

FOCUS ON YALE MEDICINE

New Frontiers in Molecular Pharmacology and Medicine: A Celebration

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On October 24, 2003, the Yale School of Medicine inaugurated its new wing for the Department of Pharmacology with a star-studded symposium titled "New Frontiers in Molecular Pharmacology and Medicine." In the world of academia, this is as close as one gets to red carpet Oscar quality spectatorship. The roster began with Tony Hunter of the Salk Institute, Joan Steitz of Yale, Jack Dixon of UCSD, Robert Weinberg of MIT, Joseph Goldstein of University of Texas Southwestern and winner of the 1985 Nobel Prize in Medicine, Stuart Schreiber of Harvard, and ended with Paul Greengard of Rockefeller University and winner of the 2000 Nobel Prize in Physiology.

HISTORICAL PERSPECTIVES ON YALE PHARMACOLOGY

The Department of Pharmacology at Yale has a renowned history since its inception in the 1940s by William Salter. Most notably, it has led the world in the study of cancer chemotherapy and neuropharmacology. Indeed, modern cancer

chemotherapy took flight at Yale in 1942 when Alfred Gilman and Louis Goodman discovered the first anticancer drug for lymphoma when they demonstrated the effects of nitrogen mustard in reducing transplanted lymphosarcoma in mice (Gilman et al., 1963).

In 1953, Arnold Welch came to Yale from Oxford to become the departmental chair. He took over an anemic department and began to recruit young scientists who would prove to be the best in the country. John Vane shared the Nobel Prize in 1982 for his work on prostaglandins and prostacyclin and the mechanism of action of aspirin. William Prusoff discovered the first specific antiviral drug to be used in man, 5-Iododeoxyuridine (IUdR) for the treatment of ocular herpes and later found the first drug against human immunodeficiency virus, 3'-deoxythymidin-2'-ene (d4T) (Lin TS et al., 1987). In neuropharmacology, Jack Cooper, Robert Roth, and Floyd Bloom led the research effort and wrote the *Biochemical Basis of Neuropharmacology* in 1970, a book that is in its Ninth Edition and can still be

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Arnold Welch

A key transitional moment in Yale Pharmacology history arrived with its new chair in 1953, Arnold Welch. With his arrival from Oxford, Welch transformed the department from a traditional focus on physiology to a mechanistic one based on biochemistry. Among his many talents was an ability to see and recruit new talent to the department. These include William Prusoff, John Vane, Jack Cooper, Alan Sartorelli and Bob Handschumacher. After leaving Yale in 1967, Welch went to the Squibb Institute for Medical Research where his research led to development of the first



ACE inhibitor CAPTOPRIL. Welch then proceeded to St. Jude Children's Research Hospital in Memphis, and finally, at 75, to the National Cancer Institute where he was hired as a cancer expert for coordination of the National Cooperative Drug Discovery Groups, and deputy director of the Division of Cancer Treatment. Welch received the prestigious Torald Sollmann Award in Pharmacology from the American Society for Pharmacology and Experimental Therapeutics. He passed away in 2003 after an amazing 94 years — many of them spent doing landmark research in the area of cancer pharmacology.

found on the bookshelf of any neuropharmacologist.

In 1967, Murdoch Ritchie was appointed Chairman of the department and worked in collaboration with William Douglas on the firing properties of non-medullated afferent fibers and with Paul Greengard on the mode of action of local anesthetics. Greengard went on to share the Nobel Prize in 2000 with Arvid Carlsson and Eric Kandel for his work on dopamine and other “slow” transmitters which act by protein phosphorylation and allow signal transduction in the nervous system. Alan Sartorelli, John Perkins, and Len Kaczmarek also served in as chairmen of the department until the arrival of Joseph Schlessinger in 2001.

OLD THEMES, NEW IDEAS

As Alan Sartorelli puts it, “Pharmacology is the study of drugs — but that can be accomplished in many, almost any, ways.” Indeed, Yale Pharmacology is becoming increasingly

multidisciplinary in this goal. The department today emphasizes a number of different areas including neurochemistry, neurophysiology, psychopharmacology, viral and microbial chemotherapy and clinical pharmacology. In addition, there is ongoing research into the mechanisms behind signal transduction, carcinogenesis, drug resistance, and differentiation.

Joseph Schlessinger joined the Pharmacology department as Chairman in 2001. Schlessinger heads a team of dynamic researchers focusing on many different areas of pharmacology — many of whom use signaling in order to address questions in either cancer or neuropharmacology. Investigators involved in signaling are Anton Bennett, William Sessa, Elias Lolis, and Barbara Ehrlich. Bennett is interested in the role protein tyrosine phosphatases play in cellular processes such as mitogenesis, apoptosis, cell movement and differentiation. Sessa focuses on how endothelial nitric oxide synthase is regulated in the context of normal physiology and in disease and the application of pro-

teomics to discover new targets to regulate blood vessel function. The structure-function relationships of chemokines is being investigated by Lolis, while Ehrlich is interested in the mechanisms behind cell regulation of intracellular calcium concentration.

In the area of signaling and neuropharmacology, Angus Nairn works on the characterization of the basal ganglia phosphoprotein DARPP-32 and the possibility of developing drugs that specifically affect phosphoproteins or their targets. Ya Ha uses x-ray diffraction to study how membrane proteins carry out complex biological functions on the surface of neuronal cells and how changes in these proteins cause neurodegeneration. Jim Howe studies glutamate receptors, Gary Rudnick focuses on neurotransmitter transport, and Len Kaczmarek's research aims to understand the nature of the biochemical changes that occur in neurons. Priscilla Dannies examines the process by which protein hormones and neuropeptides are concentrated into secretory granules.

Among the Pharmacology faculty members that study cancer are Karen Anderson, David Calderwood, Yung-Chi Cheng, and Alan Sartorelli. Anderson does

research that interfaces signaling and cancer by developing an understanding of enzymatic reactions and receptor-ligand interactions at a molecular level. Calderwood, the newest recruit to Pharmacology, studies molecular control of integrin signaling as intergrins regulate cell adhesion, growth and migration. Cheng focuses on cancer and viral chemotherapy and studies the functional roles and properties of virus-specific proteins in order to design selective antiviral compounds. DiGiovanni leads the research on the molecular signaling underlying breast cancer and its treatment. Sartorelli's lab studies the mechanism of action behind multi-drug resistance and DNA base methylating and chloroethylating agents.

DIRECTIONS FOR THE FUTURE

The symposium "New Frontiers in Molecular Pharmacology" was a celebration of the new areas that exist in pharmacological research. Tony Hunter opened the symposium with a talk entitled "Signaling by Phosphorylation in the Age of Genomics." In 1979 the Hunter lab discovered the phosphorylation of tyrosine

Joseph Schlessinger

Joseph Schlessinger joined the Pharmacology department as William H. Prusoff Professor and Chairman in 2001. Schlessinger came to Yale from the New York University school of Medicine where he was chair of Pharmacology and director of the Skirball Institute of Biomolecular Medicine. Schlessinger has been honored with many awards including the Hestrin Prize (1983), the Levinson Prize (1984), the Drew-Ciba



Prize (1995 with G. Blobel and A. Levine), the Antoine Lacassagne Prize (1995) and the Taylor Prize (2000 with T. Hunter and T.

Pawson) for his work on receptor tyrosine kinases. In addition, Schlessinger is a member of the National Academy of Science and a fellow of the American Academy of Arts and Sciences. He has been ranked in the top twenty most cited scientists in science for the past two decades for his work on receptor tyrosine kinases and the signaling pathways that these receptors activate.

residues, leading to role of tyrosine kinases in signal transduction and cell growth and development.

Joan Steitz then discussed SnoRNP biogenesis in mammalian cells and the mechanism behind the release of the snoRNA from the intron before processing. The Steitz lab is interested in the structure and function of small ribonucleoprotein complexes.

Jack Dixon is interested in the interaction between bacterial pathogens and mammalian signal transduction systems. He spoke on the Yersinia effector YopT, a protein that is assembled and injected out of bacteria into mammalian cells. YopT cleaves Rho GTPases from the membrane causing disruption of the actin cytoskeleton in host cells.

Bob Weinberg provided insight to the group on his lab's research on telomerase, an enzyme that cleaves the telomeres at the end of chromosomes in cancer cells.

This enzyme is a target in cancer therapy because the preservation of the telomeres in the cancer cells allow for immortalized proliferation.

Joseph Goldstein, recipient of the 1985 Nobel Prize with Michael Brown for their discoveries concerning the regulation of cholesterol metabolism, spoke about his research on regulated intramembrane proteolysis. Together, Dr. Brown and Goldstein discovered that cell surface receptors mediate the uptake of low-density lipoprotein and their research has led to treatment and prevention of atherosclerosis.

Stuart Schreiber spoke on the need to use small molecules to understand the chromatin signaling network. His lab focuses on development and application of diversity-oriented organic synthesis and the development of ChemBank, a suite of informatic tools and federated databases

Alan Sartorelli

Alan Sartorelli, the Alfred Gilman Professor of Pharmacology at Yale School of Medicine is in many ways a renaissance man. Since his arrival at YSM on September 1, 1961, Sartorelli has served as the Chairman of Pharmacology (1977-1984, 1998-2000) and Director of the Yale Comprehensive Cancer Center (1984-1993) while mentoring a long line of prolific researchers in basic mechanisms of neoplastic differentiation and chemotherapeutic resistance. Sartorelli has given the scientific community an appreciation for the importance of the hypoxic environment in tumors and the



need for drugs that target this region within the tumor. His many scientific affiliations include membership in the American Association for Advancement of Science, the

Institute of Medicine of the National Academy of Science, past President of the American Association for Cancer Research, and past President of the Association of American Cancer Institutes. Yet closer to Sartorelli's heart than the ASPET Award in Experimental Therapeutics, the ASPET Otto Kraye Award, or the AACR Bruce F.

Cain Memorial Award, is his love for music and opera. An avid singer for more than five decades, Sartorelli claims *La Traviata* by Verdi as his favorite composition.

William C. Sessa

William C. Sessa began his scientific journey with a degree in Pharmacy from the Philadelphia College of Pharmacy and Sciences. After finishing his degree, Sessa set out on an extensive tour of the East coast, moving from Pennsylvania to Rhode Island for a masters degree, New York for a Ph.D., and then onto London, England at St. Bartholomew's Hospital Medical College working under Yale alumnus Sir



John Vane to study enzymes responsible for generating intracellular arginine — a precursor for the gaseous second messenger, nitric oxide. He then did a second post-doctoral fellowship at the University of Virginia on the molecular cloning of nitric oxide syn-

thase. He found a home in Connecticut in 1993 when he joined the Department of Pharmacology at the Yale School of Medicine with his lab in the Boyer Center for Molecular Medicine. Sessa is now a Professor of Pharmacology and leads the Vascular Cell Signaling and Therapeutics program at Yale. In 1996, Sessa won the Established Investigator Award from the American Heart Association, and he was honored with the John J. Abel Award in Pharmacology in 2000 from the American Society of Pharmacology and

Experimental Therapeutics. Sessa is developing a program in vascular cell signaling and therapeutics in order to study the molecular control of blood vessel regulation and then determine novel strategies to treat cardiovascular diseases and cancer.

aimed to promote the development and use of chemical genetics.

Yale alumnus Paul Greengard's lecture, "Signal Integration in the Brain," was a fitting way to wrap up a symposium celebrating Yale Pharmacology — past and present. Greengard integrated the story of dopamine signaling pathways in the central nervous system and its application to major neurological and psychiatric disorders such as Parkinson's disease, schizophrenia, attention deficit hyperactivity disorder, and drug abuse. Greengard and his protégés have beautifully developed the dopamine story at Yale and Rockefeller University over the past three decades. In particular, he focused on a molecule called Dopamine and cAMP Regulated Phosphoprotein with molecular weight = 32 kD (DARPP-32) which is located at a critical

junction point in the integration and differential regulation of dopamine signaling pathways. Greengard concluded his talk with the summary that "DARPP-32 plays an essential role in mediating the actions and interactions of numerous neurotransmitters, therapeutic agents and drugs of abuse in many brain regions, including the neostriatum, hippocampus, and cerebral cortex."

With the 21st century comes a need for academic research in pharmacology to expand the traditional borders and find new ways to address biological questions. "New Frontiers in Molecular Pharmacology and Medicine" highlighted a few of the exciting angles that can be used in order to conquer disease. With a new chairman, new laboratory space, and four new assistant professors, the depart-

ment of Pharmacology at Yale is well prepared to continue making strong contributions in the field of pharmacology.

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