

# Small creature, big potential

Cherry Farrow on the snail that may provide a breakthrough in the fight against chronic pain

**Thursday February 12, 2004**

**The Guardian**

For thousands of years, medical research has depended on plants, animals and microbes to understand and treat human disease. Now increasing attention is being paid to animals for sources of new medicines. One of the most unlikely and beautiful is a small, deadly mollusc - the cone snail.

There is growing excitement among scientists that this marine snail may provide a breakthrough in the development of a series of new painkillers. Cone snails may contain more medicines than any other animal.

A new synthetic drug, Prialt, is now at an advanced stage in clinical trials for the treatment of what is classed as intractable pain - unremitting, untreatable pain. Prialt, derived from the venom or conotoxin of the snail, may be 1,000 times stronger than morphine but without the tolerance or addiction usually associated with opiates.

Cone snails live in shallow tropical waters, on reefs, in mangrove swamps and mud flats. There are thought to be approximately 500 species, although research has focused mainly on three.

The snails have a little harpoon or fleshy foot from which they inject a lethal cocktail of toxins into their prey - other molluscs, worms and fish. They can "shake" the cocktail and create a new mix of changing proportions so their victims cannot develop immunity. Each species has evolved to produce its own set of toxins, about 100, which means there could be as many as 50,000 conotoxins in all.

This is unprecedented in the biological world, says Aaron Bernstein, who is currently conducting research at Harvard Medical School.

"It's the sheer diversity of the chemicals they make. The cone snail is young in evolutionary terms - only 50m years old - yet each has evolved a different number of toxins. Compare this to the 10,000 known alkaloids in plants, which we have been looking at for centuries," he said.

Research into cone snails started 20 years ago. Experiments suggest that conotoxins could treat muscle spasticity, following spinal injury and epilepsy, that is resistant to traditional medicines. A broad spectrum anti-epileptic agent is currently in the first stage of clinical trials.

For years, scientists have searched for a medicine that is very specific, effective at low doses and does not cause side effects of addiction or tolerance. Having to keep increasing doses to achieve the same results has always limited the long-term effectiveness of the opiates used for treating severe pain. Conotoxins do not behave like that -they are very potent in small concentrations, as trials carried out on patients with Aids and cancers have shown.

"Most conotoxins are small peptides, 10 to 40 amino acids in length. They are exquisitely selective about their receptor binding sites," says Bernstein. "This makes them powerful tools for understanding how cells work, as well as a rich source for discovery of new medicines. What is remarkable about them is this ability to be so selective."

Studies suggest that conotoxins could be used to treat muscle spasticity following spinal injuries and possibly prevent cell death during strokes or head injuries. They may also help in the treatment of small-cell lung cancer. By detecting the antibodies, conotoxins can provide an early diagnostic test for some types of cancer.

But it is in the treatment of "untreatable" pain that conotoxin research is furthest advanced. The first large-scale trials show just how effective the new painkiller in its synthetic form may prove to be. Trial results showed no evidence of tolerance or addictive behaviour and in feasibility studies with Aids and cancer patients with chronic pain there was relief in more than half of the patients.

All this from a small marine snail that may, in the words of Eric Chivian, founder and director of the Centre for Human Health and Global Environment at Harvard Medical School, "contain the largest and most clinically important pharmacopoeia of any genus

in nature."

However, the reefs, mud and swamps in which they thrive are all under threat from over-fishing, pollution, mangrove clearance for coastal development, shrimp farming and "bioprospecting" - for private collections as well as the biomedical industry. Millions of cone snails are imported into the US and Europe every year.

"We cannot find any country that monitors this trade," says Chivian. "Although a number of researchers are careful about moving quickly to synthesise the toxins they need, others may not be. No one knows how many and what species are being sacrificed for research and for the ornamental trade in their shells," he says. Global warming is also damaging their ocean habitat. "The loss of species deprives us of invaluable tools for biomedical research. They can give us the insight into health and illness," he adds. "So just as we are appreciating the remarkable potential of the cone snail, they are coming under intense pressure."