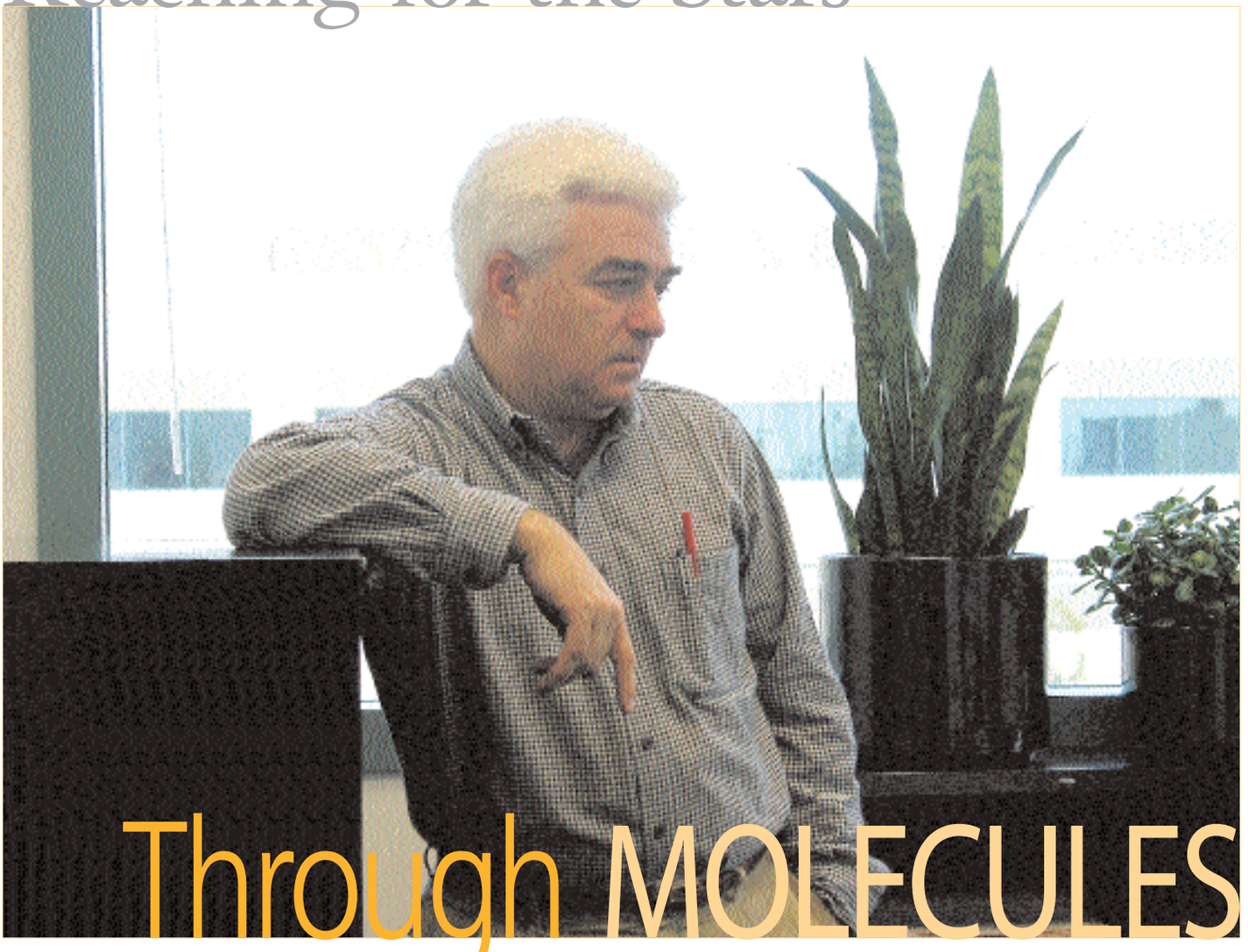
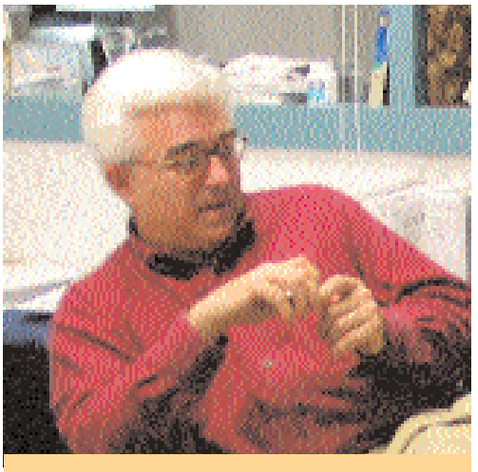
By Kim Ribbink

Reaching for the Stars



Through MOLECULES

As co-founder, executive VP, and chief scientific officer of Rigel Pharmaceuticals, **Dr. Donald G. Payan** intends to have his company become the **brightest star among those hunting for new drugs**.



Bill Creger and Alex Luncan were the ones who many years ago set me on this course, and who knows if I hadn't met them whether I would have done something different.

LIFE'S BIGGEST DECISIONS OFTEN CAN BE ATTRIBUTED TO COINCIDENCE. In the mid-1960s, Dr. Payan arrived in California to study physics and math at Stanford University, fresh from boarding school in Switzerland. The experience of leaving orderly, conservative Switzerland and arriving in the brave new world of 1960s California was, he says, like landing on the moon.

Upon arriving at the university, his first priority was to find a place to live, which was proving to be complicated. He was beginning to despair when he overheard a conversation in a hotel elevator about a real estate agent who had a connection to a university faculty member.

He raced to the real estate agent who introduced him to a professor. The professor had just rented a room to another student, but mentioned that a family across the street also rented rooms. That was the home of Bill Creger, a professor of hematology, now a dear friend to Dr. Payan, and the man who for years urged Dr. Payan to go into medicine, and who helped him eventually to get his residency at Massachusetts General Hospital.

"It was a true Thomas Hardy moment — listening to a conversation amid the crossing of two worlds," Dr. Payan says. "That elevator ride led me to Bill Creger and into medicine."

However, Dr. Payan wouldn't have even been on that elevator, had it not been for Alex Luncan, a prominent economist, family friend, and a big influence on Dr. Payan's career. Mr. Luncan was the one who convinced the young Payan to study in California, rather than England or the East Coast, where his family traditionally had been educated.

"Bill Creger and Alex Luncan were the ones who many years ago set me on this course, and who knows if I hadn't met them whether I would have done something different," he comments.

With a stellar background of extensive research experience and the solid launch of one biotech company behind him, Dr. Payan is embarking on a new voyage of innovation and discovery — leading the functional genomics company Rigel into the future. Rigel was named for the brightest star in the constellation Orion — the hunter.

As the founder of Rigel Inc., an upcoming biotechnology company, Dr. Payan has a depth of research experience behind him from his years in academia and hospital research, and his numerous writings, as well as business savvy from having established another biotech company some years earlier, Khepri Pharmaceuticals Inc., which later was acquired by Arris Pharmaceutical Corp.

Rigel's drug-development strategy uses the science of functional genomics to develop small-molecule drugs. Functional genomics is the process of identifying potential drug targets based on a prerequisite demonstration of effect on a specific cell function.

Under Dr. Payan's guidance, Rigel is taking a "portfolio approach" to drug development. The company's strategy is to develop products in its pipeline to the point where preliminary safety and efficacy have been established in human trials, in other words through Phase II clinical-trial research. The reason for this approach is these phases of research are more predictable and expedient to manage than late-stage trials, and also require fewer financial resources.

The company also has chosen to focus on areas of the clinical arena that have significant markets as well as unmet therapeutic needs. These include respiratory diseases such as asthma and allergy, hepatitis, and cancer.

Dr. Payan has set Rigel on a path of research and discovery that is, while highly innovative, also deeply practical. That approach, he says, is true to his nature.

"I was always pragmatic and focused on getting a drug into the clinic and showing that it works, and I wasn't too hung up on theoretical or theological arguments as to why it would or would not work," he explains.

Practical DISCOVERIES

Dr. Payan's penchant toward practical science led him first to the study of physics and math.

"When I went to Stanford, I had a somewhat arrogant view to biology so I majored in physics, which I believed to be the mother of all sciences. I then went to graduate school for physics at MIT," he says.

He became interested in the possibilities of medicine in the 1970s when molecular aspects of medicine and molecular biology were in their ascendancy. Further cementing his growing interest in the area was the death of a close friend.

"I went to a number of very interesting lectures by Max Perutz, one of the fathers of crystallography and was fascinated by the subject and began to spend a lot more time reading about biology," he says. "Then my roommate in graduate school developed melanoma and within six months died. The convergence of these experiences made me stop and think about what it was that I wanted to do. I decided that with medicine I could potentially have an impact on human disease. That was when I returned to Stanford as a medical student."

With his medical degree completed, Dr. Payan returned to Harvard to do his internship and residency at Massachusetts General Hospital, followed by a fellowship in infectious disease, then further research in allergy-immunology. Dr. Payan developed a particular interest in the interactions between the immune system and the nervous system.

"In the early 80s, what got me really excited was the concept that mediators, which traditionally had been thought to play a very limited role in certain systems, in fact influenced cell types outside areas that they were traditionally thought to work," he explains. "By that I mean peptides and lipid mediators were thought to only play a role in the immune system, but it was emerging that they could play a role in the nervous system as well. Now it's clear that the cross talk between the immune system, in terms of inflammatory mediators, and the nervous system in either direction can be significant in areas such as CNS and joint inflammation. It was that new appreciation that got me very excited and got me started in my early work."

Some years later, during a sabbatical, a new area of research began to fascinate Dr. Payan and became the launching point for a new career.

While working in the laboratory of Dr. Richard Scheller, now head of research at Genentech, he worked with another post-doctoral student to clone a molecule called agrin, which plays a role in the clustering of acetylcholine receptors in the neuromuscular junction.

"We found that the activity of agrin was responsible for the clustering of receptors — a fairly small part of a very large molecule," he explains. "The rest of the molecule was made up of protease inhibitor domains — small protein elements that were known to be inhibitors of proteases."

According to Dr. Payan, it was during further research into proteases that he began to realize the role they played, not just as the generic destroyers of protein, but also as interesting drug targets in their own rights.

"That was very exciting to me, and I formed a company — Khepri — around this research," he says.

New BEGINNINGS

Khepri Pharmaceuticals, which later was acquired by Arris, was established with a focus on the discovery and development of novel drugs based on proteases and protease inhibitors. In particular, the company focused on cysteine proteases, which Dr. Payan describes as an area that had been poorly examined and where new biological research was revealing interesting new drug targets.

"At Khepri we were the first to clone, express, and make small molecules against some interesting targets called Cathepsin K and Cathepsin S," he says.

Cathepsin K has been demonstrated to play a key role in bone resorption, while Cathepsin S inhibitors were shown to have potential applications in treating inflammation and autoimmune disease, including rheumatoid arthritis, asthma, atherosclerosis, and COPD.

"Khepri, although it ended up being bought by another company, was a real success story scientifically, because we rapidly identified some key targets, validated them, and developed small molecules; the basis of those targets are now the substance of programs at Merck for osteoporosis and at Aventis for inflammation," Dr. Payan continues.

It was the merger of Khepri and Arris, however, that led Dr. Payan to explore other opportunities since he did not enjoy the dynamics of the new company and felt that the execution of the merger wasn't very successful.

Dr. Payan's experience at Khepri provided him with a firm grounding in the biotech industry, and he describes the company as his business-school education.

"Khepri was a real eye-opener in terms of how to raise money, how to sell deals to large pharmaceutical companies who are your early customers, and how to pick people for management positions," he says. "When I was running a lab at the university I was the top dog and everyone else did what I wanted or they moved on. Whereas managing a biotech company, I couldn't manage it that way or it wouldn't last very

Validation through science

DONALD G. PAYAN, M.D., PH.D. — RESUME

1996-PRESENT. Founder, executive VP, research, chief scientific officer, and director, Rigel Inc., South San Francisco, Calif.

1995-1996. VP, Arris Pharmaceutical Corp., South San Francisco, Calif.

1994-1995. Executive VP, research and development founder, Khepri Pharmaceuticals Inc., South San Francisco, Calif.

1992-1994. Executive VP, chief scientific officer, and founder, Khepri Pharmaceuticals Inc., South San Francisco, Calif.

1998-PRESENT. Adjunct professor of medicine and surgery, University of California, San Francisco

1992-1997. Adjunct associate professor of medicine, University of California, San Francisco

1989-1992. Associate professor of microbiology and immunology in residence, University of California, San Francisco

1989-1992. Associate professor of medicine in residence, University of California, San Francisco

1986-1988. Associate director, Division of Allergy and Immunology, University of California, San Francisco

1986-1989. Assistant professor of microbiology and immunology in residence, University of California, San Francisco

1985-1992. Assistant investigator, Howard Hughes Medical Institute, San Francisco

1984-1989. Assistant professor of medicine in residence, University of California, San Francisco

1982-1984. Instructor of medicine in residence, University of California, San Francisco

1981-1985. Associate, Howard Hughes Medical Institute, Boston (1981-1982), San Francisco (1983-85)

1973-1976. Research assistant, Department of Anesthesia, Stanford University Hospital, Stanford, Calif.

EDUCATION:

1970. B.S., Physics/mathematics - Stanford University

1970-1972. Teaching Fellow in Physics, Massachusetts Institute of Technology, Cambridge, Mass.

1972-1977. M.D., Stanford University School of Medicine, Stanford, Calif.

1977-1978. Intern in Medicine, Massachusetts General Hospital, Harvard Medical School, Boston

1978-1979. Junior Resident in Medicine, Massachusetts General Hospital, Harvard Medical School, Boston

1979-1980. Senior Resident in Medicine, Massachusetts General Hospital, Harvard Medical School, Boston

1980-1981. Fellow in Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston

1981-1982. Allergy-Immunology Research Fellow, Harvard Medical School at the Brigham and Women's Hospital, Boston

1989-1990. Sabbatical leave, Department of Biological Sciences, Stanford University, Stanford, Calif.

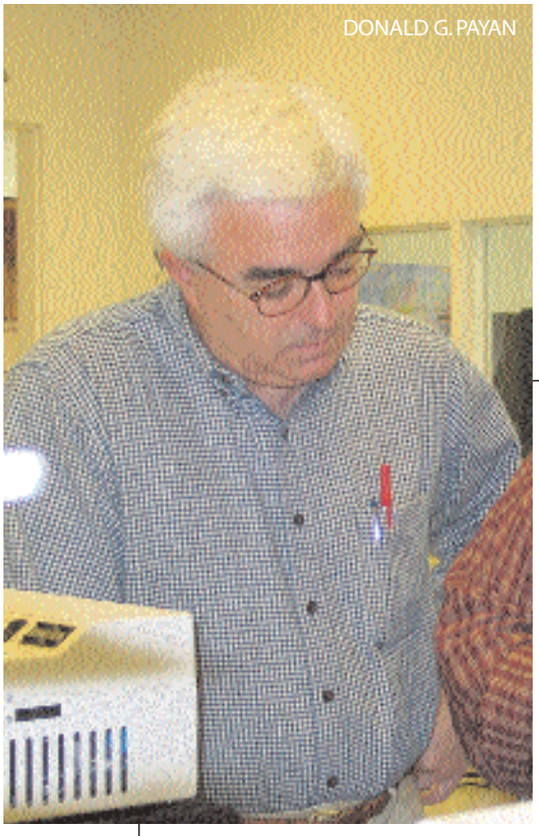
long. Khepri also taught me a lot about the timing of finances, how to deal with investors, what kind of investors you want or don't want, how to focus on projects, and how to pick projects."

Emphasis on the FUNCTIONAL

With his on-the-ground business education behind him, Dr. Payan began looking around for new opportunities, and during conversations with a colleague, decided the way forward was functional genomics.

Thus Rigel was born. "Rigel's focus is to improve drug development by letting the cell tell us what's important for changing function," Dr. Payan says.

At the same time the human genome project was gaining prominence, Rigel was formed, and Dr. Payan was quick to realize the problems that could arise in using the human genome as a starting point for drug discovery. Trying to link a gene to a disease process, which many in research were attempting to do, would require sifting through every gene in the human genome.


DONALD G. PAYAN

Thus Dr. Payan set his new company forward by using proprietary technology first developed at Stanford that enables Rigel to address many of the limitations of traditional genomics-based drug discovery by bypassing the need to know the identity or sequence of the genes to discover new drug targets and ultimately, the small-molecule drugs that regulate them. The integration of proprietary and established genomics tools allows the company's researchers to start with the "answer" to drug discovery (biological function) and then come up with the "question," in contrast to traditional genomics approaches, which begin by identifying genes (the question) that they hope will lead them to the answer (function).

The company's focus has been on primary human cells and on broad-based cellular responses that characterize maladies such as airway inflammation, or small-blood vessel growth, or tumor growth or responses to certain mediators.

"We started out by using retro-viruses, since they are very effective agents at infecting cells, and designed them so that we could make a library of retro-viruses," Dr. Payan explains. "In each retro-virus there is a piece of a gene, and our approach has been to distribute them randomly across the library. That creates a library of a billion different pieces of a gene. We can then infect a billion human cells, and then using fluorescent techniques, find those few cells where a piece of the gene alters the disease response from the disease aspect back toward normal. This approach points the way toward those targets that might be the Achilles heel in a pathway that controls the disease response.

"This approach allows us to design complex, more physiologically relevant cell-based assay and then determine what gene controls a specific cell-based assay without prejudice of choosing one target family over another."

Rigel's integration of proprietary and traditional genomics technologies has enabled the company to rapidly identify novel drug targets.

"This approach has turned out to be very successful," Dr. Payan says.

Starting from a strong vantage point

IN AN EXCLUSIVE INTERVIEW WITH PHARMAVOICE, DONALD PAYAN, M.D., PH.D., FOUNDER, EXECUTIVE VP, RESEARCH, CHIEF SCIENTIFIC OFFICER, AND DIRECTOR OF RIGEL INC. TALKS ABOUT THE MOVE FROM ACADEMIA TO INDUSTRY, THE OVER-HYPE OF THE GENOMICS PROJECT, AND HIS APPROACH TO LEADING A COMPANY.

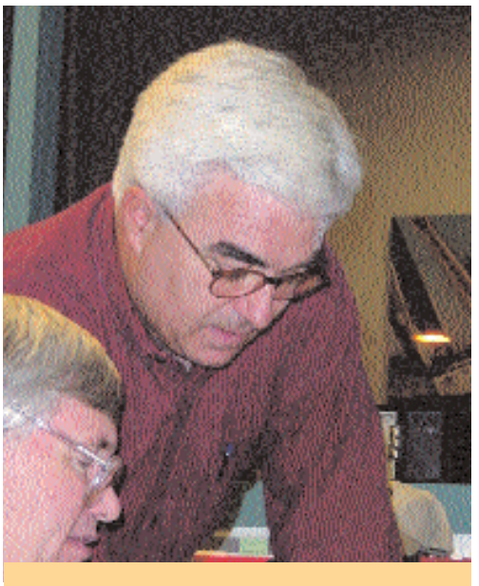
HAS THE INDUSTRY BEEN OVERLY OPTIMISTIC ABOUT LINKING THE HUMAN GENOME PROJECT TO DRUG DEVELOPMENT?

The industry greatly oversold genomics to the public and the financial institutions were only too happy to capitalize on that point. During a meeting several years ago, when someone was boasting about how many targets they had, I somewhat sardonically pointed out that they were a lot worse off than they were 20 years ago because scientists now have to figure out what these targets do, and target validation is not a straightforward process. It takes a convergence of many different kinds of biologies that allows researchers to decide whether or not a target is a good drug target. Some failures in drug discovery have been because companies rushed targets into screening and small molecules into the clinic without really understanding the fundamental properties of these targets.

The big challenge for genomics going forward is the biology of disease — taking these genes and somehow working through, in a systematic way, what these targets do into these pathologic processes, but this takes time. Biology is inherently slow and inherently messy, and we and others have put together methods to try to get the "no" answers quickly, but the "yes" answers take longer. So it helps to be starting out from what we believe is a stronger vantage point because of the method we use for identifying and validating targets.

WHERE IS THE GREATEST POTENTIAL FOR FUNCTIONAL GENOMIC-BASED DRUG DEVELOPMENT?

It's important to approach this in terms of tissue specificity and activity in disease states. In which case, functional genomics will be able to deliver impact in most disease processes, be they infectious disease,



Dr. Payan has set Rigel on a path of research and discovery that is, while highly innovative, also deeply practical. That approach, he says, is true to his nature.

"We've found many novel targets this way. We also have found targets that have been known for many years, but nobody quite knew what they did, so that we have a new disease-based context in which to identify old targets."

Both of Rigel's early projects — the mast cell project, which is the key to allergic diseases, and its oncology project — have benefited from the company's focus on broad-based cellular responses.

"As we discovered new targets we were able to study their biology extensively, and through high-throughput screening and chemistry, we discovered small molecules against these targets," he continues. "This fall, we entered the clinic in England for one of our allergic compounds, R112 to treat allergic rhinitis, and we've already completed Phase I." (For additional details, see box on page 48.)

It is the company's innovative approach to functional genomics, as well as the fact that it has gone from a standing start to getting its own compound into the clinic in just five years that Dr. Payan says sets it apart from many other companies.

"Our functional genomics program has produced small molecules, and I don't know of any other genomics company that has achieved that," he says. "Other genomics companies have produced protein therapeutics and antibody therapeutics. But for creating oral drugs, which represent the lion share of the pharmaceutical market today, most functional genomics companies are still behind us in terms of delivering the goods from a therapeutic point of view."

The company has 12 programs under way that examine the biological mechanisms of asthma/allergy, autoimmunity, transplant rejection, rheumatoid arthritis/inflammatory bowel disease, hepatitis C, and tumor growth. Rigel has identified 23 new drug targets, seven of which have generated potential drug compounds.

From a team of one TO A GROWING COMPANY

At the outset, Dr. Payan was the company's only employee, taking on the roles of CEO, chief scientific officer, and chief operating officer. After eight months, he brought on board Jim Gower as CEO, raised money for the company, and Rigel Inc. was formed in the spring of 1997. Two years later, Brian Cunningham came on board as chief operating officer, leaving Dr. Payan with the titles chief scientific officer and executive VP. Today, Rigel has about

inflammation, or pulmonary disease. The greatest benefit comes in those cases where there is a fairly reasonable, logical path that can be followed from cell to disease process. That's where Rigel's target validation has been better than most because we validate targets in primary human cells, and we validate those targets in the context of validated disease processes. This approach doesn't work as well in conditions that aren't closely linked to a single cellular system. A good example of the latter is depression. While there are some molecular mechanisms that are known to be associated with mechanisms that control depression, it's a greater stretch. The opposite is true in, for example, a mast cell. Based on cumulative literature over the last 30 years, we know that if we prevent the release of such mediators as histamine and TNF in mast cells, we will have a profound effect on airway inflammation. So the number of dots that need to be connected are fewer, making it very viable, though not always straightforward, to make a causal linkage between the cell-based system and human disease and develop a drug against a specific target.

HOW MUCH OF AN ADJUSTMENT DID YOU FIND GOING FROM ACADEMIA TO THE PHARMACEUTICAL INDUSTRY?

It's not that different. In academics, to get funded researchers have to do good science, tell a good story, and ask for money from their peers, which are the groups at the NIH, and other grant bodies. In business, researchers have to do good science, the company has to tell a good story, and then ask for money from investors. It's important to do quality work and pitch it to people who control the purse strings. Obviously in the university, researchers can work on problems that may not have an obvious commercial extension whereas clearly in biotech if companies don't work on something that has a commercial extension they won't be around for very long.

WHAT IS YOUR MANAGEMENT STYLE?

I try to articulate where we want to go, what the big picture is, and form the best team that will allow us to get there but then let the team figure out what the best route is — always allowing for taking advantage of expediency and serendipity. It's my job to provide my team with the resources and it's their job to figure out how to connect the dots. So I'm fairly forceful with designing the ultimate goals — right now for Rigel that means filing two INDs next year – and then it's a case of picking very strong people to execute those goals, and to play the role of listening, questioning, perhaps challenging certain approaches. But I stay out of the day-to-day stuff because it's not a practical way to run things.

Undoubtedly, one of Rigel's greatest strengths is having a founder with an eclectic interest in, and knowledge of, different areas of medical research.

160 employees, and Dr. Payan now is able to lead his team of scientists to focus on the day-to-day science management.

"The scientific team that Don has assembled is representative of his diverse background and experience," says Susan Scher, M.D., VP of strategic relations. "He has been really good at bringing in diverse groups of people, which is important because our research is focused in several different areas. Assembling these different groups in a company this young and small has really paid off in terms of research."

The company's financial resources derive from two sources — public equity and pharmaceutical partnerships. At the start of 2002, the company placed about 7.5 million shares of Rigel stock, raising about $31 million. Current partnerships include Johnson & Johnson Pharmaceutical Research, Novartis, and Pfizer. Rigel also announced an agreement with Daiichi Pharmaceuticals Co. to pursue research related to protein degradation, a new strategy for treating cancer.

With its team and business plan in place, Dr. Payan says Rigel's goals are to take its molecules through Phase II trials, and then find a big pharma or other commercialization partner rather than to incur the expense of large Phase III studies.

"Many biotech companies have put one molecule into the clinic and doggedly pursued that to the bitter end," he says. "With all of their eggs in one basket, that's a huge risk. We estimate that we can move five products or more into Phase II testing for the same price of taking one. This makes a lot more sense, it is a much better strategy for survival, and we can do it because of the robustness of our technology platform."

Dr. Payan says the goal is to file two INDs in 2003, and two in 2004. Therefore, starting at the end of 2004 the company will have molecules coming out of Phase II. In late 2002, Rigel filed its IND for R112 and expects to begin clinical testing in the U.S. in January.

Undoubtedly, one of Rigel's greatest strengths is having a founder with an eclectic interest in, and knowledge of, different areas of medical research. He has conducted research into, and written papers on a number of subjects, from leukotrienes and lymphocytes to peptides and lymphocytes, to peptide receptors to protease receptors, to proteases, to kinases, and more recently on inflammation and genomics.

It is this variety, Dr. Payan believes, that allows him to bring a fresh perspective to various areas of research.

"My thesis advisor at MIT used to tell me that the definition of a good scientist is somebody who can move into a new field and make a difference every five or six years; the definition of a bad scientist is a guy who repeats his Ph.D. the rest of his life," he says. Dr. Payan has made a career of putting that advice to good use. ✦

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

Identifying Targets

Rigel has multiple research programs under way to identify small-molecule drugs directed at a range of clinical indications. The company's three lead programs are asthma/allergy, Hepatitis C, and oncology.

ASTHMA/ALLERGY: MAST CELLS

Rigel's first drug-discovery program is focused on airway inflammation in asthma and allergic rhinitis. The company recently completed a Phase I study in the United Kingdom for its first product, a drug to treat allergic rhinitis, and has filed an IND to begin clinical testing in the U.S. The compound, R112, is the first of a new class of drugs that works against mast cells, a type of immune blood cell. Mast cells, when activated by exposure to an allergen, play a key role in initiating the inflammatory response in allergy and asthma. Rigel anticipates that R112 would be used to treat serious, chronic allergic nasal congestion, which is now most often treated with inhaled steroids. Building on its lead in drugs directed at mast cells, Rigel also is advancing a related compound for the treatment of asthma. The company plans to move this second product into clinical testing by the end of 2003.

HEPATITIS C

For hepatitis C, Rigel has identified a novel type of drug that, in initial laboratory studies, appears to block viral replication. This is significant because drugs currently on the market do not target the hepatitis C virus (HCV) itself but rather work to boost the immune system, often resulting in suboptimal treatment. A drug that directly attacks the virus could significantly improve treatment for the nearly 150 million people worldwide who are chronically infected with HCV. Rigel is nearing the completion of preclinical evaluation for its hepatitis compound and plans to begin clinical testing in the second half of 2003.

ONCOLOGY: LIGASES

Rigel's third lead drug-development program focuses on a new type of cancer target called ligases. These are enzymes that mediate the degradation of proteins, which in turn affects many important cellular functions, including cell division. In the past few years, ligases have become the subject of intense interest among oncology drug researchers. Rigel has a research and development program that the company expects will begin producing clinical candidates in 2004.