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Rob Ashley of AmpliMed discusses the discovery and development of Imexon

Interviewed by Steve Carney

Could you give our readers some details on the history of AmpliMed?

AmpliMed was founded in 1989 by a group of professors at the Arizona Cancer Center in Tucson. The establishment of the company was made possible by changes in State Law, allowing University employees to establish and work part time for new companies. The founders of AmpliMed were Dr. Evan Hersh, a medical oncologist; Dr. Robert Dorr, a pharmacologist and head of the pharmacy service at the Arizona Cancer Center; Dr. Dave Alberts, a medical oncologist; Dr. Bill Remers, a medicinal chemist; and Dr. Sydney Salmon, head of the Arizona Cancer Centre at the time. Initially, AmpliMed was focused on new drug delivery technology, in particular liposomes, and developed a formulation of a cancer drug in collaboration with the company Vestar that ultimately entered clinical development. However, Vestar was bought out by Nexgen and then ultimately by Gilead, and the project was dropped. Then in the mid-90s, Dr. Hersh rediscovered a drug with potential as an immune modulating agent and also as a cancer chemotherapy, called imexon. This drug, which we named Amplimexon, has formed the backbone of the company since that time.

Robert A. Ashley

Chairman, CEO and President, AmpliMed Corporation

Robert Ashley's career in the pharmaceutical industry extends over 24 years, encompassing both large and small companies. After graduating with a Masters Degree in Biochemistry from Oxford University, he joined Amersham International, where he served in numerous roles in manufacturing, development and marketing, was responsible for the launch of several new radiopharmaceutical products and served as UK Sales Manager. He then joined Squibb Corporation as Commercial Development Manager in the Diagnostics Division, and served in several marketing and business development positions of increasing responsibility within Bristol-Myers Squibb, being responsible for launching new contrast agents in various radiological specialties with a primary emphasis on improved cancer diagnosis. In 1994, he joined a venture-backed start-up company, CollaGenex Pharmaceuticals, as its second full-time employee, and served as Vice President and subsequently Senior Vice President of Commercial Development, as the company grew into a profitable, publicly-traded specialty pharmaceutical company with 160 employees and sales in excess of US$50 million. His responsibilities included research, development, regulatory, clinical, manufacturing, business development, licensing and intellectual property, along with the development of CollaGenex' business outside the United States. He was responsible for guiding CollaGenex' lead product Periostat® through the clinical development and regulatory process, and for the successful relationship between the company and the National Cancer Institute for the development of the cancer drug, Metastat®. He is the author of several scientific papers and is the inventor of several granted and pending patents.

'There was a notion at the time that if you stimulated the immune system, then you might help in the treatment of cancer'

How did you come across this drug?

Imexon was one of a class of drugs called cyanoaziridines that had been developed in the 1970s by Boehringer Mannheim as immune modulators. Boehringer ultimately decided to not take this particular drug forward into the clinic. However, a group of researchers at the University of Vienna decided to try imexon in a number of cancer patients, as there was a notion at the time that the stimulation of the immune system would help in the treatment of cancer. They tried a very low dose and a weekly regimen in a variety of different types of cancer, and observed some complete and partial

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responses and also some patients had stable disease over an extended period. However, the data were not published until the mid 80s, and then only in a review article, so they never drew the attention they deserved. Apparently the principal investigator, who was really the champion of the project, died, and so the driving force behind the project was lost and the effort was effectively ended.

However, in the early 90s, Dr. Hersh and his colleagues were responding to a request for proposal from the NIH to study immune stimulating drugs for AIDS patients, when they came across the prior imexon cancer data. Imexon was tested in Dr Hersh's lab in a mouse AIDS lymphoma model and the drug succeeded in curing the lymphomas in these animals. This got everyone interested in the potential of imexon as a cancer drug.

'...imexon is the only cancer drug under development at this time which exploits this mechanism of action.'

So how did they advance such an interesting compound?

AmpliMed resurrected the compound with the help of funding from the NCI and AmpliMed founders spent the next five years trying to work out the mechanism of action. One of the first things they found was that imexon worked in SCID mouse tumor models. This means that imexon's mechanism of action has to be independent of modulation of the immune system, because SCID mice don't have an immune system to modulate!

Could you explain the mode of action of Imexon?

With funding from a 'RAID' grant from the National Cancer Institute, the AmpliMed founders succeeded in discovering that imexon was, in their own terms, a 'mitochondrial oxidant'. Cells that are dividing rapidly and, therefore, have a highly active metabolism, produce a lot of free oxygen radicals in both the mitochondria and the cytoplasm. Cells have a variety of mechanisms to get rid of these free radicals, because they are cellular toxins and if they build up in the cytoplasm, then the cell will enter a sequence of programmed death, or apoptosis, and die. One of the mechanisms which cells have developed to protect themselves is to produce a lot of sulfhydryl-containing compounds, of which by far the most abundant is glutathione. AmpliMed scientists were able to show that imexon enters the cell and binds to glutathione and other sulfhydryl compounds, effectively preventing them from scavenging the toxic free radicals. So, particularly in the rapidly dividing cancer cell, free radical build-up in the presence of imexon leads to changes in mitochondrial membrane potential and ultimately to the mitochondria swelling and bursting. Mitochondrial proteins, in particular cytochrome *c*, are released into the cytoplasm and this activates caspase-mediated apoptosis resulting in cancer cell death. This sequence of events has been well characterized by our scientists and published in several papers in leading cancer journals. We believe that imexon is the only cancer drug under development at this time which exploits this mechanism of action.

So, what is the intellectual property position for Imexon?

Amplimexon is protected in a variety of different ways. Most importantly, the drug has been granted orphan designation by the FDA for the key indications for clinical development in the United States: pancreatic cancer, malignant melanoma, and multiple myeloma. This provides for seven years marketing exclusivity after approval. Furthermore, it is anticipated that the drug will be used in combination with other chemotherapeutics for the treatment of many cancers, and extensive preclinical work has revealed that the drug is synergistic with certain chemotherapeutic drugs, additive with others and actually antagonistic to some. These unexpected findings have led to a series of combination patents to protect the novel synergistic combinations and these are to be further developed in the clinic. There are also patents on the manufacturing of the active ingredient and the possibility of patents on the final formulation of the drug.

In view of the mode of action that you outlined, does imexon work particularly well with platinum based drugs?

Yes, we've seen synergy with platinum-containing compounds, certain alkylating agents and some tubulin inhibitors, like taxotere. A really interesting finding, for which there was no really obvious explanation, was clear synergy with antimetabolites, like gemcitabine. Recent research in Dr. Dorr's lab has discovered some of the underlying mechanisms for synergy with gemcitabine, and these were published at the recent ASCO meeting. For example, imexon is an inhibitor of ribonucleotide reductase, a key enzyme in DNA synthesis that is also a target for gemcitabine. Imexon is also a cell cycle inhibitor and in the presence of the drug cells accumulate in S phase. This is the phase of the cell cycle during which gemcitabine is incorporated in DNA and therefore in the presence of imexon it is possible to measure significant increases in gemcitabine uptake.

'These unexpected findings have led to a series of combination patents to protect the novel synergistic combinations...'

What about follow-on portfolio drugs now coming through the company?

Dr Bill Remers, our medicinal chemist, has synthesized and characterized a series of other cyanoaziridine compounds which have characteristics similar to imexon but are more potent, in some cases by several orders of magnitude, and have better physicochemical characteristics than imexon, such as better solubility, which make them easier drugs to formulate. These compounds are proprietary and we are currently selecting a lead to take into the clinic in 2006.

A second unrelated group of compounds called azonafides was also developed at the University of Arizona by Bill Remers and his colleagues and the patents are licensed to AmpliMed. This series was originally designed to get around the problems with another compound which is in clinical trials known as amonafide. This was a compound originally developed by Knoll Pharmaceuticals. It turned out to be potent, particularly in breast and prostate cancer, but unfortunately about 30% of the population was unable to tolerate the drug at doses which were effective, due to severe myelosuppression. It was discovered that the drug was metabolized in the liver by the N-acetyltransferase enzymes, NAT-1, which is a constitutive enzyme, and NAT-2,

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which is an inducible enzyme. A subset of the population has changes in these enzymes which make them rapidly metabolize amonafide. The metabolite blocks the clearance of the parent compound, so the drug builds up in the blood and damages the patient's bone marrow. Because the drug had such promising clinical results, certain companies continue to work on its development, and are trying to select susceptible patients up front and adjust the dose of the drug to avoid the side effects. In one case, the patients are administered a dose of caffeine, which is metabolized by the same enzyme system, to test for rapid acetylation. In another case, a company is screening patients genetically. Perhaps a more elegant solution to the problem is to develop a series of compounds which may maintain the efficacy of amonafide but avoids the biochemistry involved in that metabolic pathway. To this end, Dr Remers developed a series of compounds, 150 or more, and then performed extensive structure–activity work to identify a lead compound significantly more potent than amonafide but without the potential for NAT-mediated toxicity. This lead compound is called Amplizone and is headed toward the clinic early next year.

Strategically, are you going back into libraries to screen for the particular activity you have identified, to come up with other new leads?
Our compounds have been developed in academic institutions without the constraints that typically arise inside pharmaceutical companies. A typical development route in a pharma company is to identify a target, then screen numerous compounds against that target. In our case, a compound with known efficacy was immediately studied in cell lines, then in animal models to rapidly determine the best pathway for clinical development. Simultaneously, a successful effort was mounted to establish the target and the mechanism of action, and this in turn led to an understanding of the synergies observed in the preclinical models. By using this more intuitive development scheme, our University-based researchers were able to rapidly determine that imexon had the potential to be effective in man, and would likely be well-tolerated. This, along with the synergy data, suggested that, at least in principle, the drug could be used in combination with other cytotoxic drugs, which are myelosuppressive, without contributing any new toxicity. So you can, at least in principle, use full-dose gemcitabine with full-dose imexon in pancreas cancer patients. In the xenograft models, even in cells which were completely resistant to either drug by itself, the combination was extremely effective, not just in terms of growth delay, but also in terms of eliciting tumor regression. Based on that, a clinical development program was put in place, first to study the drug as a stand-alone therapy, and more recently to evaluate promising combinations. There are now two combination studies underway; one with gemcitabine in pancreatic cancer patients and one with DTIC in malignant melanoma.

'...I am a great believer in maintaining control of the clinical development function...'

So, as a company, where do you see the future for AmpliMed?
We are highly focused on the clinical development of Amplimexon, and we plan additional studies in combination with taxotere in breast, lung and prostate cancer patients and as a stand-alone therapy in multiple myeloma. However, if the pancreas cancer study we initiated early in 2005 continues to yield interesting data, and given the biochemical rationale for synergy with gemcitabine, I see us focusing even more diligently on the conduct of a registration trial for this indication, provided we can raise sufficient funds. If this is successful and we are able to file an NDA, it is possible we could have the drug approved for this indication in late 2008/early 2009. While of course a partnership to co-develop or market Amplimexon is always possible, the cancer market is sufficiently well defined such that a small company like AmpliMed could develop its own modest sales and marketing infrastructure and promote a drug, such as Amplimexon, which may have a compelling argument for widespread use.

If you were to go alone, you would probably be unique, and it would be interesting to see how successful such an approach would be, in terms of being able to generate profit.
My previous company, CollaGenex Pharmaceuticals, was involved in bringing drugs to the market in dentistry. There are more than 100,000 dentists in the United States, so this is a very expensive market to cover with a traditional pharmaceutical sales force. However, by using the data now available from various sources, which classifies healthcare professionals according to their prescribing habits, it was possible to address probably 80% of the available market for our prescription drug, with a modest sales force of less than 100. By building its own sales and marketing team, CollaGenex was able to achieve profitability within three years of market entry and with sales of less than US$50 million. This experience taught me that, if your product has reasonable margins, if you avoid building a huge and unnecessary infrastructure and if you target effectively, it is very possible to eke out solid profits from specialty pharmaceutical sales. This model is also applicable to a specialty cancer indication, such as use in combination with gemcitabine for the treatment of pancreas cancer, provided the product is novel, easy to use, and has compelling efficacy data to support it.

Leading on from that, how are you going to manufacture it out of a university department, do you outsource the synthesis and all those other downstream functions?
Yes, we outsource all of the manufacturing to companies with the skills and facilities to carry out those functions. We also outsource much of our research and development functions, but I am a great believer in maintaining control of the clinical development function by monitoring the clinical studies with in-house personnel. Functions such as data management and the statistics associated with the clinical studies are being outsourced.

'There is a continual need to manage the outsource partner...'

If you were going to set up a company again to do the same sort of thing, do you think you'd end up where you are now?
Yes. There are certain frustrations associated with outsourcing, such as the need to 'slot in' to the schedule of your outsourcing partner, particularly in areas where resources are scarce,

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such as toxicology and certain types of manufacturing. There is a continual need to manage the outsource partner, particularly to ensure that your project gets the priority it deserves. And it is a myth to think that it is inexpensive to outsource. The 'virtual' drug development model is not for every project; for example, it would not work in an environment where a lot of the expertise resides in a small number of talented scientists, or where the technologies being applied to the development of a drug are novel and proprietary. However, the flexibility that is offered by an outsourcing model and the ability to exploit skills and resources, which would never be available in house without massive investment in infrastructure and equipment, makes the outsourcing model very sensible for companies involved in the late stages of pharmaceutical development. I believe that the translation of early-stage research into clinical development and then marketable products is the area in which this model works best, and this is where AmpliMed is focused.

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Innovation drives success in Switzerland's biotech scene

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Today, it is not only Boris Becker and Ralf Schumacher who are choosing to set up home in Switzerland. A steady stream of profitable healthcare companies is selecting this country in central Europe as headquarters for healthcare-related research, development and production (Table 1). Attracted by favorable tax rulings and progressive business incentives, these companies also have access to Switzerland's highly skilled, educated and multilingual workforce. The latest to add their names to a growing list of companies with a presence in Switzerland are Celgene (new production center in the Canton of Neuchâtel) and Biogen Idec (European headquarters in Zug).

Strengths in pharmaceuticals

For years, Switzerland has been the home of innovative approaches to healthcare, built on its strong presence in the pharmaceutical industry. To a large part, this is a result of the success stories of Novartis and Roche, each with headquarters in the Basel area and each pursuing contrasting but successful business strategies in their global markets. Serono, Europe's largest biotech company, has its international headquarters in Geneva. On the strength of its portfolio in recombinant proteins, the company achieved worldwide revenues of US$2.5 billion in 2004, a performance comparable to some of the leading biotech companies worldwide. Although successful healthcare companies can be found in many regions of Switzerland, it is fair to say that the majority of early- and late-stage companies are located in the vicinity of three life-science clusters around Basel (40 companies, 4000 employees), Zürich (65 companies, 2000 employees) and the Lake Geneva region (30 companies, 5500 employees) (see map) [1]. This includes a dynamic medical technology sector, with enterprises like Medtronic (European headquarters in Tolochenaz), Phonak and Straumann.

Biotech future

A growing number of experts and opinion leaders are placing emphasis on biotechnology as the engine of growth for the healthcare industry in the years ahead. This emphasis is based on some clear-cut indicators. Last year, 26% of new active substances launched by the global pharmaceutical industry were biotech products (IMS LifeCycle New Products Focus). The Tufts Center for the Study of Drug

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