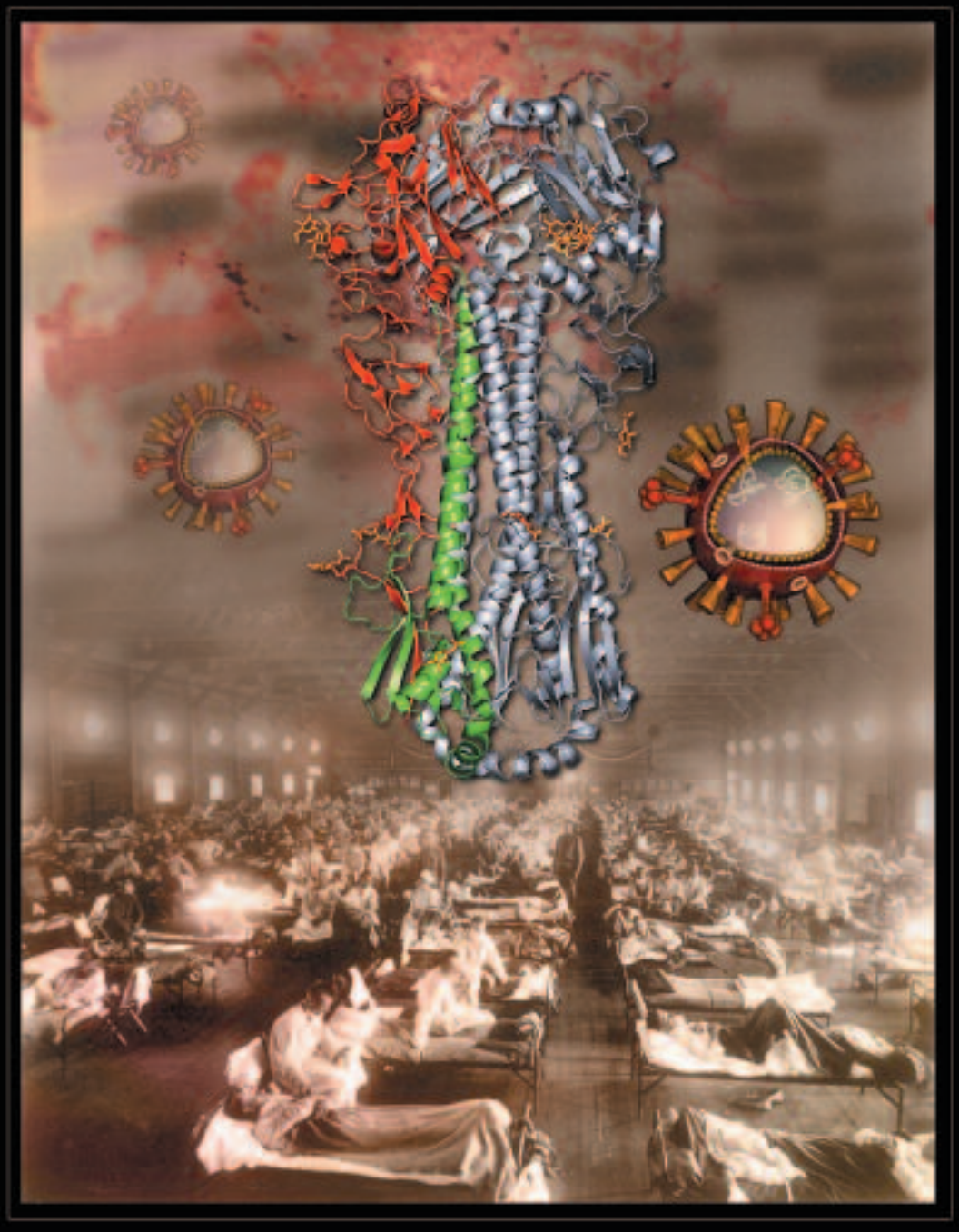
The Scripps Research Institute

Scientific Report 2004
for Scripps Florida



The Scripps Research Institute

On the front cover: *In 1918, the great flu pandemic swept the world, killing an estimated 20 million to 40 million people, making it the largest and most destructive outbreak of any infectious disease in recorded history. The cover illustrates the devastation and the scale of the epidemic that the world experienced in 1918 (photograph of influenza ward at Camp Funston, Kansas). From another army ward in Fort Jackson, South Carolina, lung biopsy material was removed from a dead soldier and fixed in formalin. A section stained with hematoxylin and eosin (overlay) shows acute bronchiolitis and alveolitis. This lung sample was recently examined by Jeffery Taubenberger, M.D., Ph.D. Using reverse transcriptase–polymerase chain reaction, he found that the sample contained influenza virus RNA, enabling deduction of the coding sequence for the viral hemagglutinin (partial sequence of the 1918 gene at top in background). From this reassembled gene, the crystal structure of the 1918 hemagglutinin was determined by James Stevens, Ph.D., in the laboratory of Ian A. Wilson, D.Phil., Department of Molecular Biology, Scripps Research. Both are members of 1918 flu consortium funded by the National Institutes of Health. Members of the consortium are using a multidisciplinary approach to understand the virulence of this extinct virus. Photos courtesy of the National Museum of Health and Medicine and Dr. Taubenberger, Armed Forces Institute of Pathology, Washington, D.C.*

This report accompanies and augments The Scripps Research Institute Scientific Report 2004. In future years, the activities of Scripps Florida will be included, but separately identifiable, in The Scripps Research Institute Scientific Reports.

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** Nobel Laureate*

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THE SCRIPPS RESEARCH INSTITUTE FLORIDA

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Biomedical Sciences and Genome Technology
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Assistant Professor
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Assistant Professor
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Bruce Pascal
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Proteomics

DRUG DISCOVERY

DMPK

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Senior Scientist
Yuanjun He, Ph.D.
Research Associate
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Research Associate

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Shipping & Receiving Specialist

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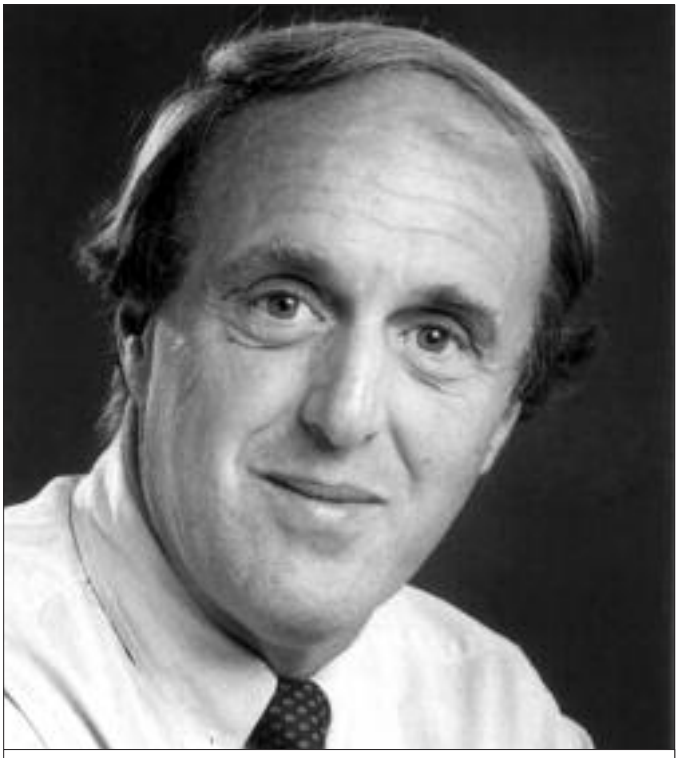
Program Administrator



Richard A. Lerner, M.D.

Scripps Florida Moves Forward

Substantial progress has been made in shaping the scientific scope of the Scripps Florida enterprise and in recruiting a strong roster of scientific faculty and administrative management. Our first announcement early this year was the recruitment of internationally renowned scientist Charles W. Weissman, a pioneer in modern biomedical research and molecular biology. Formerly a senior research scientist in the Department of Neurodegenerative Diseases at University College London, London, England, he heads the Scripps Florida Department of Infectology. Among Dr. Weissmann's research interests are the pathogens that cause malaria and tuberculosis and such prion diseases as mad cow disease.

More recently, we announced the recruitment of noted chemist William R. Roush as professor of chemistry, executive director of medicinal chemistry, and associate dean of the Florida graduate programs. Currently the Warner Lambert/Parke Davis Professor of Chemistry and chair of the Department of Chemistry at the University of Michigan, Ann Arbor, Michigan, he will begin work at Scripps Florida in early 2005. Dr. Roush is recognized for his groundbreaking research in the analysis, structural determination, and synthesis of complex, biologically active, natural products that may lead to the development of new drugs. Further, he has been a mentor to two generations of chemists, a role he will continue with Scripps Florida graduate students and postdoctoral fellows.

We have created the framework for the scientific research that will be undertaken at Scripps Florida, including developing leading-edge technologies to enable scientists to examine the basic biology of human health and find new and better treatments for a variety of devastating human diseases. These programs have been specifically designed to answer the most important questions in biology and medicine and will address such diseases as AIDS, cancer, diabetes, obesity, prion diseases, Parkinson's disease, and schizophrenia. The new research programs encompass scientific inquiry in genetic disease informatics, cancer biology, infectology, the genetics of complex diseases, proteomics, nuclear hormone receptors, drug metabolism and pharmacokinetics, diabetes and obesity, medicinal chemistry, cell-based screening, and HIV therapeutics. We have recruited more than 20 highly accomplished scientists who will carry out much of the research in these new programs. They have previously held positions and appointments at many of the finest academic institutions and private companies in the world, and we are pleased that they have made the commitment to join us at the inception of our research efforts in Florida.

Executive management expertise is critical to the efficient operation of research activities. To this end, we have appointed Harry W. Orf as vice president of scientific operations for Scripps Florida to oversee the administration and management of scientific services that will support biomedical research there. For the past 21 years, he has served as director of the molecular biology laboratories at Massachusetts General Hospital in Boston; he also is a principal associate in genetics at Harvard Medical School, Boston, Massachusetts. His management and administrative experience includes memberships on the boards of directors of several biotechnology companies.

We also appointed Will E. Ray, Ph.D., to our team as director of external affairs for Scripps Florida and as vice president for development for all of Scripps Research. Dr. Ray comes to us from the Palm Beach County Cultural Council, Palm Beach, Florida, where he was president and chief executive officer for more than 20 years.

NEW MEMBERS TO THE BOARD OF TRUSTEES

At no time in the history of the organization has strong leadership from the board of trustees been more important in making decisions that will leave an indelible mark on the future of Scripps Research. This year we have been fortunate in recruiting three distinguished and accomplished Floridians to the Scripps Research Board of Trustees.

Alexander W. Dreyfoos owns and directs the Dreyfoos Group, a private capital management firm that grew out of his previous ventures, including Photo Electronics Corporation and WPEC-TV, the CBS network affiliate in West Palm Beach, Florida.

Phillip Frost is a clinical professor of dermatology at the University of Miami School of Medicine, Miami, Florida. He also has served in leadership positions with many corporations and organizations and is currently a director of Northrop Grumman Corporation, a governor of the American Stock Exchange, chairman of the board and chief executive officer of IVAX Corporation, and chairman of the board of trustees at the University of Miami.

Lawrence F. De George is chairman and chief executive officer of LPL Investment, Inc., and LPL Group, Inc., in West Palm Beach, Florida. He also is founder and chairman of CompleTel L.L.C., a competitive local exchange carrier in Amsterdam and Paris; director of United Global Communications, Inc.; founder and chairman of Cervalis; and founder and director of Advanced Display Technologies.

The establishment of Scripps Florida is a landmark in the history of The Scripps Research Institute. With the decisions and actions taken in 2004, a governance, administrative, financial, and scientific foundation has been put in place that will support significant scientific discoveries and applications, growth, and good management for many years ahead.

BIOMEDICAL RESEARCH

Biomedical Sciences

Biochemistry

James P. Tam, Ph.D.
Professor

RESEARCH SUMMARY

HIV Entry Inhibitors

Infection by HIV-1 requires fusion of the viral and cellular membranes mediated by envelope glycoprotein gp120 and gp41. This process offers opportunities for intervention because 3-dimensional structures of critical proteins have been determined, including the protein gp41 that forms trimers-of-hairpins commonly involved in the final step of membrane fusion. A promising target is a fusion-active prehairpin intermediate that is exposed after gp120-binding with cell surface receptors. In this fuseogenic state, the prehairpin cross-links two different membranes, exposing an amino- and carboxyl-homotrimeric α-helical coiled ectodomain (N- and C-region) that eventually forms a hairpin structure of a six-helix bundle bringing the amino- and carboxyl-terminal regions of the gp41 ectodomains into close proximity enabling membrane fusion. Synthetic peptides targeting these domains are effective fusion inhibitors and constitute a new class of HIV pre-entry therapeutics. However, the first-generation peptidyl drug candidates have limitations that include high dosage and poor stability. This project focuses on developing novel protein mimetics of gp41as second-generation fusion inhibitors to improve the potency and stability of the peptide-based therapeutics. To mimic the fuseogenic conformation and the stability of the prehairpin state of trimeric coiled-coil quaternary structure, we postulate that 3-helix protein mimetics (called 3-α mimetics) as covalent-linked trimeric coiled coils can confer stable structures. We further hypothesize that 2-helix protein mimetics (called 2-α mimetics)of the C-region as covalent-linked dimeric coiled coils may increase potency by forming a 5-helix-bundle with the fuseogenic N-region of gp41. In support of these hypotheses, we show that 2-α and 3-α mimetics show protein-like properties and more importantly, potency by one to several orders of magnitude at subnanomolar concentrations. These protein mimetics represent the most potent antiviral fusion inhibitor known today.

Growth Factors and Cytokines

Corruption of signaling mechanisms is a recurring theme in disease pathogenesis. Most intervention methods have centered on disrupting upstream signaling pathways such as the ligand-receptor interactions of growth factors and cytokines on cell surfaces. In contrast, few intervention methods have been developed that block downstream intracellular targets these methods often require an invasive method such as microinjection to deliver macromolecules. This project focuses on developing a non-invasive approach for intracellular delivery using membrane-permeable protein mimetics to reach specific targets in distinct subcellular compartments. We will develop a novel platform for intracellular delivery with specific peptide cargoes and detection probes to target intracellular soluble proteins and those anchored on the inner cytoplasmic surface such as the cytoplasmic tail of transforming growth factor-α (TGF-α). Our goal is to provide an effective strategy for designing inhibitors capable of delivery to specific subcellular compartments to block signaling mechanisms relevant to human diseases. A concurrent goal focuses on developing new forms of intracellular “synthetic antibodies” to pull down specific intracellular proteins to dissect signaling pathways.

HIV-1 Synthetic Vaccines

Cumulative evidence in the past decade through immunization, antibody-binding studies and deletion mutagenesis have shown that the HIV envelope proteins gp120 and gp41 have evolved multiple structural features to evade neutralizing antibody responses in humans. This project is aimed at developing a focused approach using structure-based antigens to elicit specific and qualitatively useful immune responses. We will use a protein mimetic strategy developed to engineer two highly conserved antigens that represent intermediate states during the entry and fusion process of HIV-1 to host cells. These antigens include a discontinuous region of gp120 known as the “bridging sheet” consisting of four antiparallel β-strands (β-4 domain) and two coiled-coil helical regions (α-3 domains) of gp41. Our goals are to design and develop methods, first to mimic their tertiary and then quaternary structures to mimic bioactive conformations that may elicit quality antibodies with broad neutralizing activity. We will also develop methodology to enhance their immunogenicity of their trimeric structures. It is our intention to apply an

integrated program of design, synthesis, structural elucidation, biochemical analysis and immunological validation in small animals to develop protein mimetics as potential HIV subunit vaccine candidates.

Biographical Sketch

EDUCATION

1971 - 76: Ph.D. University of Wisconsin, Madison, Medicinal Chemistry (Advisor: Dr. Daniel H. Rich)
1968 - 71: B. S. (magna cum laude) University of Wisconsin, Chemistry

EXPERIENCE

1992 – Jan 2005: Professor, Vanderbilt University, Department of Microbiology, Immunology and Biochemistry
1992 – Jan 2005: Adjunct Professor, Vanderbilt University, Department of Biochemistry
1982 – 92: Associate Professor, The Rockefeller University, Biochemistry
1980 – 82: Assistant Professor, The Rockefeller University, Biochemistry
1977 – 80: Research Associate, The Rockefeller University, Biochemistry
1976 – 77: Postdoctoral Fellow, The Rockefeller University, Biochemistry (Advisor: Dr. Bruce Merrifield)

AREAS OF INTEREST

- Peptide and protein chemistry; abiotic protein synthesis, peptide chips for proteomics
- Design and engineering of peptides, proteins, protein mimetics, and biopolymers with unusual architectures for bioactive molecules, antimicrobial peptides, growth factors, cytokines, vaccines, enzymes and synthetic antibody
- Intracellular delivery of small peptides as inhibitors of signal transduction

AWARDS AND HONORS

2005 - Ralph Hirschman award by American Chemical Society
2003 - Rao Makineni Lecture, American Peptide Society, USA
2001 - Distinguished speaker, Kyoto Pharmaceutical University
1998 - Visiting Professor, Peking University, China
1996 – 1998: Visiting Professor, Institute of Materia Medica, Peking, China
1996 - Cathay Award, Chinese Peptide Society, China
1987 - Bachem Award for Excellence in Peptide Research
1986 - Vincent du Vigneaud Award for Young Investigators in Peptide Research, American Peptide Society, USA
1986 - Presidential Award, Triton Biosciences, Inc., USA

PROFESSIONAL ACTIVITIES

Member of American Chemical Society, American Association for the Advancement of Science, American Society for Biochemistry and Molecular Biology, The Protein Society, American Peptide Society (Councilor 1991-97, 99-05)

CONSULTANT AND SCIENTIFIC ADVISORY BOARD

Sep 2004-Mar 2006: Member of BMRC Extramural grant proposals review panel (basic research)
Aug 2004: Governance of Biomedical Research Committee, Singapore
Aug 2004: Chair, Subcommittee, Centre for Chinese Medicine, Singapore
Jul 2004: Working Committee, Centre for Chinese Medicine, Singapore
Feb 2004: A*Star Grant Review Committee, Division of Johns Hopkins Medicine in Singapore
May 2003: SARS Proposal Evaluation Committee (SPEC)
2003 - present: Expert reviewer, Professional & Research Committee, Singapore Heart Foundation
2003 - present: SAB, Asia Life Science Private Equity Company, HK
2003 – Present: BioInformatics Research Center, Member of Advisory Committee, Singapore
2002 – 2003: Advisory Board, Research Reporter, Lippincott Williams & Wilkins, USA
2002 – present: National Biosafety Committee, Ministry of Environment, Singapore
2002 – Present: Director, Temasek Life Sciences Laboratory, Singapore
2002 – Present: Chairman, Temasek Life Sciences Laboratory Search Committee,
2002 – present: Review Panel, Biomedical Sciences, A*Star, Singapore
2001 – 2003: Expert Panel, Water Reclamation Demonstration Plant Study, Public Utility Board, Singapore
1999 – 2002: Cytovax Biotechnologies Inc, USA (SAB)
1999 – 2001: Metrika, USA (SAB)
1998 – 99: Sphinx-Lilly Pharmaceutical Company, USA
1996 – 2000: Astra Pharmaceutical Company, USA
1993 – 95: Abbott Laboratory
1992 – 2000: Network Centres of Excellence, Medical Research Council of Canada

1992 – 95: Immunologic, Inc.
1991 – 93: Armour Pharmaceutical, Inc.
1990 – 91: Mallinckrodt Chemical, Inc.
1989 – 93: Study section for Bio-organic and Natural Product Chemistry
1988 – 93: AutoImmune Technologies, Inc. (Scientific Advisory Board)
1988 – 92: Applied Biosystems, Inc.
1988 – 90: Fish & Neave, Inc.
1988 – 90: Smith Kline & Beckman, Inc.
1988 – 92: Arris Pharmaceutical Corp. (Co-founder, Scientific Advisory Board)
1986 – 88: Burroughs Wellcome, Inc.
1986 – 88: General Foods, Inc.
1985 – Present: Ad hoc reviewer for NSF and NIH
1985 – 88: Vega Biotechnologies, Inc.
1984 – 90: United Biomedical, Inc. (Scientific Advisory Board)
1984 – 89: Triton Biosciences, Inc.

EDITORIAL ACTIVITIES

2001 – Present: Editorial Board member, Asia Pacific Biotech
2000: Guest Editor, Biopolymers, Peptide Science, Vol. 51(5)
1999 – Present: Associate Editor, J. Peptide Research
1997 – Present: Editorial Board, J. Peptide Research
1997, 99: Co-editor, Proceedings of The 15th American Peptide Symposium
1992 –present: Co-editor, Proceedings of The Chinese Peptide Symposium
1992: Guest editor, Int. J. Peptide & Protein Research
1989 – 96: Core expert analyst, CHEMTRACTS
1988 – 96: Editorial board, Peptide Research
1988: Editor, UCLA Symposia on Mol. & Cell. Biology, Vol. 89

INVITED LECTURES: 205
PUBLICATIONS: 287
PATENTS: 13

Biomedical Sciences

Neurobiology

John Hogenesch, Ph.D.
Professor, Biomedical Science
Director, Genome Technology

RESEARCH SUMMARY

Regulation of Mammalian Circadian Physiology

Our laboratory is interested in circadian regulation of physiology. Circadian rhythms are conserved from cyanobacteria, Neurospora, Drosophila, mice, and man, each species regulating aspects of its physiology to be in tune with the environment. In mammals, complex behaviors such as locomotor activity, and physiologies such as heme biosynthesis, hormonal signaling, and temperature rhythms are regulated by the clock. Interestingly, in all of the above species, the clock itself is regulated at the level of transcription. Several transcription factors conserved between flies, mice and man have been identified as clock components, including members of the bHLH-PAS family, CLOCK, MOP3/bMAL, PER1, PER2, and PER3, and repressor proteins called cryptochromes, CRY1 and CRY2. Along with some accessory factors, these genes work in concert to generate molecular rhythms of transcription with a period length of twenty-four hours. Currently, we are attempting to draw a link between this core transcriptional mechanism and the biological processes regulated by the circadian clock taking full advantage of the unique resources available at Scripps.

Biographical Sketch

EDUCATION

B.A., History, University of Southern California
B.S., Biology, University of Southern California
Ph.D., Northwestern University

EDUCATION/TRAINING

University of Southern California, B.A., 1989
University of Southern California, B.S., 1991, Biology
Northwestern University, Ph.D., 1999, Neuroscience
University of Wisconsin-Madison, Postdoc, 1999, Neuroscience
The Scripps Research Institute/Genomics Institute of the Novartis Research Foundation, Postdoc, 2000, Neuroscience

POSITIONS AND HONORS:

1991-2, Research Technician, Northwestern University Medical School, Chicago, IL.
1992-1998, Graduate Student, Northwestern University, Evanston, IL.
1998-9, Postdoctoral Associate, University of Wisconsin, Madison, WI.
1999-2000, Postdoctoral Associate, The Scripps Research Institute/The Genomics Institute of the Novartis Research Foundation, La Jolla, CA.
2000-2004, Program Manager of Genomics, The Genomics Institute of the Novartis Research Foundation, La Jolla, CA.
2003-2004, Assistant Professor, Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA
2004-present, Professor and Director of Genome Technology, The Scripps Research Institute, West Palm Beach, FL

PROFESSIONAL ORGANIZATIONS AND AWARDS:

Molecular Biology Training Program, Northwestern University, 1994-1995
Society of Neuroscience
FASEB 2000-2004
Member of the Scientific Advisory Board, Chemical Industry Institute of Toxicology, 2004-present
Member of the Scientific External Planning Committee, The National Center for Biotechnology, Information (NCBI), 2003-
Member of the Scientific Advisory Panel, The National Institute of Neurological Disorders and Stroke, (NINDS), The Gensat Project, 2003-present

PUBLICATIONS: 38

Biomedical Sciences

Neurobiology

Nagi G. Ayad, Ph.D.
Assistant Professor, Biomedical Science

RESEARCH SUMMARY

Generally, my laboratory at Scripps Florida focuses on understanding the role that ubiquitin mediated proteolysis plays in differentiation, cell cycle decisions, and cancer progression. My prior work has identified a novel cell cycle regulator named Tome-1, or trigger of mitotic entry. This protein is an F-box protein that associates with the SCF components Skp-1 and Cul-1 and is required for degradation of the cdk1 inhibitory kinase wee1. Interestingly, Tome-1 itself is also degraded in a cell cycle specific manner by the Anaphase Promoting Complex or APC. The discovery of Tome-1 not only identified an essential cell cycle regulator, it also uncovered a new checkpoint mechanism. Further, it established that one E3 ubiquitin ligase can target another E3 ligase for degradation, a model that is supported by my recent finding that the APC can target the SCF component Skp2 for degradation. Subsequent work from other groups has shown that Tome-1, Skp-2, and components of the APC are overexpressed in various forms of cancers, thereby highlighting the therapeutic potential of inhibiting these proteins in cancers.

In addition to identifying a role for the APC in regulating entry into mitosis and S phase, I have recently discovered that the APC is required for exiting the cell cycle and initiating neuronal differentiation. This is an extremely important finding since the role of APC mediated proteolysis in differentiation has not been discovered. One prediction is that the APC is likely to be a master regulator of differentiation since it is a master regulator of the cell cycle. I am now collaborating with Dr. Jennifer Busby to identify by quantitative mass spectrometry APC substrates turned over during differentiation of neuronal precursors. I have also initiated collaborations with Drs. Trey Sato and Josephine Harada here at Scripps Florida to look for ubiquitin ligases like the APC that will be involved in neuronal differentiation. I find this work especially exciting since it will impact the development of cancer therapy and nerve regeneration.

Biographical Sketch

EDUCATION

1999-2004, Post-Doctoral Fellowship, Department of Cell Biology, Harvard Medical School
1993-1998, Ph.D., Department of Cell Biology, Yale Medical School
BA 1992, Rutgers College, Rutgers University

TEACHING EXPERIENCE

2001-2002 Teaching Fellow, Cell Biology, Harvard University (responsible for teaching Harvard undergraduates cell biology)
1994-1996 Teaching assistant, Histology, Yale Medical School (responsible for teaching Yale Medical School students both histology and cell biology)1995-1996 Teaching assistant, Cell Biology
1994-1995 Cell Biology /Histology Tutor

RESEARCH EXPERIENCE

1/2005-Present, Assistant Professor, Biomedical Sciences, The Scripps Research Institute, Scripps Florida, Palm Beach County, Florida
1/1999-12/2004 Postdoctoral Research Associate with Dr. Marc W. Kirschner, Harvard Medical School
1993-1998 Doctoral Dissertation with Dr. Ira Mellman, Cell Biology Department, Yale Medical School
1992-1993 Biochemist, Merck & Co., Inc., Rahway NJ
1990-1992 Henry Rutgers Thesis, Dr. WilliamMoyle, UMDNJ-Rutgers Medical School

INVITED LECTURES: 9

PUBLICATIONS: 10

PATENTS: 1

Biomedical Sciences

Neurobiology

Teresa M. Reyes, Ph.D.
Assistant Professor, Biomedical Science

RESEARCH SUMMARY

Research within my lab is delineating circuitry within the brain responsible for coordinating changes in appetite and metabolism, in both healthy and challenged animals. Challenges routinely studied within the lab include acute or chronic immune activation, as well as a neurogenic stressor, such as mild restraint. In response to each of these challenges, animals demonstrate reduced appetite and changes in metabolism, however, the brain circuitry that coordinates these responses is not well defined. Multiple levels of analyses are used to address these questions, including functional neuroanatomical approaches, investigation of global transcriptional changes as well as behavioral assays. This combination of techniques employed in a range of healthy, challenged, and genetically altered animals, provides a unique opportunity to define the brain pathways that mediate this critical homeostatic process.

Biographical Sketch

EDUCATION

Ph. D 1999.-.University of Wisconsin, Madison, WI, Psychology
M.S. 1995.-.University of Wisconsin, Madison, WI, Psychology
B. S. 1992.-.University of Wisconsin, Madison, WI, Psychology

EXPERIENCE

2003-2004 - Senior Research Associate, Salk Institute for Biological Studies, Laboratory of Neuronal Structure and Function
1999-2003 - Postdoctoral Research Fellow, Salk Institute for Biological Studies, Laboratory of Neuronal Structure and Function PI: Paul E. Sawchenko
1996 - Teaching Assistant: Animal Behavior-The Primates
1992-1994 - Research Technician, Department of Biochemistry and Molecular Biology, University of Chicago PI: James A. Shapiro

ACHIEVEMENTS AND AWARDS

National Research Service Award-Postdoctoral Fellowship, National Institutes of Health
National Research Service Award-Predoctoral Fellowship, National Institutes of Health
University Fellowship, University of Wisconsin
Vilas Fellowship, University of Wisconsin
Predoctoral Fellowship, National Science Foundation
Winner of Sigma Xi Dissertation Competition
Gilchrist Award - Outstanding Undergraduate Psychology Thesis
Phi Beta Kappa
Trewartha Undergraduate Research Award

PROFESSIONAL SOCIETIES

Society for Neuroscience
Psychoneuroimmunology Research Society

PUBLICATIONS: 13; Book Chapters - 1

CONFERENCE PRESENTATIONS/ORAL: 8

CONFERENCE PRESENTATIONS/POSTERS: 9

INVITED LECTURES: 1

Infectology

Charles Weissmann, M.D., Ph.D., For.Mem.R.S.
Chairman and Professor

RESEARCH SUMMARY

The Department of Infectology of Scripps Florida will ultimately comprise groups working on various infectious or transmissible diseases. Currently the major emphasis is on prion disease, which is being studied in a mouse model, but a project aimed at discovering a drug against Leishmania, a tropical disease affecting many third world nations is also being developed, in collaboration with other institutions. Our further aim is to establish research in the hepatitis C field and one principal investigator will be starting work after our move to Jupiter. We are also committed to providing the Institute with a core facility for phage display technology.

The work is currently supported by Scripps and we have applied for a grant of $500,000 from the Arthritis Foundation to fund the phage display core.

1. Prion Disease. The questions we are addressing concern the mode of replication of the pathogenic agent, the prion. It has been established with a high degree of certainty that the major component of the prion, if not the only one, is a conformational variant of a host protein, designated PrP, and the as yet unanswered question is how the normal form is converted into the disease-causing form.

- Rather than experimenting on mice to study this issue, we use cultured cells that can be infected with prions. We have set up a cell-based assay ("Scrapie Cell Assay" or SCA) that is 10 times faster than the mouse bioassay, at least as sensitive and more precise. Because the cell line we have isolated so far is susceptible only to mouse prions of the RML strain, we are searching for cell lines susceptible to prions from other species and to different mouse strains.
- Another important question we are investigating concerns the mechanism by which prions are transferred from one cell to another. In conjunction with Peter Kloehn (Prion Unit, MRC, London) we have found that scrapie-infected neuroblastoma cells secrete infectious agent that appears to be more tractable for analysis than the agent from infected brain, which is usually used. We propose to characterize this particulate agent in detail, determine how it is produced and how it infects cells.
- We have discovered previously that prions attach very tenaciously to metal and plastic surfaces and that cells that contact such surfaces acquire prion infection. We wish to determine whether this infection is the result of a hit-and-run mechanism or whether infectious particles desorb at a low rate and then infect cells. This research is important in connection with the question how surgical instruments transmit infection and how they can be effectively sterilized or prevented from adsorbing prions.

In collaboration with E. Beutler, Scripps La Jolla, we are exploring a project aimed at discovering which genes play a role in making a host susceptible to peripheral infection by prion disease and how the immune system of the host attempts (or not) to deal with the infectious agent.

We intend to further develop the SCA to provide a even more rapid and higher-capacity assay, in collaboration with John Hogenesh, that we intend to use to screen chemical libraries for compounds that suppress propagation of prions and thus can serve as potential drugs.

Current members of the Prion Group are Dr. Chris Baker, Dr. Sukhi Mahal, Cheryl Demczyk and Alexandra Sherman, all at Scripps Florida. A further postdoctoral student is being hired for June and a Principal Investigator will join us in April.

2. Search for a drug against Leishmaniasis. Leishmaniasis is a disease prevalent in India, Nepal, Sudan Brazil and other Third World countries. Piet Borst (NKI Amsterdam) and Robert Sabatini discovered that the DNA of Leishmania contains a modified base and they isolated a protein that binds to it (JBP, J-Binding Protein). Because the protein is essential for the survival of Leishmania, we posit that if binding is prevented by a drug this could be lethal for the microorganism but not for the host. We have prepared JBP, Dr. Paul Wentworth (Scripps LaJolla and Oxford) has synthesized a fluorescently labeled oligonucleotide containing the J nucleotide and Dr. David Millar is working out a high-throughput p[rocedure for measuring the two components. We shall then screen chemical libraries for compounds that can prevent binding, optimise them and select those that have an effect on the survival of Leishmania.

Current members of the collaboration are Prem Subramaniam (Scripps Florida), Piet Borst (NKI Amsterdam), Robert Sabatini (U. of Alabama), David Millar (Scripps LaJolla) and Paul Wentworth (Scripps LaJolla, Oxford).

3. Search for a drug against hepatitis C. Hepatitis C caused by an RNA-containing virus. It affects over 170 million people worldwide and can lead to chronic hepatitis, cirrhosis and liver cancer. Dr. Donny Strosberg, who will join TSFRI in March, has identified domains of hepatitis C viral proteins that interact with each other or with viral host proteins. He intends to screen a chemical library for compounds that disrupt protein-protein interactions and search for compounds that can permeate the host cell and disrupt viral replication without damaging the host.

4. Phage display library as core function for Scripps Florida. A phage display library is a collection of recombinant phages that express a huge variety of antibody genes. By exposing the phage to a particular protein or epitope, one can isolate phage expressing an antibody to the antigen. The gene can be recovered and used to express the antibodies in quantity. This is an extremely useful tool in molecular biology, and Dr. Vittorio Verzillo (Scripps Florida), who has great experience in the field, is developing this resource. A technician will be hired to aid him.

Biographical Sketch

EDUCATION

Kantonales Gymnasium, Zürich 1946-1950
Zürich University, 1950-1961
Degrees of M.D. (1956) and Ph.D. in Organic Chemistry (1961)

FORMER POSITIONS

Assistant to Professor P. Karrer, Zürich University, 1960-1961
Postdoctoral Fellow, New York University School of Medicine, Department of Biochemistry, 1961-1963,
Instructor in Biochemistry, New York University School of Medicine, Department of Biochemistry, 1963-1964
Assistant Professor in Biochemistry, New York University School of Medicine, Department of Biochemistry, 1964-1965
Associate Professor in Biochemistry, New York University School of Medicine, Department of Biochemistry, 1965-1967
Professor extraordinarius in Molecular Biology, 1967-1970
Professor ordinarius in Molecular Biology, 1970-1999
Director of the Institute of Molecular Biology, University of Zürich, 1967-1999
Professor emeritus, University of Zürich, since 1999.
Senior Research Scientist and Visiting Professor, MRC Prion Unit, St.Mary's Hospital (1999-2001) and University College, London since 2001

AWARDS AND HONOURS

Ruzicka Prize in Chemistry (Switzerland, 1966)
Marcel Benoist Prize, Bern (1970)
Sir Hans Krebs Medaille, Budapest (1974)
Honorary Member of the American Society of Biological Chemistry (since 1979)
Otto Warburg Prize, Innsbruck (1980)
Member of the Deutsche Akademie der Naturforscher Leopoldina (since 1980)
Dr. H.P. Heineken Prize, Amsterdam (1982)
Scheele Medal, Uppsala (1982)
Foreign Member of the Royal Society (since 1983)
Honorary Member of the American Academy of Arts and Sciences (1985)
Cancer Prize (Krebspreis) of the Schweizerische Krebsliga (1987)
Jung-Preis für Medizin, Hamburg (1988)
Foreign Associate of the U.S. National Academy of Sciences (1989)
Gabor Medal of the Royal Society (1993)
Robert-Koch Medal (1995)
Datta Lectureship Award of the FEBS (1996)
Charles-Léopold Mayer Prize of the French Academy of Science (1996)
Royal Society Glaxo Wellcome Prize (1996)
Honorary Member, Dept. of Biochemistry, University of Oxford (1997)
Member of the Schweizerische Akademie der Medizinischen WIssenschaften (1997)
August-Wilhelm-von-Hofmann-Denkmünze (Gesellschaft Deutscher Chemiker, Wien 1997)
Klaus-Joachim-Zülch-Preis (Max-Planck-Gesellschaft, 1997)
Max Delbrück Medal (Berlin, 1997)
Wilhelm-Exner-Medaille (Wien, 1997)
Distinguished Service Award (Miami, 1998)
Corresponding Member of the Nordrhein-Westfälischen Akademie der Wissenschaften (1998)

Ausländisches Mitglied des Orden pour le mérite für Wissenschaften und Künste (Bonn, 1998)
Mendel Medal (Genetical Society, London, 1998)
Extraordinary Member of The Berlin-Brandenburgischen Akademie der Wissenschaften (Berlin, 1999)
Samuel Rudin Distinguished Visiting Professor (1999, Columbia University, N.Y.)
Fellow of the American Academy of Microbiology (Washington, 1999)
Visiting Professor, Rochester University (2001)
Visiting Professor, Imperial College of Medicine (1999-2002)
Betty and David Koetser Award (Zürich, 2001)
Fellow of the Academy of Medical Sciences (London, 2001)
Friedrich-Bauer-Prize for Medical Research (University of Münich, 2001)
Honorary Senior Fellow, Institute of Neurology, University College London (2004)
Warren Alpert Foundation Prize (Harvard Medical School, September 2004)

HONORARY DEGREES

Doctor honoris causa, University of Verona (1992)
Doctor honoris causa, University of Gent (1994)
Doctor honoris causa, ETH Zürich (1998)
Doctor honoris causa, University of Zürich (2000)
Doctor honoris causa, University of St.Andrews (St.Andrews, 2000)
Doctor honoris causa, Ecole Federal Polytechnique (Lausanne, 2001)

OTHER ACTIVITIES

Member of the Editorial Board of *Biochimica et Biophysica Acta* (1965-1968)
Associate Managing Editor of *Biochimica et Biophysica Acta* (1968-1980)
Member of the Editorial Board of *Gene* (1980-1983)
Member of the Editorial Board of the *EMBO Journal* (1982-1986)
Member of the European Molecular Biology Organization (EMBO) (since 1968)
Member of the Schweizerische Kommission für Molekularbiologie (SKMB) (1968-1971)
President of the Zürcher Chemische Gesellschaft (1969-1970)
President of the Schweizerische Gesellschaft für Zell- und Molekularbiologie (1970-1972)
President of the Roche Research Foundation (1971-1977)
Member of the Scientific Board of Biogen (1978-1988)
Chairman of the Scientific Board of Biogen (1984-1986)
Associate Editor of *Cell* (1983-1988)
Member of the Board of Governors of the Weizmann Institute of Science (since 1985)
President of the Ernst Hadorn Stiftung (since 1986)
Member of Scientific Advisory Board ZMB, Heidelberg (1988-1990)
Member of the Scientific Council of the Swiss National Fund (1989-1994) and President of the Section IIIA (1992-1994)
Member of the Board of Directors of F. Hoffmann-La Roche Ltd., Basel (1989-2001)
Member of the Human Genome Organisation (HUGO) (since 1989)
Member of the Academia Europaea (since 1989)
Member of the International Scientific Advisory Board of the Netherlands Cancer Institute (Amsterdam)
Member of the Scientific Advisory Board of the Roche Institute of Molecular Biology, Nutley (1993-1995)
Member of the Scientific Advisory Board of the Osaka Bioscience Institute, Osaka (1993-1998)
Member of the Scientific Advisory Board of the Institut Suisse de Recherche sur le Cancer (ISREC), Lausanne (1994-1999)
Member of the Scientific Advisory Board of Roche Molecular Systems, Alameda Ca. (1994-98)
Member of the Scientific Council of the International Human Frontiers Research Program (1994-1998)
Associate Editor of Molecular Medicine (1994-2000)
Chairman of the European Commission Group on Bovine Spongiform Encephalopathy (1996)
Member of the Board of Governors of Tel Aviv University (since 1997)
Member of the Editorial Board of the Proceedings of the Royal Society (since 1999)
Member of Board of Directors of Speedel (since 2003)
Member of the Scripps Board of Scientific Governors (2004)

SPECIAL LECTURES: 37

PUBLICATIONS: 302

ADVANCED TECHNOLOGY

Genome Technology

John Hogenesch, Ph.D.
Professor, Biomedical Science
Director, Genome Technology

RESEARCH SUMMARY

Regulation of Mammalian Circadian Physiology

Our laboratory is interested in circadian regulation of physiology. Circadian rhythms are conserved from cyanobacteria, Neurospora, Drosophila, mice, and man, each species regulating aspects of its physiology to be in tune with the environment. In mammals, complex behaviors such as locomotor activity, and physiologies such as heme biosynthesis, hormonal signaling, and temperature rhythms are regulated by the clock. Interestingly, in all of the above species, the clock itself is regulated at the level of transcription. Several transcription factors conserved between flies, mice and man have been identified as clock components, including members of the bHLH-PAS family, CLOCK, MOP3/bMAL, PER1, PER2, and PER3, and repressor proteins called cryptochromes, CRY1 and CRY2. Along with some accessory factors, these genes work in concert to generate molecular rhythms of transcription with a period length of twenty-four hours. Currently, we are attempting to draw a link between this core transcriptional mechanism and the biological processes regulated by the circadian clock taking full advantage of the unique resources available at Scripps.

Biographical Sketch

EDUCATION

B.A., History, University of Southern California
B.S., Biology, University of Southern California
Ph.D., Northwestern University

EDUCATION/TRAINING

University of Southern California, B.A., 1989
University of Southern California, B.S., 1991, Biology
Northwestern University, Ph.D., 1999, Neuroscience
University of Wisconsin-Madison, Postdoc, 1999, Neuroscience
The Scripps Research Institute/Genomics Institute of the Novartis Research Foundation, Postdoc, 2000, Neuroscience

POSITIONS AND HONORS

1991-2, Research Technician, Northwestern University Medical School, Chicago, IL.
1992-1998, Graduate Student, Northwestern University, Evanston, IL.
1998-9, Postdoctoral Associate, University of Wisconsin, Madison, WI.
1999-2000, Postdoctoral Associate, The Scripps Research Institute/The Genomics Institute of the Novartis Research Foundation, La Jolla, CA.
2000-2004, Program Manager of Genomics, The Genomics Institute of the Novartis Research Foundation, La Jolla, CA.
2003-2004, Assistant Professor, Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA
2004-present, Professor and Director of Genome Technology, The Scripps Research Institute, West Palm Beach, FL

PROFESSIONAL ORGANIZATIONS AND AWARDS

Molecular Biology Training Program, Northwestern University, 1994-1995
Society of Neuroscience
FASEB 2000-2004
Member of the Scientific Advisory Board, Chemical Industry Institute of Toxicology, 2004-present
Member of the Scientific External Planning Committee, The National Center for Biotechnology, Information (NCBI), 2003-
Member of the Scientific Advisory Panel, The National Institute of Neurological Disorders and Stroke, (NINDS), The Gensat Project, 2003-present

PUBLICATIONS: 38

Informatics

N. F. Tsinoremas, Ph.D.
Director of Informatics, Scripps Florida

RESEARCH SUMMARY

Drug Discovery Informatics Program

As part of Scripps Florida HTS program we are building the required informatics systems that would capture, manage, integrate and analyze the chemical compound screening data.

It is critical in molecular screening and lead discovery research that informatics extends beyond the power of data management, that is, storing data in a database, performing searches and visualizing results. Informatics systems that are truly effective are designed to integrate seamlessly scientific and laboratory research in biology and chemistry, technology and information science. They capture raw experimental data, the data context (biological and chemical), derived information and laboratory notebook entries, as well as human intuition and interpretation, providing an integrated platform that enables decision-making. Therefore, such data integration systems must be designed to provide flawless data exchange protocols allowing information integration which can vary widely from chemical structures to toxicology and literature while preventing any human and/or machine errors during these complex processes. Due to the increasing numbers of data points that are captured and more complex data analysis requirements, different strategies can be adopted to organize more effectively the data for efficient data capture and analysis.

More specifically we are implementing a data warehousing strategy that consists of two distinct but dynamically interconnected components: an Operational/ Transactional system and a Discovery system:

Operational systems encompass workflow and experimental design in a typical high throughput laboratory. In our infrastructure, such systems are designed to capture and manage diverse data types and formats providing a first level of integration, ranging from chemical structure and NMR spectra to experimental protocols for biological assays

The discovery systems are defined as a collection of tools, algorithms, and technologies used by scientists (statisticians, information scientists, biologists and chemists) to access and analyze experimentally-derived data in order to review project status and make critical decisions. These systems are designed to address the two most fundamental yet challenging questions in discovery research: a) what compound needs to be studied next and b) what compound needs to be synthesized next. In order to achieve the above goals, the discovery systems must support the following activities:

a. Data analysis and decision support

b. Knowledge Generation and Management

c. Data integration and access

As part of the Discovery systems we are developing intelligent software and computer science and artificial intelligence methods, to process and combine results from different HTS screens, secondary tests, lead profiling optimization, ADME and Toxicology studies.

Genetic Disease Informatics Program

Part of my group will focus on pattern recognition in sequences, structures and processes, the studying of systems ranging from single protein molecules through complex molecular interactions, and the data analysis, interpretation, and reverse-engineering of complex disease-genomic/genetic interactions in order to enhance our understanding of complex diseases.

More specifically we are interested in identifying and defining alternative splicing isoforms in drug target genes using a combination of novel bioinformatics tools and genomic technologies. The goals of this project will be initially to define the drugable genome and then study the role and function of the different protein isoforms. Currently, we have found several examples where existing drug targets show an interesting alternative splicing pattern and in many cases the “known” isoform appears to be the minor form in the target tissue. Understanding the splicing of such drug targets and using the appropriate isoform for screening and counter-screening can greatly increase the efficacy and specificity of a drug. So far, we have discovered several new isoforms in drug targets that confirm this hypothesis. In one specific instance, we have found that ion channels and more specifically sodium channels fall into this category. A significant result of this research is that we can influence the way that assay development and screening is done in these projects. In addition, as part of this program we will be studying the mechanisms of alternative splicing as they relate to environmental changes and genetic factors. The goal of this project is to understand the mecha-

nisms of alternative splicing and their role in biological pathways. Preliminary research has been done concerning the involvement of alternative splicing in disease pathways, especially those of cancer; however, no significant genome-wide studies have been performed using genomic technologies and advance bioinformatics strategies and algorithms to understand the underlying mechanisms and genetic component(s) of such pathways.

Biographical Sketch

EDUCATION

Ph.D. - Biochemistry and Molecular Biology—University of Leeds, England, 1991

BS. - Chemistry—University of Athens, Greece, 1988

PROFESSIONAL EXPERIENCE

Director and Head of Informatics. The Scripps Research Institute, Jupiter, FL. May 2004- present

Director of Genomic Discovery and Computational Genomics, Informatics. MRL Seattle, Merck & Co, February 2002- April 2004

Vice President of Genomics and Data Mining Tools. DoubleTwist Inc., March 2001- February 2002.

Director of Research. DoubleTwist Inc., July 1999-March 2001

Bioinformatics Scientist, Department of Bioinformatics, Incyte Pharmaceuticals, Feb. 1999-June 1999

Biocomputational Scientist, Department of Computational Biology, Progenitor, Inc.—1998

Research Scientist III, Department of Molecular Biology and Biochemistry, Energy Biosystems Corporation--1997 to 1998

Research Scientist, Department of Biology, Texas A&M University --1994 to 1997

Research Associate, Department of Biology, Texas A&M University -1992 to 1994

Research Fellow, University of Leeds and SERC Fellowship, Département de Physiologie Microbienne, Institut Pasteur, Paris, France - 1989 to 1991

INVENTION DISCLOSURES AND PATENTS: 8

PUBLICATIONS: 18

Proteomics

Patrick R. Griffin, Ph.D.
Professor, Drug Discovery, Scripps Florida

RESEARCH SUMMARY

Probing Protein Small Molecule Interactions by Hydrogen Deuterium Exchange

PPARγ, a ligand-dependent transcription factor and member of the nuclear hormone superfamily, is the molecular target of the drug class known as the glitazones. These compounds have been shown to improve muscle insulin resistance, a symptom or cause of type II diabetes, and are referred to as insulin sensitizers. The glitazones are widely prescribed in the type II diabetes population. However, these drugs have limited utility in use for mild insulin resistance or in patients with history of cardiovascular disease (CVD) due to specific receptor mediated side affects associated with the glitazones, such as weight gain, fluid retention, and plasma volume expansion. Unfortunately, the type II diabetes population has a higher incidence of cardiovascular disease. In addition, there is a clear link between body mass index (BMI) and the incidence of insulin resistance and type II diabetes. Thus, the search for a PPARγ modulator that improves muscle insulin sensitivity without the induction of weight gain and plasma volume expansion continues.

Recent studies using animal models of insulin resistance have shown that, indicators of weight gain and plasma volume expansion can be minimized without loss of insulin sensitization by the use of partial agonists of PPARγ, although the mechanism of this dissociation of efficacy from unwanted events is unclear. Studies in pre-adipocytes indicate that these partial agonists do not induce adipogenesis as do the full agonists and expression profiling has indicated that the gene expression patterns are different for the different functional classes of activators. Our group is developing a structure-based approach that is both rapid and sensitive to aid in the optimizing of conformational-selective modulators of PPARγ.

Amide hydrogen exchange (H/D-Ex) coupled with proteolysis and mass spectrometry has become a powerful technique for studying protein structure and dynamics, protein-ligand interactions and protein-protein interactions. Using H/D-Ex one can measure changes in solvent-accessibility and stability of a protein in the presence and absence of ligands, as determined from the rates of exchange of solvent deuterons with amide hydrogens. Our laboratory has applied amide hydrogen/deuterium (H/D) exchange mass spectrometry to detect compound-specific conformational stabilization within the ligand binding domain (LBD) of PPARγ. Ligand binding to PPARγ LBD alters amide H/D exchange rates in specific regions of the protein with differential magnitude and direction depending on the chemical structure of the ligand. This assay is currently being used to profile the nature of interactions of various PPARγ modulators and we have shown that perturbations in H/D exchange can be used to classify agonists, partial-agonists, and antagonists of PPARγ. More importantly, these H/D exchange profiles indicate that the mechanism of activation of PPARγ by full agonists, such as the glitazones, which involve recruitment of co-activators via stabilization of helix-12 or AF2 region of the ligand binding domain, is different for certain classes of partial agonists. In collaboration with the Scripps Florida Medicinal Chemistry group we are in the process of synthesizing analogs of a certain class of PPARγ partial agonist previously described in the literature in an effort to improve the pharmaceutical properties of this scaffold while using our H/D exchange assay to monitor the nature of receptor-compound interaction at the molecular level. Further investigation into the mechanism of activation of PPARγ by diverse chemotypes of PPARγ partial agonists is currently on-going. The overall goal of this work is to determine the relationship of ligand-induced receptor conformation to pharmacological response in rodent models of type II diabetes. To date, we have identified specific regions of the protein that provide sensors specific for binding mode and conformational induction for specific chemotypes. This structure-activity-relationship is important to the development of conformational-selective modulators of PPARγ.

In parallel to the PPARγ program, research is also underway to improve the technical aspects of the HD-Ex experiment. At present, a linear ion trap mass spectrometer performs mass analysis of peptide ions arising from the enzymatic digestion of the protein of interest. Measuring the mass increase of these peptides over time (as amide hydrogens exchange with deuterium) enables differentiation between slow and rapidly exchanging regions of the protein. If the iso-

topic envelope of two or more peptide fragments overlap, then useful on-exchange data cannot be obtained for these peptides. Thus, information on the region of the protein corresponding to these peptides is lost. Although sufficient for small proteins such as the PPARγ ligand binding domain (LBD) (<30 KDa) in which a small number of proteolytic peptides are generated (~50-100), the limited mass resolving power of the linear ion trap mass spectrometer prohibits the analysis of more complex samples such as proteins larger than 60 KDa or protein-protein complexes in which thousands of peptides may be generated in the proteolysis step.

To increase the dynamic range of the proteins and complexes that we can study by HD-Ex we have initiated a collaboration with Dr. Alan G. Marshall at the National High Magnetic Field Laboratory (NHMFL) site located at Florida State University (FSU). The Marshall group is widely acknowledged as the world leader in the development of Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR MS). Originally developed by Marshall and Comisarow, FT-ICR MS provides the highest resolving power and mass accuracy of any mass analyzer (a 100 fold increase over our current ion trap mass spectrometer). The resolution of FT-ICR MS allows the deuterium uptake of more proteolytic peptides to be followed during the HD-Ex experiment, and the improved mass accuracy increases the confidence of all the peptide sequence assignments.

Recently, the Scripps Florida automated HD-Ex sample preparation robot was interfaced to a 14.5 Tesla FT-ICR mass spectrometer at the NHMFL. It should be noted that this custom built 14.5 Tesla magnet is the highest field magnet ever constructed for dedicated FT-ICR MS. The HD-Ex of the PPARγ-LBD:RXRα-LBD complex (≈70 KDa) was then performed in the presence, and absence, of a PPAR-γ full agonist and retinoic acid. This data represents the first known HD-Ex analysis of how drug binding affects the structure of an entire protein complex, rather than a single protein. This work is to be presented at the 5th North American FT-ICR MS conference to be held in Key West, FL, during April 2005.

Biographical Sketch

EDUCATION

Syracuse University 12/84 - Chemistry B.S.
University of Virginia, 4/89 - Chemistry Ph.D.
Caltech, 12/91 Biotechnology - Post-Doctoral Fellowship

PROFESSIONAL EXPERIENCE

Professor Drug Discovery, Scripps Florida, 05/04 to present
Chief Scientific Officer, ExSAR Corporation, 07/02 - 05/04
Senior Director, Basic Chemistry and Molecular Profiling Proteomics, Merck, 09/01 - 06/02
Director, Basic Chemistry and Molecular Profiling Proteomics, Merck, 05/99 – 09/01
MRL Scientific Liaison - Institute for Systems Biology, Merck, 03/01 – 06/02
Senior Research Fellow, Molecular Design and Diversity, Merck, 04/96 – 05/99
Research Fellow, Inflammation Research, Merck, 12/91-04/96
Post-Doctoral Fellow, California Institute of Technology 5/90 - 12/91
Associate Scientist, Genentech, Inc. 4/89 - 4/90
Research Assistant, University of Virginia 9/85 - 4/89

SOCIETY MEMBERSHIPS

American Society for Mass Spectrometry 1985 - present
Protein Society 1985 - present
ABRF 1996 – present

ACADEMIC AND PROFESSIONAL HONORS

Dupont Chemistry Fellow, University of Virginia 1987
Dean's Fellow, University of Virginia 1988

PUBLICATIONS

Manuscripts - 66; Book chapters - 14

Proteomics

Jennifer Busby, Ph.D.
Associate Director of Proteomics, Scripps Florida

RESEARCH SUMMARY

Proteomics Core Facility

The proteomics core at Scripps Florida has general mass spectrometry capabilities for protein and peptide identification using LCMS and LCMS/MS. Current instrumentation includes a Thermo Finnigan LTQ linear ion trap and Thermo Finnigan TSQ Quantum. Expertise exists for the identification of post translational modifications, especially phosphorylation mapping. Large scale differential experiments, examining changes in both phosphorylation and protein levels, will be performed when software is available to aid in data analysis.

As a core facility the proteomics group is responsible for providing collaborative mass spectrometry services to the other faculty at Scripps Florida. These collaborative projects will necessarily drive technology development. Current efforts in technology development include automation of IMAC enrichment of phosphopeptides and creation of software for differential analysis of mass spectrometry data.

Post translational modification of proteins play an important role in cell signaling and regulation. Phosphorylation of proteins is arguably the most important of these modifications and the identification of cellular signaling pathways provides insight into protein function and behavior. This signal is often transient and may affect only a small number of proteins at any point in time. Mapping of global cellular phosphorylation states can be used in a comparative manner to identify relevant changes in critical signaling pathways between cells in different cellular states or conditions. These differences in signaling can then be viewed as potential cause/effect points, giving clarity to the complex mechanisms of the cell.

In order to examine these phosphoproteins it is necessary to enrich the sample for the phosphorylation event. In the core facility here at Scripps Florida, this enrichment is done by Immobilized Metal Affinity Chromatography (IMAC) as described in Clinical Proteomics Journal vol 1 69-80 (2004). Although the IMAC methodology is published there are several innovations that have been made to the protocol since the initial publication. In an effort to bring this important methodology to other proteomics labs in the state of Florida, I have already begun collaborations with several labs at the University of Florida. Members of these labs were invited to Scripps Florida for a weekend long tutorial on IMAC and other mass spectrometry related methods. Experiments performed that weekend will be presented at the annual mass spectrometry conference, ASMS, in June.

Biographical Sketch

EDUCATION

Ph.D. in Chemistry University of Virginia Charlottesville, Virginia
June 1996 - Dissertation Title: Identification of Biologically Relevant Peptides by nanoflow HPLC micro Electrospray Ionization Mass Spectrometry
BS in Chemistry, St. Mary's College, Notre Dame, Indiana
1993-1996 - Major: Chemistry ACS Certification Minor: Mathematics; Graduated cum laude

PROFESSIONAL EXPERIENCE

2003-2004 - Senior Research Scientist MDS Proteomics, Charlottesville, Virginia
2001-2003 - Research Scientist, MDS Proteomics, Charlottesville, Virginia
2000-2001 - Senior Scientis, Proteome Research Institute, University of Virginia, Charlottesville, Virginia
1996-2000 - Graduate Student, Professor Donald F. Hunt, University of Virginia, Charlottesville, Virginia
1995 – Undergraduate Research Fellow, Dr. Keiji Morokuma, Emory University, Atlanta, Georgia

TEACHING

1999 - Teaching Assistant, ABRF Short Course: Sequencing Peptide MS/MS Spectra
1996 – Teaching Assistant General Chemistry Laboratory
1997 - University of Virginia, Charlottesville, Virginia
1995 – Teaching Assistant General Chemistry Laboratory
1996 - St. Mary's College, Notre Dame, Indiana

TECHNICAL ABILITIES

• Expert in operation and maintenance of Finnigan

LCQ and DECA ion trap mass spectrometers
- Operator of Finnigan LTQ-FT mass spectrometer
- Antigen identification utilizing on-line column effluent splitting
- Methods development utilizing on-line microcapillary HPLC and FT-ICR mass spectrometry
- Decreased level of detection for antigen identification by an order of magnitude
- Operator of triple quadrupole mass spectrometers including various scan modes
- Operator of Sciex QStar Pulsar QTof
- Extensive use of nanoflow microelectrospray technology
- Construction and use of microcapillary columns for HPLC and affinity chromatography
- Proficient in use of separation and enrichment systems
  - HPLC
  - SCX
  - IMAC
  - CE
  - SDS Page Gels
- Peptide Synthesis
  - Extensive use of FMOC peptide synthesis methods
  - Supervised multiple lab users on Automated Peptide Synthesizer
  - Maintenance and repair of Automated Peptide Synthesizer
- De Novo and Computer based MS/MS peptide sequence analysis
  - SEQUEST
  - MS-TAG
  - Mascot
  - BLAST
- Low level sample handling including protein digestion and gel methods
- Experience in cell culture and harvesting

ACADEMIC AND PROFESSIONAL HONORS
- American Society for Mass Spectrometry
- Sigma Xi
- American Association for the Advancement of Science

PUBLICATIONS: 14

PRESENTATIONS: 5

DRUG DISCOVERY

DMPK

Patrick R. Griffin, Ph.D.
Professor, Drug Discovery, Scripps Florida

RESEARCH SUMMARY

Probing Protein Small Molecule Interactions by Hydrogen Deuterium Exchange

PPARγ, a ligand-dependent transcription factor and member of the nuclear hormone superfamily, is the molecular target of the drug class known as the glitazones. These compounds have been shown to improve muscle insulin resistance, a symptom or cause of type II diabetes, and are referred to as insulin sensitizers. The glitazones are widely prescribed in the type II diabetes population. However, these drugs have limited utility in use for mild insulin resistance or in patients with history of cardiovascular disease (CVD) due to specific receptor mediated side affects associated with the glitazones, such as weight gain, fluid retention, and plasma volume expansion. Unfortunately, the type II diabetes population has a higher incidence of cardiovascular disease. In addition, there is a clear link between body mass index (BMI) and the incidence of insulin resistance and type II diabetes. Thus, the search for a PPARγ modulator that improves muscle insulin sensitivity without the induction of weight gain and plasma volume expansion continues.

Recent studies using animal models of insulin resistance have shown that, indicators of weight gain and plasma volume expansion can be minimized without loss of insulin sensitization by the use of partial agonists of PPARγ, although the mechanism of this dissociation of efficacy from unwanted events is unclear. Studies in pre-adipocytes indicate that these partial agonists do not induce adipogenesis as do the full agonists and expression profiling has indicated that the gene expression patterns are different for the different functional classes of activators. Our group is developing a structure-based approach that is both rapid and sensitive to aid in the optimizing of conformational-selective modulators of PPARγ.

Amide hydrogen exchange (H/D-Ex) coupled with proteolysis and mass spectrometry has become a powerful technique for studying protein structure and dynamics, protein-ligand interactions and protein-protein interactions. Using H/D-Ex one can measure changes in solvent-accessibility and stability of a protein in the presence and absence of ligands, as determined from the rates of exchange of solvent deuterons with amide hydrogens. Our laboratory has applied amide hydrogen/deuterium (H/D) exchange mass spectrometry to detect compound-specific conformational stabilization within the ligand binding domain (LBD) of PPARγ. Ligand binding to PPARγ LBD alters amide H/D exchange rates in specific regions of the protein with differential magnitude and direction depending on the chemical structure of the ligand. This assay is currently being used to profile the nature of interactions of various PPARγ modulators and we have shown that perturbations in H/D exchange can be used to classify agonists, partial-agonists, and antagonists of PPARγ. More importantly, these H/D exchange profiles indicate that the mechanism of activation of PPARγ by full agonists, such as the glitazones, which involve recruitment of co-activators via stabilization of helix-12 or AF2 region of the ligand binding domain, is different for certain classes of partial agonists. In collaboration with the Scripps Florida Medicinal Chemistry group we are in the process of synthesizing analogs of a certain class of PPARγ partial agonist previously described in the literature in an effort to improve the pharmaceutical properties of this scaffold while using our H/D exchange assay to monitor the nature of receptor-compound interaction at the molecular level. Further investigation into the mechanism of activation of PPARγ by diverse chemotypes of PPARγ partial agonists is currently on-going. The overall goal of this work is to determine the relationship of ligand-induced receptor conformation to pharmacological response in rodent models of type II diabetes. To date, we have identified specific regions of the protein that provide sensors specific for binding mode and conformational induction for specific chemotypes. This structure-activity-relationship is important to the development of conformational-selective modulators of PPARγ.

In parallel to the PPARγ program, research is also underway to improve the technical aspects of the HD-Ex experiment. At present, a linear ion trap mass spectrometer performs mass analysis of peptide ions arising from the enzymatic digestion of the protein of interest. Measuring the mass increase of these pep-

tides over time (as amide hydrogens exchange with deuterium) enables differentiation between slow and rapidly exchanging regions of the protein. If the isotopic envelope of two or more peptide fragments overlap, then useful on-exchange data cannot be obtained for these peptides. Thus, information on the region of the protein corresponding to these peptides is lost. Although sufficient for small proteins such as the PPARγ ligand binding domain (LBD) (<30 KDa) in which a small number of proteolytic peptides are generated (~50-100), the limited mass resolving power of the linear ion trap mass spectrometer prohibits the analysis of more complex samples such as proteins larger than 60 KDa or protein-protein complexes in which thousands of peptides may be generated in the proteolysis step.

To increase the dynamic range of the proteins and complexes that we can study by HD-Ex we have initiated a collaboration with Dr. Alan G. Marshall at the National High Magnetic Field Laboratory (NHMFL) site located at Florida State University (FSU). The Marshall group is widely acknowledged as the world leader in the development of Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR MS). Originally developed by Marshall and Comisarow, FT-ICR MS provides the highest resolving power and mass accuracy of any mass analyzer (a 100 fold increase over our current ion trap mass spectrometer). The resolution of FT-ICR MS allows the deuterium uptake of more proteolytic peptides to be followed during the HD-Ex experiment, and the improved mass accuracy increases the confidence of all the peptide sequence assignments.

Recently, the Scripps Florida automated HD-Ex sample preparation robot was interfaced to a 14.5 Tesla FT-ICR mass spectrometer at the NHMFL. It should be noted that this custom built 14.5 Tesla magnet is the highest field magnet ever constructed for dedicated FT-ICR MS. The HD-Ex of the PPARγ-LBD:RXRα-LBD complex (≈70 KDa) was then performed in the presence, and absence, of a PPAR-γ full agonist and retinoic acid. This data represents the first known HD-Ex analysis of how drug binding affects the structure of an entire protein complex, rather than a single protein. This work is to be presented at the 5th North American FT-ICR MS conference to be held in Key West, FL, during April 2005.

Biographical Sketch

EDUCATION

Syracuse University 12/84 - Chemistry B.S.
University of Virginia, 4/89 - Chemistry Ph.D.
Caltech, 12/91 Biotechnology - Post-Doctoral Fellowship

PROFESSIONAL EXPERIENCE

Professor Drug Discovery, Scripps Florida, 05/04 to present
Chief Scientific Officer, ExSAR Corporation, 07/02 - 05/04
Senior Director, Basic Chemistry and Molecular Profiling Proteomics, Merck, 09/01 - 06/02
Director, Basic Chemistry and Molecular Profiling Proteomics, Merck, 05/99 – 09/01
MRL Scientific Liaison - Institute for Systems Biology, Merck, 03/01 – 06/02
Senior Research Fellow, Molecular Design and Diversity, Merck, 04/96 – 05/99
Research Fellow, Inflammation Research, Merck, 12/91-04/96
Post-Doctoral Fellow, California Institute of Technology 5/90 - 12/91
Associate Scientist, Genentech, Inc. 4/89 - 4/90
Research Assistant, University of Virginia 9/85 - 4/89

SOCIETY MEMBERSHIPS

American Society for Mass Spectrometry 1985 - present
Protein Society 1985 - present
ABRF 1996 – present

ACADEMIC AND PROFESSIONAL HONORS

Dupont Chemistry Fellow, University of Virginia 1987
Dean's Fellow, University of Virginia 1988

PUBLICATIONS

Manuscripts - 66; Book chapters - 14

Lead Identification HTS Assay Development

Claes Robert Wahlestedt, M.D., Ph.D.
Professor and Director of Pharmacogenomics

RESEARCH SUMMARY

In regard to basic research, we are pursuing several aspects of genomics and bioinformatics to better understand the nervous system. Genomic approaches have the potential to affect almost every aspect of neuroscience. Today most human genes have been identified. As a consequence thereof, we have assembled large numbers of novel genes and proteins (and potential drug targets), which now have to be associated with the appropriate pathways when possible, and then prioritized and validated for further work.

Focus is given to potential drug targets and pathways in the nervous system that are relevant to drug discovery efforts. At Scripps Florida, the most promising targets will be pursued for drug discovery in close interaction with chemistry efforts. Our experience from the pharmaceutical industry as well as academia will come into good use when establishing new programs at Scripps Florida.

We have also begun to build a platform for pharmacogenomics. Here we are attempting to assess the importance of differences in individual genetic backgrounds for disease susceptibility and drug reactions.

PROJECTS INCLUDE:

- Drug discovery relating to treatment of alcoholism and pain.
- Polymorphism in human genes of pharmaceutical relevance.
- Discovery and classification of non-coding RNA (incl. microRNA) in human.
- Functions of natural antisense transcripts in human and mouse.
- Large-scale production of siRNA for all human genes/transcripts.
- Investigation of LNA chemistry in antisense and siRNA, focus on in vivo.
- Identification of novel genes involved in senescence and apoptosis resistance.
- Neuronal differentiation mechanisms.

Biographical Sketch

EDUCATION

Doctor of Medicine in Pharmacology (PhD), 1987, University of Lund, Lund, Sweden

University Medical Degree (MD), class of 1984, University of Lund, Lund, Sweden

POSITIONS AND HONORS

Professor (formerly Founding Director and Department Chairman) Center for Genomics and Bioinformatics Karolinska Institutet, Stockholm, Sweden, 1997 - current

Adjunct Chief Scientist, RIKEN Genomic Sciences Center, Yokohama/Tokyo, Japan, 2004 - current

Director of various organizations, World-Wide Research: Pharmacia & Upjohn, Pharmacia Corp. and Pfizer Inc., Peapack, NJ, USA, 1997-2003

Founding director and head of Astra-Zeneca Research Centre Montreal (Drug Discovery in Neuroscience and Pain) Montreal, 1993-1997

djunct Professor of Biochemistry, McGill University, Montreal, 1995-1998

Adjunct Professor of Pharmacology and Therapeutics, McGill University, Montreal, 1995-2000

Assistant Professor, Division of Neurobiology, Department of Neurology and Neuroscience, Cornell University Medical College, New York, NY, 1989-1993

Docent (honorary title), University of Lund, Lund, 1990-

Postdoctoral period #1: Department of Pharmacology and Fidia-Georgetown Institute for the Neurosciences (Prof. E. Costa), Georgetown University, Washington, DC, 1987-1989

Postdoctoral period #2: Institute for Immunology (Prof. S. Nakanishi), Kyoto University, Kyoto, Japan, 1988

Clinical Instructor, Department of Psychiatry and Neurochemistry, University of Lund, 1986-1987

COMMISSIONS OF TRUST

Many review panels: (current)

KI- Genome Canada collaboration, coordinator

KI-RIKEN (Japan) collaboration, coordinator

Member, FANTOM consortium

KI-Pfizer collaboration, Director

Main organizer of Nobel Conference on:

G-Protein-Coupled Receptors (2003)

Novel Functional Aspects of RNA (2006)

COMMISSIONS OF TRUST: (current)

Genordia AB, Stockholm (co-founder)
Mitotech AB, Stockholm (co-founder)
Synaptogen Inc., Boston (co-founder)
Inovio A/S, Oslo (board member)
Santaris A/S, Copenhagen (SAB)
Genizon Inc., Montreal (SAB)
PainCeptor Inc., Montreal (SAB)

PUBLICATIONS: 149

Medicinal Chemistry

William R. Roush, Ph.D.
Executive Director of Medicinal Chemistry
Professor of Chemistry
Associate Dean, Graduate Program, Scripps Research Institute

RESEARCH SUMMARY

I arrived in Palm Beach on January 4, 2005, to begin my positions as Executive Director of Medicinal Chemistry, Professor of Chemistry, and Associate Dean of the Graduate Program at Scripps-Florida. I will move into the new building nearing completion on the FAU-Jupiter campus in early February, and will initiate my academic research program at TSRI at that time.

The first of my postdoctoral associates will arrive at TSRI-Florida in late January. Several members of my research group currently at the University of Michigan, Ann Arbor, MI, will move to TSRI-Florida in May. By the end of the summer, 2005, my research group at Scripps-Florida be 16-19 coworkers, consisting of 12 postdoctoral fellows and 4 (confirmed) to 7 (possible) TSRI graduate students. These individuals will perform research in the areas summarized below.

There are four major areas of research interest in my laboratory. One involves the synthesis of structurally and stereochemically complex, biologically active natural products by routes involving inter-, intra- and/or transannular Diels-Alder reactions. Specific targets that we are attempting to synthesize via this chemistry include superstolide A, quartromicin D, spinosyn A (and congeners) and FR182877A (among others). A second area involves the development of efficient methodology for the control of acyclic stereochemistry; our work on the allylboration and aldol reactions is representative of this area. Natural product targets we are attempting to synthesize in this area include tedanolide, apoptolidin, pectenotoxin C, amphidinol-2, amphidinolides C and E, scytophycin C, and reidispongiolide A (among others). A third area involves the synthesis of polyhydroxylated natural products, specifically oligosaccharide containing natural products. Durhamycin A, landomycin A and angelmicin B are major targets of these efforts. The final area concerns the design and synthesis of inhibitors of the cysteine proteases isolated from two important tropical parasites: cruzain from Trypanosoma cruzi (e.g., the causative agent of Chagas' disease) and falcipain from Plasmodium species (e.g., malaria). This program involves a collaboration with a group of molecular modelers, parasitologists (Jim McKerrow, Phil Rosenthal), protein biochemists (Charles Craik), and X-ray crystallographers (Linda Brinen) at the University of California at San Francisco. We are also involved in two other research programs focusing on the developoment of a pro-apoptotic drug-like molecules for treatment of Lupus and other autoimmune diseases (collaboration with Prof. Gary Glick of the University of Michigan). The other one involves the design and synthesis of potential anti-HIV agents (collaboration with Dr. Vassil Georgiev of the National Institute of Allergy and Infectious Diseases).

I list my research support on a separate page (in the usual NIH form). I am currently finalizing all of the paperwork to transfer three of my NIH grants to TSRI-Florida effective June 1, 2005. Those that will transfer are: AI 35709; GM 26782; and GM 38436. The dollar amounts are listed are for the current grant year only, and are direct cost dollars only; indirect costs will be paid to TSRI-Florida by the NIH agencies on top of the direct cost dollars. The competitive renewal application of NIH Grant GM 38907 received a 12.1 percentile rating. In normal years, this grant would be funded without question. However, owing to current budget problems at the NIH, a decision to re-fund this grant has not yet been made. If funded, it will begin at TSRI-Florida in June, 2005.

CURRENT RESEARCH IN PROGRESS

1. Total synthesis of stereochemically complex via asymmetric Diels-Alder technology: quartromicin, spinosyn A, cochleamycin A, FR182877, and superstolide A.
2. Total synthesis of propionate derived natural products via asymmetric crotylboration, allylsilylation, and aldol technology: tedanolide, scytophycin C, apoptolidin, pectenotoxin II and amphidinol 3.
3. Total synthesis of polyhydroxylated natural products: aureolic acid antibiotics (mithramycin), ziricin, landomycin A, and angelmicin B.
4. Design and synthesis of cysteine protease inhibitors: Trypanosoma cruzi cysteine protease (cruzain; Chagas' disease), and Plasmodium falciparum cysteine protease (falcipain; malaria).
5. Development of new synthetic methodology to support the studies defined in 1-4.

Biographical Sketch

EDUCATION

B. S., University of California, Los Angeles, 1974
Ph. D., Harvard University, 1977
Postdoctoral Fellow, Harvard University, 1977-78

OTHER APPOINTMENTS

BioInformation Associates, Principal and Consultant 1981-2001
Genzyme Corporation, Consultant 1983-97
Genzyme Corporation, Pharmaceuticals Division Board Member 1994-97
NIH Medicinal Chemistry Study Section, Ad Hoc Member 1984-88
Special NIH Study Sections, Ad Hoc Member 1984-88
Chemtracts, Expert Analyst 1986-1999
Secretary-Treasurer, ACS Division of Organic Chemistry 1990-93
Chairman, ACS Division of Organic Chemistry 1995
Alternate Councilor, ACS Division of Organic Chemistry 1999-02
NIH Medicinal Chemistry Study Section, Member 1990-93
Chairman, NIH Medicinal Chemistry Study Section 1993-95
NIGMS Council, Ad-Hoc Member 1998
Editorial Board, Organic Reactions 1991-2002
Board of Directors, Organic Reactions 1995-present
Eli Lilly and Company, Consultant 1991-oresent
Editorial Board, Encyclopedia of Reagents for Organic Synthesis 1992-2002
Editorial Board, Organic Syntheses 1993-2002
ArQule, Scientific Advisory Board Member 1994-2003
Consultant, NeXstar Pharmaceuticals, Inc. 1994-98
Organizing Committee, NSF Workshop on
Organic Synthesis and Natural Products Chemistry 1995-97
Consulting Editorial Board, Tetrahedron 1996-2002
Consultant, Parke Davis 1998-2001
Consultant, Pfizer 2001-present
Associate Editor, Journal of the American Chemical Society 1999-present
Editorial Advisory Board, Organic Letters 1999-present
Steering Committee, Challenges for the Chemical Sciences in the
21st Century, National Research Council 2000-02
Invenux, Inc., Scientific Advisory Board Member 2001-03

HONORS AND AWARDS

B.S. in Chemistry, Summa Cum Laude 1974
Phi Beta Kappa 1974
Merck Faculty Development Award 1981
Eli Lilly Grantee 1981-83
Roger and Georges Firmenich Career Development Chair in Natural Products Chemistry (MIT) 1981-84
Fellow of the Alfred P. Sloan Foundation, 1982-86
Alan R. Day Award of the Philadelphia Organic Chemist's Club, 1992
Arthur C. Cope Scholar Award, American Chemical Society, 1994
ACS Akron Section Award, 1996
Merit Award, National Institute of General Medical Sciences, 1998
Distinguished Faculty Achievement Award, University of Michigan, 1999
Paul G. Gassman Distinguished Service Award,
ACS Division of Organic Chemistry, 2002
ACS Ernest Guenther Award in the Chemistry of Natural Products, 2004

PUBLICATIONS: 223

NAMED LECTURESHIPS: 34

Medicinal Chemistry

Chris Liang, Ph. D.
Associate Director, Medicinal Chemistry

RESEARCH SUMMARY

Objectives: To discover protein kinase inhibitors as therapeutics for the treatment of human diseases such as cancer, arthritis, asthma, diabetic retinopathy, age-related macular degeneration, restenosis, and atherosclerosis.

Background: Protein kinases are a class of enzymes that catalyze the transfer of the g-phosphate from ATP to protein substrates. They play critical roles in signal transduction for a number of cellular functions. In particular, they regulate most of the "hallmarks" of cancer: cell proliferation, cell survival, cell motility/metastasis, cell cycle/division, and angiogenesis. They are also implicated in inflammatory diseases such as arthritis and asthma. The approval of Gleevec for CML (chronic myelogenous leukemia) and GIST (gastro intestino stroma tumor), and Avatin for NSCLC (non-small cell lung cancer) validated protein kinase inhibitors/antagonists as effective, non-cytotoxic anticancer agents. They provide new hope and paradigms in the long fight against cancer. There is also strong later stage clinical data suggesting that p38a MAP kinase inhibitors could be effective anti-inflammatory agents. For these reasons, protein kinases are being hotly pursued as valuable therapeutic targets and it was estimated that they constitute about 25% of all current pharmaceutical research.

Strategy: As we are building the drug discovery infrastructure in Palm Beach County, our strategy to jump start drug discovery is to improve pharmaceutical properties of known advanced protein kinase inhibitors using methods of medicinal chemistry. This strategy allows us to by-pass the lengthy drug target validation and the need of high throughput screening that is being built up.

We have studies all protein kinase inhibitors in the market, in clinical trials, or those have gone through some clinical trials or extensive pre-clinical development. It was found that one of the major hurdles that prevent many potent and selective protein kinase inhibitors from being a successful drug is the poor solubility of their chemical scaffold. Currently, the most common practice in this field is to introduce an ionizable group (amine or acid) to improve solubility. But it is unsatisfactory since it introduces new problems to the inhibitors (e.g. either increased toxicity or unacceptable protein binding), leading to the failure of many such compounds. We have developed hypothesis that may solve the solubility problem without introducing new ones. Based on the hypothesis, novel protein kinase inhibitors from different chemical scaffolds were designed. These scaffolds cover most of the protein kinase inhibitors that have advanced to clinical trials or reached market approval. The designed inhibitors are targeted against the well-validated kinase targets such as VEGFR, PDGFR, FGFR, Kit, EGFR, Her2, and p38a. Our proprietary design is aimed to further improve the drug properties of those advanced protein kinase inhibitors, thereby enabling us to develop safer and/or more effective therapeutics.

Status: Chemists in my group have synthesized nearly 200 potential drug candidates over the past half year. Most of the compounds have been tested in enzymatic and cellular assays. Their drug properties are also being evaluated. In two projects, we have found compounds that possess better in vitro properties than the best known competitors. Currently, they are undergoing further in vivo tests.

Biographical Sketch

EDUCATION

Ph. D., Princeton University (Prof. Leland C. Allen), 1985 – 1989
M.A., Princeton University, 1984 – 1985
GuangZhou English Language Center, 1983 – 1984
B.S., Wuhan University, 1979 – 1983
Short courses/training
- "Toxicology", Pharmacia continuing education class
- "Pharmacology for Chemists", ACS short course
- "Drug Metabolism", Anthony Y.H. Lu Institute
- "Champion Leadership and Team Building", The Lambton Group
- "From the Laboratory to Leadership", The Leadership Edge
- "Dynamic Presentations in a Scientific Business Setting", Deb Kaufmann & Associates

ACCOMPLISHMENTS / EXPERIENCES

SUGEN, Inc./Pharmacia/Pfizer, 1996 – 2003
Accelrys, Inc. (formerly Biosym/MSI), 1991 – 1996
Scientist, Senior Scientist
Brookhaven National Lab (Dr. Marshall Newton), 1990 – 1991
University of Georgia (Prof. Henry "Fritz" Schaefer III), 1989 – 1990

HONORS

Associate Fellow, Pharmacia Corp., 2003
John von Neumann Fellowship of Princeton University, 1986 - 1987
Fellowship of the Ministry of Education, P. R. of China, 1984 –1985

PUBLISHED PATENT APPLICATIONS: 13

SELECTED SCIENTIFIC PRESENTATIONS: 9

PUBLICATIONS: 32