

Special Chemistry Technology for the Discovery of Drugs



Helmut Thomas, Ph.D.
President & CEO

CycleniumPharma is an emerging pharmaceutical research and development company pursuing development of selected product opportunities in areas of unsatisfied medical need, while simultaneously creating a second generation macrocyclic drug discovery technology. We are building value through progression of our internal programs, and establishing collaborations with innovative pharmaceutical and biotechnology companies seeking to drug difficult disease targets.

Interview conducted by: Lynn Fosse, Senior Editor, CEOCFO Magazine

CEOCFO: Dr. Thomas, what is the concept at Cyclenium Pharma?

Dr. Thomas: The concept is to offer a special chemistry technology for the discovery of drugs against difficult disease targets that have been historically not, or only poorly, tractable with conventional small molecule chemistry, such as protein-protein interactions. In addition, we consider our technology as an attractive and economical alternative to biological drugs including therapeutic oligonucleotides, peptides, proteins and antibodies.

CEOCFO: What have you figured out? What is the technology that you can provide?

Dr. Thomas: We provide a drug discovery technology based on small-molecule macrocyclic peptidomimetics in the molecular weight range between 400 and about 750 Da. The idea behind this technology is to retain the pharmacological properties of small

peptides in the form of stable chemical entities that behave otherwise like classical small molecules. Our macrocycles are highly conformationally constrained and stereochemically defined, and follow a strict key-lock principle upon interaction with their pharmacological target. As a result, we obtain highly potent compounds with high target selectivity, low off-target activity and exceptional safety profile. We have also demonstrated high oral bioavailability of our macrocycles, a clear advantage, e.g., in comparison to biologicals, the large majority of which are parenteral drugs. Hence, our technology combines the potency and specificity of biological drugs with the convenience and economy of small molecules. We are convinced that macrocycles will, based on their unique properties, play a major role in replacing expensive biologics in the future.

CEOCFO: What is it that you are physically or chemically doing that will alter so that it performs the way you want?

Dr. Thomas: Starting out from screening hits, we optimize ring size, conformation and stereochemistry of our molecules to optimally fit the target structure and display the desired potency and pharmacokinetic and pharmacodynamic properties. This is achieved by careful combination of peptidic (typically containing two to five amino acids) and non-peptidic spacer elements that convey the targeted properties. Our macrocycles are optimized in library format by solid phase synthesis as a facile way of rapidly exploring structure activity relationships and progressing lead optimization.

CEOCFO: Where are you in the process of making it happen?

Dr. Thomas: We have rented a laboratory/office suit in the NeoMed Institute in Montreal, where we enjoy an exceptionally well equipped state-of-the art facility and stimulating multidisciplinary R&D environment, and have started to build our first macrocyclic screening library. Our goal is to produce initially 20,000 compounds within two years, half of those dedicated to protein-protein interactions and the other half with blood-brain barrier penetrating properties to allow for use in drug discovery on neurological targets. Since we started our laboratory operations on February 3rd, we have been able to complete the first 1800 compounds which will be submitted to a first round of screening shortly.

CEOCFO: Is it frustrating not being able to use what you know? What are the challenges when you are working and you know you have information that you cannot utilize?

Dr. Thomas: I am sure you are alluding to the previous MATCH technology of Tranzyme Pharma, which we were a big part of building and pioneering into late-stage clinical development, and which is no longer within Cyclenium's reach. –

Yes, it is difficult, and it is not so difficult. Difficult, of course, in a way that we cannot continue to work in a technology space that we had filed out to perfection over many years and knew how to practice very successfully on a broad range of targets. Not so difficult, as we have an opportunity to be creative and bring all of our macrocycle experience to bear in a new technology approach while eliminating weaknesses of existing technologies and focusing on promising new target areas, such as protein-protein interactions in oncology and inflammatory diseases, neurological and neurodegenerative diseases and the discovery of drugs against treatment resistant bacteria as a major current health threat worldwide. We are very familiar with the proprietary and patent estates around existing technologies and ways to avoid them. In any case, we are not looking back with regrets, but most grateful for our past experience and are excited about the opportunity to gain independence with our own proprietary technology and be successful as a company with fresh ideas.

CEOCFO: Tell us about the business side. How are you funded? Will you be seeking partnerships?

Dr. Thomas: Currently the company is being funded by a much appreciated start-up grant from Sherbrooke Innopole, and through continuous founder contributions. Our initial plan to finance Cyclenium through venture capital turned quickly out to be difficult. As a technology-based start-up company, the next inflection point is too far out for most of the venture funds we talked to, although we do have three promising early stage research programs in our pipeline that we are progressing with new chemistry technology. Hence we are exploring, as an alternative, paid drug discovery collaborations with mid-size and big pharma companies and have already been quite successful. The first agreement has been signed a couple of weeks ago. Other discussions have advanced to a stage that will likely lead to additional contracts within the next three months. Apart from that, we are still optimistic about being able to attract venture capital for the development of our own program compounds once they have reached the next optimization stage.

“Macrocycle chemistry has been on an exponential rise over the past five years or so in terms of publications and reports of success stories in drug discovery. It is generally considered the next big technology boost after anti-sense and oligonucleotide as well as monoclonal antibody technologies.” - Helmut Thomas, Ph.D.

CEOCFO: Different parts of pharma and drug development seem to be in favor with investors at different points in time. What is the marketplace or interest in your area these days?

Dr. Thomas: Although interest is generally very high in the discovery chemistry space we cover, investors are cautious and rather tend to focus these days on medical devices and products, the latter preferably at the stage of clinical proof-of concept or later. There appears to be very little appetite for platform technologies and early programs, unless they promise to be of paradigm changing value or have demonstrated broad applicability and success in development.

Different the pharmaceutical industry. We have already received very significant attention from mid-size and big pharma in search of new chemistry technologies for drug discovery, after small molecule chemistry has experienced its limits and biological drugs have seen significant resistance build up in the market primarily due to high manufacturing and therapy costs. Macrocycle chemistry has been on an exponential rise over the past five years or so in terms of publications and reports of success stories in drug discovery. It is generally considered the next big technology boost after anti-sense and oligonucleotide as well as monoclonal antibody technologies. I believe pharma has realized that macrocycles can be a very attractive alternative to biological drugs with a number of advantages regarding economy, patient compliance and efficacy. Ultimately, reports of orally bioavailable macrocycles have dramatically changed the landscape and turned the tide in favor of this technology. There is hardly any research driven pharma company out there which is not looking for access to macrocycle technology or is in the process of establishing it in-house.

Hence, I firmly believe that Cyclenium is, and will stay, in the sweet spot of drug discovery and development and will acquire a leading position in this space based on the experience of its staff in the field, previous pioneering development success with synthetic small molecule macrocycles in the clinic and past successful drug discovery collaborations with companies and organizations like BMS, Roche, Genentech and the Southern Research Institute.

CEOCFO: What are the most important lessons you have learned from previous experiences that apply at Cyclenium?

Dr. Thomas: Do what you can do best and trust yourself! Build on the unique expertise that we have in the field. Be persistent, but don't be shy to evolutionize the technology over time. Stay in a target area that is most suitable for the chemistry. Recognize limitations and don't go where conventional small molecule technology can go or where macrocycles have failed.

CycleniumPharma Inc.
4366 Michel Ange
Sherbrooke, Quebec J1N 1R6
Canada
819-571-4296
www.cyclenium.com