Emerging Medical Technologies (EMT)® Innovator of the Month

November 2013

Cognoptix, Inc.

A laser technology pioneer who helped introduce LASIK surgery and an accomplished angel dealmaker, Paul Hartung has set his sights on providing the first simple, definitive test for the early detection of Alzheimer's disease.

About Our Innovator:

E-mail Address:
PHartung@cognoptix.com

Years in the Device Industry: 25+

Specialty Areas of Focus:
Lasers, Photonics

Education:
BS and MS in Mechanical Engineering, with honors, from the Massachusetts Institute of Technology (MIT)

Hometown: Acton, MA

Marital Status:
Married, two children, 19 and 23

Hobbies: Skiing, fishing, photography, playing clarinet

About The Company:

Cognoptix, Inc.
(formerly known as Neuroptix Corporation)

Company Address:
20 Main Street, Acton, MA 01720

Company Phone: (978) 263-0005

Year Company Founded: 2001

Financing History:

- $17 million raised to date
- $20 million series D round to close in 2014; will fund pivotal clinical trials and product commercialization
- Series C: $8 million (two tranches, 2010 and 2011)
- Series B: $7 million (two tranches, 2008 and 2009)
- Series A: $2 million (two tranches, 2005 and 2007)

Investors: Inventages Venture Capital, LaunchPad Ventures, Boston Harbor Angels, Maine Angels, Granite State Angels and Beacon Angels, among other angel groups.

Actively Seeking: Strategic commercialization partners

Board of Directors: Paul Hartung, President and CEO; Richard Gill, PhD, Director; Werner Schaefer, PhD, Director; Gunnar Weikert, Director

Clinical Advisory Board: P. Murali Doraiswamy, MD (Professor, Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC); Carl Sadowsky, MD (Director of Research, Premiere Research Institute, West Palm Beach, FL); Pierre Tariot, MD (Director, Banner Alzheimer's Institute, Phoenix, AZ); and Gordon Wilcock, DM, (Hon) DSc, Professor Emeritus of Clinical Geratology, Oxford Project to Investigate Memory and Ageing (OPTIMA) Project, University of Oxford, UK)

ABOUT PAUL HARTUNG

Some people shy away from challenges, while others deliberately seek them out, driven by the desire to solve difficult problems and achieve hard-fought goals. The latter characterizes Life Science Intelligence's November 2013 Emerging Medical Technologies Innovator of the Month, Paul Hartung. Hartung characterizes himself as an engineer with the love of building and introducing products, for both Fortune 500 and start-up companies. Following his role in helping to bring the disruptive ophthalmic surgery technology, laser-assisted *in situ* keratomileusis (LASIK), onto the market, Hartung's current goal as CEO of Cognoptix is to introduce the first early-stage, noninvasive combination drug-device diagnostic test for Alzheimer's disease (AD).

Hartung, with his 30+-year career and experience spanning product development, technology invention, merger and acquisition (M&A) integration and fund raising, is up for the challenge that no one has yet been able to accomplish in addressing this costly and devastating disease. "A common thread throughout my career has been developing and introducing truly novel, complex systems within highly regulated industries," Hartung told Life Science Intelligence in an interview. His newest venture, Acton, MA-based Cognoptix, does not stray from this theme.

"We are developing a highly complex product with electromechanical, optical and software-driven components under the hood, that is simple to use," he says. Cognoptix is looking to help detect AD in its earliest stages with its combination device-drug technology, so that it can be treated early with the more than 100 new therapeutic drugs under development to slow or stop disease progress, and ultimately reduce its impact on society. In the pre-symptomatic stages of Alzheimer's disease, covert toxic changes are taking place in the brain, and abnormal deposits of neuritic amyloid plaques begin to take hold. Currently there is no noninvasive diagnostic test on the market that can diagnose the condition in this early stage.

From Mechanical Engineering to Telecommunications to the Device Space

Hartung earned his Bachelor of Science (BS) and Master of Science (MS) degrees in Mechanical Engineering from the Massachusetts Institute of Technology (MIT), where he excelled. He received the highest award given for both academic and athletic performance at the Institute, the Straight "T" award, in addition to graduating Phi Beta Kappa and receiving the College International Pour La Recherche en Productique (CIRP; the International Academy for Product Engineering) award, for his master's thesis research. Following graduation in the early 80s, he was introduced to lasers via his work at General Electric (GE), as the technology was first being introduced in the manufacture of aircraft engines. At that time, medical devices weren't yet in Hartung's crosshairs - he was focused on novel industrial applications for lasers, with a particular interest in their applications in engineering and manufacturing. Hartung then moved into product development, where he excelled at building unique scaleable operations for a number of Fortune 500 as well as start-up companies, and leading the efforts to integrate operations post-acquisition. He also sought to gain the experience and skills he would need later in general management, as a CEO, including joint ventures, strategic alliances, regulatory affairs and product launches.

The use of novel laser technology in the medical device field entered Hartung's experience in the 1990s, when he was on the start-up management team at Summit Technology. At Summit, he ran manufacturing and participated in the development, U.S. Food and Drug Administration (FDA) approval and market launch of LASIK technology. After a successful initial public offering (IPO), Summit was acquired by Alcon Laboratories in 2000 for $900 million.

Following his departure from Summit, Hartung moved out of medical device and took on a management role at the large computer networking systems company 3Com Corporation. In this role from 1995 to 2001, he facilitated several large acquisitions during the explosion of the internet and networking, including Palm Computing, U.S. Robotics and Chipcom. He also pioneered a "design anywhere/build anywhere" strategy to help 3Com manufacture and launch novel new technologies worldwide and reduce time-to-market globally (the company was acquired by Hewlett-Packard in 2010 for $2.7 billion).

Hartung then decided to re-enter the start-up world, and joined communications networking provider Winphoria Networks as vice president of operations. The successful three-year-old company was acquired by Motorola in 2003 for $179 million, during a time when almost no companies were exiting, and Hartung stayed on for another year to help assimilate operations.

Taking on the Challenge of Alzheimer's Disease Diagnosis

With the advent of wireless technology and rapid decline of the data communications and telecommunications industries in the early 2000s, Hartung once again turned his attention to the medical technology space. Via an

introduction by a corporate attorney working with Neuroptix (name later changed to Cognoptix), he met the company's co-founders, who were developing a first-of-its-kind method of early-stage AD diagnosis to allow treatment before significant neuronal loss and irreversible brain damage occurs, and were looking for someone to turn their novel scientific discovery into a business.

The sections below briefly outline Life Science Intelligence's interview with Hartung, and bring us up to speed on Cognoptix's technology and current status. The inventor/entrepreneur provides insight on changes he has seen in the fundraising environment over the years, and what he feels are the most influential drivers of the device industry going forward. He also gives some valuable advice to device entrepreneurs just starting out.

INNOVATOR Q&A

Q. What is the main motivation behind your latest venture?

A. "I consider Alzheimer's disease to be the disease of the century; it's the one major killer that has gone unabated, with no early detection or intervention available. It's a wide open opportunity. An analogy to what is needed is a cholesterol test for heart disease, or tests for precancerous cells. The understanding of the disease has increased significantly over the last decade; in 2011, for the first time there was the first recognition of the underlying pathology of the disease for clinical diagnosis. Before that, AD was only diagnosed based on symptoms, and by that time it's too late, the damage is irrecoverable, as the disease has progressed to the point where 50% of brain function is lost.

What I saw was this really exciting science, that was truly novel. To a large extent, Cognoptix owns the eye as a diagnostic site for the disease. The challenge was to figure out what's the best technology or technologies to bring to bear to practically, and in vivo, test for Alzheimer's. That's the challenge I took on."

Q. How do you feel venture capital has changed over the course of your career?

A. "Early in my career with venture-backed companies, I knew that with a good idea and a good set of PowerPoint slides, you could raise enough money to hire a hundred people, develop a technology over a couple of years, and do a lucrative exit. Those days are largely gone. The venture capital industry is not dead, as some may say, but I did find that I had to think globally to find the best fit for our technology and company, and a firm that can raise fresh funds (he secured London-based Inventages Venture Capital as an investor in Cognoptix).

Another big change that has occurred over the years is the whole realm of angel financing. It used to be that through angel groups you could raise a few hundred thousand dollars and it was difficult to bridge the gap to venture financing. Today, through syndication, angel groups particularly in the life science arena are doing multimillion-dollar financing, and they are much less risk-adverse than the venture capital community. It's an issue of control and freedom as well, as some VC firms have had the model of putting money in to launch a company from within, with their own people on the management team, and that may be fine for some entrepreneurs. Today you have to get creative with how you finance a business.

Another challenge today is coming up with ways to de-risk the basic science early on, with early human data, prior to raising venture funds. This makes it a lot easier to raise money. In a lot of cases, the ideas and the basic science are coming out of the university setting, and I think in these cases an entrepreneur should push back on the scientists that came up with the initial idea to get as much data as possible, prior to launching it as a venture. The value of the deal will go up, and the amount of ownership that you give away goes down, and it's a big win for everybody. As a founding CEO, I look for opportunities where there's already a good, validating data set that will de-risk the deal for financing purposes. This didn't used to be necessary; with a really good idea and value proposition you could muster up the funds to do it on your own."

Q. What do you feel are the most influential drivers of the medical device market today, and looking out over the next few years?

A. "Personalized medicine is getting to be a bigger and bigger deal. On one side you have the gene sequencing technology to characterize the individual, and on the other side we're starting to have lower cost medical devices, even down to the hand-held devices that can be attached to a smartphone that

can be used for personalized measurements. I would say that today there is a huge opportunity to take all the burden off the specialist and put more power in the hands of the general practitioner (GP), at the front end, who can do a better job of diagnosing diseases early (and the Cognoptix eye scan test can be used in this setting). I think there's a recognition that the GP is the first line of defense when someone is concerned about their health, and to find those changes that are putting a patient at risk for disease down the road. Traditionally the role of the GP has been fairly limited, but that's changing and they're becoming more sophisticated.

Longer term, I think a transformation will take place in personalized medicine, and more health monitoring technologies will be employed in the home setting on smart phones and other devices, so that patients don't have to go in for tests every week or month and results are results transmitted to their physician."

Q. How do you feel about being selected as Life Science Intelligence's Innovator of the Month?

A. "I am honored and delighted. There are different types of entrepreneurs, and one thing I've prided myself in is taking on the important, hard problems, and having the tenacity to realize solutions. Some entrepreneurs are always looking for the very quick win, and get frustrated if that doesn't happen. In my case, I recognize that you have to have a good plan, and have to be frugal in terms of managing finances within an organization, because you're going to run into issues along the way. I've found that how you handle the tough stuff, the unexpected roadblocks along the way, is more important in measuring the quality of an entrepreneur than the easy stuff."

Q. What advice would you give to device entrepreneurs just starting out today?

A. "First of all, follow your passion. Surround yourself with good people, and watch out for people such as investors or business partners who can be a negative influence. Be creative in terms of your approach to financing, and not only look at the science and technology, but make sure there's a good value proposition.

Also make sure that you have very good proof-of-principle data in hand or can get to relatively inexpensively in order to facilitate raising money. A choice needs to be made relative to going for angel financing versus venture financing, and part of that depends on how much money you're going to need to get to the next value step. Another thing that I did in getting Cognoptix off the ground (with Pfizer and Merck) that I recommend is to look for opportunities for nondilutive R&D funds from potential business partners fairly early on.

Lastly, be tenacious, and always in the back of your mind be thinking of a Plan B. When you face an issue, find a solution, don't let roadblocks stop you in your path."

ABOUT COGNOPTIX

AD is the sixth leading cause of death in the U.S. overall and the fifth leading cause of death for those aged 65 and older, according to the Alzheimer's Association. It is the only cause of death among the top 10 in America without a way to prevent it, cure it or even slow its progression. In the next 12 years, the number of people in the U.S. age 65 and older with AD will reach an estimated 7.1 million—a 40% increase from the 5 million in this age group who are currently affected. What's more, by 2050, the number of people age 65 and older with AD is forecast to nearly triple to a projected 13.8 million, barring the development of medical breakthroughs. In 2013, Alzheimer's will cost the U.S. healthcare system $203 billion, and this number is expected to skyrocket to $1.2 trillion by 2050. Unfortunately, patients often incur up to 50% neuronal loss and a delay of up to two years before demonstrating severe enough symptoms to achieve diagnosis by the current gold standard, which consists of a 'process of elimination' of other possible diagnoses such as stroke, trauma, Parkinson's disease, dementia and others, through extensive cognitive and physical testing. Providing the first diagnostic test for early-stage Alzheimer's is Cognoptix's lofty and admirable goal.

Cognoptix was incorporated in 2001 by Leo Chylack, MD, director of the Research Center for Ophthalmic Research, and Lee Goldstein, MD, PhD, Associate Professor of Psychiatry, Neurology, Ophthalmology, Pathology and Laboratory Medicine, & Biomedical Engineering at Boston University and former assistant professor of Psychiatry at Harvard Medical School, as well as the Director of the Molecular Aging & Development

Laboratory and Center for Biometals & Metallomics at the Brigham & Women's Hospital (BWH), Boston. The start-up operated in research and development (R&D) and IP development mode until 2004, as the founders further developed their beta amyloid protein detection technology. Drs. Chylack and Goldstein and their research team discovered that they could detect beta amyloid aggregates in the lens of the eye, and that those proteins could be measured and monitored with noninvasive tools, such as existing laser eye scanning technologies. Further research determined that suspect beta amyloid proteins could be detected in the eye prior to buildup of toxic plaques in the brains of genetically engineered Alzheimer's mice. Cognoptix has a strong and comprehensive patent portfolio covering diagnosis of beta amyloid-based diseases via ophthalmic imaging. Exclusive licenses have been acquired from UC San Diego, Massachusetts General Hospital and BWH.

Hartung was intrigued by the challenge of potentially being able to diagnose one of the most world's problematic neurological diseases, Alzheimer's disease, in its very earliest stages, via the promising new biomarker that Cognoptix's co-founders had discovered for the detection of beta amyloid proteins, which are responsible for the formation of plaques in the brains of AD patients. Hartung joining the founding group in 2004 as its first CEO, and never one to shirk a challenge, is now working on bringing the company's novel combination drug-device product through the rigors of the U.S. clinical and regulatory system, and onto the market.

Hartung started by putting together a business plan, organizing the company's initial funding and hiring an executive team. In addition, he is the inventor listed on numerous issued and pending Cognoptix patents, is personally responsible for bringing in $17 million in financing to date through an international venture capital (VC) firm and angel groups, has established development and supply chain partnerships internationally, and has secured $3 million in R&D collaborations with the pharma companies Pfizer and Merck. What's more, he was instrumental in Cognoptix receiving FDA investigational device exemption (IDE) approval for its combination device-drug product, the *SAPPHIRE II* system, which is now in human clinical trials. Cognoptix introduced its system at the July 2013 Alzheimer's Association International conference in Boston.

The SAPPHIRE II Fluorescent Ligand Scanning System

The company's software-controlled SAPPHIRE II eye scanning test is a compact, easy-to-use clinical device for *in situ* patient examination in a non-specialist doctor's office setting. It enables noninvasive quantitative measurements of beta amyloid aggregates in the supranucleus region of the human lens as a means of early detection of AD. The system, which went through several iterations during the R&D process, has a device and a drug component: the laser-based Fluorescent Ligand Scanning (FLS) device, which is an FDA Class I laser optical device that is safe for the eyes, and a proprietary, sterile, consumable ophthalmic ointment. The ointment contains a compound comprised of beta amyloid-specific small molecules, which are absorbed into the lens and bind to the amyloid aggregates that are present in the early stages of AD. It is prescribed to the patient, who applies it to the inside of their eyelid the night before their scan appointment.

During the eye scan, the SAPPHIRE II system excites the fluorescent ligands that bind to amyloid, and quantitatively measures emissions in specific anatomical locations to biochemically confirm the presence of amyloid. The binding compounds emit light in a specific, detectable range of wavelengths. If this binding increases over time, a positive diagnosis can be made, enabling clinicians to track the progress of the disease in patients by measuring levels of fluorescence – as well as potentially enabling physicians and pharmaceutical researchers to monitor the efficacy of Alzheimer's drugs in clinical trial settings. And, Cognoptix's technology has the ability to clearly separate out normal, age-related changes seen within the eye from those characteristics associated with Alzheimer's.

And, in what Cognoptix views as real market opportunity for the technology and a way to vastly improve the standard of care for patients with AD, the easy-to-administer SAPPHIRE II eye exam can be given by a general practitioner at the point of care, and takes just a few minutes to achieve a result. Today, only about 5% of patients in the U.S. are diagnosed by Alzheimer's specialists, and the remainder are diagnosed by non-specialists.

Sights Set on PMA Approval

Cognoptix's system is being regulated as a combination product, under the guidance of the FDA's Center for Devices and Radiological Health (CDRH), according to Hartung. The product is approved under an IDE to conduct clinical trials, and the device and ointment together will follow the premarket approval (PMA) pathway. In terms of product status, the company's core technology is complete, with the threshold levels of the eye scan test finalized. Cognoptix is now completing some work in the manufacturing process, packaging and design. With regard to the ointment, the company has shown that it has a nontoxic, stable, sterile, high purity product, and will be

manufacturing demonstration batches for the FDA. The ointment will be packaged in single-use dispensers.

Cognoptix has conducted two phases of clinical trials to date, in support of a PMA submission planned for late 2014. In January of this year, the company reported positive results of its proof-of-concept clinical trial in which its SAPPHIRE II eye test identified 10 mild-to-moderate Alzheimer's disease patients via a beta amyloid ("Ab") signature in their eyes. The system was able to achieve a 200% differentiation factor between a group of five healthy volunteers and five patients diagnosed with probable AD, according to Cognoptix.

Based on the strength of that trial, the company closed the second tranche of its Series C financing, which funded a subsequent 40-patient, multicenter pre-pivotal study. The company and its study investigators wanted to show definitively that the connection between AD detected via the eye and the brain, and that it can be detected *in vivo*. And, that's just what they did. This trial began in February, and this past September the company announced positive results from this trial that validate the previous proof-of-concept clinical results. In the study, the SAPPHIRE II achieved an unprecedented sensitivity of 85% and a specificity of 95% in differentiating 20 patients who were clinically diagnosed with probable (mild or moderate) AD from a group of 20 age-matched healthy volunteers. These results are superior to the reported 80% sensitivity and 80% specificity of positron emission tomography (PET) imaging of the brain, according to the study investigators. In addition, the SAPPHIRE II test was benchmarked against recently approved PET amyloid brain imaging, and it also achieved excellent correlation to this state-of-the-art technology.

According to the Society of Nuclear Medicine and Molecular Imaging, a PET scan can cost up to $4,000, depending on the type of scan performed. The SAPPHIRE II eye test is expected to be about one-tenth the cost, and it can be done at point of care in a general practitioner's office, according to Hartung.

Next, Cognoptix is preparing to file for approval of its multicenter pivotal trial, which will provide statistical validation of the efficacy of the company's technology. This study will involve approximately 400 subjects and is anticipated to start in mid-2014. The company plans to complete the trial by the end of next year, and then file for PMA approval of the SAPPHIRE II eye test. Strategically, the company is focused on approval in the U.S. first, followed by approval in other geographies.

Hartung the Fundraiser

Cognoptix has raised $17 million in finding to date, with every penny brought in by Hartung himself - no small feat, especially considering that the company's Series A round was the first syndicated angel group financing to be organized in the northeast U.S. Then, he brought in $7 million in Series B financing in late 2008, when no one was raising venture financing, from Inventages Venture Capital, one of the world's largest life science venture capital firms, with offices in London, Nassau, Hong Kong and Auckland. In 2010, Hartung orchestrated an $8 million Series C round. The company is actively forming and seeking new strategic alliances with pharma partners and academic institutes, while preparing its diagnostic platform for clinical use.

Moving in Parallel with Alzheimer's Drug Development

Cognoptix's diagnostic technology has come along at an ideal time, as knowledge about AD and treatments are advancing, and the population with this devastating and costly disease is poised to grow exponentially in the coming years. More than 100 new Alzheimer's drugs are now in development, and the ability of the Cognoptix system to easily identify and qualify patients for clinical study inclusion, as well as accurately and inexpensively track patient disease progression, may be able to provide pharmaceutical companies with a significant competitive advantage in securing new Alzheimer's drug approvals. And, it may also help identify and document differentiating drug performance attributes in Phase IV studies, according to the company.

"We have the potential of seeing evidence of AD years before symptoms arise," Hartung says. "We're looking at a paradigm shift in how we treat these patients, just as patients with heart disease and cancer have benefitted in recent years from early detection and intervention, and improved quality of life. I feel we have the ability to change the course of this disease in this century," he continues.

Comments on our new Innovator of the Month series? We'd love to hear your feedback! Send an e-mail message to Scott Pantel, CEO, Life Science Intelligence: scott@lifescienceintelligence.com