

Intellectual Property Strategic Plan

EntreMed's Best Opportunity for Securing Comprehensive IP Protection and Profitability

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Introduction

EntreMed's Best Opportunity for Securing IP Protection & Profitability

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Abstract

EntreMed is a Maryland based pharmaceutical company that does in-house research and development into oncology and anti-inflammatory drugs. The company currently has registered a number of patents and trademarks with the USPTO.

Currently the company has no products in the marketplace, but anticipates the release (possibly this year) of a least one treatment – Panzem. In the future EntreMed anticipates marketing many of the drugs currently undergoing development and clinical trials. Furthermore, the company also expects to engage in joint ventures in the near future in order to expedite and enlarge its pharmaceutical pipeline.

Recommendations Summary

- Consider non-disclosure agreements for employees engaged in joint ventures
- Partnerships for Manufacture and Marketing
- Reevaluation of Trademark Practices
- Consider licensing/selling unused intellectual property
- Register the graphical EntreMed Logo
- Consider acquiring some additional internet domain names
- Negotiate a trademark agreement with Angiogen LLC

EntreMed's Corporate Situational Breakdown

Contents

- Overview
- Products
- Finances
- Business Goals
- Competition & Risk Factors
- Strategic Partnerships

Overview

EntreMed, Inc. is a clinical-stage pharmaceutical company focused on developing next generation multi-mechanism oncology and anti-inflammatory drugs that target disease cells directly and the blood vessels that nourish them.

Products

EntreMed developed its initial drug pipeline based on extensive research in angiogenesis (the growth of new blood vessels) and its relationship to cancer. This research led to a focus on three major areas for drug candidates: angiogenesis, inflammation, and cell cycle regulation. Currently, Entremed has no products in the market. However, it has now reached Phase 2 clinical trials with two products and has a number of others under active development. The Company has made no public predictions about when these products might be ready for commercial distribution.

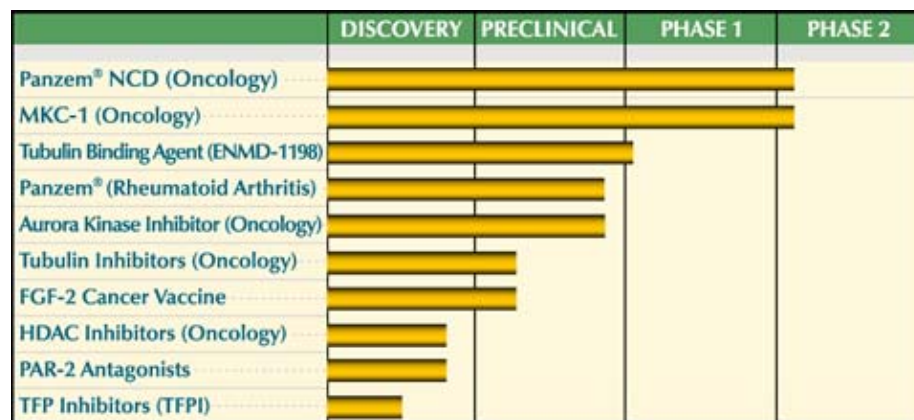


Figure 1.1 – Entremed pharmaceutical pipeline

Panzem®

Panzem, 2-methoxyestradiol or 2ME2, is EntreMed's lead clinical candidate. The 2ME2 mechanisms that are particularly relevant to the treatment of cancer involve inhibiting endothelial cell growth (antiangiogenic activity) and killing tumor cells directly (pro-apoptotic activity). Panzem was developed internally by EntreMed, and the Company owns exclusive rights to it.

MKC-1

MKC-1 is an orally-active, small molecule, cell cycle inhibitor with a unique mechanism of action. Specifically, MKC-1 arrests cellular mitosis by inhibiting a novel intracellular target important in cellular trafficking that has been shown to be involved in cell division. MKC-1 was acquired from in January 2006 when the company acquired Miikana Therapeutics, Inc., a clinical-stage biopharmaceutical company with research laboratories in Toronto, Canada.

Finances

EntreMed was founded in 1991 and had an initial public offering in June 1996 which raised \$48 million. They are listed on the Nasdaq with ticker symbol ENMD.

Since December 2004, EntreMed raised nearly \$55 million through the sale of common stock to institutional investors and through the exercise of warrants held by Celgene Corporation. The company believes that the proceeds from these transactions, together with its cash, short-term investments and projected cash inflows, will support current and planned operations well into 2007.

For 2005 EntreMed experienced a net loss of \$16,313,257 and currently has cash and short-term investment holdings in the amount of \$30,082,388. To further support the current and future operations, \$30 million in gross was raised through private placement of common stock and warrants to institutional biotechnology investors.

Recent EntreMed reports indicate that the company anticipates increasing its research and development spending in 2006.

Business Goals

EntreMed's principle goals: are to:

1. By conducting research into angiogenesis (in which its employees have expertise), develop therapeutics for the treatments of inflammatory diseases and cancer.
2. Commercialize such therapeutics, possibly through strategic partnerships or licensing arrangements.

EntreMed's plan is to pursue many product candidates simultaneously. Corporate documents indicate the company's intention to aggressively pursue co-development alliances, funded research and licensing opportunities, as well as partnerships with pharmaceutical and biotechnology companies.

Competition & Risk Factors

Competition in the pharmaceutical, biotechnology and biopharmaceutical industries is intense and based significantly on:

- results of research and development activities
- progress of our preclinical studies or clinical trials
- results of clinical trials
- changes in or terminations of our relationships with strategic partners
- changes in the focus, direction, or costs of our research and development programs
- competitive and technological advances
- establishment of marketing and sales capabilities
- manufacturing
- the regulatory approval process
- product launch

Development of products is at an early stage and is still highly uncertain. The ability of Entremed to raise funds, and the general viability of its business can easily be substantially disrupted by a fluctuation in any one of a number of critical factors:

- results of research and development activities
- progress of preclinical studies or clinical trials
- changes in or terminations of our relationships with strategic partners
- competitive and technological advances
- marketing and sales capabilities
- manufacturing
- the regulatory approval process

The most important thing to note in this discussion is that many existing and potential competitors have substantially greater financial, technical and human resources. So, in order to be competitive, Entremed will have to find inventive ways to successfully secure and commercialize its IP.

Strategic Partners

Since its founding in 1991, Entremed has pursued relationships with a number of entities in an effort to secure additional funding, and also research support.

In 1995, Entremed signed a Research Collaboration and License Agreement with Bristol-Myers Squibb Company which through fiscal year 1998 provided Entremed with \$28.5 million. In 1999, Entremed and Bristol-Myers Squibb jointly announced a modified Research and Development agreement allowing Entremed to re-assume development lead for the angiostatin protein.

One of Entremed's strongest and most successful collaborations is with the National Cancer Institute. In September 1998, the National Cancer Institute, recognizing antiangiogenic cancer therapeutics as a promising strategy in the war on cancer, signed a

Cooperative Research and Development Agreement (CRADA) with EntreMed to assist with clinical trials of Endostatin protein.

To complement in-house research and development efforts, EntreMed has entered into sponsored research agreements with outside scientists to conduct specific projects. Most of these scientists work at universities or nonprofit cancer research centers.

IP Holdings

Contents

- Overview
- Patents
- Trademarks

Overview

EntreMed owns the rights to 19 patents and has registered 3 trademarks. Our investigation has not revealed any registered copyrights.

Patents

EntreMed's patent holdings can be classified into a few sub areas

Production Methods

- 6723536 Method of producing and purifying angiostatin
- 6090617 Flow electroporation chamber with electrodes having a crystalline metal nitride coating
- 6074605 Flow electroporation chamber and method
- 5720921 Flow electroporation chamber and method

Methods for inhibiting cell proliferation

- 6805865 Compositions and methods for treating cancer and hyperproliferative disorders
- 6734163 Compositions and methods for inhibiting cellular proliferation
- 5981471 Compositions and methods for inhibiting cellular proliferation
- 5919459 Compositions and methods for treating cancer and hyperproliferative disorders
- 5814666 Encapsulated and non-encapsulated nitric oxide generators used as antimicrobial agents
- 5605885 Method for Stimulating the Immune System

Methods for treating angiogenic disease

- 6593291 Compositions and methods of use of ligands that bind components of the blood coagulation/clotting pathway for the treatment of cancer and angiogenic-based disease
- 6544947 Compositions and methods for inhibiting endothelial cell proliferation and regulating angiogenesis using cancer markers
- 6518298 Methods and compositions for inhibition of angiogenesis with EM-138
- 6413513 Compositions and methods for inhibiting endothelial cell proliferation and regulating angiogenesis using cancer markers
- 6201104 Angiogenesis--inhibiting protein binding peptides and proteins and methods of use

Other treatment methods

- 6605622 Use of anti-estrogenic compounds as anti-fungal agents
- 6239123 Use of estrogenic compounds as anti-fungal agents
- 6224902 Vaccines against sterols
- 5753260 Vaccines against sterols

Trademarks

EntreMed has 3 registered word marks (no associated graphics).

- "EntreMed"
- "The Angiogenesis Company"
- "Panzem"
- entremed.com (registered domain)

IP Utilization Analysis

Contents

- Overview
- Patent Usage
- Trademark Usage

Overview

The patents can be subdivided into 4 main areas: production methods, methods for inhibiting cell proliferation, methods for treating angiogenic disease, and other treatment methods. The first of EntreMed's production method patents involve the process to produce angiostatin which is a potential inhibitor of developing blood vessels and tumor growth. The method described involves using *Pichia pastoris* fermentation of clones with nucleic acid sequences encoding for the angiostatin protein. Next, there are three patents related to a flow electroporation chamber. The purpose of the chamber is that it provides a method for encapsulation of allosteric effectors of hemoglobin by electroporation for therapeutically desirable changes of intracellular hemoglobin.

Of EntreMed's 6 patents in inhibiting cell proliferation the first (pat. no. 6805865) and fourth (pat. no. 5919459) are related and the second (pat. no. 6734163) and third (pat. no. 5981471) are related. The first patent is a continuation of the fourth patent which involves vaccinating against growth factors that are associated with specific cancer types and hyperproliferative disorders. The second patent is a continuation of the third, they relate to the use of tissue factor pathway inhibitor to inhibit angiogenesis and angiogenesis-related diseases. The fifth patent illustrates compositions that can release nitric oxide for the treatment of microorganism-related disease states. The final patent is involved in treating people that are immunosuppressed with proteins that have prolactin-like activity.

EntreMed has 5 patents in the area of methods for treating angiogenic disease. The first patent describes the use of ligands that bind to components of the blood coagulation/clotting pathway and inhibit angiogenesis and its related diseases. The second patent (a continuation of the fourth) shows a novel use of cancer markers (like prostate-specific antigen) as inhibitors of angiogenesis. The third patent describes a method of treating diseases mediated by angiogenesis by administering a composition comprising an anti-angiogenic compound. The fifth patent involves to peptides and proteins that bind angiogenesis-related proteins that can be used in diagnostic assays and kits.

The last area is comprised of the rest of EntreMed's patent portfolio. The first two (first is a continuation of the second) patents present compounds that are useful for inhibiting the proliferation of fungi which can be used to treat infections of fungi. The third patent which is a continuation of the fourth patent describes immunoreactive vaccine compositions for immunizing humans against sterols (like cholesterol).

Patent Usage

Most of EntreMed's patents are related to angiogenesis which is the main thrust of the company.

- Panzem: Production methods for Angiostatin, methods for treating angiogenic disease
- MKC-1: Methods for inhibiting cell proliferation
- Other products pipeline: Methods for treating angiogenic disease

EntreMed has 6 patents relating to angiogenesis which are used in their main drug candidate Panzem as well as other drugs currently in their pipeline. The second leading drug candidate is MKC-1 which was obtained through the acquisition of Miikana Therapeutics. EntreMed owns the rights to 5 patents related to the area of inhibiting cell proliferation which relates to MKC-1.

In addition to these, EntreMed owns several patents in areas in which it does not currently engage in any active research there are five of these which relate principally to:

- anti-fungal medicines
- sterol vaccines (which can be used to treat high cholesterol)

EntreMed has 2 patents for using both anti-estrogenic and estrogenic compounds as anti-fungal agents. However, they are not actively engaged in further development of drugs for anti-fungal agents. In addition, EntreMed has 2 patents related to vaccines against sterols which are also not being utilized. The key factor with the anti-fungal medicines and sterol vaccines is that EntreMed's expertise and focus is in oncology and angiogenesis which do not relate to anti-fungal medicines and sterol vaccines.

Trademark Usage

EntreMed has trademarked the phrase "The Angiogenesis Company" but does not appear to use it in any of the corporate literature or on the web site. What's more, our research has identified a company named Angiogen LLC operating in Illinois. That company has registered the angiogenesis.com domain.

EntreMed has held a number of other trademarks in the past which are now no longer in use.

Recommendations

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- Overview
- IP protection under joint ventures
- Partnerships for Manufacture and Marketing
- Licensing unused IP
- Registering the EntreMed logo
- Acquiring additional domains
- Dealing with Angiogen

Overview

Based on the data presented earlier and that in the appendix section, BC Consulting now presents several recommendations designed to both protect and efficiently utilize those Intellectual assets the company currently owns.

The Principle challenges facing EntreMed to consider:

- failure to obtain additional patents
- challenge, invalidation, or circumvention of patents already issued
- failure of the rights granted under patents to provide sufficient protection
- independent development of similar products by third parties
- ability of third parties to design around patents

IP protection under joint ventures

We indicated earlier that EntreMed has become interested in pursuing industry partnerships and “co-development alliances.” Some examples of ongoing partnerships and alliances discussed earlier are the Research and Development agreement with Bristol-Myers Squibb, the National Cancer Institute, sponsored agreements with outside scientists at Universities such as University of Maryland.

It is not uncommon in such a situation that the lines between corporations blur in the eyes of researchers who are unfamiliar with the subtleties of intellectual property protection, and do not have a personal or vested interest in accounting for such property.

A large part of the value of a research-intensive organization lies in the knowledge of its employees – an aspect of intellectual property that sometimes goes unrecognized. For the past few years EntreMed researchers have presumably become increasingly skilled at their work and are likely to have developed new techniques or research methodologies in their areas of expertise. We would term such knowledge as trade secrets and recommend that the skills of EntreMed employees be viewed as a substantial corporate asset. Forming joint ventures with former industry rivals should be done with caution. It is likely that such ventures will result in the inadvertent leaking of trade secrets when EntreMed researchers interact with researchers from other entities.

We recommend that before undertaking such a venture that EntreMed perform a review of all the advanced laboratory and research techniques that have been in use at EntreMed. A feasibility study for patenting such techniques should be conducted. In addition, it may be appropriate to negotiate a contract with the partner entity in an effort to protect trade secrets. Employees should be instructed on the importance of preserving such secrets and on how to avoid revealing them unless necessary. In addition, employees can be required to sign non-disclosure agreements and non-compete agreements to protect the intellectual property of the company.

EntreMed should also review its policy toward Sponsored Research Agreements. It's important in this case to secure the rights to develop under exclusive license any discoveries resulting from these collaborations. This is typical of corporate-university relationships where the corporations provide substantial support for the scientists' laboratory, research personnel and research supplies, in return for an exclusive license.

Partnerships for Manufacture and Marketing

EntreMed currently has no capacity to market or manufacture, on a large scale, any of the products currently under development. We recommend that EntreMed actively pursue a partnership with a large pharmaceutical company now. Our research has shown that it is common for pharmaceuticals to create partnerships for marketing and distribution of their drugs. Often, domestic companies will sell the international distribution rights of their drugs to focus on domestic sales. In EntreMed's case their partnership could include marketing and distribution for both domestic and international markets. In this case, it would be wise to partner with a large pharmaceutical that has the resources and infrastructure for both international and domestic distribution. This would allow EntreMed to focus on drug discovery which is their specialty while still maintaining a revenue stream, which EntreMed currently lacks with no products on the market.

Contracts should be drafted to protect EntreMed's production processes and possibly trade secrets. The principle reason for this action arises from the fact that time-to-market is a critical concern in the pharmaceutical and biotechnology industries; waiting too long will likely result in a rushed process. Under such circumstances it is not uncommon for deals to work out in an unfavorable way for a company in EntreMed's position. We recommend that EntreMed license their drugs in their partnerships to maintain ownership versus selling the intellectual property. This is important so that EntreMed can maximize the value of their intellectual property by having a continuous revenue stream over the term of their patents to support company operations instead of a one time sale.

Reevaluation of Trademark Practices

To date every trademark EntreMed has filed for has gone unused (except for the recent addition of Panzem®). In addition, all of EntreMed's slogans have gradually moved into disuse. The current slogan, "The Angiogenesis Company," no longer appears on any company literature.

The employees of EntreMed have little or no expertise in marketing. Strategic partners will be much better equipped to handle the marketing aspects of the business. Pfizer, for example, would likely hire focus groups to study the impact of possible drug names on consumers. For these reasons we recommend that EntreMed get out of the business of product marketing and slogan making.

We believe strongly that EntreMed's best chance at profitability is to focus on its core business of research. Attempting to compete with large pharmaceutical companies with absolute advantages in marketing seems destined for failure.

Licensing Unused IP

As described in the patent usage analysis, EntreMed has 4 patents in areas outside the main focus of the company. The areas of the patents include anti-fungal compounds and vaccines against sterols. We can explore methods of earning revenue from this unused intellectual property. EntreMed can either license or sell the rights to their patents to companies that specialize in the anti-fungal medicines and vaccines against sterols. Funds could be used to increase research investments into the current pipeline or for further acquisitions of companies (similar to the purchase of Miikana Therapeutics in January 2006).

Anti-fungal patents could be licensed to any number of companies that manufacture anti-fungal medications

- Pfizer (fluconazole, Eraxis)
- Procter & Gamble (pyrithione zinc)

Consider licensing or selling sterol patents to companies that produce cholesterol lowering drugs.

- Pfizer (Lipitor)
- AstraZeneca Pharmaceuticals (Crestor)
- Merck & Schering Plough Partnership (Vytorin)

Registering the EntreMed Logo

While trademark registration protection has been acquired for the "EntreMed" name, the EntreMed Logo which appears on many of the business publications of the company is not protected.



Figure 4.1 – EntreMed Corporate Logo

We recommend EntreMed immediately seek to register the logo as a trademark. It is simply too important of a corporate symbol not to ensure the highest level of protection.

Acquiring additional domains

There are several unused domain names that we believe EntreMed should consider registering. Attempting such acquisitions after a company becomes better known often proves significantly more costly.

- entremed.net
- panzem.com
- entermed.com

Dealing with Angiogen

Angiogen was founded in 1999 which is 4 years later than EntreMed and has one main patent #6576609 (see Appendix) that covers methods and composition for generating angiostatin. Their method uses a plasminogen activator along or in combination with a free sulfhydryl donor. This production method of angiostatin patented by Angiogen could infringe upon EntreMed's patent #6723536 (see Appendix). EntreMed's patent utilizes *Pichia pastoris* for large scale purification and recovery of recombinantly-produced angiostatin. We would suggest a further investigation of the similarities between the processes because the end result product is angiostatin in both patents. Then it could be decided whether to license, create a joint partnership, or pursue litigation against Angiogen with respect to patent infringement. Some key factors to consider are that EntreMed has been in the business of producing oncology drugs that target disease cells directly and in angiogenesis being founded 4 years earlier. In addition, EntreMed is further along in clinical trials with the FDA for their angiogenesis drug Panzem than Angiogen who is a Phase I trial. Finally, since EntreMed is a publicly traded company and Angiogen is still a privately owned, there is much more transparency into EntreMed's business and IP usage.

We noted earlier that the trademark "The Angiogenesis Company" has fallen into disuse. We recommend that EntreMed consider either attempting to defend this trademark against possible infringement by Angiogen (should the EntreMed marketing department wish to resurrect the mark) or otherwise consider selling this mark to the Angiogen rather than lose it at no benefit. This trademark of "The Angiogenesis Company" could come into play during negotiations with Angiogen about the possible patent infringement.

Section

5

Appendix

Contents

EntreMed

- 19 Patents
- 3 Trademarks

Angiogen

- 1 Patent