind gut and malpighian tubule of a flea, isolated proteins encoded by such nucleic acids and isolated antibodies.

The claims are restricted to SEQ ID Nos: 7, 8, 9, 10 and 12. The patent further describes methods to protect an animal from flea infestation by administering a composition comprising an excipient and the isolated nucleic acid, isolated protein or an inhibitory compound. Such an invention would be extremely beneficial to the veterinary industry.

The claims of this patent family define *isolated* nucleic acid molecules, proteins and antibodies and are therefore, a manner of manufacture as required under the Patents Act.

The specifications also describe a use for the inventions. It is quite clear that control of fleas is a major social and public health concern and that this innovation could provide a new approach but would require major investment that could only be justified by a period of exclusivity, i.e. patent protection. A detailed search of the research literature has not been conducted however, it was noted that PubMed contains 265 articles relating to flea DNA and 460 articles relating to flea protein. Importantly, the inventors on this patent have also disseminated their findings in the peer-reviewed scientific literature[4].

2.3 Summary to Question 1

Our initial evaluation of the two patent cases presented provides no major areas of new concern. The claims of both patents define *isolated* nucleic acid molecules, proteins and antibodies and are therefore, a manner of manufacture as required under the Patents Act. The specifications also describe a use for the inventions. Importantly, both patents communicate new understanding, address unmet needs, provide a platform for investment and exploitation, and appear to be genuine innovations that could contribute to healthcare and wellbeing.

These two patent examples exemplify the importance of having claims that relate to the target, composition of matter of that target, composition of matter of materials that modulate that target and methods of use – it is this combination that secures maximum value and reduces risk for the investor. Both patents have claims granted or intended to grant in major jurisdictions such as the US and Europe and our initial review has revealed no evidence of opposition to granted claims. There does not appear to be any record of the patent holders exercising patent rights over research organisations in opposition to the "assumed" research exemption. Importantly, we could find no evidence of other parties opposing these patents, or of the existence of these patents hindering research.

As a hypothetical, we submit that if the Walter and Eliza Hall Institute were to conduct research into the PSCA or flea heads, we would not feel constrained by existing patents with respect to research activities and a quest to generate new intellectual property. Importantly, we would consider engaging with the holders of the Background IP (i.e. Agensys and Heska in these cases) to translate the new knowledge from our research. The currently published literature indicates a robust research endeavour in both areas in spite of granted patent claims.

As detailed in our submissions to the Senate Community Affairs Committee and to the Senate Legal and Constitutional Affairs Committee, research organisations exist to discover and invent and are only successful if they advance beyond existing publications and patents. We believe that the research exemption can be relied upon for most research and therefore, it would be possible to conduct research notwithstanding the existence of these patents. The Senate Community Affairs Committee conclusion that there was a lack of evidence of a negative impact of patents on research reflects our direct experience of a lack of negative impact.

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[4] Walmsley SJ, Gaines PJ. Identification of two cDNAs encoding synaptic vesicle protein 2 (SV2)-like proteins from epithelial tissues in the cat flea, Ctenocephalides felis. Insect Mol Biol. 2004 Jun;13(3):225-30

Gaines PJ, Tang L, Wisnewski N. Insect allantoinase: cDNA cloning, purification, and characterization of the native protein from the cat flea, Ctenocephalides felis. Insect Biochem Mol Biol. 2004 Mar;34(3):203-14

Gaines PJ, Walmsley SJ, Wisnewski N. Cloning and characterization of five cDNAs encoding peritrophin-A domains from the cat flea, Ctenocephalides felis. Insect Biochem Mol Biol. 2003 Nov;33(11):1061-73

Gaines PJ, Brandt KS, Eisele AM, Wagner WP, Bozic CM, Wisnewski N. Analysis of expressed sequence tags from subtracted and unsubtracted Ctenocephalides felis hindgut and Malpighian tubule cDNA libraries. Insect Mol Biol. 2002 Aug;11(4):299-306.

3. Question 2

In general terms, once a patent is granted the claims remain as valid until they are opposed in part or full by another party. Currently, approximately 1% of all granted Australian patents are opposed and this compares with the 0.5% opposition (technically "re-examination") rate in the US and 4.7% in Europe[5]. If there is no opposition from a third party this then indicates acceptance of the claims or no perceived value of the claims. In practice this is not a problem for researchers since in our considerable experience patents do not hinder research and researcher have no need to oppose patent claims in order to conduct research. In response to the second question on notice we conducted an initial search on Austlii for Patent Office decisions made between 2005 to date. A more detailed search and consequent conclusions would of course require resources beyond those currently available.

The following keywords were searched:

1. gene and/or nucleic and/or protein
2. gene and/or nucleic
3. gene and/or protein
4. nucleic and/or protein

Twenty-four patent decisions were identified (see Table 3 below). Four related to matter not related to the question raised and this enquiry. Six oppositions were unsuccessful (opposition failed), two were successful and twelve were partially successful and patent claim amendments were made.

When one considers the large number of applications that would have been granted over the same period (five years), only a small proportion do not contain patentable subject matter. WEHI has provided a response to IP Australia on the IP reforms ("Raising the Bar") and we strongly support the initiative taken by IP Australia to improve the efficiency and competitiveness of Australia's patent system by raising the standard of the system to align more closely with our main intellectual property trading partners.

It is important to understand that a third party must oppose to proposed or granted patent claims before changes are considered. The low level of changes in Australia, as for other similar jurisdictions, reflects the relatively low level of opposition.

Table 3: Examples of recent patent opposition in Australia

	Matter	Subject	Opposition
1	The Scripps Research Institute [2011] APO 24 (1 April 2011)	Hearing notice issued	NA
2	Bionomics Limited [2011] APO 21 (22 March 2011)	Hearing notice issued	NA
3	Institut Pasteur and Institut Pasteur de Tunis [2011] APO 19 (22 March 2011)	Hearing notice issued	NA
4	Schering Corporation [2011] APO 10 (4 February 2011)	Hearing notice issued	NA
5	Genentech, Inc [2010] APO 27 (15 November 2010)	Method of combination treatment – anti-Erb2 Ab + chemotherapeutic agent	successful
6	Meda Pharma GmbH & Co. KG v Arakis Ltd (CORRECTED VERSION) [2010] APO 26 October 2010)	Treatment of respiratory diseases by inhalation – glycopyrrolate in hydrophobic matrix material. Opposition successful on inventive step	successful
7	Athlomics Pt Ltd [2009] APO 20 (26 October 2009)	Determining ability of subject to compete in sporting event by evaluating molecules from blood. Claim1 novel/inventive other claims not - amend	Partially successful. Amend
8	Macquarie University v HealthLinx Limited [2009] APO 1 (14 January 2009)	Extension of time – serve evidence.	NA
9	William A Newman v Solutions-IES, Inc [2008] APO 18 (28 July 2008)	bioremediation	NA
10	Alkermes, Inc. v Nektar Therapeutics [2007]	Perforated microparticles, targeted	Unsuccessful

[5] WIPO Statistics Database (June 2010) – World Intellectual Property Indicators, 2010 (page 69)

	Matter	Subject	Opposition
	APO 39 (18 December 2007)	delivery, unsuccessful opposition - only some claims require amendment	
11	Commonwealth Scientific and Industrial Research Organisation v Monsanto Technology LLC [2007] APO 15 (20 April 2007)	Method for production of stably – transformed wheat plant – partially successful for novelty and clarity	Partially successful
12	Statens Serum Institut v Octapharma AG [2007] APO 10 (6 March 2007)	An immunoglobulin product. Opposition unsuccessful.	Unsuccessful
13	Bionomics Limited v McGill University (Corrected Version No 2) [2007] APO 6 (29 January 2007)	Inventorship decision	NA
14	Nektar Therapeutics v Advanced Inhalation Research, Inc [2006] APO 22 (9 June 2006)	Microparticles for targeted delivery of bioactive agent to respiratory tract novelty – amendments to consider	Successful. Amendment to consider.
15	Genentech, Inc v Ludwig Institute for Cancer Research and Human Genome Sciences, Inc (Corrected Version) [2006] APO 20 (5 June 2006)	VEGF protein – claims peptides, nucleic acid seqs, constructs and antibodies. Partially successful – amendments to be considered	Partially successful. Amendments to consider.
16	The Government of The United States of America, as represented by the Secretary, Department of Health and Human Services & University of Rochester v The University of Queensland and CSL Limited [2005] APO 50 (8 November 2005)	Both claim same invention and have overlapping priority dates. Whole of contents. Both can amend as each contains patentable matter	Partially successful. Amend.
17	Benitec Australia Ltd v The Carnegie Institution of Washington and The University of Massachusetts [2005] APO 49 (3 November 2005)	Genetic inhibition of double-stranded DNA. Opposition unsuccessful, a method of inhibiting expression of a target gene.	Unsuccessful
18	Novozymes A/S v DSM IP Assets BV [2005] APO 44 (11 October 2005)	A method for isolating a DNA sequence coding for a desired protein. Fair basis – lack one essential feature - measuring levels of activity of a protein of interest over background noise. Can be amended.	Successful but can amend.
19	Diversa Corporation v Maxygen, Inc. [2005] APO 43 (5 October 2005)	In vitro method for obtaining mutated polynucleotides through a process of random fragmentation. Opposition successful on one ground only, claims 22-24 lacked clarity.	Successful for one ground – claims 22-24 lacked clarity. Amend.
20	University of Rochester v The University of Queensland and CSL Limited [2005] APO 34 (13 July 2005)	Production of HPV capside protein and virus-like particles. 2 claims found to be novel and inventive only. Further citation to be considered.	Two claims novel and inventive.
21	The Government of The United States of America, as represented by the Secretary, Department of Health and Human Services & University of Rochester v The University of Queensland and CSL Limited [2005] APO 33 (13 July 2005)	Self-assembling recombinant papilloma capsid proteins. Opposition not successful – s40.	Unsuccessful
22	F Hoffman-La-Roche AG v Bresagen Ltd and New England Biolabs, Inc [2005] APO 31 (4 July 2005)	Purified thermostable enzyme. S40 issues overcome. Not successful.	Unsuccessful
23	Genentech, Inc v Grandis Deutschland GmbH – (Minor Correction) [2005] APO 20 (21 April 2005)	Human growth hormone aqueous formulation – opposition unsuccessful.	Unsuccessful
24	Syngenta Biotechnology Inc v Commonwealth Scientific and Industrial Research Organisation [2005] APO 17 (8 April 2005)	Extension for service of evidence.	NA