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From: "P.Balaram" <pb@mbu.iisc.ernet.in>

Date: Sat, May 4, 2002 2:05 pm

To: Prajna Pal <prajna@mbu.iisc.ernet.in>

Pl. print.
Balaram

----- Forwarded message -----

Date: Sat, 4 May 2002 10:45:28 +0530

From: K S Krishnan <ksk@tifr.res.in>

To: pb@mbu.iisc.ernet.in

Cc: sidd@mbu.iisc.ernet.in

Subject: DBT proposal Cone snail outline

I got your mail about CSIR . This is some blurb I had put together ..we can discuss when I am in Bangalore..I will be there tonight and will come home or lab tomorrow around 10:00 AM ..will call and fix time with you

More than 500 species of predatory Conus have been identified; ~~all~~ in the Indo pacific region. Each of these marine snails produces its own mixture of deadly conotoxins. The toxins are used by these slow moving animals to catch their prey which may be marine worms, fishes and other molluscs. The need for fast acting components for success in their predation has made these snails evolve cabals of potent and highly specific neurotoxins to exploit prey niches. The exquisite specificity of these toxins in mammalian systems that have pharmacologically diverse neuronal macromolecules allows them to block the perception of pain in animals, leaving normal sensory signals intact. Similarly highly specific drugs targeted to neuronal receptors with no side effects due to cross reactivity can be expected to be discovered.

Dr. Baldomero Olivera pioneered the research in these Contoxins. The experimental drug Ziconitide, which is a thousand times more potent than morphine in relieving chronic pain -- without any side effects, was developed by the Neurex Corporation starting from Dr Olivera's first major discovery the μ conotoxin. It is a potential treatment for intractable pain because it helps some patients who were unresponsive even to large doses of morphine. The drug, synthesized to match a toxin produced by Conus magus, is now in Phase III clinical trials involving patients who have AIDS, cancer, or severe non-malignant pain. It is hoped that Ziconitide or SNX-111 will not cause tolerance, in which patients require ever-larger doses of a drug to experience the same effects. An interesting information is that this single compound was instrumental in fetching a price of several hundred millions of dollars for Neurex Corporation when it was bought by Elan recently.

Other Conus species may soon join C. magus in the pharmacopoeia of neuromedicine. Dr. Olivera and and colleagues in collaboration with Cognetix Corporation of Salt Lake City, are testing therapeutic effects of a peptide from the marine snail, C. radiatus, in animal models for epilepsy. The peptide, called conantokin-R, appears to offer powerful protection against seizures but causes few of the behavioral side effects that trouble some users of conventional treatments. Recent studies of a toxin produced by the snail, Conus textile is approaching the end of the research pipeline.

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With more than 100 conotoxins now characterized, and perhaps thousands more awaiting detection or evaluation, those who have joined the fray expect to discover a bounty of potential conotoxin-based drugs in coming years.

But very much more than all that these toxins may prove to be a boon for the neuroscientist, the structural biologist and evolutionary biologist to probe deeper fundamental questions in biology.

Groups in Australia, Israel, China, Philippines and even Singapore have joined the fray and in Australia at least two commercial ventures have been started up with academic and biotech industry participation.

Interestingly to us a large fraction of the cone snail species are found in the coastal regions of India and are unique to this coast. The very fact that they are different species, in view of the evolutionary strategies inherent in the development of toxin cabals in these animals, promises a bounty of unprecedented value in terms of therapeutic drugs if this vast natural richness is exploited judiciously and exclusively. Our great advantage over all competition is this richness of species from Laccadives to Andamans and all of southern Indian coasts. The Marine Biology Center of the Annamali University at Porto Novo is perhaps the only institution from where a beginning on work on cone snail biology was started but which has petered away in the past few years. Some of the expertise in that institution in collecting and identifying is hoped to be input in to this project. This will be combined with strong tradition in structure determination of small peptides and ability to synthesise and modify that is the internationally proven strength of the Bangalore investigators. Bombay has built a tradition of neurobiological investigations both behavioural and electrophysiological studies which are crucial for the Pharmacological characterisation of the activities of peptides hoped to be isolated. These and Cell biological studies to be done at Bombay will be of value to understanding mechanisms of action of these molecules. In addition Molecular biological studies will in the long term circumvent the need for collecting snails and while at the same time help understand the diversity of these toxins. The investigators have proven expertise in all these areas. Dr. Baldomero Olivera who pioneered the studies in conotoxins is keen on helping the project in basic science aspects of conotoxin evolution and biology. Dr. Mani Ramswami of Utah a long time collaborator of the PI will be helping in some Neurobiological and transgenic studies in Drosophila. These foreign collaborations will be undertaken without compromising any commercial advantage that may accrue to local institutions and without transfer of material or intellectual property rights. In addition we hope to provide a feed back to conservation efforts by studying the distribution and biology of cone snails, developing tools of molecular taxonomy and ultimately suggesting measures to prevent over exploitation of the various species by uninformed collectors.

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Objectives:

Identification and structural characterisation of toxic peptides from cone snails

Preliminary Studies:

In the past few months we have done a survey of coastal regions west and east of southern India and identified about 30 species that are commonly collected by fishermen and used for making curios in shell factories in Rameswaram, Parangipettai etc. We have been able to obtain large number of live specimens from fishermen. In fact in the rocky caots of TIFR in Bombay we obtain aplenty stranded live specimens of two species and have successfully kept hem in aquaaria for over two months feeding fish and polychaetes.

We have been able to extract peptide fractions from about six species. The peptides from two of these species C. Amadis and C. Inscriptus have been charcterised MALDI and fractionated by HPLC and sizes determined.

One of the peptides has been now completely characterised and structure determined. It has potent analgesic activity in mice and kills *Drosophila* on application. This attempt has given us an opportunity to standardise the procedures for collection extraction separation and analysis and we are ready to expand this on a very large scale to cover several species.

Plan of action:

In short we will extract peptide fractions from a large number of species we can get hold of in reasonable quantities. This we expect to be at least ten species. The peptides will analysed by MALDI and purified by HPLC . Purified peptides will be used for structure determination. MALDI-TOF /MS , peptide chemistry methods will be used to determine sequence of purified peptides and NMR methods will be the mainstay of structure determination. Biological assay will be performed in mice and flies to determine toxicity and neuroactivity . Pharmacological characterisation and mechanism of action will be investigated by electrophysiology and cell biology.

In addition we have started a modest attempt at making CDNA libraries from glands and will develop ways of expressing the products of these genes. It will be both probed by consensus conotoxin sequences to develop research in expression and regulation of conotoxin genes and also we will try expressing peptides for structural studies and use for transgenic expression for in vivo functional studies with flies.

DBT is needed to fund large scale collection expeditions and facilitate permits and local help from governmental agencies in Andamas and Laccadives as well as coasts Rameshwaram etc. by providing travel and local expenses and hiring and research at Bombay and Bangalore ..support in the form of consumables, equipment and personnel. This detail we will work out.

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