

# Behind the Scenes in Pharmacognosy

## Mevalocidin: Not a Fun Guy for Weeds

by Amy Keller

On January 3, 2007, a press release issued by Mycosynthetix, Inc., announced the license of fungal-based herbicide Mevalocidin to Dow Agrosciences, LLC. CEO of Mycosynthetix and ASP member, Dr. Cedric Pearce, discusses the company's search for new pharmaceuticals in fungi, and the processes involved with the patenting and licensing of a natural product.

**How did you become interested in natural products from fungi?**

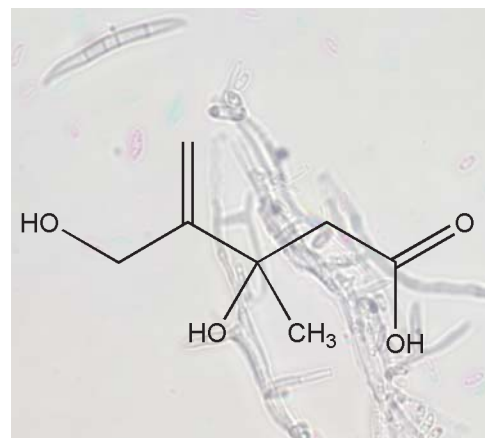
I have always been interested in microbial products and became intrigued with fungal metabolites during my tenure at the University of Connecticut, collaborating with Professors Bill Kelleher and Ralph Collins on an NCI-funded project to find new cancer agents from fungi. This interest was developed further while working at American Cyanamid's medical research division and then at MYCOsearch, a leading fungal research company in North Carolina.

Fungal metabolites, particularly those from microscopic filamentous organisms have played a leading role in the development of many modern medicines, the statins and the beta-lactam antibiotics being a few examples. The most prescribed drug in the history of medicine, Lipitor<sup>®</sup>, is based upon a fungal metabolite. When you consider that only about five percent of the one and a half million species of fungi speculated to exist has been described in the literature, then you can see what a comparatively under-investigated resource this is for a discovery program, and why we expect to continue to find new metabolites in our other programs. This point is made stronger by the observation from gene sequencing that there are often multiple polyketide synthesis genes from fungi which have fewer identified polyketides metabolites reported; therefore, even the potential of those fungi which have been characterized has probably not been fully exploited.

Mycosynthetix is a company which is focused on providing fungal metabolites for medical and agricultural use, especially to those organizations which lack microbiology and mycology departments. When we started the company, we acquired the very extensive and possibly the largest collection of diverse filamentous fungi in the world from MYCOsearch, which by that time had become the Natural Products Division of OSI Pharmaceuticals. We have maintained this collection, and added to it, as well as developed new approaches to culturing the organisms. Mycosynthetix has funded this work through grants and contracts, and we have active programs in a variety of therapeutic areas, for example anti cancer, infectious and CNS diseases.

**Who in your laboratory carried out the research?**

The people involved with this work also included Dr. Barry Katz from Mycosynthetix (now retired), the 2003 recipient of the ASP's Jack Beal Award, Dr. Christie Boros, who discovered the Emmyguyacins, is also a long time associate of Mycosynthetix. Dr Cliff Gerwick and his team at Dow AgroSciences, including natural product chemists and ASP members Drs. Paul Lewer and Carl Snipes were directly involved with this discovery.



Mevalocidin and *Fusarium nygamai*.

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Could you provide a brief explanation of the work and results in your own words? In what way does this herbicide represent a novel discovery?

SUE PEARCE



Dr. Cedric Pearce

One of our most productive collaborations has been with Dow AgroSciences, and this group has published a number of new structures from our work together. In this collaboration we provided Dow AgroSciences with extracts of our fungi, which had been cultured under a variety of condition, and these were tested for pesticide activity. Dow AgroSciences natural products group were persistent and a number of novel herbicide and insecticide metabolites were found, including Mevalocidin.

Mevalocidin is unusual for a number of reasons. First, it is a relatively simple metabolite. Usually fungal metabolites (in fact most natural products) are more complex structures. Also, it is a broadly active herbicide, whereas usually natural herbicides have a very narrow spectrum of activity, such that they have no commercial potential. Bialaphos, an *Actinomyces* product, is one exception. Of all our collaborators, the group at Dow AgroSciences was among the most persistent, and this has paid off with the discovery of Mevalocidin.

What impact does this research have on natural products or agricultural research?

Mevalocidin is another example of a natural product with commercial application. To discover a new herbicide such as this is quite unusual and may lead to more activity in this area in the future.

What is it like to have a patent and license? How does this help your company and your science for the future?

We licensed the herbicide to Dow AgroSciences expressly so that it could be developed into a commercialized product. For Mycosynthetix to enter an agreement such as this is a proof of principle for our technology, in this case the use of filamentous fungi for discovering new compounds. This is not a surprise to any member of the ASP, but I sometimes think that we could have done a better job at educating the rest of the industry. Also, when this license starts to generate revenues, we will be in a position to reinvest this in our company and into our other programs which are addressing unmet needs such as tuberculosis and cancer. Currently these are completely internally funded.

