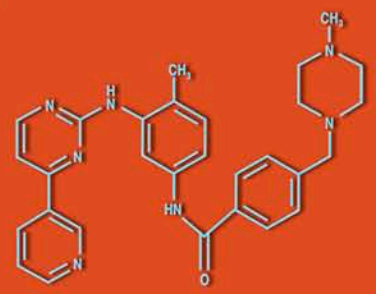
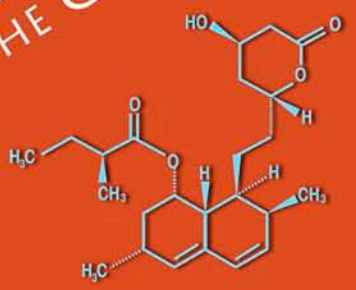
Chemistry & Biology: Partners in Decoding the Genome

March 15-16, 2004 Natcher Conference Center





National Human Genome Research Institute
and
National Institute of General Medical Sciences
of the
National Institutes of Health,
Department of Health and Human Services

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WELCOME!

The recent successful completion of the Human Genome Project, combined with remarkable advances in structural and computational biology, have provided an unprecedented opportunity to understand basic mechanisms underlying organismal complexity and pathobiology. Concurrent advances in the chemistry of small molecules have begun to provide an enormously rich toolbox with which to probe the intricacies of cellular function and dysfunction. The challenge, as in all turning points in science, is to effectively utilize the new tools to ask and answer previously insolvable problems. It is both an intellectual and a programmatic challenge.

The NIH Director's Roadmap for Medical Research (http://nihroadmap.nih.gov), and in particular the Molecular Libraries component of the Roadmap, aims to address some of these challenges. This Molecular Libraries initiative will provide funding and infrastructure for small molecule screening and probe generation, an informatics platform for archiving and utilizing small molecule data in the public sector, and technology development to expand the diversity and robustness of chemical libraries, assays, and detection technologies.

This meeting, *Chemistry and Biology: Partners in Decoding the Genome,* is a collaboration between NHGRI and NIGMS, and illustrates the scientific excitement of the Molecular Libraries initiative. The purpose of the meeting is to provide a forum for researchers who may be less familiar with the "small molecule approach" to science to experience the remarkable insights that it is yielding, and for those who are familiar with the approach to get new ideas on how chemistry and genomics can be brought together to make fundamentally new discoveries in biology and medicine.

We welcome you to this landmark meeting, and look forward to your active participation both in the meeting and in the ongoing activities of the Molecular Libraries Roadmap.

With best wishes,

Jeremy M. Berg, Ph.D.
Director
National Institute of General Medical Sciences

Francis S. Collins, M.D., Ph.D.
Director
National Human Genome Research Institute

AGENDA

MONDAY, MARCH 15, 2004:

8:30-8:45 am	Welcome – Elias Zerhouni, Director, National Institutes of Health
8:45-8:50 am	Greetings from Sponsoring Institutes – Jeremy Berg, Director, National Institute of General Medical Sciences Francis Collins, Director, National Human Genome Research Institute

Moderator: John Schwab, National Institute of General Medical Sciences

8:50-9:15 am	Francis Collins, Director, National Human Genome Research Institute *Small Molecules and the NIH Roadmap*
9:15-9:55 am	Daniel Kahne, Princeton University *Glycopeptide Antibiotics and Cell Envelope Biogenesis*
9:55-10:35 am	Stuart Schreiber, Harvard University *Dissecting Disease Biology and Advancing Medicine with Small Molecules*
10:35-10:50 am	Break
10:50-11:30 am	Craig Crews, Yale University *A Small Molecule Approach to Target Identification and Validation*
11:30-12:10 pm	Carolyn Bertozzi, University of California, Berkeley *Chemical Approaches to Studying Protein Glycosylation*
12:10-1:00 pm	Lunch

Moderator: Christopher Austin, National Human Genome Research Institute

1:00-1:40 pm	David Liu, Harvard University *An Evolution-Based Approach to the Creation and Discovery of Functional Synthetic Molecules*
1:40-2:20 pm	Roger Tsien, University of California, San Diego *Genetically and Proteolytically Targeted Sequences for Imaging from Ultrastructure to Whole Mammals*
2:20-3:00 pm	Jeremy Berg, Director, National Institute of General Medical Sciences *Chemical Approaches to Zinc Finger Protein Analysis and Design*
3:00-3:20 pm	Break
3:20-4:00 pm	Jon Ellman, University of California, Berkeley *Combinatorial Chemistry Targeting Protein Families*
4:00-4:40 pm	Gary Glick, University of Michigan *Chemistry and Biology of Immunosuppressive Benzodiazepines*
4:40-5:20 pm	Stephen Fesik, Abbott Laboratories *NMR-Based Screening of Fragment Libraries for Drug Discovery*

TUESDAY, MARCH 16, 2004:

Moderator: John Beutler, National Cancer Institute

8:30-9:10 am	Kevan Shokat, University of California, San Francisco *Chemical Tools for Deciphering Cell Signaling Pathways*
9:10-9:50 am	David Diller, Pharmacopeia *The Role of Computation When Building Collections of Millions of Compounds*
9:50-10:30 am	Virginia Cornish, Columbia University *Co-opting Nature for Chemical Diversity*
10:30-10:50 am	Break
10:50-11:30 pm	Eric Lander, The Broad Institute of MIT and Harvard TBD
11:30-12:10 pm	Dimitris Agrafiotis, 3-Dimensional Pharmaceuticals *Molecular Informatics for the New Drug Discovery Enterprise*
12:10-1:00 pm	Lunch

Moderator: Carole Bewley, National Institute of Diabetes and Digestive and Kidney Diseases

1:00-1:40 pm	Chaitan Khosla, Stanford University *Discovery and Development of New Natural Product Drugs:* *The Example of Polyketides*
1:40-2:20 pm	Baldomero Olivera, University of Utah *Conus Peptides: From Genes to Venoms to Drugs*
2:20-3:00 pm	Michael Organ, York University *New Advances in the Screening of Compound Mixtures*
3:00-3:20 pm	Break
3:20-4:00 pm	Alan Verkman, University of California, San Francisco *Drug Discovery in Academia: CFTR Chloride Channel Inhibitors and Activators for Cystic Fibrosis*
4:00-4:40 pm	Geoff Duyk, TPG Ventures *Small Molecules as Research Tools vs. Small Molecules as Drugs:* *Similarities and Differences*
4:40-5:00 pm	Closing Remarks– Jeremy Berg, Director, National Institute of General Medical Sciences Francis Collins, Director, National Human Genome Research Institute

ELIAS ZERHOUNI, M.D.

On May 20, 2002, Dr. Elias A. Zerhouni began his tenure as the 15th Director of the National Institutes of Health.

Dr. Zerhouni initiated the creation of a new research vision for the NIH which focuses the attention of the biomedical research community on new pathways of discovery, research teams for the future and the re-engineering of the clinical research enterprise.

Among his noteworthy achievements since becoming Director, Dr. Zerhouni named directors for five institutes: National Institute of Mental Health (Thomas R. Insel, M.D.), National Institute on Alcohol Abuse and Alcoholism (Ting-Kai Li, M.D.), National Institute on Drug Abuse (Nora D. Volkow, M.D.), National Institute of Neurological Disorders and Stroke (Story C. Landis, Ph.D.) and National Institute of General Medical Sciences (Jeremy M. Berg, Ph.D.). He also named a new NIH Deputy Director (Raynard S. Kington, M.D., Ph.D.), a new director of the Office of Technology Transfer (Mark L. Rohrbaugh, Ph.D., J.D.), a new Deputy Director for Extramural Research (Norka Ruiz Bravo, Ph.D.), a new Associate Director for Budget (Richard Turman) and a new Associate Director of Communications (John T. Burklow). He has also overseen the completion of the doubling of the NIH budget.

Prior to joining the NIH, Dr. Zerhouni served as executive vice dean of Johns Hopkins University School of Medicine, chair of the Russell H. Morgan Department of Radiology and Radiological Science, and Martin Donner Professor of Radiology and Professor of Biomedical Engineering.

His research in imaging led to advances in computerized axial tomography (CAT scanning) and magnetic resonance imaging (MRI) that resulted in 157 peer reviewed publications and 8 patents.

Since 2000, he has been a member of the National Academy of Sciences' Institute of Medicine. He served on the National Cancer Institute's Board of Scientific Advisors from 1998-2002.

FRANCIS COLLINS, M.D., Ph.D.

Francis S. Collins, M.D., Ph.D., a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the Human Genome Project, is director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health. With Dr. Collins at the helm, the Human Genome Project consistently met projected milestones ahead of schedule and under budget. This remarkable international project culminated in April 2003 with the completion of a finished sequence of the human genetic blueprint. Building on the foundation laid by the Human Genome Project, Dr. Collins is now leading NHGRI's effort to ensure that this new trove of sequence data is translated into powerful tools and thoughtful strategies to advance biological knowledge and improve human health. Dr. Collins is also known for his consistent emphasis on the importance of ethical and legal issues in genetics. In addition to his achievements as the NHGRI Director, Dr. Collins' laboratory has discovered a number of important genes, including those responsible for cystic fibrosis, neurofibromatosis, Huntington's disease and most recently, the gene that causes Hutchinson-Gilford progeria syndrome, a dramatic form of premature aging.

Dr. Collins received a B.S. from the University of Virginia, a Ph.D. in physical chemistry from Yale University, and an M.D. from the University of North Carolina. He is a member of the Institute of Medicine and the National Academy of Sciences.

Abstract:

Small Molecules and the NIH Roadmap

With the completion of the human genome sequence has come the opportunity, and the scientific imperative, to determine the function of the large number of proteins encoded by the genome. Recent efforts at NIH, particularly through the Director's Roadmap for Medical Research, have focused on making small molecule probe compounds available to the research community for investigating basic aspects of gene and cell function (see http://nihroadmap.nih.gov/molecularlibraries/index.asp). I will discuss the context, structure, and goals of this Molecular Libraries initiative.

DANIEL KAHNE, Ph.D.

Daniel Kahne is A. Barton Hepburn Professor of Chemistry and Professor of Molecular Biology at Princeton University. He has longstanding interests in the chemistry and biology of natural products, and has recently become interested in how natural products can be used to probe cellular pathways. Professor Kahne's research group is divided into students who develop synthetic methods to make and modify complex natural products, and students who combine some chemistry with molecular and cellular biology to address questions relating to how various natural products function. In the last five years, the Kahne group has become interested in antibiotic resistance, and has made significant contributions to understanding the mechanisms of action of glycopeptide antibiotics and derivatives that overcome glycopeptide resistance. The Kahne group has also been using glycopeptide derivatives and other antibiotics in conjunction with genetics to probe pathways involving cell wall biosynthesis and outer membrane biogenesis.

Abstract:

Glycopeptide Antibiotics and Cell Envelope Biogenesis

Glycopeptides are substrate-binding antibiotics that inhibit the final stages of cell wall biosynthesis. We have been studying derivatives of glycopeptide antibiotics that are active against glycopeptide resistant bacterial strains in order to understand the mechanisms by which these compounds act. In the first part of the talk, I will discuss our efforts to elucidate how semi-synthetic glycopeptides overcome resistance. In the second part of the talk, I will describe how efforts to use genetics to understand the mechanism of certain glycopeptide derivatives led to the identification of genes involved in the biogenesis of the outer membrane of *E. coli.* This talk will provide an example of how small molecules can be used to understand biological pathways that cannot be studied using standard genetic approaches alone.

STUART SCHREIBER, Ph.D.

Stuart L. Schreiber, Ph.D. is an Investigator at the Howard Hughes Medical Institute and Morris Loeb Professor and Chair of the Department of Chemistry and Chemical Biology at Harvard University. He is a Founder and Director of the Harvard ICCB and its affiliated and NCI-sponsored Initiative for Chemical Genetics and NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Development. He is also a member of the faculty of the Broad Institute (a joint initiative of Harvard University and MIT), and a member The Rockefeller University Board of Trustees. Dr. Schreiber is a member of the National Academy of Sciences and of the American Academy of Arts & Sciences (1995).

Dr. Schreiber is known for having developed systematic ways to explore biology using small molecules and for his role in establishing the field of chemical biology. Using his chemical approach, he has discovered principles that underlie information transfer and storage in cells. During the past twenty years, Dr. Schreiber has developed an integrated set of techniques that are systematizing the application of small molecules to biology. A key contribution was to formalize the planning of diversity-oriented synthesis (DOS). Using numerous applications of DOS along with powerful techniques for small molecule screening, many new insights into disease biology and useful small molecule probes have been discovered. To facilitate sharing of information derived from small molecules, Dr. Schreiber and ICCB created a public database named ChemBank, which was launched on the Internet in 2003.

(To learn more about these studies, visit http://www.hhmi.org/lectures, where you can receive a two-DVD set of the 2002 Holiday Lectures on Science presented by Dr. Schreiber and Dr. Eric Lander and entitled "Scanning Life's Matrix: Genes, Proteins, and Small Molecules".)

Abstract:

Dissecting Disease Biology and Advancing Medicine with Small Molecules

Academic labs are starting to transition towards the integration of small molecule synthesis, high-throughput screens, and informatics with the primary goal of illuminating principles that underlie biology and disease. The impact of this approach is substantial, in part because the concepts and technologies are being incorporated into the pharmaceutical industry's drug discovery process. Even more importantly, these efforts have identified previously unrecognized therapeutic targets whose activities can be modulated by small molecules. My lecture aims to provide insight into the development of Harvard's Institute of Chemistry and Cell Biology (ICCB), an organization dedicated to the sharing of reagents and information derived from small molecule investigations of biology, especially disease biology.

Based on the ICCB experience, three key elements are necessary for future success:
1. Marshaling the field of Chemistry in assembling a well-considered set of small molecules. Commercial compounds, although valuable for coverage of traditional drug space, are limited in other respects, while synthetic compounds produced by academic chemists offer many important advantages. Appropriate properties are achieved through new kinds of chemistry, including asymmetric synthesis, combinatorial chemistry, and diversity-oriented synthesis.
2. Unleashing the creativity of Biology to develop assays that probe disease-relevant pathways in precise and ingenious ways. Without the constraints of highly focused pharmaceutical drug discovery, the resulting assays can cover a much broader swath of biology.
3. Integrating informatics infrastructure relevant to chemical biology. We are in an excellent position to emulate the success of GenBank by drawing upon recent developments, including those resulting in ChemBank and PubChem. Scientists at the ICCB and NLM/NCBI already are coordinating efforts to establish controlled language and guidelines for information exchange.

The ultimate goal is to promote a culture where scientists share information, data, and reagents derived from the small molecule probing of disease biology.

CRAIG CREWS, Ph.D.

Craig Crews graduated from the University of Virginia with a B.A. in chemistry in 1986. Following a DAAD Fellowship in Germany, he completed his doctoral studies in biochemistry at Harvard University in 1993. As a Cancer Research Institute Fellow, he performed postdoctoral training in the Department of Chemistry and Chemical Biology at Harvard. Crews joined the Department of Molecular, Cellular, and Developmental Biology at Yale University in 1995 and currently is an Associate Professor with joint appointments in Chemistry and Pharmacology. His interests in chemical biology primarily focus on mechanisms of action of natural products. His lab has identified the molecular targets of the anti-angiogenic compound TNP-470 (methionine aminopeptidase 2), the anti-inflammatory compound parthenolide (IKK□) and the antitumor compounds eponemycin and epoxomicin (20S proteasome). Recently, in collaboration with Ray Deshaies (CalTech), his lab has developed a new technology (ProTacs) to induce protein degradation using small molecules. This methodology holds promise for the identification and validation of new drug targets. Crews is the recipient of a Burroughs Wellcome Fund New Investigator Award in the Basic Pharmacological Sciences (1996), a Donaghue Foundation Young Investigator Award (1996) and is an Arthur Greer Memorial Prize Awardee (1999). Crews currently serves on the editorial boards of *Chemistry & Biology*, *Molecular Cellular Proteomics* and *Faculty of 1000*.

Abstract:

A Small Molecule Approach to Target Identification and Validation

Each year, many promising natural products are identified as being biologically active in cell culture assays. Despite the proven *in vitro* efficacies of these compounds, development of these 'drug candidates' into clinically useful therapeutic agents is an arduous procedure, often due to issues unrelated to the compound's mechanism of action (e.g. poor pharmacokinetics, unfavorable side effects, etc.). While many of these compounds have limited therapeutic potential, investigation of their mechanisms of action can provide new information about complex intracellular signaling pathways. Moreover, these studies can serve as the starting point for the rapid development of additional efficacious compounds having more favorable pharmacological profiles. In addition, we have recently developed a new chemical genetic strategy for the identification of key components of intracellular processes.

CAROLYN BERTOZZI, Ph.D.

Carolyn Bertozzi is Professor of Chemistry and Molecular and Cell Biology at UC Berkeley, Faculty of the Materials Sciences and Physical Biosciences Divisions at the Lawrence Berkeley National Laboratory (LBNL), and an investigator of the Howard Hughes Medical Institute. She is also co-founder of Thios Pharmaceuticals, a company in the Bay Area focusing on drug development in sulfation pathways. Prof. Bertozzi's research at UC Berkeley spans the disciplines of chemistry and biology with an emphasis on studies of cell surface glycosylation pertinent to disease states. Her lab studies profiling changes in cell surface glycosylation associated with cancer, inflammation and bacterial infection, and exploiting this information for development of diagnostic and therapeutic approaches. At LBNL, Prof. Bertozzi's group works on the design of biomimetic materials for biomedical implant and nanotechnology applications. Prof. Bertozzi's awards include the Irving Sigal Young Investigator Award of the Protein Society, the American Chemical Society Award in Pure Chemistry, Merck Academic Development Program Award, Glaxo Wellcome Scholars' Award, Presidential Early Career Award in Science and Engineering, MacArthur Foundation Fellowship, Camille Dreyfus Teacher-Scholar Award, Arthur C. Cope Scholar Award, Horace S. Isbell Award in Carbohydrate Chemistry, Alfred P. Sloan Research Fellowship and the Donald Sterling Noyce Prize for Excellence in Undergraduate Teaching. She is also an elected member of the American Academy of Arts and Sciences.

Abstract:

Chemical Approaches to Studying Protein Glycosylation

A major lesson from eukaryotic genome sequencing projects is that the absolute number of genes an organism's genome encodes is not the best parameter for defining complexity of function. It appears that the complex functions associated with human health and disease are determined by combinatorial expansion of genomic information in the form of posttranslational modifications. Of these, the most complex and ubiquitous is glycosylation, highlighting the importance of glycobiology in the postgenomic era. This presentation will focus on new chemical approaches for profiling glycosylation at the systems level in both cells and living animals.

DAVID LIU, Ph.D.

David Liu was born in 1973 in Riverside, California. He met Professor E. J. Corey during his freshman year at Harvard College and performed research on sterol biosynthesis under Professor Corey's guidance throughout his undergraduate years. Following graduation from Harvard in 1994 with a bachelor's degree in chemistry, David entered the Ph.D. program at U. C. Berkeley. In the group of Professor Peter Schultz, David studied tRNAs and the enzymes that aminoacylate them, and initiated the first general effort to expand the genetic code in living cells. David earned his Ph.D. in chemistry in 1999 and became Assistant Professor of Chemistry and Chemical Biology at Harvard University in the same year. He has since received distinctions including the Arthur C. Cope Young Scholar Award, the Glaxo-Smith-Kline Chemistry Scholar Award, the AstraZeneca Pharmaceuticals Excellence in Chemistry Award, the Searle Scholars Award, the NSF CAREER Award, the Sloan Foundation Fellowship, the Beckman Foundation Young Investigator Award, the Office of Naval Research Young Investigator Award, and the university-wide Roslyn Abramson Award for undergraduate teaching at Harvard. He is currently a John L. Loeb Associate Professor of the Natural Sciences and Associate Professor of Chemistry and Chemical Biology.

Professor Liu studies the chemistry and chemical biology of molecular evolution. His research interests include (*i*) the development and application of new approaches to the evolution of biological macromolecules, and (*ii*) the development of the first approaches to the evolution of synthetic small molecules and polymers. In the first area, Professor Liu's group has developed and used new methods for diversifying proteins and nucleic acids that enable DNA sequences to randomly recombine without any sequence homology. Other research interests in this area include the evolution in living cells of RNA molecules with biological activities from random libraries, and the evolution of proteins with novel catalytic and regulatory activities. In the second area of interest, Professor Liu's group has developed a new approach to the synthesis and discovery of synthetic molecules that captures many advantages of Nature's evolution-based systems. This approach uses DNA oligonucleotides to direct the synthesis of organic small molecules and polymers in a manner that allows the DNA template associated with each synthetic molecule to be selected for desired properties, amplified by PCR, and characterized by DNA sequencing. By marrying synthetic organic chemistry with molecular biology, this work has led to the first examples of synthetic molecules undergoing the powerful processes of translation, selection, and amplification previously available only to biological macromolecules. Professor Liu and coworkers are currently using this evolution-based approach to discover both synthetic molecules and new chemical reactions with properties difficult to achieve using traditional chemical strategies.

Abstract:

An Evolution-Based Approach to the Creation and Discovery of Functional Synthetic Molecules

This lecture will summarize the development of a new approach to (*i*) controlling chemical reactivity and (*ii*) discovering functional synthetic molecules that is based on Nature's molecular evolution approach to synthesis and discovery. Insights into the nature of DNA-templated synthesis will be presented, as well as the integration of these insights into the development of multistep small-molecule syntheses programmed by DNA, DNA-templated small-molecule library synthesis, *in vitro* selections for DNA-linked synthetic molecules, and an evolution-based approach to the discovery of new chemical reactions. These studies have enabled synthetic small molecules to participate in powerful processes such as translation, selection, and amplification previously available only to biological macromolecules.

ROGER TSIEN, Ph.D.

Roger Y. Tsien was born in New York City in 1952 and received his A.B. in Chemistry and Physics summa cum laude from Harvard College in 1972. A Marshall Scholarship then took him to the Physiological Laboratory at the University of Cambridge, where he received his Ph.D. in 1977 and remained as a Research Fellow until 1981. He then became an Assistant, Associate, then full Professor in the Dept. of Physiology-Anatomy at the University of California, Berkeley. In 1989 he moved to the University of California, San Diego, where he is an Investigator of the Howard Hughes Medical Institute and Professor in the Depts. of Pharmacology and of Chemistry & Biochemistry. In 1996 he was a scientific co-founder of Aurora Biosciences Corporation, which went public in 1997 and was acquired by Vertex Pharmaceuticals in 2001. In 1999 he was a scientific co-founder of Senomyx, Inc. His most recent honors include the Davson Lectureship of the American Physiological Society (2003), the Alexander Todd Visiting Professorship of Chemistry at the University of Cambridge (2003), the Keith Porter Lectureship of the American Society for Cell Biology (2003), the Wolf Prize in Medicine (shared with Robert Weinberg, 2004), and the Grass Foundation Lectureship of the Society for Neuroscience (2004). He was elected to the Institute of Medicine in 1995 and the National Academy of Sciences in 1998.

Dr. Tsien's research has been at the interfaces between organic chemistry, cell biology, and neurobiology, starting long before such interdisciplinary efforts became fashionable. He is best known for designing and building molecules that either report or perturb signal transduction inside living cells. These molecules, created by organic synthesis or by engineering naturally fluorescent proteins, have enabled many laboratories including his to gain new insights into signaling via calcium, sodium, pH, cyclic nucleotides, nitric oxide, inositol polyphosphates, membrane potential changes, protein phosphorylation, active export of proteins from the nucleus, and gene transcription. The optical reporter molecules are also valuable in miniaturized high-throughput screening of candidate drugs in the pharmaceutical industry. His current research goals are to understand how the spatial and temporal dynamics of signal transduction orchestrate complex cellular responses such as gene expression and synaptic plasticity. These goals will require improved molecular techniques to see and manipulate small-molecule messengers, protein phosphorylation, and protein-protein interaction in live cells and organisms.

Abstract:

Genetically and Proteolytically Targeted Sequences for Imaging from Ultrastructure to Whole Mammals

Short tetracysteine motifs are genetically encoded tags, which can be labeled in live cells with membrane-permeant biarsenical dyes. Unique applications include green vs. red pulse-chase labeling of old vs. new copies of the same protein, and electron-microscopic localization and chromophore-assisted light inactivation of a chosen protein without the problems of antibody penetration. New insights into protein and organellar trafficking result from correlation of time-lapse fluorescence imaging of live cells with electron microscopy of the same cells with higher spatial resolution at a chosen time point. Directed evolution of the tetracysteine motifs has greatly improved the brightness and affinity of labeling. There is also hope for extending such *in situ* labeling to RNA not just proteins; we have discovered that certain short (38-54 nt) aptamers can specifically bind dyes and enhance their fluorescence up to 2400 fold *in vitro*. For clinical applications one would prefer not to have to introduce genes or be limited to optical detection. Arginine-rich sequences are known to mediate uptake of a wide variety of contrast agents into cells and tissues *in vivo*. We have discovered that such uptake can be prevented by appending certain polyanionic sequences and selectively re-activated by cleavage of the linker. This new mechanism offers the exciting possibility that radioactive, magnetic, and infrared contrast agents and therapeutic drugs may be concentrated in diseased tissues expressing particular extracellular proteases.

JEREMY BERG, Ph.D.

Dr. Jeremy M. Berg became director of the National Institute of General Medical Sciences (NIGMS) in November 2003. He oversees a $1.8 billion budget that funds basic research in the areas of cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, bioinformatics, and computational biology. The Institute supports more than 4,400 research grants—about 10 percent of the grants funded by NIH as a whole—as well as a substantial amount of research training grants and programs designed to increase the number of minority biomedical scientists.

Prior to his appointment as NIGMS director, Dr. Berg directed the Institute for Basic Biomedical Sciences at The Johns Hopkins University School of Medicine in Baltimore, MD, where he also served as professor and director of the Department of Biophysics and Biophysical Chemistry. In addition, he directed the Markey Center for Macromolecular Structure and Function and co-directed the W.M. Keck Center for the Rational Design of Biologically Active Molecules at the university.

Dr. Berg's research focuses on the structural and functional roles that metal ions, especially zinc, have in proteins. He has made major contributions to understanding how zinc-containing proteins bind to the genetic material DNA or RNA and regulate gene activity. His work, and that of others in the field, has led to the design of metal-containing proteins that control the activity of specific genes. These tailored proteins are valuable tools for basic research on gene function, and such proteins could one day have medical applications in regulating genes involved in diseases, as well. Dr. Berg has also made contributions to our understanding of systems that target proteins to specific compartments within cells and to the use of sequence databases for predicting aspects of protein structure and function.

Dr. Berg served on the faculty at Johns Hopkins from 1986-2003. Immediately before his faculty appointment, he was a postdoctoral fellow in biophysics at the university. His honors include a Presidential Young Investigator Award (1988-1993), the American Chemical Society Award in Pure Chemistry (1993), the Eli Lilly Award for Fundamental Research in Biological Chemistry (1995), and the Maryland Outstanding Young Scientist of the Year (1995). He also received teaching awards from both medical students and graduate students and served as an advisor to the Johns Hopkins Postdoctoral Association since its founding.

Dr. Berg received B.S. and M.S. degrees in chemistry from Stanford University in 1980 and a Ph.D. in chemistry from Harvard University in 1985. He is a coauthor of more than 100 research papers and three textbooks, *Principles of Bioinorganic Chemistry, Biochemistry (5th Edition),* and *A Clinical Companion to Accompany Biochemistry*.

NIGMS supported Dr. Berg's research from 1986-2003.

Abstract:

Chemical Approaches to Zinc Finger Protein Analysis and Design

Zinc finger domains of the Cys_2His_2 class, first discovered in *Xenopus* transcription factor IIIA, are the most abundant domain encoded in the human genome. Current analysis reveals the presence of zinc finger domains in more than 8000 proteins. Each domain of approximately 30 amino acids binds a zinc ion and forms a strand-strand-helix structure well suited for interacting with double stranded DNA. In humans, DNA-binding proteins containing these domains typically contain tandem arrays of at least three domains. Through the use of peptide ligation chemistry, it has been possible to synthesize arrays of three domains. These synthetic methods have allowed the preparation of proteins that contain unnatural or modified amino acids. These proteins have been used to expand the range of DNA sequences that can be recognized with high fidelity and to probe the effects of protein phosphorylation on DNA-binding affinity.

JONATHAN ELLMAN, Ph.D.

Jonathan Ellman received his B.S. degree from M.I.T. in 1984 where he worked in the laboratory of K. B. Sharpless. He completed his Ph.D. degree with David A. Evans at Harvard University in 1989. After an NSF postdoctoral fellowship at the University of California at Berkeley with Peter G. Schultz, he joined the faculty at the University of California at Berkeley in 1992 where he is currently Professor of Chemistry. He holds a joint appointment at University of California at San Francisco in the Department of Cellular and Molecular Pharmacology. His laboratory is engaged in the development of systematic tools to establish protein function through the design and synthesis of small molecule libraries targeting protein families. In addition, his group places a major emphasis on the development of practical and general new synthesis methods. Professor Ellman has received a number of awards, including the 2003 Society of Biomolecular Screening Achievement Award, the 2003 Scheele Award selected by the Swedish Academy of Pharmaceutical Sciences, an American Chemical Society Cope Scholar Award, and the University of California at Berkeley Department of Chemistry Teaching Award.

Abstract:

Combinatorial Chemistry Targeting Protein Families

The immense impact of genome sequencing endeavors will be realized as the biological functions of the enormous number of newly identified proteins are determined. Combinatorial chemistry can play an important role in achieving this goal by expediting the identification of potent and selective substrates and ligands for use in dissecting protein function in cells and animals. Combinatorial libraries designed to target protein families are particularly powerful because they can be efficiently and systematically leveraged against any protein within the targeted family. Here we will describe the application of synthetic libraries that target proteases, which regulate many biological processes and represent one of the most important classes of drug targets. Library methods to rapidly establish substrate specificity profiles and to identify cell permeable inhibitors will be presented.

GARY GLICK, Ph.D.

Gary Glick obtained his Ph.D. from Columbia University in 1988, studying organic chemistry under the direction of W. Clark Still. He then completed a National Institutes of Health postdoctoral fellowship at Harvard University where he studied bio-organic chemistry in the laboratory of Jeremy R. Knowles. In 1990, Dr. Glick joined the chemistry faculty at the University of Michigan in Ann Arbor, where he presently holds the Werner E. Bachmann chair in chemistry, is a professor in the Department of Biological Chemistry at the University of Michigan Medical School, and is a member of the training faculty for the Immunology Graduate Program. Dr. Glick's research interests are in drug discovery and development for autoimmune diseases; mechanisms of chemical-induced apoptosis; nucleic acid structure, folding and recognition; and molecular recognition of nucleic acids by proteins.

Dr. Glick has served and continues to serve on several boards and committees, including the Bioorganic & Natural Products Chemistry Study Section of the National Institutes of Health and the Scientific Advisory Board of the National Arthritis Foundation, Michigan Chapter. He is Co-Director of the NIH Chemistry-Biology Interface Training Program at the University of Michigan, Co-Editor of *Current Protocols in Nucleic Acid Chemistry*, and is the scientific founder of GMP|ImmunoTherapeutics, Inc.

Dr. Glick's scientific contributions have been recognized with a number of awards, including an Arthritis Investigator Award from the National Arthritis Foundation, a Junior Faculty Research Award from the American Cancer Society, a Young Investigator Award from the National Science Foundation, a Camille Dreyfus Teacher-Scholar Award, a Research Fellowship from the Alfred P. Sloan Foundation, and a Research Excellence Award from the University of Michigan.

Abstract:

Chemistry and Biology of Immunosuppressive Benzodiazepines

Developing specific and effective therapeutics for autoimmune diseases like systematic lupus erythematosus (SLE) remains challenging. Although considerable progress has been made in understanding the factors that trigger SLE pathogenesis, very few molecular targets for drug discovery have been identified and validated. We recently identified a novel lymphotoxic 1,4-benzodiazepine (Bz-423). When administered to mouse models of lupus, Bz-423 specifically induced apoptosis in disease-causing lymphocytes resulting in attenuation of disease progression and prolongation of survival. Unlike cyclophosphamide, which is the most common agent used to treat lupus, the therapeutic dosage of Bz-423 suppressed autoimmune disease without adverse non-specific toxicity or suppression of normal immune function. These data suggested that Bz-423 interacts with a target or pathway intimately related to SLE. The results of studies aimed at elucidated the mechanism by which Bz-423 functions and its cellular target will be discussed.

STEPHEN FESIK, Ph.D.

Stephen Fesik obtained his Ph.D. in Medicinal Chemistry from the University of Connecticut in 1981 and was a postdoctoral associate at Yale University in the Department of Molecular Biophysics and Biochemistry from 1981 to 1983. After his postdoctoral work, he joined Abbott Laboratories. At Abbott he developed several new NMR methods that are widely used today, including isotope-edited NMR experiments for studying molecular complexes, heteronuclear three-dimensional NMR spectroscopy, and NMR experiments that utilize ^{13}C-^{13}C magnetization transfer by isotropic mixing. He also determined the three-dimensional structures of several proteins and protein/ligand complexes. In addition to these structural studies, he developed a method for drug discovery called SAR by NMR and applied this method to identify and optimize ligands for binding to many protein drug targets. His current research interests include the use of siRNA for target identification and target validation. Dr. Fesik has published over 200 papers, trained 27 postdoctoral fellows, has been a reviewer for the NIH Biophysical Chemistry Study Section, and has served as a member of the Editorial Boards of the *Journal of Medicinal Chemistry, Journal of Biomolecular NMR, Biophysical Journal, Molecular Cell,* and *Nature Reviews Cancer* (Highlights Advisory Panel). In addition, he is a member of the Keystone Scientific Advisory Board, the Program Planning Committee and Board of Directors, the Bruker Scientific Advisory Board, and the Scientific Advisory Committee for the Cyprus Conference of New Methods in Drug Research. He has obtained several awards, including the Chairman's Award (1996) and Outstanding Researcher of the Year Award (1997) at Abbott Laboratories, the Servier Lectures Award (1998) from the University of Montreal, the ASBMB-Fritz Lipmann Award (1999), and the lifetime achievement award in nuclear magnetic resonance from EAS (2003). He is currently Divisional Vice President of Cancer Research at Abbott Laboratories where he leads a group responsible for discovering new drugs to treat cancer.

Abstract:

NMR-Based Screening of Fragment Libraries for Drug Discovery

Fragment-based approaches for discovering high affinity ligands to proteins represent useful tools for drug discovery. One of the best methods for detecting the binding of small molecular fragments that often bind weakly to proteins is NMR spectroscopy. In this presentation, the use of NMR for discovering protein ligands will be discussed, and applications of NMR-based screening for the discovery of anti-cancer compounds will be presented.

KEVAN SHOKAT, Ph.D.

Professor Shokat received his Ph.D. in 1991 from UC Berkeley with Peter Schultz and completed post-doctoral work at Stanford in 1994 before moving to Princeton University as an Assistant Professor of Chemistry and Molecular Biology. He was promoted to Associate Professor in 1998. In 1999, Shokat moved to the Bay Area where he is a Professor in the Department of Cellular and Molecular Pharmacology at UC San Francisco as well as Full Professor of Chemistry at UC Berkeley.

Abstract:

Chemical Tools for Deciphering Cell Signaling Pathways

Our laboratory focuses on the development of novel chemically based tools to decipher signal transduction pathways on a genome-wide scale. We have developed a method for producing small molecules that are specific for any protein kinase of interest in a signaling cascade by combining protein design with chemical synthesis. These highly specific inhibitors of individual kinases have revealed a number of new principles of signal transduction that have complemented genetic and biochemical studies of cell signaling. Examples where new pathways and new functions can be revealed by small molecule inhibitors of protein kinases will be highlighted. A second area of interest in our laboratory is the tracing of direct kinase substrates. We have designed and synthesized unnatural ATP analogs which are substrates of our engineered kinases but are poorly accepted as substrates of wild-type kinases. This specific nucleotide substrate of any kinase of interest allows for the radiolabelling of the direct substrates of a wide variety of protein kinases including both serine/threonine and tyrosine kinases. New methods for the isolation and identification of low abundance substrates of kinases from cells will be discussed. Once a phosphoprotein product of a kinase is identified, the specific phosphorylation site is often difficult to identify using traditional tryptic peptide phosphorylation site mapping. Using a novel strategy based on the design of tailor made proteases which specifically cleave proteins after sites of phosphorylation, we have developed a rapid means to map protein phosphorylation patterns. Finally, a potential link between the unnatural ligands of engineered kinases and a set of plant hormones, the cytokinins, will be discussed in the context of a custom designed database created for the genome wide analysis of protein kinase catalytic domains.

DAVID DILLER, Ph.D.

David Diller received his Ph.D. in mathematics from Northwestern with a specialty in partial differential equations in 1996. Recognizing greener pastures he accepted a Sloan Fellowship to move into an applied discipline. With this fellowship he spent three years as a post-doc in Wim Hol's group at the University of Washington. During this time, he was fortunate enough to be able to work on a wide range of problems including: modeling protein crystallization experiments, interpreting electron density maps, and structure based drug design. Dr. Diller has spent the last five years at Pharmacopeia. Initially, he worked in the Center for Informatics and Drug Discovery developing high throughput docking methods. Ultimately, the attraction of applying these and other methods became too strong, and as a result he moved into Pharmacopeia's molecular modeling group. He is now functioning as the group leader for molecule modeling and spends most of his discretionary time thinking about how computational chemistry, molecular modeling and bioinformatics techniques can be applied to design chemical libraries for families of targets such as kinases, GPCRs etc. and how this information can be used to benefit the downstream drug discovery process.

Abstract:

The Role of Computation When Building Collections of Millions of Compounds

Pharmacopeia began ten years ago with the premise of building large combinatorial libraries and accordingly has built a collection of over seven million compounds. With the ability to synthesize and screen so many molecules one might wonder why would computation be needed at all. In this talk we highlight how the role of computation at Pharmacopeia has changed in the last decade and how computation has been successfully applied. The computational areas discussed include diversity, ADME Tox modeling, target class library design and data mining over large amounts of historical high throughput screening data. Finally, we highlight areas where combinatorial library design can be improved to further increase its impact in the drug design process.

VIRGINIA CORNISH, Ph.D.

Virginia Cornish graduated summa cum laude from Columbia University with a B.A. in Biochemistry in 1991, where she did undergraduate research with Professor Ronald Breslow in the Chemistry Department. She then moved west to do research with Professor Pete Schultz in the Chemistry Department at the University of California at Berkeley as an NSF Predoctoral Fellow. In Professor Schultz's laboratory she helped develop a new methodology for incorporating synthetic amino acids into proteins using the protein biosynthetic machinery. In 1996, she became an NSF Postdoctoral Fellow in the Biology Department at M.I.T. under the guidance of Professor Bob Sauer. At M.I.T. she initiated an independent project that is the basis for the directed evolution program in her laboratory at Columbia. Virginia joined the Chemistry Department at Columbia in 1999, working at the interface of chemistry and biology. Her laboratory brings together modern methods in synthetic chemistry and DNA technology to co-opt biological systems for the synthesis of new materials, understanding the function of these systems by challenging their specificity at the molecular level. Her research has been recognized by numerous awards including a Sloan Foundation Fellowship, a Beckman Young Investigator Award, and an NSF CAREER Award.

Abstract:

Co-opting Nature for Chemical Diversity

Nature readily creates and screens chemical diversity for the evolution of potent natural products, enzymes with new functions, and even complex systems. Fundamental to natural evolution is genetic encoding of this diversity so that phenotype and genotype are linked. Rather than compete with Nature, our laboratory looks to co-opt biological systems to create and screen chemical diversity by bringing together modern methods in synthetic chemistry and DNA technology. Here we present two such systems. To create chemical diversity, we use synthetic aminoacyl-tRNA substrates with a purified translation system for ribosome encoded synthesis of peptidomimetics. To screen chemical diversity, we use chemical dimerizers to co-opt traditional genetic selections for reporter gene transcription to read-out enzyme catalysis. In the chemistry tradition, manipulation of these biological systems at the molecular level provides fundamental insight into their function.

ERIC LANDER, Ph.D.

Dr. Eric Lander is the Director of the Eli and Edythe L. Broad Institute of MIT and Harvard. Dr. Lander is Professor of Biology at MIT, Professor of Systems Biology at the Harvard Medical School and a Member of the Whitehead Institute. He is a geneticist, molecular biologist, and mathematician.

Dr. Lander is one of the driving forces behind today's revolution in genomics, the study of all of the genes in an organism and how they function together in health and disease. He has been one of the principal leaders of the Human Genome Project.

Dr. Lander founded the Whitehead/MIT Center for Genome Research in 1991, and the Center became part of the newly founded Broad Institute in 2003. Under Dr. Lander's leadership, the Center has developed many of the key tools of modern human and mammalian genomics and has applied them to pioneer new ways to understand the basis of disease. The Center has made its data and tools freely available to the scientific community, with the aim of accelerating progress in biomedical research.

Dr. Lander earned his B.A. in mathematics from Princeton University in 1978 and his Ph.D. in mathematics from Oxford University in 1981. In addition to his work in biology, he was an assistant and associate professor of managerial economics at the Harvard Business School from 1981 to 1990.

Dr. Lander was named a Rhodes Scholar in 1978 and received a MacArthur Foundation Fellowship in 1987 for his work in genetics. He was elected to the U.S. National Academy of Sciences in 1997, the U.S. Institute of Medicine in 1998, and the American Academy of Arts and Sciences in 1999. He has received numerous awards and honorary degrees, and has served on many advisory boards for governments, academic institutions, scientific societies, and companies.

In addition to his research, Dr. Lander is an enthusiastic teacher. He has taught MIT's core introductory biology course for a decade and, in 1992, won the Baker Memorial Award for Undergraduate Teaching at MIT. He has also lectured widely to both scientific and lay audiences about the medical and social implications of genetics, and was selected to deliver a special Millennium Lecture at the White House in 2000.

DIMITRIS AGRAFIOTIS, Ph.D.

Dimitris K. Agrafiotis is Senior Research Fellow and Team Leader of Molecular Design & Informatics at Johnson & Johnson Pharmaceutical Research & Development. He also serves as Adjunct Professor of Informatics at Indiana University School of Informatics. Dr. Agrafiotis received his B.S. in chemistry from the University of Patras, Greece, in 1985, and Ph.D. in theoretical organic chemistry from Imperial College, University of London, in 1988, under the direction of Prof. H. Rzepa. Following post-doctoral training with Prof. A. Streitwieser at the University of California, Berkeley, and Nobel laureate Prof. E. J. Corey at Harvard University, he joined Parke-Davis Pharmaceutical Research (now Pfizer Global Research) as a Senior Scientist in the Computer-Aided Drug Design group. In 1994, he moved to 3-Dimensional Pharmaceuticals where he has focused on the development of intelligent computational tools for combinatorial chemistry and structure-based drug design, serving as Executive Director of Informatics. Following the acquisition of 3DP by Johnson & Johnson, he has assumed line responsibility for the computer-assisted drug design, informatics and database groups at the Exton, Cranbury and Spring House sites, oversees the software and database systems supporting compound and screening logistics, and directs the development of a new global informatics platform for J&J PRD. His research interests span many areas of computational chemistry and biology, including computer-assisted drug design, combinatorial chemistry and organic synthesis, molecular diversity, QSAR, artificial intelligence, and software engineering. He is the author of more than 50 scientific publications and 13 patents, and is a co-inventor of 3DP's proprietary DirectedDiversity® technology. He has been a fellow of the Alexander Onassis Foundation and serves on the Editorial Board of the *Journal of Molecular Graphics and Modeling*. More information can be found at www.dimitris-agrafiotis.com.

Abstract:

Molecular Informatics for the New Drug Discovery Enterprise

The multitude of potential drug targets emerging from genome sequencing demands new approaches to drug discovery. A chemo-genomics strategy, involving the generation of small molecule compounds that can be used both as tools to probe biological mechanisms and as leads for drug property optimization, provides a highly parallel, industrialized solution. Key to the success of this strategy is an integrated suite of chemi-informatics tools that can enable the rapid and directed optimization of chemical compounds with drug-like properties using just-in-time combinatorial chemical synthesis. An effective embodiment of this process requires new computational and data mining tools that cover all aspects of library generation, modeling and design, and work effectively on a massive scale. This talk will introduce the essential elements of a convergent, computer-controlled optimization process known as DirectedDiversity®, and highlight key algorithmic advances that expand, by several orders of magnitude, the number of compounds that can be assessed as potential drugs. Our strategy for the effective integration of these tools into a coherent informatics framework for drug discovery will also be outlined. Unlike conventional approaches which involve loose integration of heterogeneous third-party tools, our strategy is based on a unified framework that allows the rapid development of powerful, inter-operable software components that share not only interfaces but also the same underlying fundamental algorithms and code.

CHAITAN KHOSLA, Ph.D.

Chaitan Khosla is a Professor of Chemistry, Chemical Engineering, and, by courtesy, of Biochemistry at Stanford University. He received his Ph.D. in 1990 at the California Institute of Technology. After completing postdoctoral studies at the John Innes Centre in the U.K., he joined Stanford in 1992. His research interests focus on the chemistry and biology of medicinally important enzymes. Over the past decade he has studied polyketide synthases as paradigms for modular biosynthesis, and has sought to exploit their properties for engineering novel antibiotics. He has co-authored over 150 publications, and is the recipient of several awards and honors including a Camille and Henry Dreyfus New Investigator Award (1991), a National Science Foundation Young Investigator Award (1994), a David and Lucile Packard Fellowship for Science and Engineering (1994), the 1997 Allan P. Colburn Award from the American Institute of Chemical Engineers, the 1999 Eli Lilly Award in Biological Chemistry and the 2000 Pure Chemistry Award from the American Chemical Society, and the 1999 Alan T. Waterman Award from the National Science Foundation. He is also the recipient of a Distinguished Alumnus Award from his undergraduate (Indian Institute of Technology) and graduate (Caltech) alma maters. He is a founder and co-Chairman of the Scientific Advisory Board of Kosan Biosciences, Inc., a public company dedicated to the discovery and development of new polyketide natural product drugs. He is also the founding President of the Celiac Sprue Research Foundation, a non-profit laboratory that merges chemistry and clinical science to improve the quality of life of Celiac Sprue patients.

Abstract:

Discovery and Development of New Natural Product Drugs: The Example of Polyketides

Although natural products have been a fertile source of new lead molecules and drugs over the past century, the pace of development of new natural product drugs has dramatically reduced within the past two decades. The reasons for this "lack of productivity" will be analyzed, and an overview of selected new technologies for remedying the situation will be presented. Polyketides are a large family of structurally diverse natural products with a broad range of biological activities. Recent studies have provided new insights into the mechanisms of biosynthesis of these complex natural products. The modularity of multifunctional polyketide synthases has been vividly illustrated through a variety of experimental approaches, which in turn have led to the engineering of numerous "unnatural" natural products. Emerging opportunities and challenges for the discovery and development of new polyketide drugs will be summarized.

BALDOMERO OLIVERA, Ph.D.

Baldomero Olivera is a Distinguished Professor of Biology at the University of Utah as well as an Adjunct Professor at the Salk Institute in La Jolla, California. He obtained his Ph.D. in Biochemistry from the California Institute of Technology in Pasadena, California.

Although the present research focus of Dr. Olivera's laboratory is the characterization of conotoxins, pharmacologically active peptides from venomous cone snails, earlier in his career, he investigated enzymes involved in DNA metabolism. He discovered and purified *E. coli* DNA ligase with Dr. I.R. Lehman, and characterized the intermediates in DNA ligation. This work revealed that NAD, the classical redox cofactor, had a radically different role as an energy source for DNA ligation. This led Olivera to characterize the pyridine nucleotide cycles of both prokaryotes and eukaryotes.

Conotoxins have had an impact on several disciplines; as standard ligands to discriminate between multiple molecular forms of ion channels and receptors, they have greatly accelerated progress in molecular neuroscience. ω-Conotoxins discovered by Olivera's lab were key in developing the calcium channel field. Several conotoxins have therapeutic application, with one close to FDA approval. Conotoxins are being investigated by laboratories all over the world and used by an ever greater number of researchers. Over 2,000 publications describe experimental work using conotoxins developed by the Olivera lab.

Abstract*:*

Conus Peptides: From Genes to Venoms to Drugs

The 500 species of carnivorous cone snails (*Conus*) use their complex venoms to capture prey and defend themselves against predators. The biologically active venom components are small, highly structured peptides ("conotoxins"), mostly 12-35 amino acids in length. A few gene superfamilies have greatly diversified to generate the >50,000 different conotoxins expressed in the venoms of living cone snails, most affecting a specific ion channel or receptor target.

Of the first 30 conotoxins isolated and characterized, three have reached human clinical trials. Although these are translation products of genes, most conotoxins can be made by direct chemical synthesis from the DNA sequence. The feasibility of using conotoxin-like peptides for small molecule drug development will be discussed.

MICHAEL ORGAN, Ph.D.

Michael Organ is Assistant Professor of Chemistry and Director of the York University Combinatorial Chemistry Facility. Dr. Organ's research has focused on synthetic efficiency and more specifically on the application of tandem-reaction methodology to improve synthetic efficiency. This methodology, focused initially on carbon-carbon bond forming methods, has been expanded to include carbon-heteroatom bond formation. There have been two areas of intense interest that have formed the backbone of his research program. The first area is tandem cycloaddition/electrophilic substitution chemistry involving allylsilane substrates that give rise to polysubstituted carbocyclic and heterocyclic compounds. The second is metal catalyzed allylic substitution and cross coupling reactions that have been combined into general sequences to prepare polysubstituted, olefin-containing products in a convergent and stereoselective fashion.

While initial studies in both areas have been concerned with methods development, progress has allowed Dr. Organ's group to undertake the synthesis of a number of natural product targets. Further, progress in tandem-reaction chemistry involving heteroatoms has also allowed Dr. Organ's group to initiate a program in the synthesis of pharmaceutically-relevant compounds. This latest initiative has resulted in the formation of collaborative projects with a number of pharmaceutical and instrumentation companies, many of which are active members of the Combinatorial Facility at York. This facility is fully equipped with all the leading edge synthetic and analytical facilities to prepare libraries of potential drug leads.

Dr. Organ has developed his research into two spin-off companies. The first, Total Synthesis Ltd. prepares libraries of compounds (usually lead development) for commercial application. The second, York Bioanalytical Laboratories, handles high-throughput analytical chemistry. He consults for a number of companies and collaborates directly with many others. He has given twenty five invited lectures and provided twelve short courses for the American Chemical Society on combinatorial chemistry in the last two years in Asia, Europe and North America. Dr. Organ has received a number of awards, the most recent being the 1999 Premier's Research Excellence Award for Ontario (Canada) and the 2002 SFI Walton Fellowship (Ireland).

Abstract:

New Advances in the Screening of Compound Mixtures

The high throughput synthesis and screening of discrete compounds has significantly diminished the need to screen compound mixtures. However, natural products and some synthetic compounds (e.g., peptides) still are supplied very effectively as mixtures. While traditional screening still evaluates mixtures on an averaged basis, frontal affinity chromatography (FAC) is capable of differentiating compounds within a mixture. By coupling FAC with mass spectroscopy detection (FAC/MS), those differentiated compounds can all be identified and their binding data individually assessed, despite their being assessed all together at the same time. Traditional methods of affixing the target protein within the affinity column include covalent methods and coordinative measures, such as avidin/biotin attachment. These methods have many problems associated with them. The presentation will outline the use of sol gel glass as a medium to entrap target proteins, rather than actually binding them to a surface, and discuss screening results obtained using the FAC/MS technique.

ALAN VERKMAN, M.D., Ph.D.

Alan S. Verkman received undergraduate degrees in biology and physics at M.I.T., a Ph.D. in physics at Harvard University and an M.D. at Harvard Medical School. His clinical training in Internal Medicine was done at the Brigham and Womens Hospital in Boston and in Nephrology at U.C.S.F. Dr. Verkman has remained at U.C.S.F. and is currently Professor of Medicine and Physiology and senior scientist in the Cardiovascular Research Institute, as well as director of the Cystic Fibrosis Research Development Program. Dr. Verkman directs a large research group funded by five NIH grants, including a MERIT award, and two program grants from the Cystic Fibrosis Foundation, including a drug discovery grant. He has authored more than 300 journal articles and 60 reviews, and is a recognized authority in membrane transporter physiology and molecular genetics. Dr. Verkman's research is focused on the biology of aquaporin water channels and CFTR chloride channels in cystic fibrosis, and the development of novel fluorescence methodology to study diffusion and protein-protein interactions in living cells. Dr. Verkman has established a unique academic drug discovery program with in-house resources to carry out high-throughput screening, combinatorial chemistry, and small animal pharmacology and efficacy testing. His recent focus in drug discovery is in the development of CFTR inhibitors as antidiarrheals, and activators of mutant CFTRs for therapy of cystic fibrosis.

Abstract:

Drug Discovery in Academia: CFTR Chloride Channel Inhibitors and Activators for Cystic Fibrosis

We have set up an academic lab-based drug discovery program with resources including high-throughput screening of a 250,000 small molecule collection, synthetic/medicinal chemistry, and small animal pharmacology/efficacy testing. The motivation for this work was the identification of inhibitors of the cystic fibrosis transmembrane conductance regulator (CFTR) for antidiarrheal applications, and activators of mutant CFTRs (including ΔF508-CFTR) for therapy of cystic fibrosis. A cell-based kinetics assay of CFTR function was developed using cells co-expressing wildtype or mutant CFTR together with a green fluorescent protein-based halide sensor. Of 150,000 compounds screened for CFTR inhibition, two validated classes of leads have emerged. The thiazolidinone $CFTR_{inh}$-172 reversibly inhibited CFTR chloride current with $K_d \sim 300$ nM by a voltage-independent block mechanism involving prolonged channel closed times. The compounds showed good specificity, not inhibiting other chloride channels or ABC transporters, and low toxicity in cell culture and rodent models. $CFTR_{inh}$-172 was effective as an antidiarrheal in rodent models of cholera (cholera toxin) and Travelers diarrhea (STa toxin). ADMET analysis indicated slow renal elimination without metabolism, and enterohepatic circulation with intestinal accumulation.

ΔF508-CFTR is the most common mutation causing CF, having defects both in channel gating and ER processing. Screening was carried out to identify 'potentiators' to overcome the gating defect, and 'correctors' to overcome the processing defect. To identify potentiators, test compounds were added 15 min prior to assay of iodide uptake in epithelial cells co-expressing ΔF508-CFTR and the fluorescent halide indicator in which ΔF508-CFTR was targeted to the plasma membrane by culture at 27 ^oC for 24 h. Out of 150,000 compounds screened, two validated classes of lead potentiators were identified. After SAR analysis and compound optimization, the best compounds of the benzothiophene class corrected defective ΔF508-CFTR gating with K_d down to 50 nM. To identify correctors, test compounds were added to cells grown at 37 ^oC at 24 h prior to assay. Six novel compound classes correct defective ΔF508-CFTR processing to levels greater than achieved by low temperature rescue, at 0.4-5 μM K_d. Correction has been verified electrophysiologically and biochemically, and analysis of correction mechanism and specificity is in progress. Our studies demonstrate the feasibility of academia-based drug discovery. The small-molecule ΔF508-CFTR activators identified here may be useful for therapy of cystic fibrosis caused by the ΔF508 mutation.

GEOFFREY DUYK, M.D., Ph.D.

Geoffrey Duyk was, until 2004, President of Research & Development at Exelixis, Inc., where he led a 550+ person group focused on the discovery and development of small molecule therapeutics. He joined Exelixis in April 1997 from Millennium Pharmaceuticals, where he was one of the founding scientific staff. As Vice President of Genomics at Millennium, he was responsible for building and leading the informatics, automation, DNA sequencing and genotyping groups as well as the mouse and human genetics group. Prior to his tenure at Millennium, Dr. Duyk was an Assistant Professor of Harvard Medical School (HMS) in the Department of Genetics and Assistant Investigator of the Howard Hughes Medical Institute (HHMI). While at HMS, Dr. Duyk was a Co-Principal Investigator in the National Institutes of Health (NIH) funded Cooperative Human Linkage Center. Dr. Duyk has been and continues to be a member of numerous NIH panels and oversight committees focused on the planning and execution of the Human Genome Project. Dr. Duyk holds a Ph.D. and M.D. from Case Western Reserve University and completed his medical and fellowship training at University of California, San Francisco. While at UCSF, Dr. Duyk was a fellow of the Lucille P. Markey Foundation and was also awarded a post-doctoral fellowship from the Howard Hughes Medical Institute.

Abstract:

Small Molecules as Research Tools vs. Small Molecules as Drugs: Similarities and Differences

Selected small molecules have long been developed as drugs in the pharmaceutical and biotechnology sectors. Most of this conference has focused on the use of this class of molecules as probes for basic biological processes, and this latter utility is the focus of much of the NIH Molecular Libraries Roadmap initiative. There is often interest in academic settings in converting small molecule research tools with interesting properties into compounds suitable for therapeutic use in humans. While this transition is highly desirable, the barriers to accomplishing it can be underestimated in settings where drug development is not routinely done. I will present a view, derived from experience in both academia and industry, of the differences in (1) types of compounds that would be useful in basic (e.g., biochemical, cell biological) mechanistic experimentation as compared to those suitable for therapeutic use; (2) types of targets that might be tractable for basic vs. therapeutic uses; (3) the steps that need to be worked through to convert a probe useful for basic research applications into a compound that can be used in humans, including ADME, Toxicology, and clinical phases.

MEDICINE

The NIH Roadmap

Elias Zerhouni

The National Institutes of Health (NIH) is at a critical moment in its prestigious history. As the 21st century unfolds, discovery in the life sciences is accelerating at an unprecedented rate. Although the sequencing of the human genome presents vast opportunities for researchers, it also creates a series of challenges that will redefine the ways that medical research is conducted and, ultimately, how research leads to improvements in health.

The 5-year doubling of the NIH budget, completed in FY 2003, both picked up the pace of discovery and heightened public expectations. As I assumed the directorship of NIH, early discussions with legislators, administration officials, and institute directors, as well as public, patient advocacy, and scientific leaders convinced me that NIH needed to examine its portfolio with an eye to identifying critical scientific gaps.

The NIH earned its reputation for success because of the vitality of its institutes, centers, and offices and because of the diverse ways in which it funds and conducts research—all fostered by decentralization inherent to its organization and funding streams. This characteristic serves the agency well and should be preserved. However, as science grows more complex, it is also converging on a set of unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches. Today, NIH research needs to reflect this new reality.

Over the past year, NIH and its leadership have been engaged in a process dubbed the "NIH Roadmap." This process was designed to ask the kind of probing questions that a complex research organization should periodically pose, especially when in transition. The roadmap was purposefully focused on efforts that no single or small group of institutes or centers could or should conduct on its own, but that NIH as a whole must address to ensure both efficient and effective discovery. This was not a reexamination of the strategic plans of each institute or the development of a wholly new comprehensive plan for the sake of being responsive to every interest and constituency. This would have led to a reasoned, but impractical, plan. Rather, the goal was to define a compelling, limited set of priorities that can be acted on and are essential to accelerate progress across the spectrum of the institute missions.

Our consultations began first with the scientific community and public constituencies, representing over 300 of the nation's biomedical leaders from academia, government, and the private sector. We asked participants to address three key questions: What are today's most pressing scientific challenges? What are the roadblocks to progress and what must be done to overcome them? Which efforts were beyond the mandate of one or a few institutes, but were the responsibility of NIH as a whole?

Through these consultations, three major themes emerged—New Pathways to Discovery, Research Teams of the Future, and Reengineering the Clinical Research Enterprise. These ideas were examined by 15 working groups, each led by institute directors, with input from the NIH Council of Public Representatives and the Advisory Committee to the Director.

In June, the NIH leadership met to make final selections of key initiatives to be launched in FY 2004 based on the following criteria: Is the initiative truly transforming—will it dramatically change the content or the process of medical research in the next decade? Would outcomes from the initiative be used by, and synergize the work of, many institutes? Can the NIH afford not to do it? Will the initiative be compelling to NIH stakeholders, especially the public? Does the initiative position the NIH to do something that no other entity can or will do?

At this juncture, working groups with thematically related initiatives were combined and reorganized into nine implementation groups (see the table) responsible for developing the proposals into tangible activities to be launched in FY 2004. The initiatives are complex, so their implementation will be gradual and tailored to specific short- and long-term goals. Some efforts will reach fruition rapidly; others will require longer incubation periods before being fully realized.

NIH ROADMAP—THEMES, IMPLEMENTATION GROUPS, AND INITIATIVES *

New Pathways to Discovery

- Building Blocks, Pathways, and Networks Implementation Group
  - National Technology Centers for Networks and Pathways
  - Metabolomics Technology Development
  - Standards for Proteomics and Metabolomics/Assessment of Critical Reagents for Proteomics
- Molecular Libraries and Imaging Implementation Group
  - Creation of NIH Bioactive Small-Molecule Library and Screening Centers
  - Cheminformatics
  - Technology Development
  - Development of High-Specificity/High-Sensitivity Probes to Improve Detection
  - Comprehensive Trans-NIH Imaging Probe Database
  - Core Synthesis Facility to Produce Imaging Probes
- Structural Biology Implementation Group
  - Membrane Protein Production Facilities
- Bioinformatics and Computational Biology Implementation Group
  - National Centers for Biomedical Computing
- Nanomedicine Implementation Group
  - Planning for Nanomedicine Centers

Research Teams of the Future

- High-Risk Research Implementation Group
  - NIH Director's Innovator Awards
- Interdisciplinary Research Implementation Group
  - Interdisciplinary Research (IR) Centers
  - Interdisciplinary Research Training Initiative
  - Innovations in Interdisciplinary Technology and Methods (Meetings)
  - Removing Structural Barriers to Interdisciplinary Research.
  - NIH Intramural Program as a Model for Interdisciplinary Research
  - Interagency Conference on the Interface of Life Sciences and Physical Sciences
- Public-Private Partnerships Implementation Group
  - Designation of a Public-Private Sector Liaison
  - High-Level Science-Driven Partnership Meetings

Reengineering the Clinical Research Enterprise

- Clinical Research Implementation Group
  - Harmonization of Clinical Research Regulatory Requirements
  - Integration of Clinical Research Networks
  - Enhance Clinical Research Workforce Training
  - Clinical Research Informatics: National Electronic Clinical Trials and Research (NECTAR) Network
  - Translational Research Core Services
  - Regional Translational Research Centers
  - Enabling Technologies for Improved Assessment of Clinical Outcomes

The author is the director of the National Institutes of Health, Bethesda, MD 20892, USA.

* For further description see www.sciencemag.org/cgi/content/full/302/5642/63/DC1

However, we will begin to implement all 28 initiatives in 2004, with a clear focus on making viable, enduring changes that will lead to improvements in health. Let me outline the themes and initiatives in more detail.

New Pathways to Discovery. This theme addresses the need to understand complex biological systems. Future progress in medicine will require quantitative knowledge about the many interconnected networks of molecules that comprise cells and tissues, along with improved insights into how these networks are regulated and interact with each other.

New Pathways to Discovery also sets out to build a better "toolbox" for today's biomedical researchers. To fully capitalize on the recent sequencing of the human genome and many new discoveries in molecular and cell biology, the research community needs wide access to technologies, databases, and other scientific resources that are more sensitive, more robust, and more easily adaptable to researchers' individual needs.

Roadmap initiatives within this theme address technologies and approaches necessary to meet contemporary research challenges, including building blocks and pathways, molecular imaging, the development of small-molecule libraries, bioinformatics and computational biology, nanomedicine, and structural biology. We will issue new Requests for Applications (RFAs) in FY 2004 for National Technology Centers for Networks and Pathways, National Centers for Biomedical Computing, Centers for Innovation in Membrane Protein Production, as well as investigator-initiated grants for related research in structural biology, metabolomics technology development, and proteomics. In addition, we will support development of new screening centers for bioactive small molecules, a publicly accessible cheminformatics reference database to be housed at NIH's National Center for Biotechnology Information, and a database and core facility dedicated to synthesizing and distributing molecular imaging probes. The agency will also begin planning a series of nanomedicine centers that will be launched in 2005. These centers will focus on quantitative measurement of biological processes at the nanoscale and the engineering of new tools to intervene at the nanoscale or molecular level. This research will help scientists construct synthetic biological devices, such as miniature, implantable pumps for drug delivery or tiny sensors to scan for the presence of infectious agents or metabolic imbalances.

Research Teams of the Future. The scale and complexity of today's biomedical research problems increasingly demand that scientists move beyond the confines of their own discipline and explore new organizational models for team science. NIH wants to stimulate new ways of combining skills and disciplines in the physical and biological sciences. The Director's Innovator Awards will encourage investigators to take on creative, unexplored avenues of research that carry a relatively high potential for failure, but also possess a greater chance for ground-breaking discoveries. In addition, novel partnerships, such as those between public and private sectors, will be encouraged to accelerate movement of scientific discoveries from bench to bedside.

Solving the puzzle of complex diseases, from obesity to cancer, will require a holistic understanding of the interplay between factors such as genetics, diet, infectious agents, environment, behavior, and social structures. To devise and use the state-of-the-art technologies developed from the roadmap effort, we will need the expertise of nontraditional teams of biological scientists, engineers, mathematicians, physical scientists, computer scientists, and others. The private sector will play an essential role in this new paradigm, and federal agencies will be required to do more collaborating with industry and each other. We recognize that the research teams of the future will look and feel vastly different from their predecessors.

Effecting these changes will require cultural and scientific adjustments and experimentation with new approaches. The implementation group responsible for the Research Teams of the Future devised a plan to meet these challenges with a series of initiatives that provide mechanisms for high-risk strategies, interdisciplinary research, and public-private partnerships. For example, it has been suggested that investigators do not submit their most innovative applications to the NIH because they think the NIH is risk-averse. We have heard that peer review typically values likelihood of success more than potential impact and that some funding decisions are too conservative. To encourage high-risk research, NIH will solicit nominations for the Director's Innovator Awards, which will provide support to a highly select group of individuals who have the potential to make extraordinary contributions. They will be evaluated in terms of their exceptional creative abilities, potential for ground-breaking discovery, evidence of focused and skillful habits of mind that predict perseverance and thorough exploration of his/her ideas, and, most important, prospects for making seminal biomedical research advances.

To build the research workforce of the future, the agency will issue RFAs to promote collaborative efforts, including Exploratory Centers for Interdisciplinary Research and Training for a New Interdisciplinary Research Workforce. These programs will be augmented by conferences and symposia on timely issues, such as methodological innovations and peer review. To expedite the formation of productive public-private partnerships, the NIH will establish a central point of contact to support and encourage NIH activities involving these partnerships.

Reengineering the Clinical Research Enterprise. Although biomedical research has succeeded in converting many lethal diseases into chronic, treatable conditions, continued success requires that the United States recast its entire system of clinical research. Over the years, clinical research has become more difficult to conduct. However, exciting basic science discoveries demand that clinical research continue and even expand, while striving to improve efficiency and better inform basic science. This is undoubtedly the most difficult but most important challenge identified by the NIH Roadmap process.

Clinical research needs to develop new partnerships among organized patient communities, community-based physicians, and academic researchers. In the past, all research for a clinical trial could be conducted in one academic center; that is unlikely to be true in the future. In these initiatives, NIH will promote creation of better integrated networks of academic centers that work jointly on clinical trials and include community-based physicians who care for large groups of well-characterized patients. Implementing this vision will require new ways to organize how clinical research information is recorded, new standards for clinical research protocols, modern information technology, new models of cooperation between NIH and patient advocacy alliances, and new strategies to reenergize the clinical research workforce.

Critics of the nation's current clinical research system have cited several factors that promote inefficiency, including poor integration of existing clinical research networks, inadequate training mechanisms for clinical investigators, inconsistent data standards and database requirements, and lack of information. In addition, successful clinical research relies on public trust, and any proposal that addresses the nation's investment in this area must be sensitive to the needs of the most important NIH constituency, the American people.

The NIH annually funds and conducts billions of dollars of clinical research—$8.4 billion in FY 2003—addressing the full panoply of public health problems that confront the nation. As such, we have a vested interest in catalyzing the transformation of policies throughout the federal government, while maintaining an emphasis on the integrity and effectiveness of federal and institutional systems of oversight. In the upcoming year, the NIH will design pilot programs for a revolutionary National Electronic Clinical Trials and Research (NECTAR) network. These pilot programs will begin to develop an infor-

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matics infrastructure that will link current and emerging clinical research information systems so that data and resources can be shared within and across clinical research networks, across studies and across institutions, reducing duplication and avoiding unnecessary overlap between trials. We expect NECTAR to help streamline clinical research and to accelerate the pace of discovery and application of clinical findings.

We intend to issue RFAs for technologies that improve assessment of clinical outcomes and for regional translational research centers. We will expand efforts to provide advanced training in clinical research, through the Institutional Career Development Award Program and the NIH Clinical Center Clinical Research Training Program. NIH Clinical Research Associates (trained and certified health-care providers) will enroll and follow patients in clinical trials, ensuring that principles of integration will become routine in the clinical research culture.

Roadmap initiatives will also be unique in the manner in which they are funded. All institutes and centers decided to create a new funding mechanism through a common pool of resources agreed upon and contributed to by all of them on the basis of the multiyear roadmap plan. The plan will be administered centrally, but executed by lead institutes or centers as appropriate on behalf of the whole of NIH. This ensures that a steady multiyear and flexible stream of funding is available and also institutionalizes a corporate process for decision-making about trans-NIH priorities. It reflects, in our opinion, a maturation of the NIH toward a more adaptive management of the NIH portfolio—an approach that will enable rapid responses to emerging opportunities that do not fit clearly within the mission of a single or small group of institutes.

The extraordinary participation of hundreds of NIH staff, extramural scientists, and the lay public in developing these initiatives is a reflection of the profound commitment of NIH and its stakeholders to do whatever is necessary to rapidly exploit the revolutionary advances of the past few years for the benefit of our people.

For more information, visit http://nihroadmap.nih.gov