# AMRAD: Pioneer of Australian biotechnology

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**Abstract** AMRAD is a biotechnology company in the human healthcare sector. Its drug discovery projects are focused on novel cytokine therapies and small molecule anti-viral treatments. The company has a portfolio of early- and late-stage projects and its strategy is to enter into collaborative arrangements with international development partners upon generating proof-of-concept data in clinical trials. AMRAD differs from the typical 'biotech model' insofar as it was initially established as a private technology transfer organisation to serve the commercialisation needs of the publicly funded founding medical research institutes. In return for shares in the company the Member Institutes gave AMRAD a first right of invitation to their research activities. Although the Member Institute arrangement remains an important asset in feeding AMRAD's R&D pipeline, AMRAD's business model has evolved from essentially a service provision role to being actively involved in the progress of new medicines through human clinical trials.

**Keywords:** Australian biotechnology, medical research institutes, technology transfer, AMRAD, WEHI, QIMR, LIF, VEGF-B

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## Introduction

The traditional model of a start-up biotechnology company, the building of an organisation around a specific piece of core technology, has recently captured the imagination of Australian investors. In recent times start-up companies are now becoming almost as commonplace in Australia as elsewhere in the world. Unfortunately, this has not always been so. In fact the lack of activity and opportunity in commercialising Australia's medical research discoveries were the major drivers behind AMRAD's formation in 1987. Over the years AMRAD has undergone a transition from its origins as a diverse technology transfer organisation to a focused biotechnology company. There are a number of factors that have driven this change but to put these in context it is helpful first to understand the environment in which AMRAD was established.

By international comparison, the Australian medical research community has been highly successful in terms of generating some of the most important and fundamental biomedical discoveries in recent times. The discovery of the colony-stimulating factors, relaxin, neuraminadase inhibitors, the role of *Helicobacter pylori* in peptic ulcer, the identification of the thymus as an important organ and elucidation of its immunological role are just a few examples of major contributions Australian researchers have made. However, up until the late 1980s these discoveries were made in a commercial vacuum. Australian entrepreneurs and investors were focused in the resources, engineering and primary industry sectors – an R&D-based pharmaceutical sector simply did not exist.

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As a consequence, the opportunities for technology transfer to local companies were limited and the development and commercialisation of medical research discoveries occurred off-shore. This concerned the leaders of Victoria's Walter & Eliza Hall Institute of Medical Research and the Howard Florey Institute of Experimental Physiology and Medicine who joined forces and successfully lobbied the Victorian State Government to create a research and development consortium in medical biotechnology. This consortium was known as AMRAD.

## The Member Institute arrangement

When AMRAD was conceived, the model involved an enterprise having the right of first offer to commercial discoveries from its Member Institutes. The arrangements were put in place even before the first employee commenced with the company. The concept of a Member Institute arose as a direct result of the founders of AMRAD seeing the need for a criticial mass of R&D to ensure that the company would be internationally competitive. Through exercising its rights by financial support of specific projects, AMRAD has assembled an intellectual property portfolio today of over 270 patent applications and granted patents, describing more than 30 inventions.

AMRAD continues to have a formal relationship with its Member Institutes through either a specific Institute Agreement or through its role as the commercialising party in the Federal Government's Co-operative Research Centre scheme. As mentioned above, the primary contractual relationship between AMRAD and its Member Institutes involves AMRAD having the first rights to all of the Institute's research discoveries with commercial potential. In return for these rights, the Institute receives shares in AMRAD. With the number of Members having been extended from the 4 founding institutes to a total of 11 by 1993, AMRAD has pre-emptive rights to research emanating from a significant portion of most of Australia's leading medical research institutes. The Member Institutes in aggregate hold approximately 6 per cent of equity of AMRAD.

From AMRAD's perspective, there are essentially three components in the relationship with its Member Institutes:

- the identification, protection and commercialisation of specific projects;
- the provision of advice to the Institutes on intellectual property protection; and
- the participation by AMRAD in the development of the Institutes' awareness of the commercial aspects of science.

Typically, on having accepted a research project that has commercial potential for further development, AMRAD enters into a formal project agreement with the Institute. The project agreement covers the usual terms including funding commitments, share of commercialisation proceeds and exclusive technology rights. Since nearly all projects via this route are relatively early stage, the chief benefit of this arrangement, from the Institute's perspective rests in the receipt of seed-funding and patent protection advice/provision that would otherwise be difficult to secure from other sources.

## Outcomes from the Member Institute arrangement

The test of the Member Institute model is best measured in terms of successful outcomes. Given the breadth of activities pursued by the Institutes, these fall into two categories:

- research reagents and enabling technologies;
- pharmaceutical targets and development candidates.

In relation to research reagents and technologies, the output of the interaction between AMRAD and the Member Institutes was such that a stand-alone reagent business, AMRAD Biotech, was established. By 1999 this business generated A$10m in annual revenue. The majority of this revenue stemmed from two products –

the sale of the cytokine leukaemia inhibitory factor (LIF) as a research reagent and commercial licences for the protein-production vector pGEX. AMRAD Biotech had an extensive catalogue of Australian-discovered research reagents/diagnostic kits and represented an important development and distribution mechanism for the Institute network. This business was recently acquired by a US company (Chemicon) following a strategic decision by AMRAD to focus on pharmaceutical R&D.

In terms of pharmaceutical development, in its relatively short history AMRAD has progressed three discoveries originating from Member Institutes into development:

- a naturally attenuated human rotavirus vaccine (RV3) for the prevention of infantile diarrhoea;
- LIF (emfilermin) for neuromuscular indications; and
- vascular endothelial growth factor B (VEGF-B) for therapeutic angiogenesis.

These discoveries emerged from programmes at the Royal Children's Hospital Research Foundation, the Walter & Eliza Hall Institute of Medical Research and the Queensland Institute for Medical Research (QIMR) respectively. Apart from RV3, which did not demonstrate a significant effect on primary end-points in Phase II clinical testing, the programmes are ongoing.

Emfilermin is currently in a Phase II trial for the treatment of chemotherapy-induced neuropathy. Emfilermin represents an interesting case study in its own right since it is presently in development as a therapeutic intervention far removed from its initial haematological indication. However, in the context of the present discussion, emfilermin is of note because it was the first project AMRAD sponsored with the Walter & Eliza Hall Institute of Medical Research. AMRAD supported the cloning of this cytokine which led to the grant of worldwide composition of matter patents, as well as a family of use patents. Over the years AMRAD has commercialised emfilermin as a research reagent (ESGRO) and as a therapeutic for thrombopoietic indications through arrangements with Sandoz and Chugai. Although the subsequent discovery of thrombopoietin led to a waning of interest in emfilermin for impaired thrombopoiesis, AMRAD regained rights and has pursued neuromuscular indications independently. Over the past four years AMRAD has assembled a comprehensive development package on emfilermin and expects to obtain the first efficacy data in neuropathy towards the end of 2001. On achieving this important milestone, the strategy is to continue and extend the neuromuscular programme with an international partner.

In parallel with AMRAD's own development activities Serono has been granted a limited option for the development of emfilermin for assisted reproduction indications. The arrangement arose from AMRAD's proprietary position on emfilermin (including granted use patents for embryo implantation) and a series of observations that women with unexplained infertility have an apparent deficiency in emfilermin levels. The fact that AMRAD had already generated a considerable package of preclinical and clinical safety data on emfilermin was instrumental in the arrangement. From a licensing point of view this posed particular challenges given AMRAD's commitment to a neuromuscular programme. Nevertheless, since the reproduction indication offered the opportunity for local rather than systemic administration, it was possible to reach a mutually satisfactory arrangement, including AMRAD retaining manufacturing rights.

VEGF-B entered the AMRAD pipeline as a partial cDNA sequence identified by scientists at the QIMR who were seeking to discover cancer genes. AMRAD's cytokine group subsequently cloned the entire sequence of the human gene, an activity that has provided a proprietary position on human VEGF-B. In collaboration with the Ludwig Institute for Cancer Research who independently discovered mouse VEGF-B, the two organisations have licensed gene therapy rights to Aventis (formerly Rhone Poulenc Rorer Gencell) and protein therapy

rights to Edwards Lifesciences (formerly Cardiovascular Division of Baxter Healthcare). VEGF-B is presently in preclinical testing for ischaemic vascular diseases with both partners. AMRAD retains direct involvement in both arrangements with ongoing technology transfer through supply of relevant research technologies and, in the case of the Edwards arrangement, supply of correctly refolded human recombinant protein.

## AMRAD today

As indicated by the examples provided above, the Member Institute arrangement has been productive and successful for both AMRAD and the specific Institute involved. However, the focus of academic institutes is not necessarily on commercial research. Nor is it sustainable from an industry perspective to rely on commercial outcomes from curiosity-driven research to maintain a pipeline of products. With this realisation, AMRAD has over the past five years actively sought out and sponsored specific drug discovery opportunities where existing expertise in the research community meets the commercial interests. In parallel it has built an internal research and drug discovery capability that complements and extends these external resources. Today the portfolio represents a mix of all of these activities and, in addition to emfilermin, the other two clinical development programmes – AM336 for chronic severe pain and AM365 for hepatitis B infection – had their origins in focused drug-discovery collaborations with the University of Queensland and Commonwealth Scientific and Industrial Research Organisation (CSIRO) respectively. AMRAD has sole responsibility for the development of both of these compounds and is aggressively advancing them through clinical trials.

The AM365 project serves as a useful example of how AMRAD has integrated its internal drug discovery activities with the external research environment. AM365 is a novel nucleoside analogue that emerged from a purpose-specific collaboration aimed at designing novel molecules against the hepatitis B virus (HBV) polymerase. AMRAD was interested in this target for commercial reasons since HBV infection remains a major worldwide health problem for which only one effective product, lamivudine (Glaxo Wellcome), has just recently become available. Under an arrangement with the Division of Molecular Science of the CSIRO the necessary expertise in nucleoside synthesis was applied with AMRAD providing the industry expertise in compound evaluation and selection. Although originally supported by a public-funding mechanism (R&D Syndicate), AMRAD continued support of the programme beyond the Syndicate period. This decision was rewarded by AMRAD's subsequent selection of AM365 as a candidate for development.

AM365 recently successfully completed Phase I clinical testing and Phase II clinical trials are planned for Q1 2001. The preclinical profile of AM365 suggests that it will be sufficiently different from lamivudine to command a commercially valuable share of the HBV market should it successfully complete the development process. However, the importance of the success of this project is far greater than the obvious potential commercial return to AMRAD and CSIRO. AM365 to some extent already is symbolic of successful technology transfer between the public and private sectors. Should it be commercially successful it will represent a major landmark as the first product to emerge from such collaboration to be clinically proven by an Australian company.

While AM365 represents the successful outcome of AMRAD's integration of its own virology resources with external chemistry resources, it is just the beginning. The campaign of target identification and drug discovery continues in a number of different guises in AMRAD. A focused selection of essential viral targets, some unique to AMRAD, are being probed with directed synthetic small molecular weight compounds. A number of these molecules have been identified as original lead compounds from which medicines may be developed. Similarly in the cytokine

programme the signal transduction and feedback mechanisms that control cytokine signalling and function are targets for the identification of new generation cytokine mimetics and antagonists.

Some of these very early drug discovery activities are dependent on basic research at the molecular and genetic level to determine their importance in controlling biological systems and their potential therapeutic utility. It is at this stage that the relationship between AMRAD and its Member Institutes/CRC collaborators completes the circle, with AMRAD contributing its own in-house scientific resources to the efforts of the academic community to provide the critical mass and complementary skills necessary to unravel the molecular and physiological pieces of the target and to discover new drug leads directed at these targets.

## The Australian environment

Reference has already been made to a recent upsurge in the number of biotechnology 'start-ups' in Australia. It is difficult to be precise as to the primary cause of this enthusiasm. The success of the Human Genome Project is frequently offered as a major driver but given that products will take a long time to emerge from this early, albeit valuable, technology, it is difficult to ascribe too much weight to this factor. Suffice to say that private and semi-private investment funds are being established across the country and they are seeking to invest in biotechnology. Recent changes to the capital gains tax structure, which removes a major disincentive to high-risk/high-return investment, has certainly been invaluable in driving this process.

On the academic side, while the Federal Government has announced a substantial increase in funding for the National Health Medical Research Council Grants Scheme, competition for these funds has never been higher. So it is understandable that academic researchers are increasingly looking elsewhere for funding. In parallel there has been increasing recognition of the need for a change in culture among the academic community towards acceptance of an entrepreneurial outlook. The combination of these events together with the increase in available funds from the private sector is proving to be a heady mix. Already this year more than 10 new companies have been established or have raised funds by listing on the Australian Stock Exchange. But, for this trend to be sustained, it is essential that success stories emerge from the sector in general. Hence the widespread interest in the success of AMRAD's development programmes, particularly those that represent examples of public and private collaborations such as emfilermin, AM336 and AM365.

In conclusion, the buoyancy of the current environment means that the medical research community's absolute need for a technology transfer vehicle such as the AMRAD of yesteryear is diminishing. This coincides with AMRAD's increasing independence from these organisations to sustain a pipeline and its evolution into a R&D biotechnology company in its own right. What this means is that while we believe the unique Member Institute model still has great importance and relevance to both parties, Australia's newly gained enthusiasm for biotechnology provides each with a vastly wider range of opportunities.