Exploring biodiversity

The Harbor Branch Oceanographic Institution (Fort Pierce, FL, USA) has been dedicated to altruistic utilization of ocean resources for more than 25 years. As a charitable, not-for-profit organization, its seven operating divisions (Aquaculture, Marine Operations, Biomedical Marine Research, Engineering, Marine Science, Marine Education and Environmental Laboratory) are largely funded by competitive outside sources ($19.9 million in 1997, representing 68% of total expenses).

Drug discovery in depth

The rich biodiversity of the marine environment is studied by the Biomedical Marine Research division. Many marine organisms, often the sessile species, have evolved unique chemical substances used for their defence, reproduction and communication, and many of these organisms may produce substances suitable for treatment of disease. The ability to access these deep-water organisms is one of the features that makes Harbor Branch's drug discovery programme unique.

After screening extracts of marine organisms, active components are purified using a combination of chromatographic techniques. The active compounds found in deep-sea sponges have promised to be the most fruitful to date. From the *Spongosorites* genus, a series of bisindole alkaloids (topsentins) have been shown to block mediators of neurogenic inflammation, and from the deep-water sponge *Discodermia dissoluta*, the potent antitumour compound discodermolide has been isolated.

Novartis backing

On 7 April 1998, Harbor Branch and Novartis Pharma (Basel, Switzerland) signed an agreement for licensing and development of discodermolide on an exclusive world-wide basis.

Dr Shirley Pomponi (Director of the Biomedical Marine Research division) first collected the deep-sea sponge in 1987. The compound was isolated and characterized by Drs Sarath Gunasekera and Ross Longley at Harbor Branch in 1990. In subsequent studies with collaborators, Dr Longley's research showed that discodermolide was effective in killing various types of human cancer cells *in vitro*, with a mechanism of action similar to that of paclitaxel (Taxol®).

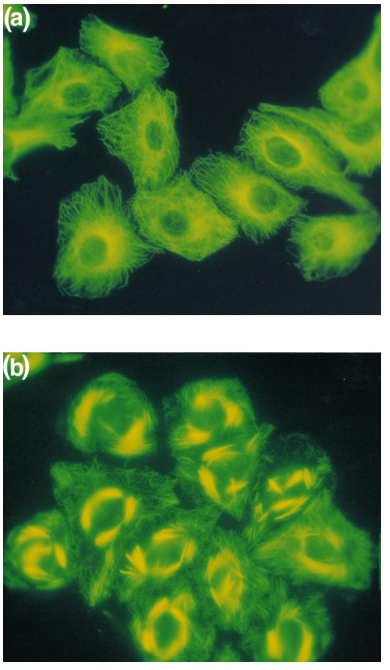
Discodermolide causes an irreversible disorganization of microtubules, which are the structural components of cells (see Figure). This results in the disruption of cellular division and induction of apoptosis. As a result of this work, Harbor Branch was awarded a grant from the NIH National Cancer Institute in 1997 for Drs Longley and Gunasekera to investigate the antitumour properties of discodermolide and its natural and synthetic derivatives.

The structure of discodermolide and its presence within a lithisid sponge led researchers at Harbor Branch to hypothesize that the compound may be produced by a symbiotic microorganism. Research is in progress to localize the compound within specific cells, isolate the symbiont responsible for production of the compound, perform genomic studies, and culture the sponge cells with their bacterial symbionts.

Identification of the genes responsible for the biosynthesis of active compounds and transfer of these genes into organisms that can be cultured easily may provide an opportunity for large-scale production of potential drugs.

Terms of the agreement

Under the terms of the agreement, Novartis is granted exclusive, world-wide rights for the development, use, manufacture and sale of discodermolide for all potential therapeutic indications. Harbor Branch will be financially supported to continue research on discodermolide, and will receive both developmental milestone payments and royalties from sales of the compound as an anticancer drug.



Human cancer cells stained with fluorescently labelled anti-α-tubulin antibody reveal the microtubules and the cytoskeletal architecture. (a) Untreated cancer cells showing cytoskeleton; the microtubules assist in the separation of chromosomes during cell division. (b) Shows the effects of discodermolide treatment. The microtubular network becomes disorganized by binding of discodermolide, and formation of microtubular bundles disrupts cell division resulting in induction of apoptosis. Photographs courtesy of Harbor Branch Oceanographic Institution.

J. Seward Johnson, Jr (Chairman of Harbor Branch) says that 'this agreement is the result of over 14 years of

 1359-6446/98/$19.00. PII: S1359-6446(98)01200-8

drug discovery research at Harbor Branch, and is the culmination of the last eight years of research on discodermolide by the Harbor Branch team. Given the exciting and promising preclinical data on discodermolide and the expertise which Novartis provide, our hope is that discodermolide will eventually surpass other chemotherapeutic agents as an effective treatment for cancer.'

The funding that will result from this venture will boost the ongoing quest of the Biomedical Marine Research division, which is not only to identify new compounds for drug discovery screening but also to develop methods for sustainable use of marine life that yield potential therapeutic agents.

Simon Fenwick

TB compounds to the rescue after heart attack?

Every year around 330,000 people in the UK and some 1.5 million in the USA suffer a heart attack. Current research on a chemical associated with tuberculosis may lead to a new drug for heart attack victims that reduces the amount of damage they sustain and allows them to resume a more normal life afterwards. The discovery was made serendipitously by two physician brothers in different disciplines who happened to discuss their individual research at a family gathering. Lawrence Horwitz, Professor of Medicine and Cardiology at the University of Colorado Health Sciences Center (Denver, CO, USA) was researching the after-effects of a heart attack, reperfusion, when the blood supply is restored. A conversation with his brother Marcus – a research worker in tuberculosis at the UCLA School of Medicine (Los Angeles, CA, USA) – led to consideration of the effects of a group of compounds called the exochelins. *Mycobacterium tuberculosis* uses the highly lipophilic exochelins as siderophores to 'soak up' iron from its surroundings. The brothers hypothesized that such a property might be useful in preventing further damage during reperfusion.

Oxidative damage

Reperfusion actually introduces high concentrations of hydroxyl radicals (•OH) to the heart tissue. The hydroxyl radicals propagate the formation of oxygen free-radical species, which cause tissue damage leading to congestive heart failure. This impairs the heart's ability to pump blood. Severe sufferers of this condition generally lose their ability to perform ordinary daily tasks that require only minimal exertion, and they tend to require frequent visits to hospital.

Numerous advances have been made in treating heart attacks in the form of angioplasty and thrombolytic drugs that rapidly reopen blocked arteries and greatly reduce the number of deaths. The very act of reopening a blocked artery, however, can lead to reperfusion injury. There is at the moment no treatment for this, although researchers have actively sought one for years.

Joint study

The two doctors decided to pursue a joint study once they had made the putative connection between the iron-scavenging compounds produced by *M. tuberculosis* and reperfusion injury caused by iron-mediated hydroxy radical formation. With funding from the National Institutes of Health and with colleagues Jovana Gobin (UCLA) and Nancy Sherman, Yinong Kong, Adrian Pike and Paul Fennessey (University of Colorado Health Sciences Center), they set about isolating the exochelins from *M. tuberculosis* and testing what effect they had on reperfusion injury. The researchers found that when blood flow is restored after a heart attack, exochelins introduced into the area actually prevented reperfusion injury in laboratory animals [Horwitz, L.D. *et al.* (1998) *Proc. Natl. Acad. Sci. U. S. A.* 95, 5263–5268].

'It's ironic that a chemical that contributes to the survival of tuberculosis bacteria may also play a critical role in helping heart attack victims', says Marcus Horwitz. 'Previous animal research has shown that after a heart attack and treatment to reopen blocked coronary arteries, up to 60% of subsequent damage to the heart is caused by reperfusion injury. We believe that exochelins could dramatically improve recovery from heart attacks', adds Lawrence Horwitz. 'The unique properties of the exochelins may also render them useful for the treatment of other diseases involving blocked arteries, such as stroke', his brother adds.

Nevertheless, the isolation of a putative drug lead of this kind and the demonstration that it works in an animal model is a long step away from producing a viable drug for treating reperfusion injury. Further research is under way.

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  1359-6446/98/$19.00. PII: S1359-6446(98)01198-2