

IN THE HIGH COURT OF AUSTRALIA
SYDNEY REGISTRY

No. S28 of 2015

BETWEEN:



YVONNE D'ARCY
Appellant

and

MYRIAD GENETICS INC
First Respondent

GENETIC TECHNOLOGIES LIMITED ABN 17 009 212 328
Second Respondent

AFFIDAVIT

I, Michael Caine, of 1 Nicholson St, Melbourne, Victoria, 3002, Registered Australian Patent Attorney, say on oath as follows:

1. I am a fellow and council member of the Institute of Patent and Trade Mark Attorneys (**IPTA**) and a partner of Davies Collison Cave, Patent and Trade Mark Attorneys (**DCC**). I was registered as a patent attorney in 1994 and became a partner of DCC in 1998.
2. During my time as a patent attorney at DCC, I have prepared and filed numerous patent applications directed to isolated biological materials, such as small molecules isolated from plants and marine organisms, as well as peptides isolated from venoms. One area where considerable research is carried out in Australia and in respect of which I have considerable knowledge is the field of conotoxins.
3. Conotoxins are short cysteine rich peptides isolated from cone snail venom which generally have from 10 to 30 amino acids and from 1 to 3 disulfide bonds. These peptides have been the subject of intensive research in Australia and have been found to interact with numerous receptors and ion channels within the human body.

Date of Document:

Filed on behalf of:

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10 March 2015

The Institute of Patent and Trade Mark Attorneys, Intervener

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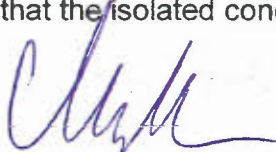
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Ref: 9110227

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4. In their natural state, conotoxins form part of the venom which comprises a complex cocktail of peptides adapted to immobilise the cone snails' prey, such as small fish or mollusks, so they can be consumed. They also help cone snails deal with predators. One conotoxin isolated from the venom of a particular fish hunting cone snail, *Conus magus*, was approved by the Food and Drug Administration in the United States in 2004 for the treatment of severe and chronic pain. That isolated conotoxin was named ziconotide and is marketed under the name Prialt.
5. In April 1998 and February 1999, prior to the FDA approval of Prialt, I prepared and filed two provisional patent applications in the name of the University of Queensland in respect of a conotoxin identified as CVID (also known as AM336) which had been isolated by researchers at the University of Queensland from another fish eating cone snail, *Conus catus*.
6. The researchers from the University of Queensland had identified a component of the venom of this cone snail which inhibited N-type calcium channels in a similar manner to ziconotide. However, the researchers believed that the high level of selectivity of this peptide for the N- type calcium channels over other calcium channels would provide advantages over ziconotide. The two provisional patent applications I filed included claims to the isolated CVID alone. With the support of the University's licensee, AMRAD Corporation Limited (**AMRAD**), a corresponding international patent application was filed in April 1999. After the filing of those patent applications, preclinical studies and clinical trials were carried out by AMRAD in relation to the conotoxin.
7. From my experience in dealing with representatives of AMRAD and the University of Queensland, I consider that AMRAD would not have funded the further research, preclinical studies or clinical trials in relation to CVID that occurred, nor that the University could have funded or arranged for such clinical trials, if there had not been patent applications on foot specifically claiming CVID, and if AMRAD and the University did not have an expectation that the isolated conotoxin would be considered to be

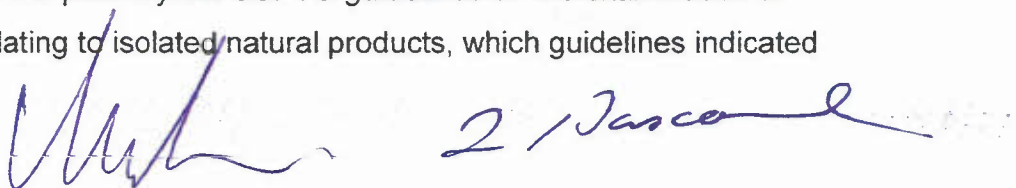


patentable subject matter, and that the patent applications would proceed to grant.

8. Further work in relation to the isolation and characterization of venom peptides from cone snails was carried out at the University of Queensland. In 1998, I was engaged to prepare two new provisional patent applications for the University of Queensland in respect of two new classes of conotoxins which had been identified by researchers at the University.
9. One of the new classes of conotoxins was named the chi-conotoxin class of which the researchers had identified two members, chi-Mr1A and chi-Mr1B. The researchers had isolated those conotoxins from the cone snail, *Conus marmoreus*. The two isolated conotoxins, chi-Mr1A and chi-Mr1B, were found by the University researchers to inhibit the human neuronal noradrenalin transporter and the researchers therefore expected them to be useful in the treatment of various human conditions and disorders, and to be useful in the treatment of pain.
10. The other new class of conotoxins identified by the researchers at the University of Queensland was named the rho-conotoxin class of which a novel conotoxin was isolated from a different species of fish hunting cone snail, *Conus tulipa*. This conotoxin was named rho-T1A. This conotoxin was found to act as an alpha-1B adrenoceptor antagonist, and for this reason the researchers expected it to be useful in treating a number of conditions and disorders in humans, including urinary and cardiovascular conditions.
11. In 1998, I filed provisional patent applications in Australia in the name of the University of Queensland that claimed the isolated conotoxins chi-Mr1A, chi-Mr1B and rho-T1A. Those isolated conotoxins were subsequently made the subject of international patent applications in the name of the University of Queensland. Through its commercialization company, Uniquest Pty Ltd, the University of Queensland then licensed those patent applications to a "spin out" company, Xenome Pty Ltd (**Xenome**).

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12. Because of the licences it held, and later because of an assignment it received of the patent applications, Xenome was able to attract considerable investment which funded further research and development in Australia in relation to these peptides. This further research subsequently lead to the identification of an analog of the peptide chi-Mr1A, named XEN2174. That analog was subsequently the subject of clinical trials carried out by Xenome in Australia and the United States.
13. From my experience in dealing with representatives of Xenome and the University of Queensland, I consider that Xenome would not have been formed if there had not been patent applications on foot claiming isolated conotoxins chi-Mr1A, chi-Mr1B and rho-T1A. I also consider that Xenome would not have been able to fund the further research in relation to chi-Mr1A and XEN2174 and the clinical trials for XEN2174 that occurred, nor that the University could have funded or arranged for such clinical trials, if there had not been patent applications on foot specifically claiming chi-Mr1A, and if Xenome and the University did not have an expectation that the isolated conotoxins would be considered to be patentable subject matter, and that the patent applications would proceed to grant.
14. In 2009, I prepared and filed an Australian provisional patent claiming another conotoxin isolated from the venom of the cone snail, *Conus catus*. This new conotoxin was named CVIE. This conotoxin was found by researchers at the University of Queensland and the University of Sydney to have improved properties relative to both CVID and Prialt. In 2010, I prepared and filed, on behalf of the Universities, a corresponding international application which ultimately lead to the filing of a patent application in the United States claiming the same conotoxin (the **US CVIE patent application**).
15. The US CVIE patent application, which included claims to the isolated conotoxin CVIE, was allowed by the USPTO and proceeded to grant on 1 July 2014. Although the application was accepted prior to the publication of the post-Myriad USPTO guidelines on the examination of inventions relating to isolated natural products, which guidelines indicated

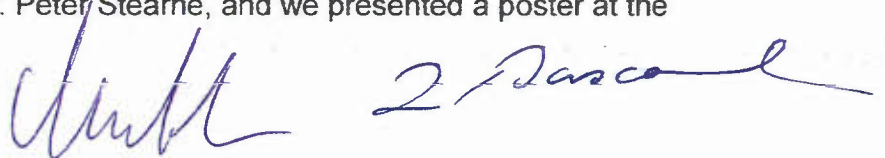
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that such inventions were not patentable, the patent proceeded to grant after the publication of the guidelines. From my experience with representatives of the Universities of Queensland and Sydney I am aware that the announced change in USPTO practice following the Myriad decision has caused significant concern and uncertainty for the Universities and has the real potential to interfere with steps taken by the them to obtain the investment necessary to conduct clinical trials in respect of CVIE.

16. In view of the importance of the field of isolated biological materials to local clients of my firm, I have attended and my firm has sponsored numerous conferences relating to isolated naturally occurring peptides, especially those which are useful as therapeutics. For example, I have attended the following Venoms to Drugs Conferences, sponsored by DCC:
- (a) Second Venoms to Drugs –Heron Island, QLD, Australia, July 2002;
 - (b) Third Venoms to Drugs –Heron Island, QLD, Australia, 28 August – 2 September 2005;
 - (c) Fourth Venoms to Drugs –Heron Island, QLD, Australia, 15-20 May 2011; and
 - (d) Fifth Venoms to Drugs –Kingscliff, NSW, Australia, 19-23 October 2014.
17. At the most recent Venoms to Drugs conference, I gave a presentation to the attendees in which I attempted to explain the consequences of the guidelines published by the USPTO for examining inventions related to isolated natural products following the decision of the Supreme Court in *Association for Molecular Pathology v Myriad Genetics, Inc.* A copy of my presentation is now produced and shown to me and marked **Exhibit MC-1**. In my presentation, I indicated that good news may be on the horizon in view of an announcement by the USPTO that they would be revising the examination guidelines which, hopefully, would allow examiners to accept patents relating to isolated venom peptides.



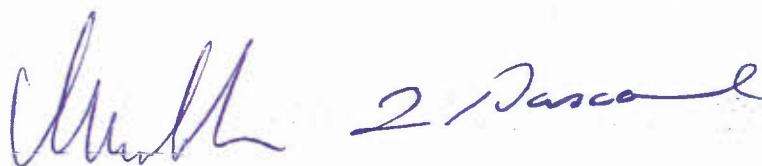
18. Since I gave my presentation, the USPTO has published revised guidelines, but it is still unclear whether the USPTO will accept claims directed towards isolated natural products such as isolated venom peptides.
19. From my experience in talking with and acting for members of the biotechnology and pharmaceutical communities in Australia, I believe that:
- (a) the lack of certainty in the US in relation to the patentability of such isolated natural products acts as a disincentive to invest in such technologies in Australia;
 - (b) although methods and uses of such natural products may be patentable, it is patents that relate to the pharmaceutical substances themselves that are valued by pharmaceutical companies and investors in pharmaceutical technologies;
 - (c) the high cost associated with obtaining regulatory approval for pharmaceutical products, which is generally understood to exceed USD\$1 billion per substance, means that patent protection for pharmaceutical substances *per se* is very important for companies considering investing in research and development of such substances for pharmaceutical use; and
 - (d) even if researchers modify isolated natural products to improve or alter their properties, and seek patent protection for such modified products, if claims to isolated natural products themselves are considered not to be patentable subject matter, they will still bear the risk that these modified compounds could be subsequently found in nature, perhaps as minor components later identified as a result of improved analytical techniques, which could invalidate their patents.
20. DCC has also been a sponsor for the Australian Peptide Conference, at least since the fourth conference which was held on Lindeman Island, QLD, Australia from 7-12 October 2001. I attended that conference with my DCC partner, Dr. Peter Stearne, and we presented a poster at the



conference relating to patent protection for drug targets, which targets include isolated natural proteins, such as receptors. In presenting the poster we explained that isolated receptors, and their use in assays and screens, can represent patentable subject matter. Davies Collison Cave also sponsored the following Australian Peptide Conferences:

- (a) Fifth Australian Peptide Conference, Daydream Island, QLD, Australia, 5-10 October 2003;
- (b) Sixth Australian Peptide Conference, Hamilton Island, QLD, Australia, 9-14 October 2005;
- (c) Seventh Australian Peptide Conference, Cairns, QLD, Australia, 21-25 October 2007;
- (d) Eighth Australian Peptide Conference, Couran Cove, QLD, Australia, 11-16 October, 2009;
- (e) Ninth Australian Peptide Conference, Hamilton Island, QLD, Australia, 16-20 October 2011; and
- (f) Tenth Australian Peptide Conference, Penang, Malaysia, 8-13 September 2013.

- 21. I attended the fifth, eighth, ninth and tenth Australian Peptide Conferences. Many of the presentations at these conferences related to peptides which have been isolated from natural sources, and the potential for these peptides to be useful as human therapeutics.
- 22. I also attended the first and second International Conferences on Circular Proteins which were held from 18-21 October 2009 and 14-17 October 2012 on Heron Island, QLD, Australia. The main focus of the circular protein conferences is a large and diverse family of cyclic peptides which have been isolated from plants. These peptides are called cyclotides. These cyclotides have been associated with a number of biological activities. Much of this research has been carried out by the University of

A handwritten signature in blue ink, appearing to read 'Charles Pascoal', is written over the bottom of the text in item 22.

Queensland and DCC have been involved in preparing, filing and prosecuting a number of patent applications relating to this technology.

23. One of those patents claimed the gene sequence for a cyclotide which exhibited insecticidal properties, and this patent has been licensed to a company with the objective of developing a plant capable of expressing (i.e. producing) a cyclotide *in situ* so as to act as an endogenously produced insecticide. From my experience in acting for the University, I believe that the patent application directed to this isolated plant gene sequence was important in allowing the University of Queensland to enter into licensing agreements with companies to develop this technology.
24. As a result of my experience in acting for and speaking with various representatives in the field of isolated biological materials in Australia, I consider that field to be particularly important to the Australian research community. This is so particularly in view of the high levels of biodiversity in Australia's native flora and fauna and the large number of research groups involved in analyzing and characterizing compounds isolated from these plants and organisms. In my experience, it is the expectation of patent protection for the isolated biological materials themselves that provides the incentive for pharmaceutical companies and other investors to support and encourage research in these areas, and to take the necessary steps to take these molecules from the laboratory to the clinic.

SWORN by the deponent Michael Caine
at Melbourne in the State of Victoria
on 10 March 2015.

Before me:

2 Pasca



IAN STANLEY PASCARL
An Australian Legal Practitioner
within the meaning of the
Legal Profession Act 2004
Davies Collison Cave Law Pty Ltd
1 Nicholson Street, Melbourne 3000

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Affidavit of Michael Caine sworn on 10 March 2015

INDEX OF EXHIBITS

EXHIBIT	DESCRIPTION	PARAGRAPH	PAGE
MC-1	<i>Copy of presentation of deponent to the Fifth Venoms to Drugs –Kingscliff, NSW, Australia, 19-23 October 2014</i>	17	10

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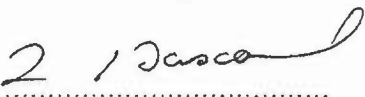
GENETIC TECHNOLOGIES LIMITED ABN 17 009 212 328
Second Respondent

EXHIBIT MC-1

This is the exhibit marked MC-1 produced and shown to Michael Caine at the time of swearing his affidavit this 10 March 2015.

*Copy of presentation of deponent to the Fifth Venoms to Drugs –Kingscliff,
NSW, Australia, 19-23 October 2014*

Before me


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IAN STANLEY PASCARL
An Australian Legal Practitioner
within the meaning of the
Legal Profession Act 2004
Davies Collison Cave Law Pty Ltd
1 Nicholson Street, Melbourne 3000

Natural Product Inventions

-Collateral damage in the war on gene patents

Michael Caine
mcaine@davies.com.au

- **Section 101.** *Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor subject to the conditions and requirements of this title.*
- USPTO Document of 4 March 2014 entitled: “Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena, & Natural Products”
- Guidelines Apply to “all claims (i.e., machine, composition, manufacture and process claims) reciting or involving laws of nature/natural principles, natural phenomena, and/or natural products.”

How to assess patentable subject matter?

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- Guidelines issued in response to two decisions of the US Supreme Court:
 - *Association for Molecular Pathology v. Myriad Genetics, Inc.*, and
 - *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*
- Question 1: Is the claimed invention directed to one of the four statutory patent-eligible subject matter categories: process, machine, manufacture, or composition of matter?
- Question 2: Does the claim recite or involve one or more judicial exceptions?
- Question 3: Does the claim as a whole recite something significantly different than the judicial exception(s)?

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Factors that weigh toward eligibility

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Factors that weigh toward eligibility (significantly different):

- a) Claim is a product claim reciting something that initially appears to be a natural product, but after analysis is determined to be non-naturally occurring and markedly different in structure from naturally occurring products.
- b) Claim recites elements/steps in addition to the judicial exception(s) that impose meaningful limits on claim scope, i.e., the elements/steps narrow the scope of the claim so that others are not substantially foreclosed from using the judicial exception(s).
- c) Claim recites elements/steps in addition to the judicial exception(s) that relate to the judicial exception in a significant way, i.e., the elements/steps are more than nominally, insignificantly, or tangentially related to the judicial exception(s).

Factors that weigh toward eligibility

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d) Claim recites elements/steps in addition to the judicial exception(s) that do more than describe the judicial exception(s) with general instructions to apply or use the judicial exception(s).

e) Claim recites elements/steps in addition to the judicial exception(s) that include a particular machine or transformation of a particular article, where the particular machine/transformation implements one or more judicial exception(s) or integrates the judicial exception(s) into a particular practical application.

f) Claim recites one or more elements/steps in addition to the judicial exception(s) that add a feature that is more than well-understood, purely conventional or routine in the relevant field.

Factors that weigh against eligibility

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Factors that weigh against eligibility (not significantly different):

- g) Claim is a product claim reciting something that appears to be a natural product that is not markedly different in structure from naturally occurring products.
- h) Claim recites elements/steps in addition to the judicial exception(s) at a high level of generality such that substantially all practical applications of the judicial exception(s) are covered.
- i) Claim recites elements/steps in addition to the judicial exception(s) that must be used/taken by others to apply the judicial exception(s).

Factors that weigh against eligibility

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- j) Claim recites elements/steps in addition to the judicial exception(s) that are well-understood, purely conventional or routine in the relevant field.
- k) Claim recites elements/steps in addition to the judicial exception(s) that are insignificant extra-solution activity, e.g., are merely appended to the judicial exception(s).
- l) Claim recites elements/steps in addition to the judicial exception(s) that amount to nothing more than a mere field of use.

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Examples provided by USPTO

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Claim 1. Purified amazonic acid.

Claim 2. Purified 5-methyl amazonic acid.

Claim 3. A method of treating colon cancer, comprising: administering a daily dose of purified amazonic acid to a patient suffering from colon cancer for a period of time from 10 days to 20 days, wherein said daily dose comprises about 0.75 to about 1.25 teaspoons of amazonic acid.

Background: Amazonic acid is contained in an amazonian cherry tree, and eating 30lbs of leaves is known to be effective in treating breast cancer. Inventor has purified amazonic acid, and has found that it can treat colon cancer. He has also made a derivative that, in addition to treating colon cancer, stimulates hair growth.

Are the claims patentable? [Claim 1 no, but Claims 2 & 3 yes]

Use of natural product drugs in the US

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Natural Product Dosages Sold in the US

IMS Health and Pharmaprojects
Professor Matthew J. Higgins, Georgia Tech

Natural Products sold in the United States From 2001-2011 (in Sales Units)

■ Tramadol	18,104,553,733
■ Clavulanic acid	5,338,207,765
■ Penicillin	3,483,851,173
■ Tetracycline	1,922,758,255
■ Taxol	1,554,822,780
■ Epogen	384,546,232
■ Adriamycin	10,433,433
■ Insulin	8,035,843
■ Vincristine	4,994,779
■ Vinblastine	1,230,034
■ Streptomycin	447,367

Total = 30,813,881,394



Where to now?

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- Good news is on the horizon!
- Following extensive public consultation the USPTO has agreed that they have gone too far with the guidelines and announced on 17 September 2014 that revised guidelines would be made available in October
- It is hoped that these guidelines will allow examiners to accept patents relating to natural products, including isolated venom peptides.
- However, until Supreme court considers the patentability of such products, or until US law is amended, there remains some uncertainty in relation to the validity of such patents in the US.

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Acknowledgements

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Justices of the Supreme Court of the United States



- Associate Justice Sonia Sotomayor,
- Associate Justice Stephen G. Breyer,
- Associate Justice Samuel A. Alito,
- Associate Justice Elena Kagan.
- Associate Justice Clarence Thomas
- Associate Justice Antonin Scalia,
- Chief Justice John G. Roberts
- Associate Justice Anthony Kennedy
- Associate Justice Ruth Bader Ginsburg.

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