Institution: Heriot Watt University

Unit of Assessment: 8 Chemistry

Title of case study: Harnessing Marine Micro-organisms for the Life Sciences Sector

1. Summary of the impact

Aquapharm is a biotechnology company founded by Dr. Andrew Mearns-Spragg that stemmed from the PhD work, supervised by Prof David Adams and Prof Grant Burgess that he conducted at Heriot-Watt University (HWU). Aquapharm seeks to harness the chemical diversity of marine micro-organisms as a source of life-enhancing pharmaceuticals and products for the food and beverages industry. Investment of >£10M has seen Aquapharm employ up to 24 staff and it currently has 8 staff based at both the European Centre for Marine Biotechnology in Oban and in Edinburgh. Aquapharm has identified >10,000 marine microbes, filed 11 patents and is developing new antibiotics that are effective against multi-drug resistant bacterial pathogens.

2. Underpinning research

Natural products make a major contribution to today's pharmacopoeia, with over two thirds of clinically used anti-bacterials falling into this category or being semi-synthetic derivatives of natural antibiotics. However, the widely-publicised problem of bacterial resistance to drugs poses a serious and growing threat to health, requiring the development of new agents to treat infections. The identification of new sources of novel biologically active microbial metabolites therefore remains a priority.

Efforts to discover antibiotics from microbes have traditionally focused on the terrestrial environment; for example soil-borne actinomycetes have proven a particularly rich source of antitumour-antibiotic compounds in the past. In contrast, the marine environment had received comparatively little attention, in part because of the long-held belief that seawater contains few microbes. The crucial contribution of the HWU team, comprising Prof David Adams (HWU, Institute of Chemical Sciences) and Prof Grant Burgess (HWU, School of Life Sciences, now at Newcastle University) , was to demonstrate that marine surfaces in fact constitute a fiercely competitive microbial environment. Organisms living in this niche can therefore be a rich source of antibacterial compounds that they themselves produce to gain a colonisation advantage.

Based on their initial insight, Adams and Burgess instigated a collaboration to study the chemical ecology of epiphytic marine bacteria and to develop a marine biotechnology programme to exploit this potentially rich source of biologically active secondary metabolites. A particular focus was to screen for compounds with activity against pathogens responsible for hospital-acquired infections.[1-6] Funding for their programme was obtained from the NERC, the Scottish Hospital Endowments Research Trust and Wyeth-Ayerst.

Through their research Adams and Burgess first confirmed that marine bacteria associated with algal surfaces can indeed produce compounds that possess antibacterial and repellent activity.[1,4] They were also able to demonstrate cross-species induction of antibacterial responses in some cases.[5,6] Moreover, by comparing culture conditions in conventional shake-flask suspensions with those in a specialist air-membrane surface bioreactor it was found that, at least with some species, production of antibacterial metabolites was dependent upon the unique physical context afforded by a biofilm environment.[5] The team investigated the metabolites responsible for antibacterial activity in a number of cases[2, 3] as well as the mechanisms of cross-species metabolite induction.

Much of this research formed part of the PhD work undertaken by Andrew Mearns-Spragg at Heriot-Watt University.[2,6] Upon completion, Dr Mearns-Spragg made direct use of the concepts and ideas developed through the Adams/Burgess collaboration to found a spin-out company, Aquapharm.

3. References to the research (* = best indicates the quality of the underpinning research)

1. K. G. Boyd, D. R. Adams, and J. G. Burgess. "Antibacterial And Repellent Activities Of Marine Bacteria Associated With Algal Surfaces." Biofouling 14, 227–236 (1999). http://dx.doi.org/10.1080/08927019909378414

2.* Z. Jiang, K. G. Boyd, A. Mearns-Spragg, D. R. Adams, P. Wright, and J. G. Burgess. "Two Diketopiperazines And One Halogenated Phenol From Cultures Of The Marine Bacterium, Pseudoalteromonas Luteoviolacea." Natural Product Letters 14, 435–440 (2000). http://dx.doi.org/10.1080/10575630008043781

3.* Z. Jiang, M-O. Barret, K. G. Boyd, D. R. Adams, A. S. F. Boyd and J. G. Burgess. "JM47, A Cyclic Tetrapeptide HC-Toxin Analogue from A Marine Fusarium Species." Phytochemistry 60, 33–38 (2002). http://dx.doi.org/10.1016/S0031-9422(02)00061-4

4. J. G. Burgess, K. G. Boyd, E. Armstrong, Z. Jiang, L. Yan, M. Berggren, U. May, T. Pisacane, A. Granmo and D. R. Adams. "The Development Of A Marine Natural Product-Based Antifouling Paint." Biofouling 19 (Supplement), 197–205 (2003). http://dx.doi.org/10.1080/0892701031000061778

5.* L.Yan, K. G. Boyd, D. R. Adams and J. G. Burgess. "Biofilm-Specific Cross-Species Induction Of Antimicrobial Compounds In Bacilli." Applied and Environmental Microbiology 69, 3719–3727 (2003). http://dx.doi.org/10.1128/AEM.69.7.3719-3727.2003

6. A. Mearns-Spragg, M. Bregu, K. G. Boyd and J. G. Burgess. "Cross-Species Induction And Enhancement Of Antimicrobial Activity Produced By Epibiotic Bacteria From Marine Algae And Invertebrates, After Exposure To Terrestrial Bacteria." Letters in Applied Microbiology 27, 142–146 (1998). http://dx.doi.org/10.1046/j.1472-765X.1998.00416.x

Grants

1. NERC, £72,980 GST/02/1633 (Burgess/Austin/Wilkinson/Adams): "Chemical Ecology of the Seaweed Surface: Antifouling Activity of Epiphytic Bacteria from Intertidal and Subtidal Seaweeds." Awarded: 1.3.1997

2. Scottish Hospital Endowments Research Trust, £39,943 (Burgess/Adams/Wright): "The effect of novel chemical inducers (signal molecules) on production of antibiotics active against multi-drug resistant hospital pathogens." Awarded: 23.2.2001

3. Wyeth-Ayerst, £98,000 (Burgess/Adams): "Chemical communication between marine bacteria." Awarded: 23.7.2001

4. NERC, £143,018, NER/T/S/2002/00586 (Burgess/Adams) "Characterisation of a biofilm specific, cross-species cell signalling system regulating the release of antimicrobial compounds and pigments in marine bacilli." Awarded: 24.2.2003

5. NERC, £30,935, NER/T/S/2003/00729 (Burgess/Adams): "Biofilm disrupting bacteria from marine bacteria" Awarded: 4.12.2003

6. NHS Chief Scientist Office, £285,000 (Austin/Jamieson/Morris/Mitchell/Schweitzer/Adams/ Mearns-Spragg): "New anti-infectives for the control of antibiotic-resistant human pathogens." Awarded: 1.12.2008

4. Details of the impact

Aquapharm is a biotechnology company that was founded in 2000 by ex-Heriot-Watt PhD student Andrew Mearns-Spragg. The company is based at the European Centre for Marine Biotechnology in Oban and has a corporate office and labs in Edinburgh. It targets applications in unmet clinical needs, for example in oncology and multi-drug resistant bacterial infections, including auto-immune diseases, tissue-damage caused by chronic and degenerative diseases. It has recently broadened its portfolio to address needs in the foods and beverages and cosmetics sectors.

Aquapharm's core business is directly linked to the marine biotechnology programme arising from the Adams/Burgess collaboration at Heriot-Watt of which the PhD work of Dr. Mearns-Spragg formed an important component. As stated by Dr. Mearns-Spragg:

"The research carried out at Heriot-Watt fundamentally established the basis of the company's core business of harnessing chemical diversity of marine micro-organisms to develop life-enhancing pharmaceuticals".

Aquapharm has now amassed a collection of over 10,000 marine microbes from which it has identified several promising lead molecules with a range of attractive properties. These include a new antibiotic compound, AQP-182, with broad spectrum activity against multi-drug resistant bacteria including multi-drug resistant *Staphylococcus Aureus* (MDRSA), multi-drug resistant *Streptococcus Pneumoniae* (MDRSP), *Clostridium Difficile* and *Enteroccocus Faecalis*. These multi-drug resistant bacteria are common causes of death in patients in hospital care units. Andrew Mearns-Spragg commented:

"We're very pleased with the output of our drug discovery platform based on marine microorganisms. From an initial screening of a small portion of our natural product library we have identified 16 novel compounds belonging to totally novel and diverse chemical classes. The most advanced compound AQP-182 has a promising pharmacological and pharmacokinetic profile which is extremely relevant for the treatment of hard to treat resistant bacterial infections."

AQP-182 is one of several compounds now in pre-clinical development at Aquapharm. Initial *in vivo* studies of AQP-182 suggest greater potency than the current 'best-in-class' drug used against MDRSA. In 2012 a further discovery of a potential anti-cancer agent was made [Text removed for publication] .

Over the last decade, Aquapharm has been successful in accessing funds to support collaborative research and development. In August 2005, Aquapharm received £1.4M funding managed by the Scottish Enterprise Investment Arm to develop new products founded on the chemical diversity of marine micro-organisms. Follow-up funding of £4M was then received in July 2007, again through Scottish Enterprise Investment Arm, and including investment from Aescap Venture, Tate & Lyle Ventures, NESTA Investments and Highlands and Islands Enterprise. In April 2010 the same partners made a further investment of > £4M. In October 2010, Aquapharm signed a joint research agreement with Leatherhead Food Research with the aim of identifying natural, marine-derived food preservatives using Aquapharm's extensive collection of marine micro-organisms.

These various funding streams and interactions have resulted in significant employment throughout the REF period, which reached a peak of 24 staff in 2010. Following a review of strategy direction in 2012, Aquapharm is aiming to re-expand from the current level of 8 employees. The company has 11 patents filed, 3 being in the current REF period: *Production of Biocompounds*; US2008293097 (27/11/2008): *Biological Production of Zeaxanthin and Carotenoid Biosynthesis Control*; US2010144003 (10/6/2010): *Induction of Microbial Secondary Metabolites*; US2011123470 (26/5/2011): *Natural Bioactive Compounds*.

In a recent development Aquapharm has entered into partnership with German industrial biotechnology firm c-LEcta, who target the identification and engineering of microorganism strains and enzymes for bio-catalytic industrial processes. Supported by €613k from the Eurostars

Research and Development (co-funded by the European Community and 33 EUREKA member countries) the Aquapharm/c-LEcta partnership has already launched its first product, a searchable genomic library using over 2,000 strains of marine bacteria. This library can be screened by potential customers from the burgeoning life sciences sector who are seeking novel biologically active microbial metabolites and enzymes with specific characteristics.

5. Sources to corroborate the impact

A senior manager, Aquapharm. Will corroborate the economic impact of the technology in terms of Aquapharm, and will be able to confirm the various collaborations and projects and the breadth of pharmaceutical applications of the technology.

Dr. Andrew Mearns-Spragg. Will confirm the connection between his PhD research, the founding of Aquapharm and its on-going business.

www.aquapharm.co.uk