THE COLLABORATIVE INNOVATION OF
COMMERCIALLIY VIABLE
MARINE-BASED NUTRACEUTICALS

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Abstract

Biotechnology is turning a traditionally low-tech industry (food) into a high-tech industry (functional food/nutraceuticals). Prior research has revealed that in varying degrees, the food industry worldwide is moving from low to high knowledge complexity, and that managerial uncertainty is being compounded by the closer fit between the functional food and the pharmaceutical industries as compared with the traditional food industry. There is thus the need to enhance managerial understanding by clarifying the nature of innovation processes in the functional food industry, including the role of R&D and collaboration.

The present investigation focuses on a particular segment of the functional food industry, viz. marine-based nutraceuticals. Two cases comprise the vehicle of understanding. The twin cases exemplify the various hurdles that thwart the fullest realization of the business potential of marine bio-actives in the pharmaceutical space. Nevertheless, the innovation of commercially viable marine-based nutraceuticals/cosmeceuticals is yet possible if the extraction route for supply is a feasible fallback option, should industrial-scale synthesis prove elusive.

Effectiveness in innovation is facilitated by the collaboration of various disciplines including epidemiology and/or folk medicine, aquaculture/fermentation, natural products chemistry, and relevant strands of medical, pharmacological, and clinical research; in this regard, the inter-disciplinary field of ethno-pharmacology rises to prominence. Universities and government research institutes may be well-positioned to drive such collaboration and reap the benefits from problem definition in addition to problem solving.

Keywords: nutraceuticals; marine biotechnology; collaboration; functional foods; natural products; aquaculture.
Introduction

The food industry has been traditionally characterized as having a low intensity of R&D, as a result of which it tends to be a downstream, consumer-oriented ‘carrier’ of new technologies that are developed in upstream, high-tech industries such as electronics (Grunert, Harmsen, Meulenberg, Kuiper et al. 1997, p. 7; Morgan et al. 2003, p. 335). A reflection of the low research intensity of the industry is the comparatively small investment in R&D. In the UK, the R&D expenditure of the food-processing sector has been estimated as 0.3% of sales intensity compared with an average intensity of 2.1% in manufacturing as a whole (Morgan et al. 2003, p. 335). In turn, the low intensity of R&D has been touted as a possible reason for the relative paucity of research into innovation in the food industry (Harmsen, 1996, as cited in Harmsen et al., 2000).

However, the research landscape is changing very rapidly: biotechnology is turning a traditionally low-tech industry (food) into a high-tech industry (functional food) (Brännback and Wikelund 2001, p. 197). While no commonly accepted definitions of the terms ‘functional food’ and ‘nutraceutical’ exist (Hobbs 2002, p. 559; Ovesen 1999, p. 809), it suffices for the present purpose to adopt the definition furnished by the 2002 Merriam-Webster Medical Dictionary: “any foodstuff enhanced by additives and marketed as beneficial to health and longevity; also called nutraceutical [a foodstuff [as a fortified food or a dietary supplement] that is held to provide health or medical benefits in addition to its basic nutritional value].”\(^1\) (In particular, we do not distinguish between the two terms strongly, as the distinction between them is becoming blurred [Hobbs 2002, p. 560].)

Given the requirement of science-based research, the functional food ‘revolution’ (Heasman and Mellentin, 2001) is being accompanied by a sea change in the level of R&D expenditure: 10-20% of revenues (Brännback and Wikelund 2001, p. 203). The differential level of R&D manifests in an order-of-magnitude increase in the rate of new product development. Although functional foods represent a market share of less than 1% of the total food and drinks market in Germany (and in the whole of Europe as well), they accounted for 19% of all innovations in that market in Germany in 1999-2000 (Menrad 2003, p. 182). Thus, after adjusting for market share, the rate of innovation in the functional food segment would appear to be nearly twenty times that of the overall food industry.

Such a heightened pace of change is ushering in a new ‘dominant logic’ (Brännback and Wikelund, 2001) in the food industry of Finland, which has been described as “a kind of Silicon Valley” of functional foods (Darrington 2003, p. 9), and elsewhere in the world. The term ‘dominant logic’ is attributed to Prahlad and Bettis (1986). It refers to how managers perceive what happens in the external business environment and bring that perception to bear upon possible changes in the knowledge base of the company, which in turn enables the company to innovate products and services for its key markets (Brännback and Wikelund 2001, p. 203).

In their study of the Finnish food industry, Brännback and Wikelund (2001) concluded that the changes in the industry, since 2000, pertained to the emergence of functional foods. Brännback and Wikelund (2001, pp. 203-204) tabulated these changes in terms of market dynamics, production processes, R&D, pricing, market communication, and competitive scope. They concluded that the Finnish food industry had moved from low knowledge complexity to high complexity. Through interviews with 11 managers from four small-and-medium-sized food companies,

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they found that the closer fit between the functional foods and the pharmaceutical industries as compared with the traditional food industry compounded managerial uncertainty (p. 205). Most managers were experiencing great frustration that the industry, of which they used to be masters and had a sound understanding, was undergoing dramatic changes. Knowledge collaboration (e.g. partnering with a biotech firm that provided a nutraceutical ingredient that the food company then commercialised) appeared to be the only viable route to business success (Brännback and Wiklund 2001, p. 203, p. 205).

The findings of Brännback and Wiklund (2001) highlight the need to enhance managerial understanding by clarifying the differential nature of innovation processes and activities in the functional food industry, including the role of R&D and collaboration. That being said, it is also important to note that thus far, the distribution of innovations in the functional food industry has been skewed towards the soft drinks, confectionery, dairy, bakery, and baby food market-segments. For instance, these segments together accounted for over 90% of innovations of functional foods in the food and drinks market in Germany during 1999-2000 (Menrad 2003, p. 182). During that period in Germany, the other segments accounted for 38% of all innovations in the food and drinks market but only 8% of functional food innovations in the same market.

As a result, the extrapolation of the insights received from sectors such as dairy would have to be tempered by the contexts of individual sectors, such as seafood, which are presently under-represented in the functional food landscape. The imperative of speaking explicitly to the sectoral context of seafood arises in the present study, which has been conducted under the aegis of an ongoing four-year project entitled ‘Determinants of innovation and growth in the seafood sector.’ The project was in turn sponsored by the New Zealand (NZ) Foundation for Research Science & Technology (FRST) expressly towards the goal of stimulating innovation-led growth in the NZ seafood sector.

Nutraceuticals and functional foods that are derived from marine life-forms constitute an emergent industry with considerable potential for knowledge creation and value-added growth in the NZ seafood sector. In a keynote address given at a recent conference of the NZ Seafood Industry Council jointly by the Chairman and the CEO of Crop & Food Research, a NZ Crown Research Institute, the two executives acclaimed the potential of aquaculture in producing unique bio-actives for the production of pharmaceuticals and nutraceuticals (Bentley and Tocker 2004, p. 4).

Against the above backcloth to the present investigation, we frame our research questions as follows: What are the salient features of innovation processes for commercially viable functional foods/nutraceuticals with specific reference to the seafood sector? In particular, what is the role of collaboration? How can such collaboration be managed?

Our operational definition of ‘innovation’ follows OECD guidelines: innovation is the introduction of a new or significantly improved product or service to the market, or the introduction of a new or significantly improved process to a business. In the manner of Harmsen et al. (2000, p. 152), who reported case study research on food companies, and in keeping with the 1980 Frascati Manual (OECD, 1981), we treat R&D (Research & Development) as being mainly the scientific steps associated with the innovation process. This process also consists of those technical, commercial, and financial steps that are needed for the successful development and marketing of new or improved products and the commercial use of new or improved processes.

The manuscript is laid out as follows. We first review the relevant literature on
innovation processes in the traditional food-processing industry as well as the functional food industry. We also briefly discuss the field of marine biotechnology in a manner that befits the objectives of the present research. Then we present the methodology for the case study research into the innovation of marine-based nutraceuticals. Following the case descriptions, we draw various implications for the innovation of such products and the management and organization thereof.

Literature review

Innovation in food

As noted earlier, research into innovation in the food industry is rather scant. Under the aegis of the UK Government’s Foresight Programme, Morgan and Blake (1999) and Morgan et al. (2003) undertook case study research into the UK food and drink industry to reveal the manifold ways in which firms have been innovative in their use of technology. The aim of Morgan et al. (2003)’s research was “to highlight innovation in the food chain and to disseminate the lessons from the processes and outcomes of this innovation to the broader sector,” (p. 335). Their analysis was at the level of specific innovations within the food chain and they profiled eight cases of product and/or process innovation.

In the 1990s, as part of a research project entitled ‘Structural change in the European food industries,’ an international group of researchers conducted collective case studies of the product development function in food-processing companies that were dispersed across six European countries (Traill and Grunert, 1997). The resulting insights were documented first by Grunert, Harmsen, Meulenberg and Traill (1997) and then by Harmsen et al. (2000) and Traill and Meulenberg (2002). A summary finding of these studies was that a food-processing firm will be mainly driven by one of three orientations (product, process, and market), which would also influence and direct the acquisition of the remaining supplementary competencies (Harmsen et al. 2000, p. 159; Traill and Meulenberg 2002, p. 6).

None of the cases examined by Morgan and Blake (1999) and Morgan et al. (2003) featured functional foods. On the other hand, the anthology of Traill and Grunert (1997) did feature a case study (Göransson and Kuiper, 1997) of Skånemejerier (Skåne Dairies), a co-operatively owned Swedish dairy company in the south of Sweden (Skåne) that has been very active in the development of functional foods. (Skånemejerier had accordingly been deemed to have a ‘product’ orientation [Traill and Meulenberg 2002, p. 3].)

Functional foods were the explicit focus of Mark-Herbert (2002, 2004), who examined the process of their innovation through four longitudinal case studies situated in Sweden, one of which featured Skånemejerier. All the four cases of Mark-Herbert involved probiotics (these are “live microbial feed supplements which beneficially affect the host animal by improving its intestinal microbial balance” [www.dictionary.com]). A summary finding of Mark-Herbert (2004, p. 714) was that the successful innovation of functional foods requires creative management that encompasses both entrepreneurial and strategic planning perspectives.

Skånemejerier had been studied by Mark-Herbert (2002, 2004) in the context of ProViva, a probiotic fruit drink that the dairy co-operative produces and markets. ProViva is based on a Lactobacillus strain, Lp299v, which had been discovered earlier by Probi AB, a research firm that specializes in probiotics. In fact, ProViva eventuated through a partnership between Probi and Skånemejerier. (The discovery and
development of Lp299v and ProViva has been narrated variously by Göransson and Kuiper [1997, 169-170], Mark-Herbert [2002, Chapter 5], Lagnevåg et al. [2003, Chapter 6], and Langlais, Janasik and Bruun [2004].

The in-house R&D-activities at Skånemejerier have been characterized as “r&D,” (Mark-Herbert 2002, p. 67): the relatively small r at Skånemejerier symbolizes the firm’s links with Probi AB (besides universities) while the large D symbolizes the vast knowledge, skills and technology within Skånemejerier that is related to handling raw materials, production, packaging, marketing, distribution, and sales. In a similar vein, Traill and Meulenberg (2002, p. 16) observed that the R&D activities at Skånemejerier are focused on development issues whilst more fundamental research is contracted to external research groups. Partnerships between entrepreneurial scientists, input suppliers, food processors, and/or medicinal supplement firms, have been necessitated in the value-chain for functional foods/nutraceuticals by the rapid growth of the sector (Hobbs 2002, p. 559).

The relationship between Probi and Skånemejerier has also been cast in the perspective of knowledge networking by Langlais, Janasik and Bruun (2004). In the analysis of Langlais et al. (2004), the identification of the Lp299v bacterium entailed ‘pioneer’ networking, wherein temporary bridges were built between distinct knowledge frameworks by using ‘boundary’ objects such as charts, simulations, pictures, concepts, etc. On the other hand, the commercialization of Lp299v (e.g. through probiotic foods such as ProViva) and the search for other similar bacilli with interesting properties entailed a measure of ‘modular’ networking wherein a central coordinator integrated/synthesized knowledge that other members produced independently. A third mode of networking is translational. Here, the members of the network communicate directly with each other by using a shared language or some other mediating structure.

Distributed innovation, wherein companies carry out innovations through collaboration with outside partners, is possible only in those fields that lend themselves to the decomposition of innovation-related tasks (Valentin and Jensen 2003, p. 277). Complex problems that manifest interdependencies between their constituent components cannot be decomposed. A corollary of decomposability is specialization and collaboration: firms such as Skånemejerier realize innovations such as ProViva by pursuing research collaboration with outside partners, e.g. Probi AB, and compensating by building stronger capabilities in manufacturing and marketing (Valentin and Jensen 2003, pp. 277-278).

The identification of Lp299v and the subsequent development of ProViva belong to that realm of food science and technology which utilizes lactic acid bacteria (LAB). Valentin and Jensen (2003) investigated the nature of distributed innovation in this field, using primarily the 180 biotech-related LAB patents that had been claimed until the year 2000. They proposed that problem processing could be split into problem definition/identification and problem solving, each of which may have differing degrees of decomposability in innovation processes. From their data, they concluded that LAB biotech R&D manifested highly decomposable problem solving but low decomposability of problem identification. Thus, firms with strong R&D integration capabilities are “advantaged by being positioned in the point of confluence (emphasis not authors’) of critical flows of opportunities that allows them repeated extractions of valuable problem definitions... once defined, these problems lend themselves to partition-friendly solution,” (Valentin and Jensen 2003, p. 280).

In most of the 180 LAB patents that Valentin and Jensen (2003) examined, the patent was assigned to only one of the R&D partners. This reflected the assignee’s
playing “a leading role in orchestrating (emphasis not authors’) the R&D producing the patent and in identifying the problems and the benefits that motivate the R&D project,” (p. 292).

In contrast with the pharmaceutical-related biotech discovery chain that prevails in the US, dedicated biotech firms were present only marginally in LAB biotech and their role emphasized problem solving over problem definition (Valentin and Jensen 2003, p. 292). While universities contributed almost half of all the inventor organizations that underlay the 180 patents, their share of patent assignments was only six percent. (However, in pharmaceutical-related applications of LAB biotech, where “information on opportunities and targets flow in decomposed forms in the public domain,” universities could play an increasing role in problem definition [Valentin and Jensen 2003, p. 296].) Unilever, Nestle, and Chr. Hansen accounted for 38% of all patent assignments (Valentin and Jensen 2003, pp. 290-291). The authors thereby concluded that only a few of the actors in LAB biotechnology were positioned at points of confluence.

With reference to Chr. Hansen, which is a world leader in cheese ingredients, Valentin and Jensen (2003, p. 294) described an example of low problem decomposability in the deployment of LAB biotechnology for reducing cheese maturation time. Through their deep understanding of the cheese maturation process, Chr. Hansen knew precisely those leverage points in the process where the most return on investment in biotechnology could be realized.

Marine biotechnology

Marine organisms, such as microalgae and invertebrates, have been acclaimed by marine biotechnologists as being a largely untapped reservoir of novel and biologically active compounds (Luiten et al. 2003, p. 429). For example, polyunsaturated fatty acids and novel lipids can be produced by marine organisms for subsequent use in nutraceuticals.

Notwithstanding this potential, prior to 2003, not a single marine natural product compound had been approved as a drug (Mendola 2003, p. 441). In the course of a review of marine pharmacology and from the perspective of bioprospecting, Faulkner (2000) discussed some difficulties that are encountered during the development of anti-cancer and anti-inflammatory agents from marine bioactives. Figure 1 depicts these difficulties as well as other challenges that are induced from Faulkner’s review of various bioactive marine natural products. An additional reason that has been cited for the dearth in the development of marine compounds as therapeutic agents is “the lack of an analogous ethno-medical history as compared with terrestrial habitats,” (Amador et al. 2003, p. 1607).

It should be noted that whilst a compound may have not yet been developed into a drug, it can still have commercial value. A case in point is pseudopterosins, which are a group of bioactive natural products extracted from the gorgonian (sea whip) _Pseudopterogorgia elisabethae_, which is found in the Caribbean. As of the time of Faulkner’s review, pseudopterosins had not been developed as anti-inflammatory drugs. However, a partially purified extract of the sea whip was being used as a ‘cosmeceutical,’ specif. an additive in cosmetic products made by Estee Lauder. The “supply problem” (Faulkner 2000, p. 141) is at play here: demand for the extract is estimated at five times the current supply. Although the gorgonians occur between 45 and 75 ft depth, diving is limited to about 60ft to allow the deep-water specimens to furnish a reservoir of breeding stock.
The logistics of expeditions for collecting organisms

Harvesting and handling several kilo-tonnes of biomass, owing to low yields of compounds

Constraints on harvest volumes due to considerations of sustainability and biodiversity conservation

The isolation and structural elucidation of marine extracts

Complexity of synthesis

Need for successful formulation of the compound for \textit{in vivo} use

\textbf{Figure 1.} A progression of challenges in developing therapeutic agents from marine bioactives (based on Faulkner, 2000).

The paucity of success stories in large-scale production and product marketing has meant that “the processing industry - the food industry and dominant players in the pharmaceutical industry - are not eager to invest in marine biotechnology,” (Luiten et al. 2003, p. 432). Luiten et al. (2003, p. 434) suggested that since it is “most often too hard to interest [the vested industrial firms in food and pharmacy] directly, pioneers [in marine biotechnology] need to co-operate with other small, knowledge-intensive firms,” whilst making “smart” choices. For instance, the product needs to fit with the portfolio of medicines/foods and/or manufacturing processes of the target food/pharmaceutical company (Luiten et al. 2003, p. 434).

\textbf{Methodology}

The genesis for the present study lay in an endeavour to showcase successful instances of value-chain innovation in the NZ seafood sector within the ambit of the FRST project noted earlier. Knowledgeable observers in the seafood industry had cited a certain farmer and processor of green-lipped mussels (GLMs) (of the species \textit{Perna Canaliculus}, which is a mollusc native to NZ) as being a prime example of value-addition in an otherwise commodity-orientated sector of aquaculture. In contrast with the legion of GLM farmers who constantly had to find and develop new markets for mussel, this firm, MacLab NZ (henceforth, MLNZ), was growing/procuring mussels precisely to meet the demand for value-added products and in particular, a nutraceutical called Lyprinol®. Subsequent investigation revealed that the value-chain for Lyprinol® appeared to create a market value of more than 100% over relatively unprocessed GLMs.
Lyprinol® is a patented and stabilised natural marine lipid extract that comprises a rare combination of lipid groups and unique Omega-3 polyunsaturated fatty acids. The value-chain for Lyprinol® is very complex. MLNZ farms mussels at various locations around NZ; to meet the growing demand, it also buys GLMs from other farmers. The GLMs are then brought to a processing plant in Nelson, NZ, wherein they are first de-shelled through a high-pressure pneumatic machine. The mussel flesh is then minced before a stabilizing agent (an organic acid) is added to it. The resulting slurry is freeze-dried and then milled to yield a powder extract. The powder is freighted to one of two locations in NZ and Germany for the extraction of marine lipids. (Stabilized mussel powder extract is also directly supplied by the MacLab group, under an exclusive contract, to a large multinational pet food and veterinary products company, which uses the powder as a nutraceutical ingredient.) The bulk lipids are then shipped to various locations worldwide where they are encapsulated.

Through both secondary data (e.g. www.lyprinol.com) and fieldwork conducted in two phases and across three locations in Australia and NZ, we developed a case study of innovation and value-chain management of Lyprinol®. The analysis proceeded at two levels. The first (higher) level spoke to the ‘breakthrough’ (or radical, revolutionary, game-changing) innovation (Veryzer 1998, p. 306) of Lyprinol® while the second (lower) level spoke to other improvements and developments in the value-chain for Lyprinol® that were relativelyincremental in nature.

The full case description is beyond the scope of the present paper. Below, we present an abridged account of the innovation process with a view towards specifying the nature of knowledge networking and collaboration that is entailed in the innovation of nutraceuticals such as Lyprinol®. We also report an auxiliary case-let of a dermaceutical called Isolutrol®.

The innovation of Lyprinol®

The name ‘MacLab’ derives from Stuart McFarlane, who helped pioneer mussel farming in NZ in the late 1960s. Alerted by interest from the US in GLM extracts for their cytotoxic properties, McFarlane found that although the cancer treatment was not successful, patients were reporting relief from arthritic pain as a welcome side-effect. This accorded with NZ folklore that coastal dwelling Maoris who regularly consumed the mussel as part of their diet suffered far less from arthritis than their inland dwelling relatives. In 1974, McFarlane launched a freeze-dried, concentrated mussel powder obtained from GLMs as an anti-arthritic product marketed as Seatone™.

In the early 1970s, two Australian businessmen who were brothers, Jim and Bill Broadbent, acquired a financial interest in certain mussel farming operations of McFarlane. They became interested in mussel extracts because of their reported anti-inflammatory properties and subsequently established a new company in Australia for distributing the extract and for registering the "Seatone" trademark worldwide.

In the early 1980s, the Broadbent brothers became major shareholders in Stuart McFarlane’s company, McFarlane Laboratories. Owing to their conviction that “there was something in the mussel which deserved investigation,” McFarlane Laboratories started researching the reported health properties of Seatone (Clark, 2000). In 1982,
they purchased a mussel powder factory in New Zealand and established a research project at the Natural Products Chemistry Division of the Royal Melbourne Institute of Technology University in Australia (“RMIT”). The company initially sought hard scientific evidence that a naturally occurring anti-inflammatory compound (a unique “marker” secondary metabolite) existed in the mussel. Such proof would supersede the hitherto inconclusive empirical evidence and help settle the medical controversy concerning the potency of mussel extracts.

In hindsight, the RMIT project was “on the wrong track” in the initial 1-2 years, being directed towards the search for aqueous (water-based) fractions instead of non-polar fractions (which Lyprinol® is comprised of). In 1983-4, a cohort of scientists that joined the Natural Products Chemistry Division of RMIT was convinced the activity of the GLM was located in lipid (non-polar) fractions. They called for a “whole new raft of funding” from McFarlane Pty. Ltd. (part of the MacLab group) to continue searching for the marker. Despite the use of a leading technology of the time, viz. high performance liquid chromatography (HPLC), the RMIT scientists were unable to isolate the active lipid fractions from GLM extract powder – one of the many challenges depicted in Figure 1.

In 1983, on a visit to Japan, Jim Broadbent met Professor Takuo Kosuge, a Professor of Pharmacology at the Shizuoka University in Japan, who specialized in natural products chemistry and had become aware of the GLM extract through a friend. Professor Kosuge offered the collaboration of his research group with the scientists at RMIT. He ran his own series of tests but also failed to isolate the active fractions.

Professor Kosuge concluded the failure to isolate the fractions owed to the oxidation of the active components: the freeze-dried mussel powder extract was unstable and with a limited shelf life and therefore needed to be stabilized in the first instance if it was to retain its potency. Indeed, oxidation has been deemed to be “one fundamental quality issue that must be considered and controlled” in the extraction of marine oils; techniques of harvesting, processing and storage impact on the oxidative stability and shelf-life of the oil product (McLean 2002, pp. 18-19; Shahidi and Kim 2002, pp. 80-81).

By developing a pharmacological screen to check the activity levels of different batches of mussel powder, Professor Kosuge himself confirmed that moisture and heat greatly impacted on the level of bioactivity. After unsuccessfully experimenting with all the recognized anti-oxidants as stabilizers, he turned to research work that he had conducted some twenty years earlier that had identified the ancient technique used by traditional Japanese fishermen to store fish in a special solution, which preserved the fish for years. Professor Kosuge then tested a variation of this solution on the mussel flesh and found that the oxidation was arrested. Thus, in keeping with the second stage of the developmental period in the innovation model of Van de Ven et al. (1999), the development of the stabilizer stemmed from the earlier setback encountered by the RMIT team in the isolation of active lipid fractions from GLM extract powder.

Subsequently, Jim Broadbent, on behalf of the present-day MacLab group, and Yoshiki Kosuge patented the above stabilization process. The MacLab group was then able to produce a stabilized mussel extract product, after also making other major changes to the production process.

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6 In contrast with primary metabolites, secondary metabolites are made for purposes other than sustaining the producing cell or organism.
Now that the mussel extract was stabilized, the RMIT scientific group were able to successfully extract selected lipids that they believed held the beneficial activity. The MacLab group’s plan was to establish a new, more effective product under a different brand name to differentiate itself from the “Seatone” product in those markets where it no longer owned the trademark.

To confirm the beneficial effects of the lipids isolated by the RMIT scientists, in 1992 the MacLab group enlisted the services of Dr. Henry Betts, Principal Scientist at the Rheumatology Research Laboratory, The Queen Elizabeth Hospital, in Adelaide, Australia. Dr. Betts had earlier established an in-vitro method of testing anti-inflammatory compounds. He then proceeded to test the fractions that the RMIT scientists had extracted.

While Dr. Betts found that two of these fractions were the most active compounds he had ever examined in his testing system, he was unable to identify them because they were not pure. He continued his work for 18 months during which time he tested the progressively purified fractions developed by the RMIT scientists. (It turns out that Lyprinol® contains a variety of active ingredients over and above the fatty acids that have been identified thus far [Halpern and Edmonds 2001, p. 26].)

At the suggestion of Dr Betts, the MacLab group approached Dr Michael Whitehouse, who specialized in testing compounds for anti-inflammatory activity in laboratory animals, for an in-vivo test of the fractions. Dr Whitehouse commenced laboratory animal studies in 1994, which confirmed the activity that Dr Betts had found in his in-vitro testing.

Lyprinol® has since been found to be much more potent than the GLM powder extracts that are prevalent in the market. Further, its use for treating asthma, besides arthritis, has also been established, which is not the case with powder extracts.

It took a further two years of intensive testing to develop the protocols for the supercritical fluid extraction process, which were then patented by the MacLab group. The group continued the original search for a ‘marker’ metabolite from among the various fractions and fatty acids that are latent in Lyprinol®. Such a ‘marker’ could pave the way for chemical synthesis and subsequent development of an anti-inflammatory drug.

The Broadbent brothers have invested a total of AUS four-five million in research into Lyprinol®. Jim Broadbent is convinced that Lyprinol® would not have eventuated had he and his company not relentlessly backed their “belief in what we were doing by putting some funding into [the research]:” in some years during the innovation of Lyprinol®, Jim Broadbent and his Australian concern were spending nearly half their income on the investment in R&D.

Hobbs (2002, p. 562) observed that innovators are often unable to undertake value-chain activities (e.g. production, marketing, and long-lasting clinical trials, such as expensive, intervention studies with high numbers of patients) beyond technology transfer given their limited access to equity capital. Thus, strategic alliances or joint ventures arise with downstream players who have the financial and human capital resources to commercialize an innovation.

In the late 1990s, the Broadbent brothers transferred their patents (except the patent for the stabilising agent) to a new holding company, Pharmalink International Limited (PIL), whilst becoming shareholders in PIL. This released capital for the MacLab group for investment in GLM farms in NZ to meet the growing demand for Lyprinol®. PIL has contracted its marketing, distribution, and production oversight functions to an affiliate, Pharmalink Marketing Australia Pty. Ltd. (PMA). Through public-domain information, the worldwide volume of sales of Lyprinol® may be
estimated to be some/several tens of million dollars p.a.

Some years after the commercialization of Lyprinol, the Broadbent brothers concluded that Lyprinol® did not contain a unique ‘marker’ that would explain its anti-inflammatory potency; rather, the various fractions and fatty acids seemed to act in a synergetic manner. Furthermore, Lyprinol® cannot be synthesized since the fractions are not completely pure. At the time of fieldwork, PMA was investigating how Lyprinol® could be progressively registered as a drug, notwithstanding the absence of a unique marker metabolite (and prospects for synthesis) and the variation in chemical composition that is inherent in natural extracts.

The case of Isolutrol®

The collaboration between Jim Broadbent, Prof Takuo Kosuge, and the RMIT group also underlay the commercial development of a dermaceutical, sodium scymnol sulphate, which has been marketed by McFarlane Pty. Ltd. as Isolutrol®. The compound had originally been discovered by Prof Kosuge in the 1980s; he had been led to this discovery after hearing about fishermen off the Japanese coast who rubbed extracts of shark’s liver on to their face to acquire clear, smooth skin.7 Research has also suggested properties in the compound that might help with some types of liver toxicity (Barclay, 2001).

Prof Kosuge awarded Jim Broadbent the rights to market the compound worldwide outside of Japan. Over a five-year period beginning 1987, the RMIT team, in collaboration with Prof Kosuge, developed a method of extracting the compound from shark bile to 99.9% purity. Tests have confirmed Isolutrol®’s efficacy in curing oily skin as well as its lack of obvious toxicological or allergenic effects.

Isolutrol® is available as a spray lotion. It is the only compound yet developed that reduces the oiliness of skin when applied topically8 – a reflection of the low rate of rediscovery of secondary metabolites that are derived from marine life-forms (Olaizola 2003, p. 460).

The global market for acne treatments has been estimated to be AU$ 2 billion p.a.9 However, given that sharks are under threat in the wild, the extraction route (from shark bile) for the manufacture of Isolutrol® is not scalable. At the time of fieldwork, synthesis on a truly large scale continued to prove elusive. Nevertheless, the presence of a confirmed marker in shark bile (i.e. sodium scymnol sulphate) leaves the door open for Jim Broadbent, who holds the rights to the chemical structure of the compound, for achieving successful industrial-scale synthesis at a later stage.

Implications of the case studies

Below we discuss the ramifications of the case studies with regard to: (i) the innovation processes of marine-based nutraceuticals; (ii) the role and nature of the requisite collaboration in such innovation; and (iii) the prominence of the emerging field of ethno-pharmacology in such collaboration.

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Innovation processes of marine-based nutraceuticals

The innovation of Lyprinol® involved, among other scientists: a pharmacologist, who specialized in natural products chemistry (Prof Kosuge); natural product chemists with expertise in HPLC (the RMIT group); a rheumatologist, who specialized in \emph{in vitro} testing (Dr Betts); and an inflammo-pharmacologist with expertise in \emph{in vivo} animal testing (Dr Whitehouse). Prof Kosuge’s ability to bridge disciplines such as natural products chemistry and pharmacology suggests that a \emph{translational} mode of knowledge networking played a pivotal, if not indispensable, part in the innovation process.

As with the cases of Mark-Herbert (2002, 2004), the initial phase was divergent, allowing for learning by discovery (Van de Ven et al. [1999, p. 16, pp. 203-204], as cited by Mark-Herbert [2002, p. 20]). Thus, the first change of direction arose when the RMIT group decided that the activity of GLMs lay in non-polar fractions. The second change of tack was prompted by the failure of both the RMIT scientists and Prof Kosuge to extract fractions, and in turn triggered Prof Kosuge’s development of a pharmacological screen, which confirmed the need to stabilize GLM flesh prior to the extraction of fractions. In turn, this beckoned the development of a stabilizing agent that was subsequently patented.

Once the RMIT scientists were able to extract fractions from stabilized mussel powder extract, the innovation process became progressively convergent. Given that the MacLab group was seeking hard evidence of the anti-inflammatory properties of GLMs, it was logical for them to contact a rheumatologist (Dr Betts) for assistance. The trial-and-error iterations between Dr Henry Betts and the RMIT research group \emph{vis-à-vis} the extraction and \emph{in vitro} testing of active fractions, as also the development of protocols for the super-critical fluid extraction process, speak to convergence in the innovation process.

With regard to functional foods, Menrad (2003) cited the limited participation of small and medium-sized food companies (SMEs), which “mostly produce functional products for market niches or offer ‘me-too’ products following the pioneering products of the multinational companies,” (p. 184). Asserting that “often these products can ‘survive’ only for a rather short time period (e.g. up to two years),” he attributed the low profile of SMEs to their lack of know-how and resources for intensive R&D activities as well as their inability to spend high sums of money on, for instance, long-lasting clinical trials (p. 184).

However, the putative advantages of organizational size (Menrad 2003, p. 184) may not hold as strongly in relation to marine extracts. To begin with, the difference in the scale of R&D between the dairy segment of the functional food market, which accounted for a fifth of all functional food innovations in Germany in 1999-2000 (Menrad 2003, p. 182), and that of marine-based nutraceuticals, such as Lyprinol®, spans at least an order of magnitude. For instance, the cost for product development and market introduction of Nestle’s LC1 yoghurt was estimated to exceed US$ 50 million. The requirement of science-based research is compounded in the innovation of functional foods by the need to ensure the bio-availability and efficacy of the nutraceutical ingredient when it is delivered in a certain functional food (Howe 2000, p. S108). On the other hand, Lyprinol® is an extract and does not contain additives.

Moreover, the numerous hurdles that can prevent marine bio-actives from realizing their fullest potential (e.g. as approved drugs that reach the pharmaceutical marketplace) are exemplified by the cases of Lyprinol® and Isolutrol®. The absence of a unique ‘marker’ in Lyprinol® curtails the product’s business potential by
thwarting the synthesis and subsequent development of a drug that could otherwise have been manufactured and marketed as anti-inflammatory medication by a pharmaceutical company under license. Unlike the case of GLMs and Lyprinol®, the ‘marker’ metabolite in shark liver bile has been isolated and had its structure elucidated (as Isolutrol®, by Prof Kosuge). However, the complicated nature of synthesis and the lack of viability of the extraction route have constrained the revenue-streams from Isolutrol® for the MacLab group and its business affiliates.

That being said, from the perspective of the MacLab group and its business affiliates (PIL and PMA), if not that of a pharmaceutical giant, Lyprinol® is still commercially viable by offering “a competitive alternative to products or compounds that are already on the market [e.g. unstabilized GLM powder extracts],” (Luiten et al. 2003, p. 434). (In the context of plant extracts, Etkin (2001, p. 181) similarly speculated that “some of the former interest [of pharmaceutical companies] in natural products would be transposed to the development of botanical complementary and alternative medicines.”) Subsequent institutional innovation (e.g. legislation for functional foods/nutraceuticals [Kalaitzandonakes, 2000]) should work in favour of Lyprinol® by enabling it to better differentiate itself in the marketplace from other nutraceuticals, such as GLM extracts, on the basis of its superior clinical evidence.

In this manner, possibilities for the limited commercialization of novel marine natural products are yet suggested by Figure 1, all of which will likely serve niche markets in the nutraceutical/cosmeceutical space – perhaps in lieu of the pharmaceutical arena. Thus, while “the commercial source of choice for the pharmaceutical industry is synthesis, which allows the company to control all aspects of production,” (Faulkner 2000, p. 142) the extraction route remains a potential alternative for the supply of nutraceuticals, provided the source organism can be viably harvested through aquaculture/fermentation. Besides Lyprinol®, the cosmeceutical that is derived from the sea whip (Faulkner 2000, p. 138) is a case in point.

The role and nature of collaboration

In both Lyprinol® and Isolutrol®, the seed for discovery was epidemiological/folkloric evidence, namely, the differential prevalence of arthritis in coastal vs. inland Maori and Japanese fishermen’s use of shark liver extracts to acquire clear, smooth skin, respectively. This parallels the commercial development of health foods, such as those from the micro-alga, Chlorella spirulina, which can be traced back to the centuries-old history of the utilization of spirulina by natural populations in Africa and Mexico (Olaizola 2003, p. 459).

The two cases suggest that the innovation of commercially viable marine nutraceuticals/ cosmeceuticals entails collaboration across a multitude of disciplines. These include: natural products chemistry; aquaculture; epidemiology and/or folkloric medicine; and relevant strands of medical, pharmacological, and clinical research that could be governed in part by prior epidemiological evidence and/or folkloric medicine (e.g. dermatology in the case of Isolutrol®). The resulting “confluence of diverse critical flows of information” (Valentin and Jensen 2003, p. 280) will enable gainful problem definition: e.g. what fraction(s) in the GLM explain its efficacy as a treatment for arthritis, as revealed by epidemiological and/or folkloric evidence regarding coastal vs. inland Maori? As the case of Lyprinol® reveals, such definition is fruitful of business opportunity by seeking to leverage epidemiological evidence towards the discovery and development of a nutraceutical that serves a sufficiently
large market and is derived from a species that can be viably farmed through aquaculture/fermentation.

Although the need to understand folk dialects is a complication (Alino et al., 1990), public-domain literature on the use of marine organisms in folk medicine is available (e.g. of fishermen based at the Tocantins River in Brazil [Begossi and de Souza Braga, 1992] or of coastal people in central Philippines [Alino et al., 1990]). However, attempts to leverage this knowledge towards commercially viable marine natural products are not common.

Moreover, such data as are available may not be useful for discovering marine bioactives, being cast in relation to epistemologies that obtain in particular knowledge frameworks, e.g. cultural ecology. A case in point is Begossi and de Souza Braga (1992), who investigated food taboos in relation to both the use of fish for folk medicine and the piscivorous habits of fish. The authors’ research objective was to compare and contrast the fishermen’s explanations for food choices with materialistic and ideological theories of cultural ecology. Therefore, their field data might not be in a form that is usable by marine pharmacologists, which exemplifies the challenge of harmonizing objectives and integrating methodologies in trans-disciplinary research (Etkin and Elisabetsky 2005, p. 23).

The presence of distinct knowledge frameworks would necessitate translational knowledge networking (Langlais et al., 2004). Universities and government research institutes could be well-positioned to achieve the needed confluence of diverse disciplines, as well as translational networking, in the search for meaningful problem definitions and targets.

Further, it may not be really viable or even desirable to direct the innovation effort primarily towards generating interest and capital from food and industrial firms (Luiten et al., 2003), especially given that industrial synthesis may be elusive, for whatever reason. Venture capital from pioneering entrepreneurs in marine biotechnology, such as the Broadbent brothers, may be easier to attract given the management of risk through collaborative innovation as well as the lack of dependence on industrial firms for subsequent scale-up.

The salience of ethno-pharmacology

The congruence of disciplines outlined above is spoken to by the research field of ethno-pharmacology, a term that defies easy definition, being a neologism that was introduced in 1967 (Heinrich and Gibbons 2001, p. 425). As cited by Heinrich and Gibbons (2001, p. 425), Bruhn and Holmstedt (1981) defined ethno-pharmacology as “the interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by man.” (The variety of perspectives of the term is evident from the definition furnished by http://www.biology-online.org/dictionary: ethnopharmacology is “the study of differences in response to drugs based on varied ethnicity.”)\(^\text{10}\)

Etymologically, the term suggests the conjunction of medical ethnography and the biology of therapeutic action (Etkin, 1996). Notwithstanding this notion, even journals that are dedicated to the field (such as the Journal of Ethnopharmacology) feature only 4-6% of articles that straddle disciplines (Etkin and Elisabetsky 2005, p. 24). In the context of the majority of published studies that are ‘stand-alone,’ Etkin and Elisabetsky (2005, p. 24) cited the tendency of laboratories to confine their

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attention to the therapeutic potentials of various groups of plants against biological targets; there was little synthesis beyond such foundational data. As described by Etkin (2001, p. 181), “… one is left with the sense of discrete bits of research emerging from various laboratories with nowhere to go and no one to pull them together. By all appearances, no one seems to reflect much on what the larger picture might be.”

Furthermore, the ethnographic component of most published ethno-pharmacology has been deemed to be weak, if not non-existent (Etkin and Elisabetsky 2005, p. 24). Nevertheless, ethnographic evaluations of indigenous therapies, which “not only look at empirical aspects of indigenous and popular … use [of natural products], but also at the cognitive foundations of this use” (Heinrich and Gibbons 2001, p. 430), could be entailed in the innovation of commercially viable nutraceuticals. Besides clarifying, for example, the requisite dosage schedules, such evaluation also unravels the symbolism underlying ritual therapies. Heinrich and Gibbons (2001, p. 430) cited an example from their ethno-pharmacological research wherein the consumption of a certain yellow petal at the end of a treatment arose not from any pharmacological effect (at that dosage) but from the petal’s symbolization of the bread of the Last Supper according to Christian mythology.

Folkloric therapies represent intellectual property of the concerned indigenous peoples, and their use and commercial exploitation are increasingly being safeguarded following the 1992 Rio Convention on Biological Diversity (Etkin and Elisabetsky, 2005; Heinrich and Gibbons, 2001). With increasing methodological and theoretical exchange across the disciplines that intersect with ethno-pharmacology (Etkin and Elisabetsky 2005, p. 25), such safeguards can enable non-decomposable problem definition and the protection of indigenous knowledge through patents.

Summary

With recourse to two case studies, one being the principal case study and the other serving as an auxiliary, we have examined the innovation of marine-based nutraceuticals as well as the role of the embedding context of marine biotechnology. While several potential pitfalls thwart the fullest realization of the business potential of promising leads, it is yet possible to discover and develop commercially viable marine natural products that serve various niches. The key is to manage the risk of development by enabling collaboration across several disciplines and to conserve capital by initiating the search for meaningful problem definitions through epidemiological and/or folkloric evidence, which has seemingly been underutilized for this purpose.

Our investigation also highlights the differential aspects of the successful innovation of marine-based nutraceuticals as compared with functional foods such as ProViva. A major consideration in the former is the need for a fallback route, i.e. extraction from the source organism that is grown through aquaculture/fermentation, given the relatively high likelihood of failure of industrial-scale synthesis. In turn, the imperative of a viable fallback entails the participation of scientists from aquaculture and allied disciplines early in the discovery process.

Two directions for further research are suggested by the present study. The first speaks to additional investigations of innovations in the functional food/nutraceuticals space that highlight the influence of context and thereby clarify the situational aspect of the management of innovation. The other direction speaks to the specification of
institutional structures and mechanisms whereby the intellectual property of indigenous peoples is protected and inter-disciplinary collaboration is gainfully realized, with particular emphasis on ethno-pharmacology, given that it will likely be the hub of meaningful problem definitions.

References


