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A Wild Ride

New focus and financing sets
EntreMed back on track.

Ted Agres
Contributing Editor

For biotech companies, challenges are a way of life. But for *EntreMed, Inc.*, a clinical-stage pharmaceutical company developing anti-angiogenesis oncology drugs, life has been a roller coaster of challenges. The company began in 1991 and went public in 1996. Following a report in the *New York Times* in May 1998, *EntreMed's* stock quadrupled overnight from \$12 to around \$51 per share. By the following year, it was trading at less than half that.

Things began to turn around in 2003. *EntreMed* entered into a partnership with rival *Celgene Corp.*, selling rights to its thalidomide analogs in exchange for equity ownership and cash. *EntreMed* also implemented a new strategy of focusing on small molecules and expanding research to include cell cycle regulation, inflammation, and kinase inhibition. In January 2006, *EntreMed* acquired *Mikana Therapeutics*, a small biotech company developing novel cell-cycle inhibitors.

With 57 employees, *EntreMed* has two lead compounds in multiple Phase II clinical trials in oncology: *Panzem®* NCD (2-methoxyestradiol or 2ME2) and *MKC-1*. Products in preclinical development



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—James S. Burns, president and CEO, *EntreMed, Inc.*

include 2ME2 for inflammatory diseases and ENMD-981693, a multi-target kinase inhibitor. The company expects to file two investigational new drugs (INDs) this year.

Contributing Editor *Ted Agres* discussed company strategy with *James S. Burns*, president and CEO; *Carolyn Sidor, MD, MBA*, vice president and chief medical officer; and *Marc Corrado*, vice president for corporate development, at *EntreMed's* corporate offices in Rockville, Md.

DD&D: *EntreMed has been through difficult times. Over the years you've had to lay off staff, freeze wages, and take other severe measures to stay afloat. Is that typical of most biotechs?*

Burns: Not to the extreme this company has been through. We've been through a near-death experience, going through a transition from being a pure research-oriented organization to ultimately becoming a business- and development-focused organization. You have rise periods where you work on promising technologies and then you have lull periods where you try to develop that technology, and then you have rise periods again when you start to see some preclinical data. Some companies have real extreme cycles.

DD&D: *Like when the New York Times writes about you on the front page and the stock soars, only to crash afterwards.*

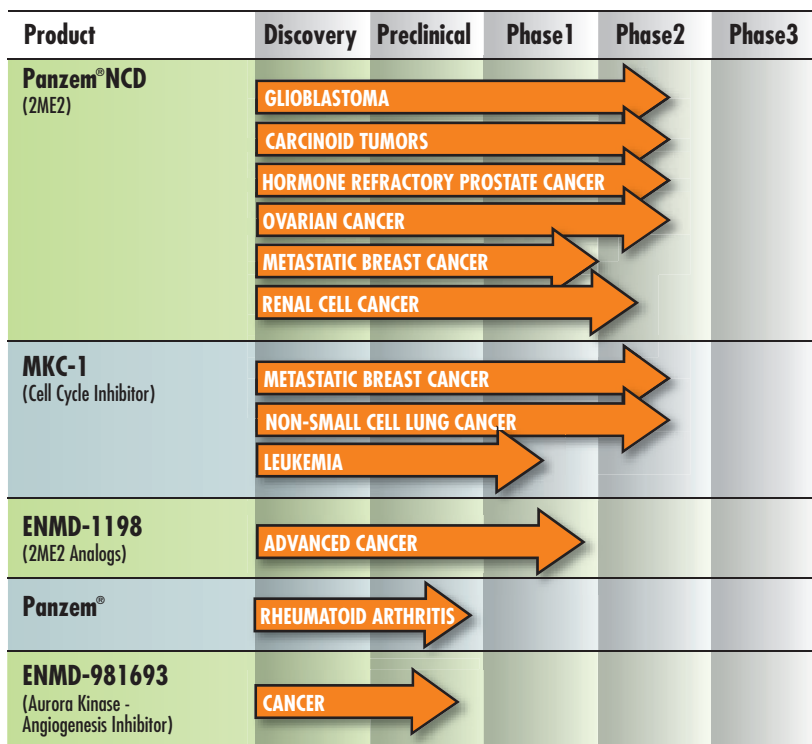
Burns: (Laughs) Right. EntreMed is now a very different company.

DD&D: *What are the main differences between then and now?*

Burns: One way is in terms of strategy. When I came in three years ago, my mandate from the board was to build a drug development company that could commercialize drugs with big pharma, big biotech, or on its own, by building off the core scientific expertise the company had since its inception in 1991 with the inhibition of angiogenesis [endostatin and angiostatin] that Judah Folkman developed [Harvard University, Children's Hospital, Boston].

In trying to get the company to move from being focused on research and into development, we had to do a number of things. We had to eliminate those programs that were not central to the focus. From a research perspective, since the company had started by working on anti-angiogenesis compounds, that included a lot of applications that were not oncology.

EntreMed PIPELINE



So, some peripheral programs, like drug-eluting stents or endometriosis, had to be cut.

Our new programs started in mid-2004. First, we focused on oncology and also saw some opportunities for inflammatory diseases. Second, we focused on small molecules. All of our compounds are oral and they all work through multiple mechanisms of action. Not only are they anti-angiogenic, they are anti-proliferative. So we started to rebuild the company by bringing forward this legacy scientific expertise in angiogenesis and cell-cycle regulation.

DD&D: *For a lot of biotech companies a key decision is whether to develop or acquire compounds. What is your philosophy?*

Burns: We knew that drug development is risky and cancer drug development is very risky. In 2005, we took our lead drug candidate, Panzem, into early stage clinical trials. But we thought we needed a pipeline with multiple compounds so we could improve the probability of success. So

we started a strategy of bulking up the pipeline in mid-stage and began looking for other compounds in early clinical to late-stage preclinical development to supplement what we had. We combed through the industry looking for opportunities, culminating in the acquisition, in January 2006, of Miikana Therapeutics. They had one compound in the clinic and two others that looked very interesting in various stages of discovery.

DD&D: *That acquisition decision seems risky and bold for a company like EntreMed, which for so long had been cash-strapped and experienced many ups and downs.*

Corrado: From the outside, you might perceive it as a risky endeavor. But when you look at the details, there were some promising assets that for us were difficult to walk away from. There's clear interest right now for Aurora kinase and multi-target kinase inhibitors. We are establishing relationships now to get the ball rolling with big pharma. There's also clear interest for HDAC inhibi-

tion and we will probably look for a partner in the next several months. So perhaps yes, this may have been a risky endeavor, but it was very manageable. When you look at the economics, when you look at the scientists, we came out on top.

DD&D: *How do you plan to handle relations with other pharmaceutical or biotech partners?*

Corrado: It's a little premature to give guidance on

the responsibilities of parties in any collaboration. ENMD-981693 has shown indications of potential in a variety of tumor types. So that tells us we will need a partner to not only



"It's a little premature to give guidance on the responsibilities of parties in any collaboration."

— Marc Corrado, EntreMed

finance, but also contribute to the development. We definitely envision having a role in clinical development and probably having a role in the commercialization. To be honest, it will depend a lot on what data comes out in the next six to 12 months and what kinds of offers we get.

DD&D: *How will you handle manufacturing?*

Burns: We currently outsource the manufacturing of the API [active pharmaceutical ingredient] so we envision continuing to outsource. We don't contemplate internal manufacturing. That's a whole other business, and there are plenty of groups out there with the expertise.

DD&D: *What about distribution and marketing?*

Burns: It'll be almost on a compound-by-compound basis. If we do co-development and co-commercialization with big pharma, we would probably share the distribution.

DD&D: *What makes EntreMed unique?*

Sidor: Many of our molecules were found to be active before we knew why, whereas most of the things coming to the clinic now are either very well defined, like monoclonal antibodies, or they're designed to hit a variety of specific


kinases. Some of our molecules, including Panzem, are natural metabolites. So we've almost had to do reverse engineering to determine what's relevant about where and how they work. When most other pharmaceutical and small biotech companies decide to in-license small molecules from universities, they often know the mechanism. In our case, we knew the activity and made the decision on that basis.

DD&D: *When you came on board, EntreMed was*

already a public company. What are the benefits and challenges that come from being public?

Burns: For the most part, it has been a benefit because we have more financing

flexibility with more types of financing vehicles open to us than do private companies. We can do public and private transactions in a public setting. But being public also presents challenges because costs are higher due to reporting requirements from the SEC, Sarbanes-Oxley, and other kinds of documentation requirements.

Also, you are always in a position to give guidance, to let the market know what you expect to accomplish on a quarter-by-quarter basis, year in and year out. Whether you meet that guidance is a measure of your credibility. The trickle down is that the R&D part of the company gets more realistic about what they can and can't do in a certain period of time. It forces everybody to take a critical look, so people are not over-promising or over-speculating. It forces you to be disciplined and transparent. 

Contributing editor Ted Agres, MBA, is a veteran science writer in Washington, DC. He writes frequently about the policy, politics, and business aspects of life sciences.

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