Bio-business in brief: the case of conotoxins

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A recent report in Science[1] states that rotaviruses (the cause of many a diarrhoea) lead to 20–60 deaths a year in the United States and about 600,000 in the developing world. This is one of the many disturbing health statistics that differentiates the developed from the developing world. If we are to see the gap narrow significantly within our lifetime, Indian researchers and entrepreneurs need to engage more with drug development. Indigenous drugs are significantly cheaper than those made elsewhere and increase our 'health security'. Their production also helps build the nation's capabilities and economic competitiveness. In an effort to contribute to this process, this article focuses on conotoxins as drug candidates.

Keywords: Bio-business, conotoxins, drug development, patents.

MARINE snails have the prettiest shells on their backs and the deadliest poison in their sting. The potent armamentarium of the *Conus* snails includes conotoxins, a fascinating series of peptides. The peptides possess pharmacological properties that make them valuable tools for pain therapy and certain disorders of the central nervous system. How a naturally occurring molecule becomes a drug and what the commercial potential of these peptides might be will be discussed later. First, let us describe the conotoxins.

Structure and function

The peptides are merely 10–40 residues and therefore smaller than most known protein toxins. These linear peptides tend to be girded by several disulphide bonds making them structurally rigid. They also have a large number of post-translational modifications, some of which are unusual. This has given rise to about 50,000 sequences in the estimated 500 species[2].

Each sequence targets a particular ion channel, receptor or transporter. Based on their specificity the conotoxins have been grouped into several classes, outlined in recent reviews[3,4]. The omega-conotoxin class of peptides targets and blocks voltage-sensitive Ca^{2+}-channels, thereby inhibiting neurotransmitter release. The alpha- and psi-conotoxins target and block nicotinic acetylcholine receptors, causing ganglionic and neuromuscular blockade. Mu- and delta-conotoxins block voltage-sensitive Na^{+}-channels of muscles. The kappa-conotoxin blocks voltage-sensitive K^{+}-channels, and these may also cause enhanced neuronal excitability. The gamma-conotoxin targets a voltage-sensitive nonspecific cation channel, and sigma-conotoxin antagonizes the serotonin $5HT_3$ receptor. Most recently, rho conotoxins, which target alpha-adrenoceptors, have been identified.

Besides the disulphide-rich conotoxins, other peptides (with fewer, even no disulphide bonds) are also found in cone snail venom. Amongst these, the conopressins are vasopressin receptor antagonists and the conantokins are N-methyl-D-aspartate receptor antagonists.

The high specificity of these toxins has been the basis for their use as research reagents or pharmacological leads. Although peptides as drugs are likely to be less toxic than chemical compounds, they suffer from the disadvantages of (a) being subject to proteolytic digestion *in vivo* and of (b) being more flexible than smaller chemical compounds and therefore having less binding affinity to their target[5]. In the case of conotoxins, the multiple disulphide bonds address the latter issue. Another method to reduce the flexibility of a peptide is to cyclize it, i.e to form an amide bond between the amino and carboxy terminii of the peptide. Several naturally occurring peptides are found to be cyclized[5]. In an attempt to increase the structural rigidity and pharmacological effectiveness of conotoxins further, scientists have used linkers of 2–15 residues for cyclization. The cyclized state also eliminates the action of exopeptidases, which require a free N- or C-terminus for action. Furthermore, a 'linker' provides an additional 'handle' on the molecule, that does not interfere with the primary biological effect of the peptide, but provides a place for functionalizing the molecule to improve biophysical properties. In some cases, this handle reduces side effects and improves BIOAVAILABILITY (words in capitals are defined or explained in the glossary.).

The publicly available comprehensive review by Terlau and Olivera[2] provides more details about the different conotoxins and their respective activities.

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Conotoxins and drug development

Based on their modes of action, it might be expected that these toxins would be effective analgesics or useful in the treatment of epilepsy, Parkinson's disease, schizophrenia, etc.

But how does one go from a snail on a beach to a medicine on a shelf? What goes into identifying a compound that could serve as a 'lead' in drug discovery? A typical procedure for isolating, purifying and characterizing a naturally occurring peptide is the following: the sequential extraction of components into various solvents, fractionation of the different mixtures by HPLC, mass spectrometric and other amino acid analyses of individual peaks, followed perhaps by NMR-based structure determination. *In vivo* targets are identified by behavioural studies as well as binding or other assays. By way of ratification, the putative peptide may be synthesized in the laboratory and its behaviour by HPLC and mass spectrometry compared with that of the isolated peptide. The special features of conotoxins add to the chemist's task in terms of having to (a) identify residues with post-translational modifications and (b) decipher the disulphide connectivity. Additionally, some of the conopeptides with only one disulphide linkage may have inter-convertible conformations on the chromatographic column[6].

One conotoxin was approved for marketing in the US by the Food and Drug Administration (FDA) as a drug in late 2004. Prialt – generic name ziconotide – is 1000 times stronger than morphine, and is non-addictive. It is prescribed as an intrathecal infusion, i.e. an infusion directly into the spine. Alarming as this may sound, it is prescribed for an even more alarming condition, for patients with unremitting chronic pain for whom morphine becomes less effective with time. Work on Prialt started at Neurex Corporation, California, which was subsequently taken over by Elan Pharmaceuticals a company based in Ireland. It was developed further by Elan, and is now manufactured and marketed by the same company. Recently, Elan transferred marketing rights in Europe to Eisai Inc., a company with roots in Japan.

A competitor to Elan is Cognetix, based in Utah. It is working on a conotoxin code-named CGX-1160. This was in Phase II clinical trials in 2005, and the company had planned to initiate a larger study in 2006 (www.cognetix.com). A few companies in Australia also have an interest in these peptides. Metabolic Pharmaceuticals, Xenome and CNSBio have conotoxin drug candidates (ACV1, Xen-2174 and AM336 respectively) in various stages of drug development. That there are three Australian companies working in this area would indicate that there is a 'locational advantage' of being near the source of the toxins. Nevertheless, the source of the peptides is only the beginning of a long journey to the clinic. This is confirmed by the fact that Cognetix organized an international supply of the peptides, resulting in a war chest of 78 granted patents (more on patents below) and more than 50 at the stage of application (www.cognetix.com). Two molecules reached Phase 1 trials, that is a trial in which a drug candidate is tested on humans for the first time, only to be put on hold due to toxicity.

Although a cyclized conotoxin has not yet been approved as a drug, the cyclization approach has been used to good effect with a different peptide. The approved drug Integrilin, based on the peptide barbourin from the venom of rattlesnake *Sistrurus*, inhibits platelet aggregation by specifically binding to the integrin GPIIb/IIIa.

Drug development often involves partnerships. This is illustrated by the collaboration of Cognetix with Baldomero Olivera, the 'father' of the field. His ties with Cognetix reflect how academia and companies have worked together in this field, as so often happens in biotech drug discovery.

Conotoxins: the Indian scenario

In terms of the source of the toxins, up to 30% of known *Conus* species are to be found in shallow tropical Indian waters, giving us as strong an advantage as Australia in this regard. Also, Indian scientists have turned their attention to marine cone snails in recent years. Whereas other groups have worked on whole venom, the groups of K. S. Krishnan (TIFR, Mumbai and NCBS, Bangalore), P. Balaram, S. P. Sarma, S. K. Sikdar (IISc, Bangalore), Anil Lala (IIT, Mumbai) and Mani Ramaswamy (Trinity College, Dublin) have collaborated to identify and study the molecular constituents of the venom. The Centre for Advanced Study in Marine Biology at Annamalai University and Unichem are also involved in these studies. Their findings have appeared in the last few years[6–8] and include descriptions of novel peptides. They have also FILED for a patent on a novel conotoxin that modulates sodium channels (see below).

Thus expertise in the basic sciences exists in India and any company wanting to work on conotoxins should perhaps first approach these researchers. Furthermore, an institute does not have to wait for a patent to be GRANTED to transfer a technology. Through the efforts of the Technology Transfer offices of their respective institutions, this research, which is an early stage technology, could be transferred to any company that wishes to pursue these peptides.

Conotoxins and intellectual property

With an increasing body of scientific evidence pointing towards the potential of these toxins for the treatment of a wide variety of neurological disorders, there has been an explosion of filing of PATENTS in this area. A list of conotoxin patents is publicly available (http://grimwade.biochem.unimelb.edu.au/cone/conpaten.html).

Box 1. Structure of a patent. Also, basic aspects of patent searching and drafting are mentioned briefly.

Structure of a patent

A patent application is usually divided into five sections. (a) The Title and Abstract help in searches by patent offices and the general public. (b) This is followed by the Background Description that helps in understanding the invention. (c) Then comes the Description or Summary of Invention which forms the basis of the claims of the application. (d) What would be called 'Methods' in a research paper are included in the Examples in a patent application. The section comprising Examples or Figures supports the claims. (e) Finally come the Claims, the most important part of the patent application, which define the scope of protection for an invention.

Patent search and patent drafting

Before applying for a patent, it is advisable to do a PRIOR ART search. This is done to establish that an invention is novel, to identify patent claims that one may inadvertently infringe, to monitor developments in the field, to identify competitors or partners for strategic alliances. Various patent offices such as the United States Patent and Trademarks Office (USPTO), Australian patent office (IP Australia), European Patent Office (EPO), New Zealand Patent Office (IPONZ) and World Intellectual Property Organization (WIPO) provide access to their databases for on-line searching. In addition, there is a resource called CAMBIA Patent Lens (www.patentlens.net), an initiative of a non-profit called CAMBIA. This site is powerful because it is in the public domain and because it helps to search for patent applications and granted patents across certain patent offices at one go. The offices covered here are those of Australia (AU) and the United States (US), the European Patent Office (EPO), and the Patent Cooperation Treaty (PCT) application.

To write a good patent, one should read and understand several patents in the field of invention. This needs to be done anyway to search for prior art. The claims are tricky to read and write. Interpreting the claims is a difficult task, so it is better to seek the advice of a patent attorney to determine the significance of the patent specifications. And while drafting a patent, a missing word or replacing a word with a seemingly similar one, can render a claim useless. This is one reason why the wording of patent claims is repetitive. Patent attorneys are good at writing these. Therefore, it is best to have an experienced attorney review any patent application before filing.

As stated above, one of the reasons patent claims are repetitive is because specific words have unambiguous meanings in this context. This reduces the chance for misinterpretation by the patent office. A second reason why some claims are repetitive is because one set of claims may be for the PROCESS and the other for the PRODUCT. Since both the process, a method by which a particular product is obtained, and the product per se are patentable, the claims get repetitive. A third reason for repetitiveness is that some claims are INDEPENDENT and others DEPENDENT. It is seen that the first claim is independent and stands on its own. A series of claims built on this independent claim are called dependent claims. Each claim is evaluated on its own merit and therefore, if one of the claims is rejected, it does not mean that the rest of the claims are invalid. It is therefore important to make claims on all aspects of the invention to ensure that the applicant gets the widest possible protection for his invention.

The first US patent on conotoxins was granted to Olivera and coworkers in 1984. This DISCLOSED for the first time the biological activity and chemical structure of three homologous toxic peptides and the process of synthesis in the laboratory.

Several patents have since been granted for various classes of conotoxins. More recently, in February 2006, a US patent was granted for cyclized conotoxins, in which Craik and co-workers describe the processes for the synthesis of the cyclic peptides and also their pharmaceutical uses.

Coming to the companies working with conotoxins, Neurex Corporation, Menlo Park, CA was granted a patent for inventing a method of producing analgesia and enhancing opiate analgesia in mammals using omega-conotoxins in 1994. As obtained by a search using Cambia's Patent Lens (see below), in all, 19 patents have been granted to Neurex and 12 to Elan with respect to omega-conotoxins. However, it should be noted that most of these patents are CONTINUATION-in-part or DIVISIONAL applications.

Cognetix has 21 US patents to its credit and on most of these patents Olivera is one of the inventors. The patent most recently granted to Olivera and co-workers was on October 2005 (a divisional application of US Patent No. 6,265,541). Here they CLAIMED uses of alpha-conotoxins for treating disorders by targeting neuronal nicotinic acetylcholine receptors.

Box 1 outlines the usual structure of a patent. Box 2 is a verbatim rendition of the claims of a patent (US Patent No. 6,727,226) pertaining to conotoxins. Note how the claims are phrased to obtain the best coverage and the best defensive position possible. Note also that each claim can be only one sentence. We also list in Box 3, the claims in the patent application entitled 'A novel

Box 2. The title of US Patent No. 6,727,226 is 'Mu-conopeptides'. The claims of this patent are reproduced here in their entirety.

What is claimed is:

1. An isolated peptide comprising the amino acid sequence Xaa–Asn–Cys–Cys–Asn–Gly–Gly–Cys–Ser–Ser–Lys–Xaa–Cys–Arg–Asp–His–Ala–Arg–Cys–Cys (SEQ ID NO:211), wherein Xaa at position 1 is Gln or pyro-Glu and Xaa at position 12 is Trp or bromo-Trp.
2. The isolated peptide of claim 1, wherein Xaa at position 1 is pyro-Glu and Xaa at position 12 is Trp.
3. An isolated mu-conopeptide propeptide comprising the amino acid sequence Gly–Ser–Met–Met–Ser–Lys–Leu–Gly–Val–Leu–Leu–Thr–Val–Cys–Leu–Leu–Leu–Phe–Pro–Leu–Thr–Ala–Leu–Pro–Leu–Asp–Gly–Asp–Gln–Pro–Ala–Asp–Arg–Pro–Ala–Glu–Arg–Met–Gln–Asp–Asp–Ile–Ser–Ser–Asp–Glu–His–Pro–Leu–Phe–Asp–Lys–Arg–Gln–Asn–Cys–Cys–Asn–Gly–Gly–Cys–Ser–Ser–Lys–Trp–Cys–Arg–Asp–His–Ala–Arg–Cys–Cys–Gly–Arg (SEQ ID NO : 210).
4. A method for treating or preventing disorders associated with voltage gated neuronal sodium channel disorders which comprises [sic] administering to a patient in need thereof a therapeutically effective amount of a peptide of claim 1 or a pharmaceutically acceptable salt thereof.
5. The method of claim 4, wherein said disorder is a neurologic disorder.
6. The method of claim 5, wherein said neurologic disorder is Amytrophic Lateral Sclerosis.
7. The method of claim 5, wherein said neurologic disorder is head trauma.
8. The method of claim 5, wherein said neurologic disorder is epilepsy.
9. The method of claim 5, wherein said neurologic disorder is a neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia.
10. The method of claim 9, wherein said neurotoxic injury is associated with stroke, cerebrovascular accident, brain or spinal cord trauma, myocardial infarct, physical trauma, drownings, suffocation, perinatal asphyxia, or hypoglycemic events.
11. The method of claim 4, wherein said disorder is pain.
12. The method of claim 11, wherein said pain is migraine, acute pain, persistent pain, chronic pain, neuropathic pain or nociceptive pain.
13. The method of claim 12, wherein the pain is phantom limb pain, neuroma pain or pain associated with trigeminal neuralgia, diabetic neuropathy, and post-herpetic neuralgia.
14. The method of claim 11, wherein said pain is burn pain.
15. The method of claim 4, wherein said disorder is myofacial pain syndrome, chronic muscle spasm, or spasticity.
16. A method of alleviating pain which comprises administering to a mammal that is either exhibiting pain or is about to be subjected to a pain-causing event a pain-alleviating amount of a peptide of claim 1 or a pharmaceutically acceptable salt thereof.
17. The method of claim 16, wherein the peptide is administered as a local anesthetic.
18. The method of claim 16, wherein the peptide is administered as an occular anesthetic.

conotoxin modulating sodium channels' by Krishnan and Balaram (hereafter, the 'K&B application'). We examine this patent application, and compare it to two other (granted) US patents related to conotoxin peptides, Patent Nos 6,767,896 and 6,727,226 (hereafter '896 and '226 respectively).

(1) The title of the K&B application states that a novel conotoxin is the subject of the patent application. Whereas both the words 'new' and 'novel' are acceptable for academic papers, they are not allowed in patent applications, as they create undue pressure on the patent office to confirm that the invention is new. Thus, uninformative as the following titles may sound, patent '896 is entitled 'Conotoxin peptides' and patent '226 'Mu-conopeptides'. There is also another reason why titles are general. It is to keep it as BROAD as possible to avoid the implication that it is a NARROWLY defined patent.

(2) The K&B application lists a 'Field of Invention'. This is optional. Many patents do not have this section because it is part of the cover page of the patent

Box 3. The patent application from conotoxin research in India is entitled 'A novel conotoxin modulating sodium channels' has PCT publication no. WO 2005/030801 A1, available at patentlens.net. The inventors are K. S. Krishnan (TIFR, NCBS) and P. Balaram (IISc). The claims of this patent are reproduced here in full.

We claim:

1. A substantially pure peptide having the amino acid sequence CKQAGESCDIFSQNCCVG-TCAFICIE-NH2 (SEQ ID NO 1).
2. A substantially pure peptide of claim 1, wherein the peptide is used [sic] a sodium channel modulator.
3. A process of preparing substantially pure peptide of claim 1, comprising of:
   (i) isolation of the peptide, and
   (ii) purifying the peptide by chromatographic methods.
4. A process of preparing substantially pure peptide of claim 3, wherein the peptide in step (i) is isolated from venoms of a molluscivorous snail.
5. A process of preparing substantially pure peptide of claim 4, wherein the molluscivorous snail is *Conus amadis.*
6. A process of preparing substantially pure peptide of claim 3, wherein the purification step (ii) is carried out by HPLC (High Performance Liquid Chromatography).
7. A substantially pure peptide of claim 1, wherein the peptide is used for treatment of neurophysiological and neurological disorders.
8. A substantially pure peptide of claim 7, wherein the peptide is used for treatment neurophysiological and neurological disorders n schizophrenia, epilepsy, bipolar disorder or in syndromes that affect the nervous system.
9. A pharmaceutical composition comprising a peptide having the amino acid sequence CKQAGESCDIFSQNC-CVG-TCAFICIE-NH2 (SEQ ID NO 1) with or without pharmaceutically acceptable carriers.

application in the section entitled 'Int. Cl'. Nevertheless, since the latter is in code, in this case IPC: C07K 141435, A61K 38117, therefore spelling it out in the 'Field of Invention' makes it easier for the reader.

(3) The background description is a little short, at around 400 words. Both '226 and '896 have background descriptions of around 1000 words each. It is advisable to write a thorough description as there is no second chance to add new information to the application once it is filed. The only changes subsequently permitted are amendments to claims.

(4) Unlike summaries in academic papers, patent summaries are quite long. Perhaps this derives from legal 'briefs' which may not be brief! The summary in the K&B application is around 100 words, whereas those in '226 and '896 are around 1650 and 1800 words respectively. We find that the kinds of disorders that the peptide of the K&B application might treat are listed in the claims but not in the summary. A summary will be the subject of future prior art 'searches'. Therefore, it should not merely contain statements of the invention but also include potential uses thereof.

(5) Although the K&B application does seek protection for 'pharmaceutically acceptable carriers', it has omitted to make one claim that is made quite often, that of 'pharmaceutically acceptable salts or solvates' of the peptide in question. Both aspects help broaden the scope and the protection of the patent, should the peptide be converted into a drug.

(6) Another aspect that could have been included for protection is the use of a cyclizing linker. Thus, an additional claim might read as follows: 'A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 which may or may not include a cyclizing linker'.

(7) The amounts and methods of administering a drug is yet another aspect that could have been claimed. Thus, patent '896 has a claim relating to the amounts to be administered, a broad range of '0.001 mg/kg to about 250 mg/kg'. Also, separate claims regarding administration as an intrathecal injection, as an intracerebroventricular injection and administration by a pump. Each of these facets increases the strength of the protection afforded by the patent.

(8) Claims 3–6 will probably not be allowed, since they are commonly used methods. The other two patents have not listed these methods in their claims.

(9) In claim 7, instead of clubbing neurophysiological and neurological disorders, these could perhaps have been separated. Thus, if for some reason one medical use cannot be allowed, in case they are the subjects of separate claims, then at least one use can still be granted. If they are clubbed, both will be disallowed.

(10) Probably the K&B application could have had several other potential uses listed in the claims. Also, several other variants, either in terms of amino acid

sequence, or modifications of the side-chains, could have been protected.

Patents are a step en route the market. Although we do not have much of a tradition in India, of converting academic science into marketable products, this will change. We need to strengthen our patent applications to make them an effective first step.

Conclusion

One conotoxin is already an approved drug. From tropical waters to Utah and California, and onward to Ireland and mainland Europe, the conotoxins have travelled widely in their path to the clinic. Much remains to be done to determine whether the disulphide bonds of the peptides and amenity to cyclization makes them reasonably reliable drug precursors or scaffolds for drug design. Since there is no dearth of medical need in the areas of pain, convulsive disorders, stroke, neuromuscular block and cardio-protection for all of which the conotoxins have shown hints of activity in the laboratory, let us look forward to more of their numbers making the full journey.

Glossary

Bioavailability: It is the amount of drug that reaches the blood stream. When a drug is given intravenously, bioavailability is 100%. However, if it is given orally bioavailability is less as there is incomplete absorption from the gut and metabolism takes place before it reaches the blood.

Broad claim: A broad claim is drafted to cover all scopes of the invention as it allows the patent owners to exclude others from practising their invention. A narrow claim is more precise, covering a limited number of aspects of the invention. However, it is better to make the individual claims narrow, since each claim will then have a lower chance of being rejected. By having multiple narrow claims, one can have broad patent protection.

Claim: A claim defines the invention. One can have several claims per patent. Each claim is a single sentence. Claim 1 provides a broad definition of the invention, without too many specific details. Claim 2 refers to claim 1, thereby including all the features of claim 1 and adds another detail. Subsequent claims keep adding one feature each, thereby covering a broad area by including more and more specifics. A particular set of words tends to be used while drafting a patent. For example 'said' means 'the', 'comprised of' means 'includes'. This is because these words have been used in the past and interpreted in known ways and the attorneys have confidence in using them again. Using well-accepted words helps predict how the patent office examiner, competitor's patent attorneys and, in case of a conflict, a judge, interpret the claims.

Continuation application: It is a second application for the same invention having additional claims and is filed before the first application is abandoned or is granted. It is useful when it is anticipated that some of the claims may be rejected by the patent examiner or when the inventor wants to cover new areas.

Dependent claim: A claim that refers back to a preceding claim. In the example in Box 2, claim 2 is dependent on claim 1 and claim 5 depends on claim 4.

Disclosed: A patent is a contract between the government and an individual. In exchange for monopoly rights embodied in the patent, an inventor has to reveal or disclose all the details of his/her invention so that his/her invention can be reproduced by any skilled person.

Divisional application: If two independent inventions are covered in one patent application, then the patent examiner may ask the inventor to restrict the application to one of the inventions. If the inventor wishes to protect the other invention and not abandon it, he/she can file another application called a divisional application without losing priority.

Filed: A patent is stated to have been 'filed' once the application is submitted to the patent office.

Granted patents: Once the patent office has 'granted' the patent, it comes into force and can be commercially exploited. A granted patent may also be referred to as an allowed or issued patent.

Independent claim: A claim that does not refer back to or depend on another claim, e.g. claim 1 and claim 3, in Box 2.

Invention: Any object, process or technique which is novel is called an invention.

Narrow claim: See broad claim.

Patent: It is a 20-year exclusive right given to the inventor to use the invention commercially. Granting a patent confers a 'negative right' on a patent owner, because he/she may legally exclude competitors from using his/her invention. However, his/her own freedom to use the patent depends on other pre-existing patents. To get a patent, the invention must be new, it must involve an inventive step and it must have an industrial application. A discovery (of something occurring in nature) cannot be patented.

Prior art: It is the information relevant to the patent application that has been disclosed to the public. This could be by means of published/unpublished patent applications, scientific publications, talks, posters at scientific meetings, etc. A prior art search is done by the inventor to determine whether his/her invention is novel.

Process patent: A process for producing a product can be patented and is called a process patent. Process patents are of particular importance in the pharmaceutical industry and other chemical industries.

Product patent: Patent protection for physical products such as antibodies, recombinant proteins, vectors, etc.

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