

Halaven – the New Zealand connection

UC Chemists' research work assists cancer drug breakthrough

On 15 November the US Food and Drug Administration approved for use a new drug eribulin mesylate (Halaven) for treatment of refractory breast cancer.¹ The CEO of Eisai Co., Ltd (the parent company of US-based Eisai Inc., the makers of this drug) has said that Halaven could command a US\$1-billion/year market when it is approved for treatment of other cancers.² This synthetic compound has a crucial connection with work started in 1983 by the University of Canterbury chemists Emeritus Professors John Blunt and Murray Munro.

From a deep-water collection of marine sponges off Kaikoura, post-doc Dr Rob Lake identified one sample (then referred to as yellow-slimy, but subsequently characterised as a *Lissodendoryx* species) that yielded an extract with exquisitely potent activity against cultured cancer cells (work done by Gill Ellis at UC), and in an animal model provided a remarkable life extension (T/C) of 250%. In 1988 Rob Lake eventually identified the active compound as halichondrin B, which had just become known from work by a Japanese group in 1985³ and later also identified by a group in Arizona from a range of different sponges in 1991 and 1993.⁴ Rob Lake's work was not published until 1994, after further work at UC by post-doc Marc Litaudon and PhD student Jo Hart had identified a new version of the halichondrin, isohomohalichondrin B.⁵ Subsequent publications in 1997⁶ and 2009⁷ revealed a range of other halichondrins from studies by Marc Litaudon and PhD students Rachel Lill and Sarah Hickford.

The US National Cancer Institute (NCI) were very interested in obtaining a large supply of halichondrin B to extend studies they had initiated which indicated a novel mode of action for this compound in arresting the growth of tumor cells. The yields of this compound from the Japanese and US collections of sponges were extremely small, whereas the NZ *Lissodendoryx* sponge had a ten-fold better return, typically 0.4 mg/kg of sponge. The NCI then organized a contract with the UC group to supply much larger quantities of the halichondrin B. Following ROV-based surveys conducted by Dr Chris Battershill (previously a post-doc at UC) at NIWA which established a likely population of about 289 ± 90 tonnes of the sponge at Kaikoura, approval was given by the New Zealand Government for the collection of 1,000 kg of the sponge by deepwater dredging.⁸ Extraction of the sponge was carried out by Dr Stephen van Eyk at New Zealand Pharmaceuticals <<http://www.nzp.co.nz/>> in Palmerston North, a company whose CEO then was Dr Richard Garland and manager Dr Selwyn Yorke, all three being UC chemistry graduates. Final purification of 310 mg of halichondrin B was achieved at UC by Sarah Hickford. This supply to the NCI enabled them to carry out xenograft experiments in mice, the early results of which caught the attention of the Eisai Company in 1998. In partnership with Professor Kishi at Harvard University, whose initial synthetic work on halichondrin B was funded by the NCI through a competitive R01 grant, Eisai had been exploring the synthesis of analogs⁹ of halichondrin B following Prof Kishi's successful total synthesis of this compound in 1992.¹⁰ A head to head comparison in late stage xenografts at NCI of two of the Eisai analogues, the future eribulin and its diol precursor, with the New Zealand-supplied halichondrin B, showed that eribulin was a much better candidate for development as an anticancer drug.¹¹ Accordingly, Eisai, who were about to drop their project, continued with the development of eribulin, initially in conjunction with the NCI, through successful clinical trials leading to the latest outcome of approval of eribulin mesylate as a drug. Dr David Newman, the current Chief of the Natural Products Branch at the NCI, and who organized the New Zealand supply contract and the subsequent collaborations with Eisai, has said that "Without the New Zealand material and the work done in New Zealand, none of the future development would have occurred."

The halichondrins are very complex molecules and have continued to be the subject of effort in many labs world-wide directed at the total synthesis of these compounds. Professor Kishi's group was the first to complete a total synthesis.¹⁰ A very recent success, providing the shortest synthesis to date, has also been reported by Prof Andy Phillips (a chemistry PhD graduate from UC) now at Yale University, but with the

halichondrin work done at Colorado.¹² He has said that information from research on the acid-catalysed reactions of the halichondrins published by UC PhD student Jo Hart in 1996¹³ was critical to his ability to complete his total synthesis.

This release to market of Halaven is another example of the value of the study of natural products in the development of drugs for human and animal use. A recent example is Taxol[®] which also took many years for development from the original discovery of the natural product, and the expenditure of several \$100 m, to get a product to market.

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