Gene Patents and Patents granted over Biological Materials: *Their Impact on the Provision and Cost of Diagnostic Services and Medical and Scientific Research in Australia*

A Submission to the

Senate Community Affairs Committee

Inquiry into Gene Patents

Part Two

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Introduction

The purpose of Part Two of this two part Submission is to inform the members of the *Senate Community Affairs Committee* of six examples of gene patents granted by IP Australia and provide evidence of how these patents have, do, and may impact on (i) the provision and cost of healthcare; (ii) the progress in medical research and, (iii) the health and wellbeing of the Australian people.

They are, however, the tip of the iceberg. According to Auspat, IP Australia's online patent searching service, as at 16 February 2009 15,042 Australian gene patents have been granted. These patents are classified by IP Australia as falling within the international patent classifications C12N15 and C12Q1/68. There may well be more. Attached at the end of this Introduction is a list of 100 of the most recent examples of gene patents granted in Australia.

Accordingly, this part of this Submission is not a comprehensive study. Frankly, there is only so much one person can do in the short time made available to prepare submissions. Nonetheless, the members of the Committee can read this part of the Submission in the knowledge that the histories and lessons which they provide can be extrapolated more broadly. Thus, it will become readily apparent that much more needs to be done if this Committee is to get to the bottom of the problem which gene patents have created for Australia, its economy, its people and its medical and scientific community.

The TRIPS Agreement and, indeed, the very legislation upon which the *AU Patents Act, 1990* is derived from, the *Statute of Monopolies, 1623*, requires patent monopolies to be granted only for things that are 'inventions'. Not only that to be a patentable invention, an 'invention' must be new, novel and industrially applicable. These are the four conditions of patentability and each of these four must be satisfied if an exception to the general rule against monopolies is to be made.

The grant of a patent monopoly in Australia is significant. It has ramifications for the economy, society and the progress of science and technology in this country. As Justice Breyer of the US Supreme Court has said, 'sometimes too much patent protection can impede rather than "promote the Progress of Science and useful Arts"'.

Our forefathers understood that monopolies are antithetical to economic and industrial progress and that is why the *Statute of Monopolies* became the law in 1624. That they made an exception for 'manners of new manufacture', provided that they were not 'contrary to law nor mischievous to the state by raising prices or commodities at home, or hurt of trade, or generally inconvenient', being the operative words in the *AU Patents Act, 1990 (Cwth)*, should not be overlooked as being some antiquated idea that is meaningless in today's modern world. There is wisdom in those words. Indeed, it would be fair to say that our entire western capitalist system is built upon the notion that free competition should be encouraged because it is that form of competition that provides the incentive for cheaper and better products and the technologies that enable them.

So the obvious contradiction between free competition on the one hand and a patent monopoly on the other means that the two can only exist if the system that creates patent monopolies is carefully calibrated and balanced. If it is not, then the patent system threatens the very basis of our western capitalist economic system.

Unfortunately, the six examples are not exceptions to the rule, but are illustrative of the state of the patent system in Australia and the rest of the world. Today, patent systems everywhere, not just here in this country, are under severe stress. They are inefficient, expensive and incapable of being the patent gatekeeper. Not only that, the courts, which are supposed to augment their patent gatekeeping role, are also inefficient and so expensive that they are not

doing so. The very few patent cases that do make it to the courts are reserved for wealthy and sophisticated litigants who can afford to spend the millions of dollars that lawyers and experts cost. The courts are the modern battlefields in which armies of specialised lawyers and experts are brought together, and paid handsomely, to fight for their clients' cause. These clients are mostly multi-national corporations whose interest in patent monopolies is not to reward the inventor, who usually is an employee, but to achieve as broad a patent monopoly as possible so as to operate without competition.

It cannot be ignored that in 1624 the period of a patent monopoly was 14 years. Today it is 20 years. Why so? Simply because in 1963 the draft European Patent Convention, which was signed in 1973 by EEC countries (which included the UK) and which became one of the templates for TRIPS in 1995, said so. There was no economic analysis and no consideration of the impact of such an extension on society, the economy or scientific and technological progress.

Each of the six patents in Part 2 of this Submission confirm that the patent system in Australia is incapable of providing the balance that is demanded by a western capitalist economic system.

They also demonstrate that the organs of the Australian government, the departmental agencies through which the laws of the Commonwealth are administered, have systematically failed to protect Australia's national interest by hesitating to act within the powers provided to them under the *AU Patents Act, 1990.* Thus they are unable to ameliorate the negative impact which these patent monopolies have had, and still have, on the provision of healthcare and on medical and scientific research and development in Australia.

The fault is not just that of IP Australia. The fault is also that of the Commonwealth and State Departments of Health. It is also that of the Federal Court of Australia. It is also that of the High Court of Australia. It is also that of the patent attorneys and patent lawyers who have put their self interest before the interests of their country. Indeed, what these six patents demonstrate is that there exists a systemic failure of catastrophic proportions. The impact that the grant of these patents have had, are having and may have in the future, and the failure to ameliorate their impact has yet to be assessed, measured and accurately costed but it would not be an exaggeration to suggest that the cost must run into billions both in actual monies unnecessarily spent in the provision of healthcare and in lost opportunities.

One can only hope that this Committee will act rapidly and decisively to ensure that the Government takes the necessary steps to redress this appalling state of affairs.

Search Results

Your search for **(C12N15/* IN IPC OR C12Q1/68 IN IPC) AND standard IN TY AND (approved IN ST OR sealed IN ST OR ceased IN ST OR expired IN ST)** returned **15042** results. Here are the first 5000 results.

	Application number	Title	Applicant(s)	Filing date	Application status	Earliest priority date	PCT number	First IPC mark
4801	2004237922	Secreted and transmembrane polypeptides and nucleic acids encoding the same	Genentech, Inc.	2004-12-14	SEALED	1998-12-16		C12N15/12
4802	2004237923	Secreted and transmembrane polypeptides and nucleic acids encoding the same	Genentech, Inc.	2004-12-14	SEALED	1998-12-16		C12N15/12
4803	2004299829	Corn plant MON88017 and compositions and methods for detection thereof	Monsanto Technology LLC	2004-12-14	SEALED	2003-12-15	PCT/US2004/041723	A01H5/10
4804	2004240157	Caspase-8 interacting proteins	Yeda Research & Development Co. Ltd	2004-12-15	SEALED	1998-12-24		C07K14/47
4805	2004240199	Conserved Neisserial antigens	Novartis Vaccines and Diagnostics S.r.l.	2004-12-17	SEALED	1999-04-30		C12N15/31
4806	2004242423	Synthases	The Salk Institute for Biological Studies; University of Kentucky Research Department	2004-12-17	SEALED	1998-09-18		A01H5/00
4807	2004299336	Cytochrome c protein and assay	GE Healthcare UK Limited	2004-12-17	SEALED	2003-12-19	PCT/GB2004/005317	C07K14/80
4808	2004299519	Brachyspira pilosicoli 72kDa outer-membrane protein and diagnostic and therapeutic uses thereof	Spirogene Pty Ltd	2004-12-17	SEALED	2003-12-19	PCT/AU2004/001783	A61K38/04
4809	2004240212	Human ubiquitin ligase E3 for the modulation of NF-kappaB	Signal Pharmaceuticals, LLC.; Yissum Research Development Company of the Hebrew University of Jerusalem	2004-12-20	SEALED	1998-12-10		C12N15/09
4810	2004240248	Method for diagnosing, imaging, and treating tumors using restrictive receptor for Interleukin 13	The Penn State Research Foundation	2004-12-21	SEALED	1998-04-03		C12N15/09
4811	2004303629	Methods for detection of Mycobacterium tuberculosis	Department of Biotechnology; All India Institute of Medical Sciences	2004-12-22	SEALED	2003-12-23	PCT/IN2004/000396	C12Q1/68
4812	2004303676	Unsaturated fatty	Suntory Limited	2004-	SEALED	2003-12-	PCT/JP2004/019196	C12N9/10

		acid synthase gene originating in marchantiales plant and utilization of the same		12-22		22		
4813	2004242462	Nucleic acid ligands to hepatocyte growth factor/scatter factor (HGF/SF) or its receptor C-Met and to integrins	Gilead Sciences, Inc	2004-12-23	SEALED	1999-07-29		C07H21/04
4814	2004303601	Gene expression technique	Novozymes Biopharma DK A/S	2004-12-23	SEALED	2003-12-23	PCT/GB2004/005462	C12N15/67
4815	2004242465	Fibroblast Growth Factor-Like Polypeptides	Amgen Inc.	2004-12-24	SEALED	1999-09-07		C12N15/00
4816	2004242526	Optical Sorting Method	Medical Research Council	2004-12-30	SEALED	1999-01-07		C12N15/10
4817	2004242533	Large circular target-specific antisense nucleic acid compounds	Welgene, Inc.	2004-12-30	SEALED	2001-03-08		C12N15/63
4818	2005200008	Soluble receptor BR43x2 and methods of using	ZymoGenetics, Inc.	2005-01-04	SEALED	1999-01-07		C12N15/11
4819	2005200044	Human monoclonal antibodies against TGF-beta II receptor and medicinal use thereof	Japan Tobacco, Inc.	2005-01-06	SEALED	1999-11-18		C12N15/02
4820	2005200042	A Protein-Ig Fusion, Method of Making Same, and Compositions Thereof	Biogen Idec MA Inc.	2005-01-07	SEALED	1998-12-17		C12N15/09
4821	2005203861	Method of producing sterile plant, plant obtained by using the same and use thereof	National Institute of Advanced Industrial Science and Technology; Japan Science and Technology Agency	2005-01-07	SEALED	2004-01-07	PCT/JP2005/000155	A01H1/00
4822	2005200142	Megsin Protein	Miyata, Toshio; Kurokawa, Kiyoshi; Tokai University Educational System	2005-01-13	SEALED	1997-09-22		C12N15/12
4823	2005200237	Neutrokine-alpha and neutrokine-alpha splice variant	Human Genome Sciences, Inc.	2005-01-20	SEALED	1999-02-23		C12N15/09
4824	2005200250	Human monoclonal antibodies to dendritic cells	Celldex Therapeutics, Inc.	2005-01-21	SEALED	2000-05-08		C07K16/28
4825	2005200270	Nucleic acid sequences to proteins involved in isoprenoid synthesis	Calgene LLC	2005-01-21	SEALED	1999-04-15		A01H5/00
4826	2005200279	Transgenic Animals for Producing Specific Isotypes of Human Antibodies Via Non-Cognate	Amgen Fremont Inc.	2005-01-24	SEALED	1999-06-10		A01K67/00

		Switch Regions						
4827	2005209926	Modified human four helical bundle polypeptides and their uses	Ambrx, Inc.	2005-01-28	SEALED	2004-02-02	PCT/US2005/003537	C07H21/04
4828	2005211362	Modified human interferon polypeptides and their uses	Ambrx, Inc.	2005-01-28	SEALED	2004-02-02	PCT/US2005/002599	C07K1/00
4829	2005210006	Screening assays	Novartis AG	2005-02-04	SEALED	2004-02-05	PCT/EP2005/001168	C12N15/11
4830	2005200515	Human antibodies that bind human IL-12 and methods for producing	Abbott GmbH & Co. KG	2005-02-07	SEALED	1999-03-25		C07K16/24
4831	2005210362	Method of detecting nucleic acid and utilization thereof	Fuso Pharmaceutical Industries, Ltd.	2005-02-08	SEALED	2004-02-09	PCT/JP2005/001840	C12N15/10
4832	2005200548	Protein Switches	Gendaq Limited	2005-02-09	SEALED	1999-05-28		C12N15/10
4833	2005200622	Cell culture process for glycoproteins	Genentech, Inc.	2005-02-11	SEALED	1999-04-26		C12N9/64
4834	2005200670	Adsorption of nucleic acids to a solid phase	F. Hoffmann-La Roche AG	2005-02-15	SEALED	2004-02-20		C12N15/09
4835	2005214135	Desaturase enzymes	The University of York	2005-02-17	SEALED	2004-02-17	PCT/GB2005/000549	C12N9/02
4836	2005322640	Compositions for use in identification of bacteria	Ibis Biosciences, Inc.	2005-02-18	SEALED	2004-02-18	PCT/US2005/006133	C07H21/02
4837	2005215910	P53 wild-type as biomarker for the treatment with mTOR inhibitors in combination with a cytotoxic agent	Novartis Forschungsstiftung; Novartis AG	2005-02-22	SEALED	2004-02-23	PCT/EP2005/001849	C12Q1/68
4838	2005200827	Allele-specific siRNA-mediated gene silencing	University of Iowa Research Foundation	2005-02-24	SEALED	2002-08-05		C12N15/00
4839	2005200828	siRNA-mediated gene silencing with viral vectors	University of Iowa Research Foundation	2005-02-24	SEALED	2002-08-05		C12Q1/68
4840	2005200846	Probe matrix-based device for identifying microorganisms	Gen-Probe Incorporated	2005-02-25	SEALED	1999-05-03		G01N33/53
4841	2005200998	Diagnosis and therapy of cancer using SGP28-related molecules	Agensys, Inc.	2005-03-04	SEALED	1999-10-28		G01N33/574
4842	2005221763	Barley for production of flavor-stable beverage	Carlsberg A/S	2005-03-09	SEALED	2004-03-11	PCT/DK2005/000160	C12C1/18
4843	2005201060	Phosphatidylinositol 3-kinase P110 Delta Catalytic Subunit	ICOS Corporation	2005-03-10	SEALED	1996-11-25		C12N15/54
4844	2005201125	Non-stochastic generation of genetic vaccines	Verenium Corporation	2005-03-15	SEALED	1999-02-04		C12N15/00

		and enzymes						
4845	2005201212	Recombined porcine adenovirus based viral vaccines and vectors	Ecole Nationale Veterinaire De Maisons Alfort; Merial	2005-03-21	SEALED	1999-02-11		C12N15/86
4846	2005201289	Inhibiting formation of atherosclerotic lesions	President and Fellows of Harvard College	2005-03-24	SEALED	1999-02-12		C12N15/11
4847	2005226595	Mussel bioadhesive	POSTECH Foundation; POSCO	2005-03-25	SEALED	2004-03-26	PCT/KR2005/000888	C12N15/12
4848	2005201365	Use of modified chimeric polypeptides	Regeneron Parmaceuticals, Inc.	2005-03-31	SEALED	1999-06-08		C12N15/12
4849	2005228283	Detection instrument with the use of polynucleotides mapped on barley chromosome	Japan Science and Technology Agency	2005-03-31	SEALED	2004-03-31	PCT/JP2005/006825	G01N37/00
4850	2005228446	Method to determine responsiveness of cancer to epidermal growth factor receptor targeting treatments	The General Hospital Corporation; Dana-Farber Cancer Institute, Inc.	2005-03-31	SEALED	2004-03-31	PCT/US2005/010645	C12Q1/68
4851	2005230820	Cytokinin oxidase sequences and methods of use	Pioneer Hi-Bred International, Inc.	2005-03-31	SEALED	2004-04-02	PCT/US2005/010615	C12N15/82
4852	2005201464	Gene encoding flavone synthase	International Flower Developments Proprietary Limited	2005-04-06	SEALED	1999-01-29		C12N15/52
4853	2005201467	Mutations associated with iron disorders	Billups-Rothenberg, Inc.	2005-04-06	SEALED	1999-03-26		C12Q1/68
4854	2005231862	Neisseria gonorrhoeae detection	The State of Queensland acting through Its Department of Health	2005-04-06	SEALED	2004-04-08	PCT/AU2005/000500	C12Q1/68
4855	2005235182	TLR ligand and IL-1 response-injured animal model	Japan Science and Technology Agency	2005-04-15	SEALED	2004-04-20	PCT/JP2005/007304	A01K67/027
4856	2005278123	Canine Pancreatic Lipase	IDEXX Laboratories, Inc.	2005-04-15	SEALED	2004-04-16	PCT/US2005/012645	C12N9/20
4857	2005201735	Methods and compositions for use in gene therapy for treatment of Hemophilia	The Children's Hospital of Philadelphia	2005-04-26	SEALED	1997-03-14		A61K48/00
4858	2005201799	Osteoprotegerin binding proteins and receptors	Amgen Inc.	2005-04-27	SEALED	1997-04-16		A61K31/70
4859	2005201777	A Method for Direct Nucleic Acid Sequencing	ASM Scientific, Inc.	2005-04-28	SEALED	1999-03-10		C12Q1/68
4860	2005201826	Immune responses against HPV antigens elicited by compositions	Nventa Biopharmaceuticals Corporation	2005-04-29	SEALED	1997-08-05		C12N15/70

		comprising an HPV antigen and a stress protein or an expression vector capable of expression of these proteins						
4861	2005330566	Nuclease resistant external guide sequences for treating inflammatory and viral related respiratory diseases	Yale University	2005-04-29	SEALED	2004-04-29	PCT/US2005/015038	C12N15/11
4862	2005241020	Use of IL-17 expression to predict skin inflammation; methods of treatment	Schering Corporation	2005-05-02	SEALED	2004-05-03	PCT/US2005/014720	C12Q1/68
4863	2005241093	MN/CA IX/ CA9 and renal cancer prognosis	Institute of Virology of Slovak Academy of Sciences	2005-05-04	SEALED	2004-05-04	PCT/US2005/015587	C12Q1/68
4864	2005201901	Direct expression of peptides into culture media	Unigene Laboratories Inc.	2005-05-05	SEALED	1997-04-16		C12N1/00
4865	2005201916	G protein-coupled receptor up-regulated in prostate cancer and uses thereof	Agensys, Inc.	2005-05-05	SEALED	1999-10-05		C12N15/12
4866	2005247341	Methods and compositions for the treatment of uveitis	The Government of The United States of America as represented by The Secretary of The Department of Health and Human Services	2005-05-05	SEALED	2004-05-06	PCT/US2005/015761	A61K31/7088
4867	2005202131	CXCR3 chemokine receptor, antibodies, nucleic acids, and methods of use	Theodor-Kocher Institute; Millennium Pharmaceuticals, Inc.	2005-05-17	SEALED	1996-09-10		A61K31/7105
4868	2005202143	Transmembrane protein expressed in prostate and other cancers	Agensys, Inc.	2005-05-18	SEALED	1999-04-12		A01K67/027
4869	2005202165	Methods for generating polynucleotides having desired characteristics by iterative selection and recombination	Maxygen, Inc.	2005-05-18	SEALED	1995-11-30		C07K14/00
4870	2005245919	Maize multidrug resistance-associated protein polynucleotides and methods of use	E.I. Du Pont De Nemours and Company; Pioneer Hi-Bred International, Inc.	2005-05-19	SEALED	2004-05-20	PCT/US2005/017472	C12N15/82
4871	2005202234	Cotton cultivar DP 611 BGII/RR	D&PL Technology Holding Company, LLC	2005-05-23	SEALED	2004-09-20		A01H5/00
4872	2005202229	Cytokine Receptor Chain	Genetics Institute, LLC; Johns Hopkins University	2005-05-24	SEALED	1998-12-14		A61K38/00

4873	2005202240	Genomic Sequence of the purH Gene and purH-Related Biallelic Markers	Serono Genetics Institute S.A.	2005-05-24	SEALED	1999-03-24		C12Q1/68
4874	2005202246	Vascular adhesion molecules and modulation of their function	Laboratoires Serono S.A. Coinsins	2005-05-24	SEALED	1999-03-11		C12N15/12
4875	2005202259	Novel plant expression constructs	Monsanto Technology LLC	2005-05-25	SEALED	1999-12-16		C12N15/00
4876	2005202311	Alteration of flowering time in plants	Wisconsin Alumni Research Foundation	2005-05-27	SEALED	1999-02-25		C12N15/82
4877	2005202386	Recombinant influenza viruses for vaccines and gene therapy	Wisconsin Alumni Research Foundation	2005-05-27	SEALED	1999-04-06		C07K14/11
4878	2005250055	Binding moieties based on shark IgNAR domains	AdAlta Pty Ltd	2005-06-02	SEALED	2004-06-02	PCT/AU2005/000789	C07K14/46
4879	2005202417	Artificial human chromosome containing human antibody Lambda light chain gene	Medarex, Inc.; Kirin Pharma Kabushiki Kaisha	2005-06-03	SEALED	2001-05-11		C12N15/09
4880	2005202423	Cotton cultivar 00S07	D&PL Technology Holding Company, LLC	2005-06-03	SEALED	2004-07-27		A01H5/00
4881	2005250142	Biomarkers for the prediction of responsiveness to clozapine treatment	Novartis AG	2005-06-03	SEALED	2004-06-04	PCT/EP2005/006002	C12Q1/68
4882	2005202459	Plant regulatory sequences for control of gene expression	Monsanto Technology LLC	2005-06-06	SEALED	1999-09-16		C12N15/00
4883	2005202462	Evolution of whole cells and organisms by recursive sequence recombination	Maxygen, Inc.	2005-06-07	SEALED	1997-01-17		C12Q1/68
4884	2005254984	Method for nucleic acid analysis	GE Healthcare Bio-Sciences Corp.	2005-06-09	SEALED	2004-06-10	PCT/US2005/020378	C12Q1/68
4885	2005202657	Method and means for modifying gene expression using unpolyadenylated RNA	Commonwealth Scientific and Industrial Research Organisation	2005-06-17	SEALED	1999-08-13		C12N15/63
4886	2005202658	Control of gene expression	Commonwealth Scientific and Industrial Research Organisation	2005-06-17	SEALED	1998-03-20		C12N15/11
4887	2005257596	PNA chip using plastic substrate coated with epoxy group-containing polymer, method of manufacturing the PNA chip, and method of detecting single nucleotide polymorphism using the PNA chip	LG Life Sciences, Ltd.	2005-06-21	SEALED	2004-06-24	PCT/KR2005/001920	B01J19/00

4888	2005202730	Mutated cyclin G1 protein	University of Southern California	2005-06-22	SEALED	2000-05-02		C12N15/12
4889	2005202768	Transgenic Mammals Having Human IG LOCI Including Plural Vh and Vk Regions and Antibodies Produced Therefrom	Amgen Fremont Inc.	2005-06-24	SEALED	1996-12-03		C12N15/00
4890	2005202773	Specific genetic modification of the activity of trehalose-6-phosphate synthase and expression in a Homologous or heterologous environment	Vlaams Interuniversitair Instituut voor Biotechnologie v.z.w.(VIB)	2005-06-24	SEALED	1998-10-15		C12N15/54
4891	2005327983	Methods of protecting plants from pathogenic fungi	Pioneer Hi-Bred International, Inc.	2005-06-30	SEALED	2004-06-30	PCT/US2005/023327	C12N15/82
4892	2005202946	Enhancement of expression of a single-stranded, heterologous nucleotide sequence from recombinant viral vectors by designing the sequence such that it forms intrastrand base pairs	Targeted Genetics Corporation	2005-07-05	SEALED	1999-08-09		C12N15/00
4893	2005202972	Proteins comprising conserved regions of neisseria meningitidis surface antigen NhhA	The University of Queensland	2005-07-07	SEALED	2000-01-25		C07K14/22
4894	2005203028	Method for the production of glycerol by recombinant organisms	E.I. Du Pont De Nemours and Company; Genencor International, Inc.	2005-07-12	SEALED	1996-11-13		C12N15/53
4895	2005274974	Salivary transcriptome diagnostics	The Regents of the University of California	2005-07-15	SEALED	2004-07-21	PCT/US2005/025138	C12Q1/68
4896	2005203138	Methods and products for manipulating uncoupling protein expression	University of Vermont and State Agricultural College	2005-07-19	SEALED	1999-06-23		C12N15/00
4897	2005263591	Genetically engineered pyrroloquinoline quinone dependent glucose dehydrogenase comprising an amino acid insertion	F. Hoffmann-La Roche AG	2005-07-19	SEALED	2004-07-20	PCT/EP2005/007844	C12N9/04
4898	2005265443	DNA coding for polypeptide participating in biosynthesis of pladienolide	Mercian Corporation; Eisai R & D Management Co., Ltd	2005-07-19	SEALED	2004-07-20	PCT/JP2005/013541	C12N15/52

4899	2005203173	Super-antigen fusion proteins and the use thereof	Healthbanks Biotech Co., Ltd.	2005-07-21	SEALED	2004-07-21	C07K19/00
4900	2005203184	Methods for identifying combinations of entities as therapeutics	CombinatoRx, Incorporated	2005-07-21	SEALED	2000-07-07	A61K45/00

This data is current as of **2009-02-15 18:00 AEDT**.

1. AU624,105 – NANBV Diagnostics and vaccines

Preliminary

Patent Applicant: Chiron Corporation (Chiron), a US corporation

Current Patent Owner: Novartis Vaccines and Diagnostics, Inc, a US corporation (subsidiary of Novartis AG, a Swiss corporation. Partial acquisition (42.2%) completed in 1995. Final acquisition (100%) completed in 2006).

Earliest Patent Application Date: 18 November 1987 (United States)

Australian Patent Application Date: 18 November 1988.

Australian Patent Grant Date: 28 September 1992

Patent Monopoly Period: 18 November 1988 to 18 November 2008

Current Status: Expired

Title: *NANBV Diagnostics and vaccines*

Technical Field: The invention relates to materials and methodologies for managing the spread of non-A, non-B hepatitis virus (NANBV) infection. More specifically, it relates to diagnostic DNA fragments, diagnostic proteins, diagnostic antibodies and protective antigens and antibodies for an etiologic agent of NANB hepatitis, i.e., hepatitis C virus.

Granted Claim 1: (1992)

'A purified HCV polynucleotide'.

See schedule A1 for all claims

Amended Claim 1: (1997)

'A polypeptide in substantially isolated form comprising a contiguous sequence of at least 10 amino acids encoded by the genome of hepatitis C virus (HCV) and comprising an antigenic determinant, wherein HCV is characterized by:

(i) a positive stranded RNA genome;

(ii) said genome comprising an open reading frame (ORF) encoding a polyprotein; and

(iii) said polyprotein comprising an amino acid sequence having at least 40% homology to the 859 amino acid sequence in Figure 14.'

See schedule A1 for all claims

Pre-grant Opposition: No

Post-grant Litigation: Yes. *Murex Diagnostics Australia Pty Ltd v Chiron Corporation* Australian Federal Court, NSW District Registry, Action No: NG 106/1994.

Result of Litigation: Settled on 28 August 1996 during trial conducted by Burchett J. Murex permitted to supply HCV immunodiagnostic assay in Australia.

Hepatitis

Prior to 1989 there were three classified forms of hepatitis. They were hepatitis A, B and non A non B (NANBH). However, as a result of the discovery and characterisation of the causative agent of NANBH in 1987 by scientists at Chiron working in collaboration with scientists at the US Centers for Disease Control (CDC), and the subsequent verification of their work by scientists in the US and around the world, by 1989 NANBH had became classified as hepatitis C. Today the categories of hepatitis are A, B, C, B with D, E and G,

although there is some evidence to suggest a category of hepatitis infection known as non A, B, C and E. Hepatitis G is not known to cause hepatitis in humans.

The causative agents of hepatitis A, B, C and E are viruses. The causative agent of NANBNCNE hepatitis has not been identified.

Hepatitis means inflammation of the liver. It is a human disease, though not exclusively.

Relevant History

The work that led to the discovery of HCV began in 1983. It was completed in 1987.

In 1981 Chiron was incorporated by a group of scientists that were at the University of California in San Francisco. It was a small start up company and its management had employed Dr Michael Houghton, a young PhD, who had for ten years been a research scientist at Searle Research & Development in England.

In November 1982 Dr Houghton arranged to meet Dr Bradley, a virologist with a worldwide reputation, from the CDC. Bradley had published a number of scientific papers that demonstrated that he had access to biological materials that were likely to contain the causative agent of NANBH. He also had undertaken experiments with the objective of creating biological materials that would be rich in the likely causative agent of NANBH. To do this he had used the CDC's primate laboratory. It was estimated that the cost, at the time, to maintain a single chimpanzee in the CDC's laboratory to be in the order of US$100,000 per year. Dr Houghton proposed to Bradley that they entered into an 'open collaboration', the objective of which 'was to clone HCV', as Houghton subsequently confirmed in testimony he gave to the Australian Federal Court on 9 July 1996. Dr Bradley was someone that Houghton needed if he was to have any chance of identifying the causative agent of NANBH. Apart from knowing nothing himself about hepatitis, having spent the previous four years working with interferons, Houghton was a molecular biologist not a virologist.

Thus in 1983 formal collaboration between the CDC, a publicly funded US government agency, and Chiron commenced. The idea was to combine Dr Houghton's molecular biological skills with Dr Bradley's skills as a virologist. Cloning the causative agent required access to biological materials that were known to contain the candidate agent and Houghton knew that if anyone could provide these, Bradley could.

Four years later, a relatively short period of time in the world of molecular biology in the 80s, the crucial discovery was made. By this time the estimated value of the exclusive biological materials used in the experiments conducted at Chiron's laboratories and developed and supplied by Dr Bradley's team was US$8,000,000. Of course, there was much more to the collaboration than that.

Despite the collaboration (as part of which the CDC never charged Chiron for the supply of its biological materials nor for the services of Dr Bradley and his highly trained team at the CDC) neither Chiron nor Dr Houghton communicated to the CDC or Dr Bradley that the causative agent of HCV had been cloned in January 1987. Indeed, it was not until May 1988, when Chiron made a public announcement that its scientists, alone, had discovered and verified the causative agent of hepatitis C, that the CDC and Dr Bradley learned that Chiron had filed patent applications which did not name him as a co-inventor.

Understandably, these events led the dispute between Chiron, the CDC and Dr Bradley over inventorship towards litigation; which although narrowly avoided by an agreement reached between the parties in 1990, flared up again when Dr Bradley discovered that the effect of the agreement was not as he had understood it to be. Unfortunately, he had been unrepresented at the time but when he sued Chiron and some of its officers in the US courts to vitiate the agreements on grounds of duress and mistake, his legal action was summarily dismissed for technical reasons.

The CDC on the other hand did not want to get involved. Essentially, the US government

officials who had brokered this very poor settlement with Chiron had either moved on to other positions or were disinterested. In effect, Chiron paid the CDC US$1.9 million for $US8 million worth of materials. Why the CDC did so, when it was obvious that Chiron was about to earn many millions of dollars more from its 'invention', beggars belief. And while Dr Bradley had received US$337,500 from Chiron, this was only a fraction of what Dr Bradley was entitled given his expectation that an independent review of his role in the discovery of HCV would confirm his status as a joint inventor.

Frustrated by Chiron repeatedly refusing to license it to 'legally' make use of HCV biological materials on reasonable commercial terms, F Hoffmann La Roche AG (Roche), a Swiss company, even went to the extraordinary length of offering to acquire from Bradley his non-US inventorship rights to the 'invention' which Chiron claimed exclusively, but which Bradley claimed as his. Having obliged Roche, Dr Bradley then found himself involved in another round of litigation in the US, this time brought by Chiron against Roche and him.

In the midst of all of this litigation, Roche continued to pursue its Opposition in the European Patent Office (EPO) which it had instigated (along with other organisations) in 1993 after the EPO had granted Chiron its first European HCV patent (EP 0,318,216). Although Roche had failed before the Opposition Division of the EPO, it appealed the decision to the Technical Appeal Board of the EPO. Eventually, the appeal was heard in June 2000 and in a surprising result Chiron's claims to HCV proteins and their use were revoked. Effectively, Chiron was no longer able to prevent Roche from making and supplying an HCV immunoassay (antibody diagnostic) in Europe. But the Technical Appeal Board had, in its decision, maintained some aspects of Chiron's claims over the use of the genome of HCV in DNA-based diagnostics.

The stalemate between Roche and Chiron was only resolved when Novartis AG, which in 1995 acquired 42.2% of Chiron, intervened. Finally, Roche was granted a license to make and supply HCV diagnostics around the world and as part of that resolution Dr Bradley was forced to agree to disclaim forever his rights as a joint inventor of HCV.

Inconsistency between the EPO and the UK Courts over the validity of Chiron's HCV patent

By 1988 a rift had developed between the EPO and the UK courts over the interpretation of article 52 of the European Patent Convention. Article 52 EPC and s.1 *UK Patents Act, 1977* deal with patentable subject matter. They are virtually identical provisions.

The rift became apparent in the context of gene patents when both the UK Patents Court and the UK Court of Appeal in *Genentech Inc's Patent* (*Genentech*) held that isolated t-PA, a purified form of tissue plasminogen activator (the human protein that dissolves blood clots in the body), was not an 'invention' within s.1(1) *UK Patents Act, 1977*. Indeed, the UK Court of Appeal's decision, handed down in October 1988, contradicted the memorandum, released by the EPO, the USPTO and the Japanese Patent Office (JPO) in June of that year [see Part 1 p 64], which stated in effect that isolated biological materials were capable of being 'inventions' because in that form they were different from naturally occurring biological materials.

Acting in accordance with the EPO policy and contrary to the binding authority of the UK Court of Appeal in *Genentech*, the British Patent Office granted Chiron a British patent, GB 2,212,511, in 1992. Chiron then sued Organon Teknika Ltd, Murex Diagnostics Ltd and United Biomedical, Inc for infringement and in June 1993 the trial came before Aldous J in the UK Patents Court. In response, the Defendants had counterclaimed to revoke the British patent on a number of grounds, including that isolated HCV genetic and protein materials were not, as per the decision in *Genentech*, inventions.

In October 1993 Aldous J handed down his decision which upheld the validity of the patent in respect to all claims, except the claims to the use of isolated HCV biological materials in HCV vaccines. These he held invalid because the patent did not provide sufficient information to enable the skilled person to make an HCV vaccine without undue

experimentation. Sitting with Aldous J had been Dr Sidney Brenner, a noted molecular geneticist, who with the consent of the parties was appointed a Scientific advisor.

The Defendants then appealed the decision to the UK Court of Appeal.

In August 1993 the EPO granted Chiron a European patent, EP 0,318,216, with virtually identical terms to that granted by the British patent office. Immediately, Chiron brought patent infringement proceedings against Organon, Murex and UBI in The Netherlands and Germany. The Dutch courts at the time were issuing orders for injunctions, which were known as 'pan-European injunctions', that is, they purported to apply across the international borders of countries that were members of the European Union (EU). This uniquely Dutch remedy is no longer available, but Chiron used it then to obtain injunctions to enjoin the defendants from infringing the European patent. Naturally, they relied heavily on the decision of Aldous J and, predictably, the Dutch court granted the pan-European injunction.

In the meantime, as noted earlier, Roche and a number of other companies, which included Organon, Murex and UBI, had filed Oppositions with the EPO against the grant of the European patent.

While in the UK the appeal was moving closer to a hearing date, in early 1995 certain information concerning the relationship of the court appointed scientific advisor and Chiron came to the knowledge of the Defendants' lawyers. What they had discovered was that Dr Brenner had, subsequent to the trial before Aldous J, been appointed to the scientific advisory board of Lynx Therapeutics, Inc (Lynx), a US corporation, of which Chiron was the sole source of funds. Thus, when the time came to consider whether Brenner should be appointed as a scientific advisor to the UK Court of Appeal, the Defendants opposed on the basis of what they knew, namely, as Sir Thomas Bingham MR (the chief justice of the UK Court of Appeal) said, 'that he was said to have some involvement with, and some investment in, a company in which Chiron, the Plaintiffs, were also investors'. In spite of the Defendants objections the UK Court of Appeal ordered Dr Brenner's appointment. Subsequently, further information came to the attention of the Defendants lawyers. Once again the Defendants objected, this time asking the UK Court of Appeal to reconsider the appointment. The new information was described by Sir Thomas as follows:

> It is pointed out that a Dr Martin, a Chiron man (if I can so describe him), had become the Chairman of Lynx; that Lynx was described as a "satellite" company in the Chiron firmament; that a Dr Rutter was a director of Lynx; that there was a collaboration agreement between Chiron and Lynx; that the work which Lynx was doing was work related indirectly to the subject-matter of this patent; that Chiron had an investment in Lynx and was providing financial support; that Chiron had the expectation of profit from its investment in Lynx and that Dr Brenner himself had a financial interest since he was a shareholder in Lynx, had collaborated in its research and stood to gain financially from Lynx's performance. He is, as we understand, a director of Lynx. Material was put in to suggest that the value of Chiron's investment in Lynx was very substantial and greatly in excess of the sum which Chiron had actually paid.

But Sir Thomas was unconvinced that a man such as Dr Brenner would be capable of acting other than fairly and independently. He said:

> Is there the slightest risk that the expert would act otherwise than with total independence in performing the function for which he is retained, or could any reasonable person suppose that there was such a risk? To my mind the answer to both those questions is, emphatically, no.

Unfortunately, Sir Thomas's decision was made four years before the House of Lords ruled that a judge should be disqualified where the 'decision would lead to the promotion of a cause in which ***the judge was involved together with one of the parties***' [*R v Bow Street Metropolitan Stipendiary Magistrate and others, ex parte Pinochet Ugarte (No 2)* [1999] 1

All ER 577 (see p 44 of Part 1)]. Clearly, had Sir Thomas had the benefit of the Lords decision in *Pinochet* he may have decided otherwise. Certainly, Dr Brenner was not a judge, but he literally sat with the trial judge and had meetings with him beyond the ears of the lawyers for the parties. Thus he was in a position to influence the judge on matters of fact. However, even though the issue of whether isolated biological materials were patentable subject matter as a matter of law was debatable, it was foreseeable that the way Dr Brenner characterised the scientific facts to the judge would play an important role in the way the judge interpreted the law. Accordingly, it was appropriate that the same rules that applied to a judge should have applied to him.

So with Dr Brenner at their side the judges in the UK Court of Appeal upheld Aldous J's decision that isolated HCV biological materials were patentable subject matter. In doing so the Court supported the policy adopted by the European Patent Office (EPO) in June 1988. Thus the appeal judges (like Aldous J did) accepted that the processes involved in the 'isolation' of a naturally occurring HCV materials so changed those materials that their treatment as 'inventions' - not 'discoveries' - was justified as a matter of law.

The problem was that their reasoning (which was probably based upon a misconception of the facts that Dr Brenner may have allowed proactively or by silence) was irreconcilable with the earlier UK Court of Appeal decision in *Genentech,* and no reasoning was proffered by the appellate judges to explain away the obvious conflict between these two decisions, other than to say that the *invention issue* 'was not argued as it was accepted [by the Appellants] that it was not open [to them]… in the light of the judgments of Purchas and Dillon LJJ in Genentech'.

But this statement was, unfortunately, incorrect. In truth, Purchas LJ invalidated Genentech's patent on the basis that the isolated t-PA claims were 'not inventions' while Dillon LJ held otherwise. Indeed, it was Purchas and Mustill LJJ, not Purchas and Dillon LJJ, who made up the majority in *Genentech* and they held that the claims to isolated biological materials were *not* inventions because at the end of the day, as a matter of fact, the process of the *isolation* of t-PA (which were the materials in issue in that case) did not change what it was, namely, the same as the t-PA that existed in nature. This Mustill LJ made clear in the following passage from his decision:

> It is true that the word "recombinant tissue plasminogen activator" may be a useful turn of phrase, but this should not be allowed to disguise the fact that "recombinant" describes, not the product itself, but its history. It is I believe, a failure to acknowledge this which has compounded the already substantial difficulties of relating these unusual claims to the framework of patent law, and which have diverted attention away from the fact that the success of Genentech lay, not in the invention of a new substance -- for protein molecules with the amino acid sequences shown in figure 5 and the functional characteristics set out in the specification have existed since far into the distant past -- but in the accomplishment for the first time of a method of creating that substance. Wrapped up as it may be in the product claims, I believe that in truth what Genentech have invented (if they have invented anything at all) is a process. (Emphasis added)

So the appeal judges' incorrect and therefore ambiguous statement shed no light on their reasoning to hand down a conflicting decision.

Even more confusing was that Dr Brenner had played the same role in the UK Court of Appeal in *Genentech* as he had in *Chiron*. So how could it be that the same court, constituted by different judges, but with the same scientific advisor, and dealing with essentially the same issue about different biological materials (t-PA and HCV), could come to such irreconcilable conclusions?

By this stage, however, Organon and UBI had capitulated to Chiron. This had resulted in the withdrawal of their HCV immunodiagnostic assays from the European market leaving only Murex, which had, in the meantime, opened up a new litigation front by seeking to revoke

Chiron's Australian HCV patent (AU 624,105). While the Australian case was moving towards a trial there was still some time to go before the case would be ready to be heard.

In the UK it was left for Murex to file an application for leave to appeal to the Appellate Committee of the House of Lords, the highest appellate court in the UK. One of the grounds on which leave was sought was:

> The patent as currently formulated should have been held invalid as not being directed to an invention, but to a discovery; or to a known concept instead of the inventive solution required to bring it about.

Murex's application was successful but they were awaiting a hearing date when the trial in the Australian litigation commenced in June 1996.

That litigation, as it was to turn out, was to have lasting ramifications for Chiron and Murex because on 28 August 1996, some nine weeks into the trial, Chiron suddenly and without any explanation offered to withdraw all its litigation worldwide against Murex and with no payment by Murex of Chiron's legal costs. Chiron agreed to walk away from an enforceable order for its UK legal costs worth some £12 million. In addition, Chiron agreed to grant Murex a worldwide license that enabled it to continue making and selling its HCV serotyping assays throughout the world and its HCV immunoassays in Australia. Why this occurred will be discussed in the next section but, needless to say, while it was an excellent result for Murex and particularly for the health system of Australia it resulted in the withdrawal of Murex's appeal to the House of Lords.

This was just as well for Chiron because in October 1996 the House of Lords handed down its decision in *Biogen, Inc v Medeva plc*. This was an important decision being the first House of Lords decision concerning a gene patent after the *Genentech* and *Chiron* decisions.

In a separate but concurring decision, as an addendum to Lord Hoffmann (the author of the unanimous decision), Lord Mustill wrote:

> I have had the opportunity to read in draft the speech of my noble and learned friend Lord Hoffmann, and agree both with the conclusion that the appeal should be dismissed and with the reasons for that conclusion. ….
>
> There is however one matter which I should mention: namely, the necessity or otherwise for a valid patent to concern an invention, as well as satisfying the conditions expressed in paragraphs (a) to (d) of section 1(1) of the Act. This question was not contested before the House, although some reference was made to it in debate, for it was agreed (rightly in my opinion) that it has no bearing on the present appeal. My reason for referring to it is simply to make clear that in concurring with all your Lordships in the reasons for dismissing the appeal I should not be taken to accept, without full argument, that the need for an invention would always be academic, or that no such need is expressed by the words of section 1(1): nor indeed do I understand my noble and learned friend as advancing any conclusion to that effect. Certainly, in the great majority of cases, there will be no need to complicate the enquiry by looking outside the four conditions. The traditional law of patents is, however, in the course of adapting itself to new technologies, beyond contemplation when the foundations of that law were established. This process is not without strain, and I believe that in some instances a close conceptual analysis of the nature of patentability will not be a waste of time. ***Such a case was Genentech Inc's Patent where the claim was for a product already existing in nature, a subject far distant from the mechanical and chemical inventions to which so much of traditional patent law relates. There may well be others in the future***.
>
> My Lords, my purpose in adding this footnote to the speech of my noble and learned friend is not of course to express any opinion, one way or the other, on the correctness of the reasoning outlined at pages 261-266 of

> the report of Genentech Inc's Patent. The intention is only to emphasise that when a dispute does arise on which this question may have a bearing it will merit study leading to a definitive answer. (Emphasis added)

The reason why Lord Mustill added this addendum was to open the field for testing the legal boundaries of 'invention' under s.1(1) *UK Patents Act, 1990*.

Thus in preferring to leave 'the question' of whether 'something which satisfies the conditions of patentability can be called an invention' to when 'it arises', Lord Hoffmann, nonetheless confirmed that the issue of 'invention' was important because '[o]nly if this question receives an affirmative answer would it be necessary to go on to consider whether the invention satisfies the prescribed conditions for being "patentable"'.

So, given that the 'invention' issue was not before their Lords and content to leave that to another day, Lord Hoffmann turned to a secondary condition of patentability – inventive step; namely, whether there was an inventive step involved in producing a recombinant plasmid that could synthesise two antigens (that is, HBV proteins that antibodies reacted to) of the hepatitis B virus (HBV)?

In this respect although the plasmid was new and artificial it had been made in accordance with the molecular biological techniques first pioneered by Stanley Cohen and Herbert Boyer in 1973. So the techniques themselves were not in anyway 'inventive'. Nonetheless, it was argued by Biogen's lawyers that there was an inventive step because there were certain unresolved 'uncertainties' which meant that there was no guarantee that these techniques would work without some modifications. Biogen's lawyers argued that these modifications were inventive.

Interestingly, Aldous J, the trial judge in *Chiron*, was also the trial judge in *Biogen*. While in *Chiron* the UK Court of Appeal supported his reasoning, a differently constituted UK Court of Appeal in *Biogen* did not. In *Biogen* he held that there was an inventive step in 'the idea or decision to express a polypeptide displaying HBV antigen specificity in a suitable host', but the UK Court of Appeal was to disagree, with Lord Hoffmann saying that 'so stated, the concept was obvious'.

That said, Lord Hoffmann considered Aldous J's description of the inventive step to be inaccurate. In his opinion, there was more to the inventive step than that, but rather than 'pursue the question of whether this amounts to an inventive step for the purposes of patent law' he was 'content to assume, without deciding, that [the invention defined in claim 1] was not obvious'.

On the basis of that assumption, Lord Hoffmann then turned his mind to whether the patent made an adequate disclosure so as to justify the claim to such an invention. This issue, known to patent lawyers as 'sufficiency', is not a secondary condition of patentability but is an issue that nonetheless goes to the very heart of the patent system – whether the information which the inventor gives to the State justifies the patent monopoly. Thus, the issue was whether the breadth of the scope of the patent monopoly to *all ways* of making the recombinant plasmid that housed the genetic sequence of the HBV antigens was justified. If it was not, then the patent was insufficient and therefore invalid.

With respect to the law on this issue Lord Hoffmann was critical of Aldous J's reasoning which, he said, followed 'his earlier decision in *Chiron Corporation v Organon Teknika Ltd* [1994] FSR 202 … that it would be enough if the specification enabled *one* embodiment to be made'.

In other words, Aldous J had held in *Chiron* that so long as the patent explained to the ordinary skilled reader how to make the 'invention' in one way, that was enough to justify a patent that covered *all* ways of making the same invention. Indeed, Lord Hoffmann was critical of the European Patent Office [EPO] for taking a similar approach. He said:

> I think that in concentrating upon the question of whether Professor

> Murray's invention could, so to speak, deliver the goods across the full width of the patent or priority document, the courts and the EPO allowed their attention to be diverted from what seems to me in this particular case the critical issue. It is not whether the claimed invention could deliver the goods, but *whether the claims cover other ways in which they might be delivered: ways which owe nothing to the teaching of the patent or any principle which it disclosed*.

On the facts of the case Lord Hoffmann accepted 'the judge's findings that the method was shown to be capable of making [HBV] antigens and … that it would work in any otherwise suitable host cell', but in answer to the question '[d]oes this contribution justify a claim to a monopoly of *any* recombinant method of making the antigens?' Lord Hoffmann responded:

> In my view it does not. The claimed invention is too broad. Its excessive breadth is due, not to the inability of the teaching to produce all the promised results, but to the fact that the same results could be produced by different means.

In terms of the impact which these kinds of patents can have on scientific and medical progress, it is important that this Committee note his Lordship's view:

> It is inevitable in a young science, like electricity in the early nineteenth century or flying at the turn of the last century or recombinant DNA technology in the 1970s, that dramatically new things will be done for the first time. The technical contribution made in such cases deserves to be recognised. *But care is needed not to stifle further research and healthy competition by allowing the first person who has found a way of achieving an obviously desirable goal to monopolise every other way of doing so.* (See Merges and Nelson, On the Complex Economics of Patent Scope (1990) 90 Columbia Law Review 839.)
>
> I would therefore hold that [the patent] did not support the invention as claimed in the European Patent and that it is … invalid. (Emphasis added)

Postscript to the Chiron's European HCV patent 0,318,216

It was not the UK courts that brought Chiron's stranglehold over HCV immunodiagnostics in Europe to an end, but the Technical Board of Appeal of the European Patent Office (TBA). In June 2000 the TBA heard an appeal in the Opposition filed by F Hoffman La Roche AG (Roche) when EP 0,318,216 was first granted to Chiron in 1993. It had taken seven years for the Opposition to reach this stage and during this time Chiron had succeeded in closing down the HCV immunodiagnostic production of Organon Teknika and United Biomedical, Inc through patent litigation. Now Chiron faced the TBA in Munich, which is where the EPO is headquartered, and witnessed the almost complete destruction of the very patent that had caused so much damage to the healthcare systems of Europe and the businesses of at least three companies.

Perhaps the gravity of the situation in Europe had been communicated to the EPO via diplomatic or governmental channels, but whatever the cause of the EPO's change of heart, the TBA decision handed down in writing on 8 February 2001 [TBA Case No T0188/97 – 3.3.4] made it clear that all of the claims as granted to Chiron in 1993 were invalid. That Chiron was able to maintain the patent at all was due to its ability within the European patent system to file amended claims after the grant of a European patent. This Chiron did and as a result five completely new claims to HCV nucleic acid diagnostics were substituted. So while the patent survived the Opposition, the scope of the patent monopoly was very different and much more narrow.

It should be noted that the very claims which the UK Patents Court and the UK Court of Appeal held as valid under the EPC equivalent, the *UK Patents Act, 1977*, was determined by the EPO to be invalid. True, the patent in issue before the UK courts was one granted by the British Patent Office (GB 2,212,511), but by the time argument in the Opposition appeal was

heard by the TBA, Chiron had relinquished the British patent for the European patent (EP, 0,318,216 – which had the same claims) with the expectation that the EPO would never revoke EP 0,318,216 or narrow the scope of the patent monopoly to exclude HCV immunodiagnostics. In what can only be described as a most confusing state of affairs, the patent claims held to be valid by the national courts in the UK, The Netherlands and Germany and which led to the closing down of HCV immunodiagnostic production of Organon, Murex and UBI during the intervening period, were ultimately revoked by the granting patent office, the EPO.

The Impact of the Australian Litigation

The Australian litigation commenced in March 1994 and, rather than being a repeat of the UK litigation, it was quite different; in Australia, unlike in the UK, it was open for the patent to be declared invalid on the basis that Bradley was an inventor from whom Chiron had not secured his rights when it applied for and was granted the Australian patent. Thus the evidence leading up to the invention, including the relationship between Chiron and the CDC and between Houghton and Bradley, was relevant.

More importantly was the role that Dr Brenner had played as a scientific advisor when he sat with both Aldous J and the UK Court of Appeal. This issue became germane during the trial in the Australian litigation when Chiron's lawyers sought to rely on the findings of fact and law made by the British judges in the *Chiron* decisions. This presented Murex's lawyers with an opportunity to challenge the reliability of these decisions.

The Brenner subpoena

Although I was Murex's principal Australian lawyer I was not given access to the documents which had been presented to the UK Court of Appeal ('the Brenner/Chiron/Lynx documents') until mid-August 1996 but, once seeing the documents for the first time, I formed the view that there was a real likelihood that an Australian judge would find Dr Brenner's appointment as a scientific advisor to the UK Court of Appeal to have been improper. I thereupon drafted a Notice to Produce, the effect of which required Chiron to produce all documents relating to or concerning Dr Brenner and his association with Lynx.

Chiron's reaction was revealing. Rather than simply comply with the Notice to Produce, it sought to have the Notice set aside.

On 21 August 1996, merely a week before the worldwide litigation between Murex and Chiron was to come to an end (and which was not thought possible at that time), legal argument was heard by Burchett J. In support of the Notice to Produce, I brought to Burchett J's attention the contents of the Brenner/Chiron/Lynx documents.

Having heard the argument, Burchett J handed down an *ex tempore* decision (Latin: at the time) in which he said:

> It is accepted that Murex's point was raised in the Court of Appeal, and that it was rejected. But it is suggested that the law in England is not identical with that in Australia on this point, and that in any case rejection on the facts then known should not bar the raising of the matter on such facts as may be ascertained now. It should be appreciated, counsel argue, that *the appearance in question here is not just of Dr Brenner sitting with the President and founder of Chiron; but of his being a director of a company which had a concern in the development of patents, so that, it is urged, there may be an appearance of his having been both pro Chiron and pro the interests of patentees in general*.

Burchett J then referred to the decision in *Livesey v The New South Wales Bar Association* (1983) 151 CLR 288 at 293-294 which held:

> (A) judge should not sit to hear a case if in all the circumstances the

> parties or the public might entertain a reasonable apprehension that he might not bring an impartial and unprejudiced mind to the resolution of the question involved in it.

Accordingly, Burchett J dismissed Chiron's motion and ordered Chiron to comply with the Notice to Produce, which Chiron duly did. However, buried among the documents was a document that I had not seen before. This document is subject to a confidentiality order and so its contents cannot be disclosed without the permission of the Federal Court of Australia, however, the document suggested that something untoward had happened *prior to* Aldous J handing down his decision in October 1993. This was not known by the UK Court of Appeal when it heard argument on the Defendants application to have Dr Brenner's appointment rescinded.

Significantly, within a day of the document's production, Chiron contacted Murex's lawyers in London through an intermediary, Johnson & Johnson, a US company and a silent partner in Chiron's HCV immunoassay business, to see if the Murex board was interested to settle out-of-court. That overture was immediately taken up and within 24 hours settlement discussions had begun in San Francisco.

In the meantime, Robert Blackburn, Chiron's Vice President and Chief Patent Counsel, was due to be cross examined in the Australian litigation. I was instructed by Michael Warren, the chairperson of the Murex board, that Chiron's board was most concerned to ensure that Mr Blackburn was not questioned about the contents of this document. Accordingly, Mr Warren also instructed me not to have David Catterns QC press Blackburn on oath until such time as it was clear that the settlement discussions had failed. For the first time in my legal career I had my mobile phone turned on in a courtroom so that I could instruct counsel, Mr Catterns QC, promptly once I had received instructions from Mr Warren. When the phone call came it was to advise me that the case was over. Mr Blackburn was released from the witness box.

Thus, within a week, the worldwide patent litigation battle that had been waged in many countries for over four years and which had brought Murex close to bankruptcy was over. News of the settlement was broadcast on ABC national television on the *7.30 Report* on the evening of 29 August 1996.

Clearly, had the Australian litigation proceeded further, not only would Mr Blackburn have been cross examined over the contents of the document but Chiron would also have had to produce the persons mentioned in it for cross examination.

It is a matter of speculation as to what would have happened had the worldwide patent litigation between Chiron and Murex not settled so abruptly, but it is important to note that Chiron's first US patent for HCV immunoassays had not yet been granted by the USPTO. Had the case in Australia proceeded further and resulted in adverse findings of fact on (a) the issue of inventorship or (b) the UK decisions made by Aldous J and the UK Court of Appeal (having been possibly tainted by Dr Brenner's association with Chiron), it is very possible that the USPTO would never have granted Chiron US patent 5,698,390 on 16 December 1997.

Events in Australia after the Murex litigation (1997-2008)

In February 1997 Chiron substituted the originally granted patent claims in Australia (AU 624,105 and which were the subject of the revocation action) for a new set of claims. These new claims were identical or nearly identical to the claims granted in 1993 in EP 0,318,216.

It should further be noted that despite the fact that the EPO invalidated these very claims in June 2000, IP Australia did nothing about the Australian patent even though it has power under the *AU Patents Act, 1990* to do so. As a result, until the patent expired on 18 November 2008, Chiron (and its new owner, Novartis) maintained a patent monopoly which the EPO had repudiated some eight years earlier.

Neither Chiron nor Novartis has had to pay compensation to Organon or UBI nor any other

organisation or person detrimentally affected by the enforcement of, what was, an invalid patent monopoly over HCV immunodiagnostics.

The Impact of Chiron's HCV patent on the Australian Health Sector

Although IP Australia did not grant Chiron AU 624,105 until September 1992, the exclusive rights which Chiron acquired at that time effectively commenced some 4 years earlier (which is the reason why the patent monopoly period of 20 years commenced on November 18, 1988). Therefore, between the time that the patent application become known (or open for public inspection) and the sealing of the patent, Chiron had the right, under the *AU Patents Act, 1990,* to sue in respect of anything done within Australia that would have amounted to an infringement of the patent once granted.

While this appears fair and reasonable given that the patent monopoly is, in effect, backdated to the date of application in Australia, it must be appreciated that it would not have been easy for third parties to gauge the scope of the patent monopoly, as the final claims would not be known until IP Australia published a notice confirming the acceptance of the patent application, some three to four months prior to the grant date. Therefore, those that may have been tempted to institute research into this field and would therefore infringe Chiron's 'ungranted' patent in Australia during this period (when it was not even known if a patent would even be granted) would have had to base their research on a reliance of the patent claims as applied for (which in this case, made almost no difference since the claims as applied for and the claims as originally granted were virtually identical). Had Chiron's Australian HCV patent application been subjected to the same objections raised by the EPO with regard to Chiron's European HCV patent application during pre-grant examination, almost certainly a different set of claims would have resulted.

No other patent office in the world granted Chiron the patent claims that IP Australia granted. They were the broadest claims imaginable.

This is a significant issue in terms of assessing the efficiency of Australia's patent law because if a third party in Australia had been in a position to undertake HCV research prior to grant, they would, as Professor Blumberg said in his affidavit filed in the *Murex v Chiron* Australian litigation, have been 'deterred from conducting research on HCV because the patent is, in effect, *intimidating*.' The question to ponder is this: is this a desirable outcome when it is possible that the patent may not have been granted? Furthermore, what if instead of 4 years of uncertainty over the possible claims of the patent, as in this case, that period had been even longer?

The Original Patent Claims (as granted)

There were 39 claims originally granted. These included claims to isolated or purified biological materials that are identical or substantially identical to HCV as it occurs in nature:

> Claim 1: A purified HCV polynucleotide
>
> Claim 10: Purified HCV.
>
> Claim 12: A purified HCV polypeptide.
>
> Claim 18: A monoclonal antibody directed against an HCV epitope.
>
> Claim 19: A purified preparation of polyclonal antibodies directed against HCV.
>
> Claim 28: A polypeptide containing an HCV epitope produced by the method of claim 27.

Then there were claims to the *use* of these materials in vaccines:

> Claim 32: A vaccine for treatment of HCV infection comprising an immunogenic polypeptide containing an HCV epitope wherein the

immunogenic polypeptide is present in a pharmacologically effective dose in a pharmaceutically acceptable excipient.

Claim 33: A vaccine for treatment of HCV infection comprising inactivated HCV in a pharmacologically effective dose in a pharmaceutically acceptable excipient.

Claim 34: A vaccine for treatment of HCV infection comprising attenuated HCV in a pharmacologically effective dose in a pharmaceutically acceptable excipient.

As well as claims to the *use* of these materials in HCV diagnostics.

Claim 22: A kit for analyzing samples for the presence of polynucleotides derived from HCV comprising a polynucleotide probe containing a nucleotide sequence from HCV of about 8 or more nucleotides, in a suitable container.

Claim 23: A kit for analyzing samples for the presence of an HCV antigen comprising an antibody directed against the HCV antigen to be detected, in a suitable container.

Claim 24: A kit for analyzing samples for the presence of an antibodies directed against an HCV antigen comprising a polypeptide containing an HCV epitope present in the HCV antigen, in a tuitable container.

Claim 25: A polypeptide comprised of an HCV epitope, attached to a solid substrate.

Claim 26: An antibody to an HCV epitope, attached to a solid substrate.

Claim 29: A method for detecting HCV nucleic acids in a sample comprising:

(a) reacting nucleic acids of the sample with a probe for an HCV polynucleotide under conditions which allow the formation of a polynucleotide duplex between the probe and the HCV nucleic acid from the sample; and

(b) detecting a polynucleotide duplex which contains the probe.

Claim 30: An immunoassay for detecting an HCV antigen comprising:

(a) incubating a sample suspected of containing an HCV antigen with a probe antibody directed against the HCV antigen to be detected under conditions which allow the formation of an antigen-antibody complex; and

(b) detecting an antigen-antibody complex containing the probe antibody.

Claim 31: An immunoassay for detecting antibodies directed against an HCV

(a) incubating a sample suspected of containing anti-HCV antibodies with a probe polypeptide which contains an epitope of the HCV, under conditions which allow the formation of an antibody-antigen complex; and

(b) detecting the antibody-antigen complex containing the probe antigen.

There were, of course, claims to the *use* of these materials in other applications as well as claims to *derivatives* of these materials such as these below:

Claim 2: A recombinant HCV polynucleotide

Claim 3: A recombinant polynucleotide comprising a sequence derived from an HCV genome or from HCV cDNA.

Claim 4: A recombinant polynucleotide encoding an epitope of HCV.

Claim 5: A recombinant vector containing the polynucleotide of claim 2, or claim 3, or claim 4.

Claim 6: A host cell transformed with the vector of claim 5.

Claim 11: A preparation of polypeptides from the HCV of claim 10.

Claim 14: A recombinant HCV polypeptide.

Claim 16: A recombinant polypeptide comprised of an HCV epitope.

Claim 17: A fusion polypeptide comprised of an HCV polypeptide.

This claim structure is typical for gene patents. Indeed as one becomes familiar with gene patents, a pattern emerges that demonstrates how the patent attorney profession quickly adopt drafting styles that are deemed acceptable to patent offices.

AU Patent 624,105 and the Australian Health Sector

The most immediate and obvious effect of the grant of AU 624,105 was on those health service providers that were involved in the provision of whole blood or blood products. Until the release of the first generation HCV immunodiagnostics it was difficult for whole blood and blood product providers to screen out sources of blood that were contaminated with the cause of non-A non-B hepatitis (NANBH). Indeed, it was well documented in the scientific and medical literature at the time that the most likely cause of post-transfusion NANBH (PT-NANBH) was, as the name suggests, the transfusion of whole blood or blood products.

Understandably, the announcement by Chiron on 10 May 1988 [see Chiron press release in schedule B] that its scientists, alone, had identified and characterised the causative agent of NANBH was unexpected. The achievement was hailed by blood banks and blood product providers around the world as being a wonderful achievement. Virologists around the world, including in Australia, heaped praise and awards on those involved in making the discovery. In 1992 Dr Bradley from the CDC and Drs Houghton, Choo, Quo and Overby from Chiron and Dr Alter from the US national Institutes of Health (NIH) were jointly awarded the *Karl Landsteiner Memorial Award*. This award was presented to these men for 'recognizing the clinical implications of post-transfusion non-A, non-B hepatitis, physiochemically characterizing an agent not yet visualized, developing a novel approach to the molecular cloning and characterization of the genome of the causative agent of hepatitis C, and expressing virus-specific proteins that formed the basis for the first hepatitis C antibody test.' In 1993 Drs Bradley and Houghton shared the *Robert Koch Prize* in recognition for their work to isolate, characterise and clone HCV. In 1994 Drs Bradley, Houghton, Choo and Kuo were awarded the *William Beaumont Prize* in Gastroenterology and Dr Bradley alone was the recipient of the *Priscilla Kincaid-Smith Award* given by the Royal Australasian College of Physicians. In 2000 Drs Houghton and Alter were awarded the *Lasker Clinical Medical Award*.

Therefore there is no doubt that these scientists did excellent research and made a significant discovery in the isolation, characterisation and cloning of HCV.

That said, it did not justify the grant of a patent to Chiron over the isolated and purified HCV biological materials nor, indeed, to the use of those materials in respect of every strain of HCV in diagnostics and in vaccines.

The following is an account of what transpired after Chiron's announcement on 10 May 1988 and how these events were to impact directly upon Australia.

Chiron and Ortho Diagnostic License Abbott Laboratories

On 17 August 1989 Chiron and Ortho Diagnostics Systems Inc (Ortho), a US corporation which was (and is) a fully owned subsidiary of Johnson & Johnson (J&J), entered into a number of written agreements, the effect of which was to license Abbott Laboratories (Abbott), a US corporation, with respect to the manufacture, supply and distribution of hepatitis immunodiagnostics around the world. The license agreement was directed to hepatitis diagnostics covered by Chiron's hepatitis patents anywhere in the world and it

defined hepatitis extremely broadly, effectively including anything that caused hepatitis.

The intention of the parties was described in the principal agreement as follows:

> The parties intend that their activities under this Agreement generally shall be directed toward optimising the profit of each of them under this Agreement while at the same time developing a strong, efficient, effective and growing presence in the markets for Products worldwide.

The word 'Products' was defined to mean as follows:

> Product shall mean any and all Immunoassays, Immunoassay kits or Immunoassays test configurations (excluding the instrument portion thereof), the manufacture, sale or use of which utilize or contain Antigens or Antibodies.

The words 'Antigen' and 'Antibodies' were defined to mean:

> Antigens shall mean Hepatitis Antigens and Retrovirus Antigens
>
> Antibodies shall mean Hepatitis Antibodies and Retrovirus Antibodies.

The terms 'Hepatitis Antigens' and 'Hepatitis Antibodies' were defined to mean:

> (a) Hepatitis Antigens shall mean any peptide, polypeptide or ligand and all proteins which react Immunologically with antibodies which are Immunologically reactive with Hepatitis B virus, Delta antigen, Hepatitis A virus, Hepatitis C viruses, or any other virus that is at any time classified as a hepatitis virus by the International Committee on the Taxonomy of Viruses (or by any body that replaces that committee).
>
> (b) Hepatitis Antibodies shall mean any and all antibodies or fragments thereof or other anti-ligands Immunologically reactive with any of the viruses referenced in Paragraph (a) above except those listed in Exhibit F.

Clause 9.2 of this Agreement placed an obligation on Ortho to notify Chiron of any infringement of any of Chiron's hepatitis patents and unless Chiron sued the infringer within 90 days, Ortho had the right to sue and Chiron was obliged to cooperate.

Even more importantly, clauses 6 and 7 mandated Ortho to acquire all the biological ingredients for its hepatitis immunoassays from Chiron.

These same conditions applied to Abbott.

Murex Diagnostics Australia Pty Ltd and IMTC

Murex Diagnostics (Australia) Pty Limited (Murex) was a member of a group of companies controlled by International Murex Technologies Corporation (IMTC). Murex was an importer, supplier and distributor of Murex products which were manufactured by Murex Diagnostics Limited, a UK company, at its manufacturing plant in England.

In February 1992, IMTC acquired all the operating assets and assumed certain related liabilities of the diagnostics division of The Wellcome Foundation Limited (Wellcome). This acquisition significantly altered the scope of IMTC's business. Employees increased by 620 and over 600 new products were added, resulting in a corresponding increase in annual revenues from US$2.5 million in 1991 to US$72 million in 1992. As a result of this acquisition, IMTC was converted into a research and development company with a blood banking operation selling products through an international distributor network that supported a direct sales force in 35 countries and a distributor network in more than 100 countries.

Part of the assets that IMTC acquired from Wellcome was its HCV R&D and immunodiagnostics technology which had been developed using a strain of HCV known as HCV1b. This was different to the strain of HCV which Drs Bradley, Houghton, Choo and Kuo had identified in 1987. The Chiron strain of HCV was HCV1a, predominantly found in North American populations. Thus the HCV strain that Murex's HCV immunoassays used

came from a different source. Moreover, the HCV immunoassay had been developed by its own scientists at its own laboratory. It was not a case of Murex merely producing a copy of the Chiron, Ortho or Abbott HCV immunoassays, all of which used biological materials derived from the North American strain of HCV (HCV1a) as the active ingredient.

The Reaction of Chiron (and its licensees) to Murex in Australia

During 1993 Murex entered the Australian market to supply HCV immunodiagnostics to the Australian health sector. Murex enjoyed some considerable success, partially due to the competitive pricing of its HCV immunodiagnostics, which was AU$1.50 per test lower than Abbott or Ortho's price. This prompted Abbott to report Murex's activity to Chiron which, in turn, prompted Bill Gerber, Chiron's President, to write to Robert Blackburn, Chiron's Vice President and Chief Patent Counsel, on 25 November 1992. Gerber wrote:

> In Australia, Murex won the HCV business at Sydney and Hobart blood banks: a total of 600,000 draws per year. They bid $1.50 per test lower than Abbott of [sic] Ortho. The Melbourne, Perth and Adelaide blood centers [sic] are out for bid, and Murex is bidding at those sites as well. Marcia asked if you would be willing to write a letter to the Directors of those centers [sic] informing them of our patent application, and of the probability if the patent issues that Murex would have to withdraw its product from the market. I told her that we cannot say anything that could be construed as a threat by Murex, and that what we could say might not be terribly helpful, but she would like us to do our best. The names and addresses of the individuals are attached. Please let me know what we can do. Thanks.
>
> [The complete document is in schedule B1]

It should be noted that as a result of Murex's entry into the market, the price per test was $1.50 lower than the test supplied by Chiron's licensee, Abbott.

The same internal memorandum explained that Marcia was Marcia Thomas, 'the newly-appointed vice president of Abbott's Diagnostics Division'.

In response to that internal memorandum, on 22 January 1993 Blackburn wrote to the directors of every blood transfusion service in Australia. His letter stated the following:

> We understand that you are accepting tenders for the supply of HCV immunodiagnsotics Kits. We would like to call to your attention Chiron's Australian patent no. 624,105, which broadly covers HCV immunodiagnostics kits and methods, as well as Chiron's pending Australian patent application nos 52783/90 and 76510/91, directed to improved HCV immunodiagnostics.
>
> The only suppliers of HCV immunodiagnostics licensed by Chiron are Ortho Diagnostic Systems and Abbott Laboratories. Therefore, we ask you to limit your consideration to these authorized [sic] suppliers. Thank you in advance for your cooperation in this matter.
>
> [The complete document is in schedule B2]

It is not known how many responses Blackburn received to this letter, but it is known that he did receive one from Prof Robert Beal, the Director of the South Australian Red Cross Blood Transfusion Service. He wrote on 3 February 1993 as follows:

> Thank you for your letter of 22 January 1993. It is helpful to have the appropriate patent numbers available for reference should this be necessary.
>
> After discussion of all of the factors involved, including the Chiron patents, this Service has entered into an arrangement with Abbott to continue to supply HCV immunodiagnostic material.

[The complete document is in schedule B3]

On 5 October 1993 Aldous J handed down his decision in the *Chiron v Organon, Murex and UBI* in the UK Patents Court and although Chiron maintained its British HCV patent GB 2,212,511 over HCV immunodiagnostics, he refused to grant Chiron any relief because he had found in favour of the Defendants in respect to their defence that the Agreement, referred to earlier contravened s.44 *UK Patents Act, 1977*. Specifically, s.44(3) provides:

> In proceedings against any person for infringement of a patent it shall be a defence to prove that at the time of the infringement there was in force a contract relating to the patent made by or with the consent of the plaintiff or pursuer or a licence under the patent granted by him or with his consent and containing in either case a condition or term void by virtue of this section.

As we already know, Chiron and the Defendants then appealed that decision to the UK Court of Appeal, but in the meantime, Chiron and Ortho modified their Agreement so as to overcome the Court's objections and then, once again, applied for a further injunction relying on Aldous J's decision on the merits of GB 2,212,511. In February 1994 Chiron was successful and was granted an injunction enjoining the Defendants from manufacturing and supply their HCV immunodiagnostics in the UK.

The injunction had a drastic impact on Murex as it was forced to close down its HCV immunoassay production plant in the UK. Murex had, already made provision for this contingency and had managed to ensure that its distributors had sufficient stock of HCV immunoassays until it was able to restart production in Morocco.

Abbott Diagnostics, one of Chiron's licensees in Australia, was keen for Chiron in Australia to capitalise on its success in the UK and so on 12 February 1994 John Ruberry, an Abbott manager, wrote to Mr Blackburn as follows:

> Thank you for your response regarding the above issue. Obviously we are ecstatic with the result of the court case, congratulations!
>
> We are extremely keen to take up your offer to write/fax to the appropriate Blood Bank Directors with regards to the outcome of the court case against Murex. In particular, would you be able to include in your correspondence the comment you made in your message to me, viz. "Murex's manufacturing plant has been shut down and they can no longer supply kits from the UK".
>
> The list of Blood Banks and fax numbers are attached.
>
> This communication to these Blood banks coming directly from CHIRON, would be of significant benefit to us, in that ABBOTT will be seen to be at 'arms length' and behaving in an [sic] professional manner.
>
> Once again, if you could fax your communicade [sic] the the [sic] Directors as a matter of urgency, we will be in a strong position to reclaim from MUREX any lost HCV business, before MUREX have a chance to impliment [sic] any "recovery strategy" they may be working on.
>
> This urgency is highlighted by the fact that Melbourne, Adelaide, Perth and Sydney are all right in the middle of their review processes to award new contracts for next year's supply of screening tests. These Blood banks represent in excess of 75% of the Australian market.
>
> [The complete document is in schedule B4]

What Mr Ruberry had not anticipated was that Murex's board had already made the decision to challenge Chiron's HCV patent AU 624,105 and preparations were well advanced by this time.

In March 1994 Murex commenced proceedings in the Federal Court of Australia seeking the revocation of Chiron's Australian HCV patent AU 624,105 [*Murex Diagnostics (Australia) Pty Ltd v*

Chiron Corporation Federal Court of Australia, NSW District Registry, NG 106 of 1994]. In due course Chiron filed a cross-claim seeking damages and injunctions for patent infringement.

This correspondence clearly shows that Abbott was agitating Chiron to take advantage of its patent monopoly to put Murex out of the HCV immunodiagnostics business in Australia. That it did so is reprehensible given that without Murex there was no non-Chiron licensed HCV immunoassay available on the Australian market at that time. Had Chiron succeeded in achieving in removing Murex it would have placed Australian doctors and, importantly, the Australian health services in an very difficult situation. The issue was not merely the price that they would have had to pay for Chiron licensed HCV immunoassays, which would have undoubtedly increased in that event, but the loss of their access to a secondary confirmatory HCV immunoassay that was vital as a diagnostic tool.

HCV Immunodiagnostic Issues in Australia

In the course of preparing and in conducting the case that Murex brought against Chiron, as the solicitor of record for Murex and IMTC I had cause to meet various virologists and clinicians in Australia. One of these was Ass Prof Stephen Locarnini.

At the time, between 1994 and 1996, Prof Locarnini was the Director of the Virology Department at the Victorian Infectious Diseases Reference Laboratory (VIDRL) at Fairfield Hospital (Fairfield) and had been since March 1991. He was an expert in hepatitis having also held the position of Director of the Hepatitis Research Unit of the MacFarlane Burnet Centre for Medical Research between 1989 and 1991 and since May 1993 had served as the Chairperson of the National Health and Medical Research Council (NHMRC) Task Force on Hepatitis C (Hepatitis C Task Force).

Having become acquainted with Prof Locarnini's qualifications I formed the view that he was an informed and independent expert who I could rely upon to provide the Australian Federal Court with accurate and impartial evidence on the state of hepatitis C diagnostics in Australia.

Prof Locarnini agreed to provide affidavits in the *Murex v Chiron* litigation. In summary his evidence was as follows:

- The Hepatitis C Task Force reported to the NHMRC and the Australian Health Minister's Advisory Committee (AHMAC). The Hepatitis C Task Force was set up to address some of the complex public health issues that are evolving with respect to hepatitis C. The NHMRC reports to the Chief Medical Officer of the Federal Department of Health, which in turn reports to the Federal Minister for Health. The NHMRC is the body which oversees the Australian health medical research community as well as general health of the community. The other body is the AHMAC which is a committee of representatives of State Health Departments interacting on a formal basis with the Federal Department of Health.
- Fairfield was the major centre for the study of infectious diseases in Victoria. In other States infectious disease units were established at all the major teaching hospitals. Patients with infectious diseases were treated at those hospitals. Fairfield had proven to be a valuable resource, as it focused on infectious diseases as they evolved. In other States of Australia, such as New South Wales, there was no single major centre for infectious diseases. Consequently, it was much more difficult to do studies, for example, of 100 consecutive admissions of hepatitis C patients, as had been conducted at Fairfield in the past, because in the other States it could take years to get a hundred consecutive admissions. In terms of laboratories conducting research on infectious diseases, Fairfield was unique in Australia because it had clinical resources as well as the laboratories.
- The laboratories underpinned the diagnostic functions of the hospital in terms of making those clinical laboratory diagnoses. Clinical specimens serve as excellent resources for the conduct of basic research and enable studies to be undertaken. The

laboratories have existed since 1948.

- Viral hepatitis is a disease of the liver. It is a common disease throughout the world. It is now accepted by hepatitis workers in Australia that there are five primary aetiological agents of viral hepatitis. It is suspected that there are more, however they are yet to be identified.
- The primary aetiological agents of viral hepatitis in 1994 were hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV). The principal aetiological agents of hepatitis are either enterically transmitted or parenterally transmitted. HAV and HEV are enterically transmitted i.e., the virus is transmitted by the faecal-oral route. HBV, HCV and HDV are parenterally transmitted i.e., the virus is transmitted through the transfer of blood, blood products or body fluids.
- These five aetiological agents of viral hepatitis were known to lead to acute hepatitis, but only the parenterally transmitted hepatitis viruses were commonly associated with persistent infection and the development of chronic sequelae which included chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma.
- In 1994 confirming the diagnosis of acute viral hepatitis involved several steps:

  (a) The demonstration of acute hepatitis based largely on the pattern of serum biochemistry with dramatic (preferably at least ten fold) elevations in serum alanine aminotransferase levels (ALT);

  (b) The exclusion of non-viral causes, usually on the basis of history, physical findings and associated laboratory data;

  (c) Identification of the responsible viral agent and, preferably, the source of infection;

  (d) If the clinical features or biochemical tests are in any way atypical, early ultrasound hepatic imaging should be arranged;

  (e) Serological tests are now routinely available for diagnosis of hepatitis A, B, C, D and E as well as other uncommon viral causes of hepatitis such as the Epstein-Barr virus, cytomegalovirus, herpes simplex virus and human herpesviruses 6 & 7.
- In 1994 it was known that HCV was the major cause of parenterally transmitted NANBH. There were at least 100 million HCV carriers in the world and the number of new cases each year has been estimated to be 175,000 in the United States and Western Europe collectively and 350,000 in Japan.
- In 1994 infection with HCV occurred predominantly by blood or blood products and also infrequently by sexual intercourse as well as from infected mothers to their babies.

Geographic Issues

- While the development of HCV immunodiagnostics was an important step in controlling the spread of hepatitis C there were problems that needed to be addressed that were unique to Australia. Specifically, the problem that he had as a medical virologist in setting up hepatitis C testing in Victoria was that only approximately 45% of persons infected with hepatitis C were HCV1a; 5-10% were HCV1b; and 45% were HCV3a.
- In this respect it is relevant for the Committee to note that Chiron's HCV patent AU 624,105 only disclosed the genome (genetic sequence) of 77% of HCV1a, yet the patent monopoly granted by IP Australia covered the complete genome of HCV1a together with all the genomes of any virus that was capable of inducing symptoms

that were hepatitis C-like.

- One source of this demographic data was a report prepared by the Hepatitis C Task Force entitled *Report On The Epidemiology, Natural History And Control Of Hepatitis C* and tabled with the NHMRC in November 1993. The report referred to studies from Western Australia which showed that of the 23 Australians in one study, 13 of 23 (56%) were infected with HCV1, 3 of 23 (13%) were infected with HCV2; and 7 of 23 (31%) were infected with genotype 3. The study conducted at Fairfield in Victoria showed that 45% were 1a; 10% were 1b; and 45% were 3a. The significant point, it was found, was that genotype 3 was an important strain in Australia.
- The Hepatitis C Task Force recommendations contained in the November 1993 report focus on the laboratory diagnosis of hepatitis C, case definitions, epidemiology and control mechanisms of hepatitis C in Australia. The Hepatitis C Task Force, after receiving submissions and reviewing the literature, indicated that a number of important public health issues had come to light. The Hepatitis C Task Force found that Australian strains of hepatitis C were probably different from strains circulating in the northern hemisphere. Consequently, the first recommendation of the report was that Australian research laboratories '*be encouraged to undertake full nucleotide sequence studies on Australian strains of hepatitis C virus*'. The reason for this recommendation was that cases of post-transfusion hepatitis C were occurring in the community that were being missed by the existing, 'second generation' screening tests. The reason for this is unknown at the time. The Ortho/Abbott second generation screening kits were introduced in Australia in May 1991. The Abbott 'third generation' screening kits were being introduced in 1994.
- The concern of the Hepatitis C Task Force was the strong and unequivocal evidence indicating that, despite the use of second generation HCV immunoassays as supplied in Australia, there were antibody negative HCV infectious blood donors in Australia. So in the opinion of the Hepatitis C Task Force there was sufficient evidence to indicate that there were genotypes of hepatitis C in Australia which was not being detected by then available HCV immunoassays.

HCV Immunoassay performance

- Due to the fact that by 1996 (a) HCV immunoassays had not achieved sensitivity above 90% and (b) the numbers of indeterminant diagnostic results that had been recorded, virologists believed that many of the immune responses to HCV infection were conformation dependent. In other words there were nuances of the three-dimensional folding of the HCV proteins which were critical to antibody detection and this subtly affected the performance of *all* HCV immunoassays. Moreover, there was also evidence emerging that some third generation immunoassays, such as those produced by Abbott Laboratories, had no greater sensitivity than the second generation immunoassays, even though the manufacturer had included more HCV genetic material as the active ingredient.
- In a letter published in the *Medical Journal of Australia* Vol. 163 on 2 October 1995 entitled *A positive hepatitis C enzyme immunoassay antibody test in a low risk population: what does it mean?,* the authors stated as follows:

> The introduction of screening of all blood donations for antibodies to the hepatitis C virus (anti-HCV) by enzyme immunoassay (EIA) has reduced the number of cases of post transfusion hepatitis C. Current third generation EIAs typically include antigens from the structural region (capsid) as well as one or more antigens from the non-structural region of the virus (NS3, NS4 or NS5). Such assays are highly reliable among individuals with risk factors for or symptoms and signs of hepatitis C virus infection, but the false positive rate remains a significant problem when a low risk population (such as blood donors) is screened....A definitive

diagnosis cannot be made from a positive anti-HCV EIA test result in a healthy asymptomatic individual with no risk factors for HCV infection and a normal ALT." (Emphasis added)

- A significant finding by the authors of that same letter was that with the third generation anti-HCV EIA a repeatedly reactive test result was 'interpreted as false positive reactions in approximately 75% of cases'.
- Fairfield used the Murex HCV immunoassay as a secondary test. This was a prudent and necessary procedure. By way of example, in the case of HIV, Fairfield used up to *ten* tests on the one sample to confirm its status as truly positive. With hepatitis C, as with HIV, all HCV antibody reactive samples detected in the screening had to be tested in another test and a positive result had to be obtained with the other test before the result was classified as positive.
- Accordingly, it was a necessary policy for a reference laboratory like Fairfield to have more than one diagnostic test available. This was in the best interests of public health, especially true for hepatitis C where there were present in Australia at least three genotypes of HCV. Genotype differences were more likely to cause false negatives in immunoassays which meant that in 1996 blood donors with HCV infection could have been missed when screened and infected blood could have been transmitted to other persons.

Implications of HCV Immunoassay performance

- The implications of an unacceptably high level of false positives on the Australian blood donor pool was extremely serious. Blood banks in Australia and elsewhere were losing blood donors permanently. This meant that the source of blood needed on a daily basis by the Australian community, and other communities, was being seriously threatened. Once a blood donor was labelled as an HCV-indeterminate or HCV positive, their blood was excluded from the blood supply, even though they may have been truly negative for HCV. In other words, blood donors were being falsely labelled as 'HCV positive' when in fact they were not, because of the inadequacies of the HCV immunoassays.
- The fact that third generation HCV immunoassays were giving such results was unacceptable. *It meant in a low risk group, such as blood donors, the HCV immunoassays that were available in 1995 were detecting something other than HCV and giving false positive results in up to 75% of cases*. It had been five years since the first HCV immunoassays were first used in Australia and the manufacturers of these kits had not yet produced a kit which was as sensitive and specific as the test kits for HIV (which was 99% accurate). This was clearly unsatisfactory.
- What must be understood is that the test results from HCV immunoassays needed to be interpreted before a final conclusion could be reached as to whether a person did or did not truly have HCV. It was not simply a matter of testing a person's blood with a test kit. The background of that person was relevant. If that person came from a high risk group, such as injecting drug users, and a positive result was obtained, then one could have concluded with a high degree of certainty that it was a true positive result, but if a person was from a low risk group, such as blood donors, the same was not true.
- 'It has to be remembered', testified Prof Locarnini, 'that a positive diagnosis drastically affects peoples lives. Once people are labelled HCV positive, their blood is lost to the community if they are a blood donor; they are referred to a liver clinic; their private lives are affected; their relationships are affected; their insurance policies are affected; their quality of life is affected. In the case of a false positive, this to me is unacceptable and a great deal of research must be undertaken to encourage improvement in the specificity of these tests.'

- He also testified: 'When you contrast the developmental history of HIV tests with HCV tests the reasons for my concern are more readily apparent. With HIV the specificity and sensitivity was in the high 90s very quickly together with a confirmatory strategy that worked with the Western Blot. That has not happened with HCV, so clinical laboratories have had to struggle with the false positives issue. In my opinion the current anti-HCV tests are better than no test, but that is not the point. Once you have a test, the test needs to be highly sensitive and specific and the current tests are not as sensitive nor specific as they need to be.'

Prof Locarnini was not alone in raising these issues with me. There were other Australian and overseas scientists who had been reporting in the scientific and medical journals that there were serious problems with regard to the accuracy of the available HCV immunoassays.

While it was true that a test was better than no test, that was, as Prof Locarnini said not the point, as Dr Nicholas Crofts confirmed in his evidence in the *Murex v Chiron* litigation.

Like Prof Locarnini, Dr Crofts was from Victoria. Between 1994 and 1996 he was employed at the Macfarlane Burnet Centre for Medical Research as a medical epidemiologist and was a member of the NHMRC's Hepatitis C Task Force. He also came across as an independent expert in infectious diseases and I believed that he would provide the Federal Court of Australia with expert and impartial evidence on hepatitis C and its impact.

In regard to the impact that false positive results were having on blood banks, Dr Crofts advised me as follows:

> During discussions I had with Dr John Barbara, Head of the North London Blood Transfusion Service, Dr Phillip Mortimer, Director of Virology at the Central Public Health Laboratories and Professor Richard Tedder I was told that in the UK, *the Health Department made a decision*, that was a carefully discussed and calculated decision, *not to use the first generation HCV assays when they were first released by Ortho in 1990*. The UK blood banks did not start screening for HCV until the second generation assays were introduced, some eighteen months later. This meant that during that period there were a number of people that were potentially infected with HCV as a result of receiving blood transfusions. *The justification for this decision was based on the concern of the UK blood banks that too many blood donors would be lost from the already over stretched blood supply. They recognised that the first generation tests would produce too many false positives and that would place enormous pressures on the UK blood supply to keep up with demand for blood.* There was also concern about the potential misunderstanding that could occur in explaining to HCV positive blood donors that they may not in fact be truly HCV positive. The social consequences of positive results that could not be confirmed also influenced their decision. (Emphasis added)

By contrast, said Dr Crofts: 'The Australian blood banks did not hesitate in 1990 to introduce HCV screening because of the potential for litigation. Most Australian blood banks at that time were being sued with respect to HIV transmissions in the 1980's.'

This decision, while expedient in terms of dealing with the litigation brought against Australian blood banks, was not necessarily the right decision, according to Dr Crofts. In his opinion, 'the Australian blood banks [could not] afford to lose regular blood donors unnecessarily' and he gave, as an example, the Melbourne Blood Bank which had, he said, 'blood reserves of one day.'

Again, like Prof Locarnini, Dr Crofts confirmed that there was a critical need for more than the Chiron-licensed HCV immunoassays in Australia. He testified:

> One of the **significant deficiencies** in HCV testing in Australia at the moment is that all of the anti-HCV assays except for assays manufactured by and supplied by Murex use exactly the same genotype (1a) proteins. I have been informed by my colleagues that these assays are

> manufactured or supplied by Chiron licencees. Murex uses proteins from strain 1b. *However, we also need in Australia, HCV assays that use proteins from other strains such as genotypes 2, 3 and 6 because we have a very diverse ethnic population base. HCV 1 and 3 are the most prevelant. HCV 6 is mostly in the Asian community.* (Emphasis added)

Beyond the 'sensitivity' issue over HCV immunoassays were the effects which other components had on their performance and reliability. Dr Crofts confirmed that 'the same assay [would] work differently with different sera because of cross reactivity with contaminants in the sera.' Furthermore, according to Dr Crofts, the ability of any specific HCV immunoassay to detect antibodies that were produced in response to HCV infection depended upon 'different antibody window periods'. He said: 'Between the time a person is infected and the time that detectable antibodies are produced to infection there is a window when these types of assays cannot be used to detect infection.' One way of dealing with the shortcomings of HCV immunodiagnostics was to use an 'antigen test', that is, a nucleic acid assay that would detect HCV proteins, but in 1995, according to Dr Crofts, that was 'not yet possible with HCV'.

Impact of HCV on the Australian people and the cost of HCV treatment

Dr Crofts made it clear that containing the spread of HCV infection and developing an effective treatment for this disease was a serious issue for Australian health authorities. He estimated that there were at least 100,000 people infected with HCV whose long term prognosis was not good. According to Dr Crofts:

> Those infected people can live for another twenty or thirty years and not all of them will die of liver failure, but the same sort of numbers will die from HCV as will die from HIV infection. The period of illness with HCV is much longer and some people will need very expensive medical treatment, such as a liver transplant to keep them alive. The impact on the community in terms of social and economic cost is, in my opinion, at least equal to HIV and yet we know much less about HCV than what was known about HIV for the corresponding period.

In terms of the reason for his belief that the cost of HCV infection to the Australian community would be as high as that for HIV, he said:

> There are many reasons for this including the level of government intervention and the political priority given to HIV as compared to HCV, but in my opinion**, there has been a significantly lower level of cooperation with HCV assay manufacturers than there was with HIV in all respects.** The consequences of this are now being understood. While with HIV the increase in infections has fallen with HCV it is still rising. At the present moment in Australia that is rising at a level of 8,000 to 10,000 people per year. When you extrapolate this into social and economic cost terms, the cost is very significant.

He concluded that:

> **It [was] against the best interests of the Australian community** that only one type of anti-HCV assay be permitted to be manufactured and supplied using the same antigen produced in the same way.

In terms of the estimated cost on Medicare he referred me to a study, which at that stage was in the process of publication in the Medical Journal of Australia. The study described in that paper formed the basis of a report to the Commonwealth Department of Health. According to the authors of this study, of which he was one:

> For every 1,000 chronic carriers of HCV there is an implied $14.32 million in health care spending over the years as sequelae become manifest, with cumulative total costs of approximately half a billion 1994 dollars after 60 years. If the estimated 10,000 new HCV infections in injecting drug users in Australia per year continue for the next 60 years, total health care costs

will be around $4 billion over that period. [Brown, K and Crofts, N (1995) 'Health care costs of a continuing epidemic of hepatitis C virus infection among injecting drug users', *Medical Journal of Australia*, 22 (3), 384-388]

Reaction of Health Departments to Chiron HCV Patent AU 624,105

Despite the fact that the *Murex v Chiron* litigation in Australia had received considerable publicity (on ABC national television it was featured as major stories on programs such as *Lateline*, *Quantum*, the *7.30 Report* and in national and major city newspapers) not once did anyone from any State or Federal Department of Health contact me or Murex about the patent issues raised by the litigation, nor was any offer made by them to provide the Federal Court of Australia with information that would have assisted Burchett J to assess the impact of Chiron's patent on Australian society and the economy.

Moreover, when the European Patent Office (EPO) upheld the appeal brought by F Hoffmann La Roche AG (Roche) against the grant of the corresponding patent in Europe (EP 0,318,216) and invalidated the claims which in February 1997 came into effect in Australia by way of a voluntary amendment made by Chiron, no action was taken by any State or Federal Department of Health to challenge the validity of those claims in the Australian courts. Furthermore, despite the ability of these same departments to take advantage of the Crown Use provisions in the AU Patents Act, 1990 [s.163], at no stage did they avail themselves of this option.

2. AU600,650–Polypeptides of erythropoietin

Preliminary

Patent Applicant: Kirin-Amgen, Inc (Amgen), a US corporation

Current Patent Owner: Kirin-Amgen, Inc.

Earliest Patent Application Date: 30 November 1984 (United States)

Australian Patent Application Date: 11 December 1984.

Australian Patent Grant Date: 23 August 1990

Patent Monopoly Period: 11 December 1984 to 24 April 2006 (21 years 4 months 13 days). The term was extended by IP Australia on 7 June 2000 pursuant to s.70 *AU Patents Act, 1990*.

Current Status: Expired

Title: *Polypeptides of erythropoietin*

Technical Field: Disclosed are novel polypeptides possessing part or all of the primary structural conformation and one or more of the biological properties of mammalian erythropoietin ("EPO") which are characterized in preferred forms by being the product of procaryotic or eucaryotic host expression of an exogenous DNA sequence. Illustratively, genomic DNA, cDNA and manufactured DNA sequences coding for part or all of the sequence of amino acid residues of EPO or for analogs thereof are incorporated into autonomously replicating plasmid or viral vectors employed to transform or transfect suitable procaryotic or eucaryotic host cells such as bacteria, yeast or vertebrate cells in culture. Upon isolation from culture media or cellular lysates or fragments, products of expression of the DNA sequences display, e.g., the immunological properties and in vitro and in vivo biological activities of EPO of human or monkey species origins. Disclosed also are chemically synthesized polypeptides sharing the biochemical and immunological properties of EPO. Also disclosed are improved methods for the detection of specific single stranded polynucleotides in a heterologous cellular or viral sample prepared from, e.g., DNA present in a plasmid or viral-borne cDNA or genomic DNA "library".

Amended Claim 1: (1994 – voluntary)

'A purified and isolated polypeptide having the primary structural confirmation and one or more of the biological properties of naturally-occurring erythropoietin and characterized by being the product of prokaryotic or eukaryotic expression of an exogenous DNA sequence'.

See schedule A2 for all claims

Further Amended Claim 1: (1999 – Federal Court of Australia)

'A purified and isolated polypeptide having the primary structural confirmation and ~~one or more of the biological properties~~ possessing a biological property as herein defined of naturally-occurring erythropoietin and characterized by being the product of prokaryotic or eukaryotic expression of an exogenous DNA sequence'

See schedule A2 for all claims

Pre-grant Opposition: Yes (23 November 1990). **Opponents:** Board of Regents of University of Washington and Genetics Institute, Inc. **Resolved:** Opposition dismissed (19 October 1995). *Kirin-Amgen Inc v Board of Regents of University of Washington and Genetics Institute, Inc* (1995) 33 IPR 557 (25 June 1998).
On line: http://www.austlii.edu.au/cgi-bin/sinodisp/au/cases/cth/APO/1995/61.html

Post-grant Litigation: Yes. *Genetics Institute, Inc v Kirin-Amgen, Inc (No 3)* (1998) 41 IPR 325, Federal Court of Australia, Victorian District Registry, Action No VG 868 of 1995.
On line: http://www.austlii.edu.au/cgi-bin/sinodisp/au/cases/cth/FCA/1998/740.html

Result of Litigation: Opposition upheld-Amendment to claims ordered. **Application for leave to Appeal to Full Federal Court:** Refused: *Genetics Institute Inc v Kirin-Amgen Inc* [1999] FCA 742 (7 June 1999)
On line: http://www.austlii.edu.au/cgi-bin/sinodisp/au/cases/cth/FCA/1999/742.html

Erythropoietin (Epo)

It is a protein, more specifically a hormone, that is produced naturally in the human body (and other mammals). Its function is to control red blood cell production. It is produced by the kidney.

Medical Use of Erythropoietin

Erythropoietin stimulates bone marrow to produce red blood cells. As a medicine it is given to patients to treat anaemia. Thus, renal patients and cancer patients can be prescribed a coarse of treatment with erythropoietin medicines. Cancer patients that are undergoing chemotherapy will have a reduced number of white and red blood cells and will, as a result, suffer from anaemia. It is sometimes given as an alternative to a blood transfusion. The period of treatment is about 1 month.

Erythropoietin is a clear liquid and is injected under the skin, usually in the thigh or abdomen.

Erythropoietin medicines are known by a variety of trade marks such as Epogen (Amgen), Eprex (Johnson and Johnson) Recormon (Boehringer Mannheim) and Aranesp (Amgen).

For more information see: http://en.wikipedia.org/wiki/Erythropoietin

Cost

Details of the cost of treatment of Australian patients with erythropoietin medicines will be accessible from the Department of Health in each State and Territory in Australia. These details are not generally available from publicly accessible databases. However, it is known that Eprex and Recormon were approved by the Therapeutic Goods Administration in Australia (TGA) in 1991 and 1998 respectively.

In the absence of AU 600,650, and other related patents granted to Amgen, it would have been possible for Australian pharmaceutical companies to supply erythropoietin medicines at lower prices. It is not possible to provide this Committee with an estimate of savings at this time. However, it should be possible for the Committee to ask the Departments of Health to provide such estimates.

Relevant History

According to Arthur Sytkowski [Sytkowski, Arthur J (2004) *Erythropoietin*: Verlag GmbH & Co KGaA: Weinheim, Germany]

> The discovery of erythropoietin (Epo) was not a single event that can be credited to one individual or even a group of investigators in a particular year. Rather, it was a process of slow, deliberate unmasking of the molecule that began in the nineteenth century. … Perhaps the earliest recorded observation relating to Epo was that of Jourdanet who observed in 1863 that persons living at high altitude had more viscous blood.

Indeed the process of discovery and scientific experimentation meant that by the 1970s the function of Epo was well known. Moreover, it was known that it was produced in the kidneys and there were various assays available for its measurement. Also, most of the protein structure (amino acid sequence) of human Epo was known.

The human Epo gene was cloned by two groups around the same time. Those two groups were headed by Dr Lin at Amgen and Dr Fritsch at Genetics Institute. Dr Lin's group was the first, having done so in October 1983. Dr Fritsch's group, using a similar technique to Dr.

Lin's, isolated the gene in July 1984.

In the context of the biotechnological revolution that had started in the 1970s with Cohen and Boyer's new biotechnological process, once the human gene that contained the genetic sequence that coded for human Epo was discovered Amgen and Genetics Institute (GI) filed US patent applications over the same gene. This did not, however, present a problem for the USPTO, which, as explained in Part 1, had adopted a specific policy that supposedly justified the patentability of the human Epo gene on the basis of its isolation, and so eventually granted US patents to both corporations.

- GI was granted US patent 4,677,195 entitled *Method for the purification of erythropoietin and erythropoietin compositions* on 30 June 1987.
- Amgen was granted US patent 4,703,008 entitled *DNA sequences encoding erythropoietin* on 27 October 1987.

That Amgen's patent was granted after GI's (despite the fact that Amgen's patent application was filed on 13 December 1983 whilst GI's was filed on 3 January 1985) was due to Amgen's first three (associated) patent applications being rejected by the USPTO examiners. These rejections had the effect of slowing down the progress of Amgen's patent sufficiently that GI's issued first. But the date of the actual cloning of the Epo gene was not necessarily decisive in determining priority since under US patent law, where the 'first-to-invent' rule still applied, it was the 'first to conceive and reduce the invention to practice' that was deemed to be the first and true inventor. The issue of priority, however, was not yet in issue, so both patents were granted.

Not content with this result, on the very day that the USPTO granted US 4,703,008 Amgen sued GI and its licensee, Chugai Pharmaceuticals (Chugai), a Japanese corporation, for patent infringement in the US Federal District Court for the District of Massachusetts [*Amgen, Inc v Chugai Pharmaceutical Co Ltd and Genetics Institute* Civil Action No 87-2617-Y]. The following day, GI and Chugai sued Kirin-Amgen, a US corporation and a joint venture company of Amgen and the Japanese Kirin Brewery for patent infringement of US 4,677,195 in the US Federal Court for the Southern District of California. Essentially these two cases mirrored each other and were, as described by Judge Young, a Federal District Court judge in the Massachusetts litigation, 'a battle over turf' [*Amgen, Inc v Chugai Pharmaceutical Co and Genetics Institute, Inc* (1989) 706 F. Supp. 94].

The 'turf' was the human Epo gene and the Epo protein which it coded for.

Understandably, since both had patents over the same thing, neither party sought to challenge their respective opponent's patent on the ground that there was no patentable subject matter within s.101 *US Patents Act, 1952*. Thus the issue as to whether it was actually possible, as a matter of legal principle, to patent the human Epo gene and its corresponding protein in their isolated and purified forms was not raised and not argued. The result meant that both the Massachusetts and South Californian Federal District Courts *assumed* that the patents concerned 'inventions'. However, whether they were or not was another matter entirely.

It should be noted that here was a situation where neither the policy which the USPTO adopted to justify the grant of these patents, nor the validity of the patents themselves granted on the basis of this policy, was subject to judicial review or scrutiny. By January 1989 the Massachusetts Federal District Courts had granted a preliminary injunction against GI and Chugai with the result that they were enjoined from 'among other things, exporting, shipping or delivering to others certain recombinant erythropoietin' in the United States. Then, in what can only be described as an absurd situation, in February 1989 the Southern California District Court handed down a preliminary decision that found Amgen to have infringed GI's patent. In the midst of this litigation the 'public interest' over the production of purified erythropoietin eventually forced the Massachusetts Federal District Court to lift the preliminary injunction on the condition that GI and Chugai deposited 'all profits on the sale of Epo' with the Court.

That, however, was not the end of the US litigations. The Massachusetts litigation then proceeded to produce findings of fact that confirmed that both the human Epo gene and the corresponding protein in the isolated and purified forms that were claimed as 'inventions' were identical to the naturally occurring human Epo gene and its corresponding protein. On 5 May 1989 Federal Magistrate Saris held:

> … the overwhelming evidence, including Amgen's own admissions, establishes that [natural erythropoietin] and [recombinant erythropoietin] are the same product. The [erythropoietin] gene used to produce [recombinant erythropoietin] is the same [erythropoietin] gene as the human body uses to produce [natural erythropoietin]. The amino acid sequences of human [natural erythropoietin] and [recombinant erythropoietin] are identical. … There are no known differences between the secondary structure of [recombinant erythropoietin] produced in a Chinese hamster cell and [erythropoietin] produced in a human kidney. Amgen's own scientists have concluded that by all criteria examined, [recombinant erythropoietin] is the "equivalent to the natural hormone." [*Amgen, Inc v Chugai Pharmaceutical Co and Genetics Institute, Inc* (1989) 11 USPQ2D 1466]

Accordingly, both US patents were, for all practical purposes, claiming 'natural phenomena' as 'inventions' (something inherently excluded as patentable subject matter) but, in what was reminiscent of *The Emperor's New Clothes* by Hans Christian Andersen, this fact was not mentioned by anyone, including the so-called 'inventors', the biotechnology companies, their patent attorneys, the USPTO examiners and finally by two US Federal District Courts themselves.

Eventually, on 9 May 1989 the USPTO declared an 'interference' between the two granted patents. The issue thereupon became priority over the 'invention', which seemed logical enough except that no one stopped to ask whether there ever was an 'invention' in the first place.

With the 'priority' issued now flagged to be resolved by the USPTO, the respective litigants continued their course and eventually, in an attempt to overcome the stalemate produced by the corresponding preliminary decisions, agreed to a single trial to be conducted at one forum before a US Federal Magistrate. The trial took place in Boston between 7 August 1989 and 19 October 1989 with closing arguments on 9 November 1989. The Magistrate handed down her decision on 11 December 1989. [*Amgen, Inc v Chugai Pharmaceutical Co and Genetics Institute, Inc* (1989) 13 USPQ2D 1737].

In the context of this Inquiry it is worth taking the Committee to the decision that was handed down by Federal Magistrate Saris because it reinforces the point just made above – that everyone was content to avoid confessing to the fact that the 'invention' was the Epo gene. Thus she explained as follows (these are her words):

- The ***quest for the EPO gene*** began at the California Institute of Technology when Dr. Rodney Hewick sequenced erythropoietin obtained from Dr. Eugene Goldwasser to 26 amino acid residues in the fall of 1980. Dr Hewick took the sequence with him to GI when he was employed to work there in 1981; (Emphasis added)
- The sequence derived by Dr. Hewick was presented at the 23rd annual meeting of the American Society of Hematology in San Antonio, Texas, on December 6, 1981, by Dr. Goldwasser. Also, the sequence was published in June 1983 in an article by Drs. Sue and Sytkowski;
- When Dr Lin joined Amgen (6 August 1981), he began to work on the Epo project which was already underway. He was project leader of the Epo project from 1981 through 1984;
- Dr Marty Cline, a professor from the University of California, Los Angeles, and a member of Amgen's Scientific Advisory Board, was involved with the Epo project.

During the September-October 1981 time frame, Dr Lin discussed with Dr Cline his strategy for the Epo project, and in particular "the general approach" of using two sets of probes to screen genomic libraries;

- On April 28, 1982, Dr Lin wrote a memorandum concerning an Epo project team meeting on April 23, 1982. Lin wrote: "We urgently need a second region of amino acid sequence to confirm our clones." Later in the memorandum, after describing the alternative routes to looking for the Epo gene, Lin stated: "But it is agreed that confirming genomic clones with a probe from a second region of amino acid sequence is more direct and less [*37] time consuming." At the time, Amgen already had a number of putative Epo genomic clones, and **needed to find a way to identify which was the *real* Epo gene**.
- [Regardless], by the end of 1982, Lin felt like a 'lonesome soldier', because the company felt so frustrated with the Epo project and felt it was dead; no one at the company wanted to touch it.
- [Nonetheless Lin continued and he] obtained additional tryptic EPO fragments from Dr Goldwasser at the end of August, 1983. Dr. Por Lai's department sequenced the fragments provided by Dr. Goldwasser. The probes designed from these fragments were successful. Lin designed three sets of "fully degenerate" probes, called EpV, EPO-17, and EpQ, in September, 1983, and ordered them from a branch of Amgen in Boulder, Colorado which synthesizes oligonucleotide probes. Each set of probes had 128 different sequences. The EpV probes, ordered on September 2, 1983, were from amino acid region 46-52. The EpQ probes, ordered on September 24, 1983, were from region 86-91. EPO-17 covered the amino acid sequence region 18-23.

What Magistrate Saris was describing here were the techniques that Lin was using to develop 'probes' that were constructed from various fragments of the Epo protein which would bind to Epo nucleic acids (DNA) much like a magnet would act toward iron filings (although this is a crude analogy, nonetheless that was the idea – to create a biological magnet that would attract very specifically to the Epo genetic material). The reason why this idea was being pursued was that it was well known that there was a *relationship* between a nucleic acid sequence (DNA) of the gene and the amino acid sequence of the protein. Saris continued:

- Lin used the following method to clone the gene. First, he "plated out" the genomic library in "phage," which is a virus that infects bacteria, and fixed the DNA onto a filter. He obtained the genomic library from Dr. Maniatis. He then screened or "probed" the library by exposing the filter to the EpV set of oligonucleotide probes to determine which portions of the DNA the probes would "hybridize" or bind with. The probes carried a radioisotope tag which would signal hybridization. After hybridization, Lin washed off the non-specific hybridization signal, and took an x-ray of the filter. The area of hybridization showed up as a black spot in the film. Then, Lin cooked the filter to remove the probes, and applied the EpQ set of probes taken from a different region of the EPO internal amino acid sequence. He followed the same hybridization and x-ray procedure. He then matched up the two films; where the black spots were the same, there was a good chance the EPO gene had been isolated. Lin then matched the dark spots on the film with the original plate that contained the phage and picked out the portions of the phage which corresponded to the spots. Those portions contained the clones with the positive hybridization signals. Then, Lin went through a rescreening and dilution process to make sure the phage did not contain contamination from a neighboring phage. **This is how Dr. Lin isolated the EPO gene and pulled it out of the genomic library.**

This description confirms that Dr Lin was a gene hunter *not* an inventor. Where he did display some innovation, it was not in respect to anything done to 'invent' the Epo gene, rather, it was in respect to the molecular genetic techniques used to discover or isolate the Epo gene. **The invention, if indeed there ever was one, was to the specific technique or**

process that he devised to isolate the Epo gene, not the Epo gene itself. That may have given him the right to claim to being the inventor of that specific process, but not to claim to have been the inventor of the Epo gene (whether in an isolated form or not).

Unfortunately, it was obvious that once the process that Lin had employed was known any competent molecular geneticist would be able to replicate that process and isolated the Epo gene themselves; indeed, once the Epo gene sequence itself was published not even that step would have been necessary. So Amgen, along with many others who sought to profit from this knowledge, were keen to characterise the inventive step to the invention of the isolated Epo gene to be the *process* that was employed to isolate it. And as attractive as that argument was, and may even still be to proponents of gene patents, the fact is that it ignored the reality – the Epo gene, whether isolated or not, was identical or substantially identical to that same gene as it existed in its natural environment, i.e., in the human body.

The problem for Saris was that she had to resolve the issue of priority of invention assuming that there was an invention. Thus all she could do was accept the fiction that there was an 'invention' so as to determine which of the two groups was first to 'simultaneously' conceive and reduce to practice that invention, described as the Epo gene in an isolated form.

In this respect Saris said:

> It is true that Amgen held an advantage over the other companies because it alone among the commercial biotechnical companies had access in usable amounts after 1981 to urinary source Epo, which was a "rather rare commodity," from Dr Goldwasser, the primary person who had that material. But, that fact, although making for an unequal playing field with respect to the opportunity to reduce the invention to practice, does not undermine this court's determination that the doctrine of simultaneous conception and reduction to practice is applicable.

Her reference to the 'unequal playing field' was a direct reference to the *relationship* between a gene and the protein that it coded for – so physical access to erythropoietin (the protein and its amino acid sequence) was essential to being able to locate the human Epo gene that held the genetic instructions for the protein's biosynthesis. In this respect Amgen held the advantage. Of course, it raises the ultimate question: if the 'invention' was 'the gene', how could it have been an inventive step for Lin to reach the 'invention' when the amino acid of the protein provided the *obvious* route?

The truth was that any competent molecular geneticist anywhere in the world would have eventually found the Epo gene so long as they had access to sufficient quantities of naturally occurring Epo. Amgen had just that because of Dr Goldwasser. Incidentally, Dr Goldwasser had quantities of naturally occurring Epo as a result of his being the recipient of US publicly funded research grants.

Regardless, she held:

> In any event, even assuming that the doctrine of simultaneous conception and reduction to practice does not apply here, and that the conception was sufficiently complete and operable in 1981, the court would still reach the same conclusion that Dr Lin has priority over Dr Fritsch as the inventor of the "purified and isolated" DNA sequence encoding erythropoietin because Dr Lin conceived the approach first of using two sets of fully degenerate probes from two different regions to screen a genomic library.

Predictably, Saris's decision was appealed to the CAFC.

Once again the 'invention' condition of patentability was not in issue, but Lourie J, who wrote the CAFC's unanimous decision, stated that 'neither Fritsch nor Lin invented Epo or the Epo gene'. This statement suggested that he saw that the Emperor was not wearing any clothes but, like everyone else, did not take this further.

The CAFC judges took it upon themselves to provide patent protection to an industry which

they believed needed that form of protection. It was not because it was legally mandated (which it wasn't), but because the political feeling at the time was that university generated research should be commercialised through whatever means possible. The *Bayh-Dole Act, 1980,* which was the direct result of the US stockmarket success of Genentech, Inc in 1976, was interpreted by the CAFC as a Congressional directive towards encouraging the fledgling US biotechnology industry. Clearly this judicial activism suited the USPTO, the US biotechnology industry and the US government of the day, all of whom were quite prepared to ignore hundreds of years of patent law on the basis that the ends justified the means.

So, adopting the Massachusetts Federal District Court's approach, the CAFC resolved the issue of priority of invention by focusing on the experimental route that was devised and adopted by the two competing groups, on the basis that it was *this* work that was the crucial step to the formation of 'a complete mental conception of a purified and isolated DNA sequence encoding EPO.'

Lourie J opined that '[a] gene is a chemical compound, albeit a complex one' and since chemicals were considered patentable subject matter it followed that genes should be. Prof Rebecca Eisenberg, a US patent law professor confirmed that this opinion was common, given that 'patents on the genes encoding these proteins promised exclusivity in the market for the protein itself, equivalent to the protection that a pharmaceutical firm obtains by patenting a new chemical compound that can be used as a drug.' She suggests that owing to this viewpoint the CAFC 'turned to prior cases considering patents on chemicals in resolving disputed issues about how patent law should apply to DNA sequences.' [Eisenberg, R S (2000) Re-Examining The Role Of Patents In Appropriating The Value Of DNA Sequences, *Emory Law .Journal*, 49 (3), 783-800, 784-5]

But this approach, which was subsequently reinforced in two CAFC decisions in *In re Bell* (1993) 991 F.2d 781 and in *In re Deuel* (1995) 51 F.3d 1552, is presently under review. The US Supreme Court in *KSR v Teleflex* (2007) 550 US 398 held that the test which the CAFC applied in determining whether the 'inventive step' condition had been satisfied was indeed wrong. In the context of biotechnology and specifically 'gene patents', this US Supreme Court ruling has already had a significant impact. The USPTO and the US Board of Patent Appeals and Interferences has since held in *Ex parte Kubin and Goodwin* (App. No. 2007-0819: Bd. Pat. App. Int. 31 May 2007) that isolating the gene in issue in that case was obvious, because 'there was a reasonable expectation that at least one [molecular genetic method] would be successful'.

Prof Rai, a US patent law professor, has summarised the current situation in the US:

> On the face of it, *KSR* could have a greater impact on biologic protein therapeutics than it does on the small molecule drugs typically manufactured by the pharmaceutical industry. According to *In re Kubin*, … *KSR* calls into question the Federal Circuit's much-criticized *In re Deuel* decision. In that 1995 case, Judge Lourie established a bright-line rule that *methods* for finding DNA sequences did not represent appropriate prior art for *product* claims to such sequences. The BPAI decision in *Kubin* states that, after *KSR*, product claims to DNA sequences should be considered obvious if the method for finding the DNA sequence was routine in the art. Whether or not the BPAI is correct in holding that *KSR* speaks directly to the question, the Federal Circuit may take up the invitation to overturn a case that has long been criticized as technologically and doctrinally indefensible. [Rai, A (2008),'Building a Better Innovation System: Combining Facially Neutral Patent Standards With Regulation of End Product Therapeutics', *Houston Law Review*, 45 (forthcoming)]
> On line: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1160198

Prof Rai's critique of *Bell* and *Deuel* as being 'technologically and doctrinally indefensible' is a reference to Lourie J's reasoning in both of those cases. In her opinion, Lourie J not only misconstrued the correct legal test for obviousness (lack of inventive step), as the US Supreme Court implied he had in *KSR*, but misconstrued the scientific *relationship* of the amino acid sequence of a protein to the genetic sequence of the gene that codes for that

protein. Specifically, Prof Rai argues that Lourie J's decisions in *Bell* and *Deuel*, which treated gene patent inventions as 'just another species of chemical compounds', ignores the fact that 'although DNA sequences represent chemical compounds, *they are more fundamentally carriers of information'*. She maintains, as the USPTO has also pointed out, that:

> … because of the informational link between proteins, amino acids, and DNA, knowledge of the protein's complete or partial amino acid sequence can be used to obtain the desired DNA sequence. To put the point another way, the current state of scientific knowledge renders the DNA sequence for a given protein obvious once the protein's complete or partial amino acid sequence is known. [Rai, Arti K., (2000) 'Addressing the Patent Gold Rush: The Role of Deference to PTO Patent Denials'. USD School of Law, Public Law Working Paper No. 05 and Law and Economics Research Paper No. 02. Available on line: http://ssrn.com/abstract=223758]

The CAFC heard oral argument in *Ex parte Kubin and Goodwin* (Case. No. 2008-1181) on 8 January 2009 and a decision is expected before June 2009. That decision may then be subject to a further appeal to the US Supreme Court.

The Australian Litigation

The parties in the US patent litigation eventually brought their dispute to Australia once IP Australia published a Notice of Acceptance of Amgen's Australian patent application on 23 August 1990. That prompted both the University of Washington (Washington) and GI to file an Opposition to the grant of a patent on 23 November 1990.

The Australian Opposition

Despite much of the technical and scientific evidence concerning the 'invention' already being before the US courts, it took about four and a half years to bring the Opposition before IP Australia for oral argument. Why this extraordinary amount of time elapsed is not known, but eventually oral argument before Mr David Herald, a Deputy-Commissioner of Patents, took place at IP Australia between 28 and 31 March 1995.

The Role Played by Australian Patent Lawyers and Patent Attorneys

It is relevant for this Committee to note the identity of the patent lawyers and patent attorneys involved in this Opposition because not only were some of them (Dr Bennett AC and Dr Pickering) appointed to the ALRC Advisory Committee on Gene Patents some seven years later, but Dr Pickering (a patent attorney representing GI) was, at the time, also representing Chiron in the *Murex v Chiron* litigation which was then proceeding to trial in the Federal Court of Australia. It should be mentioned that Dr Bennett QC was acting for Murex.

Dr Pickering's involvement in this Opposition is specifically relevant in that it may help to explain why the issue of 'invention' was not raised in the Opposition as a ground of invalidity. In this regard it must be remembered that 'invention' had been raised as a ground of invalidity with respect to the Chiron HCV patent – a patent which Dr Pickering had drafted and which he was duty bound to protect.

It also highlights the part of Dr Bennett QC who, while acting for Kirin-Amgen in this Opposition, was also acting for Murex in the *Murex v Chiron* litigation. Perhaps it might be said that Dr Bennett QC was not conflicted, since the issue of 'invention' was not raised in this Opposition. Furthermore, to the extent that she acted for Murex, she was one of two QCs and her specific brief was deal with the role that Dr Bradley had played in the discovery of HCV, not to the legal issue of whether Chiron's patent related to being an invention or not. Nonetheless, she was in and out of two philosophical camps simultaneously.

Clearly, 'invention' was a significant and relevant issue with respect to both the Epo and HCV patents, especially in the absence of any Australian court authority. That it had been formally raised only in the *Murex v Chiron* litigation suggests that there was a strategic reason

for the issue not to be raised in this Opposition. None of the evidence filed by the parties nor the arguments presented to IP Australia in the Opposition dealt with the issue of whether or not there was an 'invention'. This is noteworthy in view of what Mr Herald did when it came to delivering his decision some six months later in October 1995.

The Role Played by IP Australia: Mr Herald's Decision

Two points to note were that Mr Herald expressly referred to 'the US District Court in *Amgen Inc v Chugai Pharmaceutical Co Ltd* 13 USPQ2d 1737', so it cannot be said that he was unaware of it. He also raised the issue of 'invention' when it was not a ground of opposition.

As already discussed, the US District Court in that US litigation had held that the isolated Epo gene and the purified Epo were identical in every way to the naturally occurring Epo gene and Epo as found in a human body. However, when looking at the same patent in this jurisdiction, Mr Herald found that claims 33 and 34 claimed a 'DNA sequence' which was 'directed to molecules which have been deliberately changed from the naturally occurring form'. On this basis he concluded that Amgen's patent disclosed an 'invention'.

Why Mr Herald would do this is not known, but there would have been some motivation for him to make a statement which he must have known would have been interpreted by patent attorneys and others (including Justice Burchett in the pending *Murex v Chiron* litigation) as signalling that IP Australia was favourably inclined to the view which he had expressed. In order to do this, however, he had to make a finding of fact that would support it. Such a finding, given his direct reference to the US litigation, would have to contradict the US finding. In other words it would have to be false.

This decision has had a direct impact on the cost of erythropoietin to Australian hospitals and consequently to the healthcare budgets of all Australian State governments.

The Appeal to the Federal Court of Australia

This decision was then appealed to the Federal Court of Australia and it was heard by Heerey J. He handed down his decision in *Kirin-Amgen, Inc v Genetics Institute No 3* on 25 June 1998.

Once again the Committee is reminded that none of the grounds of appeal raised the issue of 'invention'. GI confined the appeal to very specific technical issues concerning the way the patent and the claims were drafted.

Thus no challenge was made to Mr Herald's gratuitous ruling on the issue of 'invention', and neither was Heerey J invited to nor did he seek to deal with that issue.

Heerey J did, however, order that some of the claims be amended.

The Application to the Full Federal Court of Australia for leave to appeal

The decision of the Full Federal Court was handed down on 7 June 1999. Leave was refused. The claims were then amended by IP Australian as per the order of Herrey J.

The Impact of AU 600,650 on Australia's Healthcare System and Economy

Even before Australian patent 600,650 was sealed, becoming operational on 24 June 1999 (*some 16 years after it was first applied for*), it was having an effect on the healthcare system and economy of Australia. In terms of the healthcare system, the cost of Epogen, Eprex and Recormon, being trade marks for erythropoietin medical products supplied to Australian hospitals, had the most immediate impact.

Unfortunately, I do not have access to the files of IP Australia, the Therapeutic Drugs Administration, the Departments of Health of the States, the Federal Department of Health and Amgen Australia Pty Limited. Accordingly, I am not in any position to provide this Committee with accurate information regarding the cost of these products over the (almost)

22 year life of this patent in Australia, but in 2003 the combined worldwide sales of erythropoietin medicines (in that year alone) amounted to US$10.1 billion [IMS World Review: on line http://panopharma.com/world_pharma_sales_2003.aspx], so it can safely be assumed that the overall cost must be vast.

Had this patent not been granted by IP Australia, it would have been possible for the Federal and State Departments of Health to have sourced erythropoietin products from generic manufacturers, some of which may very well have been Australian.

The Committee should note that although this patent has been expired for about three years, the effects of the lack of an indigenous medical and research capacity in erythropoietin production, which this patent monopoly ensured, is being felt in this country in subtle ways. Medical and scientific researchers in Australia who are in receipt of research funds provided by Amgen, either directly or through their universities and institutions, are publishing scientific papers that are questioning the safety, efficacy and the bioequivalent properties of erythropoietin products that are not manufactured by Amgen and its former licensee, Johnson & Johnson.

An example of this type of influence is confirmed by the scientific paper which was written by Dr Simon Roger and published in the Australian medical journal, *Nephrology*. In his paper, entitled *Biosimilars: How similar or dissimilar are they?* [*Nephrology* (2006) **11**, 341-346] Dr Roger, who was then with the Renal Unit of the Gosford Hospital at Gosford in NSW, a hospital funded by NSW Health, wrote that 'the imminent expiry of patents on biological medicinal products, such as epotein alfa in 2006, has significant implications for nephrology in Australia'.

He went on to say that while the 'nephrology community' in South-East Asia had accepted 'generic chemical medicines as being identical to the original trademarked product', he warned his Australian readers that 'the issue of biosimilars (similar biological medicinal products)' was 'quite different'. Indeed he made the point that 'biopharmaceuticals are inherently more complex, difficult to manufacture and have greater process-related variability that can impact efficacy and safety'.

This is an informative paper for a number of reasons.

First, it was a paper that Dr Roger wrote having disclosed that he accepted research funds from Amgen, Jansen-Cilag (a Swiss based subsidiary of Johnson & Johnson) and F Hoffmann La Roche (via its German subsidiary Boehringer Mannhiem). Each of these companies has supplied licensed erythropoietin medicinal products to Australian hospitals since as early as 1991 when J&J's product, Eprex, was approved by the Therapeutics Goods Administration in Australia. Amgen possibly provided Epogen, its erythropoietin medicinal product, earlier than this on some experimental or trial basis. (According to the South Australian Health Commission 1988/89 Annual Report [on-line at: http://www.publications.health.sa.gov.au/cgi/viewcontent.cgi?article=1011&context=sahc] amounts of Epo were made available in Australia in 1988-9 'on a trial basis during the year for a limited number of people undergoing renal dialysis who met the criteria established by the Renal Services Advisory Committee.')

Secondly, as was pointed out in Part 1 of this Submission (Section 2 p 11), as early as 1908 it was recognised that trademarked medicines could continue to have an impact on the prescribing decisions of doctors after the patent over the active ingredient had expired. This was of concern to the Swan Committee when it examined and reported on the patent law in the UK between 1945 and 1947 and whose report, which dovetailed the introduction of the National Health Service (NHS) in 1948, led to the *UK Patents Act, 1949*, which in turn led to the *AU Patents Act, 1952* just as the PBS came into operation here. Thus Dr Roger's specific referral to 'trademarked' erythropoietin medicinal products and his suggestion that generic versions may not be as safe or efficacious is reminiscent of the findings of the Inquiries conducted in the UK during the 1950s into how to constrain the cost of the National Health

Service budget and which found that pharmaceutical companies were using their sales forces to influence British doctors into prescribing trademarked medicines. [See also Part 1 of this Submission (Section 5 pp 27-35)]. While today companies such as Amgen, J&J and Roche may not be as overt as the British pharmaceutical companies in the 1950s, but is it not inconceivable that Dr Roger may have been influenced to the view he expresses in this paper on the basis of a long standing relationship between him, his hospital and these companies. Sure enough, at the end of his paper he did properly note the financial assistance that he had been provided by these companies, which included 'travel assistance to attend the 2005 Biosimilars Workshop in Singapore', but the level of assistance did not stop there. Dr Roger also acknowledged the assistance provided by Peter Tobin (described as a medical writer from Janssen-Cilag) who gave Dr Roger 'editorial assistance' in writing this paper. Dr Roger also confirmed that he was 'also a member of Roche Pharmaceuticals biosimilars advisory consultants'.

One would reasonably think that this level of financial and professional assistance will inevitably influence or bias health professionals into believing or acting in ways that are favourable to those organisations that provide that assistance.

Thirdly, and most relevantly, is the point of his paper: that Australian health professionals should not assume that generic biomedicinal products are bioequivalent. Regardless of the fact that Dr Roger may have been influenced towards this view, it may be that he is correct. Unfortunately, what his message suggested is that Australian Departments of Health should continue to pay higher prices for the trademarked biopharmaceuticals if they are to ensure the safety of Australians.

The Committee is reminded that society's preparedness to pay higher prices for patented products is conditional on the patent owner providing, in the patent, all information that would enable others to reproduce the invention after the expiry of the patent, which in the case of pharmaceuticals, must be such as to enable the production of that pharmaceutical exactly. The suggestion, which Dr Roger makes, that generic manufacturers are unable to do this implies a lack of adequate disclosure in the granted patent.

In this instance, Amgen's broad patent, which was granted by IP Australia over the very Epo gene and protein (and not just to Epo as a medicine), legally prevented any Australian organisation from reproducing these materials without the prior approval of Amgen. Indeed, to make and use anything that came within the scope of the patent monopoly without Amgen's approval was an infringement. And this would have applied even if the research had have been done for purely experimental purposes, because as the law presently stands in Australia, there was a serious possibility that Amgen would have sued anyone and anything which posed a threat to its exclusive market.

The truth is, there is no seamless transition from patented process to generic production because third party R&D is 'illegal' before the patent expires. Thus as matters stand at the present time, in the absence of any pre-existing production capacity, any generic producer either obtains Amgen's know-how immediately when the patent expires, or it would, according to Dr Roger, have to undertake significant research and development before it could supply commercial quantities of generic erythropoietin that was *bioequivalent* to the Amgen licensed-trademarked versions. Of course, Amgen is unlikely to simply hand this information, which is commercial-in-confidence, to a generic manufacturer.

Surely, given that Australia's Therapeutics Goods Administration (TGA) has in its possession all information necessary to enable the generic manufacture of a bioequivalent erythropoietin product, once Amgen's patent expired that information should have become freely available to the public so that any generic manufacturer could utilise it for the purpose of manufacturing and supplying erythropoietin to Australian hospitals. Apart from making it more likely that generic erythropoietin was bioequivalent to Amgen's erythropoietin, such a policy, should it have been in place in 2006, would have facilitated lower prices for erythropoietin products for Australian hospitals and healthcare institutions.

Apart from which, as matters presently stand, rather than facilitating the domestic biopharmaceutical production of erythropoietin, which is what Amgen's patent should be doing now that it has expired, the issue over the bioequivalence and the difficulty in accessing Amgen's know-how, is having the exact opposite effect. Dr Roger noted that although the European market alone, in 2004, was estimated to be worth $US2.3 billion:

> … an Australian-based pharmaceutical company, Mayne Pharma, reported that it would not continue development of a biosimilar epoetin alfa with its Croatian collaborator Pliva, due to increasing clinical program costs, although the biosimilar had shown encouraging phase I results and substantial progress had been made.

It would seem, therefore, in the absence of a generic substitute, that the cost of these *imported* trademarked biopharmaceuticals to Australian hospitals means that Australian Federal Health budget will continue to balloon as they are supplied at prices higher than they would otherwise be. This not only effects Australia's balance of payments, but does not lead to the development of an Australian biopharmaceutical industry which will employ Australian scientists and skilled workers.

What this example has demonstrated is how Australian patents which are directed to things that are not inventions have been used to deliberately suppress the development of Australian know-how that would enable the development of an Australian biopharmaceutical industry, much like US patents granted to German chemical companies in the period prior to WWI were used by them to suppress the development of an indigenous US chemical industry (See Part 1 of this Submission, pp 11-13).

From the TGA's website

The Australian community expects that medicines and medical devices in the marketplace are safe and of high quality, and of a standard at least equal to that of comparable countries. The objective of the *Therapeutic Goods Act 1989*, which came into effect on 15 February 1991, is to provide a national framework for the regulation of therapeutic goods in Australia to ensure the quality, safety and efficacy of medicines and ensure the quality, safety and performance of medical devices.

The regulatory framework is based on a risk management approach designed to ensure public health and safety, while at the same time freeing industry from any unnecessary regulatory burden.

Essentially therapeutic goods must be entered on the Australian Register of Therapeutic Goods (ARTG) before they can be supplied in Australia. The ARTG is a computer database of information about therapeutic goods for human use approved for supply in, or exported from, Australia.

The *Therapeutic Goods Act 1989*, Regulations and Orders set out the requirements for inclusion of therapeutic goods in the ARTG, including advertising, labelling, product appearance and appeal guidelines. Some provisions such as the scheduling of substances and the safe storage of therapeutic goods, are covered by the relevant State or Territory legislation.

The Therapeutic Goods Administration (TGA) is a unit of the Australian Government Department of Health and Ageing and is responsible for administering the provisions of the legislation.

The TGA carries out a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard. At the same time the TGA aims to ensure that the Australian community has access, within a reasonable time, to therapeutic advances.

3. AU 686,004 – In vivo mutations and polymorphisms in the 17q-linked breast and ovarian cancer susceptibility gene

(Note: this patent is 1 of 4 BRCA patents. The other patents are: AU 691,331, 691,958 and 773,601)

Preliminary

Patent Applicant: Myriad Genetics (Myriad), a US corporation; Centre de Recherche du Chul, a Canadian organisation; and Cancer Institute, a Japanese organisation.

Current Patent Owner: As above

Earliest Patent Application Date: 7 June 1995 (United States)

Australian Patent Application Date: 11 August 1995

Australian Patent Grant Date: 11 June 1998

Patent Monopoly Period: 11 August 1995 to 11 August 2009

Current Status: Current (expires on 11 August 2015)

Title: *In vivo mutations and polymorphisms in the 17q-linked breast and ovarian cancer susceptibility gene*

Technical Field:

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer, in particular, breast and ovarian cancer. More specifically, the invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer.

Granted Claim 1:

'An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19.'

See schedule A3 for all claims

Pre-grant Opposition: No

Post-grant Litigation: No

BRCA 1 Gene Mutations

BRCA 1 is a gene located on human chromosome 17. Mutations to this gene have been associated with breast and ovarian cancer. For more details see: http://en.wikipedia.org/wiki/BRCA1

Relevant History

It was Prof Mary-Claire King, a professor of genetics and epidemiology at University of California at San Francisco (UCSF) who, in 1990 and after sixteen years of receiving publicly funded research, discovered that hereditary breast and ovarian cancers were linked to a gene on human chromosome 17.

The head start that Prof King had given scientists by narrowing the search down to one human chromosome was invaluable. In May 1991 Dr Mark Skolnick, a scientist from the

University of Utah, and Mr Peter Meldrum, a venture capitalist, formed Myriad Genetics, Inc. Within a year Prof Walter Gilbert had joined Myriad as a 'founding scientist' and became Vice-Chairman of the company's board of directors, as had Mr Kevin Kimberlin, another venture capitalist whom Prof Gilbert already knew. Prof Gilbert and Mr Kimberlin had founded Biogen, Inc in 1978.

Myriad was formed for a specific purpose: to identify the gene on human chromosome 17 that was linked to breast and ovarian cancer and then patent the gene for the purpose of controlling the genetic diagnosis of breast and ovarian cancer. Ironically, the promoters of Myriad were all men. But they realised that there was a fortune to be made if they could control the patent rights to the genetic marker of these human diseases – two human diseases that effected mostly women.

On the basis that the conventional wisdom at that time was the first and only prize goes to those who isolate the gene, Skolnick considered Prof King's contribution to scientific and medical knowledge as incidental. Skolnick's experience in the 1980s, after he discovered the link between neurofibromatosis and chromosome 17, made him determined to win the race to this gene and patent it. According to Skolnick: 'it was a bit of a disappointment [in the 1980s] to be left out of really the final prize of discovering what was the gene that caused the disease [neurofibromatosis] that we'd been working on now for ten years.' That prize, 'the real fruit', believed Skolnick, was in: 'isolating and discovering the underlying gene.'

By 1991 there was no doubt about what was to be done with this genetic information. Whoever it was that isolated the gene to breast and ovarian cancer would use that information to monopolise the market for a genetic test to those diseases. It was hardly surprising therefore that Skolnick was: 'able to convince investors that we had a reasonable chance of finding that gene.' Of course they did - King had given them a good road map to the 'treasure' – the gene.

Thus, in his own words he described the 'prize' to be 'that gene'. This was no more than a treasure hunt – one that took place after King had given everyone the map to where the treasure was buried. What helped Skolnick find it before anyone else was his team and their tools. Skolnick subsequently said:

> We took an approach that used what are called bacterial artificial chromosomes, or BACs, where some of the competitors used yeast artificial chromosomes, or YACs, and as fate would have it, there was a hole, not well covered by YACs, where the BRCA1 gene was, and it was covered by BACs. So were we lucky that it was covered by the reagent we chose to use, are we, were we smart in choosing a reagent that covered the gene? Is the cup half full, is the cup half empty?

Of course, there was more too it than that. What Skolnick failed to mention was the millions of dollars of public research funds given to his university together with the goodwill of thousands of American Morman families that had given his university their personal and private family histories and biological materials so that he could promote the common good.

But all Skolnick was interested in was 'the prize' - the 'the whole gene' - and once his team at the University of Utah had isolated it they went about patenting it so that they could exclusively control it and maximise the price of breast and ovarian cancer diagnostics. But, again, there was more to it than that. What Skolnick and his cohorts planned to do was the use the patent over this gene as a mechanism to extract millions of biological samples and the data that these samples would provide to continuing mapping the gene for mutations that would be linked to breast and ovarian *and other cancers such as prostate cancer*.

Thus by using the patent over the gene for one specific purpose, Skolnick and Myriad hoped to extend their patent position beyond the BRCA genes by identifying gene mutations on those genes that relate to other human illnesses and diseases. And this data would have come to Myriad without cost because the revenues generated by Myriad in performing the breast and ovarian gene test would have more than compensated it for the R&D in searching for

mutations in the BRCA genes to other human illness. These, of course, would have been patented as well.

Myriad called the breast and ovarian cancer susceptibility gene on chromosome 17 'BRCA 1'. It is a 220-kilodalton nuclear phosphoprotein and in its normal state suppresses the production of tumours. However inherited mutations to this gene impair this natural function and in this altered state it accounts for about seven to ten per cent of all breast and ovarian cancers. Women who have inherited mutations to this gene have a lifetime risk of breast cancer of between 56 and 87 per cent and a life time risk of ovarian cancer of between 27 and 44 per cent. One thing is clear: no one invented the gene containing these mutations. They are a natural by-product, albeit deleterious, of human reproduction.

Despite this, on 2 December 1997 the USPTO granted Myriad its first US patent over this gene and its genetic mutations. US 5,693,473, entitled *Linked Breast and Ovarian Cancer Susceptibility Gene* defined the principal invention to be: '[a]n isolated DNA comprising an altered BRCA1 DNA having at least one of the alterations set forth in Tables 12A, 14, 18 or 19 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID. NO:1.'

There was no question about what it claimed as an invention – the human gene with genetic mutations called BRCA1. The relevant DNA was isolated, but essentially and practically this was a claim to DNA that contained the very same genetic information that exists in the genomes of some people, as a result of which some in turn are predisposed to breast and ovarian cancer. This DNA was not something that the named inventors either conceived of or invented or made. They merely discovered the gene that contained these genetic mutations on human chromosome 17 - the very same chromosome that only a few years earlier King had identified and linked to breast and ovarian cancers.

In Europe it took the European Patent Office (EPO) until 28 November 2001 to grant Myriad EP 0,705,902, entitled *17q-linked Breast and Ovarian Cancer Susceptibility Gene*. This patent concerned the same invention as did US 5,693,473, but it was the second European patent to issue, the first being EP 0,699,754 entitled *Method for Diagnosing a Predisposition for Breast and Ovarian Cancer* and granted on 10 January 2001.

Claim 1 of the '902 patent defined the invention as:

> An isolated nucleic acid which comprises a coding sequence for the BRCA1 polypeptide defined by the amino acid sequence set forth in SEQ. ID. NO:2, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ. ID. NO:2'. Claim 2 defined it as: '[a]n isolated nucleic acid as claimed in claim 1 which is a DNA comprising the nucleotide sequence set forth in SEQ. ID. NO:1 from nucleotide 120 to nucleotide 5708 or a corresponding RNA.

SEQ. ID. NO:1 is the genetic sequence that corresponds to the human BRCA1 gene. It is a double-stranded molecule made of cDNA (complementary DNA) consisting of 5914 base pairs (that is the sequence of nucleotides A, T, G, and C in base pairs that Watson and Crick deduced to be in a helical formation). SEQ. ID. NO:2, on the other hand, is the amino acid sequence for the protein that is coded for by the nucleotide sequence of SEQ. ID. NO:1. It consists of 1864 amino acids.

Again there was no question about what these two claims were about – the BRCA1 gene with genetic mutations and the protein that the gene coded for. Again both naturally made, except that the cDNA was replicated by humans. Apart from this the genetic information contained in the molecule described as SEQ. ID. NO:1 was identical to the defective human gene.

As an aside, while US 5,693,473 listed Donna Shattuck-Eidens, Jacques Simard, Francine Durocher, Mitsuuru Emi, and Yusuke Nakamura as the sole inventors, EP 0,705,902 listed Donna Shattuck-Eidens as an inventor but not any of the other inventors named on the US patent, but it did list Mark Skolnick, David Goldgar, Yoshio Miki, Jeff Swensen, Alexander

Kamb, Keith Harshman, Sean Tavtigen, Roger Wiseman and Andrew Futreal.

The reason for this discrepancy is that on 20 January 1998 the USPTO granted Myriad its second US patent, US 5,710,001 entitled *17q-linked breast and ovarian cancer susceptibility gene.* Claim 1 defined the principal invention to be:

> A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises gene comparing a first sequence selected from the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.

Indeed all of the claims in US 5,710,001 were to methods. None were to the BRAC 1 gene or the protein that it coded for. Nonetheless US 5,710,001 corresponded to EP 0,705,902 but in name only. The claims, or the inventions as defined in those claims, were quite different. US 5,693,473 actually corresponded more closely to EP 0,705,902 and even more confusingly EP 0,699,754 corresponded more closely to US 5,710,001. So the relevant US and European patents over the BRCA 1 *gene* were US 5,693,473 and EP 0,705,902 and over the *diagnostic method* for screening breast and ovarian cancer they were US 5,710,001 and EP 0,699,754. (There are legal implications that flow from this, but these will not be discussed here: they are mentioned because it is relevant to understand why the titles of the US and EP patents to the same inventions differed.)

Ignoring the patents to the diagnostic methods and focusing only on the patents over the BRCA 1 gene, it is fair to say that what Myriad had patented was a cause of human disease in the form of a defective human gene. Accordingly it has a 20 year patent monopoly on the components of that gene and the protein that it codes for. It may not own the BRCA 1 gene in the sense that one does in terms of physical property; after all, those people who carry that gene in their genomes own that gene and the potential consequences. However, in the sense that Myriad can control what others can do with the genetic information contained within the genetic components of the gene, for all intents and purposes it has the exclusive rights to the BRCA 1 gene and the corresponding protein for 20 years. That is the legal effect of these two patents in the US and throughout Europe. At least it was - Myriad did not get its own way in Europe; powerful opponents objected to Myriad's European patents and that fight is continuing.

Dr Gert Matthijs from the Centre for Human Genetics, University of Leuven, Belgium in a paper he wrote, entitled *The European opposition against the BRCA gene patents* [Familial Cancer (2006) Vol 5, 95-102], starts with this summary:

> Several professionals – mostly those who are familiar with gene patenting, including the experts at the European Patent Office (EPO) - have been wondering why the patents on the familial breast cancer genes BRCA1 and BRCA2 have caused such a fuss. The explanation is simple. Firstly, breast cancer is closer to the public than rare diseases. Secondly, the licensing policy of Myriad Genetics, the United States based company that (co-)owned four European patents on the BRCA1 and BRCA2 genes, has upset geneticists and other medical practitioners. Myriad Genetics had opted to strictly exert its monopoly right on the genes. This was unprecedented in the field of genetic testing.
>
> Confronted with the BRCA1 monopoly, the European laboratories had several options. The first would have been to do nothing and see what would happen. In 10–15 years, the problem will be solved anyway

> because most of the patents on genes will have expired by then. To stop testing was an alternative that was quickly dismissed by most laboratories. The cost of the commercial test – not reimbursable in most countries –would exclude a large group of women from testing.

At the time that his paper was published the Opposition had been successful in so far as the EPO had invalidated Myriad's patent to the use of BRCA1 gene mutations in genetic tests, but Myriad had appealed that decision. Unfortunately, in November 2008 the Technical Appeal Board of the EPO reversed the decision to revoke the European patent, and although this was a blow to the Opponents, the patent claims that were allowed by the TBA have left many geneticists in Europe confused and puzzled as to what the practical boundaries of that patent monopoly actually are. According to Dr Matthijs, '[i]t becomes unclear at which point during the analysis practitioners like myself would start to infringe the patent.'

According to an article that was published in *Nature* soon after this decision was made, entitled *Europe to pay royalties for cancer gene* and subtitled *BRCA1 patent decision may be ignored in clinics*, 'clinical geneticists do not agree with monopolies on diagnostic testing of genes for such diseases because they believe they block the competition that could lead to the development of better, cheaper products.' [Nature (4 December 2008) Vol 456, 556] The same article confirmed that in the US, where Myriad hold very broad patents over both BRCA1 and BRCA2 genes (a gene on human chromosome 13), the company charges US$3,120 'for a full analysis of both genes', whereas in Europe, where the patents have been so far ignored by 'large academic institutions and hospitals' that cost is US$1,900. Unfortunately, the TBA's ruling now means that Europeans must pay the higher price or risk patent infringement litigation.

The Impact of the BRCA1 Gene Patent in Australia

On October 2002 Genetics Technologies Ltd (GTL), a publicly listed Australian company headquartered in Melbourne (but effectively controlled by Dr Mervyn Jacobson, its largest shareholder), negotiated an exclusive license from Myriad to all BRCA1 and BRCA2 patents (there are four in total) that had been granted to Myriad and various other organisations (in respect of two such patents, the US Department of Health being one of the patentees).

Soon after, GTL sought to enforce its newly acquired patent rights in Australia. As a result of this, and after receiving representations through the Federal Minister for Health with respect to GTL's demands, on 17 December 2002 Daryl Williams AM QC MP, the then Federal Attorney-General, wrote to Prof David Weisbrot, President of the Australian Law Reform Commission (ALRC), directing the ALRC 'to undertake a review of intellectual property rights over genes and genetic and related technologies, with a particular focus on human health issues.'

The ALRC duly undertook this Inquiry 'in accordance with section 21 of the *Australian Law Reform Commission Act 1996*' and on 29 June 2004 provided Philips Ruddock MP, the then Federal Attorney-General, with its report entitled *Genes and Ingenuity: Gene Patenting and Human Health* (ALRC 99, 2004). This report is discussed in Part 1 of this Submission and, for the reasons given, it is respectfully recommended that this Committee ignore that report (Part 1, pp 43-49).

In the meantime, in May 2003 and in response to the announcement of the ALRC Gene Patent Inquiry, GTL publicly announced that it would not enforce its exclusive patent rights to the Myraid BRCA patents. Indeed, this decision was described by Mr Jacobson as a 'gift to the people of Australia'. Regardless of this gesture, the ALRC continued with its Inquiry.

Unfortunately, the ALRC's report failed to recommend that the *AU Patents Act, 1990* be amended so as to make it clear that isolated biological materials, such as human genes and proteins, even those synthesised using biotechnological techniques, were to be excluded from patentability. Indeed, neither the Howard nor Rudd governments appeared concerned to respond to the ALRC's report, at this stage.

Not surprisingly, and believing that the dust had settled, on 11 July 2008 GTL wrote to all Australian laboratories and institutions advising them that GTL had changed its mind and decided to enforce its patent rights and asked that they cease and desist, within 7 days, from continuing to undertake BRCA breast and ovarian gene testing.

This then reopened the public debate. Various newspaper articles appeared at about this time after the Cancer Council of Australia brought GTL's action to the attention of various journalists. The publicity that followed soon indicated that the debate over the patenting of human genes and the impact which these patents had had and were having on the provision of healthcare in Australia was far from being resolved. Various representations were then made to Nicola Roxon, the Federal Minister for Health, and discussions were had between the Ministry for Health and GTL. As a result, on 29 September 2008, GTL wrote another letter to the laboratories advising them that the litigation deadline of 6 October 2008 had been extended to 6 November 2008.

On 10 October 2008 GTL released its 2008 Annual Report. In a letter written by Henry Bosch AO, in his capacity as the non-executive chairman, Mr Bosch confirmed that 'on 18 September 2008, the Board of GTG received a Notice of Intention to Move a Resolution from a substantial shareholder seeking to remove a majority of Directors from the Board, and to appoint one new Director'. Mr Bosch also identified that shareholder as Mervyn Jacobson ApS, being the 'holder of 49 million shares in GTG' and controlled by Dr Jacobson.

On 22 October 2008 Senator Heffernan raised 'the patent problem with BRCA1 and BRCA2' before the Senate Community Affairs Committee.

Subsequent events, including an investigation by the ACCC, caused GTL to announce a further delay of the litigation deadline of 6 November 2008 to sometime in 2009.

On 11 November 2008 Senator Parry moved a Motion in the Senate referring to the Senate Community Affairs Committee an Inquiry, the terms of reference ask the Committee to report on 'the impact of the granting of patents in Australia over human and microbial genes and non-coding sequences, proteins and their derivatives, including those materials in an isolated form'. The Motion was passed.

On 12 November 2008 Senator Heffernan rose to speak to the Senate to thank the Senate 'for its generosity in agreeing to an inquiry into the impact of gene patents on the provision of health care in Australia.'

On 19 November 2008 GTL held its AGM at which various resolutions were put to the meeting. Having been passed, Mr Bosch and a number of other directors were removed from the Board. Included in this purge was Mr Ohanessian, the CEO.

On 2 December 2008 GTL issued a public announcement that on 24 November 2008 the new Board had completed its review of GTL's 'recent decision to enforce its BRCA testing rights' and that it had decided 'to immediately revert to its original decision to allow other laboratories in Australia to freely perform BRCA testing'.

Clearly, in view of GTL's last public announcement, that company, at least, will not seek to enforce its rights as an exclusive licensee in Australia. While this is an important concession on the part of GTL, it does not extinguish the rights of Myriad and the other patentees in Australia. It is therefore feasible that GTL's rights may be removed either by voluntarily relinquishing them to Myriad or by Myriad electing to rescind them. Thereafter, Myriad would be free to enforce its Australian patents. In either event, the potential for patent litigation remains an issue for Australian laboratories that currently perform BRCA gene testing.

In this respect, the Health Minister's letter of 8 December 2008, in response to a letter to her from the Cancer Council of Australia of 29 October 2008 inviting her to invoke the 'Crown Use' provisions under s.163 *AU Patents Act, 1990* so as to shield Australian laboratories from the threat of patent litigation, was problematic. In her letter, the Minister wrote that while 'she

shared' the CCA's concerns about this 'important and sensitive issue', she felt that she was unable to invoke the powers provided under s.163 AU Patents Act, 1990 because 'the Commonwealth does not have any direct involvement in genetic testing for BRCA 1 and 2' and so her 'Department', which had been 'working with the State and Territory Governments in attempting to find a solution' to the 'ultimatum of 7 July 2008', was in a 'quandary'. She confirmed that her 'Department had considered this option' but her understanding was that as 'all BRCA1 and 2 testing in Australia is carried out either by State owned or funded or privately owned laboratories' that '[s]ection 163 of the Patents Act 1990 [was] not available to the Commonwealth because it does not own or directly fund any laboratory which carries out such testing.' She did, however, suggest that 'this option may be available to the State Governments involved'.

To date, the only known direct action by any State Government over GTL's 'ultimatum of 7 July 2008' was an indemnification that the Victorian State Government had provided the Peter MacCallum Cancer Centre. This was confirmed by Ms Addison, from the Federal Department of Health, in answer to a question put by Senator Heffernan during a Senate Community Affairs Committee Hearing on 22 October 2008. [Hansard, Senate, 22/10/08. CA15].

As far as can be ascertained, no State or Federal Department of Health or other government department or agency has sought to challenge the validity of any BRCA gene patent in the Federal Court of Australia. Moreover, despite being advised, the ACCC has failed to act. IP Australia has failed to re-examine any of the BRCA patents, ignoring the power it has under the *AU Patents Act, 1990* to do so.

Thus, as matters presently stand, any one who makes or uses or researches BRCA1 and BRCA2 isolated biological materials or who uses such materials in the performance of a diagnostic test from breast and ovarian cancer in Australia without the authority of the patentees is at risk of patent litigation. Accordingly, until such time as these patents are re-examined by IP Australia and revoked or challenged in the Federal Court of Australian and revoked, they remain a real and significant threat to every laboratory in Australia that is performing BRCA1 and BRCA2 testing.

In terms of the impact of these patents on the Australian healthcare system, should Myriad seek to enforce these patents, the most immediate and obvious impact will be in terms of cost; and the situation in Europe, the US and Canada, where the patents are being enforced, provide Australians with hard evidence of the likely result. This cost, however, is not confined to the dollar value of each test performed, which will, undoubtedly, be substantially higher. Rather, it includes the opportunity cost for Australian laboratories to gather important scientific data with respect to the BRCA gene mutations. That data is vitally important to improving the reliability of BRCA gene testing because these genes are complex and the lack of significant genetic markers that universally apply to all people means that there is a real need for this data to be shared among laboratories. This aspect is a very real issue because of the licensing strategy that Myriad has in place in the US, which demands that all BRCA testing be performed by Myriad. The centralisation of this data by a private corporate entity creates issues concerning access to that data and the cost of that access, because control of databases can be effected through copyright law.

Geneticists have confirmed that BRCA gene mutations can be racially significant. For instance, it is scientifically accepted that in Ashkenazi Jewish women two BRCA gene mutations, 185delAG on the BRCA1 gene and 6974delT on the BRCA2 gene, are specific markers of breast and ovarian cancers. As such, during the course of the Oppositions before the EPO, Myriad voluntarily amended one of the European patents so that in Europe the patent monopoly for the BRCA genetic test applies only with respect to the 6974delT gene mutation on the BRCA2 gene. It is therefore conceivable that there are other BRCA gene mutations, yet to be discovered, that will be reliable markers of breast and ovarian cancers in women of other ethnic backgrounds, and this is particularly significant in countries such as Australia where those backgrounds will not be homogenous. Indeed, the patterns of

immigration to Australia suggests that a variety of racially important markers may be critical to achieving reliable diagnosis of these cancers in Australian women.

It is important, therefore, for Australian laboratories in publicly funded hospitals and research institutions to continue performing BRCA diagnostic testing so that a better and non-exclusive roadmap to the BRCA genes may be created.

In addition, there is evidence to suggest that gene mutations on the BRCA genes may be markers for other types of cancers, such as prostate cancer. In as much as this appears to be the case, it is vitally important to the health and welfare of Australians that Australian medical and scientific researchers be allowed unfettered access to BRCA genetic materials and the proteins which they code for. It must be recognised that access to these materials goes well beyond their use for the diagnosis of breast and ovarian cancers. To explain what is meant by this, one needs to examine the claims in AU 686,004 in more detail. Going to claim 15 (see *schedule A3* for a complete list of claims) for instance, it is clear that the patent monopoly in Australia extends to proteins that are coded for by the BRCA1 gene and which may be useful in an anti-cancer treatment or vaccine. Specifically, it should be noted that the claim is not limited to a specific human disease and so the claim is capable of being interpreted broadly so as to include within the scope of that monopoly the use of those proteins in the treatment of *any* type of cancer. Claim 15 reads as follows:

> Use of a polypeptide as defined in any one of claims 10 to 12 and 14 as an immunogen for antibody production.

The patent specification also states:

> The present invention also provides variant BRCA1 polypeptides substantially free of other proteins which are encoded by a mutant BRCA1 locus as defined above and use of such polynucleotides as an immunogen for antibody production, preferably monoclonal antibody production.

The specification provides examples of the kinds of medical applications which this claim may be directed to, such as, 'rational drug design', 'gene therapy' and 'peptide therapy'. The problem with the patent specification which IP Australia vetted and examined, oblivious to the impact of its decision to grant the patent with such a claim, is that it contains no information that would enable the skilled addressee to make proteins that would act as 'an immunogen for antibody production'. Indeed, the patent specification merely *speculates* about the potential referring to '[t]he hope for a new generation of specifically targeted antitumor drugs may rest on the ability to identify tumor suppressor genes or oncogenes that play general roles in control of cell division'.

The implications of such a claim for investors in medical and scientific research of this kind are obvious. It means that they would need to ensure that they had a license from Myriad first, to undertake research into anti-cancer therapies and second, to cover the situation, if and when they identify proteins that would be therapeutically useful, that would enable them to commercially exploit those proteins. Apart from the transactional costs associated with having to deal with Myriad and negotiate the appropriate licenses, these hypothetical investors would probably have to share the revenues generated from this exploitation and ownership of any patents with Myriad. And all because Myriad discovered a human gene and some mutations that were positive markers in a population of women that had a family history of breast and ovarian cancers.

Rational investors, however, would most likely react by choosing not to invest. After all, they would bear the risk and expense of developing the anti-cancer therapies, but Myriad would be entitled to a share and would probably be able to control the research, and the exploitation of that research, using what are known as reach back provisions in the license agreements which would be required as a result of this patent.

4. AU2001265698 – Mutation associated with epilepsy

Preliminary

Patent Applicant: Bionomics Limited, an Australian company headquartered in South Australia

Current Patent Owner: As above

Earliest Patent Application Date: 20 June 2000 (Australia)

Australian Patent Application Date: 20 June 2001

Australian Patent Grant Date: 3 September 2006

Patent Monopoly Period: 20 June 2001 to 20 June 2021

Current Status: Current (expires on 20 June 2021)

Title: *Mutations associated with epilepsy*

Technical Field:

The present invention is concerned with a human genetic mutation which is associated with a form of epilepsy. This genetic mutation is a mammalian DNA molecule encoding a 'mutant receptor subunit' of the inhibitory neurotransmitter GABA has been isolated. The mutation of the GABA receptor subunit disrupts the functioning of an assembled GABA receptor which, in turn, is the trigger for an epileptic episode.

Granted Claim 1:

'An isolated mammalian DNA molecule encoding a mutant y-aminobutyric acid (GABA) receptor subunit, wherein a mutation event selected from the group consisting of point mutations, deletions, insertions and rearrangements has occurred and said mutation event disrupts the functioning of an assembled GABA receptor, or an otherwise functional fragment or homologue thereof.'

See schedule A4 for all claims

Pre-grant Opposition: No

Post-grant Litigation: No

5. AU2004200978 – A diagnostic method for epilepsy

Preliminary

Patent Applicant: Bionomics Limited, an Australian company headquartered in South Australia

Current Patent Owner: As above

Earliest Patent Application Date: 27 March 2003 (Australia)

Australian Patent Application Date: 4 October 2004

Australian Patent Grant Date: 4 June 2006

Patent Monopoly Period: 4 October 2004 to 4 October 2024

Current Status: Current (expires on 4 October 2024)

Title: *A diagnostic method for epilepsy*

Technical Field:

A method for the diagnosis of severe myoclonic epilepsy of infancy (SMEI) in a child, comprising detecting an alteration in the SCN1A gene, including in a regulatory region of the gene, in a patient sample, and ascertaining whether the alteration is known to be SMEI associated or non-SMEI associated or, if not known to be either, determining the likelihood that it is a SMEI associated alteration.

Granted Claim 27:

'An isolated nucleic acid molecule encoding an altered SCN1A subunit of a mammalian voltage-gated sodium channel, wherein the alteration gives rise to an SMEI phenotype and has the sequence set forth in any one of SEQ ID NOS: 1-25.'

See schedule A5 for all claims

Pre-grant Opposition: No

Post-grant Litigation: No

Epilepsy (in general)

Epilepsy is a term that refers to a mammalian affliction, a characteristic of which is the recurrence of sudden seizures. It is considered to be a neurological disorder, estimated to affect about 50 million people throughout the world. It most commonly afflicts young children or adults over the age of 65 years and some forms of epilepsy are transient, not lifelong. The causes of epilepsy are many, just as the types of epilepsy vary (there are over 40 different epilepsy syndromes). Consequently, not all forms of epilepsy are the same and the types of seizures experienced during an epileptic episode also vary. About 5% of epileptics suffer from non febrile seizures. Seizures can be partial, during which a sufferer may or may not lose consciousness, or generalised, during which consciousness is lost. Generalised seizures are classified by their effect on the sufferer such as atonic (a mild form commonly called 'drop seizures' because the loss of muscle control cause the sufferer to fall), but include forms known as absence, myoclonic, clonic, tonic and tonic-clonic. However, there are some epilepsy syndromes of unknown localisation.

For more information see: http://en.wikipedia.org/wiki/Epilepsy

Epilepsy (patent specific forms)

The specific epileptic syndromes which are the subject of these two Australian patents are classified as 'idiopathic epilepsies' because their causes are *genetic*.

Each patent thus describes idiopathic epilepsies in almost exactly the same terms.

> The idiopathic generalized epilepsies (IGE) are the most common group of inherited human ~~epilepsies~~ epilepsy and do not have simple inheritance. Two broad groups of IGE are now known-the classical idiopathic generalized epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and the newly recognized genetic syndrome of generalized epilepsy with febrile seizures plus (GEFS+) (Scheffer and Berkovic, 1997 ; Singh et al. , 1999).
>
> [The underlined words are in the 2004 patent but not the 2001 patent. The deleted word is in the 2001 patent but not in the 2004 patent. Otherwise the paragraph is identical in both patents.]

Indeed, what becomes apparent on reading the patent specifications is that although their subject matter are different, in that one is principally directed to a gene whereas the other is principally directed to a diagnostic method, substantial parts of the respective specifications are identical or substantially so. Perhaps, this can be explained on the basis that the named

inventors in both patents are to some degree overlapping. Perhaps too, the parts of the specification that are identical are descriptive of this classification of epilepsy or describe aspects of genetic science and recombinant DNA methodologies.

However, what distinguishes these two patents from each other, apart from their principal claims, one being to a genetic mutation and the other to a diagnostic method to a genetic mutation, is that they concern two different forms of 'idiopathic epilepsies', which in turn are caused by different human gene mutations. This is the reason why both patents share so much of the same text and are word-for-word identical. The differences in the text occur when the patent is describing the genetic source of the two types of idiopathic epilepsies discussed.

Thus the key distinction between these two 'inventions' are the human gene mutations that are associated with the idiopathic epilepsies described in the patent specifications.

AU 2001265698

The earlier patent (the 2001 patent) identifies the cause of epilepsy as a 'mutant y-aminobutyric acid (GABA) receptor subunit'. GABA is said to be 'the most abundant inhibitory neurotransmitter in the central nervous system'. So, a mutation to this 'receptor subunit', which is a human protein, means that the way that the body interacts with GABA is suboptimal and it is this that the patent suggests to be the cause of one form of idiopathic epilepsy. Accordingly, claim 1 of the 2001 patent defines the 'invention' to be 'an isolated mammalian DNA molecule' that encodes this mutant receptor subunit.

There is no question as to what the invention is supposed to be. It is the human gene, or that part of the human gene, that codes for the mutant receptor subunit. True, the claim is limited to that gene or genetic material in an isolated form, but given that it is the genetic information which that genetic material possesses that is important, since it is this information that instructs the body to make the mutant receptor subunit, whether the gene is isolated or not makes no practical or material difference.

The patent, as is typical of gene patents, also claims the use of these genetic materials, and the proteins which they code for, in various applications that include methods for the production of other biological materials, such as antibodies that are 'immunologically reactive' to these proteins (claim 75), and in turn these antibodies, which are also naturally occurring, are claimed in their use various applications, such as diagnostic assays, have their potential use in therapeutic treatments.

In this respect, the patent monopoly extends to the use of these naturally occurring biological materials in 'gene therapy' (claim 79) and as components in 'a medicament for the treatment of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity' (claim 81).

This is a truly impressive list of illnesses. Yet, the patent specification contains little practical information that would explain to the skilled addressee how to do anything of the kind and certainly presents no supporting data.

AU 2004200978

The later patent (the 2004 patent), on the other hand, identifies the cause of 'severe myoclonic epilepsy of infancy (SMEI)' as mutations to the human SCN1A gene. The patent specification suggests that as these mutations, or 'alterations' as the patent describes them, 'lead to more severe changes to the SCN1A protein', they increase the 'likelihood that the patient has SMEI'. Moreover, the patent suggests that the 'likelihood' of SMEI is 'increased even further if it can be shown that the alteration is a de novo change rather than one that it inherited from the patients parents or relatives, or that the alteration in the SCN1A gene is one that has previously been associated with SMEI.'

Clearly, the *key* to the diagnosis of SMEI are the SCN1A genetic or protein materials used as

components in the test and not any specific underlying diagnostic technology. That this is the case is confirmed by a disclaimer in the patent that 'there exists a number of assay systems that can be used to test for the existence of an SCN1A alteration'. Indeed, the patent asserts that 'the invention is not limited by the examples [of the diagnostic technologies] that are provided' therein. Even more specifically, the patent states that 'the specific method … is not critical and may include enzyme-linked immunosorbent assays (ELISA)…fluorescent enzyme immunoassays (FEIA or ELFA) … and radioimmunoassay (RIA).'

The patent specification further labours the point about how key the 'SCN1A alterations' are in the test's performance by pointing out that the 'utility of the diagnostic assay in providing a likelihood that an individual may be affected with SMEI' are the 'mutations in the SCN1A gene in individuals that have been clinically diagnosed with SMEI'. These specific mutations are then defined in various sequence data tables which are referenced as SEQ ID NOS: 1-25; 26-48; 49-53 and 54-58. These are so voluminous that they make up 458 pages of the total patent document which consists of 521 pages, thus 88% of the patent specification is simply made up of the sequence data of the SCN1A gene mutations.

Needless to say, although the patent commenced with claims that define the invention to be 'a method for determining the likelihood that a patient suspected of SMEI does or does not have SMEI' with some 26 claims to this effect, claims 27 to 30 are ultimately directed at the SNC1A DNA, the sequence of which is contained in the tables already mentioned. Furthermore, claims 35 to 38 are claims to proteins coded by the genetic sequences in those tables. Then there are claims to antibodies as well as the uses of these biological materials in various treatments, therapies and medicaments.

That the key to the invention is little more than the *SCN1A mutations*, is reinforced by the patent, which although covering all possible uses of the biological materials (as defined by or derived from the DNA sequence data) in the claims, provides virtually no instruction to the skilled addressee as to how to use that data to treat SMEI in the specification.

In so far as the patent does contain information that a skilled addressee would find useful in producing a diagnostic assay, apart from the DNA sequence data there is nothing new or inventive disclosed. In fact, it would be fair to say that the use of the application of that data in various diagnostic assays was obvious to the skilled addressee.

The Impact of these patent in Australia

On 21 June 2000 Bionomics Limited (Bionomics), the patent owner of both of these patents, made a public announcement advising that it had filed two provisional patent applications 'describing two genes responsible for separate forms of epilepsy in two different families'. Bionomics' public statement also advised that the initial research that led to these patent applications emanated from 'the laboratory of Professor Sutherland', who was described as 'one of Australia's most internationally recognised geneticists'. Professor Sutherland was, at the time, the holder of a professorial chair from the University of Adelaide's Department of Paediatrics at the Women's and Children's Hospital (WCH), both publicly funded institutions. The statement also advised that 'work conducted by the University of Melbourne' (UM) and the 'intellectual property relating to this research' had been licensed from both the WCH and UM.

On 13 December 2000 Bionomics publicly announced that it had been 'successful in attracting R&D Start Grant funding' from the 'Federal Government agency AusIndustry'. The announcement confirmed that the company was 'a world leader in the discovery of genes associated with epilepsy' and that 'the additional funds provided by this R&D Start Grant' would be used to undertake this research.

While these announcements only dealt with the 2001 patent, not the 2004 patent, it is the case that Bionomics was greatly assisted, direct and indirectly, through the receipt of significant amounts of public funding. The role that earlier public funded research played in assisting

Bionomics was confirmed in a public announcement made on 3 December 2002. In that announcement the company stated:

> The Company has benefited from a very close and productive collaboration with Melbourne University and the Women's and Children's Hospital in Adelaide since it's inception where the teams led by Professor Sam Berkovic and Professor Grant Sutherland have achieved significant advances in understanding the genetic causes of epilepsy.

On 13 May 2004 the WCH issued a public statement, entitled 'World-first common epilepsy gene discovery', advising that '[s]cientists at the Women's and Children's Hospital, in collaboration with Bionomics Limited, the University of Melbourne and a US group in Tennessee … identified the first 'susceptibility' gene for the common forms of epilepsy'. That announcement also confirmed that 'the work was funded by a Federal R&D Start grant that was matched with funding from Bionomics'.

There is, of course, no suggestion that Bionomics acted inappropriately. Indeed that it collaborated with leading university researchers and received government funding for R&D was entirely consistent with the then Federal government policy which, more or less, remains the policy today.

One might even suggest that the public announcement made by Bionomics on 27 September 2004 that it had entered into a license with a major US diagnostic laboratory in respect of, what was then, the patent application of the 2004 patent was a positive result for an Australian biotechnology company. No doubt the news would encourage further private investment in Bionomics and the fledgling biotechnology sector in Australia. Accordingly, Bionomics confirmed that the US licensee would 'pay … upfront fees on signing, milestone payments linked to sales targets and royalty payments on net sales.'

Unfortunately, within months of this announcement Bionomics made another public announcement that was not so positive for Australian hospitals and clinicians. On 8 November 2004 it announced that it had granted the 'worldwide testing and marketing rights, including exclusivity for Australia and New Zealand, to new epilepsy tests' to Genetics Technologies Limited (GTL). This is the same company that had the exclusive license to the BRCA gene patents in Australia. Although to some this might be considered to be a win-win result for Australian ingenuity and the economy, as events transpired it was not.

Subsequently, on 3 November 2005 Bionomics announced that it had 'licensed two genetic tests for the diagnosis of epilepsy to Laboratory Corporation of America', one of the largest diagnostic service providers in North America. This was also good news for Bionomics.

The good news from Bionomics continued. On 11 April 2006 it announced that it had been granted an Australian patent. This was a reference to the 2001 patent. Bionomics advised the public that:

> The granted patent relates to the link between mutations in the GABA-A receptor and epilepsy. The patent covers the use of several mutations in diagnostics; drug screening and potential new treatments for CNS disorders associated with GABA-A receptor dysfunction, in particular epilepsy.

Apart from the fact that the company confirmed that the patent 'covered several mutations', being a clear reference to the human gene mutations that are thought to be responsible for the type of epilepsy induced by a dysfunctional GABA-A receptor, the statement made some rather misleading statements. While it may be the case that the patent did cover the use of these mutations in the 'potential new treatments for CNS disorders', the patent did not, in fact, disclose any information that would enable anyone to actually make use of those gene mutations other than in diagnostics, and, frankly, that was hardly the kind of innovation that could have been regarded as inventive. That was just planly obvious. Everyone who knew anything about genetic testing knew how to use the genetic and protein materials to make

diagnostics. The only thing that was new were the gene mutations and the link to the CNS disorder. This was nothing more than a wonderful example of Australian science but, at the end of the day, there was no invention. Of course, Bionomics did not raise this as a possibility in its announcement. Its management was quite content to mislead the public into believing that it had valuable intellectual property in the form of this patent.

Consequences of these patents on the Australian healthcare sector and the Australian economy

What does this mean for Australia?

First, it means that medical and scientific research into this specific form of epilepsy is now controlled by Bionomics, particularly since the broad patent monopoly has given it the right for 20 years to control all manner of 'potential new treatments for CNS'. After all, what reasonable investor will invest in a field of research over which *every conceivable* medical and scientific application (most of which are speculative) is already patented?

Secondly, it means that Australia's molecular geneticists are unable to make or use those gene mutations to produce even better and cheaper diagnostic tests for CNS disorder. Further medical and scientific research into gene mutations may reveal other gene mutations not already discovered by scientists who were working with the public funded institutions in collaboration with Bionomics. In any event, it was and is within the competence of Australian molecular geneticists to make these tests using the DNA sequence of the gene mutations, which were discovered, once this information was published in the scientific literature.

Thirdly, it means that the benefit of public monies given to Bionomics and its collaborators in the form of grants of various kinds have been reserved exclusively for Bionomics and its shareholders. There was nothing in any public announcement made by Bionomics or any Australian institution or government agency to the effect that Australia's public investment in this R&D would be repaid or that Australian hospitals or laboratories would be given free access (or even substantially discounted access) to the end results of that R&D. Perhaps it was thought to be enough for an Australian company to be generating revenues for the Australian economy, but how could this be so, when at the same time, the Australian public would have to pay commercial prices for those CNS diagnostic tests? Is this not a case of double dipping, in which the Australian taxpayer pays twice for the same thing?

Fourthly, it means that other Australian medical and scientific researchers have gained the impression that the grant of patents over genes linked to human disease is legal. The law in this country requires patents to be granted for inventions as defined in the *AU Patents Act, 1990*. At the time that this patent was granted, although IP Australia had interpreted the law so that it could grant these patents, there was no judicial authority to support its interpretation. This was, and remains, significant because the *AU Patents Act, 1990* expressly provides (a) that no patent is guaranteed to be valid and (b) nothing that IP Australia does can make it accountable to anyone. Therefore, valuable medical and scientific resources in Australia have been directed towards the making of discoveries in the expectation that these would be the subject of a valid and enforceable patent.

Finally, it means that Australian hospitals are unable to access these tests for reasonable prices because of the licensing policies of Bionomics. An example of this is given in respect of the diagnostic test which is the subject of the 2004 patent.

On 29 November 2008 an article was published in the Sydney Morning Herald entitled *Sick Babies Denied Treatment in DNA Row*. The article's author, the newspaper's Medical Editor, Julie Robotham, wrote about a situation that faced Westmead Hospital, one of Sydney's major public hospitals. According to Ms Robotham, Dr Deepak Gill, head of neurology at the Westmead Children's Hospital, 'said he would test at least 50 per cent more infants for the SCN1A gene - which would diagnose the disabling Dravet syndrome - if the hospital could conduct the test in-house.'

In other words, by being prevented by the 2004 patent (which was exclusively licensed to

GTL) from making its own in-house tests (which would not only save thousands of dollars from the NSW Health's budget, but would encourage further medical and scientific research into better diagnostics), Dr Gill was being forced to *ration* the test when there was a clear need for the test in the diagnosis of a childhood disorder that was affecting Australian children, their families and the health system of this country. How ironic, that a discovery that had been made possible through the grant of public moneys to Australia's leading scientists at some of Australia's leading institutions resulted in Australian public hospitals being unable to benefit in a practical way from that research.

It is worth including Ms Robotham's two excellent articles in this submission.

Sick babies denied treatment in DNA row

Julie Robotham Medical Editor

November 29, 2008

BABIES with a severe form of epilepsy risk having their diagnosis delayed and their treatment compromised because of a company's patent on a key gene.

It is the first evidence that private intellectual property rights over human DNA are adversely affecting medical care.

Deepak Gill, head of neurology at the Children's Hospital at Westmead, said he would test at least 50 per cent more infants for the SCN1A gene - which would diagnose the disabling Dravet syndrome - if the hospital could conduct the test in-house.

But rights to the gene are controlled by the Melbourne-based Genetic Technologies, which has already threatened to stop public hospitals testing for breast cancer gene mutations, and the hospital will not risk a similar problem.

Specialists are sending blood samples to Scotland, and only babies whose seizure patterns closely resemble Dravet syndrome are tested. This means children with slightly different symptoms may be treated with the wrong medicines for months, potentially retarding their development.

"It's frustrating that we can't get the test done readily," Dr Gill said. "If we could include it as part of the work-up, we could identify them early."

At present the diagnosis is often delayed until the child is 12 to 18 months old. This is after the optimum time for treatment with strong drugs that are unsuitable for most babies with epilepsy but are used for infants with Dravets to control severe seizures that can damage the brain. Standard childhood epilepsy medications are ineffective with Dravets and may worsen it, Dr Gill said.

The situation comes amid growing concern among doctors and medical researchers over the ethics of granting private ownership to human DNA. A Senate inquiry announced this month will investigate the effects of gene patenting on health-care.

SCN1A is the most important epilepsy gene discovered, Dr Gill said, and is abnormal in about 70 per cent of children with Dravet syndrome, which affects about one in 30,000 babies - almost 10 per cent of infant epilepsy cases.

About one in 20 children have a seizure when they develop a fever, though only a minority had epilepsy, Dr Gill said. The Scottish laboratory conducts SCN1A testing for all of Britain. Dr Gill said the price of the test - about $1800 - was similar to that offered by Genetic Technologies, but he had more confidence in the expertise of the Scottish laboratory, run by a pediatric neurologist.

Dr Gill said patenting the gene "may have helped initially to define and produce the test, but in 2008 it's not helping kids right now to access the test".

John Christodoulou, director of the Western Sydney Genetics Program, based at the same hospital, said his laboratory could not risk SCN1A testing in case Genetic Technologies - which licenses the gene patent from an Adelaide biotechnology firm, Bionomics - later barred him from testing or imposed a prohibitive royalty.

Condition critical for sick hospital

Julie Robotham Medical Editor

March 7, 2009

BED numbers have been slashed this week at Sydney's biggest hospital, in a round of ward closures aimed at reining in a $70 million blow-out in the region's health spending.

Ten of 16 operating suites have been closed and elective surgery has been cancelled, with staff forced to take leave, sources said. Forty-three cardiology and heart surgery beds have shut since late last year, said medical and nursing staff, culminating last week in the closure without notice of the heart surgery ward - which staff found empty and locked when they arrived for work.

The unprecedented axing of about 70 beds comes after the *Herald* revealed in late January that Sydney West Area Health Service, which oversees Westmead, owed $26 million to creditors – more than any other region and almost a quarter of NSW Health's outstanding debt to suppliers at that time.

Neurosurgery and general surgery beds have also closed, said the sources, while casual nursing shifts have been curtailed across the entire hospital, as displaced permanent staff are redeployed into vacancies on the roster.

The closures represent about 9 per cent of Westmead's total capacity, and are the biggest round of cuts at a single hospital to strike the beleaguered state health system.

The chairman of the hospital's Medical Staff Council, Andrew Pesce, said the closures were by far the most severe the flagship teaching hospital had seen. "It's a quantum leap [compared with] the modest bed closures usually built around [public] holidays," Dr Pesce said.

Coming a month before Easter and without any promise that beds would reopen or surgery resume, the closures were the equivalent of an extra Christmas closedown, said Dr Pesce - referring to the practice of selectively suspending services during the holiday period to save money.

"If things continue the way they are going, the morale of the place will become so low that doctors and nurses will start leaving," he said. Hospital managers were not solely to blame because NSW Health gave them "unrealistic budgets".

Public hospitals had traditionally been insulated from state spending cuts, Dr Pesce said, but NSW's wider financial crisis meant they were no longer receiving favourable treatment.

Health accounts for about one-third of the state's spending, and had blown out by about $300 million at the time of November's mini-budget. Area health services were ordered to save $943 million over four years.

6. AU2002048844 – Methods and compositions for use in gene therapy for treatment of hemophilia

Preliminary

Patent Applicant: The Children's Hospital of Philadelphia, a US public funds-assisted health institution

Current Patent Owner: As above

Earliest Patent Application Date: 14 March 1997 (US)

Australian Patent Application Date: 12 March 1998 (patent parent application)

Australian Patent Application Date: 19 June 2002 (current patent child application)

Australian Patent Grant Date: 26 May 2005

Patent Monopoly Period: 12 March 1998 to 12 March 2018

Current Status: Current (expires on 12 March 2018)

Title: *Methods and compositions for use in gene therapy for treatment of hemophilia*

Technical Field:

Includes a composition comprising a recombinant adeno-associated viral vector comprising at least two adeno-associated virus inverted terminal repeats, a promoter/regulatory sequence, isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions and a transcription termination signal, and methods of use thereof.

Claim 1 (as applied for – defacto applicable until 27 January 2005 (publication date of patent acceptance)):

'A composition comprising a recombinant adeno-associated virus vector comprising at least two adeno-associated virus inverted terminal repeats, a promoter/regulatory sequence, isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions and a transcription termination signal.'

Claim 1 (as granted – legally applicable between 27 January 2005 and 15 December 2005):

''A ~~composition~~ method of treating hemophilia in a mammal comprising ~~at least two adeno-associated virus inverted terminal repeats, a promoter/regulatory sequence, isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions and a transcription termination signal~~:

(a) providing a virus, said virus comprising a recombinant adeno-associated virus vector (rAAV), said rAAV comprising a nucleic acid encoding Factor IX operably linked to an expression control element; and

(b) administering an amount of said virus to a mammal wherein the Factor IX is expressed at levels having a therapeutic effect on said mammal and wherein said therapeutic effect is an increase in coagulation of blood.'

Claim 1 (as voluntarily amended on 15 December 2005 – legally applicable from 16 December 2005 and 12 March 2018):

'A method of treating hemophilia in a mammal comprising:

(a) providing ~~a virus, said virus comprising~~ a recombinant adeno-associated virus vector (rAAV), said rAAV comprising a nucleic acid encoding Factor IX operably linked to an expression control element; and

(b) administering an amount of said ~~virus~~ rAAV to a mammal wherein said Factor IX is

expressed at levels having a therapeutic effect on said mammal and wherein said therapeutic effect is an increase in coagulation of blood.'

See schedule A6 for all claims

Pre-grant Opposition: No

Post-grant Litigation: No

Haemophilia (in general)

According to the patent specification:

> Hemophilia is a disease of humans and other mammals wherein a gene encoding a blood coagulation factor contains a mutation such that the encoded protein does not function normally in the cascade process. Specifically, the hereditary disease, hemophilia B, is characterized by a mutation in the gene encoding the blood coagulation protein, Factor IX (F.IX). F.IX is reviewed in High et al. (1995, "Factor IX" In: Molecular Basis of Thrombosis and Hemostasis, High and Roberts, eds., Marcel Dekker, Inc.).

It is also useful to read Dr Katherine High's (one of the named inventors) description of haemophilia. In her paper entitled *Gene Transfer as an Approach to Treating Hemophilia* [*Circulation Research* (2001) 88, 137-144] she writes:

> Hemophilia is an X-linked bleeding diathesis resulting from a deficiency of blood coagulation factor VIII (F.VIII) (hemophilia A) or factor IX (F.IX) (hemophilia B).
>
> Clinically, the disease is characterized by frequent spontaneous bleeding episodes, mostly into joints or soft tissues. Bleeding can also occur into other critical closed spaces, such as the intracranial space or the retroperitoneal space, where it can be rapidly fatal. Hemophilia A occurs in 1 in 5,000 male births; hemophilia B is less common, occurring in 1 in 30,000 births. Still, hemophilia is one of the most common genetic disorders, and prevalence of the disease is the same in all populations studied.
>
> Hemophilia is classified as mild, moderate, or severe on the basis of circulating levels of clotting factor; severe disease is defined as 1% of normal levels, moderate as 1% to 5%, and mild as .5%.
>
> Life expectancy for individuals with hemophilia increased dramatically with the introduction of clotting factor concentrates in the 1960s, but contamination of these with hepatitis viruses and later with human immunodeficiency virus (HIV) has had devastating effects for the hemophilia population. Thus, in the 1950s, the leading cause of death in hemophilia was fatal bleeding episodes, whereas today the two leading causes of death are HIV-related disease and end-stage liver disease. Other disadvantages of the present protein-based therapy include the expense of the product, which can reach $50,000 to $100,000 per year for an individual with severe disease, and the inconvenience of managing a chronic disease with a medication that must be infused intravenously.
>
> These considerations have fueled an interest in developing a gene-based approach to treating hemophilia.

For more information see: http://en.wikipedia.org/wiki/Haemophilia

Relevant History

On 14 March 1997 Dr Katherine High and Dr Roland Herzog were named as inventors on a US patent application filed by The Children's Hospital of Philadelphia (CHP) in which they asserted that that they had made an 'invention' for the treatment of haemophilia in humans.

Specifically they stated:

> There is a long felt and acute need for methods of delivering F.IX to mammals having hemophilia, in particular, to humans having hemophilia, such that a therapeutic effect is achieved. The present invention satisfies this need. (Emphasis added)

Yet, a decade later, in a scientific paper written by Dr High and published in *Hematology*, the peer reviewed journal of the American Society of Hematology, *Update on Progress and Hurdles in Novel Genetic Therapies for Hemophilia* [*Hematology Am Soc. Hematol. Educ. Program* 2007, 466-72 (2007)], she confirmed that her invention had failed to deliver on that promise.

The question which must be asked in light of her admission is this: back in 1997 had it not occurred to Dr High that she was premature in applying for a patent? One might be forgiven for thinking not, given that the USPTO granted the CHP US 6,093,392 on 25 July 2000, but some two years later, when it should have been apparent that her 'invention' had failed to produce a practical and useful treatment for haemophilia in humans, why did the CHP persist with an Australian patent application in which the very same assertion that Dr High and Dr Hertzog made in 1997 was repeated? Indeed, why did IP Australia even grant the Australian patent when by May 2005 the scientific literature (which was available to patent examiners) was reporting [see for example Arruda et al, (2001), 'Safety and efficacy of factor IX gene transfer to skeletal muscle in murine and canine hemophilia B models by adeno-associated viral vector serotype 1', *Blood*, **103**(1), 85-92 (1 January 2001)] that clinical trials using, what can only be described by this time as Dr High's hypothetical form of treatment, was failing to produce the same effect in humans as it had in mice and dogs?

While it is true that Dr High may have had cause to believe in 1997, based on experiments carried out on animals, that gene therapy had the potential to provide a new and better form of treatment in humans, the problem was that subsequent studies were unable to replicate the same level of performance. Unfortunately, Dr High seemed unable to accept this. In an article that was published in 2001, she wrote that 'that data derived from animal studies will serve as a reliable guide to results in humans'. Moreover, she tried to convince her colleagues, based upon these clinical trials, that 'these trials have ushered in a new era of treatment for hemophilia that holds the promise not only of improved treatment for bleeding disorders but for a variety of other genetic diseases as well.' [High, K (2001), 'Gene Transfer as an Approach to Treating Hemophilia', *Circulation Research*, **88**, 137-144]

That said, by the time her paper, *Gene Transfer for Hemophilia*, was published in August 2005, Dr High seemed to appreciate that her idea of using gene therapy to treat human haemophilia was years away from becoming a reality. [High K (2005), *Journal of Thrombosis and Haemostais*, **3**, 1682-1691]

In her retrospective account of the medical treatment of haemophilia, she confirmed that in the ten years since the patent application was filed no significant medical advance had been made in the treatment for haemophilia, and that, indeed, the only practical and useful treatment for haemophilia was, in 2007, exactly the same as it had been in 1997. Dr High wrote in 2007:

> The goal of gene therapy for genetic diseases is to bring about long-lasting expression of the missing or defective gene, i.e., to effect a "cure," defined in the case of hemophilia as the ability to maintain hemostasis without significant ongoing medical intervention. Current management, by intravenous infusion of clotting factor concentrates, either prophylactically or on demand, is a highly effective treatment, but clearly falls short of this long-term goal. Advances that would likely be considered improvements by most consumers would include products that required less frequent infusions, those that could be taken orally rather than intravenously, and those that are less expensive than the currently marketed concentrates, which may cost in the range of $50,000 to $100,000/year for an adult with severe disease.

A quick comparison back to the patent specification is illuminating, for not only have the costs of the intravenous treatment remained the same, but evidently, so has the form of treatment. The patent states:

> Current therapy for hemophilia involves the intravenous injection of a preparation of clotting factor concentrates whenever a bleed occurs. This treatment is cumbersome, inconvenient and very expensive. The average patient pays approximately $100,000 per year for the concentrate alone. Further, because the concentrate is only administered to the patient intermittently, patients remain at risk for life-threatening bleeds which are fatal if treatment is not timely administered.

This, of course, raises an obvious question: why did the USPTO and IP Australia grant CHP patents for an invention that is neither practical nor useful and which, at best, was only hypothetical on 14 March 1997? Indeed, it is fair to say that all that Dr High and Dr Herzog had was an *idea* that gene therapy could be used to treat human haemophilia; they most certainly did not have an invention to that effect. Importantly, in their patent application they failed to produce any scientific data to support their claim to having invented a gene therapy to treat human haemophilia. That seemed not to matter to either the USPTO or IP Australia.

So, if one of the justifications for the grant of a patent is that the information which it contains will add to the body of knowledge of other ingenious people, surely those people should be given information that is reliable, accurate and realistic? Undoubtedly, the answer should be in the affirmative. Yet having survived the pre-grant examination process in both the USPTO and IP Australia, both patent granting authorities granted the CPH patents that provided unreliable, inaccurate and unrealistic claims to an invention. Do we have a problem with the patent system in both countries? The answer must be in the affirmative.

The Impact on Australia

Clearly, this patent had no effect on the cost of the healthcare system in Australia given that there is no gene therapy for human haemophilia but, given that the patent will not expire until March 2018, it is possible that if in the intervening time such a therapy materialises that there will be an impact on cost.

But the impact on Australia is not merely one of cost, nor should it be.

Beyond the issue of the higher cost of medicines and treatments which patents inevitably cause, is the impact which they have on the direction that medical and scientific research may take. In the past, the kinds of results which Dr High and Dr Hertzog believed in 1997 to offer promise in the treatment of a human illness would have been published in the scientific literature, and their experiences and thoughts would have informed their colleagues throughout the world, including in Australia, of the potential for gene therapy. In the past, their colleagues would have been free to then take that research further. They may have tested the results and through the rigorous process of external scientific assessment either supported the ideas or not. Unfortunately, Dr High and Dr Hertzog instead decided to apply for a patent in Australia and, due to the lack of any rigorous pre-grant examination their patent application, turned this hypothesis into a granted patent. Even so, it would have become known to Australian scientists in August 1998, when the Australian patent application was published and open for public inspection, that a patent application had been filed. Therefore, and given that the patent application claimed to have *invented* a ‘composition comprising a recombinant adeno-associated virus vector comprising at least two adeno-associated virus inverted terminal repeats, a promoter/regulatory sequence, isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions and a transcription termination signal’, it is plausibly the case that Australian scientists may very well have been persuaded not to undertake research in this field.

Thus far, if anyone is encouraged to undertake further research, they are required to seek the permission of the CHP. This will involve them in negotiating some form of license

agreement, contributing to the costs of the proposed research and requiring them to devote precious time to legal machinations. The end result may be a license that will most certainly require them to share the ownership of any intellectual property which they develop as a result of their own research with the CHP; a very costly way for the rest of the world to help put some substance onto the preposterously premature idea that the CHP has patented in Australia.

Conclusion

The Australian patent system has systemically failed to achieve the objectives that Barry Jones, the Minister for Science, said it would. Mr Jones told the Australian Parliament in June 1989 that the *AU Patents Act, 1990* would:

(a) foster indigenous innovation;

(b) reduce unnecessary social costs;

(c) improve the efficiency of the administration of the patent system; and

(d) make it harder to get a patent by strengthening the standards of novelty and inventiveness.

Yet, as these six examples show, in the past 20 years the exact opposite has occurred.

Taking Chiron's HCV patent first and keeping in mind the Minister's stated objectives, what impact has it had on Australia?

First, the patent prevented indigenous innovation in the field of HCV diagnostics by making it illegal for anyone not authorised by Chiron and its partner Ortho to undertake research in the field of HCV immunodiagnostics in Australia. By adopting a licensing policy that restricted licenses to five organisations worldwide – a policy designed to maximise prices of HCV diagnostics assays - it was impossible for Australian scientists to legally synthesise these materials using standard and well known molecular biological techniques and processes. That Chiron did not sue any Australian research institution for patent infringement reflects this. The potential illegality was enough to deter any research because what the patent claimed as an invention was the very foundation stone upon which that research would be supported – the HCV proteins and genome in an isolated form.

Secondly, it increased social costs by (i) substantially raising the cost of screening blood donated by Australians freely to Australian blood transfusion services; (ii) reducing the potential blood donor pool in Australia by the adoption of a deliberate policy that restricted its licensees to supply in Australia HCV immunodiagnostics that produced false positive detections of HCV in low risk populations; (iii) ensuring that medical and scientific research in Australia with regard to HCV was subject to control by Chiron through the patent monopoly that extended to isolated HCV biological materials; and (iv) unnecessarily contributing to the cost of the provision of healthcare throughout Australia through the higher than normal prices that applied to products that used HCV biological materials.

Thirdly, it demonstrated the inefficiency of the administration of the patent system both domestically and internationally. The decision of the European Patent Office, some 7 years after IP Australia granted Chiron the HCV patent, to revoke the very claims that were (a) upheld as valid by various courts throughout Europe and (b) that led to the removal of HCV immunoassays that competed with Chiron's licensed HCV immunoassays in Europe nearly sending a British company (Murex Diagnostics Limited) to the wall, is testimony to this. That aside, the lengths to which Chiron sought to extend its patent monopoly around the world to cover things that (a) were not 'inventions' and (b) were to 'inventions' but which, nonetheless, were not patentable, such as to non-existent HCV vaccines, and the complicity that the British and European Patent Offices played in granting Chiron these patents, reinforces the point made here.

In Australia, the failure of IP Australia to restrict the patent monopoly to what was *lawful*, thus ensuring that the social contract between Chiron and Australia was fair and in the best interests of Australia (within the limits of Australia's international obligations), demonstrates that it too was complicit in helping Chiron achieve its worldwide objective. Even more, by its *inaction* after the European Patent Office had revoked the very claims which Chiron had voluntarily inserted in 1997 into its Australia HCV patent, IP Australia displayed gross

negligence.

Finally, this patent monopoly demonstrated just how easy it was for Chiron to 'get a patent'. Not only was the patent monopoly over something that no one invented, namely isolated HCV biological materials, but, in terms of the practical application of those materials, while some of those applications were so obvious that any skilled person in Australia could have made HCV immunoassays without difficulty, others were so speculative, such as with regard to vaccines, that the paucity of data contained in the patent meant that it would have taken a skilled person another 30 man years of research to achieve a practical and useful result.

The same criticisms can be levelled at Amgen's patent over erythropoietin - a patent that operated in Australia for nearly 22 years because some of the claims were to erythropoietin as a biopharmaceutical and so it was subject to a special allowance that enables such patents to have a maximum life of 25 years. So how did this patent impact upon Australia?

First, the patent prevented indigenous innovation by making it illegal for anyone not authorised by Amgen to undertake research in the field of erythropoietin biopharmaceuticals in Australia. Like Chiron, Amgen's licensing policies made it impossible for Australian scientists to synthesise erythropoietin using standard and well known molecular biological techniques and processes. Again, that Amgen did not sue any Australian research institution for patent infringement is no cause for complacency. The potential illegality involved in making the very materials that would have been used in medical and scientific research was enough to deter that research because what the patent claimed as an 'invention' was the erythropoietin gene and proteins in isolated forms.

Secondly, it too increased social costs by (i) substantially raising the cost of kidney dialysis and cancer treatment; (ii) ensuring that medical and scientific research in Australia with regard to erythropoietin biopharmaceuticals was subject to control by Amgen through the patent monopoly that extended to isolated erythropoietin biological materials; and (iii) unnecessarily contributing to the cost of the provision of healthcare throughout Australia through the higher than normal prices that applied to products that used erythropoietin biological materials in their production.

Thirdly, it also demonstrated the inefficiency of the administration of the Australian patent system. That it took 16 years for the patent administrative system to grant Amgen a patent, which in any event was invalid because it granted a patent monopoly over 'natural phenomena', reinforces this point. Moreover, at no time did IP Australia address the issue of 'invention' through the judicial avenues which were open to it, either during the course of the appeal to the Federal Court, or separately.

Similarly, the other four patents have in one way or another, although perhaps not as dramatically as these two examples, have cost this country more than they have or can possibly contribute.

To make matters worse, during the past 20 or so years no Commonwealth or State Department of Health applied to use powers available to them to ameliorate the negative effects of these powers. Section 163 provides the Commonwealth and State governments with 'Crown Use' powers. They have never been invoked. Furthermore, on no occasion has any Commonwealth or State government agency challenged the grant or the validity of any of these six patents.

What is amply demonstrated by these examples is that if the patent system is to be made to function properly, so that it is balanced and well calibrated, then IP Australia must be made accountable to an independent Commonwealth government agency that will not only audit IP Australia to ensure that it acts within the law, but that it will actively monitor the grant of patent monopolies in Australia and their impact and, in appropriate cases, challenge those patents in a specialised court that is composed of judges who are expert in patent law. In this respect it is important that the judges of such a court not be selected from solely from the barrister profession, but that they also come from other spheres of the legal profession and

academia. It is also important that non-lawyers, such as economists, engineers and scientists, also actively participate in this review process because patent law is not simply about granting patents as a reward for ingenuity – they have the capacity to impact (and as in these cases negatively) upon society, the economy and Australia's capacity for scientific and technological innovation.

Schedule A1

Patent Claims (Granted)

AU 624,105

AU Patent 624,105 CLAIMS (as granted)

1. A purified HCV polynucleotide.
2. A recombinant HCV polynucleotide.
3. A recombinant polynucleotide comprising a sequence derived from an HCV genome or from HCV cDNA.
4. A recombinant polynucleotide encoding an epitope of HCV.
5. A recombinant vector containing the polynucleotide of claim 2, or claim 3, or claim 4.
6. A host cell transformed with the vector of claim 5.
7. A recombinant expression system comprising an open reading frame (ORF) of DNA derived from an HCV genome or from HCV cDNA, wherein the ORF is operably linked to a control sequence compatible with a desired host.
8. A cell transformed with the recombinant expression system of claim 7.
9. A polypeptide produced by the cell of claim 8.
10. Purified HCV.
11. A preparation of polypeptides from the HCV of claim 10.
12. A purified HCV polypeptide.
13. A purified polypeptide comprising an epitope which is immunologically identifiable with an 5 epitope contained in HCV.
14. A recombinant HCV polypeptide.
15. A recombinant polypeptide comprised of a sequence derived from an HCV genome or from HCV cDNA.
16. A recombinant polypeptide comprised of an HCV epitope.
17. A fusion polypeptide comprised of an HCV polypeptide.
18. A monoclonal antibody directed against an HCV epitope.
19. A purified preparation of polyclonal antibodies directed against HCV.
20. A particle which is immunogenic against HCV infection comprising an HCV polypeptide having an amino acid sequence capable of forming a particle when said sequence is produced in a eukaryotic host, and an HCV epitope.
21. A polynucleotide probe for HCV.

22. A kit for analyzing samples for the presence of polynucleotides derived from HCV comprising a polynucleotide probe containing a nucleotide sequence from HCV of about 8 or more nucleotides, in a suitable container.

23. A kit for analyzing samples for the presence of an HCV antigen comprising an antibody directed against the HCV antigen to be detected, in a suitable container.

24. A kit for analyzing samples for the presence of an antibodies directed against an HCV antigen comprising a polypeptide containing an HCV epitope present in the HCV antigen, in a tuitable container.

25. A polypeptide comprised of an HCV epitope, attached to a solid substrate.

26. An antibody to an HCV epitope, attached to a solid substrate.

27. A method for producing a polypeptide containing an HCV epitope comprising incubating host cells transformed with an expression vector containing a sequence encoding a polypeptide containing an HCV epitope under conditions which allow expression of said polypeptide.

28. A polypeptide containing an HCV epitope produced by the method of claim 27.

29. A method for detecting HCV nucleic acids in a sample comprising:

(a) reacting nucleic acids of the sample with a probe for an HCV polynucleotide under conditions which allow the formation of a polynucleotide duplex between the probe and the HCV nucleic acid from the sample; and

(b) detecting a polynucleotide duplex which contains the probe.

30. An immunoassay for detecting an HCV antigen comprising

(a) incubating a sample suspected of containing an HCV antigen with a probe antibody directed against the HCV antigen to be detected under conditions which allow the formation of an antigen-antibody complex; and

(b) detecting an antigen-antibody complex containing the probe antibody.

31. An immunoassay for detecting antibodies directed against an HCV antigen comprising:

(a) incubating a sample suspected of containing anti-HCV antibodies with a probe polypeptide which contains an epitope of the HCV, under conditions which allow the formation of an antibody-antigen complex; and

(b) detecting the antibody-antigen complex containing the probe antigen.

32. A vaccine for treatment of HCV infection comprising an immunogenic polypeptide containing an HCV epitope wherein the immunogenic polypeptide is present in a pharmacologically effective dose in a pharmaceutically acceptable excipient.

33. A vaccine for treatment of HCV infection comprising inactivated HCV in a pharmacologically effective dose in a pharmaceutically acceptable excipient.

34. A vaccine for treatment of HCV infection comprising attenuated HCV in a pharmacologically effective dose in a pharmaceutically acceptable excipient.

35. A tissue culture grown cell infected with HCV.

36. The HCV infected cell of claim 35, wherein the cell is of a human macrophage cell line, or is of a hepatocyte cell line, or is of a mosquito cell line, or is of a tick cell line, or is of a mouse macrophage cell line, or is an embryonic cell.

37. The HCV infected cell of claim 35, wherein the cell is of a cell line derived from liver of an HCV infected individual.

38. A method for producing antibodies to HCV comprising administering to an.individual an isolated immunogenic polypeptide containing an HCV epitope in an amount sufficient to produce an immune response.

39. A method for producing antibodies to HCV comprising administering to an individual the polypeptide preparation of claim 11, wherein the preparation contains at least 1 immunogenic polypeptide, and the administering is of an amount sufficient to produce an immune response.

Schedule A2

Patent Claims (Final)

AU 600,650

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A purified and isolated polypeptide having the primary structural conformation and possessing a biological property as herein defined of naturally-occurring erythropoietin, and characterized by being the product of procaryotic or eucaryotic expression of an exogenous DNA sequence.

2. A polypeptide according to claim 1, further characterized by being free of association with any mammalian protein.

3. A polypeptide according to claim 1, wherein the exogenous DNA sequence is a cDNA sequence.

4. A polypeptide according to claim 1, wherein the exogenous DNA sequence is a manufactured DNA sequence.

5. A polypeptide according to claim 1, wherein the exogenous DNA sequence is a genomic DNA sequence.

6. A polypeptide according to claim 1, wherein the exogenous DNA sequence is carried on an autonomously replicating circular DNA plasmid or viral vector.

7. A polypeptide according to claim 1, possessing the primary structural conformation of human erythropoietin as set forth in Table VI.

8. A polypeptide according to claim 1, possessing the primary structural conformation of monkey erythropoietin as set forth in Table V.

9. A polypeptide according to claim 1, which has the immunological properties of naturally-occurring erythropoietin.

10. A polypeptide according to claim 1, which has the in vivo biological activity of naturally-occurring erythropoietin.

11. A polypeptide according to claim 1, which has the in vitro biological activity of naturally-occurring erythropoietin.

12. A polypeptide according to claim 1, further characterized by being covalently associated with a detectable label substance.

13. A polypeptide according to claim 12, wherein said detectable label is a radiolabel.

14. A purified and isolated DNA sequence encoding erythropoietin, said DNA sequence selected from the group consisting of:

(a) the DNA sequences set out in Tables V and VI; and

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(b) complementary sequences of the DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (a).

15. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 14 in a manner allowing the host cell to express said polypeptide product.

16. A polypeptide product of the expression of a DNA sequence of claim 14 in a procaryotic or eucaryotic host.

17. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

18. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding monkey erythropoietin.

19. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to any one of the claims 14, 17 or 18 in a manner allowing the host cell to express erythropoietin.

20. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to any one of claims 14, 17 or 18.

21. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 20.

22. A cDNA sequence according to claim 17.

23. A manufactured DNA sequence according to claim 14.

24. A manufactured DNA sequence according to claim 23 and including one or more codons preferred for expression in E. coli cells.

25. A manufactured DNA sequence according to claim 24, coding for expression of human species erythropoietin.

26. A manufactured DNA sequence according to claim 25, including the protein coding region set forth in Table XIV.

27. A manufactured DNA sequence according to claim 23 and including one or more codons preferred for expression in yeast cells.

28. A manufactured DNA sequence according to claim 27, coding for expression of human species erythropoietin.

29. A manufactured DNA sequence according to claim 28, including the protein coding region set forth in Table XXI.

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30. A DNA sequence according to claim 17 covalently associated with a detectable label substance.

31. A DNA sequence according to claim 30, wherein the detectable label is a radiolabel.

32. A single-strand DNA sequence according to claim 30.

33. A DNA sequence coding for a polypeptide or polypeptide analog of naturally-occurring erythropoietin.

34. A DNA sequence coding for [Phe^{15}]hEPO, [Phe^{49}]hEPO, [Phe^{145}]hEPO, [His^{7}]hEPO, [Asn^{2}des-Pro^{2} through Ile^{6}]hEPO, [des-Thr^{163} through Arg^{166}]hEPO or [Δ27-55]hEPO.

35. A DNA sequence according to claim 33, which is a manufactured sequence.

36. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 33 or claim 34.

37. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 36.

38. A polypeptide product of the expression in a procaryotic or eucaryotic host cell of a DNA sequence according to claim 17 or claim 33.

~~39. A non-naturally occurring glycoprotein product of the expression in a non-human~~ eucaryotic host cell of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing human bone marrow cells to increase production of reticulocytes and red blood cells ~~and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.~~

40. A procaryotic or eucaryotic vertebrate cell transformed or transfected with a DNA sequence according to any one of the claims 14, 17-19 or 22-35, said cell being capable of being propagated in vitro continuously and which upon growth in culture is capable of producing in the medium of its growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.

B+

41. A transformed or transfected vertebrate cell according to claim 40, capable of producing in excess of 500 U erythropoietin per 10^6 cells in 48 hours.

42. A transformed or transfected vertebrate cell according to claim 40, capable of producing in excess of 1,000 U erythropoietin per 10^6 cells in 48 hours.

43. A transformed or transfected vertebrate cell according to claim 40, being a mammalian or avian cell.

44. A transformed or transfected vertebrate cell according to claim 43, being a COS-1 cell or CHO cell.

45. A synthetic polypeptide having the continuous amino acid sequence as set forth in Table V and possessing a biological property as herein defined of naturally-occurring monkey erythropoietin.

46. A synthetic polypeptide having the continuous amino acid sequence as set forth in Table VI or a polypeptide selected from V-P-D-T-K-V-N-F-Y-A-W-K-R-M-E-V-G, K-E-A-I-S-P-P-D-A-A-S-A-A, V-Y-S-N-F-L-R-G-K-L-K-L-Y-T-G-E-A-C-R-T-G-D-R or peptide sequences set forth in Table VI which are delineated by intron sequences and which correspond to amino acid residues -23 to 26, 27 to 55, 56 to 115 or 116 to 166, and possessing a biological property as herein defined of naturally-occurring human erythropoietin.

47. A process for the production of a polypeptide having the primary structural conformation and possessing a biological property as herein defined of naturally-occurring erythropoietin, said process comprising:

growing, under suitable nutrient conditions, procaryotic or eucaryotic host cells transformed or transfected with a DNA vector according to claim 20 or claim 36, and isolating desired polypeptide products of the expression of DNA sequences in said vector.

48. An antibody substance characterised by immunoreactivity with erythropoietin and with a synthetic polypeptide having a primary structural conformation substantially duplicative of a continuous sequence of amino acid residues extant in a naturally-occurring erythropoietin, wherein the production of said antibody substance was induced by and the antibody substance is immunoreactive with a synthetic polypeptide having the amino acid sequence selected from:

V-P-D-T-K-V-N-F-Y-A-W-K-R-M-E-V-G

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K-E-A-I-S-P-P-D-A-A-S-A-A

V-Y-S-N-F-L-R-G-K-L-K-L-Y-T-G-E-A-C-R-T-G-D-R.

49. An antibody according to claim 48, which is a monoclonal antibody.

50. An antibody to claim 48, which is a polyclonal antibody.

51. A pharmaceutical composition comprising an effective amount of a polypeptide according to any one of claims 1, 16, 38 or 39, and a pharmaceutically acceptable diluent, adjuvant or carrier.

52. A method for providing erythropoietin therapy to a mammal comprising administering an effective amount of a polypeptide according to any one of claims 1, 16, 38 or 39.

53. A method according to claim 52, wherein the therapy comprises enhancing hematocrit levels.

54. A purified and isolated DNA sequence as set out in Table V or VI or the complementary strand of such a sequence.

55. A polypeptide product of the expression of a DNA sequence according to claim 54 in a procaryotic or eucaryotic host cell.

DATED this 18th day of March, 1996

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Schedule A3

Patent Claims (Final)

AU 686,004

Claims:

1. An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19.

2. An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a mutant BRCA1 polypeptide, said DNA containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No: 1 one or more mutations set forth in Tables 12, 12A and 14.

3. An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a polymorphic BRCA1 polypeptide, said DNA containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more polymorphisms set forth in Tables 18 and 19.

4. A nucleic acid probe wherein the nucleotide sequence is a portion of a nucleic acid as claimed in any one of claims 1 to 3 including a mutation or polymorphism compared to the nucleotide sequence set forth in SEQ.ID No: 1 selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19.

5. A replicative cloning vector which comprises an isolated DNA according to any one of claims 1 to 4 and a replicon operative in a host cell for said vector.

6. An expression vector which comprises an isolated DNA according to any one of claims 1 to 4 wherein the coding sequence for said mutant or polymorphic BRCA1 polypeptide is operably-linked to a promoter sequence capable of directing expression of said coding sequence in host cells for said vector.

7. Host cells transformed with a vector as claimed in claim 5 or claim 6.

8. A method of producing a mutant or polymorphic BRCA1 polypeptide compared to the BRCA1 polypeptide having the amino acid sequence set forth in SEQ.ID No:2 which comprises (i) culturing host cells as claimed in claim 7 containing an expression vector encoding said polypeptide under conditions suitable for production of said polypeptide and (ii) recovering said polypeptide.

9. A method as claimed in claim 8 which further comprises labelling the recovered polypeptide.

10. A preparation of a polypeptide substantially free of other proteins, said polypeptide being a mutant or polymorphic BRCA1 polypeptide compared to the BRCA1 polypeptide having the amino acid sequence set forth in SEQ.ID No:2 which is obtainable by expression of a nucleotide coding sequence derived from the nucleotide sequence set forth in SEQ.ID No:1 by incorporation of one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19.

11. A preparation of a polypeptide as claimed in claim 10 which is a mutant BRCA1 polypeptide obtainable by expression of a nucleotide coding sequence derived from the nucleotide sequence set forth in SEQ.ID No:1 by incorporation of a mutation set forth in Tables 12, 12A and 14.

12. A preparation of a polypeptide substantially free of other proteins, said polypeptide being an antigenic fragment of a polypeptide as defined in claim 10 or claim 11 having a mutation or polymorphism compared to the BRCA1 polypeptide having the amino acid sequence set forth in SEQ.ID No:2.

13. A preparation as claimed in any one of claims 10 to 12 wherein said polypeptide is labelled.

14. A polypeptide as defined in any one of claims 10 to 12 which is in the form of a fusion protein.

15. Use of a polypeptide as defined in any one of claims 10 to 12 and 14 as an immunogen for antibody production.

16. A use as claimed in claim 15 wherein one or more antibodies produced are subsequently labelled or bound to a solid support.

17. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germline alteration in the sequence of the BRCA 1 gene in a tissue sample of said subject compared to the nucleotide sequence set forth in SEQ.ID No:1 or a wild-tyle allelic variant thereof, said alteration indicating a predisposition to said cancer being selected from the mutations as set forth in Tables 12, 12A and 14.

18. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus, which comprises determining whether there is a mutation in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in SEQ.ID No.1 or a wild-type allelic variant thereof, said mutation being selected from the mutations as set forth in Tables 12, 12A and 14.

19. A method as claimed in claim 17 or claim 18 which comprises analyzing mRNA or protein of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele as defined in claim 1.

20. A method as claimed in claim 19 wherein the mRNA encoded by the BRCA1 gene in said sample is investigated.

21. A method as claimed in claim 20 wherein mRNA from said sample is contacted with a BRCA1 gene probe under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

22. A method as claimed in claim 17 or claim 18 wherein a BRCA1 gene probe is contacted with genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene and hybridization of said probe is determined.

23. A method as claimed in claim 21 or claim 22 wherein said probe is an allele-specific probe for a mutant BRCA1 allele as defined in claim 1.

24. A method as claimed in claim 17 or claim 18 which comprises determining whether there is a mutation in the BRCA1 gene in said sample by observing shifts in electrophoretic mobility of single-stranded DNA from said sample on non-denaturing polyacrylamide gels.

25. A method as claimed in claim 17 or claim 18 wherein all or part of the BRCA1 gene in said sample is amplified and the sequence of said amplified sequence is determined.

26. A method as claimed in claim 17 or claim 18 wherein oligonucleotide primers are employed which are specific for a mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

27. A method as claimed in claim 17 or claim 18 wherein all or part of the BRCA1 gene in said sample is cloned to produce a cloned sequence and the sequence of said cloned sequence is determined.

28. A method as claimed in any one of claims 17 to 20 which comprises determining whether there is a mismatch between molecules (1) BRCA1 gene genomic DNA or BRCA1 mRNA isolated from said sample, and (2) a nucleic acid probe complementary to human wild-type BRCA1 gene DNA, when molecules (1) and (2) are hybridized to each other to form a duplex.

29. A method as claimed in any one of claims 17 to 20 wherein amplification of BRCA1 gene sequences in said sample is carried out and hybridization of the amplified sequences to one or more nucleic acid probes which comprise a wild-type BRCA1 gene sequence or a mutant BRCA1 gene sequence as defined in claim 1 is determined.

30. A method as claimed in claim 17 or claim 18 which comprises determining *in situ* hybridization of the BRCA1 gene in said sample with one or more nucleic acid probes which comprise a wild-type BRCA1 gene sequence or a mutant BRCA1 gene sequence as defined in claim 1.

Schedule A4

Patent Claims (Final)

AU 2001265698

Claims

1. An isolated mammalian DNA molecule encoding a mutant γ-aminobutyric acid type A ($GABA_A$) receptor subunit, wherein a mutation event selected from the group consisting of point mutations, deletions, insertions and rearrangements has occurred and said mutation event disrupts the functioning of an assembled $GABA_A$ receptor, or an otherwise functional fragment or homologue thereof.

2. An isolated mammalian DNA molecule encoding a mutant γ-aminobutyric acid type A ($GABA_A$) receptor subunit, wherein a mutation event creates a phenotype of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity.

3. An isolated mammalian DNA molecule as claimed in claim 2 wherein the subunit is a $GABA_A$ gamma subunit.

4. An isolated mammalian DNA molecule as claimed in claim 3 wherein the gamma subunit is the gamma-2 subunit.

5. An isolated mammalian DNA molecule as claimed in claim 4 wherein said mutation event occurs in the nucleotides encoding an extracellular region of the gamma-2 subunit.

6. An isolated mammalian DNA molecule as claimed in claim 5 wherein said mutation event abolishes or reduces diazepam potentiation of the GABA response.

7. An isolated mammalian DNA molecule as claimed in claim 6 wherein said mutation event occurs in the nucleotides encoding a benzodiazepine binding domain.

8. An isolated mammalian DNA molecule as claimed in claim 7 wherein said mutation event occurs in the nucleotides encoding the large extracellular loop of the gamma-2 subunit.

9. An isolated mammalian DNA molecule as claimed in any one of claims 4 to 8 wherein the mutation is a point

mutation.

10. An isolated mammalian DNA molecule as claimed in claim 9 wherein the point mutation results in substitution of a highly conserved amino acid residue with another amino acid residue.

11. An isolated mammalian DNA molecule as claimed in claim 10 wherein said mutation event results in replacement of a highly conserved arginine at residue 43 of the mature gamma-2 subunit.

12. An isolated mammalian DNA molecule as claimed in claim 11 wherein said mutation event results in replacement of the highly conserved arginine with a glutamine.

13. An isolated mammalian DNA molecule as claimed in claim 12 wherein said mutation event is a G-A nucleotide substitution at position 471 of the gamma-2 subunit.

14. An isolated mammalian DNA molecule as claimed in claim 13 having the nucleotide sequence set forth in SEQ ID NO:1.

15. An isolated mammalian DNA molecule as claimed in any one of claims 1 to 13 in which one or more additional mutation events selected from the group consisting of point mutations, deletions, insertions and rearrangements have occurred.

16. An isolated mammalian DNA molecule as claimed in claim 15 wherein said one or more additional mutation events are point mutations which result in conservative amino acid substitutions.

17. An isolated mammalian DNA molecule comprising the nucleotide sequence set forth in SEQ ID NO:1.

18. An isolated mammalian DNA molecule consisting of the nucleotide sequence set forth in SEQ ID NO:1.

19. An isolated mammalian DNA molecule as claimed in claim 4 wherein said mutation event occurs in the large cytoplasmic loop between the third and fourth transmembrane domains of the $GABA_A$ gamma-2 subunit.

20. An isolated mammalian DNA molecule as claimed in claim 19 wherein said mutation event is a point mutation.

21. An isolated mammalian DNA molecule as claimed in claim 20 wherein said mutation event is a C→T nucleotide substitution at position 1394 of the gamma-2 subunit.

22. An isolated mammalian DNA molecule as claimed in claim 21 wherein said mutation event results in the introduction of a stop codon at position 351 of the encoded mature gamma-2 subunit protein.

23. An isolated mammalian DNA molecule as claimed in claim 22 which has the nucleotide sequence set forth in SEQ ID NO:2.

24. An isolated mammalian DNA molecule as claimed in any one of claims 19 to 22 wherein one or more additional mutation events selected from the group consisting of point mutations, deletions, insertions and rearrangements have occurred.

25. An isolated mammalian DNA molecule as claimed in claim 24 wherein said one or more additional mutation events are point mutations which result in conservative amino acid substitutions.

26. An isolated mammalian DNA molecule comprising the nucleotide sequence set forth in SEQ ID NO:2.

27. An isolated mammalian DNA molecule consisting of the nucleotide sequence set forth in SEQ ID NO:2.

28. An isolated mammalian DNA molecule as claimed in claim 2 wherein said mutation event occurs in a $GABA_A$ delta subunit.

29. An isolated mammalian DNA molecule as claimed in claim 28 wherein said mutation event is a point mutation.

30. An isolated mammalian DNA molecule as claimed in claim 29 wherein the point mutation results in replacement of an arginine residue at position 172 of the encoded mature protein.

31. An isolated mammalian DNA molecule as claimed in claim 30 wherein the arginine residue is replaced with a cysteine residue.

32. An isolated mammalian DNA molecule as claimed in claim 31 wherein said mutation event is a C→T nucleotide substitution at position 658 of the delta subunit.

33. An isolated mammalian DNA molecule as claimed in claim 32 is which the nucleotide sequence is as set forth in SEQ ID NO:3.

34. An isolated mammalian DNA molecule as set forth in any one of claims 30 to 32 in which one or more additional mutation events selected from the group consisting of point mutations, deletions, insertions and rearrangements have occurred.

35. An isolated mammalian DNA molecule as claimed in claim 34 wherein said one or more additional mutation events are point mutations which result in conservative amino acid substitutions.

36. An isolated mammalian DNA molecule comprising the nucleotide sequence set forth in SEQ ID NO:3.

37. An isolated mammalian DNA molecule consisting of the nucleotide sequence set forth in SEQ ID NO:3.

38. An isolated mammalian polypeptide, said polypeptide being a mutant γ-aminobutyric acid type A ($GABA_A$) receptor subunit, wherein a mutation event selected from the group consisting of substitutions, deletions, truncations, insertions and rearrangements has occurred and said mutation event disrupts the functioning of an assembled $GABA_A$ receptor, or an otherwise functional fragment or homologue thereof.

39. An isolated mammalian polypeptide, said polypeptide being a mutant γ-aminobutyric acid type A ($GABA_A$) receptor subunit, wherein a mutation event creates a phenotype of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or

migraine and/or obesity.

40. An isolated mammalian polypeptide as claimed in claim 39 wherein the subunit is a $GABA_A$ gamma subunit.

41. An isolated mammalian polypeptide as claimed in claim 40 wherein the gamma subunit is the gamma-2 subunit.

42. An isolated mammalian polypeptide as claimed in claim 41 wherein said mutation event occurs in an extracellular region of the gamma-2 subunit.

43. An isolated mammalian polypeptide as claimed in claim 42 wherein said mutation event abolishes or reduces diazepam potentiation of the GABA response.

44. An isolated mammalian polypeptide as claimed in claim 43 wherein said mutation event occurs in a benzodiazepine binding domain.

45. An isolated mammalian polypeptide as claimed in claim 44 wherein said mutation event occurs in the large extracellular loop of the gamma-2 subunit.

46. An isolated mammalian polypeptide as claimed in any one of claims 40 to 45 wherein said mutation event is a substitution.

47. An isolated mammalian polypeptide as claimed in claim 46 wherein said mutation event results in replacement of a highly conserved arginine at residue 43 of the mature gamma-2 subunit.

48. An isolated mammalian polypeptide as claimed in claim 47 wherein said mutation event results in replacement of the highly conserved arginine with a glutamine.

49. An isolated mammalian polypeptide as claimed in claim 47 having the amino acid sequence set forth in SEQ ID NO:4.

50. An isolated mammalian polypeptide as claimed in claim 48 in which one or more additional mutation events selected from the group consisting of substitutions, deletions, truncations, insertions and rearrangements have occurred.

51. An isolated mammalian polypeptide as claimed in claim 50 wherein said one or more mutation events are

conservative substitutions.

52. An isolated mammalian polypeptide comprising the amino acid sequence set forth in SEQ ID NO:4.

53. An isolated mammalian polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:4.

54. An isolated mammalian polypeptide as claimed in claim 40 in which said mutation event occurs in a large cytoplasmic loop between the third and fourth membrane spanning domain of the gamma-2 subunit protein.

55. An isolated mammalian polypeptide as claimed in claim 54 wherein said mutation event is a truncation.

56. An isolated mammalian polypeptide as claimed in claim 55 wherein the deletion is from position 351 of the mature gamma-2 subunit.

57. An isolated mammalian polypeptide as claimed in claim 56 having the amino acid sequence set forth in SEQ ID NO:5.

58. An isolated mammalian polypeptide as claimed in claim 57 in which one or more additional mutation events selected from the group consisting of substitutions, deletions, truncations, insertions and rearrangements have occurred.

59. An isolated mammalian polypeptide as claimed in claim 58 wherein said one or more mutation events are conservative substitutions.

60. An isolated mammalian polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:5.

61. An isolated mammalian polypeptide as claimed in claim 39 wherein the subunit is a $GABA_A$ delta subunit.

62. An isolated mammalian polypeptide as claimed in claim 61 wherein said mutation event occurs in an extracellular region of the $GABA_A$ delta subunit.

63. An isolated mammalian polypeptide as claimed in claim 62 wherein said mutation event occurs in the large extracellular loop of the $GABA_A$ delta subunit.

64. An isolated mammalian polypeptide as claimed in any

one of claims 61 to 63 wherein said mutation event is a substitution.

65. An isolated mammalian polypeptide as claimed in claim 64 wherein said mutation event results in replacement of an arginine at residue 172 of the mature delta subunit.

66. An isolated mammalian polypeptide as claimed in claim 65 wherein said mutation event results in replacement of an arginine with a cysteine.

67. An isolated mammalian polypeptide as claimed in claim 66 having the amino acid sequence set forth in SEQ ID NO:6.

68. An isolated mammalian polypeptide as claimed in any one of claims 62 to 66 in which one or more additional mutation events selected from the group consisting of substitutions, deletions, truncations, insertions and rearrangements have occurred.

69. An isolated mammalian polypeptide as claimed in claim 69 wherein said one or more mutation events are conservative substitutions.

70. An isolated mammalian polypeptide comprising the amino acid sequence in SEQ ID NO:6.

71. An isolated mammalian polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:6.

72. An isolated mammalian polypeptide, said polypeptide being an assembled $GABA_A$ receptor including a subunit as claimed in any one of claims 38 to 71.

73. A method of preparing a polypeptide, said polypeptide being a mutant subunit of a $GABA_A$ receptor, comprising the steps of:

(1) culturing host cells transfected with an expression vector comprising a DNA molecule as claimed in any one of claims 1 to 37 under conditions effective for polypeptide production; and

(2) harvesting the mutant $GABA_A$ receptor subunit.

74. A method as claimed in claim 73 further comprising

the step of allowing the mutant $GABA_A$ subunit and other $GABA_A$ subunits to assemble into a mammalian $GABA_A$ receptor and harvesting the assembled receptor.

75. An antibody which is immunologically reactive with a polypeptide as defined in any one of claims 39 to 73, but not with a wild-type $GABA_A$ receptor or subunit thereof.

76. An antibody as claimed in claim 75 wherein the antibody is selected from the group consisting of polyclonal, monoclonal, chimeric, single chain antibodies and antibody fragments such as F(ab')2 and Fab.

77. A method of treating epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity, comprising the step of administering a wild-type $GABA_A$ receptor or receptor subunit and/or an isolated DNA molecule encoding a wild-type $GABA_A$ receptor or receptor subunit to replace $GABA_A$ receptor activity in a patient in need of such treatment.

78. A method as claimed in claim 77 wherein receptor function is restored through the incorporation of truncated $GABA_A$ receptors into the cell membrane.

79. A method as claimed in claim 77 wherein a wild-type $GABA_A$ receptor or a $GABA_A$ receptor subunit is introduced by gene therapy.

80. A method as claimed in claim 79 wherein a wild-type $GABA_A$ gamma or delta subunit is introduced.

81. The use of a wild-type $GABA_A$ receptor or receptor subunit and/or an isolated DNA molecule encoding a wild-type $GABA_A$ receptor or receptor subunit in the manufacture of a medicament for the treatment of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity.

82. A method of treating epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity, comprising administering an antibody to a mutant $GABA_A$ receptor as defined in claim 72.

83. A method as claimed in claim 82 wherein the antibody is selected from the group comprising of polyclonal antibodies, monoclonal antibodies, chimeric, single chain antibodies and antibody fragments such as F(ab')2 and Fab.

84. The use of an antibody to a mutant $GABA_A$ receptor as defined in claim 72 in the manufacture of a medicament for the treatment of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity.

85. A method of treating epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity, comprising administering a DNA molecule which is the complement of any one of the isolated mammalian DNA molecules defined in claims 1 to 37 to a subject in need of such treatment.

86. The use of a DNA molecule which is a complement of an isolated mammalian DNA molecule as defined in any one of claims 1 to 37 in the manufacture of a medicament for the treatment of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity.

87. The use of an isolated mammalian DNA molecule as claimed in any one of claims 1 to 37 for the diagnosis of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or

migraine and/or obesity.

88. The use of a polypeptide as defined in any one of claims 38 to 72 in the diagnosis of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity.

89. The use of an antibody as claimed in either claim 75 or 76 in the diagnosis of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity.

90. A method for the diagnosis of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity, comprising the steps of:

(1) obtaining DNA from a subject suspected of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or migraine and/or obesity and/or Alzheimer's disease; and

(2) comparing the DNA sequence of a subunit of the $GABA_A$ receptor of said DNA to the DNA sequence of the corresponding subunit of the wild-type $GABA_A$ receptor.

91. A method as claimed in claim 90 wherein each DNA fragment is sequenced and the sequences compared.

92. A method as claimed in claim 90 wherein the DNA fragments are subjected to restriction enzyme analysis.

93. A method as claimed in claim 90 wherein the DNA fragments are subjected to SSCP analysis.

94. A method for the diagnosis of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity, comprising the steps of:

(1) obtaining a $GABA_A$ receptor from a subject

suspected of epilepsy and/or anxiety and/or manic depression and/or phobic obsessive symptoms and/or Alzheimer's disease and/or schizophrenia and/or migraine and/or obesity; and

(2) comparing a subunit of said receptor with the corresponding subunit of the wild-type $GABA_A$ receptor.

95. Use of a polypeptide as defined in any one of claims 38 to 72 in the screening of candidate pharmaceutical agents.

96. Use as claimed in claim 95 wherein high-throughput screening techniques are employed.

97. A genetically modified non-human animal transformed with an isolated DNA molecule as defined in any one of claims 1 to 37.

98. A genetically modified non-human animal as claimed in claim 97 in which the animal is selected from the group consisting of rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs and non-human primates such as monkeys and chimpanzees.

99. The use of a genetically modified non-human animal as claimed in either one of claims 98 or 99 in the screening of candidate pharmaceutical compounds.

100. The use of a host cell transformed with a DNA molecule as claimed in any one of claims 1 to 37 in the screening of candidate pharmaceuticals.

101. A host cell transformed with a DNA molecule as claimed in any one of claims 1 to 37.

102. An expression vector comprising a DNA molecule as claimed in any one of claims 1 to 37.

Schedule A5

Patent Claims (Final)

AU 2004200978

2004200978 01 Nov 2005

Claims

1. A method for determining the likelihood that a patient suspected of SMEI does or does not have SMEI, comprising:

(1) testing a patient sample for the existence of an alteration in the SCN1A gene of the patient, including in a regulatory region of the gene;

(2) (a) terminating the process with an inconclusive diagnosis if no alteration is found; or

(b) identifying the alteration;

(3) ascertaining whether the alteration, when one is detected, is known to be SMEI associated or non-SMEI associated or is not known to be either;

wherein (a) a diagnosis which will indicate a high probability of SMEI is made where the alteration is known to be SMEI associated;

(b) a diagnosis which will indicate a low probability of SMEI is made where the alteration is non-SMEI associated; or

(c) further analysis is undertaken to establish whether the alteration is a SMEI associated or a non-SMEI associated alteration.

2. A method as claimed in claim 1 wherein the alteration is one of those alterations identified as SMEI associated in Table 3.

3. A method as claimed in claim 1 wherein the alteration is one identified of those alterations identified as non-SMEI associated in Table 3.

4. A method as claimed in claim 1 wherein the likelihood that the alteration is a SMEI associated alteration is established through:

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considering genetic data for parents and/or relatives; and

establishing whether the alteration has arisen *de novo* or is inherited.

5. A method as claimed in claim 4 further comprising establishing whether the alteration would result in a major disruption to the protein.

6. A method as claimed in claim 5 wherein the alteration is a truncating mutation.

7. A method as claimed in any one of claims 4 to 6 comprising establishing a diagnosis which will indicate a low probability of SMEI in the case of an inherited mutation and indicate a high probability of SMEI in the case of a *de novo* mutation, and a very high probability of SMEI where a *de novo* mutation would result in a major disruption to the protein.

8. A method as claimed in any one of claims 1 to 7 comprising performing one or more assays to test for the existence of an SCN1A alteration and to identify the nature of the alteration.

9. A method as claimed in claim 8 comprising:

(1) performing one or more assays to test for the existence of an alteration in the SCN1A gene of the patient; and, if the results indicate the existence of an alteration in the SCN1A gene,

(2) performing one or more assays to identify the nature of the SCN1A alteration.

10. A method as claimed in claim 8 or 9 wherein one of the assays is a DNA hybridisation assay.

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11. A method as claimed in claim 10 wherein an SCN1A gene probe, an SCN1A exon-specific probe, or an SCN1A allele specific probe is hybridised to genomic DNA isolated from said patient.

12. A method as claimed in claim 8 or 9 wherein one of the assays is high performance liquid chromatography.

13. A method as claimed in claim 8 or 9 wherein one of the assays is an electrophoretic assay.

14. A method as claimed in claim 8 or 9 wherein the sample DNA to be tested is quantitatively amplified for at least one exon of the SCN1A gene to produce amplified fragments and the length of the amplification products for each amplified exon is compared to the length of the amplification products obtained when a wild-type SCN1A gene is amplified using the same primers, whereby differences in length between an amplified sample exon and the corresponding amplified wild-type exon reflect the occurrence of a truncating alteration in the sample SCN1A gene.

15. A method as claimed in claim 8 or 9 wherein one of the assays incorporates DNA amplification using SCN1A allele specific oligonucleotides.

16. A method as claimed in claim 8 or 9 wherein one of the assays is SSCP analysis.

17. A method as claimed in claim 8 or 9 wherein one of the assays is RNase protection.

18. A method as claimed in claim 8 or 9 wherein one of the assays is DGGE.

19. A method as claimed in claim 8 or 9 wherein one of the assays is an enzymatic assay.

20. A method as claimed in claim 19 wherein said assay incorporates the use of MutS.

21. A method as claimed in claim 8 or 9 wherein one of the assays examines the electrophoretic mobility of the SCN1A protein of the patient.

22. A method as claimed in claim 8 or 9 wherein one of the assays is an immunoassay.

23. A method as claimed in claim 8 or 9 wherein one of the assays is DNA sequencing.

24. A method for determining the likelihood that a patient suspected of SMEI does or does not have SMEI, comprising:

(1) testing a patient sample for the existence of an alteration in the SCN1A gene of the patient, including in a regulatory region of the gene;

(2) (a) terminating the process with an inconclusive diagnosis if no alteration is found; or

(b) identifying the alteration;

(3) ascertaining whether the alteration, when one is detected, is as laid out in Table 3 as SMEI associated or non-SMEI associated, or is not known to be either;

wherein (a) a diagnosis which will indicate a high probability of SMEI is established if a SMEI associated alteration as laid out in Table 3 is identified,

(b) a diagnosis which will indicate a low probability of SMEI is established if a non-SMEI associated alteration as laid out in Table 3 is identified, or

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(c) further analysis is undertaken to establish if the alteration is a SMEI associated or a non-SMEI associated alteration.

25. A method of determining the appropriate treatment for a SMEI patient comprising performing one or more of the methods claimed in any one claims 1 to 24 and correlating the diagnosis reached with known indications and contra-indications for SMEI patients.

26. A method of determining the likelihood of adverse results from treatments of a SMEI patient including drug treatments and vaccinations comprising performing one or more of the methods as claimed in any one of claims 1 to 24 and correlating the diagnosis reached with known indications and contra-indications for SMEI patients.

27. An isolated nucleic acid molecule encoding an altered SCN1A subunit of a mammalian voltage-gated sodium channel, wherein the alteration gives rise to an SMEI phenotype and has the sequence set forth in any one of SEQ ID NOS: 1-25.

28. An isolated nucleic acid molecule encoding an altered SCN1A subunit of a mammalian voltage-gated sodium channel, wherein the alteration gives rise to a non-SMEI epilepsy phenotype and has the sequence set forth in one of SEQ ID NOS: 49-53.

29. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in any one of SEQ ID NOs: 1-25, 49-53.

30. An isolated nucleic acid molecule consisting of the nucleotide sequence set forth in any one of SEQ ID NOs: 1-25, 49-53.

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31. An expression vector comprising a nucleic acid molecule as claimed in any one of claims 27 to 30.

32. A cell comprising a nucleic acid molecule as claimed in any one of claims 27 to 30.

33. A genetically modified non-human animal comprising a nucleic acid molecule as claimed in any one of claims 27 to 30.

34. A genetically modified non-human animal as claimed in claim 33 in which the animal is selected from the group consisting of rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs and non-human primates such as monkeys and chimpanzees.

35. An isolated polypeptide, said polypeptide being an altered SCN1A subunit of a mammalian voltage-gated sodium channel, wherein the polypeptide has the amino acid sequence set forth in one of SEQ ID NOS: 26-48 and the alteration gives rise to an SMEI phenotype.

36. An isolated polypeptide, said polypeptide being an altered SCN1A subunit of a mammalian voltage-gated sodium channel, wherein the polypeptide has the amino acid sequence set forth in one of SEQ ID NOS: 54-58 and the alteration gives rise to a non-SMEI epilepsy phenotype.

37. An isolated polypeptide comprising the amino acid sequence set forth in any one of SEQ ID NOs: 26-48, 54-58.

38. An isolated polypeptide consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 26-48, 54-58.

39. A sodium channel that incorporates an SCN1A subunit as claimed in any one of claims 35 to 38.

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40. A method of preparing a polypeptide comprising the steps of:

1) culturing a cell as claimed in claim 32 under conditions effective for polypeptide production; and

2) harvesting the polypeptide.

41. A polypeptide prepared by the method of claim 40.

42. An antibody which is specific for an isolated polypeptide as claimed in any one of claims 35 to 38 or 41, said polypeptide being an altered SCN1A subunit of a mammalian voltage-gated sodium channel, or a sodium channel as claimed in claim 39.

43. An antibody as claimed in claim 42 which is selected from the group consisting of a monoclonal antibody, a humanised antibody, a chimeric antibody or an antibody fragment including a Fab fragment, (Fab')2 fragment, Fv fragment, single chain antibodies and single domain antibodies.

44. The use of a nucleic acid molecule as claimed in any one of claims 27 to 30 for the screening of candidate pharmaceutical compounds.

45. The use of a polypeptide as claimed in any one of claims 35 to 38 or 41, a sodium channel as claimed in claim 39, or an antibody as claimed in claim 42 or 43 for the screening of candidate pharmaceutical compounds.

46. The use of genetically modified non-human animal as claimed in claim 33 or 34 or a cell as claimed in claim 32 in the screening of candidate pharmaceutical compounds.

47. A method of treating epilepsy, including SMEI, comprising administering a selective antagonist, agonist or modulator of a polypeptide as claimed in any one of

2004200978 01 Nov 2005

claims 35 to 38, or a sodium channel as claimed in claim 39 to a patient in need of such treatment.

48. The use of a selective antagonist, agonist or modulator of a polypeptide as claimed in any one of claims 35 to 38, or a sodium channel as claimed in claim 39 in the manufacture of a medicament for the treatment of epilepsy, including SMEI.

49. A method of treating epilepsy, including SMEI, comprising administering an isolated nucleic acid molecule which is the complement (antisense) of a nucleic acid molecule as claimed in any one of claims 27 to 30 and which encodes an RNA molecule that hybridizes with the mRNA encoding an altered SCN1A protein to a subject in need of such treatment.

50. The use of an isolated nucleic acid molecule which is the complement (antisense) of a nucleic acid molecule as claimed in any one of claims 27 to 30 and which encodes an RNA molecule that hybridizes with the mRNA encoding an altered SCN1A polypeptide in the manufacture of a medicament for the treatment of epilepsy, including SMEI.

51. A method of treating epilepsy, including SMEI, comprising administration of an antibody as claimed in claim 42 or 43.

52. The use of an antibody as claimed in claim 42 or 43 in the manufacture of a medicament for the treatment of epilepsy, including SMEI.

53. A method of treating epilepsy, including SMEI, comprising administering an antibody, as claimed in claim 42 or 43, administration of an agonist, antagonist or modulator of a polypeptide as claimed in any one of claims 35 to 38, or a sodium channel as claimed in claim 39, or

2004200978 01 Nov 2005

administration of a DNA molecule which is the complement of a nucleic acid molecule as claimed in any one of claims 27 to 30 and which encodes an RNA molecule that hybridizes with the mRNA encoding an altered SCN1A protein, in combination with administration of the wild-type SCN1A, to a subject in need of such treatment.

54. The use of an antibody, as claimed in claim 42 or 43, use of an agonist, antagonist or modulator of a polypeptide as claimed in any one of claims 35 to 38, or a sodium channel as claimed in claim 39, or use of a DNA molecule which is the complement of a nucleic acid molecule as claimed in any one of claims 27 to 30 and which encodes an RNA molecule that hybridizes with the mRNA encoding an altered SCN1A protein, in combination with the use of the wild-type SCN1A, in the manufacture of a medicament for the treatment of epilepsy, including SMEI.

Dated this 1st day of November 2005
BIONOMICS LIMITED
By their Patent Attorneys
GRIFFITH HACK
Fellows Institute of Patent and
Trade Mark Attorneys of Australia

H:\maraR\Keep\Speci\P52305 1/11/2005

Schedule A6

Patent Claims (Final)

AU 2002048844

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating hemophilia in a mammal comprising:

(a) providing a recombinant adeno-associated virus vector (rAAV), said rAAV comprising a nucleic acid encoding Factor IX operably linked to an expression control element; and

(b) administering an amount of said rAAV to a mammal wherein the Factor IX is expressed at levels having a therapeutic effect on said mammal and wherein said therapeutic effect is an increase in coagulation of blood.

2. The method of claim 1, wherein said recombinant adeno-associated virus vector is administered by injecting said vector into at least two sites in the mammal.

3. The method of claim 1, wherein said recombinant adeno-virus vector is administrated at a dose of between about 1×10^8 to about 5×10^{16} viral vector genomes per mammal.

4. The method of claim 1, wherein said mammal is a human and said Factor IX is a human Factor IX.

5. The method of claim 1, wherein said expression control element is selected from the group consisting of a cytomegalovirus immediate early promoter/enhancer, a skeletal muscle actin promoter and a muscle creatine kinase promoter/enhancer.

6. The method of claim 1, wherein said vector further comprises a portion of intron 1 of a Factor IX gene.

7. The method of claim 1, wherein said nucleic acid encoding Factor IX comprises a mutation which reduces binding of Factor IX encoded thereby to collagen IV as compared to a Factor IX lacking the mutation, wherein the mutation replaced a lysine residue with an alanine residue in the fifth amino acid position from the beginning of mature Factor IX.

8. The method of claim 1, wherein said mammal is a human.

9. The method of claim 1, wherein the administering is to a muscle tissue of the mammal.

10. The method of claim 2, wherein said recombinant adeno-associated virus vector is administered by injecting said vector into at least six sites in the mammal.

11. The method of claim 6, wherein said portion of intron 1 of a Factor IX gene is from about 0.3 kb to about 1.7.

12. Use of a composition comprising a recombinant adeno-associated virus vector (rAAV), said rAAV comprising a nucleic acid encoding Factor IX operably linked to an expression control element; and a pharmaceutically acceptable carrier, in the manufacture of a medicament for the treatment of haemophilia in a mammal.

acceptable carrier, in the manufacture of a medicament for the treatment of haemophilia in a mammal.

13. The use according to claim 12, wherein said virus comprising said recombinant adeno-associated virus vector is administered by injecting said vector into at least two sites in the mammal.

14. The use according to claim 13, wherein said virus comprising said recombinant adeno-associated virus vector is administered by injecting said vector into at least six sites in the mammal.

15. The use according to claim 12, wherein said virus comprising said recombinant adeno-virus vector is administered at a dose of between about 1×10^8 to about 5×10^{16} viral vector genomes per mammal.

16. The use according to claim 12, wherein said Factor IX is a human Factor IX.

17. The use according to claim 12, wherein said expression control element is selected from the group consisting of a cytomegalovirus immediate early promoter/enhancer, a skeletal muscle actin promoter and a muscle creatine kinase promoter/enhancer.

18. The use according to claim 12, wherein said vector further comprises a portion of intron 1 of a Factor IX gene.

19. The use according to claim 18, wherein said portion of intron 1 of a Factor IX gene is from about 0.3 kb to about 1.7 kb in length.

20. The use according to claim 12, wherein said nucleic acid encoding Factor IX comprises a mutation which reduces binding of Factor IX encoded thereby to collagen IV as compared to a Factor IX lacking the mutation, wherein the mutation replaces a lysine residue with an alanine residue in the fifth amino acid position from the beginning of mature Factor IX.

21. The use according to claim 12, wherein said mammal is a human.

22. The use according to claim 12, wherein the administering is to a muscle tissue of the mammal.

23. The method of claim 1, wherein said virus is not significantly contaminated by wild-type AAV.

24. The use of claim 12, wherein said composition is not significantly contaminated by wild-type AAV.

25. The method of claim 1, wherein said virus comprises less than 1 infectious unit of wild-type AAV per 10^9 genomes of AAV-F.IX.

26. The use of claim 12, wherein said composition comprises less than 1 infectious unit of wild-type AAV per 10^9 genomes of AAV-F.IX.

27. A method according to any one of claims 1 to 11 and 23 to 25, substantially as hereinbefore described with reference to the examples.

28. Use according to any one of claims 12 to 22 and 26, substantially as hereinbefore described with reference to the examples.

Dated this eleventh day of November 2004

The Children's Hospital of Philadelphia
Patent Attorneys for the Applicant:

F B RICE & CO

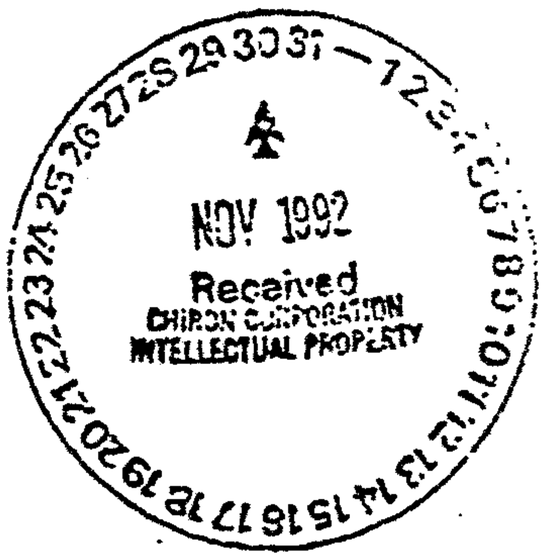
5

Schedule B1

Abbott Internal Memorandum

25/11/1992

Memo #WGG921125.1
November 25, 1992



CHIRON CORPORATION
INTERNAL MEMORANDUM

TO: Bob Blackburn

FROM: Bill Gerber Bill

CC: Pierre Cassigneul
Jack Goldstein
Ed Penhoet

SUBJECT: Abbott Patent Requests

Marcia Thomas, the newly-appointed vice president of Abbott's Diagnostics Division, visited the other day. Among the issues high on their list was patent prosecution. They were particularly interested in the European situation, where Murex' ELISA HCV test was recently approved by the Paul Ehrlich Institute, and Behring has introduced an HCV ELISA test. They are also seeing disturbing signs of loss of market share and price erosion from the increasingly large numbers of competitors. Their experience is similar to Ortho's. Is there anything we can do to speed approval at the EPO?

They also brought up Japan, making the same points that Hiro Hoketsu did in his letter. I appreciate your update on that situation, and will anticipate that we will have approval or be involved in an appeal in the first quarter of '93.

In Australia, Murex won the HCV business at Sydney and Hobart blood banks: a total of 600,000 draws per year. They bid $1.50 per test lower than Abbott of Ortho. The Melbourne, Perth and Adelaide blood centers are out for bid, and Murex is bidding at those sites as well. Marcia asked if you would be willing to write a letter to the Directors of those centers, informing them of our patent application, and of the probability if the patent issues that Murex would have to withdraw its product from the market. I told her that we cannot say anything that could be construed as a threat by Murex, and that what we could say might not be terribly helpful, but she would like us to do our best.

The names and addresses of the individuals are attached. Please let me know what we can do. Thanks.

Schedule B2

Chiron letter to Dr Pat Coglin
22/01/1993

CHIRON

22 January 1993

Dr. Pat Coghlan
Melbourne Blood Transfusion Service
Cnr Kavanagh and Ralston Streets
SOUTH MELBOURNE VIC 3205
AUSTRALIA

Dear Dr. Coughlan:

We understand that you are accepting tenders for the supply of HCV immunodiagnostics kits. We would like to call to your attention Chiron's Australian patent no. 624105, which broadly covers HCV immunodiagnostic kits and methods, as well as Chiron's pending Australian patent application nos. 52783/90 and 76510/91, directed to improved HCV immunodiagnostics.

The only suppliers of HCV immunodiagnostics licensed by Chiron are Ortho Diagnostic Systems and Abbott Laboratories. Therefore, we ask you to limit your consideration to these authorized suppliers. Thank you in advance for your cooperation in this matter.

Sincerely,

Robert P. Blackburn
Vice President & Chief Patent Counsel

RPB:gmr

CHIRON CORPORATION • 4560 Horton Street • Emeryville, CA • 94608-2916 • 510-655-8730
LAW DEPARTMENT • General Fax: 510-654-5360 • Intellectual Property Fax: 510-655-3542

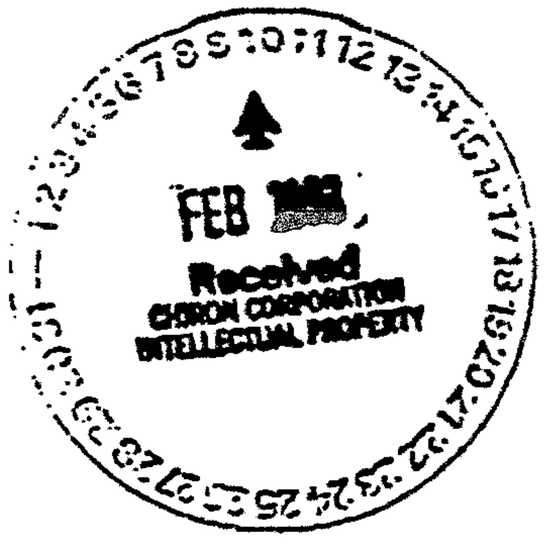
Schedule B3

South Australian Blood Transfusion Service letter to Chiron

03/02/1993

AUSTRALIAN RED CROSS
BLOOD TRANSFUSION SERVICE
South Australian Division

301 Pirie Street, Adelaide, SA 5000
Telephone: (08) 223 1333
Facsimile: (08) 223 7280
International Code 618 -



Ref: RB:dc/39

3 February 1993

Mr Robert P Blackburn
Vice President & Chief Patent Counsel
Chiron Corporation
Law Department
4560 Horton Street
EMERYVILLE CA 94608-2916

Dear Mr Blackburn,

Thank you for your letter of 22 January 1993. It is helpful to have the appropriate patent numbers available for reference should this be necessary.

After discussion of all of the factors involved, including the Chiron patents, this Service has entered into an arrangement with Abbott to continue to supply HCV immunodiagnostic material.

Yours sincerely

Prof Robert Beal
DIRECTOR

p.c. Mr P Sandeman, Metropolitan Division, SAHC.

Schedule B4

Abbott Facsimile to Mr Robert Blackburn
12/02/1994

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aaaaa a
a a
aaaaaaaaa

Facsimile Transmission

ABBOTT DIAGNOSTICS DIVISION -- AUSTRALIA
Marketing
142 Wicks Road,North Ryde,NSW,2113
P.O.Box 394,North Ryde,NSW,2113
Australia

Telephone: (ISD-61 2) 8571066

Facsimile: (ISD-61 2) 8571122

TO: ROBERT P. BLACKBURN

PAGES SENT: 2

FROM: JOHN RUBERRY

RE: UK INJUNCTION AGAINST MUREX

DATE: 12/02/94

Thank you for your reponse regarding the above issue. Obviously we are ecstatic with the result of the court case, congratulations!

We are extremely keen to take up your offer to write/fax to the appropriate Blood Bank Directors with regards to the outcome of the court case against Murex. In particular, would you be able to include in your correspondance the comment you made in your message to me, viz. "Murex's manufacturing plant has been shut down and they can no longer supply kits from the UK".

The list of Blood Banks and fax numbers are attached.

This communication to these Blood Banks coming directly from CHIRON, would be of significant benefit to us, in that ABBOTT will be seen to be at 'arms length' and behaving in an professional manner.

Once again, if you could fax your communicade the the Directors as a matter of urgency, we will be in a strong position to reclaim from MUREX any lost HCV business, before MUREX have a chance to impliment any "recovery strategy" they may be working on.

This urgency is highlighted by the fact that Melbourne, Adelaide, Perth and Sydney are all right in the middle of their review processes to award new contracts for next year's supply of screening tests. These Blood Banks represent in excess of 75% of the Australian market.

I look forward to your response.

Best Regards,

JOHN RUBERRY.

Dr Anthony Keller	Director Red Cross Blood Bank 290 Wellington Street Perth WA 6000	Fax: 09 325 9930
Dr Gordon Whyte	Director Red Cross Blood Bank Cnr Kavanagh & Balston Streets South Melbourne VIC 3205	Fax: 03 686 1768
Professor Robert Beal	Director Australian Red Cross Blood Transfusion Service 301 Pirie Street Adelaide SA 5000	Fax: 08 223 7280
Dr Brenton Wylie	Chief Executive Officer (BTS Director) Red Cross Blood Transfusion Service 153 Clarence Street Sydney NSW 2000	Fax: 02 229 4372
Dr Ian Young	Director Red Cross Blood Transfusion Service 480 Queen Street Brisbane QLD 4000	Fax: 07 832 6025
Dr Richard Kimber	Chairman of National Blood Transfusion Committee C/- Institute Medical & Veterinary Science Frome Road Adelaide SA 5000	Fax: 08 232 4690
Dr J T Kennedy	Medical Director Blood Transfusion Service 44 Melville Street Hobart TAS 7001	Fax: 002 352820

Schedule B5

Chiron Corporation Press Release
10/05/1988

RELEASE DATE: IMMEDIATE

CONTACT: Ginger Rosenberg
Associate Director, Marketing and
Business Development
Chiron Corporation
(415) 655-8730

or

Larry Kurtz
Vice President, Group Manager
Burson-Marsteller
(415) 392-9200

CHIRON CLONES HEPATITIS NON-A, NON-B VIRUS WHICH MAY ALLOW SCREENING FOR PREVIOUSLY UNDETECTABLE DISEASE

WASHINGTON, D.C., May 10, 1988 -- Scientists at Chiron Corporation (NASDAQ:CHIR) have identified, cloned and expressed proteins from a long-sought blood-borne hepatitis non-A, non-B virus, and have developed a prototype immunoassay that may lead to a screening test for hepatitis non-A, non-B antibodies, the company announced here today.

The research was carried out in part under the auspices of The Biocine Company", a joint venture of Chiron and Ciba-Geigy, which is responsible for researching, developing, manufacturing and marketing any vaccine, and with support from its partner Ortho Diagnostic Systems, a subsidiary of Johnson & Johnson, which will market any immuno-diagnostic products which result.

Despite widespread, intensive research efforts dating back more than 15 years, neither the virus nor the antibodies from the virus have been identified, and thus this serious disease has been transmitted partially through blood transfusions. Now that the virus has been discovered, work on a vaccine can begin.

-more-

Blood-borne hepatitis non-A, non-B is another major type of hepatitis, different from hepatitis A and hepatitis B, the viruses of which have previously been identified. Blood-borne hepatitis non-A, non-B is transmitted through contaminated blood or blood products, via blood transfusions or other close personal contact.

In the acute form, from which patients may fully recover, symptoms can range from mild to severe jaundice, fever, nausea, loss of appetite and fatigue. In the chronic form, infected patients at high frequency develop chronic liver disease, including cirrhosis.

Prior to 1986, according to National Institutes of Health estimates, up to 10 percent of the three million patients receiving transfusions annually in the U.S. were infected by blood-borne hepatitis non-A, non-B. Some 50 percent of those infected developed chronic hepatitis, and 20 percent of those, or 30,000 people each year, eventually developed cirrhosis of the liver.

Blood banks in the U.S. currently screen for hepatitis B with a specific immunoassay. In 1987, blood banks began screening to eliminate a portion of non-A, non-B infected blood using two tests that substitute for actual identification of the virus. The first test screens for hepatitis B anticore antibodies to identify people at high risk; the second, called ALT, indicates liver damage.

This surrogate testing has reduced the incidence of post-transfusion hepatitis non-A, non-B by 40 to 60 percent. Still, 90 to 95 percent of transfusion-related hepatitis is caused by the blood-borne non-A, non-B virus and almost 1,500 people each week receiving transfusions in the U.S. contract chronic hepatitis non-A, non-B.

"Solving blood-borne hepatitis non-A, non-B has been one of the toughest challenges in the world of infectious disease," said Edward E. Penhoet, president and chief executive officer at Chiron. "Our discovery and subsequent work is a significant first step that we expect will have major impact for the millions of people receiving transfusions each year. Longer term, we believe our discovery will lead to a vaccine and therapeutics for this serious disease."

-more-

Chiron estimates that the hepatitis non-A, non-B testing market in the U.S. is approximately $85 million annually. Pre-clinical trials of an antibody test are underway. The company expects an Investigative New Drug (IND) application for its immunoassay kit to be filed with the U.S. Food and Drug Administration later this year.

Chiron has begun manufacturing scale-up of the viral protein through yeast fermentation in its manufacturing facility in Emeryville, California, where the company is headquartered.

When approved and available, blood banks will be able to apply a relatively simple assay procedure, using a plate coated with the virus protein, to screen for blood infected with hepatitis non-A, non-B virus. Antibodies from the infected blood bind to the plate, which is then rinsed -- if the antibodies are present, a second coating of indicator antibodies will signal a color. The immunoassay kit will be marketed by Ortho Diagnostic Systems, Chiron's partner in immuno-diagnostic products.

A team of scientists consisting of Michael Houghton, Ph.D., Qui-Lim Choo, Ph.D., George Kuo, Ph.D. and Amy Weiner, Ph.D., cloned the virus in 1987. They collaborated with Daniel Bradley, Ph.D., of the Center for Disease Control in Atlanta, who supplied non-A, non-B infected materials. Later in 1987, the team expressed the virus protein and confirmed that antibodies for the virus are present in the blood of individuals with blood-borne hepatitis non-A, non-B. The extremely small numbers of the virus present in infected patients prolonged the discovery process, particularly compared to other hepatitis viruses and the AIDS virus, all of which are present in larger numbers and were discovered relatively faster.

Houghton, the project leader, presented the research results at a scientific seminar May 9 at the University of California at San Francisco. The process of discovery involved screening millions of clones to find a single viral clone.

-more-

"The discovery of the blood-borne hepatitis non-A, non-B virus reinforces Chiron's leadership in the overall field of hepatitis," said Penhoet. "It follows similar breakthroughs in hepatitis A, hepatitis B and hepatitis D or delta, and demonstrates our scientific prominence in a critical area of infectious disease."

In July 1986, the FDA approved marketing of a vaccine for hepatitis B that uses recombinant DNA technology developed by Chiron. Chiron licensed the basic technology to Merck & Co., Inc., which manufactures and markets the product as Recombivax HB®.

Chiron scientists have also cloned and expressed the proteins that form the hepatitis A virus shell, and research is underway to develop a vaccine. Houghton's team previously discovered the structure of the hepatitis D virus, a type of hepatitis virus occuring as a satellite to hepatitis B which increases the severity of the disease.

The discovery of the blood-borne hepatitis non-A, non-B virus was part of a major research effort in virology underway at Chiron and its joint venture, The Biocine Company, to research, develop, manufacture and market a new generation of synthetic vaccines. Subsequent vaccines will be marketed by The Biocine Company, which combines the recombinant DNA technology of Chiron with Ciba-Geigy's proprietary technology in adjuvants, which enhance the immune response to vaccines.

Additional applications of the research may include: confirmed clinical diagnosis of patients with symptoms of blood-borne hepatitis non-A, non-B and monitoring during therapy; investigation of vaccines; and investigation of therapeutics to control chronic carriers.

Currently, cases of blood-borne hepatitis non-A, non-B are diagnosed by exclusion -- that is, people who have hepatitis symptoms but who do not test positively for other viruses such as hepatitis A or B are assumed to have hepatitis non-A, non-B. Also, the virus can be present in people who have never had transfusions -- for example, of the blood donors carrying the virus, an estimated 90 percent have never been transfused. Thus the virus can be transmitted efficiently other than via transfusion, presumably through blood transmission or close personal contact.

"The discovery and cloning of a blood-borne hepatitis non-A, non-B virus is clearly a scientific achievement of great importance," said William J. Rutter, Ph.D., chairman of Chiron. "It affirms again the promise of recombinant DNA technology in developing solutions to the world's major health problems. We intend to complete and publish the research results in the near future and share the knowledge with our scientific colleagues."

Chiron Corporation develops therapeutic and diagnostic products for the health care market using recombinant DNA and other techniques of modern biology. The company emphasizes four areas of product development: vaccines, therapeutic hormones and growth factors, therapeutic enzymes and related diagnostics. Ciba-Geigy is a major international pharmaceutical company. Johnson & Johnson is a major international pharmaceutical and health care products company.

# # #

Schedule C

Decision of Burchett J

Federal Court of Australia

Murex v Chiron NG 106/1994

21/08/1996

FEDERAL COURT UNREPORTED JUDGMENTS

MUREX DIAGNOSTICS AUSTRALIA PTY LTD v CHIRON PTY LTD and ANOR; CHIRON CORPORATION v MUREX DIAGNOSTICS AUSTRALIA PTY LTD and ORS

No. NG 106 of 1994

FEDERAL COURT OF AUSTRALIA

NEW SOUTH WALES DISTRICT REGISTRY

GENERAL DIVISION

21 August 1996, heard;

21 August 1996 , delivered

CATCHWORDS: PRACTICE and PROCEDURE - apprehended bias - difference between Australian and English statement of the principle - application to an expert sitting as scientific adviser with a court.

JUDGES: BURCHETT J

Burchett J:

Murex (as I shall call the Applicant) issued a notice to produce covering certain documents relevant to the relationship between Chiron Corporation (Chiron) and a Dr Brenner. Chiron has taken out a motion to set this notice to produce aside. The basis on which the motion is brought is that the documents, it is said, cannot be relevant to any question reasonably arising in the case. Counsel accepts that he has to go that far, and that the onus resting on Chiron is similar to that arising in a case to which the principle of General Steel Industries Inc. v Commissioner for Railways (NSW) (1964) 112 CLR 125 applies.

The issue put forward by Murex, which Chiron thus seeks to dismiss out of hand, relates to the role of Dr Brenner as scientific adviser to Aldous J, and later as scientific adviser to the Court of Appeal, in the English proceedings concerning the United Kingdom equivalent of the patent with which I am

concerned. Murex points out that, in his opening in the present case, senior counsel for Chiron relied on the English decision, not only as determining, at least persuasively, legal questions, but also as persuasive on matters of fact. Furthermore, there is a pleading which may or may not properly raise certain questions of issue estoppel founded upon the English judgment. That pleading has not been abandoned, and indeed, if it is not effective, counsel for Chiron has indicated an intention to seek leave to amend Chiron's pleadings to replace it with an effective allegation of the same kind. Counsel for Murex says that, if the English case is to be relied on at all, he should be entitled to impugn it for bias or the appearance of bias. On behalf of Murex, evidence has been tendered on the motion to show prima facie that Dr Brenner, while adviser to one or both of Aldous J and the Court of Appeal, was sitting, as a director, on the board of a company, together with the President and founder of Chiron, which owned a significant part of the shareholding of the company in question; that this company, to which Dr Brenner was also a scientific consultant, had a collaboration agreement with Chiron; and that Dr Brenner stood to gain financially, to some degree, from that collaboration, and from his association with the company. In this situation, Murex says that the principle of apprehended bias, as understood in Australia, would apply to bar Dr Brenner from participating, even though merely as a scientific adviser, in the internal deliberations of a court in which Chiron was litigating matters close to the collaboration in question.

Reference was made by counsel for Murex to some words with which the judgment of the Court of Appeal, which is reported, but not fully, in (1996) Fleet Street Reports at 204, was brought to a conclusion. These particular words, for some reason, were omitted from the report in the Fleet Street Reports. They are:

> "In short without him" -
>
> I interpolate that is Dr Brenner - "in this unfamiliar field our understanding of the facts would have been insufficient."

It is accepted that Murex's point was raised in the Court of Appeal, and that it was rejected. But it is suggested that the law in England is not identical with that in Australia on this point, and that in any case rejection on the facts then known should not bar the raising of the matter on such facts as may be ascertained now. It should be appreciated, counsel argue, that the appearance in question here is not just of Dr Brenner sitting with the President and founder of Chiron; but of his being a director of a company which had a concern in the development of patents, so that, it is urged, there may be an appearance of his having been both pro Chiron and pro the interests of patentees in general.

In considering the question thus put before me, I have had regard to some of the case law in Australia which has referred to a possible difference between the law in Australia and the law in England in this particular respect. I referred to some of the decisions, and particularly to the decision of the High Court in Vakauta v Kelly (1989) 167 CLR 568, in Australian and Overseas Telecommunications Corporation Ltd v McAuslan (1993) 47 FCR 492 at 494-495. I there drew attention to the fact that, in Vakauta v Kelly, Brennan, Deane and Gaudron JJ made it plain they considered the judge with whom that decision was

concerned would not have been biased in fact; but they nevertheless held, at 573-574 of the report, that his comments were such as "to cause 'reasonable apprehension' on the part of a lay observer that the judgment itself was, 'in the end', affected by bias." I went on to refer to the accepted test in England of "a real danger of bias" or "a real danger of injustice", being the test laid down by the House of Lords in The Queen v Gough [1993] AC 646 at 670 and 673. In Vakauta v Kelly, in another passage at 571, Brennan, Deane and Gaudron JJ spoke of preconceived views that "could threaten the appearance of impartial justice." The principle that was adopted was that stated in Livesey v The New South Wales Bar Association (1983) 151 CLR 288 at 293-294:

> "(A) judge should not sit to hear a case if in all the circumstances the parties or the public might entertain a reasonable apprehension that he might not bring an impartial and unprejudiced mind to the resolution of the question involved in it."

In another judgment of my own, which is unreported, Carr v McDonalds Australia Limited, delivered on 21 October 1994, I referred to a decision of the Court of Appeal of New South Wales in Australian National Industries Ltd v Spedley Securities Ltd (in Liq) (1992), 26 NSWLR 411, where the then president, now Kirby J of the High Court, referred (at 419) to:

> "(T)he stringency which is required, by decisions of the highest courts, of all those who exercise judicial office or have equivalent functions in Australia. Although it was formerly necessary to demonstrate a 'probability' or 'real likelihood' that a reasonable observer would apprehend bias by pre-judgment on the part of the judicial officer concerned, such is not now the case in this country. By repeated decisions of the High Court the test is now expressed in terms of possibilities, that is, whether the parties or the public 'might entertain a reasonable apprehension that the judge might not bring an impartial and unprejudiced mind to the resolution of the question involved' ... ".

In my opinion, having regard to these statements of the law, the point raised by Murex cannot be rejected without a hearing as hopeless. So to hold, of course, is not to say that ultimately it will find favour with this or any other court. That is a matter which can only be determined when the full circumstances which the parties choose to put before the court are known. But the point simply cannot get a hearing, at least a hearing of the kind for which our procedures provide, unless the notice to produce is enforced.

I do not think that Mr Catterns's failure to cite authority in support of apprehended bias, as distinct from fraud, as a vitiating factor in respect of the binding force of a judgment, is necessarily fatal to the point. I think that the point, if pursued by the parties, can only be determined after all the evidence that is to be tendered upon it has been heard.

ORDER:

Accordingly, I dismiss the motion and I direct that the notice to produce be answered.

I desire to add that, after my reasons had been delivered ex tempore, Mr Catterns did cite the following

authority with respect to the avoidance of a judgment upon a relevant ground other than fraud: Jet Holdings Inc v Patel [1990] 1 QB 335 at 345.

Representation:

Counsel for the applicant and the first cross-respondent: Mr DK Catterns QC and Miss KJ Howard

Solicitors for the applicant and the first cross-respondent: Banki, Palombi, Haddock and Fiora

Counsel for the third cross-respondent: Dr AC Bennett SC and Miss KJ Howard

Solicitors for the third cross-respondent: Banki, Palombi, Haddock and Fiora

Counsel for the first and second respondents and the cross-claimant: Mr FM Douglas QC and Mr AJ Bannon

Solicitors for the first and second respondents and the cross-claimant: Allen Allen and Hemsley