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IN THIS ISSUE

New Gene Therapy: Take Two Pills and Call Me Tomorrow

By Amy Forrest

Stanford has granted a license to Ariad Gene Therapeutics, Inc. (Cambridge, Mass.) for a method of gene therapy that promises to revolutionize the treatment of diseases like osteoporosis, chronic anemia, hemophilia, diabetes, hypertension and coronary artery disease.

Using "regulated gene therapy," invented by Gerald Crabtree and David Spencer, biologists at Stanford's Howard Hughes Medical Institute (HHMI), and Stuart Schreiber, a Harvard chemist, synthetic compounds are orally administered to patients to regulate their bodies' production of therapeutic proteins.

For example, a diabetic may receive genetically engineered cells that produce insulin when she takes a pill and cease production when she takes a different pill, thus freeing her from several painful insulin shots each day.

Mona Wan, the OTL Associate who negotiated the license, is happy with the result. "We marketed it to several companies," she says, "but Ariad combined the infrastructure of an established company with the capital and focus of a venture capital firm, evidenced by Ariad's decision to organize a company around the technology."

Continued on Page 2

Mention Stanford biologist Gerald Crabtree's new method for "regulated gene therapy," described in the November 12 issue of Science *and widely publicized since, and you'll get a smile. "We never get tired of talking about it," he says. "We think of it as our baby."*

The (Very, Very, Very) Little Refrigerator that (Still) Could

By Eric Grunwald

The "microminiature refrigerator" (MMR), developed over ten years ago by physics professor William Little and licensed by OTL to his company MMR Technologies, Inc., has not exactly been a big seller. But thanks to a scientific development twenty years ago in the Soviet Union, the MMR may soon become ubiquitous in computers and workstations.

Little first began thinking about the MMR over 20 years ago during his research on superconductivity. He says the smallest refrigerators then available (called "miniature") dissipated 10-50 watts. But since most superconducting devices only dissipate a few milliwatts, Little says "it didn't make a lot of sense" to use such large refrigerators.

So he developed an idea for a tiny one using a phenomenon known as the Joule-Thomson Effect, in which a gas is allowed to expand through a porous plug or fine capillary tube at high pressure and, as a result, suffers a slight drop in temperature.

In such a refrigerator, the Joule-Thomson Effect snowballs on itself in what is known as a "counterflow heat exchanger." In this setup, the gas – in this case, nitrogen – is pumped through tiny capillaries into larger ones, reducing the pressure and thus cooling the gas about 10°.

The cooled gas is then directed back past the incoming gas, cooling it before it in turn encounters the larger capillaries, thus resulting in a further temperature drop, and so on. In Little's device, this process would continue until the nitrogen liquified at a temperature of 77°K (or -196° C; 0° C = 273° K), and refrigeration would be complete.

"When we started," Little says, "we had no technology and no market. So our goal was to get the technology to work and then build a market we could survive on."

Continued on page 3

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New Gene Therapy: Take Two Pills...

Continued from page 1

In an interesting twist, Wan negotiated the bulk of the agreement with Amy Porter of Ariad, formerly a Senior Associate at OTL. According to Wan, "Amy knew the constraints implicit in licensing from the university side" and was familiar with Stanford policy.

Wan says the negotiation was long, which is not unusual for a technology with such a potentially significant impact, particularly when further data are necessary to support the patent application prior to solidifying company interest.

The licensing process was complicated, however, by the geographical location of the inventors, the large number of parties involved (Stanford, Harvard, HHMI, and Ariad), and the fact that the technology itself had very specific development requirements.

As Wan explains, Stanford and Harvard agreed about these requirements, easing the negotiations somewhat.

The co-ownership of the technology, however, "slowed the decision making process, because we needed to keep all parties informed, and we required approval from several sources at each step of the process."

"It is such a significant technology," Wan summarizes, "we wanted to make sure everybody's interests were reflected."

Current gene therapy involves removing a patient's cells, inserting genetic material into them to induce the production of proteins that combat disease, and then returning the cells to the patient's bloodstream each time therapy is required.

"Regulated gene therapy" is less invasive and allows greater specificity. In the ideal case, a patient will take a pill to activate the production of therapeutic proteins, then take another to deactivate it.

Crabtree and Schreiber had collaborated for years on intracellular communication and knew that specific proteins in the surface of a cell act as receptors, reacting to chemical signals that move past in the bloodstream.

These proteins pass the signals on to genes in the cell nucleus, instructing the genes to produce therapeutic proteins. The inventors thus needed a compound that would activate this signalling, as well as a way to get the compound inside the cell.

Building on previous research done by Charles Zucker and Mike Hall on FK506, an immunosuppressive drug used to prevent rejection in organ transplants, and their own research, they created a compound "small enough to pass through the cell surface that isn't detrimental to anything else" and that provided the necessary signals.

A similar compound based on a modified FK506 molecule causes protein production to cease.

With previous procedures, genes could be modified but the production of therapeutic proteins could not be regulated.

As Schreiber explains, "The power of chemistry in biology is that you're not limited to the natural system. Through chemical synthesis, you can configure artificial systems that will do whatever you want them to do."

Crabtree and Schreiber plan to use this development in their future research to decipher cellular patterns of communication. Crabtree says that the precise manipulation allowed by this new process will "illuminate the cell's compensation for genetic defects and help [us] to interpret the results of mutation at the cellular level."

This, he explains, will provide the scientific world greater understanding of the roles played by specific genes in the life of a cell.

All parties involved think Ariad Gene Therapeutics is just the company to fulfill their varied interests. Wan believes Ariad won't try to pigeonhole the technology as strictly biological or chemical and that Ariad recognizes the duality inherent in creating chemical compounds that solve biological problems.

Inventor Crabtree agrees that a "major advantage of Ariad is that they will be able to support both the chemical and biological sides of the project" and says the inventors are satisfied with Ariad's direction for developing their invention.

For example, David Baltimore, a Nobel laureate who Crabtree says "has a defined expertise that will be very helpful in developing this technology" will be a scientific advisor for the project.

Describing Ariad's view, Amy Porter says, "We see [this technology] as the perfect extension of work we've been doing in signal transduction and small molecule drug design, and we know that with our in-house expertise we have the potential for commercial success."

Underscoring the importance of the invention, she adds, "We wouldn't have spun off the subsidiary company to prove its potential if it were not such a special technology."

License Agreements Signed 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: 270	Agis Pharmaceuticals; Antivirals; Hybridon; Houston Biotechnology; Myco Pharmaceuticals; Research Genetics; Signal Pharmaceuticals; Syntello Inc.; Oncor, Inc.; Terrapin Technologies; Upstate Biotechnology; Plant Genetic Systems Int'l	Non-exclusive
S78-077	"Protein Production at...Site"	Protein expression	Eli Lilly	Option
S82-007	"Amplification of...Genes"	Biological tool	IDEC Pharmaceuticals	Option
S83-018	"Data Readout Using Tunnel Current"	Digital memory (storing images, etc.)	Canon, Inc.	Non-exclusive
S85-043, et. al.	"A New Approach to Digital Reverberation"	Music synthesis	Ahead Inc.	Option
S87-057, et. al.	"Endothelial Molecules and the Control of Leukocyte..."	Therapeutic, diagnostic products	LeukoSite	Non-exclusive
S88-149A	"Homing Receptor for Lymph Nodes and Peyer's Patches"	Immunotherapy	Cell Genesys, Inc.	Exclusive
S92-147	"Regulated Gene Therapy Using Orally Admin'd..."	(See article, page 1)	Ariad Gene Therapeutics	Exclusive
S93-198	"Monoclonal Antibodies..."	Diagnose toxoplasmosis	Hi-Titer, Inc.	Non-exclusive

The (Very, Very, Very) Little Refrigerator that (Still) Could

Continued from page 1

So Little "spent two desperate years trying to get [the MMR] to work." He began by going to his colleagues in the Integrated Circuits Laboratory at Stanford to learn how to etch onto a silicon wafer the tiny capillaries for transmitting gases.

Unfortunately, the very thing that made silicon easy to etch — its crystalline structure — was what also made it an excellent thermal conductor, thus rendering it unusable for the refrigerator, since cold and heat could move in and out uncontrollably.

"We needed an amorphous material," says Little, and a perfect candidate was glass. And to make capillaries in glass, it was necessary to use "isotropic etching," a process in which a jet of compressed air shoots fine particles of alumina — "sandblasting, basically," Little says.

The problem with that, however, was that it etched away not only the glass, but the photomask that patterned the capillaries to be cut as well. The solution to this problem came to Little not in the lab, but at his old Spanish-style house in Palo Alto. "We had these old iron gates," says Little, "and we were having them sandblasted for repainting.

"So I asked the guy what the hardest thing to sandblast was, and he said the yellow stripes in the middle of the road. Since the paint is latex-based, the sand just bounces right off. I said, 'Thank you very much,' and went back to the lab."

Little had remembered a process used by a printer he had known in Scotland, where he did graduate work, in which the printing block had been treated with fish glue. "So I tried to get fish glue, but I couldn't," he says. "But," he continues, "the important element in the fish glue was gelatin, so I went to Safeway and got some Knox's unsweetened gelatin, and it worked perfectly." (He says MMR now uses a specialized gelatin for the same effect.)

Thus, MMR had their technology; now they had to find their market. The most obvious was in universities and industrial research labs, where people were doing research similiar to Little's and where he originally envisioned the MMRs going.

But the venture capitalists funding the company also saw applications in the military, such as for infrared detectors used in night vision. According to Little, though, "it takes seven to ten years to get into the military market. They only use technologies that have been established."

For example, the Sidewinder missile utilizes a refrigeration technology developed over thirty years ago.

Says Little, "Ours was flat and didn't fit into the cylindrical slot [in the missile] used by the conventional cooler. We did research and showed ours worked better, but there was no need."

Thus the military market never developed, and, according to Little, MMR "couldn't sell enough to

Continued on page 4

Revenues from Equity to Go to Fellowship Fund

Stanford's Board of Trustees has approved a policy under which a Graduate Fellowship Fund will be created for royalties generated through the liquidation of equity acquired under license agreements. The policy is designed to allow Stanford to benefit from taking equity while avoiding conflicts of interest.

OTL has received approval from the University to take equity (to be managed by the Stanford Management Company) in six companies as part of license issue fees. Money from the sale of the equity will go to the Fund, which is to be administered by the Dean of Research and Graduate Policy.

The (Very, Very, Very) Little Refrigerator that (Still) Could *Continued from page 3*

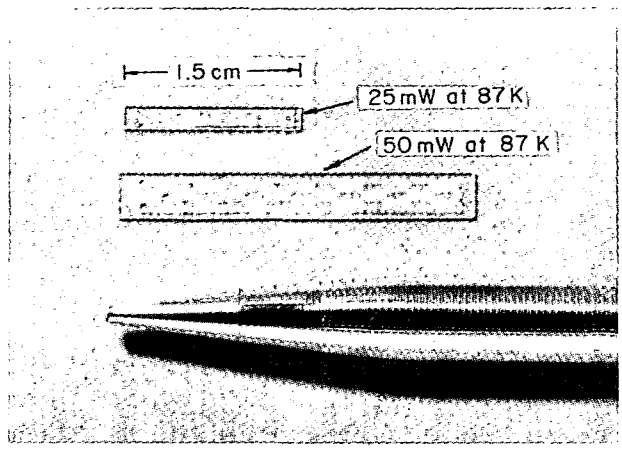
survive." Nevertheless, he says, "we were in a unique position. We had our foot in the door."

The key to success, he felt, was to supply instruments that could use the refrigerator, such as for sampling the concentrations of impurities in silicon wafers or measuring important characteristics such as the mobility of charge carriers in semiconductors.

Little says the company can supply "cooler, smaller, and quieter" refrigerators for $1,000, and instruments using them can sell for $10-$20,000.

But even with an array of instruments, Little says MMR is still "a hand-to-mouth operation."

Since the company was started ten years ago it has sold between three and four thousand of the devices. "We still don't sell a lot," he says.



Smaller than a pen, colder than the Arctic Circle, able to liquify nitrogen in a matter of seconds, it's the MMR! Thanks to a "cocktail" made in the USSR and a compressor like the one on your refrigerator at home, you may soon have an MMR on your desk. Story begins onpage 1.

But all of that may change in the next few years, thanks to a couple of innovations. The first Little describes as a "cocktail" of gases used in the USSR but never noticed here. "A friend in Holland put me on to it," he says.

Little and his colleagues don't yet know exactly why, but using the mixture in the MMR instead of plain nitrogen increases its refrigeration capacity by a factor of 10. "The refrigerators are rated at a quarter of a watt, but with this we can get one to two watts," he says.

The other innovation, ironically, comes from the relatively giant refrigerators found in most kitchens. Little discovered that the small compressor found on the back of such refrigerators is perfect for pumping gases through the MMR.

"It's incredible how cheap they are," Little says, citing a price of $56. "And they run for twenty years without maintenance. One company has built over a hundred million of them, and fifty million are still running. I know people who have them on their old refrigerators out in their garages, still working after thirty years."

With the addition of one plumbing part, Little says he will be able to build a microminiature cryogenic refrigerator that costs only a few hundred dollars. He and his colleagues demonstrated one a year ago and have since obtained funding to build a more readily manufacturable model.

With such an improvement, Little believes his MMRs will have application in work stations, minicomputers, and even desktops, resulting in a two- to five-fold enhancement in speed.

"What most people don't realize," he explains, "is that most of the junctions in a microprocessor are running at the boiling point for water (100°C). And they're spec'd at 125°C — that's not much head room. If you can take them down and run them at room temperature or below, you could drive them much faster."

According to Little, manufacturers now use "thermal management" to deal with the heat; i.e., carrying it off, mainly with fans. Computer chips such as Intel's 486 have fans attached directly to them.

The key is to get manufacturers to switch, but Little says that won't be easy. "They hate it," he says. "Liquid coolant is totally foreign to them." But he does believe that "as people get more familiar with this technology, they'll use it more."

But while Little would love to see that happen, he is happy with what he has already achieved. "I have a very strong interest in basic science," he says, "so it's satisfying to me just to see other people using [the refrigerators]."

Finally, asked why he didn't name his company "Little Refrigerators," Little says with a small chuckle, "It never occurred to me."

Correction

In the last issue, Mr. George Comstock was reported to have founded Adobe Systems. Mr. Comstock kindly called to inform us that he in fact founded Diablo Systems, another Silicon Valley company.

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