

B STANFORD TECHNOLOGY BRAINSTORM



THE NEWSLETTER OF STANFORD UNIVERSITY'S OFFICE OF TECHNOLOGY LICENSING (OTL)

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(IF = Inside Flap)

Eating Away at Vascular Disease: Cooke Pharma & HeartBar®

by Rich Scholes

In 1988, a small group of scientists gathered in Keystone, Colorado, to share their research findings on the biological effects of endothelium-derived nitric oxide (NO), a potent vasodilator. Dr. John Cooke, then an assistant professor of medicine at Harvard, presented his finding that the ability of the vessel wall to produce NO was impaired in animals fed a high cholesterol diet. Later Salvador Moncada—a brilliant investigator from Wellcome Research Laboratories—announced a finding that held significance for the future of cardiovascular therapy: the amino acid L-arginine is the precursor to NO.

"I thought we might be able to improve vascular relaxation in the hypercholesterolemic animals simply by giving them the precursor to NO. When I got back to my lab we tried this experiment and it worked. Administration of L-arginine to the animals improved the ability of their blood vessels to

relax," said Cooke. Little did he know that their research on arginine would become the backbone of his first entrepreneurial endeavor.

In 1995, Cooke licensed the arginine technology from Stanford's Office of Technology Licensing (OTL) and started Cooke Pharma (CP). Now ten years since their research began, he has collected an expert scientific staff and handpicked a management team for CP.

Together they have developed the HeartBar® which contains the active ingredient L-arginine and numerous nutrients necessary for optimal vascular health. Available in Cranberry, Peanut Butter, and (tasty) Original flavors—and built on the technology that won last year's Nobel Prize in Medicine—HeartBar enhances the vessel's production of NO, improves blood flow, and effectively relieves the symptoms of heart and vessel disease.

CP has completed clinical trials on their prod-

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ICO Helps Bring Two Worlds Together

By Glennia Campbell and Sara Nakashima

Stanford has a long-standing history of working with industry, from receiving generous gifts of funds and equipment from Fortune 500 companies, to sponsored research in many fields, to licensing core technology to start-up companies. Many faculty are interested in working with industry because good university-industry relationships provide students with "real world" problems to solve, give students potential employment opportunities, and facilitate the transfer of research results to the public.

The Interface

In early 1997, Charles Kruger, the Dean of Research, and Katharine Ku, Director of OTL, first conceived of the Industrial Contracts Office (ICO) to facilitate Stanford's sponsored research interface with the corporate world. Since intellectual property issues are often the most significant area of negotiation, it seemed reasonable to have the ICO nestled within OTL. Except for clinical trials, the ICO has responsibility for negotiating research contracts with industry and signing such agreements on behalf of Stanford.

Although relationships between Stanford and

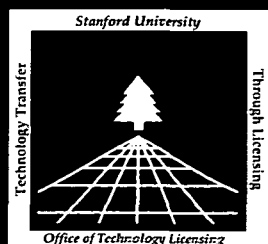
industry must be mutually beneficial in order to be successful, there are some significant "cultural" differences between any university and a company. Like most universities, Stanford's mission has often been summarized in three words: Teaching, Learning, and Research. Most companies have a business focus on a particular product line or market niche. A university's primary goal is to generate and disseminate knowledge to benefit the public, while a company's emphasis is on producing a return on investment for its investors and shareholders.

Many companies share the university's goal of benefiting the public through scientific endeavors, training the next generation of scientists and professionals, and finding solutions to today's technology problems. In that common space, there is ample opportunity for universities and companies to work together.

How to Begin – on either side

Many companies learn about Stanford research projects and academic interests through conference presentations or scholarly publications. Companies often contact a faculty member directly to initiate discussions about mutually interesting

Continued on page 4



HeartBar...*Continued from page 1*

uct and met regulatory guidelines for marketing it as the first medical food for the dietary management of vascular disease. After finishing test marketing of the medical food, the CP team recently began national distribution of the HeartBar in major drugstore chains including Walgreens and Longs Drug Stores. HeartBar is already available over-the-counter in 30,000 stores nationally.

Humble Beginnings

Although the scientific community seemed initially skeptical when Cooke published his findings on the effects of L-arginine, but Cooke continued his work. He moved to Stanford in 1990 and successfully demonstrated that dietary arginine served to enhance NO-dependent vasodilation and limit atherosclerosis (the progressive narrowing and hardening of arteries). In preclinical trials, he showed that consuming arginine even seemed to cause regression of atherosclerosis. Other scientists later confirmed his findings.

After a few years of additional research, Cooke and others discovered why people with atherosclerosis or risk factors for atherosclerosis (e.g. high cholesterol) need more L-arginine. The blood of these individuals contains high levels of an inhibitor of NO production. By consuming enough L-arginine, it out-competes the inhibitor to create NO and enhance vasodilation. Cooke and his fellow researchers had shown that dietary arginine promotes vascular health in patients with cardiovascular disease.

NO Commercials?

Though pleased with their findings, Cooke also hoped the technology could be commercially de-

A Sampling of Licenses Granted by OTL in the Last Quarter

Docket(s)	Title(s)	Uses	Licensee(s)	License Type
S89-001	"Microfabricated Cantilever Stylus"	Atomic Force Microscopy	Team Nanotech	Non-exclusive
S92-066	"Mercury Microelectrode Array"	Heavy Metal Sensor	Orion Research	Field Exclusive
S93-199	"Ultrasonic Air Transducer"	Medical Ultrasound	CBYON, Hewlett-Packard Sensant	Non-exclusive
S97-072	"GENSCAN"	Gene Identification	Ariad, Biogen, LION, RPR Gencell	Non-exclusive
S97-235	"Topical Genetic Immunization"	Vaccine Delivery	Maxygen	Exclusive
S99-007	"SUTECH Microarray Database"	Identifying Genes & EST's	Axys, Onyx, Tularik	Non-exclusive

veloped to improve public health. He disclosed his findings to Stanford's Office of Technology Licensing (OTL), and together they identified and contacted prospective licensees.

Committed to the cause, Cooke interacted with many of the companies about his research and flew to several to share his findings with company scientists. Meanwhile, OTL filed a patent application on medical use of arginine. But after extended interactions with a handful of companies, no one chose to license the invention.

Founding Cooke Pharma

With no licensee but still committed to the invention's development, Cooke decided to start a company and took a license himself. In classic Silicon Valley style, Cooke Pharma began in his Palo Alto garage in 1996.

Initially Cooke imagined CP as a virtual company that would promote the technology until it was acquired by a larger pharmaceutical company. After many months of calling and meeting with companies, no corporate partner emerged to develop the technology. But in the midst of his hundreds of visits, calls and drafts of his business plan, Cooke decided that, with the information and know-how he had collected during his discussions, he would develop the technology himself. Rather than searching for a developer, Cooke began visiting companies, individuals, and venture capital firms in search of investors.

The Funding Challenge

As Cooke notes, funding Cooke Pharma wasn't smooth sailing. "There were five times we ran out of money." But as he noted, to succeed you have to "go over, around or under every hurdle you face."

Cooke initially invested \$75K of his own money and CP earned another \$25K. Cooke spent this fund the first year writing business plans, making calls and visits, and paying his secretary. With the money

dwindling, a group of private investors from the Philippines invested \$750,000 in early 1997. This was enough to hire a small research team and to begin testing prototypes of the arginine-enriched HeartBar. With a patent, a product, and a small but favorable clinical trial, Cooke was able to entice some professional managers to join part-time late in 1997. But in early 1998, money was again short.

However, this time they had a strong management team in place that was able to attract "real" money. Over the course of the next year, CP successfully raised almost \$6 million from a Japanese corporate investor and Silicon Valley private investors. This money enabled them to bring on full-time management and to perform test marketing of HeartBar in Sacramento early this year.

Once again, the till was low, but with their positive test market results, CP convinced venture capital investors to commit \$12.5 million for the company's national launch of HeartBar. As Cooke notes, with their national launch now underway, "CP's future is a marketing play" as they educate doctors and individuals about the benefits of HeartBar.

Cooke encourages entrepreneurial graduate students and his fellow faculty: "If you have an idea, talk to OTL...talk with faculty. Don't be discouraged. Be innovative with obstacles; take advantage of the wealth of knowledge in Silicon Valley. Use the resources."

Keys to Success

There are multiple reasons for the success of

vascular Medicine at Stanford and therefore can only spend one day a week pursuing his non-Stanford responsibilities. He has four children. He cares for patients in the Stanford Hospital and teaches courses in the Medical School. He frequently publishes on his research and is a prolific inventor of Stanford technologies.

When asked how he could be successful in each of his numerous responsibilities, Cooke praises his supportive family, without whom he could not have done it. He also attributes his success to working nights and weekends and the many helpful people who gave him priceless advice and assistance during his development of CP.

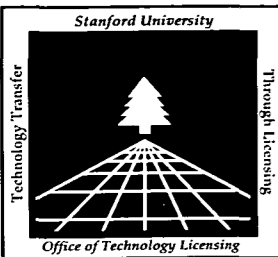
As Cooke notes, success requires determination. Of the hundred plus venture capital firms, corporations, and individuals whom Cooke approached for technical development and funding, many found the bugs in his proposal. "If they turn you down, figure out why; don't go away feeling beaten. If it's really a novel idea you will have people say it won't work. Figure out why."

Finding Mildred

Walley's promotion of HeartBar is as innovative as Cooke's technology. During their test market, Dr. Joseph Kozina, a Sacramento cardiologist, prescribed the HeartBar to Mildred Mineau, a 78 year old woman with several heart problems. Though Mildred had received extensive treatment for her condition—including open heart surgery—she still experienced severe angina (chest pain that results from inadequate delivery of oxygen to the heart), often upwards of two dozen episodes a day. In the KOVR-TV Channel 13 piece on HeartBar, Mildred's cardiologist explained he prescribed her two bars a day because he had nothing else to offer her.

After four weeks of her twice daily diet of HeartBars, Mildred's symptoms dramatically decreased. She experienced only one or two episodes of minor pain per day. She continues her HeartBar regimen and is pleased to have "so much energy." Tasks that had become laborious, Mildred now does with ease. The report on Mildred by KOVR-TV caused Sacramento sales to surge, leading Walley to the idea of a "Find Mildred" campaign. Cooke Pharma sales representatives have begun their national crusade to bring local media attention to the usefulness of the HeartBar and to find "Mildred" in their area.

To learn more about HeartBar, please contact Darlene Walley at (650) 594-5961, or go to www.cookepharma.com. ▲



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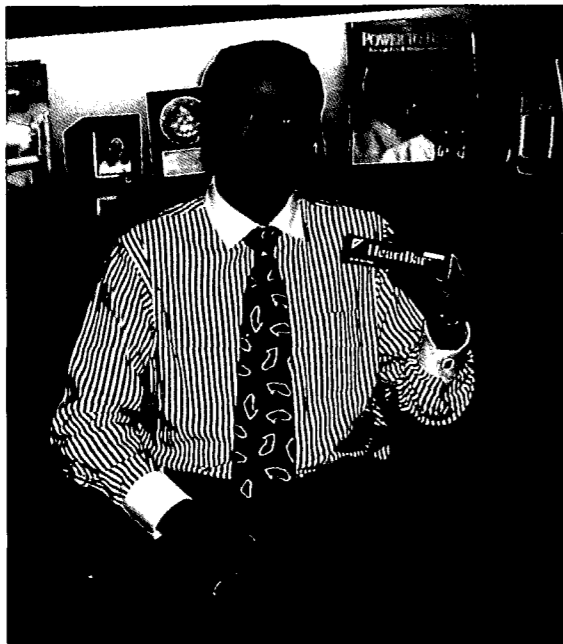
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Dr. John Cooke with the fruits of his labor- the HeartBar®

Second Invention Challenge

Minimally Invasive System for Treatment of the Arthritic Knee

The second annual invention challenge once again provides a sticky problem for an ingenious person or team to solve. This year the challenge is to develop a better system for minimally invasive treatment of the arthritic knee.

One of the goals of the contest is to break down barriers between medicine and engineering. A team composed of people with backgrounds in each of these areas would most likely be optimal to develop a better system.

Last year 12 entrants participated in the contest to develop a better anastomosis device. Of these, three teams won prizes (see *Brainstorm*, Summer 1999). OTL filed a patent application for the first prize winner's device.

The prize for the winning entry this year will be \$2,500. Some entries will be considered by OTL for potential patenting and licensing.

Informational meetings will be held in mid-October. The contest is open to Stanford faculty, staff and students and is sponsored by OTL and the Medical Device Network. Please visit MDN's web site at <http://mdn.stanford.edu/events/default.asp#INVENTIONCHALLENGE> for more information, or contact Sandra Miller at (650)498-7856 or smiller@cvmed.stanford.edu. ▲

Start-Up Seminar

OTL is hosting another start-up seminar on November 8, 1999, from 3 to 5 pm at Fairchild Auditorium. Keep your eyes open for information to be distributed through e-mail and posted around campus.

The first start-up meeting occurred in April, 1999 (see *Brainstorm*, Summer 1999). At the seminar, three entrepreneurs (Guy Kawasaki, Lawrence Steinman and John Cioffi) advised potential future entrepreneurs of good and bad practices in starting a company.

If you have any questions, please contact Sandra Bradford at sandra.bradford@stanford.edu. ▲

Brainstorm now online!

After a short hiatus, *Brainstorm* is once again fully up-to-date online at <http://www.stanford.edu/group/OTL/bsindex.html>. If you would prefer to receive *Brainstorm* in PDF format by e-mail rather than a hard copy by mail, please contact Rich Scholes at rich.scholes@stanford.edu or (650) 725-9115 with your request. ▲

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OTL is providing this as a service to Stanford students. Each advertisement will be approximately 1/4 of a page. The company can either supply its own description or we can build one for you.

Brainstorm's current circulation is around 3,000 issues per quarter, and it is distributed widely around the Stanford campus as well as to companies and other universities across the world.

The first issue is free. If your company decides to continue the advertisement, the cost is either \$150 per issue or \$500 for one year (four issues).

For more information, please contact Rich Scholes at rich.scholes@stanford.edu or (650) 725-9115.



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Working With Industry in Sponsored Research

Continued from page 1

areas of research. If a company is interested in sponsoring the research through a formal contract, the faculty member should contact the ICO.

The professor should prepare a statement of work for the proposed research to be funded by the company, along with a budget that includes both direct and indirect costs of completing the project. This information is routed through the proper administrative channels and then on to ICO. ICO will negotiate the terms of the agreement for the faculty member and sign the resulting contract.

The Cultural Differences

Intellectual property, licensing options, confidential information, and publication rights are the primary points of discussion in the Sponsored Research Agreement between Stanford and the sponsor.

Generally, companies want rights to intellectual property either as a means of ensuring a proprietary position in the marketplace ("we have something our competitors don't have") or for allowing freedom of action ("we don't want to be sued for using your inventions"). As a non-profit institution of public trust, Stanford has an obligation to ensure that intellectual property developed in the course of Stanford research is transferred to the public for society's use and benefit. In this context of diligent technology transfer, Stanford is willing to grant either a non-exclusive royalty-free license or an exclusive royalty-bearing license to inventions that arise from the sponsored research. Like most universities, Stanford does not give title to inventions to the sponsor, whether corporate or government.

Some companies take the position that they must have ownership of anything that Stanford researchers discover during the course of sponsored research because "they are paying for it." Companies who have successful university-industry relation-

ships understand that they are funding the *research* and not the acquisition of intellectual property through a sponsored research agreement.

Two other issues that may come up during the negotiation between corporate sponsors and Stanford are **confidentiality** and **publication**. Stanford is an open environment, where free exchange of ideas and information among colleagues is an essential and long-standing policy. Although many companies highly prize confidentiality, no program of research that requires secrecy may be conducted at Stanford under University policy (see <http://www.stanford.edu/dept/DoR/RPH.html> for all of Stanford's Research Policies).

The University is committed to the principle that faculty may publish the results of their research in a meaningful and timely manner, guided only by scientific objectivity and academic freedom. The right to publish is the hallmark of academic freedom, and Stanford cannot agree to provisions in a contract that prevent publication, require changes to the content of a particular publication or approval by the sponsor prior to publication, or designate Stanford research results as confidential to the company.

The Common Space

Since its inception, the ICO has signed more than 120 sponsored research agreements, 40 collaboration agreements, and 400 Material Transfer Agreements. Clearly, there is common space where the two cultures can successfully come together for mutual research benefit.

The Industrial Contracts Office focuses on facilitating the relationship between Stanford and industry by negotiating agreements that foster long-term business relationships with sponsors and that are consistent with Stanford policy. For more information about the process from initiation through completion, Agreement terms, and examples of sponsored research at Stanford, please visit the ICO website at www.stanford.edu/group/ICO, or call us at (650) 723-0651. ▲



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