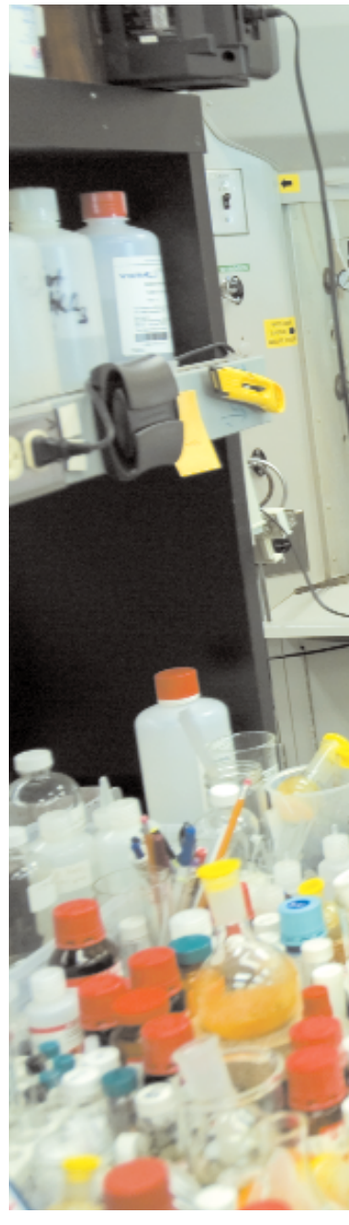
BY KIM RIBBINK

From his years in medical school and throughout his career, **PETER MILNER, M.D.**, has questioned conventional wisdom, always looking for new ways to approach diseases and the drugs that treat them.

IT IS THAT INQUISITIVENESS, COMBINED WITH AN ENTREPRENEURIAL SPIRIT, THAT LED DR. MILNER TO FORM ARYX THERAPEUTICS, A COMPANY THAT IS SEEKING TO BECOME THE INDUSTRY STANDARD FOR SAFER DRUGS.



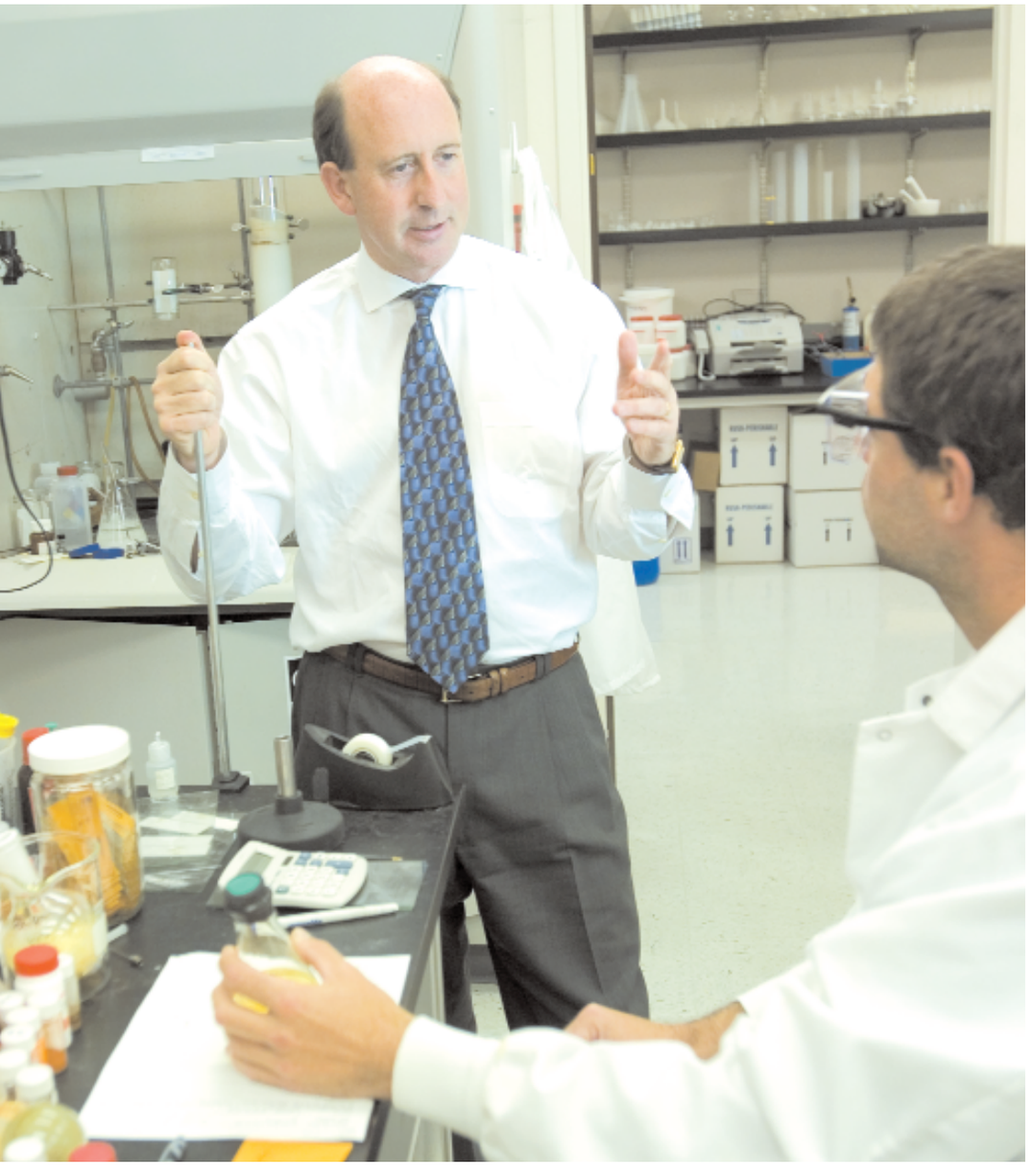
Peter Milner

IN SEARCH OF

REAL SOLUTIONS

Invention comes naturally to Peter Milner, M.D. From his years in academia to practicing medicine to creating life-sciences companies, Dr. Milner has sought answers to difficult questions and has looked for real solutions to the problems patients face.

"The experiences that I have had through my years in medicine and being an entrepreneur really shape what I do," says Dr. Milner, the cofounder, president, and CEO of ARYx Therapeutics Inc. "The opportunities that we seek at ARYx are based on real-time experiences in medicine and at the bedside."



ARYx is an emerging, privately held biopharma company with a focus on improving today's drugs by making proven therapies safer through its retrometabolic drug-design technologies. The company's goal is to treat significant medical needs unresolved by currently available therapies because of limitations in drug design and metabolism problems.

Dr. Milner founded ARYx in 1997 with Pascal Druzgala, Pharm.D., Ph.D., VP of research and chief scientific officer. Dr. Milner says even before founding the company he was looking for a way to address the problems of medicinal chemistry.

"I was looking for the next new thing," he says. "I wanted to do something that made medicinal chemistry simple, explicable, and predictable because there is a real limitation with conventional drug design."

In working with Dr. Druzgala, Dr. Milner recognized that there were opportunities to improve drug safety through the redesign of many good drugs that were forced to be withdrawn from the market after approval, such as Propulsid, Rezulin, and Baycol. More recently, Vioxx, Serzone, and Celebrex have made headlines because of questions about their safety.

"These were billion-dollar drugs, which after approval were discovered to have safety issues that caused them to be withdrawn from the market," he says. "In fact, a study published in 2002 by the *Journal of the American Medical Association* found that 10% of the 548 drugs that were approved by the FDA from 1975 through 1999 were withdrawn from the market or relabeled with a black-box warning because of safety."

AN ENTREPRENEUR IN THE MAKING

"When I was at medical school and practicing medicine in England and at Johns Hopkins in the United States, where I did my residency, I recognized that there were limitations in current knowledge," he says. "I always thought mechanistically and physiologically about diseases. I questioned the very basis of the pathophysiologic process."

The constant probing and desire for a deeper level of understanding of both diseases and their treatments are the platforms on which

Dr. Milner has built his career as a scientist and entrepreneur.

Aside from ARYx Therapeutics, Dr. Milner also founded CV Therapeutics, a biopharmaceutical company focused on the application of molecular cardiology to the discovery, development, and commercialization of novel, small-molecule drugs for the treatment of cardiovascular diseases.

Dr. Milner also has played a key role in several other small companies. He helped found Lifeline Technologies Inc., a biotechnology company focused on the use of natural products for improving human health. He also is on the scientific advisory board of ConjuChem, a biotechnology company with a type 2 diabetes drug in Phase II testing.

Dr. Milner's desire to delve deeper into medical problems was influenced, in part, by his late father, Jeremiah Milner, an industrialist who founded ML Laboratories. Mr. Milner also was the inventor of Extraneal, a sterile peritoneal dialysis solution used for chronic kidney failure, which is now marketed by Baxter International.

"I helped with many of the patents developed by ML Laboratories and some of the associated business deals," Dr. Milner says. "We learned some very painful lessons about who to trust, and those lessons have helped me in the companies I've formed."

Success as a scientific entrepreneur has as much to do with business acumen as it does with discovery, Dr. Milner believes.

"As an inventor and entrepreneur there are two key considerations for success," he says. "The first is knowing when to let go. Inventors, naturally, want to nurture their discoveries and take them as far as they can so their vision will be recognized. The second is turning that invention into something that has financial value."

Lessons Learned Along The Way

IN AN EXCLUSIVE INTERVIEW WITH PHARMAVOICE, PETER MILNER, M.D., COFOUNDER, PRESIDENT, AND CEO OF ARYX THERAPEUTICS INC., TALKS ABOUT THE PEOPLE WHO HAVE INSPIRED HIM, THE WAY HE SEEKS TO INSPIRE OTHERS, WHAT THRILLS HIM MOST ABOUT THE LIFE-SCIENCES INDUSTRY, AS WELL AS THE CHALLENGES THE INDUSTRY FACES.

WHO ARE THE PEOPLE WHO HAVE PLAYED AN IMPORTANT ROLE IN GUIDING YOU TO WHERE YOU ARE TODAY?

There are two people who had a significant influence on me. The first was my father, who died 15 years ago. He was a gentle, creative person with a fine business mind, and he was a great inventor. But he wouldn't reach out to experts. For example, he wouldn't consult a lawyer on legal issues; he thought he knew it all. The lessons I learned from him were twofold: one was how to conduct myself and the other was what not to do. I've never made a decision in business, either with my own money or anyone else's money, without adequately listening to lawyers, which is critical in business. The second person who had a major influence was Dr. Victor McKusick, who was the chief of medicine at Johns Hopkins and the father of human genetics. He won the Lasker Prize (considered by some to be the American Nobel Prize). At 83 years of age, he is the most-quoted man in medicine. He brought me from Liverpool to Johns Hopkins because I was interested in genetics. I learned more about medicine and science from him than anyone. Even though he wasn't a bench scientist, he had a catalogue-like memory and, in fact, is the author of the biggest catalogue of genetic diseases. Dr. McKusick pulled me out of obscurity and put me on the fast track at Johns Hopkins in medicine. If he hadn't done that I wouldn't be where I am today. I'd probably be some doctor in a small town in England.

WHAT MOST INSPIRES YOU ABOUT THE LIFE-SCIENCES INDUSTRY?

I look at the revolutionary changes that have happened in my own time. I spent 12 years away from working in emergency rooms, between 1984 and 1996, and in those years I noticed something incredible. In 1996 I was working in an emergency room and saw a patient who had come in for some problem, who was also diagnosed as schizophrenic, but he behaved in the same way as any other patient. This astounded me because 12 years earlier when I was working with schizophrenic patients they'd be taking the old-generation antipsychotics, such as mellaril and perphenazine, which had poor efficacy and seriously damaged their basal ganglia. These patients would have psychotic mentation, plus because of the damage to their basal ganglia, they would have Parkinson's disease. So I would be treating a 24-year-old guy who was shaking with Parkinson's and having hallucinations. When I started to practice again in 1996, I saw people whose mentation and psychosis were completely under control with the newer generation drugs such as olanzapine, risperidone, and clozapine. These atypical antipsychotics made a dramatic change in medical practice.

In cardiology, the introduction of stents, and especially drug-eluting stents, has changed medical practice as well. I like being part of this change, and I believe there are huge opportunities in drug invention around safety and efficacy.

HOW WOULD YOU DESCRIBE YOUR MANAGEMENT STYLE?

I would say my management style is modeled on

This requires an organized structure and system of capital that allows for entrepreneurs and inventors to be rewarded. It also takes learning from past experiences.

At CV Therapeutics, for example, Dr. Milner says he learned that being willing to share ideas was as important as the invention.

"Learning to share concepts, credit, and patents became a critical testing point; 1% of something that's valuable is worth more than 100% of something that's worth nothing," he says. "There are many inventors who can't cross that Rubicon; they are wary of sharing their patents for fear that their ideas will be stolen. I've learned that, although there is a danger of being taken advantage of, net-net being willing to share ideas has been to my advantage. While I've made mistakes, I've chalked those up to experience and now I can take those learnings, as well as the experiences of the management team, and lead toward success."

ROLE OF A LEADER

Having been issued 22 patents and 39 applications worldwide and having been published widely in peer-reviewed publications, Dr. Milner has established his credentials as a scientist and inventor. The real test, he says, was how he would prove himself as a company leader.

"I was a bad manager when I started off, and through the advice of colleagues and friends I've learned how to manage," he says.

Dr. Milner notes developing management skills is not part and parcel of the skill set commensurate with a background in medicine.

"From day one, doctors are taught to swim solo," he says. "In an emergency room, it's essential for a physician to be able to make a decision without looking for guidance. That's not the optimum fit for business or management, where the best decisions are made collectively and by listening to the advice of the right people."

Dr. Milner has had to learn to step back from much of what comes naturally to him, which is scientific research and discovery.

"It's important that I don't try to do the job of everyone else, including the scientists," he says. "As much as I view myself as a scientist and physician, my job now is being a CEO."

Having the scientific background does give Dr. Milner a broader perspective on how the company's technology can be put to best use and consensus building. I ask very direct questions, and I expect everyone at a senior level, not necessarily at the top level, to be able to answer these questions about what they're doing and why they're doing it.

I foster a culture of constructive criticism rather than dissent. There's a fine line there. One can disagree with the opinions of other people around the table, but when the company as a group decides to do something, managers are either on board or they're not. People who sit on the sidelines and say, "I told you it was going to fail," are poison to organizations. And many organizations tolerate this; I won't. I don't want an in crowd and an out crowd; what I look for are managers who might not have agreed with a decision, but back the decision thereafter. So when any employee of the company talks to any one of those managers, he or she gets the same opinion on the matter.

My management style is open, but there are definitely closed-door discussions during which things are decided.

WHAT ARE SOME OF THE TOUGHEST CHALLENGES FACING THE INDUSTRY, AND WHAT CAN LEADERS SUCH AS YOURSELF DO TO HELP OVERCOME THOSE DIFFICULTIES?

The first challenge is parallel imports from Canada, which are going to poke a big hole in the revenue of a lot of major pharmaceutical companies. It's a difficult issue to address because the American public has the right to have drugs as cheaply as possible and certainly as cheaply as the Europeans do. In the past 10 years, innovation in the pharmaceutical industry has moved into the United States. Novartis has moved its research headquarters to Boston, GlaxoSmithKline has essentially become a U.S. company, AstraZeneca is becoming a U.S. company. Swiss, British, and French companies are migrating to the United States because this is where the profit center is. In Germany, the government put a clamp on pricing, then it progressively has ratcheted down reimbursement over the last five to 10 years, decimating German pharmaceutical companies.

Price controls are the death knell of innovation. Somebody has to pay for innovation and right now it's the American public. There has to be a shared responsibility for that on a global basis. The Europeans have to start paying more for their drugs. I don't know precisely how this should be done, but that is one of the big challenges.

The second big challenge is that industry profits are viewed to be somewhat obscene in the eyes of a lot of social activists. Of course pharma needs profits to generate new invention, but when drugs fail after approval or late in development, it's very hard to justify the need for vast profits. A major figure at the FDA said in a private forum, "It's very hard for me to argue against Canadian imports if drug company X has three drugs that fail in Phase III because of liver toxicity."

Pharmaceutical companies need to put in place systems that can weed out failures at an early stage and build pipelines at an earlier stage. For the most part, pharma companies have waited until the late stage to in-license a product because it minimizes the cost. Now, they need to find a better way to funnel products into their early pipelines that weren't invented in-house.

WHAT DO YOU PREDICT FOR THE INDUSTRY'S FUTURE?

I see big pharmaceutical companies becoming biotech companies. Who would have thought 10 years ago that Roche or Lilly would have top-selling biologicals? Right now there's a headlong rush, and rightly so, for monoclonal antibodies and recombinant products.

Ten years ago, nobody would have believed that disease-modifying proteins given through IVs would be some of the top-selling drugs in the pharmaceutical industry. There is a premium price for disease-modifying proteins. But there's still a huge opportunity for once-a-day therapies that alleviate symptoms. To take advantage of that opportunity, pharma companies need to put in place systems that can weed out failures from success at an early stage, and they need to build those into the pipelines at an earlier stage.

what else is happening in the field. But it is the CEO's ability to set the tone and vision for the company and to address both the opportunities and threats to best ensure the company's success.

"A CEO has three critical powers," he says. "There's the power of persuasion, the power of the purse — in other words, I can veto anything that's in a budget or develop a budget — and there's the power of the peer group, which is essential. Whether it's the management team, the research and development teams, the business development teams, or the finance teams, these people come together based on their collective respect for each other. Building a peer group has nothing to do with being a physician, scientist, or businessman; it has everything to do with common sense and developing camaraderie."

To ensure that camaraderie is nurtured and maintained in the organization, Dr. Milner focuses on making sure his management team

Working Backward for Safety

ARYx Therapeutics is building its product franchise on the back of retrometabolic drug design.

The company's ARM technology (ARYx RetroMetabolic) analyzes the parent structure and degradation products of known drugs and creates new drug candidates that are chemical analogs that use different metabolic pathways for elimination and excretion. The ARM approach to drug design begins with the creation of a nontoxic, easily excreted end product. This information is then used to engineer new molecules, or analogs, that maintain the efficacy of the parent structure but with a better safety profile.

"We take an existing drug and, based on modifications that have been made to that drug by other researchers, we know what part of the molecule is active and what part is not as important for activity," says Peter Milner, M.D., cofounder, president, and CEO of ARYx. "We can then modify the back end of the molecule, the part that's not as responsible for activity, to create a nonburdensome, metabolic, or elimination pathway."

The features ARYx scientists look for in a breakdown product are that it is nontoxic, that it is rapidly eliminated from the body, and that it is water soluble.

MOLECULES BY DESIGN

"The operational difference between ARYx and other companies is that most companies design a conventional drug, put it into animals or tissue culture, then into man, and wait to see what happens," Dr. Milner says. "We design a weak point into the molecule to determine where it will break, so to speak. So we know exactly what the molecule should do in the body. And so far, we have found in all our animal and human tests that what we thought should happen to the molecule does happen."

ARYx has put its approach to the test in three targets. The first is ATI-2042, an amiodarone analog for the treatment of atrial fibrillation and ventricular arrhythmias. Amiodarone has served as the gold standard in the treatment of atrial fibrillation since its launch, although its usage has been complicated and limited by toxic side effects resulting from accumulation of the drug with long-term use. ATI-2042 has been engineered with a specific half-life so that the drug converts into a metabolite that is inactive, nontoxic, water soluble, and rapidly eliminated. ATI-2042 is in Phase II clinical trials.

"Our new drug has the same pharmacological properties as amiodarone, but has a totally different clearance; it is safer and doesn't accumulate in the body," Dr. Milner says.

ARYx's second project is ATI-7505, an analog of cisapride for the treatment of diabetic gastroparesis and gastroesophageal disease (GERD). Cisapride, which was marketed by Janssen Pharmaceutica under the brand name Propulsid, was a category leader before it was voluntarily withdrawn because of its serious cardiac liabilities. ATI-7505 is devoid of the off-target pharmacology underlying the cardiac liability associated with cisapride. ATI-7505 is in Phase I clinical trials.

ATI-5923 is the company's third product. It is a proprietary anticoagulant designed to prevent stroke in atrial fibrillation patients and to treat deep-vein thrombosis. The drug has similar efficacy to warfarin (best known as the drug Coumadin) and depletes certain clotting proteins in the blood, thereby reducing the risk of stroke. Although warfarin is the most widely prescribed anticoagulant on the market, in cases where the therapeutic effect is minimal, clots can form; in cases where the therapeutic effect is exaggerated, dangerous bleeding can occur. This means the drug must be monitored weekly or monthly. The ATI-5923 warfarin analog will have the same pharmacological profile but with a more reliable metabolism, which should reduce the instances of under or over anticoagulation. ATI-5923 is expected to enter the clinic this year.

"ATI-5923 is a reengineered version of Coumadin, which has been around for years but is problematic because it has a very steep, nonlinear dose-response curve and this makes it very hard to regulate," Dr. Milner says. "We've reengineered warfarin to preserve the same efficacy, but have flattened its dose-response curve to make it much more user-friendly."

SAFETY ADVANTAGES

Dr. Milner says there are two inherent safety advantages to ARYx's molecules; one is that they are designed to break down in the body without burden, and two they break down into safe fragments.

"The most significant result of our research is that we've found this process can be done repeatedly," he says.

works harmoniously, which leads to positive results throughout the organization.

"Nurturing the team and maintaining the vision are the practical areas where I can make a difference," he says. "There are people, other than myself, who can run budgets, invent drugs, develop drugs, but in terms of leadership there are things that I have the experience to be able to speak to."

Above all, a leader must be secure enough to accept and adapt to change, including his or her own position, Dr. Milner notes. That's particularly important in the pharmaceutical industry where change is a way of life.

"Change has always been part of my mantra, and I think people who embrace change do well," he says. "The industry and its leaders need to learn how to respond to change."

For Dr. Milner, as for all company leaders, there are professional challenges to contend with, most notably budgetary issues, including which programs to fund, which to cut, and where to invest resources.

"When we cut a project, we almost always wish we didn't have to do so," he says. "The day an executive can say, 'I'm glad we cut that project because it was lousy' the company has too much money. The best balance is to have adequate resources but a lean enough budget so money is being spent on the highest yield opportunities. Managing portfolios requires multifactorial decisions with a lot of input from different people — commercial, drug development, toxicology, and regulatory."

Fortunately, at this point in its business development, ARYx has not yet had to make the tough decision to discontinue a research project, having demonstrated success with its technology in three out of three cases.

"The company is in a great position in terms of potential products," he says. "Our challenge is to triage the development opportunities and spend the minimum amount of money on each to prove that the drug is viable so as to attract partners as a worthwhile investment."

SEIZING THE DAY

After leaving CV Therapeutics in January 1996, Dr. Milner spent some time working as an independent consultant to the pharmaceutical and biotechnology sectors. He was responsible for organizing and implementing preclinical and clinical development programs and arranging the sub-licensing of two drugs under contractual agreements with two separate biotechnology companies.This experience gave him a perspective on some issues that were arising within the industry.

I was looking for the next new thing.
I WANTED TO DO SOMETHING THAT MADE MEDICINAL CHEMISTRY SIMPLE, EXPLICABLE, AND PREDICTABLE
because there is a real limitation with conventional drug design.

"The chemistry of inventing drugs defied the logic of many of the pharmaceutical companies' senior managers; they were frustrated because they couldn't control the invention process," Dr. Milner says. "Unlike marketing functions, where it's possible to equate a certain amount of spending to an expected return in terms of sales, with drug invention companies can spend $5 billion on research and not come up with a drug."

As a result, some leading company executives began to search for a way to automate the discovery process through such technologies as high-throughput screening, combinatorial chemistry, and target validation.

"This approach started in the early 1990s, and I believed this was a fundamental mistake for the industry," he says. "Something that is on the border of human understanding cannot be automated. One can't hope to push a button and expect a drug to come out."

Recognizing this gap between research and product development as an opportunity, Dr. Milner decided to establish a company with the goal of simplifying medicinal chemistry. In March 1997, he and Dr. Druzgala founded ARYx Therapeutics, which is based on Dr. Druzgala's own design concepts to streamline the drug-development process.

Their first difficulty came in finding the resources to get ARYx started. At the time, in 1997 and 1998, there either was not enough capital available or venture capitalists were more attracted to other technologies.

"Ultimately, we funded the company with money from friends and family and were able to raise about $2.5 million from 1997 to 2002," Dr. Milner says. "We also received $25 million in nondiluted funds from a pharmaceutical company."

With the money the company raised, ARYx set to work to refine the platform, apply for and get patents, apply the technology, understand where the technology best applied, and bring forth targets that were ready for development. Thereafter, in 2002 Dr. Milner was able to raise $2.5 million in venture capital as part of a Series C financing. In June 2004, the company announced it had completed a $55 million Series D financing. That money has been invested in several promising clinical programs. (See box on page 46, for more information.)

Among these programs is ATI-7505, which is an analog of cisapride in Phase I trials for the treatment of diabetic gastroparesis and gastroesophageal disease (GERD). (Cisapride was formerly marketed by Janssen Pharmaceutica under the brand name Propulsid.)

Dr. Milner describes the company's ability to rid HERG, or IKr, liability in cisapride as the defining moment for the company. Cisapride was found to lead to drug-induced long QT syndrome (LQTS), a cardiac abnormality that can lead to loss of consciousness or sudden death. Drug-induced LQTS is usually caused by medications that block a cardiac potassium channel in the heart known as HERG or IKr, which is abnormal in inherited LQTS.

"Cisapride was a good drug, but patients died when the drug was taken in conjunction with other treatments, such as erythromycin or fluconazole; blood and tissue levels of cisapride went up about 40 fold in the heart, which would cause arrhythmia and death," Dr. Milner says. "When we set out to alter the metabolism of cisapride, we found that the very site in the molecule that we were trying to alter was also the site of the electrical activity. We had all the assays set up and the know-how to be able to do this. The result is a great drug that has all the beneficial properties of cisapride; and so far, in clinical trials, it appears that we have completely altered the metabolism and have eliminated the cardiac liability."

This discovery was a seminal moment for the company, Dr. Milner says.

"I think everybody — the board, the venture capitalists, the management, the scientists, the drug-development people — believed at this point the company would be around for the long term based on the achievement of those results," he says.

While Dr. Milner is proud of what the company has achieved to date, he believes the opportunities for ARYx's technology are vast.

"We've been picking the low-hanging fruit to reengineer, in other words drugs that are clearly good opportunities because they are known to be good drugs with problematic side effects," he says. "But our longer-term goal is not to be restricted to other companies' failures. Our technology can be applied de novo to newly invented drugs for whole new therapeutic categories but we're not in a position to do that yet. We need to have more mileage under our belt in terms of success with the drugs we have in development."

According to Dr. Milner, the company is still in what he refers to as the walking phase, but quickly headed for the running phase, which is Phase III trials and partnerships around these drugs, with the eventual sprint being to implement ARYx's technology in newly discovered targets.

"While we do set expectations and goals for the company in both the near and long term, we don't want to get too far ahead of ourselves and set too high a goal for next year," he says. "We have lofty goals for the long term but we want to get there in an iterative, step-by-step fashion. If we try to run before we can walk then we might stumble and hurt ourselves."

The goal, Dr. Milner says, is to own the drug-safety arena.

"Through our design concepts, we're creating drugs that don't interfere with efficacy, but that enhance safety," he says. ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

From Questions to Invention

PETER MILNER — RESUME

MARCH 1997— PRESENT. Cofounder, President, and CEO, ARYx Therapeutics Inc., Santa Clara, Calif.

FEB. 1996 — DEC. 1999. Consultant and Scientific Advisory Board Member, Aderis Pharmaceuticals Inc., Richmond, Va.

JAN. 1996 — DEC. 1999. Independent Consultant, Los Altos Hills, Calif.

MAY 1996 — JULY 1997. Consultant and Member of the Board of Directors, Orbon Corp., San Mateo, Calif.

1995 — PRESENT. Clinical Assistant Professor of Medicine, Stanford University, Palo Alto, Calif.

SEPT. 1992 — JAN. 1996. Cofounder, Executive Director, CV Therapeutics, Palo Alto, Calif.

1988 — 1992. Assistant Professor of Medicine and Independent Investigator, Washington University, St. Louis.

1988 — 1990. Instructor in Medicine, Department of Medicine, Washington University, St. Louis.

1986 — 1988. Research Fellow in Medicine, Department of Medicine, Washington University, St. Louis

1984 — 1986. Clinical and Research Fellow in Cardiology, University of Virginia, Charlottesville, Va.

1982 — 1984. Resident in Internal Medicine, The Johns Hopkins Hospital, Baltimore

1981 — 1982. Intern in Internal Medicine, The Johns Hopkins Hospital, Baltimore

EDUCATION

1980. M.B., Ch.B., University of Liverpool, United Kingdom

1978. B.Sc. Biochemistry, University of Liverpool, United Kingdom

BOARD MEMBERSHIPS AND PROFESSIONAL SOCIETIES

MAY 1998 — PRESENT. Member, Board of Directors, Lifeline Technologies Inc., St. Louis

MAY 1996 — PRESENT. Member, Scientific Advisory Board, ConjuChem, Montreal, Canada

JUNE 1994 — PRESENT. Editorial Board, *International Journal Of Oncology*, Athens, Greece

1988 — PRESENT. Fellow of the American College of Cardiology

1988 — 1992. Council Member, American Federation of Clinical Research

1988 — 1999. Fellow of the Royal Society of Medicine, United Kingdom

1986 — 1994. Member, American Federation of Clinical Research

1983 — PRESENT. Member, American Heart Association

JAN. 1980 — OCT. 1989. Part-Time Advisor to Chairman of the Board, ML Laboratories Plc., London

FEB. 1976 — NOV. 1999. Member of the Board of Directors, Milner Scientific (MSMR), Liverpool, United Kingdom, and Milner Research Ireland Ltd. (MRIL), and Diarmuid Investments, Roscrea, Ireland