MICHAEL FAMULOK AND WALDEMAR KOLANUS

CHEMISTRY IN BIOLOGY: LIFE SCIENCES' FUTURE

Mingling of disciplines will greatly facilitate progress in the postgenomics era

It is estimated that the complete human genome will be known by 2003 or even earlier. Already, the various genome projects have generated an enormous amount of data. These data still have to be translated into a precise understanding of how genes and proteins function in normal and in diseased states. In the meantime, data-acquisition technologies such as multiplex sequencing arrays or so-called DNA chips have been pushed to very high standards. However, the development of similarly powerful technologies for the functional validation of biologically active molecules has not been able to keep up.

From these observations, it becomes evident that for the time being, looking at DNA—in whatever sophisticated fashion—will not suffice to address many disease-related cellular functions. There is an optimistic mood about the possibility to deduce relevant information about the role of a given gene in a certain disease largely, if not solely, by analyzing RNA or protein expression patterns and subsequently using intelligent bioinformatics. Although this process may be used at some point, there currently is no convincing, generally applicable concept of how it might be achieved. On the other hand, we believe that the precise tools of molecular dissection that come from the armament of chemistry will become indispensable to these endeavors. And when we say this, we refer to not the formulas of pills but the use of high-end research.

The sequence information of the various genomes currently is used broadly to identify regulatory patterns of gene expression. However, information derived from messenger RNA levels cannot be reliably connected to the function of the resulting protein. Proteomics comes into play at this point; it holds the promise that the shortcomings of comparing mRNA patterns may be overcome by analyzing whole-cell protein levels. Of course, this idea does not take into account the fact that many of the important carriers of information at the protein level—protein modification, for example—are not detected when the cellular expression of different proteins is compared.

One could think of ways to cope with these insufficiencies, but then another even more important argument muddies the waters: The very idea of interfering with signal networks that control important disease-related cellular functions relies on not all proteins of a given network being equally important. It is generally thought that information flux inside the cell is structured hierarchically so that there are centrally important checkpoint genes in pathways (for example, that control proliferation and apoptosis), and then there are more peripheral pathways. The quest is to gain functional information about the genes that are important.

All of the aforementioned approaches will be used to assemble invaluable databases. But then, the databases have to be exploited to gain functional information in a rapid, parallel, high-throughput fashion. The goal, therefore, must be to develop chemical probes that are able to target the function of a certain protein directly in the cell by an agonistic or antagonistic mechanism. Even more than that, optimally, they should also be able to directly identify the protein on which they act. At first, the use of antisense and RNA-interference tech-

CROSSING THE GAP **Kolanus (left), a biologist by training, and Famulok (right), a chemist by training, are focusing their talents at the interface of biology and chemistry in the belief that cooperative work will lead to insightful discoveries in the life sciences.**

CONTRIBUTING TO "NEW VOICES IN CHEMISTRY":

Samuel Abrash
David Adams
David Allen
Kevin Anderson
Kristi Anseth
Mark Aubart
Scott Auerbach
Shenda Baker
Kim Baldridge
Joe Barchi
Clifton Barry
Stacey Bent
Jeremy Berg
Debora Bergstrom
Carolyn Bertozzi
Philip Bevilacqua
Armen Boldi
Carsten Bolm
Joan Brennecke
Julia Burdge
Derrek Burrows
Mark Bussell
Gary Calabrese
Erick Carreira
Ben Chew
Dominic Chiapperino
Jean Chmielewski
Elaine Cohen-Hubal
Wilfredo Colón
Vicki Colvin
Jeanine Conklin
Pete Connolly
Robert Continetti
Fabrice Cornille
Virginia Cornish
Jeffrey Crow
Kit Cummins
Marcos Dantus
Mark Davis
Shannon Davis
Peter de Koning
Julio de Paula
Joseph DeSimone
Carl Decicco
Victoria DeRose
Todd Dickinson
Alexander Dömling
Peter Dorhout
Jennifer Doudna
Anne Eldrup
Christopher Evans
Michael Famulok
Dan Feldheim
Jerald Feldman
Shawn Feng
Richard Fitch
John Fourkas
C. Daniel Frisbie
Alois Fürstner
Brian Gibney
Susan Glassmeyer
David Goldstein
Carlos Gonzalez
Eric Green
Donna Griffin
Serge Halazy
David Hansen
John Hartwig
James Heath
Nicola Heron
Don Hilvert
Doug Hobbs
Edward Hodgkin
Amir Hoveyda
Jim Hutchison
Nancy Jackson
Mathieu Joanicot
Neil Kelleher
Shana Kelley
Shaheer Khan
Chaitan Khosla
Laura Kiessling
Waldemar Kolanus
Mary Korpusik
Roland Krämer
Tore Land
Tom Leckta

niques seem to fulfill all these demands: Oligonucleotides can be easily designed on the basis of genetic information, they can be introduced into cells, and they can efficiently interfere with gene function. However, this approach does not provide information about the quality of a protein as a drug target and whether it may be possible to target the protein antagonistically, let alone agonistically. The same argument applies for so-called reverse genetics and knock-out technologies. Instead, this kind of information can be achieved only by direct interaction with the protein target in the context of the living cell.

Looking at DNA—in whatever sophisticated fashion—will for the time being not suffice to address many disease-related cellular functions.

For such approaches, it is necessary to apply and further develop technologies by which molecules that fulfill these demands can be rapidly generated and applied inside cells—that is, molecules without any bias about their nature, whether they are easy to synthesize, or whether they can be directly applied as drugs. All they need to do is be functional in living systems and exert their function by agonistic or antagonistic mechanisms. Several approaches based on peptide or nucleic acid aptamers serving as high-affinity interactors for biomolecules are promising. These molecules may not immediately qualify as drugs—at least not in most cases—but they already can be applied in biological systems and used to obtain information about the function of a cellular target.

Synthetic organic chemistry in concert with molecular biology will further establish additional methods and tools for genomics, proteomics, ribonucleomics, metabolomics, transcriptomics, and whatever other kinds of "-omics" are still to be created. Chemists will increasingly concentrate on developing new synthetic approaches for the precise modification of biological macromolecules to expand the scope of molecular probes that are applicable to real-time analyses of cellular dynamics, biomolecular signals, and complex biological interaction networks in single cells as well as for the precise targeting of a certain cellular compartment.

The important required features of such molecules or families of molecules are straightforward generation of high diversity, bioapplicability, the ability to withstand evolutionary pressures in living systems, and recoverability from biological systems. They need not only be cells. The recent use of peptide aptamer/phage display libraries for probing vascular surfaces in living animals proves that such evolutionary methods are, in principle, fit to be applied even at the organismic level. Indeed, this has to be the goal: functional chemical probing of biomacromolecules in a context that really qualifies as "in vivo." Already, a fantastic amount of genetic information is available on various model organisms that should help initiate more endeavors in these promising directions at the interface between chemistry and biology.

In 1907, Emil Fischer pointed to exactly this strong relationship and fruitful correlation between these two disciplines: "In its early youth, organic chemistry was so closely connected with biology. I do consider it not only possible but desirable, that the close connection of chemistry with biology ... should be reestablished, as the great chemical secrets of life are only to be unveiled by cooperative work."

This wise statement is even more relevant today. The interface of biology, chemistry, and physics is perhaps the most dynamic and most rapidly growing area of science. We imagine that the increased collaboration of chemical and biological expertise will greatly facilitate and accelerate progress in the life sciences in the postgenomic era. Those researchers who are willing and able to cross the gap between chemistry and biology will be rewarded handsomely. They will experience the excitement that is created by gaining insights in both disciplines that would not have been obtained by either discipline alone.

Michael Famulok *is a professor of bioorganic chemistry and biochemistry at the University of Bonn, Germany. He received a doctoral degree in chemistry from the University of Marburg, Germany, in 1989. He completed a one-year postdoctoral fellowship at Massachusetts Institute of Technology followed by a two-year postdoctoral fellowship in the department of molecular biology at Massachusetts General Hospital and in the department of genetics at Harvard University. Famulok began his research career at the Institute of Biochemistry at Ludwig Maximilians University, Munich, Germany.*

Waldemar Kolanus *is an associate professor of biochemistry in the Gene Center at the University of Munich, Germany. He received a doctoral degree in biology from the University of Hannover, Germany, in 1990. He completed a three-year postdoctoral fellowship in the department of molecular biology at Massachusetts General Hospital.*