BY KIM RIBBINK

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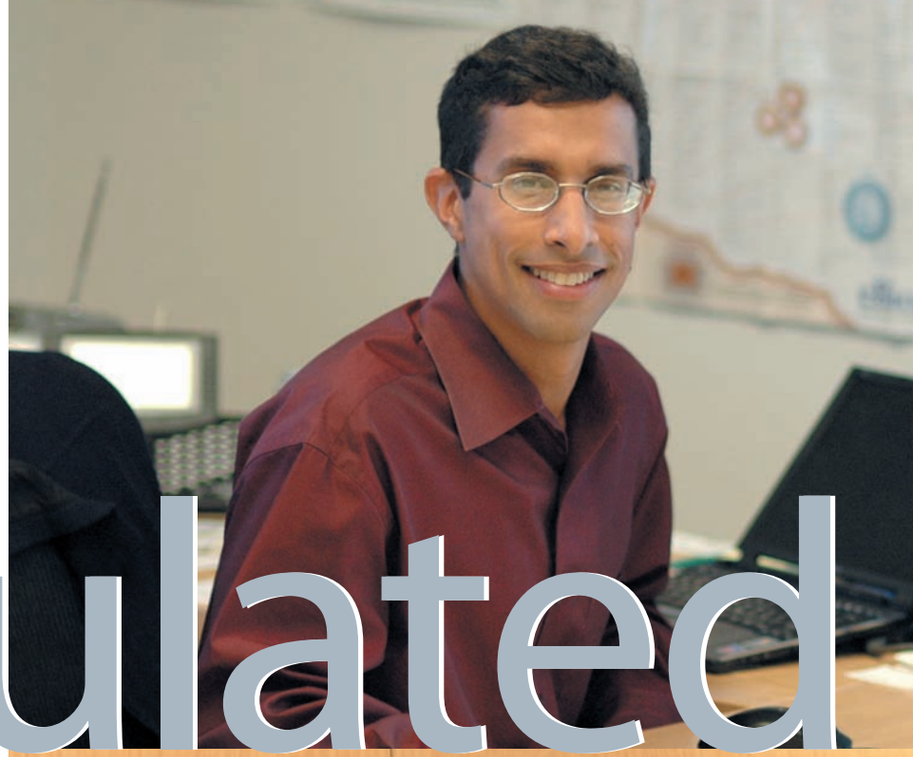
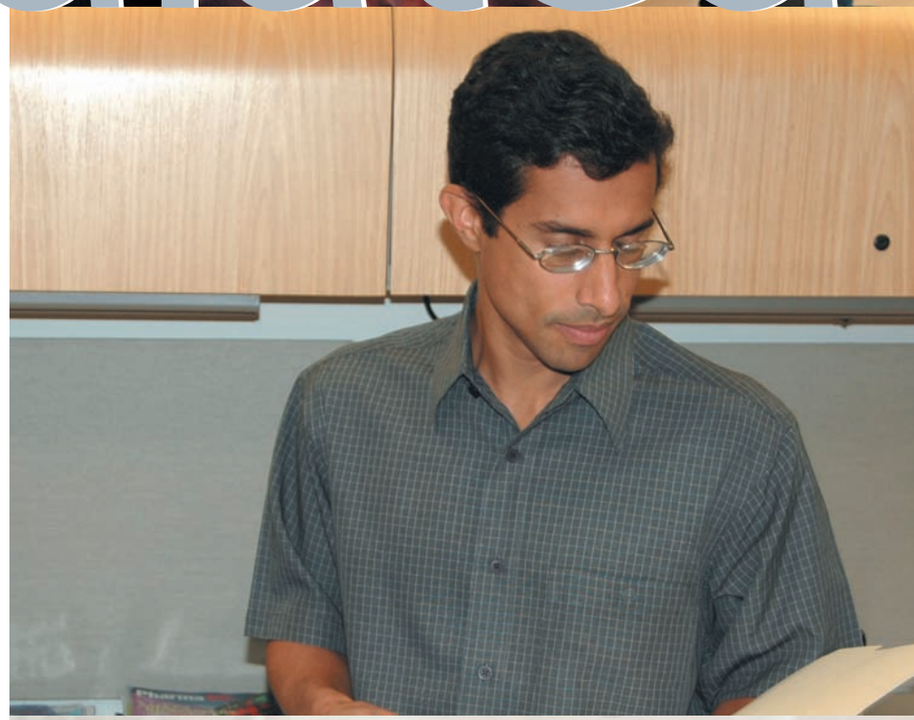
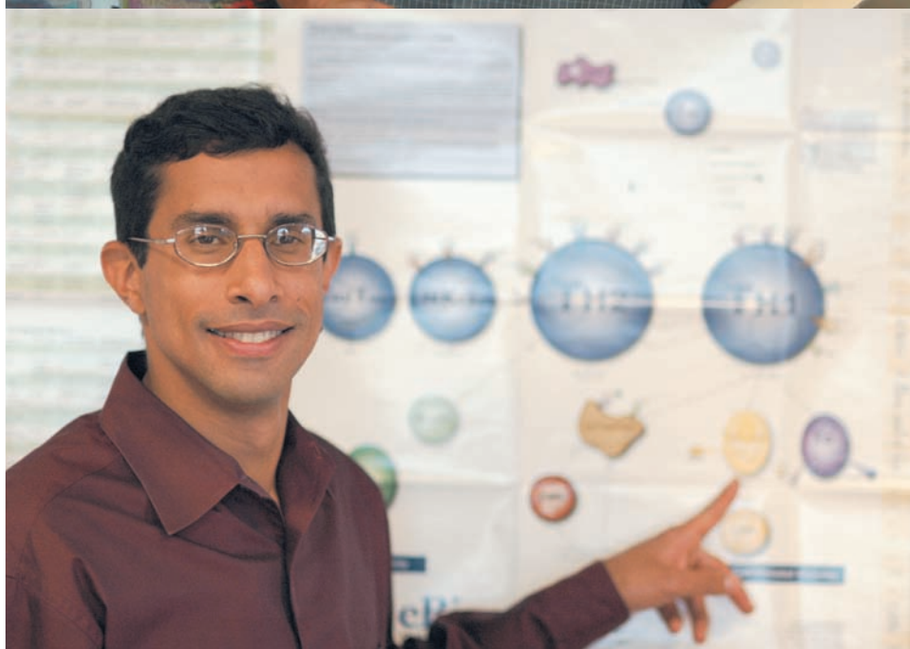






In a business climate in which caution and proven outcomes dominate, Bassil Dahiyat, Ph.D., is a daring and enthusiastic exception to the rule. Risk is not a word that frightens the young entrepreneur.

He founded his own company, Xencor Inc., directly after completing his Ph.D., based on the protein design automation he helped develop for his thesis. With no experience, Dr. Dahiyat went about learning the new language of business.

"I wasn't shy about reaching out and asking for help from people who had started biotech companies before me, from the people who I ran into, from patent lawyers, corporate lawyers, investors, the board directors I managed to secure early on," he says. "I got a lot of help from a lot of people but it was still very much a challenge, learning on the fly."

In the early days of Xencor, some of the initial challenges were closing the first round of investments of $3.5 million, while at the same time finding a location for the company and hiring the first group of scientists.

"At first, the biggest problem was defining the goals that would be commercially meaningful, because what might seem important at the outset may not be so significant after a few months," Dr. Dahiyat says. "That hurdle was definitely a result of my being new to running a business — coming right out of the scientific community into starting the company."

Beyond that, what made establishing Xencor such a tall task was that it was being built around a newly emerging area — protein design and protein engineering.

"We had to ask ourselves many questions, such as how were we going to define a business around protein design; how were we going to get customers; were we going to have to generate our own drug candidates; and what were the important milestones to reach," he says. "When we started nine years ago, it was an open field. We had the opportunity to define the arena and learn as we went along the way."

And though building the company was demanding, Dr.

Risks

With little more than his Ph.D. thesis and a dream of creating a truly groundbreaking technology, **Bassil I. Dahiyat, Ph.D.**, founded Xencor Inc., learning the business ropes along the way. Nine years later, Dr. Dahiyat remains as enthusiastic as ever about the potential for breakthrough drug candidates through protein therapeutics.

Dahiyat's enthusiasm for sailing uncharted waters has not been dampened in any way. His intention for Xencor is to draw on scientific discoveries to develop drugs and technologies that are truly innovative and groundbreaking.

"Even though this goal means taking bigger risks, we have the chance of making a big difference by creating drugs and impacting biology in ways that haven't been done before and helping people who couldn't have been helped before," he says.

The biotherapeutics company is developing protein and antibody therapeutics using its proprietary protein design automation technology platform. Thus far, the company has successfully developed two proprietary classes of protein drug candidates: XmAb antibody therapeutics and XPro protein therapeutics. In addition, because Xencor can engineer the affinity and specificity of protein-protein interactions, it is generating entirely new therapeutic mechanisms of action.

Building BLOCKS

Science has always been something Dr. Dahiyat enjoys — learning how the world works and how things operate — and so biomedical engineering was a draw for him because of both the applied engineering and mathematical elements.

"I remember being excited when I was a kid hearing about this new company called Genentech, which was doing genetic engineering and using tools to manipulate biology — actually making changes and building things," he says.

He completed his bachelor of science and his master's in biomedical engineering at Johns Hopkins before going onto the California Institute of Technology (Caltech) for his Ph.D. in chemistry. It was at Caltech where he helped develop the theoretical basis and computational methods for the automated design of proteins. During his years of study, he was awarded scholarships and worked as a lab assistant, and along the way he received a National Defense Science and Engineering Graduate Fellowship.

Dr. Dahiyat continues to draw extensively on his studies from his undergraduate and postgraduate years.

"What I do is extremely technical and what I learned — about biology, about chemistry, about quantitative analysis — at Caltech and at Johns Hopkins are hugely important all the time because Xencor is a very scientific, technically oriented company," he says. "There are a great deal of important scientific issues that I have to understand and be able to make reasonable decisions about."

His background in engineering also has been an advantage, since it is a discipline that trains people to be objective and quantitative, Dr. Dahiyat maintains, which has been invaluable to him in business.

But he admits that starting a biotech company was far different from how he imagined it would be.

"I didn't realize just how competitive the industry is; there are so many companies scrambling for partnering dollars, for financing from the investment community, and even for the same patients in clinical trials," he says. "When we started out, I had no idea how much time would have to be spent thinking how competitors might impact the business, what actions would be needed to compete and to improve our technology, and ultimately how to ensure that we are communicating the advantages of our technology to potential partners."

Along the way, Dr. Dahiyat has learned the ins and outs of running a company — from intellectual property law, to closing deals, to developing a succinct financing strategy, to compiling a comprehensive product development strategy, to managing the staff, to ensuring the plans are executed.

"Starting a business was an awakening, and now nine years later the biotech industry has grown so much since we started, that in the scheme of things we've been around for a decent amount of time," he says.

Having weathered the storm of building a business from scratch, Dr. Dahiyat strives to

smooth the way for other up-and-comers through participating in an organization called Entretec, which tries to support entrepreneurship in the Pasadena, Calif., area.

"Entretec is a networking organization that helps young companies get financing, sets up events for them to get visibility, and so forth," Dr. Dahiyat says. "I know that when I started out, having access to an organization such as this would have been hugely helpful. It's about the simple things: finding an insurance company for health benefits or a real-estate broker to find a building. These are the types of activities that can eat up time and not allow you to concentrate on the strategic aspects of building a business."

Acting on an INSPIRATION

The impetus for starting Xencor came from Dr. Dahiyat's desire to solve real-world problems.

Having developed a tool for protein engineering along with Dr. Stephen Mayo, his adviser at Caltech, the new doctoral graduate was enthusiastic about exploiting his success.

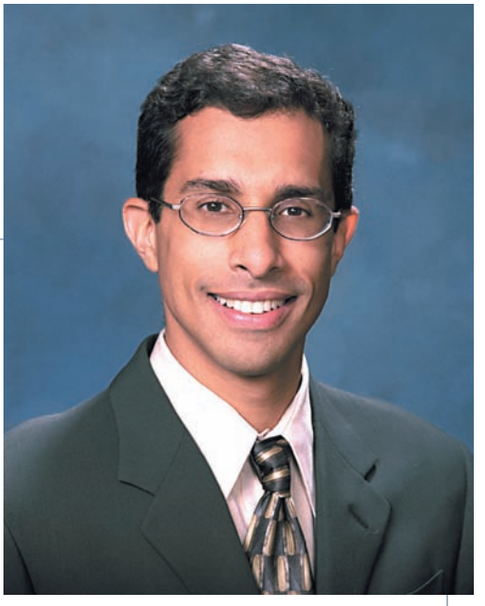
"By the end of my Ph.D. we'd had some success at building tools that could help design proteins, and while this is fairly rudimentary science today, back then it was quite an advance," Dr. Dahiyat says. "Naturally, I wanted to move beyond what we were doing, and somewhat naively decided, why not, let's start a company."

With Dr. Mayo's enthusiastic support and involvement in creating Xencor, Dr. Dahiyat took the first steps of founding a company.

A crucial early move was to hire people who were experts in their various fields. From Xencor's inception, Dr. Dahiyat was the company's president and CEO, but he stepped aside into the chief scientific officer role for a couple of years, from 2003 to 2005, to allow someone with commercial and business experience to lead the company. When that CEO left 18 months later for personal reasons, Dr. Dahiyat, his management team, and the board of directors decided it made sense for him to return to the helm.

"By that time, I'd gained a lot of experience in business, and furthermore, since the organization had matured during that time, we had more people on the scientific side who were able to focus on the technology, allowing me to focus more on the commercial side," Dr. Dahiyat says.

Over the years, Dr. Dahiyat and his senior-management team have forged several important partnerships with companies such as Roche, Eli Lilly, Genentech, MedImmune, and Centocor, alliances that Dr. Dahiyat



BUMPS IN THE ROAD

IN AN EXCLUSIVE INTERVIEW WITH PHARMAVOICE, BASSIL I. DAHIYAT, PH.D., FOUNDER, PRESIDENT, AND CEO OF XENCOR INC., TALKS ABOUT HIS BIGGEST CONCERNS FOR YOUNG BIOTECH COMPANIES AND FOR THE WORLD AT LARGE.

AS THE VENTURE-CAPITAL COMMUNITY INCREASINGLY TAKES A MORE CONSERVATIVE STANCE TOWARD BIOTECH INVESTMENT, THE PRESSURE IS ON FOR YOUNG, INNOVATIVE COMPANIES THAT WANT TO CHART THEIR OWN COURSE.

FOR BASSIL DAHIYAT, PH.D., FOUNDER, PRESIDENT, AND CEO OF XENCOR INC., THIS IS ONE OF THE BIGGEST PRESSURES THAT START-UPS FACE TODAY.

"The financing environment for biotechnology has had a fundamental change from how it was when I started out nine years ago, and, from what I've heard from others, what it was 15 or 20 years ago," he says. "Back then there was an investment environment fueled by the dream of creating life-changing drugs using incredibly exciting technologies — genetic engineering and molecular biology."

WHILE DR. DAHIYAT BELIEVES THE DREAM IS STILL ALIVE, THE INVESTMENT COMMUNITY IS MUCH MORE RISK-AVERSE AND IS FOCUSED ON HAVING A COMPANY THAT CAN MAKE A SPECIFIC DRUG CANDIDATE AND ACHIEVE FINANCIAL SUCCESS RATHER THAN INVESTING IN COMPANIES THAT CAN HAVE BROADER FLEXIBILITY AND GO IN MANY DIFFERENT WAYS.

AND THOUGH HE MAINTAINS THAT LACK OF FOCUS IS A BAD THING, THIS CAUTIONARY APPROACH TO INVESTMENT IS CREATING PROBLEMS FOR A NUMBER OF YOUNG BIOTECH COMPANIES, SUCH AS XENCOR, FORCING THEM TO SPEND TIME CHASING INVESTMENT DOLLARS RATHER THAN DEVOTING THE TIME NEEDED TO EXPAND THE BUSINESS.

"I truly believe the genomics revolution as it was in the late 1990s could not happen today; the investment climate is much more stringent," he says. "Today, investors wouldn't take fliers on what later proved to be groundbreaking technology but at the time had no solid evidence that it would be."

BEYOND FINANCE, DR. DAHIYAT BATTLES WITH THE SAME PERVASIVE ISSUE THAT SO MANY COMPANY LEADERS HAVE TO FACE — THE TOUGH REGULATORY ENVIRONMENT.

"It is hard to get drugs approved; there are very stringent, high hurdles, as there should be," he says.

BUT PART OF THIS IS A RESULT OF PRESSURE FROM THE PUBLIC AND FROM CONGRESS TO BE VERY CAREFUL ABOUT ISSUES SUCH AS DRUG SAFETY.

"There's not a good understanding among the general public and politicians about how drugs really behave and what it means to develop a safe and efficacious drug," he says. "This environment puts a lot of political pressure on regulatory agencies, and it makes the regulatory process take even longer. That's the biggest risk for a biotech company — it just can't last long enough to get its drug past the finish line."

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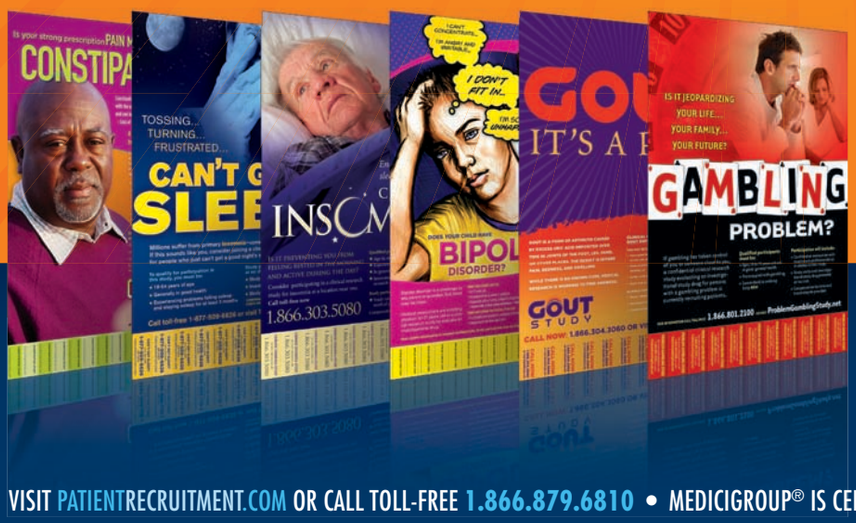

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attributes to Xencor's flexibility in adapting the technology to meet the needs of other companies.

"It became clear to us that we needed to think more about identifying our partners' needs rather than focusing on how great our technology is," he says. "Partners look for real candidate leads that emerge from a new technology not just information on how to sift through a lot of different candidates."

It was critical that the company differentiate itself from its competitors, and, to that end, Xencor started to invest in building its own molecules and lead candidates. Xencor began by focusing its technology on engineering the constant regions of antibodies and now because it builds its own complete antibody candidates, the company is engineering the entire molecule, including the variable regions. Antibodies are immune system-related proteins called immunoglobulins, and each antibody has what is referred to as constant and variable regions. The variable region gives the antibody its specificity for binding antigen; the constant region determines the mechanism used to destroy antigen.

"We realized there was a way we could potentially create a significant differentiation if the science bears out, and that is engineering in the Fc region, which is part of the constant

NEW BOUNDARIES

BUILT ON A FOUNDATION OF RATIONAL AND COMPUTATIONALLY BASED METHODS TO ENGINEER PROTEINS, XENCOR HAS ESTABLISHED A NICHE POSITION FOR ITSELF WITH A TECHNOLOGY THAT MAKES IT POSSIBLE TO DRAMATICALLY REDUCE THE TIME AND EFFORT IT TAKES TO CONDUCT PROTEIN RESEARCH.

The company was built on software that Bassil Dahiyat, Ph.D., helped develop while working on his thesis at the California Institute of Technology. Since then, Xencor has greatly expanded upon that technology and developed a system, the Protein Design Automation (PDA) platform technology, that enables the company to rapidly examine very large numbers of possible ways to change a protein and then draw up a short list of candidates that can reasonably and quickly be handled in the laboratory.

"The classic way to engineer a protein for improved binding would be to randomly make several million protein variants in a test tube and employ assay methods to quickly, though fairly coarsely, sort them to come up with winners," says Dr. Dahiyat, Xencor's founder, president, and CEO. "But we've designed a method whereby we can actually look at large numbers in the computer and whittle them down to a few dozen or a few hundred to actually take into the lab."

The beauty of such an approach means the company can focus experimental screening resources on the few hundred best protein variants. The accuracy of these validated design algorithms filters out all but the most likely variants for use in complex, expensive, and pharmaceutically relevant assays for lead selection. Furthermore, by having the computational engine sort through very large possible sets of changes to a protein, the company can cover a large amount of ground in changing the properties of the protein and in finding new intellectual property to patent.

Dr. Dahiyat says the company has been able to move forward thanks to a realization it made in the first year or two of operations.

"It was one of those Eureka moments when we realized we don't need to make the computer model perfect; that is we don't need to have the computer tell us exactly what the best protein sequence is going to be to make a drug, which is very difficult; we just have to get it to be pretty close," he says. "What makes this technology unique is that nobody had ever bridged the computational and experimental system, and it's the computational part that is really the unique driver."

To date, the company has had several breakthroughs with its PDA suite of technologies, including: a completely novel therapeutic protein, XPro1595, the company's lead drug candidate that inhibits tumor necrosis factor (TNF) for the treatment of rheumatoid arthritis; protein therapeutic variants that Eli Lilly has licensed to enable development of a promising drug candidate; several antibody candidates, including XmAb2513, which have improved potency and other traits; and a comprehensive suite of optimized Fc domain compositions of matter that drive antibody partnerships with major biotechnology and pharmaceutical companies.

Dr. Dahiyat says he is excited about the set of monoclonal antibody candidates that the company is creating for cancer.

"The most advanced one is targeting Hodgkin's disease, and we think it could really be exciting because it is the first use of what could potentially be a very broadly applicable and powerful technology for improving antibody drug potency," he says.

Xencor's technology, known as XmAb, aims to engineer the Fc region of the antibody to heighten interactions of the antibody with the immune system; in other words, this gives antibodies more tumor-killing power by improving their capacity to recruit the immune system against cancer cells.

"We realized if we could engineer that region of the antibody to improve how it engages these critical immune receptors and how it recruits immune function to the site of its action, we could potentially make much more effective antibody drugs," Dr. Dahiyat says.

Already, the company has some compounds that it is planning to take into the clinic. And this has generated a fair amount of excitement with partners. Further down the line, Xencor will look to pursue more of these targets as the biology becomes better understood.

"We didn't invent this hypothesis; people have known about the constant region for years," he says. "We were just the ones who had the protein design tools to exploit it."

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hese are exciting times. We are finding out whether our big bet on taking a cutting-edge and risky approach to tackling a truly new biology is going to pay off. **None of this might work, we don't know that yet, but we have the opportunity to work on something that could really change the face of medicine based on technologies that nobody conceived five or 10 years ago; that's inspiring.**

region, the opposite of what others had been doing," Dr. Dahiyat says.

According to research conducted by the company, engineering the Fc region of monoclonal antibodies (mAbs) increases their toxicity to cancer cells, potentially improving the utility of targeted cancer therapies. (For more information about Xencor's technology and research, see box on page 58.)

"Nine years ago, when we started out, this type of research was not on the radar screen, and for the first three or four years there wasn't a lot of interest by the pharmaceutical industry for manipulating or designing proteins," Dr. Dahiyat says. "Now it's a high priority for everybody."

Riding the ROLLERCOASTER

Over the past six years or so, Dr. Dahiyat has been spreading the word about Xencor's technology at various seminars and symposia.

"These conferences give me a chance to talk to people about what's exciting to me — the work we're doing here, the technology we've created, the science we've done, and the opportunities to create new products to treat disease," he says. "I love to convey my excitement and to get other people excited too."

The potential of scientific discovery and the opportunity to develop groundbreaking technologies truly motivates Dr. Dahiyat.

"Who would have thought 60 years ago that the genetic code was contained in four letters or that it would be possible to translate this surprising and elegant science into something that really can help people," he says.

Undoubtedly the science and research a company does, and the outcomes of that work, are paramount to its success, but as important are the people within a company and how they contribute to the ultimate goals.

To help staff members achieve their full potential, Dr. Dahiyat encourages and strives to ensure open, honest communication.

"We operate in a very fast-paced environment with very complex scientific issues, business issues, and product-development issues," he says. "Therefore it's critical that everyone is able to communicate openly, quickly, and honestly."

With a goal of establishing the company's technology and drug candidates, Dr. Dahiyat focuses on managing and coordinating the efforts of his staff and ensuring they have what they need to do their jobs.

"My job is to take all the information, and results and feedback that come to us from our own programs, our own scientists, our partners, our business development efforts and activities, and from the financial community, and aggregate them together so we can formulate a strategy," he says.

Part of that strategy is to start putting the company's products to the test, and later this year the company hopes to dose its first patient with the first Xencor-designed drug.

"These are exciting times; we're finding out whether our big bet on taking a cutting-edge and risky approach to tackling a truly new biology is going to pay off," Dr. Dahiyat says. "None of this might work, but we have the opportunity to work on something that could really change the face of medicine, based on technologies that nobody had conceived five or 10 years ago; that's inspiring." ✦

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

THE ENGINE ROOM

BASSIL DAHIYAT – RESUME

2005 — PRESENT. President and CEO, Board of Directors, Xencor Inc., Monrovia, Calif.
2003 — 2005. Chief Scientific Officer, Board of Directors, Xencor Inc., Monrovia, Calif.
1997 — 2003. President, CEO, and Founder, Board of Directors, Xencor Inc., Monrovia, Calif.

EDUCATION

1992 — 1997. Ph.D., Chemistry, California Institute of Technology. Thesis: Protein Design Automation: Principles and Practice. Advisor: Dr. S. L. Mayo, Division of Biology
1990 — 1992. M.S.E., Biomedical Engineering, Johns Hopkins University
1987 — 1990. B.S., Biomedical Engineering, Johns Hopkins University. Departmental and General Honors

AWARDS

2005. World Economic Forum Technology Pioneer – Corporate Delegate
2004. International Achievement Summit Delegate
2003. MIT Technology Review TR100 – World's Top 100 Young Innovators

SOCIETY AFFILIATIONS

American Chemical Society
Protein Society
American Society of Biochemistry and Molecular Biology

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