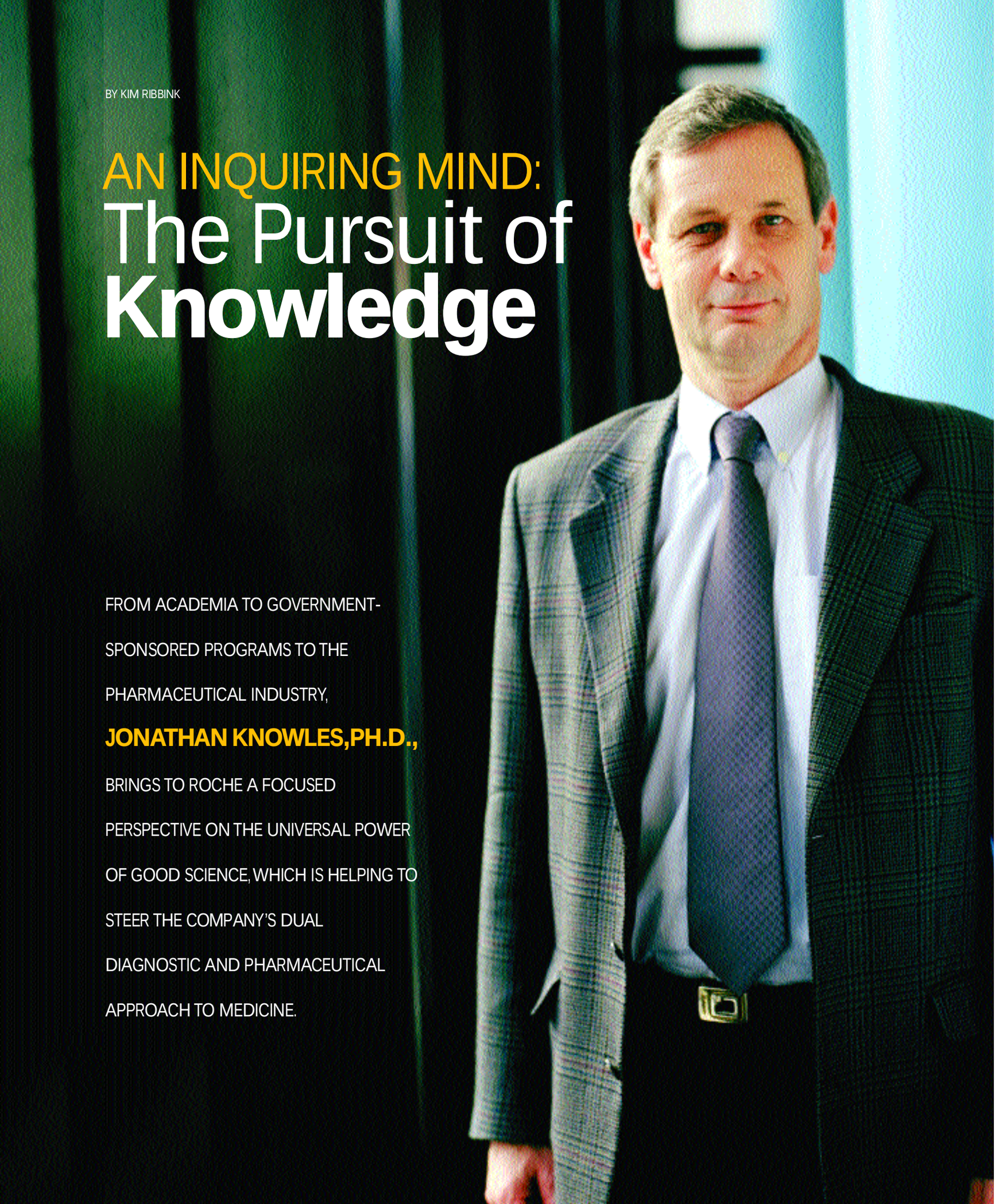
BY KIM RIBBINK

AN INQUIRING MIND: The Pursuit of Knowledge



FROM ACADEMIA TO GOVERNMENT-SPONSORED PROGRAMS TO THE PHARMACEUTICAL INDUSTRY, **JONATHAN KNOWLES, PH.D.,** BRINGS TO ROCHE A FOCUSED PERSPECTIVE ON THE UNIVERSAL POWER OF GOOD SCIENCE, WHICH IS HELPING TO STEER THE COMPANY'S DUAL DIAGNOSTIC AND PHARMACEUTICAL APPROACH TO MEDICINE.

THE PATH TO DRUG DISCOVERY IS EXTREMELY LONG AND COMPLEX, and according to Jonathan Knowles, Ph.D., director of global research at Roche, at the heart of that journey is good science. Dr. Knowles believes that good science is predicated on the basis of asking good questions and challenging long-held premises to influence the fundamental issues underlying medicine. Dr. Knowles also believes that good science crosses cultural boundaries and is a global rather than regional concept.

"Science and medicine are universal and people have the same motivations around the world," he says. "The difficulty of creating effective medicines often is underestimated."

During his career, Dr. Knowles has gained a global perspective and has been involved in most aspects of drug discovery having worked for academic institutions in Europe, Japan, and the United States. He also spent 12 years at a government-sponsored research center in Finland before taking a position at Glaxo in Switzerland. Today, he oversees research of the Roche Group and specifically the research at Roche's four centers of excellence, which are located around the world. His responsibilities take him from his base in Basel, Switzerland, to Japan, other parts of Europe, and the United States, where he spends about one week every month.

"I would like to think this exposure to different cultures gives me a broader range of possibilities of interaction; I am very comfortable in different cultural environments," he says. "For instance, I am as comfortable in California as I am in Japan, not to mention Switzerland."

Dr. Knowles' affinity for adapting to different cultural environments is a definite asset, as more than 56 nationalities are represented by the people who work in the company's Basel headquarters alone. For Dr. Knowles, this makes Roche the ideal place to work.

Roche employs more than 69,000 people worldwide and markets products in more than 150 countries.

Such diversity poses certain challenges, but these challenges have more to do with prioritization than with science, such as in deciding which area or areas to focus the company's research efforts on to benefit patients and the company as a whole.

"There's a growing understanding in the company that we can only be successful by working together," Dr. Knowles says. "Neither the company nor patients benefit if some areas are unbelievably successful and others aren't."

For Roche, working together means not only integrating ideas and strategies across departments and divisions within the company, but also with outside partners, be they industry, academia, or other entities. Only then, Dr. Knowles believes, can good science result in new and more efficacious medicines or other healthcare solutions.

Science and medicine are universal and people have the same motivations around the world. The difficulty of creating effective medicines often is underestimated.

The Mechanisms of SCIENCE

From an early age, Dr. Knowles was interested in the way things work — be they clocks or sailing ships — and consequently how to make them work better. That interest later translated into gaining an understanding of why people get sick and what can be done to make them better. The answers to many of those questions, Dr. Knowles says, lie in genetics. After completing an undergraduate degree in molecular genetics, he went on to receive a Ph.D. in mitochondrial genetics, which is the genetics of energy generation, investigating how biological systems generate energy.

"In the context of biology, genetics, if done right, provides the answers to why things go wrong or right in the context of a particular environment and often provides information about the environment," Dr. Knowles says. "This is one of the primary tools to understanding what's wrong and how to fix the problem."

His research at various institutions led Dr. Knowles to hypothesize that the most important problem to be solved in biology and medicine was gene regulation, which he believed would lead to the creation of better medicines. With that in mind, he spent a year in Finland working with a couple of groups on gene expression in Drosophila, a fruit fly. At this point in his career, fruit fly heat-shock gene expression was one of the best understood and provided the best opportunity to develop a novel approach for identifying the actual proteins, or switches, that turn genes on and off.

The plan was to take a position at the Albert Einstein Medical School in the United States after the year in Finland, but a broadly defined opportunity to lead a biotechnology group applying molecular biology to biotechnology was offered to Dr. Knowles. Unable to turn down such an opportunity, Dr. Knowles remained in Finland, spending a total of 12 years in the country, the majority of the time at the Biotechnical Laboratory of the Technical Research Center, a government-funded research center in Helsinki.

"I had a very exciting 12 years in Finland working on a range of scientific questions — from creating new antibiotics and peptides in medicines in collaboration with European pharmaceutical companies to improving the lager process involved with producing beer," he says.

Dr. Knowles says this experience taught him how to manage science and prepared him for his move into the pharmaceutical industry

as director of the Glaxo Institute for Molecular Biology in Geneva. As with the Helsinki position, Dr. Knowles says the job at Glaxo once again presented a fairly open-ended opportunity, this time working on applying molecular biology to drug discovery.

"Originally when I went to the Glaxo Institute, molecular biology was really about shuffling genes," he says. "Increasingly, it became clear that molecular biology, when combined with automation and sophisticated informatics, particularly epidemiology, could go further; molecular biology could actually help us to understand not simply why mice are different, but why people are different and why some people get some diseases and other people don't."

Dr. Knowles says his work in the area led to some exciting developments while at Glaxo, including the creation of the genetics division within the company's research and development unit. One of the achievements at Glaxo that Dr. Knowles is most proud of is his part in developing the Glaxo Institute in Geneva.

"During the 10 years I was at the Institute, the work equaled the output from some of the better academic institutes in Europe in terms of the publication and citation index," he notes.

According to Dr. Knowles, this was particularly important because the Institute was on the cutting edge in terms of influencing the future of medicine and the future of science.

The institute later was sold by Glaxo and is now the main research headquarters for Serono, one of Europe's biggest biotech companies.

While the work at Glaxo inspired Dr. Knowles, he believed there was one important

DR. JONATHAN KNOWLES

Inspirational Pursuits

IN AN EXCLUSIVE INTERVIEW WITH PHARMAVOICE, JONATHAN KNOWLES, PH.D., TALKS ABOUT WHAT INSPIRES HIM, HOW HE HOPES TO INSPIRE HIS COLLEAGUES, AND THE PARALLELS BETWEEN NATURE, RELAXATION, AND THE PURSUIT OF EXCELLENT SCIENCE.

WHAT IS IT ABOUT THE RESEARCH AND DEVELOPMENT PROCESS THAT YOU FIND MOST INSPIRATIONAL?

Good medicines and diagnostics aren't made by accident, but through the best possible science. I'm very excited by diversity and by excellence and the opportunity, in collaboration with my colleagues around the world, to work on some of the most exciting experiments in science and medicine. If my colleagues and I are successful, we bring relief of suffering to many millions of people around the world — that's inspiring.

ARE THERE PEOPLE WHO HAVE INSPIRED YOU AND HELPED LEAD YOU TO WHERE YOU ARE TODAY?

There are many, but if I start with my early career, my Ph.D. supervisor at the University of Edinburgh, Geoffrey Beale, who will be 90 very soon, taught me two things. One is the critical importance of asking the right question, and the other is with the right question genetics can provide the answer. In terms of management interfaces, my boss in Finland, Tor-Magnus Enari, taught me a lot about the management of science, the management of people, the management of different stakeholders, and how to manage large groups of scientists. He was a master.

HOW DO YOU BELIEVE YOU INSPIRE THOSE WITH WHOM YOU WORK AND WHO YOU OVERSEE?

I have a sense of optimism, which translates into very ambitious goals. When I moved to Finland there was a bit of reluctance. I had people tell me, "This is more difficult to do in Finland, you don't understand." My response was, "I simply couldn't care. We have marvelous resources, we have a fantastic environment here in Scandinavia, let's get on and do it." And we did. I have ambitious goals combined with a sense of optimism. And when I'm not under time pressure, I would like to think I'm fairly sympathetic and capable of listening to people.

GIVEN THE PRESSURES OF THE JOB, WHAT DO YOU FIND HELPS YOU TO RECHARGE YOUR BATTERIES AND MAINTAIN THE FOCUS THAT IS REQUIRED FOR THE COMPANY'S R&D SUCCESS?

I like to go for a quiet walk where I can see plants, animals, and birds; I find nature inspirational. There are a lot of parallels between plants in spring and companies expanding and societies being created, the redirection of resources, prioritization of leaves versus storage. I find biological metaphors very applicable to economics and society. I also like what I would call life-threatening activities, such as skiing, sailing, and flying small airplanes. I enjoy these because they demand intensity and focus. When I think about the bigger issues at work, these activities give me a broader perspective in terms of creating options and more ways of looking at things.

element missing: the application of of genetics to diagnostics. That emphasis on the dual roles of pharmaceuticals and diagnostics, he says, was one the major attractions to joining Roche.

Internal OVERLAPS

As director of global research at Roche, Dr. Knowles oversees the company's research strategy. Central to that is finding synergies for product development within Roche's pharmaceutical and diagnostics divisions.

Dr. Knowles says while a pharmaceutical and a diagnostic product may look very different and serve somewhat different purposes, the science underlying the creation of the two products is, remarkably, similar.

Dr. Knowles' ensures that there is an understanding between the two divisions so each partner understands how they might create products or derive benefits from accessing the other's understanding — both clinical and preclinical.

"We often find that we can form a joint group between diagnostics and pharmaceuticals to do the same experiment," he says. "For instance in oncology, we have a joint proteomics group whose mission is to identify patients who might be at risk of developing cancer so they can be treated early or physicians can identify which treatments would be most appropriate for which patients on the basis of the proteins found in the tumor or in the serum from blood samples."

The value of such collaborations is apparent from the research done at Genentech Inc. in the area of breast cancer. Roche is the majority shareholder of Genentech, which operates as a publicly traded, independent legal entity as part of the Roche group.

The discovery of HER2 (human epidermal growth factor receptor2), the protein found on the surface of cells, led to both a diagnostic and a medicine, Dr. Knowles explains.

While a pharmaceutical and a diagnostic product may look very different and serve somewhat different purposes, the science underlying the creation of the two products is remarkably the same.

In 1998, Genentech received approval from the FDA to market the humanized monoclonal antibody Herceptin as a first-line therapy in combination with paclitaxel and as a single agent in second- and third-line therapy for patients with metastatic breast cancer who have tumors that overexpress the HER2 protein.

Roche has exclusive marketing rights to Herceptin outside the United States.

Herceptin is designed specifically for HER2 positive patients and, as clinical trials have shown, careful selection of these patients results in improvement in survival, quality of life, and a better use of clinical resources. The availability of Herceptin means HER2 testing is an essential part of breast-cancer management today.

"The diagnostic gives the prognosis that a patient with a breast tumor overexpressing HER2 has, on average, only a three-year life expectancy, and those with a breast tumor that does not express HER2 have a life expectancy of seven years," he says. "In this case, one scientific discovery led to both a diagnostic and the medicine Herceptin. That's a piece of early genomics."

These types of dual projects are central to Roche's R&D endeavors and are helping the company identify not only the best medicines but also which medicine will benefit which patients.

"The challenge we have going forward is to identify which patients should get which medicine, and that's where diagnostics come in," he says. "The more precisely we can identify the right medicine for the right patient, the more efficient the healthcare profession becomes, and therefore the more research dollars we can devote to developing better medicines for other patients."

Roche already has found some further success with this strategy with Pegasys, a pegylated interferon, which was approved in the United States in December 2002. The FDA approved combination therapy with Pegasys (peginterferon alfa-2a) and Copegus (ribavirin) for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of

Genetic Research Successes Over Time

SINCE 1998. The collaboration between Roche and deCODE has resulted in the identification of genes associated with a multitude of diseases.

MARCH 1999. The companies announced progress in more specifically locating the chromosomal region where an osteoarthritis disease-causing gene is located.

AUGUST 2000. The companies announced successful mapping of a novel gene that contributes to late-onset Alzheimer's disease.

NOVEMBER 2000. The companies announced successful mapping of the gene linked to progressive arterial occlusive disease, a narrowing of the arteries of the arms and legs.

FEBRUARY 2001. The companies announced drug targets identified through analysis of a gene linked to schizophrenia, which was identified in October 2000.

cirrhosis (Child-Pugh class A). Pegasys and Copegus combination therapy was granted priority review designation by the FDA and Pegasys was approved as combination therapy for the treatment of adults with chronic hepatitis C (HCV) Oct. 16, 2002.

"We developed Pegasys using diagnostics, instead of looking at the efficacy of the drug at the end of the treatment, which takes a year," Dr. Knowles says. "We also looked at interim measures of success after three months. After three months we can evaluate individual patients to determine if they should continue taking Pegasys because the drug is treating HCV effectively. We also know if patients should stop, because the probability of successfully treating their HCV is small."

Dr. Knowles is passionate in his belief that the future of medicine is in the interplay between pharmaceuticals and diagnostics, and he, along with other senior executives at Roche, has helped drive that message throughout the company.

In 1997, Roche acquired the diagnostic and pharmaceutical businesses of the Boehringer Mannheim Group, creating the world's largest diagnostics company — Roche Diagnostics Corp. Roche continues to place significant focus on the diagnostics side of the business. This April, for example, Roche Diagnostics announced plans to invest $135 million and create about 600 new jobs at its Indianapolis campus during the next 10 years. In the next several years, the company expects growth and expansion of its research and development, laboratory, manufacturing, distribution, information technology, and corporate headquarters operations in support of five diagnostics business areas: diabetes care, central diagnostics, applied sciences, molecular diagnostics, and point of care.

External COLLABORATION

The science that comes out of a pharma or biotech company does not exist in a vacuum, but is rather the result of collaborations, partnerships, and understanding across industry, academia, and government-sponsored programs, Dr. Knowles says.

He warns against the tendency to regard the pharmaceutical industry as something of a world unto itself.

"The pharmaceutical industry, like other industries, is part of society; it exists to serve people," he says. "If an industry serves society well, it will be successful; if it doesn't it won't. At a fundamental level, it's very important for people in science, particularly in industry, to have a broad understanding of how science works in all parts of the world and different communities. It's extremely important for scientists in industry to understand the motivations and the constraints of academia to allow effective interface."

This deep-seated understanding of the power of collaboration in science has served Dr. Knowles well in his career. And it is a view that he has brought to, and shares with, his colleagues at Roche.

In recent years, Roche has stepped up its partnerships and collaborations and is now the industry leader in product-based deals and a leader in research or technology deals. Last year, through its newly formed licensing business development group, Roche entered into 25 partnerships in a variety of therapeutic areas.

One of the most groundbreaking collaborations is with an Iceland-based organization called deCODE, a biotech company created by a group of researchers to understand genetic risk in common disease. Dr. Knowles explains the partnership gives Roche access to deCODE's findings, which are extraordinarily detailed thanks to certain aspects unique to Iceland. (See box on page 54 for more details.)

"For 1,200 years, one of the main interests of people living in Iceland has been their genealogy; so the public domain has all of the family trees going back 1,200 years," he says. "Because Iceland is part of Scandinavia, the country has an extremely coherent medical database, so all medical information about all residents is stored in a coherent fashion, which is not true for many hospitals around the world let alone a whole nation. Under the leadership of Kári Stefánsson, who is CEO of deCODE, based in Reykjavik, the company has the largest genotyping center in the world. Putting all these things together, deCODE has been able to uncover many significant genetic risk factors."

The significance of deCODE's knowledge base is that healthcare professionals can identify people at risk for diseases, and researchers are better able to identify new drug targets to help treat or prevent those diseases.

This exchange of information works both ways. Many years ago, Roche acquired the rights to polymerase chain reaction, or PCR, a molecular biology technique that allows for quick replication of DNA, and decided to grant licenses across the board. That decision, Dr. Knowles says, ensures that PCR is broadly used for the benefit of science and medicine.

Increasingly, with the development of some new approaches in biology, the science of academia and industry are brought much closer together. Dr. Knowles offers as an example early work done on restriction enzymes, which started with studies into why some bacteria phages infected some bacteria but not others.

"The answer to that question gave birth to recombinant DNA and protein medicine," he says. "It's hard to imagine that starting off

MAY 2001. The companies announced the isolation of the gene causally involved in cerebrovascular disease, or stroke.

MAY 2001. The companies announced the successful mapping of a gene linked to type II diabetes.

SEPTEMBER 2001. The companies announced the successful mapping of a gene whose variant forms contribute to obesity.

SEPTEMBER 2001. The companies announced the successful mapping of a gene strongly linked to all forms of clinical anxiety.

NOVEMBER 2001. The companies announced the successful mapping of the first gene with genome-wide significant linkage to rheumatoid arthritis outside the major histocompatibility complex region.

JANUARY 2003. Scientists announced the identification of variations in a specific gene that confers significant increased risk of osteoporosis.

with an esoteric piece of microbiology would lead to protein medicines, but in fact it did."

With the advent of genomics and proteomics, the opportunities for collaborations have expanded since these tools are used in academic and industrial laboratories in much the same way.

Down the ROAD

The way forward, Dr. Knowles believes, can only lie in collaborative work, sharing information, and ultimately using genomics and proteomics to develop products that will tell scientists more about a disease and which medicines are appropriate for which patients.

At Roche, the momentum has been toward working with external partners and interdepartmentally to develop innovative new drugs to treat illness, as well as develop diagnostics that will help pinpoint the right medicine for the right patient. For example, in July the company is launching a gene chip to measure genetic variations in P450s, which essentially predict the metabolism of different drugs.

Among the products in Roche's pharma pipeline is R411, which is an integrin antagonist for asthma that is in Phase II trials.

"This is a medicine that instead of stopping the disease after it's started, in other words after the lymphocytes have infiltrated the lung, prevents lymphocytes from entering the lung," Dr. Knowles says. "We have very good primate data; we're now in the middle of a large Phase II study and in about nine or 10 months we'll know if the compound really works in people."

Also in Phase II is R667, which Dr. Knowles says appears to be very efficacious in reconstructing lungs affected by emphysema.

Roche also is looking at a drug currently indicated for the treatment of non-Hodgkins lymphoma, Rituxan (rituximab) — which is known as MabThera in Europe — as a therapy for rheumatoid arthritis.

"MabThera originally was designed through a collaboration between Genentech and IDEC to remove B cells, which is what non-Hodgkins lymphoma is," Dr. Knowles explains. "We're following some preliminary observations made in the United Kingdom. We've carried out a medium-sized Phase II trial, which demonstrated that when B cells are removed from rheumatoid arthritis patients there is a dramatic effect on the progression of the disease. The study switched the whole philosophy about rheumatoid arthritis away from T cells to B cells, at least in part. We're now awaiting the results of Phase III studies."

Other significant milestones for Roche are the company's plans to make two tons of Fuzeon this year. Fuzeon (enfuvirtide), which was created in collaboration with Trimeris Inc., is the largest synthetic peptide ever produced and is designed to block HIV fusion. The product was approved in March in both the United States and Europe and represents a new class of anti-HIV medications. Demand for Fuzeon is expected to be high.

These discoveries add to Roche's numerous therapeutic areas, which include anemia, cardiovascular diseases, central nervous system disorders, dermatology, genitourinary disorders, infectious diseases, inflammation, metabolic disorders, oncology, respiratory diseases, transplantation, and virology.

For his part, Dr. Knowles helps turn all this research into a successful reality by bringing several defining management characteristics to the table.

"One is an insistence that we define success," he says. "It's always possible to be more definite about what success looks like, and the clearer we are about how we identify success, the more likely it is that we will achieve success.

"The other defining characteristic is that I make sure that if there are benefits that one group or individual can bring to another that they work together because they will create more than if they work individually," he says.

Dr. Knowles says he is proud of the work done in research and development at Roche, adding that he believes the company has a portfolio that in terms of quality and quantity is one of the better ones in the industry.

The challenge going forward for the pharmaceutical industry as a whole, Dr. Knowles says, is creating safe medicines, and demonstrating the safety and efficacy of these medicines using all of the powers of modern science. ✦

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

Worldwide Journey

JONATHAN KNOWLES — RESUME

1997–PRESENT. President of Global Pharmaceutical Research, F. Hoffmann-La Roche Ltd.

1997–PRESENT. Member of the Genentech Board

1998–PRESENT. Member of the Corporate Executive Committee of the Roche Group

1995–1997. Research Director, Glaxo Wellcome Europe, responsible for all preclinical research at the four European sites at Verona, Paris, Madrid, and Geneva — 500 people

1989–1997. Director of the Glaxo Institute for Molecular Biology, Geneva, Switzerland

1986–1989. Research Professor and Head of Molecular Biology at the Biotechnical Laboratory, VTT, Helsinki, Finland

1980–1986. Head of the recombinant DNA group at the Biotechnical Laboratory, VTT, Helsinki, Finland

1979. Visiting Assistant Professor, Albert Einstein College of Medicine, N.Y. Appointed Docent of the University of Helsinki

1978–1980. EMBO fellowship to Department of Medical Chemistry and Department of Genetics, University of Helsinki, Finland

1975–1977. Royal Society European Exchange Fellowship at Centre de Génétique Moléculaire, CNRS, Gif-sur-Yvette, France, with Professor P. Slonimski and Dr. J. Beisson

1975. EMBO short-term fellowship at Centre de Génétique Moléculaire, CNRS, Gif-sur-Yvette, France

1973–1974. S.R.C. Post Doctoral Research Fellow with Professor G.H. Beale, F.R.S., Department of Genetics, University of Edinburgh, Scotland

EDUCATION

1973. Ph.D. in Genetics of Mitochondria with Professor G.H. Beale F.R.S., University of Edinburgh, Scotland

1969. 1st Class Honours Degree in Molecular Genetics, University of East Anglia, England

Scientific Advisory Boards and Review Committees