Marine-based Nutraceuticals: A case study

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May 9, 2005.
OUTLINE

- Research goal and objectives.
  - Choice of MacLab NZ.

- Background to marine natural products.

- Literature review.
  - Functional food vs. nutraceuticals.
  - The functional food industry and market.
  - Knowledge & innovation management, value-chains.

- Innovation and commercialization of Lyprinol®.

- Key findings.
  - Innovation of nutraceuticals.
  - Value chain dynamics (esp., clinical testing, market development).
  - Distinctiveness of marine natural products.

- Lessons for the seafood sector.
Value-Chain Innovation

Research questions.

◆ What forms do innovations in seafood industry supply chains assume?
◆ What factors underpin successful innovation?
◆ What barriers need be overcome?
◆ More generally [in light of the public-good nature of the research], how can innovations in the value-chains for seafood be stimulated?

A key objective: showcase exemplars.
Choice of MacLab NZ

MacLab NZ grows/procures GLMs precisely to meet demand for high value-added products (esp., Lyprinol®).

- Patented and stabilised natural marine lipid extract comprising a rare combination of lipid groups and unique Omega-3 polyunsaturated fatty acids that are extracted from the GLM through a patented supercritical fluid extraction process using liquefied CO₂.

R&D-intensiveness of the nutraceuticals/functional foods industry.

- Finnish food industry: new product development < 2% of turnover.
- Global pharmaceutical industry and biotechnology companies: 15-20% and 36% (Brännback & Wiklund 2001, p. 199).
- Functional foods: < 1% market-share in the whole of Europe; 19% of all innovations in the German food and drinks market in 1999-2000 (Menrad 2003, p. 182).

Research objectives.

- Showcase a successful case study of innovation and value-chain management in an emergent industry.
- Add to the literature on the innovation of nutraceuticals and functional foods and the value-chains thereof.
Background to Marine Natural Products

- ‘Natural product’ has various meanings: e.g., ‘secondary metabolite.’
- Late start in the study of marine natural products (Bergman et al., circa late-1940s).
- Key challenge: *very low yields* (often the $10^{-4}$–$10^{-6}$% range on a wet-weight basis).
  
  - Need kilo-tonnes of freshly-harvested biomass material to support a successful clinical development program (Mendola 2003, p. 441).
  
  - Large harvests threaten biodiversity conservation (Faulkner 2000, p. 140).
Considerable promise that is unfulfilled

- Ocean life is richly diverse (Wijffels 2003, p. ix).
  - A source of bioactive compounds with pharmaceutical potential (Munro et al., 1999).
- Only a few firms produce and market marine nutraceuticals/pharmaceuticals on a large scale: Luiten et al. (2003).
- Prior to 2003, no marine natural product compound had been approved as a drug (Mendola 2003, p. 441).
  - Only two chemical analogues had been approved as drugs.
- A vicious cycle: R&D not forthcoming (Luiten et al., 2003).
- Low rate of innovation in functional seafood.
- Bridging the gap between isolation in the lab and commercialization: multi-disciplinary design groups (e.g., Aqua-Production Park).
Various difficulties in the development of anti-cancer and anti-inflammatory agents from marine bioactives.

- “Far from romantic” expeditions for collecting organisms, especially deep-water (Faulkner 2000, p. 136).
- The supply problem.
- Difficulties in isolation and structural elucidation of marine extracts; thwarts synthesis.
- ‘Academic’ synthesis vs. ‘industrial’ synthesis (Munro et al., 1999); many marine bioactives are so complex that they require multi-step syntheses.
- The compound may be either poorly transported or unstable when administered subcutaneously; hence, even if synthesized, need to successfully formulate for in vivo use.
“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).”

  - Greater market acceptance for food-like product.
  - Technological (Has a special component been added or removed?).
  - Legislative (E.g., health claims).
The Functional Foods Industry and Market

- Worth US$ 60 billion p.a., growing 10% p.a.
- The US has a 50% share of the global market for functional foods; in turn, functional foods have a 2% share of the US food market.
- Fragmented market: Central and Northern European countries evince more interest than the Mediterranean region (Menrad 2003, p. 182).

Four key dynamics:
- Commercial promise (e.g., higher margins).
- Global character of the value-chain (Brännback & Wiklund 2001, p. 199).
- A societal shift from therapeutic to preventive health.
**Functional Foods Industry, Market, contd: Regulation**

- **Need for institutional innovation**: Kalaitzandonakes (2000, pp. 1-2).
  - Trans-Tasman Therapeutic Products Agency to regulate medicines, complementary healthcare products in Aust/NZ.

- **Need to harmonize health claims** (e.g., the US).
  - Advertising (FTC) versus food labels (FDA); FTC more flexible.

- **Exploiting loopholes**: “supplements” as opposed to food.

- **FOSHU** (Foods for Specified Health Uses) system in Japan.
Knowledge & Innovation Mgmt and Value-chains


K&IM and Value Chains, contd.

- Need partnerships between entrepreneurial scientists, input suppliers, and food processors and/or medicinal supplement firms: Hobbs (2002).
  - *ProViva*, a probiotic fruit drink.
    - Probi AB, a research firm that specializes in probiotics.
    - Skånemejerier, a co-operatively owned Swedish dairy company, which engages in “r&D” (Mark-Herbert 2002, p. 67).

  - Added to salmon feed to facilitate pigmentation.
  - *Haematococcus* astaxanthin cannot compete on cost.
  - Average consumers unwilling to pay a premium.
  - New market (human nutraceuticals) opening up given the molecule’s antioxidant characteristics.
K&IM and Value Chains, contd.

- Need knowledge networking to overcome *trans-epistemic* challenges (Langlais et al., 2004).

- Modes of knowledge networking.
  - *Modular*: central coordinator.
  - *Pioneer*: temporary bridges are built using ‘boundary’ objects such as charts, simulations, pictures, etc.
  - *Translational*: members communicate directly with each other by using a shared language or some other mediating structure.

- *ProViva*.
  - Identification of the Lp299v bacterium: *pioneer* networking.
  - Commercialization of Lp299v: *modular/pioneer* networking.
First-generation GLM extracts.
- Relief from arthritis a side-effect for cancer patients.
- Maori folklore and related epidemiological findings.
- Broadbent brothers established McFarlane Mktg (Aust) Pty for distributing and registering “Seatone” worldwide.
- Enormous publicity, considerable sales in the UK.
- Early study results (some involving laboratory rats) were inconclusive and inconsistent.
- Scathing editorial in the Lancet (1980): “… perhaps the most definite statement that can be made is seatone has shown little in the way of side-effects. This could, of course, reflect its degree of therapeutic activity.”
Lyprinol®: Stabilized GLM extracts

- Early 1980s, Broadbents became major shareholders.
- 1982-: Established a research project at RMIT’s Natural Products Chemistry division.
  - The search for a ‘marker.’
  - Initial two years: stopped searching for aqueous fractions.
    - ‘Defatted’ powder has been shown to have no activity.
  - RMIT scientists unable to isolate active lipids despite using HPLC.
  - Professor Takuo Kosuge ran own series of tests, failed.
  - Kosuge developed a pharmacological screen for bioactivity, concluded freeze-dried GLM powder extract was unstable, had to be stabilized.
  - After repeated failures, Kosuge turned to an age-old technique of Japanese fishermen.
Lyprinol®: Identification, Extraction of Active Fractions

- Dr Henry Betts, U. of Adelaide.
  - *In vitro* testing of anti-inflammatory compounds.
  - Iterations with RMIT.

- Dr Michael Whitehouse.
  - *In vivo* testing of anti-inflammatory activity in laboratory animals.

- Protocols for the supercritical fluid extraction process.

- “Externality effects can … damage the reputation of other firms by weakening the credibility of the [nutraceuticals] industry,” (Hobbs 2002, p. 564).
  - Focus on lipids in lieu of powders.
Lyprinol®: Product Commercialization

  - Product capability: user-perceived benefit(s).
    - Lipid, not powder; asthma in addition to arthritis.
  - Technological capability.
    - Stabilization of mussel flesh prior to freeze-drying; protocols that extract lipids without damaging the active fractions.
- US FDA’s classification of new drugs (therapeutic potential and chemical composition) coincides with the customer benefits and product technology dimensions (Korescu et al., 2003).

  - PMA’s MD had been involved in the nutraceuticals business in Australia for twelve years.

- Marketing strategies.
  - House-brands for natural healthcare products companies.
  - PR/advertising (Sam Riley, Jana Pittman).
  - Channels: e.g., Asian food shops.
# A Knowledge Networking Perspective of the Innovation and Commercialization of Lyprinol®

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<td>KR 1 plus pharmacology.</td>
<td>How can GLM powder extract be stabilized?</td>
<td>Drawing upon prior research into folkloric preservatives.</td>
<td>Translational</td>
<td>Formation of KR 3. The development of a stabilizer and subsequent successful extraction of active fractions.</td>
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<td>KR 5 plus clinical researchers, including specialists in complementary therapies.</td>
<td>How can Lyprinol® be successfully commercialized as a nutraceutical?</td>
<td>Value-chain partnerships with investors, marketers of nutraceutical products, functional food and nutrition specialists, etc.</td>
<td>Modular</td>
<td>Commercialization of Lyprinol®, development of markets, continued clinical research, pursuance of registration as a drug, etc.</td>
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**Legend:** KR - Knowledge Regime; TC – Transepistemic Challenge; KN – Knowledge Networking.
Lyprinol®: Ongoing Developments

- Cost reductions and productivity gains in mussel farming and the production of GLM powder extract.
  - Contractual price for powder.
- Backward integration to gain greater control over supply.
  - Partnerships with local iwi.
- Aquacultural innovations.
  - Deep-water catching of spat.
  - Offshore mussel farming.
  - Selective breeding (Cawthron Institute).
  - Can GLMs be grown outside of NZ?
Lyprinol®: Ongoing Developments, contd.

- Cf. *Haematococcus* astaxanthin.
  - Continuous improvement to produce *Haematococcus* biomass with higher final astaxanthin content.
  - Expansion of production into China with lower land, labour, and energy costs (Olaizola 2003, p. 465).

- Production ramp-up of GLMs in pace with market and demand development for Lyprinol®.

- HPP technology: greater yield; market diversification.

- Leveraging processing equipment: e.g., freeze-drying.
Discussion of Principal Themes

- Innovation of nutraceuticals.
  - "What started, in all of the cases, as an interesting research project grew into something other than what was the inspiring need at start," (Mark-Herbert 2004, p. 716).
    - Search for a marker resulted in Lyprinol®.
  - Initial, divergent phase, followed by a convergent phase of discovery and development.
  - Additional functional foods.
    - Functional dog food.
  - Need luck! (Getting top scientists on board.)
    - Robert Borland/Theo Macrides at RMIT.
    - Takuo Kosuge at Shizuoka Uni.
    - Michael Whitehouse (on secondment at Adelaide U.).
    - The ‘silver bullet’ marker is elusive!
“Regrettably, mainline medical journals have in the past shown frequent bias to highlighting negative reports about ineffective or toxic [natural] products …,” (Butters & Whitehouse 2003, p. 105).

Studies upholding the potency of plant stanol esters (that feature in Benecol™) in cholesterol reduction (e.g., Miettinen et al., 1995) have appeared in prestigious journals.

The products that are widely available in the marketplace (e.g., unstabilized powders) may be considerably inferior to those used for published clinical trials (e.g., stabilized powders): Gresham’s Law as paraphrased by Butters & Whitehouse (2003).
Distinctiveness of Marine Natural Products

- Points of departure for discovery and development are the marine organisms and the interest they evoke.
- Access to raw material inputs is especially critical.
- “The lack of an analogous ethno-medical history as compared with terrestrial habitats” is another reason why “the development of marine compounds as therapeutic agents is still in its infancy,” (Amador et al. 2003, p. 1607).
Success of Lyprinol®.
  ◆ Relatively easy availability of GLMs for testing and subsequent commercialisation.
  ◆ Relatively higher yields of lipids (about 0.02%, which is 200 times the upper limit of the range of typical yields of $10^{-4} - 10^{-6}\%$ for secondary metabolites [Mendola 2003, p. 441]).
  ◆ Lyprinol® is a complex of over 30 compounds!
  ◆ Prior ethno-medical evidence comparing coastal and inland Maori and related epidemiological evidence.

Lowering of input costs and the ramping up of production in line with market demand are some key drivers in the management of the value-chain for marine-based nutraceuticals and functional foods.
Lessons for the Seafood Sector

- Need for research collaboration.
  - Firms that attempt to introduce innovations that are ‘new to the market’ (e.g., Lyprinol®) than ‘new to the firm’ (e.g., powder extract) are far more likely to engage in co-operative arrangements (Tether, 2002).
Risk associated with radical innovations is apparent at two stages: development and introduction (Korescu et al., 2003).

- Development stage: “When and whether a process directed at creating breakthroughs will materialize into actual, ready-for-market innovations.”
- Introduction stage: “Extent and time frame of consumers’ adoption of the product,” (Korescu et al. 2003, p. 84).

Cf. Isolutrol.

- Shark bile used by Japanese fishermen to treat oily skin.
- Compound identified as Sodium scymnol sulphate, also treats some forms of liver toxicity.
- RMIT able to extract to 99.9% purity, but the extraction route is not scalable.
- Large-scale synthesis still elusive.
Lyprinol® vs. Isolutrol®

- Either way “need a lot of luck:” neither product has fully realized commercial potential.

- **Lyprinol®.**
  - No unique ‘marker’ metabolite; thwarts synthesis and drug development.
  - Extraction route is viable.
  - *Institutional* innovation (e.g., legislation) should enhance prospects, as would increased awareness of the importance of anti-inflammatories.

- **Isolutrol®.**
  - Presence of a marker – but very hard to synthesize.
  - Extraction route not very commercially viable.
  - Possibly less risk at the introduction stage.
Some prior evidence (folkoric, epidemiological) to underpin/guide the research (coastal vs. inland Maori, Japanese fishermen).

Focus on source organisms that can be viably farmed – the extraction route is a viable *fallback* option to synthesis.

- By-product utilization.
  - Low hurdle return on investment that is required from offal-derivative, nutraceutical by-products (Barclay, 2001).
  - Easily available for testing, commercialization, and long-term market development.

Need for flexible knowledge networking.

Collaboration between at least four disciplines is indicated.

- Traditional medicine, folkloric wisdom (possibly combined with some epidemiological data).
- Natural products chemistry.
- Aquaculture.
- Specific medical and clinical research disciplines.
An Approach for Managing Risk

1. Along with natural product chemists, search traditional medicinal and folkloric knowledge bases (e.g., from islands in the S. Pacific that rely on seafood), and related epidemiological evidence, for ideas for marine bioactives with commercial potential as nutraceuticals.

   - Begossi & de Souza Braga: usefulness of fish species for folk medicine of fishermen in the Tocantins River in the Amazon region.

2. Screen ideas on the basis of the size of the potential market(s).

3. As applicable, evaluate the feasibility of farming the source organism(s) and/or harvesting them in the wild in a sustainable way.

4. Screen ideas yet again on the basis of yield factors and cost as well as reliability and scalability of farming/harvesting the source organism(s).

5. In parallel,
   - Embark on the search for ‘marker’ metabolites; if they can be isolated and elucidated, investigate methods for industrial-scale synthesis.
   - Establish scientific documentation of therapeutic efficacy through research collaboration between natural product chemists and relevant medical/pharmacological and clinical specialist researchers as dictated by traditional medicine/folklore.