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