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IN THIS ISSUE

"Amati Phone Home" – Cioffi Sending Clear, Strong Signals

"We were a curiosity, a joke," says Electrical Engineering Professor John Cioffi. But now he, his students, and OTL are the ones who are smiling, for Amati Communications – the company Cioffi founded with technologies he invented and licensed back from Stanford – is now on the verge of revolutionizing telecommunications hardware.

The technology, called Discrete Multi-tone (DMT), was named the American standard for telephone line technology by the American National Standards Institute (ANSI) in 1993, and soon received the same distinction in Europe.

And the technology is spreading, for good reason. DMT can transmit up to six movie-quality video signals over a phone line simultaneously. DMT also speeds up computer access to the Internet by a factor of a thousand; what previously took fifteen minutes to download now takes seconds.

The DMT story started in 1986, when Cioffi won a Presidential Investigator Award from the National Science Foundation, which included a

Continued on page 2

Electrical Engineering Professor John Cioffi is smiling because with his DMT technology, he can speed up his access to the Internet by a factor of a thousand -- and yours, too!

Transplant Drug Hoping for Tolerance in Patients, Market

A drug based on a series of Stanford inventions aimed at preventing the human body from rejecting transplanted organs has passed Phase II of clinical trials, making it one of the furthest along of any licensed Stanford invention currently in clinical trials.

Invented in the laboratories of Carol Clayberger and Alan Krensky and licensed to SangStat Medical Corporation of Menlo Park, the inventions work through peptides — compounds derived from proteins — that block the ability of the organ recipient's T-cells (the "soldiers" of the body's immune system) to recognize and attack the new organ.

What Clayberger and Krensky found in the lab was even better than they expected. "The surprising finding was not that our technique works, because theoretically it should work," says Clayberger, an Associate Professor of Immunology in Cardiothoracic Surgery and Pediatrics.

"What was surprising is that we can use one peptide for all patients, instead of requiring a different 'cocktail' of peptides for each patient."

"There were approximately 50,000 organ transplants worldwide last year," explains Krensky, Clayberger's husband and a Professor of Pediatrics whose focus is nephrology (the study of kidneys), particularly children requiring transplants. "The biggest problem with transplants is rejection, so my interest is to find a way to give these children long and productive lives when they otherwise wouldn't have either.

"Most transplanted organs experience rejection, of which there are two types: acute and chronic. Acute rejection, which occurs immediately, can be staved off with cyclosporin and steroids, plus a couple of drugs that came out just last year."

However, adds Clayberger, "since the treatments for acute rejection are potent immunosuppressors — that is, they suppress the

Continued on page 3

Stanford University
Technology Transfer Through Licensing
Office of Technology Licensing

STANFORD TECHNOLOGY BRAINSTORM

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Stanford Technology BRAINSTORM is published quarterly in order to provide information about OTL and general information of interest to the licensing community, both within and outside Stanford.

OTL's services are available to any Stanford faculty, students, or staff who invent technologies which may benefit the public or be of commercial value.

To learn about a specific technology or to disclose one of your own, contact us at the above address.

"Amati Phone Home" ...

Continued from page 1

substantial research stipend. With that, plus matching funds from companies, Cioffi and his students set about finding a way to send digital television signals over phone lines.

"Although people with scientific expertise knew it was fundamentally possible," Cioffi says, "no one knew how to do it." Cioffi's group explored three techniques, one of which seemed especially promising.

Then Cioffi saw a brochure that he says "changed my life." Circulated by Stanford, the brochure described a program sponsored by University Technology Transfer International (UTTI) for transferring technology out of the University into start-up companies.

"I just happened to look at it as it crossed my desk, and on a lark I submitted a proposal. It was one of two that was funded, and we were scheduled to receive $250,000."

UTTI went bankrupt in 1990, with Cioffi's lab having received only half of the funding. But, he says, "we had enough momentum and enough contacts to continue on our own with careful spending."

By then Cioffi had made his initial disclosure to OTL, and OTL Senior Licensing Associate Joe Koepnick filed a patent application. Cioffi, meanwhile, approached such companies as Northern Telecom and AT&T.

They were not interested in funding further research, but Koepnick wasn't surprised. "These companies had billions invested in fiber optics," he says, "and this does compete with fiber optics."

Cioffi offers an additional explanation: "It was a University project, the wild ruminations of a professor." But in 1991 he obtained, somewhat serendipitously, a contract to build a working system from an Israeli company called ECI.

"They were a small company," says Cioffi, "but they had contracted with the Deutsches Bundespost [DB — the German postal and telephone service] to install phone lines in the former East Germany, where there were few."

ECI had overestimated the capabilities of conventional technology and had underquoted their bid. "But they had heard of our technology," Cioffi says. "So they could either take a financial hit from the DB, or take a risk with us."

They took the risk. "ECI saw something in our technology that others hadn't," says Cioffi. So with the contract from ECI, he founded Amati, negotiated an exclusive license with Stanford for the four existing patents, and set about making the system.

Since Amati had no venture capital funding, Koepnick agreed to keep the licensing fees low in exchange for a chunk of equity in the company. "If you make the fees too high, they can't afford it, and it's not going to happen," says Koepnick. "Equity is a good way for us to be flexible, because if the company succeeds, Stanford still gets a return."

The products for ECI were extemely successful. "They actually exceeded the requirements," says Cioffi. "The Bundespost was very happy."

Now that the technology had been proven, at least for providing cheaper and faster phone service, Northern Telecom decided to fund Amati for a prototype of an Asymmetric Digital Subscriber Lines (ADSL) modem to transmit TV signals.

But with fiber optics then considered the inevitable wave of the future, Amati and its technology were still not taken seriously. "Here was the University professor who would get smiles, even laughs," Cioffi says. "Northern Telecom wouldn't even let us say publicly that they were funding us.

"We were told by every phone company, 'No way. It will be all fiber optics.' They were wrong. Even a friend of mine at Pacific Bell said that, and now they're using ADSL."

There was one big step left, however — the key event in DMT and ADSL history, says Cioffi — and that was going up against the established technologies to prove DMT to the phone companies and to ANSI, which was scheduled to decide the national standard in January of 1993.

"It was essentially a bake-off," says Cioffi, "open to anyone who wanted to put up their technology. All other companies were basically promoting a version of AT&T's CAP technology, which could transmit 1.5 megabits per second.

"I believed DMT could do four times that, so in our proposal I said we could do six megabits per second." The difference between DMT and CAP, explains Cioffi, is that CAP sees all phone lines as the same.

"But no two phone lines are exactly alike," he says. "They're of different lengths, or some have radio-signal noise, impulse noise, crosstalk noise, etcetera. But CAP sends the same signal over all of them. Sometimes it gets lucky and the signal is close to optimum; other times it's not so lucky, and performance is severely degraded."

With DMT, however, "we have intellegent transceiver modems on each end. Both sides learn about the line and tell each other about it and change their signals accordingly. They assess the phone line as a bunch of different little modems, tens to hundreds

Continued on page 4

A Sampling of Licenses Granted by OTL in the Last Quarter

Docket(s)	Title(s)	Uses	Licensee(s)	License Type
S74-043	"Cohen-Boyer Recombinant Technology"	DNA Cloning – Production of proteins Total number of DNA licensees: 353	Medical Enzymes; Lexicon Genetics; Digital Gene Technologies; Scriptgen Pharmaceuticals; Receptor Biology; Atherogenetics; Calydon, Inc.; Research Biochemicals Int'l; Vitro Diagnostics	Non-exclusive
S81-026	"Phycobiliproteins (PE)"	Diagnostics	Cedarlane Laboratories	Non-exclusive
S81-035	"MINOS" (Software)	Optimization	Daiwa, Duxbury	Non-exclusive
S85-043	"Waveguide"	Sound synthesis	Virtual Music Ent.	Non-exclusive
S93-087, S94-052	"Genetic Footprinting:..."; "...plasmid JW4303"	Gene analysis; Expression plasmid	Genome Therapeutics	Non-exclusive
S93-113	"Virtual Design Team"	Engineering design	VITE	Exclusive
S93-131	"MAb for RANTES...Protein"	Research reagents	PeproTech, Inc.	Non-exclusive
S93-160	"...Multiple Alleles in...Genes"	Detecting mutations	Chiron	Non-exclusive
S94-144	"STRUCTAL" (Software)	Protein analysis	Bioscape	Non-exclusive
S96-076	"Infomaster"	Internet	Epistemics	Non-exclusive

Transplant Drug Hoping for Tolerance in Patients, Market

Continued from page 1

body's immune system — patients are open to infections and viruses. Many of them end up back in the hospital, and many die.

"In chronic rejection," she continues, "the graft fails in different ways, over the longer term — say, five years — and patients often need a retransplant.

"So current immunosuppressive therapy is good for the short term, but we thought that if we could apply a treatment around the time of the transplant that could induce permanent tolerance for the new organ, these other problems would go away."

So far, so good. SangStat's product, Allotrap® 2702, recently passed Phase II of clinical trials, which is primarily a safety trial but includes some data on efficacy. "The data suggest that the drug only affects cells having to do with transplantation, which means it wouldn't otherwise suppress the immune system," says Clayberger.

"Progress on Allotrap® is good," agrees Philippe Pouletty, founder and CEO of SangStat. "It is a candidate with promise, though we haven't yet proven it. That will require additional clinical trials."

Such caution is not surprising from a man in Pouletty's position, though his long-time interest in the technology suggests he is more excited than he's letting on. As a post-doctoral fellow in 1986 and 1987 in the Stanford lab of John Boothroyd, Pouletty invented his own, unrelated technology, which OTL licensed to GeneProbe.

It was also in 1987 that he learned of Clayberger and Krensky's approach through their papers in *Nature*. Following his fellowship, Pouletty went back to his home country of France, then returned to the U.S. to start SangStat.

"I used technologies I had developed at SangStat, and some I had licensed from other academic groups," he says. The Clayberger-Krensky technology, however, had already been licensed to another company. "But that company had done nothing with it in two years," says Pouletty, "so I convinced OTL to negotiate with SangStat."

After all, SangStat was a company dedicated to transplant technologies. Moreover, says Pouletty, "to build a company takes excitement, and this technology met my pre-existing level of excitement."

Since taking the license, SangStat has moved the technology forward quickly. "To have taken it on in 1991 and gotten it to Phase II already is pretty fast," says Licensing Associate Mona Wan, who negotiated the license with SangStat. "A drug usually takes five to ten years to develop, then it goes to clinical trials."

A number of factors account for the drug's speed through development and the trials, according to Pouletty and Clayberger. First, the company's experience with transplant drugs has meant a quicker turn-around for this one. "It can go through the same pipeline as our other drugs," says Pouletty. "We already have the expertise for transplant drugs. It's much easier than doing trials and tests in multiple fields."

Second, says Clayberger, "the compound is relatively easy to make, with none of the problems typically associated with genetic engineering and compound synthesis."

Third, the process hasn't shown any toxic side effects so far.

Pouletty adds a final reason for Allotrap's progress: the continued contributions of Clayberger and Krensky, who consult for SangStat.

"Our collaboration has been very good," agrees Clayberger. "SangStat does development, and we do basic research. There's not a lot of overlap or competition with each other."

Continued on page 4

"Amati Phone Home" – Cioffi Sending Clear, Strong Signals

Continued from page 3

of times per second, and find the sweet spot on the line. They are very adaptive."

Cioffi's claim of six megabits generated much excitement, but, he says, "people were saying we had no chance against AT&T." But when the tests were finished, DMT had performed as Cioffi predicted, and the verdict was unanimous: DMT was the new American standard.

Despite its clear advantages, Cioffi says there is no guarantee DMT will be used universally, because of the momentum of old technologies and the unwillingness of technology vendors to change.

But, he says, "it's close to a lock that DMT will be used on a wide scale. It's been transferred enough and there are enough companies using it that I think it will survive and flourish."

A promising example is Australia, which, says Cioffi, "is witnessing a ruthless competition between phone and cable companies, and the phone companies are rolling out thousands of DMT systems to provide broadcast video. That could eventually turn into millions of systems."

OTL's Koepnick isn't surprised. "This technology has two things going for it. The first is that almost every conceivable customer has a phone line; you won't have to run any new cables. The second is Cioffi." Koepnick says he had never met an inventor or a professor with more energy. "He radiated energy when I met him," he says. "And the percentage of his disclosures we've licensed is unprecedented." Of Cioffi's seven disclosures, five are licensed (one to Philips Electronics) and two other licenses are in the works.

"Amati wouldn't have happened without Cioffi," says Koepnick. "This is the way technology transfer works in the best case: you have involvement by the inventor and a champion within the company who is driven to make it happen. Ideally, as in this case, they're one and the same."

Cioffi is equally praising of Stanford and OTL. "There's no way this would have happened without Stanford — from the support to apply for the UTTI grant to allowing me to take a sabbatical, and from OTL giving us very reasonable licensing fees to being patient when we couldn't pay them on time.

"I hope the University gets back a big return, which it deserves."

OTL Fiscal Year 1995-96

(Preliminary Figures)

Total Income: $43.74 Million (M)

Cohen-Boyer DNA Patents:

- **Total Income: $31.49 M**
- **New Licenses: 44**
- **New License Income: $373,631**

All Other Technologies:

- **Total Income: $12.25 M**
- **New Licenses: 92**
- **New License Income: $1,266,500**

Companies in which Stanford took equity: 5

Distribution:

- **OTL Budget: $1.8 M**
- **Research Incentive Fund: $3.2 M**

Transplant Drug Hoping for Tolerance...

Continued from page 3

Pouletty also cites university technologies as a "big positive for a young company," explaining, "Discovery research is very expensive. With university technologies we don't have to reinvent the wheel. Plus, with such researchers' names behind us, our own papers have better credibility."

As for OTL, Pouletty says, "Having been on both sides of the [licensing] fence — as both inventor and licensee — I've been pretty pleased with the way OTL has acted. Other universities are not as easy to work with. Stanford is on the very good end of the licensing spectrum."

One valuable element of the license with Stanford was equity. "I've done deals with equity many times," says Pouletty.

"Equity is valuable to both sides. It's valuable to the company because of cash flow, and it's valuable to the university because the stock can become valuable many years before there are royalties."

For OTL's Wan, half the battle — finding a licensee — was won five years ago. "A major part of the struggle in finding a licensee is having a 'champion' within a company who will push for the technology," she says. "In this case, our champion was the company's CEO. You can't do much better than that."

As for the inventors, Clayberger says, "We certainly have no proof yet, but it's very exciting."

Krensky agrees. "The chances that something developed in the lab will develop into a drug are always small," he says, "and I've been skeptical of this each step of the way.

"But that it's come this far is dramatic, and this is only the first in a line of better drugs all based on this line of inquiry."

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