Health and Medicine: Challenges for the Chemical Sciences in the 21st Century

Organizing Committee for the Workshop on Health and Medicine, Committee on Challenges for the Chemical Sciences in the 21st Century, National Research Council

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CHALLENGES FOR THE CHEMICAL SCIENCES IN THE 21ST CENTURY

HEALTH AND MEDICINE

ORGANIZING COMMITTEE FOR THE WORKSHOP
ON HEALTH AND MEDICINE

COMMITTEE ON CHALLENGES FOR THE CHEMICAL SCIENCES
IN THE 21ST CENTURY

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Preface

The Workshop on Health and Medicine, held in Irvine, California, on December 2-4, 2002, was the last of six workshops that will make up the study *Challenges for the Chemical Sciences in the 21st Century*. The task for each workshop was defined as follows:

Each workshop—and its subsequent report—will address a series of common themes:

- Discovery: Identify major discoveries or advances in the chemical sciences during the last several decades.
- Interfaces: Identify the major discoveries and challenges at the interfaces between chemistry/chemical engineering and such areas as biology, environmental science, materials science, medicine, and physics.
- Challenges: Identify the grand challenges that exist in the chemical sciences.
- Infrastructure: Identify the issues and opportunities that exist in the chemical sciences to improve the infrastructure for research and education, and demonstrate the value of these activities to society.

The Workshop on Health and Medicine brought together a diverse group of participants (see Appendix D) including speakers on a variety of issues and challenges for the chemical sciences as they relate to health and medicine. The presentations served as a starting point for discussions and comments by the participants. The workshop participants were then divided into small groups that met

periodically during the workshop to further discuss and analyze the issues. Each group provided its discussions to the workshop as a whole.

This report is intended to reflect the concepts and opinions discussed at the Workshop on Health and Medicine; it is not intended to be a comprehensive overview of all the potential challenges for the chemical sciences in health and medical technology. Additionally, the report is a meeting summary and not a consensus report.

This study was conducted under the auspices of the National Research Council's Board on Chemical Sciences and Technology, with assistance provided by its staff. The committee acknowledges this support.

Douglas A. Lauffenburger
Christopher T. Walsh
Co-chairs,
Organizing Committee for the Workshop
on Health and Medicine

Acknowledgment of Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their participation in the review of this report:

Paul Bartlett, University of California, Berkeley
Cynthia Burrows, University of Utah
Joel Huff, Merck & Co., Inc.
Laura Kiessling, University of Wisconsin
Dorothy Margolskee, Prospect Ventures
Anna Maria Pyle, Yale University
Ian Tomlinson, Dow Chemical Company

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Gregory Petsko, Brandeis University. Appointed by the National Research Council, he was responsible for making certain

that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Contents

Executive Summary

The Challenges for the Chemical Sciences in the 21st Century Workshop on Health and Medicine was held on December 2-4, 2002, at the Arnold and Mabel Beckman Center in Irvine, California. The goal of the workshop was to identify and discuss new tools and approaches, new methods in synthesis and development, new directions in manufacturing and delivery, and major accomplishments and challenges in the chemical sciences relating to health and medicine. There were 12 speakers tasked to address their research areas and how they pertain to the workshop themes. The workshop presentations were as follows:

- "Systems Biology and Global Analytical Techniques," Leroy Hood, The Institute for Systems Biology
- "Structural Proteomics and Drug Discovery," Stephen W. Kaldor, Syrrx, Inc.
- "Challenges in Nucleic Acid Chemistry," Gerald F. Joyce, The Scripps Research Institute
- "Biochemical Complexity," Barbara Imperiali, Massachusetts Institute of Technology
- "Chemical Biology," Peter B. Dervan, California Institute of Technology
- "Biotechnology," Peter G. Schultz, The Scripps Research Institute
- "Synthetic Challenges," Samuel Danishefsky, Columbia University and Memorial Sloan-Kettering Cancer Center
- "Cell/Tissue Engineering," Linda G. Griffith, Massachusetts Institute of Technology
- "Bioinformatics," Sangtae Kim, Eli Lilly and Company
- "Drug Delivery," W. Mark Saltzman, Yale University

- "Medicinal Chemistry," Paul S. Anderson, Bristol-Myers Squibb Company
- "Bioprocessing," James R. Swartz, Stanford University

There were also breakout sessions in which participants in the workshop expressed their views about the various topics. The following report is a compilation of participant views and speaker presentations and is not intended to be a comprehensive review of research efforts in the area of health and medicine. Additionally, the report is a meeting summary and not a consensus report.

NEW TOOLS AND APPROACHES FOR DISCOVERY, DIAGNOSTICS, AND PREVENTION

The advancement of science in the health and medicine arena has brought about many new tools and approaches for drug discovery, diagnostics, and prevention of disease. There are a number of efforts underway to increase the throughput of DNA sequencers, which would allow for multiple genome comparisons. This technology could eventually give rise to predictive, preventative medicine based on an individual's genetic makeup. DNA is also being exploited for its informational and chemical properties to create nanoscale machines that will lead to powerful new approaches to chemical and biological problems. Although oligonucleotide drugs have been in existence for a number of years, it was only recently that viable drug candidates emerged to successfully treat disease. The increased understanding of their mechanism of action (e.g., role of antisense RNA and RNA interference in disease treatment) has led to new therapeutic candidates and better methods to minimize the unwanted side effects of these drugs.

High-throughput approaches, such as combinatorial chemistry, proteomics, and informatics, are now at the forefront of scientific discovery. These advances are a direct result of the development of new synthetic strategies and deciphering of entire genomes. The ability to effectively screen thousands of compounds in search of a lead target molecule has given rise to many new therapeutic agents. The highly automated nature of this approach has dramatically decreased the amount of time required to synthesize, purify, and characterize a compound. This has enabled researchers to pursue rational drug design. Parallel processing and miniaturization has also played a large role in decreasing the time needed to express and purify proteins. This, coupled with high-throughput microcrystallization techniques, has led to large-scale structure determination. In addition, recent advances in tandem mass spectrometry have allowed scientists to analyze protein expression from entire genomes, which has aided in identification of proteins expressed in response to various cellular stressors. There have also been advances in co-expression techniques aimed at deciphering intracellular localization and protein-protein interactions.

NEW METHODS IN SYNTHESIS AND DEVELOPMENT FOR PHARMACEUTICALS

Since the market for leading therapeutic drug classes is over $350 billion per year, there is a great demand to pursue new methods in synthesis and development. This demand must take into account the fierce competition in an industry that is experiencing considerable cost pressures. In the face of this challenge the ultimate goal of the pharmaceutical industry is to find safe, effective medicines. The traditional approach of the pharmaceutical industry is to identify a therapeutic target, link the chosen target to a defined biological mechanism, discover a lead compound that works by this mechanism, and optimize the lead for potency and selectivity of the biological activity. The increased use of outcome studies to establish the therapeutic value of new medicines prior to choosing a target has raised this process to a new level of sophistication. Once the target has been selected, linking this to a specific biological mechanism provides focus for the discovery effort. Identification of the lead compound has benefited from the advent of high-throughput screening methods that enable a large number of compounds to be screened in a relatively short time. Recent advances in stereoselective synthetic chemistry have better facilitated the making of lead analogs. These lead compounds can then be subject to a variety of substrate binding and toxicological tests to ensure the efficacy of the drug.

There have been many drug discoveries that illustrate how focusing on the action of a drug has facilitated the discovery process. This has been made easier by rapid structural analysis of target macromolecules by X-ray crystallography, NMR spectroscopy, and mass spectrometry.

On a macromolecular scale, research in tissue engineering has focused on the development of nonimmunogenic materials to serve as scaffolds for regeneration in damaged tissues. This technology is also being applied to generate skin for severe burn victims. There is current research in the development of synthetic bone grafts, which interact with cells in the body in a manner that attracts those required for healing. At present, polymer scaffolds can be used to grow bone and cartilage. The ultimate vision in the field of tissue engineering is to create artificial organs that can viably replace damaged organs and can be used in drug testing. A more tractable possibility is the development of tissue chips that can serve as a medium for tissue-specific drug testing. These chips comprise polymer-supported human cells that retain the functions normally associated with intact organs. The success of this technology would greatly enhance the efficiency of drug testing for therapeutics when sufficient animal models are unavailable. This could also eliminate the need for animal testing altogether, which would solve the long time ethical debates about using animal models for testing purposes.

NEW DIRECTIONS IN MANUFACTURING AND DELIVERY

With the rapid increase in the availability of biological information in the post-genomic era, there is an increased need to produce and deliver new pharmaceuticals and diagnostic systems. As new, complex chemicals are identified, challenges arise in the large-scale manufacturing and precise delivery of pharmaceuticals to the desired site of action. This challenge is further increased by the intense federal regulation of pharmaceutical manufacturing. The Food and Drug Administration not only must approve a drug but also the process by which it is made. A small change in manufacturing could lead to a reevaluation of the entire synthetic process, thus requiring further costly and time-consuming clinical trials. This is especially true for such biological compounds as proteins, since minute changes in manufacturing can lead to variations in post-translational modifications as well as possible tertiary structure modifications.

In response to the demand for decreased cost and increased efficiency of pharmaceutical manufacturing and delivery, many new advances have been made. Some of these include large-scale controlled cultivation of animal and plant cells, production of therapeutic proteins and first generation systems for their controlled release, development of more effective delivery methods of complex pharmaceuticals, and the development of improved membrane and chromatographic methods used in separation. There have also been considerable developments in theoretical, experimental, and computational techniques designed to increase drug yields.

There are a variety of new manufacturing processes that may provide promise in surmounting the obstacles present in modern pharmaceutical manufacturing. Hybrid manufacturing processes that utilize chemical synthesis as well as biocatalysis are being developed to remove potentially harmful forms of a pharmaceutical that are not therapeutically active. The directed evolution of proteins is facilitating the use of catalytic enzymes in nonaqueous environments. These processes are increasingly being developed simultaneously with discovery to reduce the time it takes for a product to reach the market.

ACCOMPLISHMENTS

In recent years there have been tremendous accomplishments by chemists and chemical engineers in the area of health and medicine. The discovery of safe and effective medicines in both the pharmaceutical and biotechnology industries is a testament to this. Some of these include angiotensin-converting enzyme inhibitors for hypertension and cholesterol biosynthesis inhibitors for the control of cholesterol levels. These advances would not have been possible without the application of biochemical and bioprocess science approaches. The design of scalable protein separation processes that are reproducible across many clinical trials has been critical to success in the biotechnology sector. In addition, advances in

diversity-oriented synthesis methodologies have produced both small focused libraries and very large libraries for screening new disease targets. Optimization of these combinatorial methods may aid in developing effective new therapeutics.

The chemical sciences have not only played a major role in drug discovery but also in drug delivery and disease pathophysiology. Novel controlled release devices fabricated from synthetic polymers have been instrumental in delivering organic and protein therapeutics to patients. Quantitative analysis of the cellular mechanisms of drug delivery, uptake, and degradation has led to significant advances. The modeling of these molecular processes in cells has aided drug delivery and provided insight into the mechanism of disease states.

The emergence of new molecular technology has provided a gateway to seemingly limitless exploration of chemical biology and biomolecular engineering, which are the fusion of chemistry and chemical engineering with the field of biology. The most prominent example of this is the decoding of the three billion DNA base pairs of the human genome. These new technological advances have changed much of the chemical sciences from hypothesis-driven science to discovery science. The enormous amount of biological information now available has enabled scientists to implement a systems approach to biological problems. It is now possible to employ a top-down approach when looking at biological processes. Chemical biology applies chemical-scale molecular approaches to elucidate biological processes. Small molecule inhibitors have been used in conjunction with protein engineering to investigate the biological role of a particular protein. These approaches offer promise for dissecting biological pathways, which may lead to future therapeutics.

CHALLENGES

Although there have been significant advances in chemistry and chemical engineering with respect to health and medicine, the ever increasing wealth of information in this area has posed significant future challenges for scientists. There are a myriad of complex biological processes that scientists have yet to understand. These processes will most likely become more complicated as science reveals more pieces of the puzzle. The committee has highlighted some of the challenges that were discussed in the workshop.

- There is a continued need in health and medicine for advances in synthetic techniques.
- Advances in measurement and imaging that improve understanding of biological function at the molecular level will aid progress in chemical biology.
- Advances that reduce the cost of bringing new drugs to market and lengthen the profitable lifetime of existing drugs are vital in providing the benefits of new developments to the public.

- Research in nanotechnology shows promise for impact in health and medicine.
- The development of an appropriate chemistry and chemical engineering curriculum is a challenge that must be met to adequately provide the education needed to do interdisciplinary research across the chemistry and biology divide.
- Innovation requires the sharing of information across novel technologies and chemistry and biological efforts. Therefore, improvements in data access, data management, and data manipulation are critical for future successes in health and medicine.

Perhaps one of the greatest challenges to the increasingly interdisciplinary fields of chemistry and chemical engineering is the development of a curriculum that can adequately provide the education needed to do research across the chemistry-biology divide. It is unclear whether current programs provide the background knowledge necessary to do interdisciplinary research. Scientists are required to know a tremendous amount of information to understand both chemical and cellular processes. There must be balance between the breadth and depth of knowledge between these fields. In addition to the education of scientists, there must be continued efforts to educate the general public about the importance and relevance of science at the interface of chemistry and biology. Educating the public about the significance of this work will aid in bolstering continued federal support for research in this area.

The pharmaceutical and biotechnology industries must continue to evolve to meet the ever increasing demand for safe, effective therapeutics. However, they must accomplish this goal while finding cheaper R&D alternatives and increasing their success rate, which must be accomplished in part by developing further advances in bioprocessing techniques that will provide faster time-to-market capabilities. More efficient processes must be created to decrease costs while maintaining new drug discovery.

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New Tools and Approaches for Discovery, Diagnostics, and Prevention

With recent advances in the chemical sciences there has been an explosion of information in genomics, proteomics, informatics, and high-throughput screening. This has led to an ever increasing need for new tools and approaches to effectively create and manage the large amounts of information that are being obtained in the postgenomic era. Concomitant with the increase in biological information, interdisciplinary fields have emerged in the chemical sciences in order to fully exploit all areas of research. One such field, systems biology, does not use the traditional reductionist approach to chemical problems. Instead the scientist looks at biological problems as the whole of its components, which is made possible by the various technological advances in the chemical sciences.

DNA SEQUENCING

New tools and technology in the chemical sciences have advanced DNA sequencing. The automated florescent DNA sequencer has led to the completion of the human genome project. There has been roughly a 6,000-fold increase in the throughput of DNA sequencing with a significant decrease in cost from its inception in 1986. There are current efforts to increase the throughput another 3,000- to 6,000-fold, which can be accomplished by single molecule DNA sequencing. This new approach will open the world of genomes to comparative analysis, which in turn will allow predictive and preventative medicine based on an individual's specific genomic makeup (see Sidebar 1.1).

There are other new and innovative approaches to DNA sequencing in development. The 2002 Nobel Prize winner in physiology, Sydney Brenner, has developed a technique whereby a million cDNA sequences can be affixed on separate

Sidebar 1.1
The DNA Sequencing Revolution
Excerpt from "Systems Biology and Global Analytical Techniques"
Leroy Hood
The Institute for Systems Biology

Since the 1986 publication of the automated fluorescent DNA prototype, an increase of approximately 6,000 times the throughput of DNA sequencing has occurred coupled to a significant decrease in cost. Applied Biosystems, a company set up to commercialize these instruments, then took nearly five years and $75 million to make the DNA sequencer a robust instrument. It took another 10 years and several hundred million dollars to create the high-throughput production line that led to finishing the human genome project. Extrapolation from today to five to seven years in the future yields another 3,000- to 6,000-fold increase in throughput and at least a thousand-fold decrease in cost. Therefore, an entire human genome could be sequenced in an afternoon for less than $10,000, a feat that opens up the whole world of genomes for comparative analyses and the possibility that we will do genetic mapping of humans by complete sequence analysis. As a result we would be able to characterize the three billion nucleotides of the genome instead of just the 300 or 3,000 features by genetic markers.

beads and amplified for 16 to 20 base pairs simultaneously in a flow cell. This results in roughly a million sequences in about six hours. This particular technique is important in analyzing a discreet transcriptome of a particular cell type. Another innovative approach to genome sequencing developed in the laboratory of Leroy Hood uses inkjet technology to synthesize oligonucleotide arrays. The current model has the ability to synthesize 60 to 70 mers in very high yield in a short time. This technology may lead to the synthesis of large genes or even gene families.

DNA NANOTECHNOLOGY

An emerging field that is attempting to exploit the information content of DNA is DNA-based nanofabrication. The idea is to achieve instructed fabrication by using the information contained in DNA to construct higher-order complexes and to control motion by using the chemical properties of the DNA. There are a number of examples of using DNA scaffolds to demonstrate controllable molecular motions. One such example used a DNA structural motif termed the

"paranemic crossover" that was able to rotate 180 degrees depending on which oligonucleotide was added to the solution. DNA nanotechnology is a promising new field of science that certainly will lead to powerful new approaches to chemical and biological problems.

NUCLEIC ACID THERAPEUTICS

Nucleic acid therapeutics was first proposed using antisense technology in the late 1970s. This technology has since evolved into preclinical and clinical trials. Antisense DNA binds to target mRNA through Watson-Crick pairing, which prevents the RNA from being translated into protein. The formation of a DNA-RNA heteroduplex initiates the enzyme RNase H to cleave the RNA portion of the heteroduplex. While theoretically sound, the advancement of this technology has been very slow. A newer approach using antisense employs the mechanism of RNA interference (RNAi). RNAi uses the ability of higher eukaryotic cells to cleave double-stranded RNA, presumably in defense of a viral infection. The double-stranded RNA is enzymatically cleaved into smaller fragments known as small interfering RNAs (siRNAs), which in turn initiate the cleavage of the mRNA that corresponds with the sequence of the siRNAs. RNAi technology is still not completely elucidated. In order for this technology to be effectively incorporated into a viable therapeutic alternative, RNAs must be inhibited from inducing an interferon response in the cell.

COMBINATORIAL CHEMISTRY

Combinatorial chemistry has emerged as one of the most productive new approaches to drug discovery. The technology of creating and testing large amounts of compounds to ascertain which ones contain the desired biological activity has spawned many new approaches to synthesis and design. It can provide access to ligands to probe a biological process (e.g., ligands that inhibit a target protein of interest, promote a phenotype of interest, or act as a sensor). Many new assays have been developed to effectively screen molecular libraries. The screens typically are immunoassays, enzyme reactions, cell-based assays, or any number of other specialized tests chosen for the specific disease or molecule being studied. The synthetic process in combinatorial chemistry usually employs many automated techniques, such as robotics, to synthesize thousands of unique chemical compounds or oligonucleotides with predetermined atomic structure that are categorized in a database or library. The ultimate goal of this technology in the area of health and medicine is to enable researchers to pursue rational drug design, whether using molecular libraries to discover new drugs or in oligonucleotide therapeutics. Combinatorial methods are now also being employed in the biotechnology sector in the areas of proteomics and bioinformatics.

STRUCTURAL PROTEOMICS

One of the fields of science that is benefiting the most from recent advances in the chemical sciences is structural proteomics, which is the global analysis of proteins. There are presently only about 15,000 structures deposited in the Protein Data Bank, of which roughly 4,000 represent unique protein folds spanning 1,500 protein families. Although these numbers are growing every day, the predicted number of protein families in our proteome is on the order of 20,000-50,000. These numbers depict the challenge that lies ahead for chemists and biologists in understanding the complex mechanisms in the human body. There are only a limited number of proteins that have been marketed due to structure-based discovery techniques. Timely access to molecular structures has historically been one of the major drawbacks. Parallel processing, miniaturization, and automation have greatly decreased the amount of time it takes from protein purification to structure determination. In particular, the use of robotics, nano- and picoliter-scale crystallization techniques, and high-throughput automated imaging systems to detect viable crystals has greatly increased the speed at which protein structures are elucidated. In nuclear magnetic resonance spectroscopy there has been limited success with automated structure determination programs. There have also been new advances in pulse sequences that greatly reduce the number of scans needed to obtain structural data under certain conditions, thereby decreasing costly data acquisition time. In addition, innovative tandem mass spectrometry techniques allow detailed characterization of proteins without having to undergo the potentially painstaking task of structure determination. These advances have dramatically improved efforts to look for biologically active compounds that thwart disease.

PROTEIN EXPRESSION ANALYSIS

Since there is no analog to polymerase chain reaction (PCR) for proteins, it is difficult to analyze the expression patterns of proteins in response to various phenotypic conditions. New techniques using mass spectrometry have been able to help associate protein expression with genomic DNA in response to various cellular stressors. A technique called “isotope coded affinity tagging” (ICAT) in combination with mass spectrometry was used by Leroy Hood and colleagues to analyze the galactose expression system and create a snapshot of the global interactions of a series of different systems present in a yeast cell. A protein engineering technique called Expressed Protein Ligation has been developed that introduces sequences of unnatural amino acids, posttranslational modifications, and biophysical probes into proteins of any size through the chemoselective addition of a peptide to a recombinant protein (see Sidebar 1.2).

Sidebar 1.2
Genetic Code Expansion
Excerpt from "Biotechnology"
Peter G. Schultz
The Scripps Research Institute

Every known form of life has the same genetic code containing the same common 20 amino acids, with a few rare exceptions. Logical questions from chemists may follow: "Why these 20? What would it be like if it were not these 20? If we find life on another planet, will the same 20 be present?" With only 20 amino acids there is a limitation with what can be done with proteins. Presently enough is known about these systems that they are actually amenable to chemical synthesis, but different starting materials in the cell need to be dealt with. If one wants to make proteins and change the genetic code of a living cell, the components of the protein biosynthetic machinery must be used: the DNA that transcribes the message that is translated on the ribosome by a set of adapter molecules, the tRNAs that translate the triplet codons in the genetic code, the polypeptide, and the amino acids in the polypeptide sequence.

Peter Schultz and colleagues have been successful at expanding the genetic code by incorporating additional amino acids. An *E. coli* that has a 21-amino-acid genetic code, in which the additional amino acid is benzophenone, is one example. A second example is the introduction of a keto amino acid: an important functional group in chemistry that was missing from the genetic code. Schultz and colleagues successfully added the keto group with fidelity of 99.99 percent. There is no difference between the benzophenone and keto amino acids and alanine, since the yields of protein are identical. Kilograms of proteins can be produced with these unnatural amino acids, allowing selective modification of proteins in the case of the keto due to the unique functional group. Furthermore, the unique genetic code can be modified with fluorescein to create a molecular-level probe. Schultz would like to create molecular resolution tags and probes that can be used to image any event in a living cell.

PROTEIN STRUCTURE ANALYSIS

Although protein structure determination is critical to understanding the process of an enzyme, it often does not adequately address real-time protein-protein interactions in vivo, which is imperative when attempting to decipher the inner workings of the cell. Co-expression tags can aid in detecting protein localization and interactions in the cell. Barbara Imperiali and colleagues have developed a new, less obtrusive class of expression probes that bind lanthanide ions to impart luminescent effects. This enables these co-expressed proteins to be monitored by

protein-protein interaction assays. The small size of these probes aids in minimizing any steric interactions between the probe and the proteins of interest.

MICROFLUIDICS

To circumvent the increasing cost and increase the efficiency of research and development in health and medicine, there is an increasing trend toward miniaturizing reactions and reaction conditions. Microfluidics is the study of reaction conditions and fluid flow in microenvironments. Many scientists are investigating this type of "lab on a chip" technology where compounds can undergo complicated reaction schemes in a microenvironment. This new technology affords the possibility of having multiple laboratory functions, such as purification, immobilization, sorting, and detection, carried out on a single chip, enabling the capacity to perform multiple parallel analyses in a faster and often more accurate microreaction.

MOLECULE DELIVERY

One of the challenges in studying intracellular interactions is successfully delivering the molecule of interest to its site of action. There have been many new approaches and advances in this arena. One such advance is in the area of caged phosphopeptides. Phosphopeptides that represent phosphorylation sites in various kinases have been designed to examine the effect of the liberated phosphopeptide on cell migration. Typically, the phosphopeptides can be cleaved by photolysis of the cage upon migrating to the site of action in the cell. Although promising, there is still much research to be done before this approach can be widely used in medicine. There are many new and innovative approaches to drug delivery that are currently under investigation.

2

New Methods in Synthesis and Development for Pharmaceuticals

Annual sales in the pharmaceutical industry have been growing in the double-digit range for many years. These numbers are expected to decrease in the future because of patent expirations on major products, pressure to reduce healthcare expenditures, larger spending on sales and marketing, and the increased cost of research and development. Because the market for the leading therapeutic classes of drugs is over $350 billion per year, there is considerable incentive to pursue opportunities for new drug discovery. These opportunities must be addressed, however, in the face of fierce competition in an industry that is consolidating and experiencing considerable pressure on pricing. These factors will require intelligent and efficient management of the significant risks and costs associated with pharmaceutical research and development.

Finding safe, effective medicines has always been the goal of the pharmaceutical industry. Better understanding of the biochemical mechanisms for diseases has improved the scientific basis for drug discovery. It is anticipated that genomics, proteomics, and bioinformatics will further enhance the drug discovery process by providing a more advanced understanding of disease processes and revealing new opportunities for successful intervention with drugs (see Sidebar 2.1). These new tools, along with others such as high-throughput screening, combinatorial chemistry, and micro array technology have required significant capital and human resource investments before the capture of clear value in productivity. Subsequently, costs and risk in drug discovery increase before it can be established that the new tools and technologies improve the efficiency of the process. This is a challenge for the industry because cost effectiveness and affordability of product are vital issues in drug discovery and development.

The pharmaceutical industry of today evolved largely from the chemical in-

Sidebar 2.1
The Trend toward Personalized Medicine
Excerpt from "Bioprocessing"
James R. Swartz
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The genomics revolution is working toward personalized medicine, requiring precise diagnostics and rapid, inexpensive drug production. Instead of providing one drug to serve a population, the possibility exists to provide multiple drugs to serve that population by being more specific to each individual patient. No product is on the market to capitalize on personalized medicine for any illness, and no technology exists that can provide rapid production, low cost, and high quality therapeutics. B-cell lymphoma provides an example; each patient has a different B-cell receptor, so each patient needs a different vaccine. The hypothesis is that if the variable region of the B-cell receptor can be expressed and fused to an immune-stimulating molecule and given to the patient, antibodies will be stimulated and attack the disease. Cell-free synthesis is being examined to potentially isolate the diseased cells to a DNA template in a few days, produce the protein in a few hours, then purify, formulate, test, and release the remedy in about one week. The result would be personalized medicine with the required reduction in time and expense.

dustry. As these roots would suggest, chemistry was a key component of early drug discoveries that were focused on pain management and the treatment of inflammation and infectious diseases. Advances in science related to the structure and function of DNA, as well as powerful methods for manipulating DNA and making proteins, has led to a more balanced partnership for drug discovery between chemistry and biology. Understanding the structure and function of these biopolymers has provided a common language for the partnership to use for strategic and tactical purposes. The result was a commonly used process for drug discovery. This process focused initially on four key points: (1) selection of a therapeutic target, (2) linkage of the chosen target to a defined biological mechanism of drug action, (3) discovery of a lead compound that worked by this mechanism, and (4) optimization of the lead for potency and selectivity of the biological activity. Pursuit of this scheme revealed the importance of including other considerations in the optimization process at an early time point. Thus, drug absorption, distribution, and metabolism (ADMET) and certain safety studies were incorporated into the selection process for potential drug development candidates. Questions related to "what the drug does to the body" and "what the body does to the drug" are addressed in this scheme. While these additional studies add time and expense to the discovery phase of the process, justification for this comes

from higher-quality compounds being entered into the more expensive development phase of the overall process that leads to a new drug.

Selection of a therapeutic target based on unmet or undermet clinical need is an important early step in drug discovery. Increased use of outcome studies to establish the therapeutic value of new medicines has raised target choice to a new level of sophistication. Third-party players may require a study of this type for reimbursement. Because outcome studies can be difficult to design and expensive to execute, it is important to carefully research this issue as part of the initial project proposal.

BIOLOGICAL PATHWAYS

The explosion of information regarding biological pathways, such as gene and protein expression, modulation and regulation, and cell signaling, raises the challenge of target selection to critical importance, given the immense effort required to discover and develop compounds. Once the therapeutic target has been selected, linking the target with a specific biological mechanism for drug action provides focus for the discovery. To accomplish this goal it is necessary to identify the relevant biological assays. An example is provided by the work that led to the discovery and development of HIV protease inhibitors for treatment of HIV infection. This viral enzyme is required for replication. A cell-free assay in which enzyme inhibition could be measured was used to define the biological mechanism of drug action. Compounds that were active in the enzyme assay were then evaluated in cell culture systems that were subjected to HIV infection. Compounds that act by this mechanism and can achieve an adequate concentration in these cells would be expected to inhibit viral replication in a concentration-dependent manner. Thus, data from these two assays provided a useful coupling between the mechanism of drug action and the expected response. Medicinal chemists used data from these assays to guide progress from early lead compounds to clinically effective drugs.

SCREENING

Leads for drug discovery are frequently identified by screening collections of compounds available from synthesis or by isolation from natural sources. In that these collections or libraries of compounds may be large (> 100,000), high-throughput screening methods and equipment have been developed to facilitate the work. In certain cases it has been possible to generate a lead by modifying the structure of a substrate involved in the biological mechanism that is being studied. Medicinal chemists who use synthetic organic chemistry and a variety of design tools and techniques pursue optimization of lead molecules for therapeutic properties. The two central issues faced by the medicinal chemist are “what to make” and “how to make it.” The how-to-make knowledge is derived largely

from synthetic organic chemistry. Because many drugs have at least one stereo center, recent major advances in synthetic methods addressing this issue have been of particular importance to medicinal chemistry. Parallel methods for rapidly making analogs of leads have been useful in some cases. Multiple factors are involved in deciding what to make. In as much as most drug molecules interact noncovalently with their macromolecular targets, steric, electronic and solvation factors make important contributions to the interaction energy. Design of biologically active molecules is not an exact science. Nonetheless, structure activity relationships derived from laboratory experiments and modeling data frequently contribute to the decisions about which drug to pursue. More recently, information obtained from NMR and X-ray structures of target macromolecules with and without complexed ligands has aided the design process.

While design of drug-like molecules for target affinity and selectivity is important, these molecules must also be optimized for pharmacokinetic, metabolic, physical, and toxicological properties. As a result, p450 metabolic profiling, cassette dosing in animals, cellular toxicity measurements, and the assessment of protein binding and solubility properties have become routine in the ranking of candidate compounds. The inclusion of these studies in the early phase of drug discovery has improved the quality of compounds selected for further development work. Because of their value, these data have rapidly become a significant part of the information base used by medicinal chemists to recommend compounds for development.

MECHANISM OF DRUG ACTION

Focusing on the mechanism of drug action has facilitated the discovery process. Angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists have greatly improved therapy for the treatment of hypertension. Better control of cholesterol biosynthesis through the use of HMG-CoA reductase inhibitors has reduced the incidence of coronary heart disease by more than one-third. Bone resorption inhibitors have provided effective therapy for the treatment of osteoporosis. Leukotriene receptor antagonists have improved the quality of life for patients with asthma. Serotonin agonists with receptor subtype specificity have provided effective treatment for migraine headache. Improved therapy for depression and schizophrenia also has been derived from agents that have receptor subtype profiles that differ from earlier drugs of these types. The discovery of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors has dramatically improved prospects for patients infected with HIV. While the therapeutic advances of the last quarter-century are impressive, many opportunities and challenges remain. Better drugs are needed to treat cancer, dementia, obesity, diabetes, and infectious diseases. As this short and certainly not all-inclusive list would suggest, there is no shortage of opportunities for new drug discovery.

Organizational structures and relationships that will facilitate teamwork and open sharing of information must be developed and used in order to achieve success in the complex world of drug discovery. The workforce must be able to function as an interdisciplinary team, consisting of chemists, biologists, and scientists who specialize in molecular modeling, computational analysis, structure determination, drug metabolism, pharmaceutics, safety assessment, and all aspects of informatics. Because there are many tools that the team uses, such as high-throughput screening, combinatorial chemistry, genomics, and proteomics, produce large amounts of data, the team must have access to the resources needed to process this information. Open access to all information is important to encourage boundary crossing in the search for innovative solutions in each drug discovery project.

Structural analysis of target macromolecules using protein X-ray crystallography and NMR spectroscopy has already had a positive impact on drug design. Powerful computational programs and modeling techniques have enhanced the utility of these methods. It is likely that this trend will continue as new science evolves. Mass spectrometry, particularly in the fields of bioavailability and metabolism, has been key to rapidly obtaining information that is very useful in the candidate optimization process. While the promise of proteomics, genomics, and bioinformatics is yet to be realized, the potential of this new science to significantly facilitate drug discovery is real. The continuing advances of synthetic organic and analytical chemistry are also important to the pharmaceutical industry. Advances in parallel synthesis have the potential to rapidly expand the diversity of compounds available for study as new drugs. New chemistry that makes production of drugs more efficient has obvious commercial value. Continuing investment in all of the science that supports the advancement of knowledge at the interface between chemistry and biology is critical to achieving the full value of what we have already learned.

TISSUE ENGINEERING

Research in tissue engineering has focused on developing nonimmunogenic materials to serve as scaffolds for regeneration of damaged tissue. This technology is now being applied to generate skin for severe burn victims to decrease the time required for healing and in cases where the damaged area is too large to cover with normal grafts of skin from another part of the patient's body. One relatively low-cost approach uses an "artificial skin" to cover the burned area. The need for skin grafts and scarring is greatly reduced. Another approach uses "living skin," a synthetic matrix with cells in the matrix, but the current cost of this material renders it impractical and cannot yet compete with approaches that do not involve the external use of cells. There are many potential applications of the technology that will require the development of new polymer matrixes with

superior properties that will be absorbed or encourage adhesion of the appropriate cells and permit the development of blood vessels for oxygen transport.

Research is underway to develop materials for synthetic bone grafts. Patients with osteosarcoma often require removal of large sections of bone. Currently the only option for replacement is cadaver bone. These grafts carry the potential of disease transmission, require an available source of replacement bone, heal slowly, and are weaker than the bone that was replaced. A totally synthetic scaffold for growth of new bone will need to interact with cells in the body in a manner that attracts those cells required for healing to the wound site (e.g., the cells for depositing bone and those for forming the blood vessels needed to carry oxygen to the new tissue). This might be accomplished by designing new materials that interact with adhesion receptors on cells and the development of drugs that promote cell migration and proliferation. The set of molecular tools available is limited at this point, and additional work is needed to identify and characterize new receptors and molecules that stimulate cell migration and growth. The ligands that interact directly with cell surface adhesion receptors must be clustered to achieve their maximum effect. New synthetic procedures are needed to produce biocompatible polymers for which the concentration and presentation of ligands for adhesion of specific types of cells can be precisely controlled.

Polymer scaffolds can be used to grow bone and cartilage at the present time. One of the visions in the field of tissue engineering, which is well beyond the capabilities of current technology, is to be able to grow organs such as a kidney, heart, or liver on polymer templates. Fully developed organs are large complex structures with a complex vascular network to deliver oxygen and nutrients. Early experiments have highlighted problems associated with supplying oxygen to cells as newly growing tissue becomes more than a few microns thick.

A more tractable application of the technology for growing heart, liver, kidney, or lung tissue may lie in the development of "tissue chips" for drug development. For example, hepatitis C is the leading cause of liver transplants in the Western world. Attempts to develop new drugs for hepatitis C have been frustrating because the virus infects only humans and chimpanzees and efforts to propagate the virus outside animals have been unsuccessful. In a related vein, liver toxicity from drugs such as acetaminophen or consumption of poisonous mushrooms can result in death. The mechanisms that lead to necrosis and death are just now being elucidated in mice. Related studies cannot be done in humans, and an understanding of these diseases is being hampered by the lack of good models for how humans, not mice, respond to infection, or to the chronic or acute insults that result in liver damage. Similar problems are encountered with other organs.

The development of tissue chips comprising polymer-supported human cells that retain the functions normally associated with intact organs such as the liver would allow drug development to proceed with human tissue rather than resorting to animal models. Several advantages of such a development are immediately

apparent. For example, research related to drug development and toxicity assessments would not require the heavy reliance on the current practice of test animals. Ultimately, costs for drug development could be lowered, the effects of drugs on specific human tissues could be readily assessed, and ethical concerns about the use of animals in drug screening would be eliminated. In any event, the technological problems to be solved are immense. A liver cell only remains a liver cell when it is in constant contact with its neighboring hepatic cells. Without the constant signals that cells get from their neighbors, they loose their sense of place and the related behavior they exhibit in intact tissue. One possible approach is to perfuse matrix-supported cells with the appropriate signaling molecules. How closely their properties mimic those of cells in an organ could be assessed by transcriptional profiling. The first step would involve chips consisting of a single cell type, but normal tissue often contains several different cell types and ultimately one would want to construct complex matrixes containing all the cells found in the tissue in a proper spatial arrangement.

Several hurdles must be overcome to develop this technology. A new generation of three-dimensional materials must be synthesized that permit different cell types to bind to specific regions of the support with high spatial selectivity. Small molecules that support the signaling between cells typically found in organs must be identified and synthesized. Manufacturing techniques must be developed to make the technology cost effective. The scientists and engineers who develop this technology must have a firm base in chemistry and chemical engineering and be broadly trained so they understand the special challenges posed by working with tissue. Most undergraduate and many graduate programs are not designed for the breadth of exposure needed to tie together such different fields while retaining the in-depth training in a subdiscipline. Thus, the curricula offered by colleges and universities will also need attention.

ACCESS TO INFORMATION

More than ever innovation requires the sharing of information across novel technologies, chemistry efforts, and biological fields – information that becomes fragmented when spread across academic labs and small biotech companies. Dealing with fragmentation of scientific knowledge is critical for future successes in the fields of health and medicine. In addition to keeping abreast of new insights, access has become a challenge. One solution has been to place information in the public domain (although protecting intellectual property often delays disclosure or constrains use); another has been to establish cross-company and -university alliances. The need for biotech alliances with large pharmaceutical companies is acknowledged by small private companies, both for the shared learning and financial support that large partners can provide. From the large pharmaceutical perspective, “enabling technologies” have been fair game for licensing-in for

many years. A more recent revelation is that alliances of small biotech companies and universities are equally important to bring chemical and biological innovation into large pharmaceutical companies. In a similar vein, collaborations across small biotech companies and universities may become much more the norm for cross-discipline integration. Current alliance structures are not efficient; new approaches are needed.

3

New Directions in Manufacturing and Delivery

Manufacturing and delivery are integral parts of the expensive, risky, and lengthy drug development cycle (roughly 15 years and $800 million for a new drug) regulated by the Food and Drug Administration. The cost of pharmaceuticals to U.S. consumers is rising rapidly (15 percent per year) and is a major factor in the rate of increase in healthcare costs. There is pressure to control prices of pharmaceuticals, which requires more efficient systems for drug development, manufacture, and delivery. Advances in chemical technology are effectively shifting healthcare cost from medical labor to medical technology. Considerable progress has been made in the last 20 years in manufacturing and delivery of pharmaceuticals and biomedical devices.

A major opportunity to control costs resides in more efficient processes for manufacture of new pharmaceuticals and development of new delivery systems that release drugs at a target site, at a predetermined rate, over a predetermined time. Spatial and temporal control of drug delivery may extend the life of older drugs by avoiding side effects while delivering higher concentrations to a local site. Extending the useful life of a pre-existing drug may reduce costs as well. Diagnostic systems that identify disease earlier will likely reduce treatment costs by requiring less drugs and other medical intervention.

Recent advances that have improved manufacturing and delivery include development of

- large-scale, controlled cultivation of animal and plant cells;
- efficient production of therapeutic proteins and first generation systems for their controlled delivery;
- more effective methods for synthesis of new and more complex pharma-

ceuticals, such as solid-phase synthesis, chiral catalysts, oligosaccharide chemistry, catalytic antibodies, and enzymes better adapted to specialized environments;

- improved membrane and chromatographic methods to separate and purify complex molecules more effectively;
- theoretical and experimental techniques to engineer cellular metabolism ("metabolic engineering") in order to produce biochemicals at higher yields or novel products;
- biomaterials that act as scaffolds for tissue engineering or as improved matrixes;
- computational and bioinformatic tools to assist in drug discovery and in development of manufacturing processes; and
- first generations of tissue-engineered products (artificial skin and cartilage).

MANUFACTURING CHALLENGES

The challenges to the manufacturing process arise from the increasing cost of R&D, the need to develop information systems that exploit benefits from genomics and bioinformatics, pressure on pricing and fierce competition in the industry, the relatively inefficient output of new products due to failure in clinical trials, technical barriers for targeted delivery, and the crude ability to control complex biological processes such as cellular differentiation and organization. While many of these challenges apply to both pharmaceuticals made by chemical synthesis and bioprocesses, there are also separate issues based on mode of manufacture. Production of therapeutic proteins from mammalian cells is particularly challenging. Many of these new products require intricate post-translational processing steps (e.g., addition of oligosaccharides) to be effective. Currently we do not understand how to scale up these processes to maintain uniform glycosylation (i.e., same oligosaccharide modifications) at all scales of production. Many of these products, such as therapeutic antibodies, may be required in large amounts. These current production processes are inefficient and require large facilities.

Overcoming these challenges will require a better understanding of how culture conditions can be manipulated to improve productivity in mammalian cells while maintaining a consistent product, or we must seek alternative production systems. Examples of alternative systems include yeast (*Pichia pastoris*), insect cell systems, transgenic plants, or transgenic animals. All of these alternatives present barriers in terms of authenticity of the product (e.g., human-like form), cost (especially for transgenic animals), and ability to meet regulatory standards for reproducibility. Additionally, use of transgenic animals brings up the unresolved issue regarding the potential of contamination (e.g., prions) from diseased animals to patients and the fact that prions are extremely difficult to detect analytically.

There are also manufacturing challenges related to nonprotein natural prod-

ucts from plants and marine organisms. While one example of a large-scale (75,000 L) bioreactor system exists (for production of the anticancer agent Taxol from plant cell culture), extension to other valuable, complex, nonprotein pharmaceuticals is yet to be established. Many marine products, particularly from marine bacteria and algae, show promise in clinical trials. Some of these compounds are too complex for large-scale production using traditional synthetic organic chemistry, and established methods for large-scale culture of the producing organism do not exist. In some cases the metabolic engineering of easy-to-grow cells may provide an effective alternative. The ability to do rational metabolic engineering needs to be improved through a more fundamental understanding of cellular metabolism and its interaction with the external environment.

In other cases hybrid manufacturing processes, the practice of combining chemical synthesis and biocatalysis (e.g., enzymes), are being developed to produce pharmaceuticals of increasing purity (particularly chiral purity). Removing potentially harmful forms of the pharmaceutical that are not therapeutically active is increasingly important. In many cases biocatalysts must be modified to perform satisfactorily in a nonbiological environment (e.g., in the presence of high levels of an organic solvent). The availability of such biocatalysts is often dependent on advances in protein engineering (e.g., "directed evolution"). Another biomanufacturing challenge is the production of organized tissues using tissue engineering. While processes to produce tissue-engineered skin have been commercialized, it is clear that the economic viability of these manufacturing processes must be improved. An increasingly more precise understanding of how to manipulate cellular organization and differentiation will support development of more effective manufacturing processes. Further, challenges in the manufacturing process are an effective separation, on a large scale, of complex and sensitive molecules. While both chromatographic and membrane methods have greatly advanced and are particularly important for the recovery and purification of therapeutic proteins, new advances will be needed to increase throughput and efficiency while reducing cost. Many of these advances will come through new materials and modes of operation.

The manufacturing process needs to be identified early in the drug development process. With advances in combinatorial methods and genomic technologies, the number of possible drug leads has expanded dramatically. Advances in high-throughput screening and parallel synthetic methods, coupled with the ability to generate crystal structures or nuclear magnetic resonance structures of a protein target with and without a ligand, place synthetic chemists in a position to contribute further to generation of more chemicals for evaluation as possible pharmaceuticals. Consequently, methods to predict which of these drugs are going to be effective in the clinic are increasingly critical. Bioinformatics and computational modeling are expected to play increasingly significant roles in drug target validation, including preclinical pharmacology and toxicology. In fact, early attempts to combine discovery with simultaneous optimization of potency, selec-

tivity, optimization of Adsorption-Distribution-Metabolism-Elimination-Toxicity (ADMET), and safety is the key to reducing the time from discovery to product (which may dramatically decrease cost). Formation of such human surrogates can improve the fraction of drug leads that become actual products.

NEW DELIVERY OPPORTUNITIES

New technologies are being developed to deliver drugs to people more effectively and safely. Synthetic polymers are being used as a delivery system for drugs. They are biocompatible, which means that material can be implanted into tissues with little biological response. For example, ethylene-co-vinyl acetate, an industrial polymer, is inert when implanted in tissues throughout the body. It is hydrophobic, biocompatible, and nondegradable. These kinds of materials last a long time in the body, do not change, and can be used to make physical matrixes in which a drug of interest is encapsulated or dispersed throughout a continuous polymer phase. The five-year implantable birth control system Norplant is the best known example. One of the major advances over the last few decades has been to miniaturize these systems and make them into tiny particles that can be injected. This is usually accomplished with degradable polymers such as poly (lactide-co-glycolide), which will degrade over the course of several months once exposed to water. One can change the rate of release of the drug from this material by changing how it is fabricated. These particles can be injected and used to release drugs locally. It is now routine to make ~1 micron particles that have functional DNA within the solid matrix.

Biomedical imaging is a technology that will greatly impact drug delivery. Two-photon microscopy has been used to visualize the dynamics of nerve growth hormone (NGF) diffusion in brain slices, for example. These direct measurements allow for monitoring of mechanisms of transport in the tissue and recording changes that occur with conjugation of the protein. NGF and other proteins can be stabilized in tissue by conjugation to polymers such as polyethylene glycol (PEG). Another method for increasing the effective volume of treatment is to split the delivery system up into small units and spread them out over a larger volume. By changing the spacing between the units, one could spread out active agent over some larger volume in the brain, being careful not to get the sources too far apart leaving regions untreated. This is another opportunity to match drug delivery systems with imaging science. Many diseases are not only local, but occur in complex geometries. In these cases, one could envision approaches in which multiple microscopic delivery systems are arranged into a spatial configuration that matches the disease process.

Knowledge of material synthesis from the microelectronics industry can be used to create smarter delivery systems (see Sidebar 3.1). For example, people have been using electronic materials in the brain for a long time. These materials can be made into drug delivery systems by putting microfluidic channels into the

Sidebar 3.1
Smarter Drug Delivery Systems through Microelectronics
Excerpt from "Drug Delivery"
W. Mark Saltzman
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Material synthesis knowledge from the microelectronics industry could be used to make smarter drug delivery systems. For example, electronic materials, such as stimulation recording devices and neuroprostheses, have been used in the brain for some time. These materials can be made into drug delivery systems by putting microfluidic channels into the material. Drug delivery can proceed by injection of fluids; tight control over delivery can be achieved due to external control with a fluid phase. Another approach is to enable the material to turn delivery on and off at various times. With DNA, for example, a microelectrode in the material can be used to create a local voltage difference that modulates the rate of release of the drug from the material: the drug releases quickly when the voltage is on and slowly when the voltage is off. One of the advantages of the overall approach of using microelectronic materials is that the drug delivery system can be easily combined with a probe that senses local conditions, such as local conditions of voltage or chemistry, allowing release of a drug in response to that local condition.[1]

[1]Saltzman, W.M., Olbricht, W.O. 2002. Building drug delivery into tissue engineering. Nature Reviews Drug Discovery 1:177-186.

material. Drug delivery can proceed by injection of fluids; tight control over delivery can be achieved because it is controlled externally with a fluid phase. Another approach is to enable the material to turn on and turn off delivery at various times. With DNA for example, a microelectrode in the material can be used to create a local voltage difference which then modulates the rate of release of the drug from the material: drug releases fast when the voltage is on and slow when the voltage is off. One of the advantages of this overall approach—using microelectronic materials—is that the drug delivery system can be easily combined with a probe that senses local conditions, either local conditions of voltage or chemistry, allowing release of a drug in response to that local condition.

DELIVERY CHALLENGES

Significant drug delivery challenges still exist. Intracellular delivery is an important problem because of the difficulty of getting DNA into cells. The gen-

eral approach has been to try to complex DNA with something (usually a lipid or a polymer) in order to make complexes that can enter the cell. However, once in the cell, there are other barriers. Internalized DNA often ends up in endosomes where it can be digested. There is a trend now to focus on designing systems in cell culture in situations where particles can be delivered immediately adjacent to the target cell. That is rarely going to be achievable in real tissue. There is evidence that approaches such as using receptors for targeting or using pH-dependent materials to trigger release from the endosome at the right time might be useful. Alternately, polymer particles that are ~100 nm in size can also be used to deliver agents directly to the cytoplasm of the cell. One of the advantages of this approach is that agents can be released intracellularly over time.

Degradable polymers have been in use for years and much is known about assembling them with different classes of drug molecules. However, since the methods of fabrication remain imperfect, one usually obtains a complex mixture of particles of different sizes and shapes. Matching methods of particle formation with drugs has been one of the major challenges in this area. Many different ways to make small particles are now in the literature. Unfortunately few of these methods are compatible with most drugs. Finding better ways to make controlled particles that are compatible in drug incorporation is a challenge for the future.

While injection remains the primary route for protein delivery, oral or pulmonary delivery would be less expensive and more convenient for the patient. Oral delivery for proteins requires stabilizing the protein while it passes through the stomach followed by selective uptake through the gastrointestinal tract and into systemic circulation. While some success has been observed (e.g. edible vaccines from plants where the plant material may provide protection through the stomach for a sub unit vaccine), oral delivery is still problematic. Pulmonary delivery has also shown early promise, yet issues such as the control of particle size remain barriers to a generally effective system. No generally effective method for gene therapy exists today. Although nucleotide delivery in both viral and nonviral vectors can lead to transfection, obtaining the correct dose in the right location and time frame without disturbing other cellular processes remains an elusive goal (e.g., induction of cancer due to loss of control of cell cycle arrest).

4
Accomplishments and Challenges in Health and Medicine for Chemistry and Chemical Engineering

ACCOMPLISHMENTS IN CHEMISTRY

Chemists work on molecular-scale phenomena, meaning they discover molecules that exist in nature and invent both new molecules and new materials. The molecular perspective of chemistry is fundamental to explaining complex behaviors of biological systems. Therapeutic molecules, generally small organic molecules, are the medicines that change the course and progression of many human diseases. Some of the recent contributions of chemical science to advances in health and medicine were discussed at this workshop and are summarized below.

The discovery and development of safe and effective medicines by teams of medicinal chemists in the pharmaceutical and biotechnology sectors have progressed rapidly in recent years. Some of these medicines include angiotensin-converting enzyme inhibitors for hypertension and rate-limiting enzyme inhibitors in cholesterol biosynthesis by the statin class of drugs for the control of cholesterol levels. There have also been improved therapeutics for depression and schizophrenia by receptor subtype specific ligands, as well as the HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors for the treatment of AIDS.

New medicines require new molecules, which emerge from chemical synthesis of natural products, synthetic chemical libraries, and rational design. Molecules that arise from nature teach architectural complexity and functional group density, which has evolved into a valid utility in biological systems. Some examples include lactams, statins, macrolides, taxanes, and anthracyclines. The advances in diversity-oriented synthesis methodologies have produced both small focused libraries of specific scaffolds and large libraries numbering mol-

ecules in the millions as sources for screening new disease targets for therapeutic leads. The rational design of new compounds has given rise to breakthrough products such as Gleevec, which is the first rationally designed molecule to do specifically what is was designed to do (inhibit Abl-family kinases). The continued advances in synthetic organic chemistry of both natural products and complex libraries have provided many advances in the treatment of numerous diseases and ailments.

New molecular technology, such as the invention of polymerase chain reaction (PCR) and DNA sequencers that can decode millions of DNA bases per day, has revolutionized the context of biology. This has enabled the decoding of the three billion DNA base pairs of the human genome. Additionally, multiple parallel signature sequencing analysis (MPSS) has allowed for the observation of the entire transcriptome of a particular type of cell.

Chemical biology, a fusion of the two sciences, has come to the forefront in the last decade. This is reflected, among other things, in the name change of several academic chemistry departments to departments of chemistry and chemical biology. Chemical biology applies chemical-scale molecular approaches to elucidate problems in biology and often involves the interaction of small organic molecules with biological macromolecules (DNA, RNA, proteins, membranes, and organelles). A few noteworthy discoveries discussed at the workshop include small molecules that dimerize and activate target receptor proteins, the biosynthetic incorporation of unnatural amino acids into proteins at specific sites, combinatorial biosynthesis of new antibiotics, biosensors to monitor calcium ions in cells and to localize proteins in subcellular locales, the directed evolution of proteins to create novel or improved properties, and in vitro selection of nucleic acids with specific binding or catalytic activities. Advances in protein semi-synthesis (native chemical ligation and expressed protein ligation) have also led to the creation of proteins with novel properties.

Much of the work at the biology and chemistry interface has changed from hypothesis-driven science to discovery science. Human biology is evolving from an information-poor arena to an information-rich science amenable to a systems approach, which will revolutionize medicine from being reactive to predictive to preventive.

ACCOMPLISHMENTS IN CHEMICAL ENGINEERING

Chemical engineers emphasize a quantitative analysis and design approach to the operation of molecular systems, pursuing advances in chemistry-based products and chemistry-based processes. The application of chemical engineering principles and tools to biological systems, primarily in regard to biomolecular products and biomolecular processes, including those involving cells and tissues, has contributed greatly to a number of advances in health and medicine in the last

decade. Some of these accomplishments highlighted in the workshop are discussed below.

The development of bacterial, yeast, and animal cell bioreactor technologies for production of therapeutic proteins, including monoclonal antibodies from recombinant DNA methods, has enabled this powerful new class of drugs to emerge alongside classical small molecule organics. Protein drugs are often capable of focused stimulation of desired cell functions for treatment of disease. This activity is generally not possible with small molecule organic drugs. Proteins are much more challenging to manufacture. Application of biochemical reactor analysis and design approaches, including quantitative kinetics, mass and heat transfer, and fluid mechanics, has led to a series of highly effective protein therapeutics that are presently in clinical use. Examples of these are the protein erythropoietin used for anemia, GCSF for neutropenia, interleukin-2 for boosting the immune system, TNFR for arthritis, and b-interferon for multiple sclerosis.

The design of scalable protein separation processes has been necessary to purify and concentrate these high-value products for therapeutic use. Achieving well-characterized and exceedingly pure moieties in substantial amounts in a reliable manner and across many trials is critical to clinical effectiveness and government agency approval of biological therapeutics. These separation processes are diverse in nature, in accord with the complex characteristics of biological macromolecules and cells, and typically make use of molecular recognition interactions employing additional biomolecules specifically generated for targeting particular proteins in solution or on cell surfaces.

Novel controlled-release devices derived from synthetic polymers have permitted a crucial means to deliver protein and organic therapeutics to patients. Proteins are typically rapidly cleared from the bloodstream and tissues through both relatively nonspecific and specific mechanisms, involving physiochemical transport, enzymatic degradation, and cellular uptake. Quantitative analysis of these dynamic systems of in vivo barriers, in terms of chemical engineering process models, has indicated how proteins might be more effectively introduced into the patient (i.e., in what locations and with what rates). Polymer microspheres containing proteins have been demonstrated to possess the capability for releasing the drugs in appropriate locations and with appropriate rates, resulting in improved pharmacokinetic profiles and physiological effects. However, these products generally suffer from problems of initial burst, in which a large portion of the dose is released in the first few hours.

Cell therapies have also begun to demonstrate impact in clinical medicine, requiring purification, expansion, or metabolic functions of blood and tissue cell populations in vivo or ex vivo. Applications already in practice include immune white blood cell replacement in bone marrow transplantation and extracorporeal liver cell bioreactors for enhancement of metabolic tissue function to counteract liver disease.

Determination of the most useful candidates for drugs, whether proteins or small molecules, along with how to best deliver them and diagnose conditions indicating their use, benefits from a fundamental understanding of how biomolecular mechanisms govern cell and tissue functions. In collaboration with basic biological sciences, chemical engineering approaches that model molecular processes in cells, tissues, and organs have been successfully applied to yield significant insights into pathophysiology. Prominent examples include analysis of transport phenomena that critically affect tumor diagnosis and therapy, kinetics of receptor and ligand processes regulating cell proliferation and migration, and dynamics of cell and substratum interactions involved in biomaterials colonization and immune and inflammatory system responses to host insult and injury.

CHALLENGES FOR CHEMISTRY AND CHEMICAL ENGINEERING

The scope and pace of accomplishments in chemistry at the health and medicine interfaces serve as starting points for deconvoluting the multilayered systems that make up both the normal physiology of human biology and the pathophysiology of disease. There are grand challenges at the interface of chemistry, biology, and medicine that are baffling in their complexity, such as understanding the chemical bases of thought, memory, and cognition; and how to elucidate multigenic contributions to diseases such as diabetes, obesity, schizophrenia, and degenerative diseases. The timeline of discoveries is not clear, but there is optimism that personalized and regenerative medicine will be hastened by meeting several of the short-term challenges that exist at the interface of chemistry and medicine.

Chemical engineering tools and principles, including chemical reaction kinetics, thermodynamics, fluid mechanics, and heat and mass transfer, ought to provide powerful approaches to a number of important challenges in health and medicine in the coming decade. Significant progress toward overcoming these challenges should lead to useful new products from the pharmaceutical and biotechnology industries. We highlight here some challenges that were apparent from the workshop discussion. The name of the presenter who discussed the topic is shown parenthetically after each heading.

There is a continued need in health and medicine for advances in synthetic techniques.

Chemical Synthesis (Joyce)

The synthesis of smart nanoscale materials for diagnosis by biosensing and controlled, programmable drug delivery is a current challenge for both chemists and chemical engineers. The power of chemical synthesis will need to be implemented for synthesis of molecules at the nanoscale range in order to match spe-

cific target structures. The design of self-assembling and template-mediated synthetic systems is a current frontier in synthetic chemistry. The synthesis of compounds that target specific cell types and specific regions of the cell is also an important frontier for achieving enhanced specificity with regard to mechanism of action.

Molecular Design (Danishefsky)

New advances in chemistry can lead to the generation of new compounds that can block interactions that are not commonly targeted by current drugs. These include protein–protein interactions, protein–oligonucleotide interactions, and protein–carbohydrate interactions. While genomics can identify potential drug targets, compounds that block or activate these targets will come from chemistry. In addition to continuing to develop new synthetic chemistry, there must be further advances in molecular design methodology. These are required to develop effective inhibitors of some of the attractive targets identified by advances in genomics and proteomics. Because it is known that the assembly of multiprotein complexes is required for many biological processes, the synthesis of compounds that can assemble systems of interacting proteins would be advantageous. Such compounds could be useful for controlling responses due to multiprotein assemblies in applications like vaccine development and control of cellular differentiation.

Advances in measurement and imaging that improve understanding of biological function at the molecular level will aid progress in chemical biology.

Analytical Chemistry (Hood)

Analytical chemistry challenges will continue and will drive the measurement sciences at the interfaces of chemistry, biology, and medicine. Advances in analytical chemistry will spur advances in systems biology by enabling the collection of information across a wide range of time regimes in cells, tissues, organs and individuals. Challenges for analytical chemistry will involve modularity, scalability, and dynamic range of techniques, and multisystem computational models for analysis.

Advances that reduce the cost of bringing new drugs to market and lengthen the profitable lifetime of existing drugs are vital in providing the benefits of new developments to the public.

Chemical Discovery (Anderson)

The pharmaceutical and biotechnology industries must continue to evolve to meet needs for new blockbuster medicines in an era of market consolidations, tight capital markets, and rising costs. Chemical discovery and development must increase the success rate from the current 10 percent for drug candidates in clinical trials, lower the costs (estimated at $250-$800 million per drug developed to FDA approval), and shorten the 10- to 12-year average development cycle.

Bioprocessing (Swartz)

Further advances in bioprocessing are required to lower the cost of drug manufacturing and provide for faster time-to-market capabilities in order to reap swifter benefits from new discoveries. Directions offering promise include (a) improved methods and devices for global, molecular-level analytical measurement of biochemical properties in sensitive, small-scale, high-throughput modes; (b) bioreactor scale-down to facilitate high-throughput analytics; (c) enhanced understanding of cell functions across a spectrum of organisms to increase production efficiencies of therapeutic biomacromolecules and cells; and (d) cell-free production of biochemicals to reduce capital expenses and obtain increased flexibility for process changes.

Human Organ Physiology and Pathology (Griffith)

New experimental models of human organ physiology and pathology could offer quantum leaps forward in drug discovery and development. Tissue-engineered in vitro organ surrogates could provide an ability to identify the most useful drug targets for affecting human cell function and permit true pharmacogenomic analysis by creating surrogates from a spectrum of human subpopulation genetic backgrounds. This same approach could allow toxicogenomic studies in similar manner, for off-target effects of drugs in human tissues; replacing animal studies would be a tremendous benefit for multiple reasons. Indeed, it can be projected that the impact of tissue engineering on human health care will ultimately be far greater for drug discovery and development than for patient implants.

Research in nanotechnology shows promise for impact in health and medicine.

Nanotechnology (Joyce)

Chemists could build on the DNA-based nanofabrication technologies that have led to controlled cubic architectures, informational objects based on DNA structures, DNA-fueled tweezers, and other mechanical devices. Nucleic acid

chemistry has had notable reach-through polymerase chain reaction (PCR) technology, which has revolutionized forensic science and medical diagnostics. Further advances in diagnostics using biosensors and gene amplification are in the offing and will be required to enable real-time medicine, including biodefense applications. Oligonucleotide therapeutic candidates are advancing and it is likely that RNA interference (RNAi) will have tremendous reach in the coming decade. Biosensor arrays may evolve from dumb arrays to smart arrays, using smart RNA aptamers.

The development of an appropriate chemistry and chemical engineering curriculum is a challenge that must be met to adequately provide the education needed to do interdisciplinary research across the chemistry and biology divide.

Incorporating Chemistry into Biology (Dervan)

Chemists are becoming increasingly involved in biological research. With the emergence of such interdisciplinary fields as chemical biology and systems biology, chemists are actively working on solving biological problems with chemical approaches. This requires expansive knowledge of both chemistry and biology, which may not be adequately addressed in a chemistry or biochemistry curriculum. There is, therefore, a pressing need for a revised curriculum that stresses the use of chemical approaches to address biological issues.

Chemical biology offers many challenges, among them use of chemical-scale thinking for proteomics and ligand arrays. Small molecules are being developed as regulators of gene expression, targeted, for example, at the histone acetylation and methylation enzymes, and as ligands for multisubunit complexes such as the proteasome or the spliceosome. Charting the small molecule inventory of cells, the metabolome, in a time-dependent way has predictive utility and will be an analytical chemistry challenge. The evolution of macromolecules as specific, potent therapeutic agents will require many approaches, which may range from DNA shuffling and selection to site-specific incorporation of unnatural amino acids and their subsequent selective modification.

Innovation requires the sharing of information across novel technologies and chemistry and biological efforts. Therefore, improvements in data access, data management, and data manipulation are critical for future successes in health and medicine.

Computational Models of Cell Function (breakout sessions)

Computational models of cell function emphasizing a dynamic, multivariable understanding of intracellular regulatory networks could lead to unprec-

edented work in silico drug discovery and design capability derived from molecular processes. However, a cell-level integrative-systems perspective rather than a reductionist perspective would be involved. These kinds of models could then be coupled with those at higher level in physiological hierarchy (tissue, organ, systemic) to aid in elucidating more effective delivery principles and modalities, with both pharmacokinetic and pharmacodynamic analyses becoming much more mechanism-based than empirical.

Innovative techniques for targeting therapeutics (small molecule, protein, nucleic acid, and cell) to specific, localized sites of action in the patient should bring substantial benefits in therapeutic index, enhancing effectiveness, and reducing toxicity. These techniques might comprise biochemistry-derived cell selectivity along with physical approaches for discerning and reaching particular tissue regions with minimal invasiveness.

Appendixes

A

Statement of Task

The Workshop on Health and Medicine is one of six workshops held as part of "Challenges for the Chemical Sciences in the 21st Century." The workshop topics reflect areas of societal need—materials, energy and transportation, national security and homeland defense, health and medicine, information and communications, and environment. The charge for each workshop was to address the four themes of discovery, interfaces, challenges, and infrastructure as they relate to the workshop topic:

- Discovery—major discoveries or advances in the chemical sciences during the last several decades;
- Interfaces—interfaces that exist between chemistry and chemical engineering and such areas as biology, environmental science, materials science, medicine, and physics;
- Challenges—the grand challenges that exist in the chemical sciences today; and
- Infrastructure—infrastructure that will be required to allow the potential of future advances in the chemical sciences to be realized.

B

Biographies of the Organizing Committee Members

Douglas A. Lauffenburger (Co-chair) is a professor of biological engineering, chemical engineering, and biology, co-director of the Biological Engineering Division, and director of the biotechnology process engineering center at the Massachusetts Institute of Technology. He received a B.S. from the University of Illinois and a Ph.D. in chemical engineering from the University of Minnesota. His research combines molecular cell biology with engineering approaches to improve design of cell-based technologies and molecular therapeutics. Dr. Lauffenburger's awards include the A. P. Colburn, W. H. Walker, and Food Pharmaceutical and Bioengineering Division awards from the American Institute of Chemical Engineers; the C. W. McGraw award from the American Society for Engineering Education; and the Amgen Award in Biochemical Engineering from the Engineering Foundation. He is also a member of the National Academy of Engineering, American Academy of Arts and Sciences, past president of the Biomedical Engineering Society, and a member of the NIH General Medical Sciences Advisory Council.

Christopher T. Walsh (Co-chair) is currently the Hamilton Kuhn Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. His research efforts have been directed to enzymatic catalysis, including analysis of the chemical basis of molecular transformations and the study of enzyme inhibitors. This has led to study of the mechanism of agents in various areas of molecular pharmacology, including immunosuppressive agents and antibacterial drugs. Dr. Walsh earned his A.B. from Harvard University and his Ph.D. from Rockefeller University. Dr. Walsh is a member of both the National Academy of Sciences and the Institute of Medicine. He spent the first part of his career in the

chemistry department at MIT. He sits on the board of directors and advisory board of many corporations and has won such awards as the Alfred P. Sloan Foundation Fellowship (1975), Eli Lilly Award in Biochemistry (1979), the Arthur C. Cope Scholar Award of the American Chemical Society, and the ACS's Repligen Award. Dr. Walsh has also been on the Editorial Board of the *Journal of the American Chemical Society* and is a member of the NIH General Medical Sciences Advisory Council.

Paul S. Anderson is the vice-president for drug discovery at Bristol-Myers Squibb Company. He previously held comparable positions at DuPont Pharmaceutical Company and DuPont-Merck Pharmaceutical Company. Before joining DuPont-Merck he was the vice-president for chemistry at Merck Sharp & Dohme Research Laboratories, where he served in various roles from senior research chemist through executive director of the medicinal chemistry department. Dr. Anderson received a B.S. from University of Vermont and a Ph.D. in chemistry from University of New Hampshire. He performed postgraduate studies as a National Institutes of Health postdoctoral fellow in chemistry at Cornell University. He is a former president of the American Chemical Society.

Ellen Leahy is a senior scientist in medicinal chemistry at Celera in South San Francisco, California. She earned both her B.S. and Ph.D. from the University of South Florida and was a postdoctoral scholar at the University of Pennsylvania in the laboratory of Ralph Hirschmann. Dr. Leahy has worked in the San Francisco Bay area biotechnology industry focusing on combinatorial chemistry as well as traditional medicinal chemistry programs. During the course of her career she has held positions at Affymax and Versicor and then at Axys Pharmaceuticals, which became part of Celera in 2001. She recently received the Outstanding Chemistry Alumni Award at the University of South Florida.

Michael A. Marletta is currently a professor of chemistry and biochemistry and molecular biology at the University of California, Berkeley, and a professor of cellular and molecular pharmacology at the University of California, San Francisco. He was previously on the faculty at the University of Michigan and the Massachusetts Institute of Technology. His research focuses on the interface of chemistry and biology, probing biological catalysis and other protein structure and function questions. Novel functions and mechanisms are explored for application of those properties to drug design. Dr. Marletta has a number of awards that include a MacArthur Foundation Fellowship, the State of Michigan Scientist of the Year, and the Distinguished Faculty Achievement Award from the University of Michigan. He is a member of the Institute of Medicine and a fellow of the American Academy of Arts and Sciences. He earned his A.B. at State University College in Fredonia, New York, and his Ph.D. at the University of California, San Francisco.

C. Dale Poulter is the John A. Widtsoe Distinguished Professor in the Department of Chemistry at the University of Utah. He earned his B.S. from Louisiana State University and his Ph.D. from the University of California, Berkeley. He was a National Institutes of Health postdoctoral fellow with Saul Winstein at the University of California, Los Angeles. Dr. Poulter's research combines synthetic and mechanistic organic chemistry with biochemistry and molecular biology to study the chemistry of enzyme catalysis. This work has focused on enzymes in the isoprenoid biosynthetic pathway, including those in sterol biosynthesis and protein prenylation. He has been awarded an Alfred P. Sloan Fellowship, the American Chemical Society Ernest Guenther Award, an ACS Arthur C. Cope Scholar Award, and the ACS Repligen Award. He is a fellow of the American Association for the Advancement of Science. Dr. Poulter has served on a number of ACS committees and editorial advisory boards and is the editor in chief of the *Journal of Organic Chemistry*.

Dagmar Ringe is a professor of biochemistry and chemistry at Brandeis University. Her research group studies the relationship of protein three-dimensional structure to chemical function, using a combination of design of transition-state analog inhibitors, site-directed mutagenesis, genetics, and X-ray crystallography. Dr. Ringe received her Ph.D. from Boston University.

C

Workshop Agenda

Workshop on Health and Medicine
Challenges for the Chemical Sciences in the 21st Century
National Academies
Arnold and Mabel Beckman Center
100 Academy Drive
The Auditorium
Irvine, CA 90027

Monday, December 2

7:30 Breakfast and Registration

SESSION 1: THE UNDERLYING CHEMICAL SCIENCE

8:10 Introductory remarks by organizers. Background of project.

8:15 **DOUGLAS J. RABER**, National Research Council

8:20 **RONALD BRESLOW**, **MATTHEW V. TIRRELL**, Co-Chairs, Steering Committee on Challenges for the Chemical Sciences in the 21st Century

8:25 **DOUGLAS A. LAUFFENBURGER AND CHRISTOPHER T. WALSH**, Co-Chairs, Organizing Committee, *Workshop on Health and Medicine*

8:30 **LEROY HOOD,** *The Institute for Systems Biology*
Systems Biology and Global Analytic Techniques

9:05 Discussion

9:25 **Stephen W. Kaldor,** *Syrrx, Inc.*
Structural Proteomics and Drug Discovery
10:00 Discussion
10:20 Break
10:50 **Gerald F. Joyce,** *The Scripps Research Institute*
Challenges in Nucleic Acid Chemistry
11:25 Discussion
11:45 Lunch

Session 2: Biological Chemistry

1:00 **Barbara Imperiali,** *Massachusetts Institute of Technology*
Biochemical Complexity
1:30 Discussion
1:50 **Peter B. Dervan,** *California Institute of Technology*
Chemical Biology
2:20 Discussion
2:40 Breakout Session: Discovery
Breakout question: What major discoveries or advances related to health and medicine have been made in the chemical sciences during the last several decades?
3:45 Break
4:00 Reports from breakout sessions (and discussion)
5:00 Reception
6:00 Banquet—Dinner Speaker:
Peter G. Schultz, *The Scripps Research Institute*
Biotechnology

Tuesday, December 3

7:30 Breakfast

Session 3: Synthesis and Engineering

8:00 **Samuel Danishefsky,** *Columbia University and Memorial Sloan-Kettering Cancer Center*
Synthetic Challenges
8:30 Discussion
8:50 **Linda G. Griffith,** *Massachusetts Institute of Technology*
Cell/Tissue Engineering
9:20 Discussion
9:40 Breakout Session: Interfaces
Breakout question: What are the major biomedical discoveries and challenges at the interfaces between chemistry/chemical engineering and other disciplines, including biology, information science, materials science, and physics?
10:45 Break

11:00 Reports from breakout sessions (and discussion)
12:00 Lunch

SESSION 4: UNDERLYING SCIENCE FOR PHARMACEUTICAL MANUFACTURE

1:00 **SANGTAE KIM,** *Eli Lilly and Company*
Bioinformatics
1:30 DISCUSSION
1:50 **W. MARK SALTZMAN,** *Yale University*
Drug Delivery
2:20 Discussion
2:40 Breakout Session: Challenges
Breakout question: What are the biomedically-related grand challenges in the chemical sciences and engineering?
3:45 Break
4:00 Reports from breakout sessions and discussion
5:00 Adjourn for Day

Wednesday, December 4

7:30 Breakfast

SESSION 5: MANUFACTURE OF PHARMACEUTICALS

8:00 **PAUL S. ANDERSON,** *Bristol-Myers Squibb Company*
Medicinal Chemistry
8:30 Discussion
8:50 **JAMES R. SWARTZ,** *Stanford University*
Bioprocessing
9:20 Discussion
9:40 Breakout Session: Infrastructure
Breakout question: What are the issues at the intersection of health and medicine and the chemical sciences for which there are structural challenges and opportunities—in teaching, research, equipment and instrumentation, facilities, and personnel?
10:45 Break
11:00 Reports from breakout sessions (and discussion)
12:00 Wrap-up and closing remarks
DOUGLAS A. LAUFFENBURGER AND CHRISTOPHER T. WALSH, Co-Chairs, Workshop Organizing Committee
12:15 Adjourn

D
Participants
Challenges for the Chemical Sciences in the 21st Century: Workshop on Health and Medicine

William L. Alworth, Tulane University
Paul S. Anderson, Bristol-Myers Squibb Company
Anand R. Asthagiri, California Institute of Technology
John E. Baldwin, Syracuse University
Cynthia Bamdad, Minerva Biotechnologies Corporation
Georges Belfort, Rensselaer Polytechnic Institute
Dale Boger, Scripps Research Institute
Ronald Breslow, Columbia University
Michael Burkart, University of California, San Diego
Cynthia J. Burrows, University of Utah
Alison Butler, University of California, Santa Barbara
Jeffrey Chalmers, Ohio State University
Kevin Chapman, Merck & Co., Inc.
Panagiotis D. Christofides, University of California, Los Angeles
Steven S. C. Chuang, University of Akron
Benjamin F. Cravatt, Scripps Research Institute
Samuel Danishefsky, Memorial Sloan-Kettering Cancer Center
Nancy A. Da Silva, University of California, Irvine
Edward A. Dennis, University of California, San Diego
Peter B. Dervan, California Institute of Technology
Kenneth M. Doxee, National Science Foundation
Christos Georgakis, Polytechnic University
Eric M. Gordon, Palantir Consulting
Linda G. Griffith, Massachusetts Institute of Technology
Peter Gund, Gund Discovery Services
Leroy Hood, Institute for Systems Biology
Klaudyne Hong, Berlex Biosciences
Joel R. Huff, Merck & Co., Inc.

Randy Hungate, Amgen, Inc.
Barbara Imperiali, Massachusetts Institute of Technology
Gerald F. Joyce, Scripps Research Institute
Stephen W. Kaldor, Syrrx, Inc.
Sangtae Kim, Eli Lilly and Company
Jack F. Kirsh, University of California, Berkeley
William F. Koch, National Institute of Standards and Technology
Walter Kozumbo, U.S. Air Force Office of Scientific Research
Douglas A. Lauffenburger, Massachusetts Institute of Technology
Ellen Leahy, Celera Genomics
Thomas S. Leyh, Albert Einstein College of Medicine
Craig E. Lunte, University of Kansas
Sundar Madihally, Oklahoma State University
Michael A. Marletta, University of California, Berkeley
Luigi Marzilli, Louisiana State University
Douglas D. McAbee, California State University, Long Beach
Claude F. Meares, University of California, Davis
Reginald Morales, University of Puerto Rico, Rio Piedras
Thomas H. Morton, University of California, Riverside
Larry E. Overman, University of California, Irvine
Sean Palecek, University of Wisconsin, Madison
C. Dale Poulter, University of Utah
Paul J. Reider, Amgen, Inc.
Dagmar Ringe, Brandeis University
Michael E. Rogers, National Institute of General Medical Sciences
W. Mark Saltzman, Yale University
Christine E. Schmidt, University of Texas, Austin
Peter G. Schultz, Scripps Research Institute
John W. Scott, Bristol-Myers Squibb
Michael L. Shuler, Cornell University
Scott F. Singleton, Rice University
Gregory Stephanopoulos, Massachusetts Institute of Technology
Basil I. Swanson, Los Alamos National Laboratory
James R. Swartz, Stanford University
William C. Swope, IBM
David H. Thompson, Purdue University
Mathew Tirrell, University of California, Santa Barbara
Ian A. Tomlinson, Dow Chemical Company
Joan S. Valentine, University of California, Los Angeles
Christopher T. Walsh, Harvard Medical School
Mark K. Weise, Praxair, Inc.
Chi-Huey Wong, Scripps Research Institute
Michael Zaworotko, University of South Florida

E

Reports from the Breakout Session Groups

A key component of the Workshop on Health and Medicine was the set of four breakout sessions that enabled individual input by workshop participants on the themes of the workshop: discovery, interfaces, challenges, and infrastructure. Each breakout session was guided by a facilitator and by the expertise of the individuals as well as the content of the plenary sessions. Each breakout group (color-coded blue, green, red, and yellow) was asked to address the same set of questions and provide answers to the questions, including prioritization of the voting to determine which topics the group concluded were most important. After every breakout session, each group reported the results of its discussion in plenary session.

The committee has attempted in this report to integrate the information gathered in the breakout sessions and to use it as the bases of the information contained herein. When breakout groups reported votes for prioritizing their conclusions, the votes are shown parenthetically in this section.

SESSION 1: DISCOVERY

What major discoveries or advances related to health and medicine have been made in the chemical sciences during the last several decades?

Blue Group Report

Discovery and development of new pharmaceutical agents

- Protein-based drugs

- Drug discovery
- Structure-guided drug design
- Antibiotics
- *In silico* chemistry
- Rapid roll out of AIDS therapeutics
- Drug delivery
- New anticancer drugs

Effective methods for the synthesis of new pharmaceuticals

- Synthetic strategy
- Solid-phase synthesis
- Synthetic methods
- Catalysis in synthesis (organometallic)
- Chiral catalysts
- Enzymes and bioprocessing
- Catalytic antibodies
- Combinatorial and parallel chemistry
- Polymerase chain reaction (PCR)

Medical diagnostics for prediction, detection, and distribution of disease

- Magnetic imaging
- Noninvasive imaging
- Contrast imaging
- Laser applications
- Biosensors
- Real-time analytical analysis
- Diagnostics

Development of new molecular separations techniques for analysis, identification, and processing

- Separations technology

Green Group Report

Cellular signaling (9 votes)

- Understanding signal transduction
- Intracellular sensors of biomolecules (GFP)
- Molecular probes
- Post-translational chemistry and modification

Molecular medicine (7 votes)

- Molecular mechanism of disease
- New drugs (statins)
- Structure-guided rational drug design
- Controlled release (large molecule delivery)
- Bio-engineered pharmaceutical agents

Techniques and tools (7 votes)

- In vivo imaging (MRI, PET)
- Mass spectrometry (MALDI, TOF)
- High-field and multidimensional NMR
- PCR
- Solving human genome (underlying technologies, DNA sequencing)
- Molecular modeling and dynamics
- Rapid and inexpensive diagnostics

Bioprocessing (4 votes)

- Tissue engineering (artificial skin)
- Large-scale tissue culture
- Molecular and cell separation techniques
- Metabolic networks
- Modeling biological systems

Synthetic methodologies (4 votes)

- Asymmetric synthesis
- Chemoenzymatic synthesis
- Templated synthesis
- Oligosaccharide chemistry

Combinatorial methods (2 votes)

- Molecular synthesis
- High-throughput crystallization
- Protein engineering
- Nucleic acid engineering

Red Group Report

Synthetic techniques (9 votes)

- Ability to synthesize and manufacture complex molecules
- Development of catalysts for chiral synthesis
- Solid-phase synthesis
- High-throughput synthesis and analysis
- Combinatorial chemistry

Imaging modalities (6 votes)

- Monitoring of single molecules
- Single molecule imaging
- Development of MRI
- Engineered proteins for fluorescent signaling
- Use of lasers in medicine, surgery, imaging

Spectroscopy (6 votes)

- Advances in mass spectroscopy
- NMR

Drug development (5 votes)

- Development of statins
- HIV therapy

Computational chemistry (4 votes)

- Development of computer-aided experimentation
- Development of structure-based drug design

Molecular amplification (4 votes)

- Recombinant DNA technology
- PCR

Yellow Group Report

Analytical tools (13 votes)

- NMR
- X-ray

- Mass spectrometry
- HPLC
- PCR
- DNA sequencing
- Microarrays
- Recombinant DNA
- SAMS
- Clinical diagnosis

New therapies (11 votes)

- Natural products discovery
- Chemistry of enzyme active site
- Rational drug design
- Protease inhibitors
- Cardiovascular drugs
- Cancer therapies

Chemistry of the cell (9 votes)

- RNA catalysis
- Signal transduction
- Natural product mechanisms
- Gases (e.g., O_2, NO)
- Metal ions
- Noncovalent interactions
- Focus on function and structure

Synthetic methods (7 votes)

- Selective chemical reactions
- Asymmetric synthesis and catalysis
- Synthesis on solid support
- Combinatorial chemistry

Biomaterials (2 votes)

- Synthetic membranes
- Biocompatible materials
- Controlled drug release
- Tissue engineering, use of
- Plastics
- Disposable

SESSION 2: INTERFACES

What are the major biomedical discoveries and challenges at the interfaces between chemistry and chemical engineering and other disciplines, including biology, information science, materials science, and physics?

Blue Group Report

Material science (8 votes)

- Micro and nano fabrication
- Biofunctional "smart" materials
- Drug delivery systems
- Oral delivery
- Drug formulation
- Conductive polymers (nerve regeneration)

Cell biology (7.5 votes)

- Homogeneous glycoprotein manufacturing
- Understanding cell surface
- New chemical types (natural products)
- Proteomics and metabolomics
- Genotype and phenotype correlations
- Understanding neural pathways

Information science, computer science, and mathematics (6 votes)

- Cellular modeling
- Personalized medicine (genomics)
- Dynamic theory for multiscale modeling
- Proteomics and metabolomics
- Genotype and phenotype correlations

Physics (4 votes)

- Imaging
- Single molecule studies
- Optical manipulation (tweezers)
- In vivo diagnostics

Medicine (3 votes)

- Problem of drug resistance

Agriculture (2.5 votes)

- Therapeutic proteins by transgenic plants and animals
- Improving agricultural production (feed the world)
- New chemical types (natural product discovery)

Immunology (2 votes)

- New bioprocessing techniques (transgenics)
- New vaccines

Green Group Report

Cultural barriers at the interfaces (5 votes)

- Process versus discovery versus hypothesis-driven research
- Challenge: Chemists as part of a team
- Common standards for biological data
- Mechanism versus function or property

Translational medicine (3 votes)

- Economic challenges (government reimbursement versus profit)
- Bioorganic synthesis-basic science versus clinicians
- Benefit: Clinicians can define the issue and point to technology needed

Chemists make things (1 vote)

- Natural products with unnatural function
- Manipulation of biomolecules

Training students (1 vote)

- Challenge: Education of the other sciences about what chemistry does
- Undergraduate education
- Tension between broad and deep

Red Group Report

Diagnostics (12 votes)

- Early detection of cancer
- Personalized medicine
- Health sensors
- Near real-time diagnostics in a primary care setting
- Biosignatures
- Predictive mass spectometry
- Non-invasive sensor development
- Environmental and biohazard sensing
- Medical delivery and medical ethics

Macromolecular complexes (8 votes)

- Small molecule control of macromolecular interactions
- Dynamic (time resolved) measurements at the molecular level
- Metal ion transport and bioaccumulation

Computational and systems models (7 votes)

- Computational chemistry and structure-based drug design
- Greater use of artificial intelligence and pattern recognition in diagnostics
- Better predictive models
- Systems level modeling through computation (e.g., molecular up to organism)

Improved drug formulation and delivery (5 votes)

Implants and regenerative medicine (5 votes)

Optimal development of cultural interfaces without loss of specialist training (4 votes)

- Ways to foster communication, collaboration, interdisciplinary research

Yellow Group Report

New instrumentation, miniaturization, and sensors (10 votes)

- Mechanical engineering
- Electrical engineering

- Materials science
- Physics

Computation: Structure-function modeling and bioinformatics (disconnect with language, storage, retrieval, standardization) (8 votes)

- Computer science
- Mathematics

Modeling: Noncovalent interactions; Pharmacokinetic properties (6 votes)

- Computer science
- Mathematics
- Pharmacology
- Physics

Global molecular analysis: Metabolomics, proteomics (4 votes)

- Computer science
- Systems engineering
- Electrical engineering
- Single-cell analysis (3 votes)
- Mechanical engineering
- Electrical engineering
- Physics

Single-molecule experimentation (3 votes)

- Mechanical engineering
- Electrical engineering
- Physics

Agricultural science: Safe new crops, pest-resistance (2 votes)

- Veterinary medicine
- Entomology
- Botany
- Agronomy
- Environmental science

Defining Protein Function (1 vote)

- Cell biology

- Enzymology

Cell differentiation (1 vote)

- Physics
- Biomaterials
- Electrical engineering

Noninvasive imaging (1 vote)

- Physics
- Engineering
- Clinicians
- Nuclear science

SESSION 3: CHALLENGES

What are the biomedical challenges in the chemical sciences and engineering?

Blue Group Report

New therapies (7 votes)

- Viral therapies, known and unknown
- Cancer therapies
- Gene therapy
- Personalized medicine
- Genomic diagnostics
- Reactive sensors

Exploitation of the human genome (6 votes)

- Connection of genomics with proteomics
- Protein folding
- Predictive protein and protein interaction
- "PCR" for proteins

Interface systems biology with drug discovery (5 votes)

- Systems physiology
- Tools for handling complexity in biological systems
- Intelligent drug delivery, monitoring, and feedback

- Seamless electronic tissue interfaces

Predictive ADMET (4 votes)

- Predictive biopharmaceutics
- Target selective delivery systems
- Target selective pharmaceuticals
- Green chemistry (3 votes)
- Selective transformations

Regenerative medicine (3 votes)

- Engineering functional living tissue models
- In vivo tissue regeneration
- Development of universal or immune-tolerant cell sources
- Aging

Understanding cognition (3 votes)

- Neurodegenerative diseases
- Depression, psychoses
- New mechanisms for pain control

Green Group Report

Controlled drug delivery to the site of action (5 votes)

Pure air and water for the world (5 votes)

In vivo imaging of molecular events at 1-100 nm scale (4 votes)

Develop effective antivirals (3 votes)

Robust, cheap, and reliable genetic testing for disease predisposition (3 votes)

Molecular-level model of cell with predictive capability (3 votes)

Early detection of disease (3 votes)

Molecular machines for biomedical applications (2 votes)

Programmable cell-based synthesis of organic molecules (2 votes)

Understand brain chemistry (e.g., consciousness) (1 vote)

Couple informatics with discovery-based R & D for molecular medicine (1 vote)

Red Group Report

Curing disease (10 votes)

- Host and microflora interactions: Relationship to chronic disease
- Curing viral diseases
- Prevention and cure of degenerative diseases
- Gene therapy: Making it work
- Smart nanoscale materials: Trigger delivery
- Functional cell surface modification
- Example: Drug targeting

Higher understanding of noncovalent interactions (7 votes)

- 3D Macromolecular folding and assembly
- Understanding the Ribosome
- Understanding principles of protein folding
- Membrane-bound protein structure and mechanism

Chemistry of life processes (6 votes)

- Whole cell model
- Synthetic cell
- Artificial life creation
- Understanding origin of life
- Using information from sequences of all organisms

Harnessing the immune system (5 votes)

- Harnessing of immune system to provide next generation of therapies
- Immunologically reactive structures database
- Predict immunoreactivity
- Biocompatibility of materials

Understanding brain processes (5 votes)

- Memory
- Learning
- Aging

Outreach (4 votes)

- Resource allocation
- Chemical literacy for all
- Global accessibility to medicine
- Low cost, abundant
- Increased agricultural productivity

Human surrogates for pharmaceutical testing (2 votes)

- Engineered tissue
- Computer modeling
- Understanding mechanism of differentiation and development

Yellow Group Report

Disease cures (12 votes)

- Viral, universal antibiotic, cancer, aging (prion, AD) cancer, memory
- Regulation of body parts

Genomics, proteomics, metabolomics (7 votes)

- Enhanced health, personalized medicine (prediction and prevention)
- Predict three dimensional structure from sequence
- Prediction of cellular function

Chemical basis of: (5 votes)

- Thought and memory
- Addition
- Immune system

Optimize chemical tools (4 votes)

- Ligands for every protein
- Ideal one-step, 100 percent synthesis

Livable environment (4 votes)

- Clean air, water, food
- Population balance (control)

SESSION 4: INFRASTRUCTURE

What are the issues at the intersection of health and medicine and the chemical sciences for which there are structural challenges and opportunities — in teaching, research, equipment and instrumentation, facilities, and personnel?

Blue Group Report

Need to evaluate funding model

- "One size does not fit all"
- Balance between single investigator and project grants
- Need more capital investment
- Better access to core facilities

Education and training

- Need 21st century undergraduate curriculum
- Breadth and depth; need to assure talent pipeline (recruitment, diversity)
- How to deal with evolving department structures
- Need early lab experience
- Interdisciplinary culture needs to be supported

Need to address ethical issues

Regulatory issues for personalized medicine

Better public perception of chemistry and better "marketing"

Green/Red Group Report

Working well

- Radioisotope facilities
- Entrepreneurship from investigation
- Students entering the workforce are high quality
- Some large scale facilities
  — PNNL protein fragment database, CAMS (Livermore)

Not working well

- Data mining: Management and sharing
- Academic core facilities support
- National and core facilities staffing
- Reward and mechanisms and collaborative research
- High-school outreach

Needs

- High-throughput screening facilities
- Nanofabrication facility
- Online exposure to the chemical literature for high-school and small-college students
- National forums
  - — More crossdiscipline forums
  - — Increased input from industry and younger scientists
- Education
  - — Graduate courses outside field of specialization
  - — Structure for a generalist
  - — Support for web-based courseware

Possible Solutions

- Education
  - — Build laboratory rotation into Ph.D.
  - — Support for industrial and government internships
- Facilities
  - — Grant surcharge for facilities support
  - — Central repository of instrument parts

Yellow Group Report

Information exchange (7 votes)

- Realization of the need to collaborate
- Positive academia and industry interactions (spin offs)
- Intellectual property issues
  - — Industry and university
  - — University and university (MTA)
  - — University, industry, and government
- Increase recognition of collaborations

Teaching (6 votes)

- Breadth and depth
- Emphasis of relevance of chemistry to human health
- Improved undergraduate chemical education
  - — Better laboratory course
  - — Incorporate biochemistry in curriculum earlier
  - — Promote undergraduate research
- Continued increase in funding for science education

Outreach (5 votes)

- Promotion of chemical science to the general public
- More involvement to improve K-12 science education

Equipment and facilities (4 votes)

- More access to state of the art instrumentation
- Effective maintenance and access to shared facilities
  - — Remote access
  - — Hands-on access to large-scale facilities

Research (1 vote)

- Increase funding mechanisms to encourage discovery-based research to complement hypothesis-driven research
- Enhanced postdoctoral fellowships
  - — Independent of grants
  - — Broader distribution to promote diversity

Information and data (1 vote)

- Better search capabilities
  - — Needs to be standardized
- Quality control of information
  - — Needs to be standardized
- Pooling of information