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The Alton Ochsner Medical Foundation

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Introduction

The Alton Medical Foundation, a not-for-profit organization, was founded in New Orleans in 1944. The Foundation was, from its inception, closely associated with the Ochsner Clinic, a medical group practice founded in 1941 by five former academic surgeons from Tulane University. The mission of the Foundation was to build a hospital for the care of patients from New Orleans and the region, to establish programs of postgraduate medical education, and to conduct research. Over the ensuing five and a half decades the organizations have grown, such that the New Orleans campus is now supported by 17 satellite clinics in the metropolitan area, a second tertiary care clinic has been established in Baton Rouge, 70 miles northwest of New Orleans, and this latter facility is similarly supported by four satellite facilities. In addition, the Ochsner Health Plan, a health maintenance organization, was created in 1985 as a joint venture of Ochsner clinic and the Alton Ochsner Medical Foundation. Currently, the Ochsner Health Plan serves 200,000 members throughout Louisiana. At the New Orleans campus approximately 750,000 outpatient visits and 19,000 inpatient admissions are recorded each year. Two hundred and twenty-two residents are in training at Ochsner each year in a wide variety of medical specialties.

The Ochsner Clinic and Alton Ochsner Medical Foundation were named for Dr. Alton Ochsner who originally came to New Orleans to serve as Chief of Surgery at Tulane University School of Medicine, succeeding the renowned Rudolph Matas. Dr. Ochsner was among the first to associate cigarette smoking with lung cancer and was a strong proponent of not only smoking cessation but the study of the pathogenesis and treatment of lung cancer. Because of the academic interests of Dr. Ochsner and the four other academic surgeons who founded the Ochsner organizations, research was introduced to the enterprise very early on. Two years after the Foundation was established, a biochemical research unit was put in place, and in the 1950s Dr. Albert Segaloff was recruited from Wayne State University to lead the research effort. Dr. Segaloff was a nationally and internationally recognized research scientist in the area of steroid hormone biology particularly as it influences the pathogenesis and progression of breast cancer. Until his death in 1985 he was a vigorous force not only in the biological community but also in the area of breast cancer treatment and prevention. In 1976 the Foundation recruited Dr. Edward Frohlich, at that time the George Cross Professor of Medicine at the University of Oklahoma School of Health Sciences, to direct the research effort. Dr. Frohlich, a nationally and internationally recognized expert in the study of hypertension and its sequelae, was one of the first in this country to advocate the use of beta-adrenergic blocking drugs in the treatment of hypertension, to categorize the cardiac structural alterations associated with hypertension of different forms, and to appreciate the adverse consequences of left ventricular hypertrophy on the prognosis of hypertensive individuals. Dr. Frohlich continues his activities at Ochsner as the Alton Ochsner Distinguished Scientist. He has served on numerous National Institutes of Health study panels and most recently has served on the Sixth Joint National Commission on Hypertension, helping to define optimal hypertensive therapy. Dr. Frohlich currently serves as the editor of the American Heart Association journal *Hypertension*, the editorial offices of which are located at the Foundation.

In 1986 at the direction of Foundation pres-

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Fig. 1. The Alton Ochsner Medical Foundation.

ident, Dr. George H. Porter, III, a research expansion was undertaken. This expansion was driven by the rapid pace of advance in biomedical research and by[1] the necessity that the research activity support training, patient care, and scholarship in a variety of medical disciplines. It was elected to establish a core molecular genetics laboratory base consisting of independent but mutually supporting activities. This core molecular genetics activity was then surrounded by a reconfiguration of the then operative physiology and biochemistry activities. These basic science activities were further encouraged to collaborate with a wide array of human experimental activities ongoing in the clinic and hospital. In this way it became possible to study disease mechanism on the clinical, physiologic, and molecular levels. For example, when some years ago the use of lymphokine activated killer cell therapy coupled with interleukin II was proposed as a therapy for certain cancers, the Foundation was able to link its clinical oncologists with its basic immunologists in an effort to study this therapy. Other examples of such collaboration center on the possible use of gene therapy to prevent restenosis in animal models of coronary artery disease, and the use of novel molecular amplification techniques in the detection of infections in transplantation patients, among others.

Laboratory of Molecular Genetics

The primary effort of this laboratory (Prescott Deininger, Ph.D.) is the area of human genome stability with an emphasis on the interspersed repetitive DNA family, Alu. Dr. Deininger participated in the discovery of these elements in 1980 and has carried out extensive studies of the structure, expression, and evolution of these mobile elements in the human genome since that time. Much of his ongoing research continues to focus on the mechanisms by which these elements are capable of undergoing an RNA-mediated duplication and insertion into a new genetic locus. In addition to studies of these elements and their insertion in the genome, the laboratory is pursuing evidence which indicates that the recombination among different Alu elements in the human genome is a significant cause of chro-

mosomal rearrangements, insertions, and deletions. The laboratory is developing an accurate and sensitive reporter gene system that will allow the measurement of Alu-Alu recombination and determine the influences of various genetic, environmental, and pharmacological reagents on this process. At the same time, Dr. Deininger is attempting to identify genes involved in deafness. The laboratory helped narrow the chromosomal interval associated with Ushers syndrome in the local Acadian population to a region of about 800 kilobases. This region is being explored for potential candidate genes in which the mutation causing this profound deafness and progressive retinitis pigmentosa resides. Similarly, the laboratory has mapped the gene responsible for nonsyndromic deafness in a mouse model (dn) to a relatively small region. A search is currently under way for candidate genes for deafness in this model so that an assessment can then be made whether it contributes to either of the two human deafness syndromes that have been mapped to the syntenic region of the human genome.

In the same laboratory, the effects of oxidant stress in the pathogenesis of a variety of human disorders is being studied (Jawed Alam, Ph. D.). This group is broadly interested in understanding and augmenting the mechanism by which cells protect themselves against oxidant-mediated injuries or disease. The research focuses on (*a*) the regulation of mammalian gene transcription in response to oxident stress and (*b*) the use of genes encoding antioxidant enzymes or regulators of antioxidant enzymes as therapeutic tools. Currently, the laboratory is investigating the regulation and function and heme oxygenase-1, an enzyme that catalyzes the initial step in heme degradation. The laboratory has recently identified the Nrf/Maf family of transcription factors as mediators of heme oxygenase-1 gene activation in response to oxidant stress. These proteins may represent a third major group of transcription factors, including AP-1 and NF-κB, that regulate the cellular oxidant defense response. In a second line of research, this group has also recently demonstrated that intratracheal injection of an adenovirus encoding heme oxygenase-1 prevents oxygen reduced mortality and lung inflammation in rats. Studies are currently in progress to determine the molecular mechanisms responsible for this protection.

A third group in this laboratory (Julia Cook, Ph.D.) studies the mechanisms by which the protein p53 tumor suppressor binds to DNA and regulates gene expression. p53 is the protein most often mutated in cancer. Wild-type and mutant p53 proteins are being studies with regard to transactivation of consensus sequence homologies both in transiently transfected plasmids and in integrated chromatin structures. This group has found that the ability of p53 to bind and mediate transcriptional activation through p53 homologies is profoundly affected by the integration site of the consensus sequence. The team is constructing a vector delivery system to insulate the p53 consensus sequence reporter gene constructs from effects of nearby enhancers and repressors. This system should permit repeatable, unbiased assessments of relative potencies of p53-binding sequences. This group has further designed and constructed a series of retroviral vectors that possess synthetic enhancer sequences combined with a basal cellular promoter. They have determined that each of these promoter/enhancer regions are expressed for a much longer duration than are viral promoters, yet the expression levels are greater than those observed using the basal cellular promoter alone. Their analysis of stably transfected tissue culture cells, has continued for 1.5 years.

Finally, an effort is underway within the laboratory (Janet Larson, M.D.) to utilize the techniques of gene therapy in the in utero therapy/prevention of cystic fibrosis. This effort utilizes in utero gene transfer to rescue cystic fibrosis knockout mice. The work has also suggested previously unappreciated effects of the cystic fibrosis transmembrane conductance regulator in lung development. This group is exploring both the mechanisms by which knockout mice are rescued and the mechanism by which the transmembrane conductance regulator affects lung development and resistance to infection.

Laboratory of Cellular Immunology

This laboratory (Yong Sung Choi, M.D., Ph.D.) studies cellular and molecular mechanisms responsible for the efficient production of effective antibodies and the generation of the immunological memory. To investigate this question, the laboratory has established an in vitro experimental model that mimics the in vivo microenvironment of the lymphoid follicle where memory lymphoctyes are generated. This unique in vitro model utilizes a stromal cell line (follicular dendritic cell) that has been established in this laboratory and used by a number of investigators

around the world. These tools should make it possible to identify the genes encoding the novel signal molecules that regulate the immune response. The functional analysis of these molecules should provide valuable therapeutic insights. In this effort, the Laboratory of Cellular Immunology works closely with biotechnology companies to determine the therapeutic potential of a large number of candidate human genes.

Hepatology Laboratory

This laboratory effort (Andrew Mason, M.B.B.S.) is focused on determining the etiology and pathogenesis of the autoimmune/idiopathic biliary disorders, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). The laboratory is investigating the role of exogenous and possibly endogenous retroviral agents in the pathogenesis of these disorders. A novel endogenous retrovirus from the liver of a patient with PBC has been cloned using representational difference analysis. In addition, retroviral sequences from hepatic tissue and body fluids have been analyzed and two specific clones from patients are undergoing more intensive study.

Hypertension and Cardiovascular Biology

This laboratory (Edward Frohlich, M.D.) studies the pathogenesis of hypertension and its sequelae, including left ventricular hypertrophy and renal insufficiency. Recent studies of the kidney are designed to determine whether antihypertensive therapy will prevent or reverse end-stage renal disease. These studies have demonstrated that aging exacerbates the endothelial dysfunction of hypertensive kidney disease. Furthermore, certain forms of antihypertensive therapy reverse not only the severe intrarenal and glomerular hemodynamic alterations of hypertensive renal disease but also the pathological changes and severe proteinuria. These beneficial effects of therapy seem to be specific for certain classes of antihypertensive drugs. Thus, the ACE inhibitors rapidly reverse these changes, whereas diuretics, possibly because of effects on the intrarenal renin-angiotensin system, do not. Also, the laboratory has extensively studied the renin angiotensin system, not only as a regulator of cardiovascular homeostasis but as a regulator of cellular growth (Richard Re, M.D., Julia Cook, Ph.D.). Using antisense inhibitors of angiotensinogen synthesis, the laboratory has demonstrated that autocrine production of angiotensin II can regulate growth in specific cell types, thereby lending support to the concept of physiologically relevant local renin angiotensin systems. Because autocrine angiotensin growth regulatory systems have been identified both in cells derived from the cardiovascular system and in certain neoplastic cell lines, this work is potentially relevant to the pathophysiology of both cardiovascular disease and certain forms of neoplasia.

Laboratory of Molecular Oncology

This laboratory (Om Prakash, Ph.D.) is primarily interested in the pathogenesis of HIV infection. The laboratory operates both a transgenic facility and a P3 viral isolation facility. The HIV-1 genome encodes a number of proteins; one among these is Tat. There is accumulating evidence that in addition to its role in transactivation of HIV-1 gene expression and virus replication, Tat can alter the expression of a large number of cellular genes and normal cell functions and, consequently, can contribute to the development and support of a variety of HIV-associated disorders. In view of this possibility, the laboratory generated transgenic mice that express HIV-1 Tat. The biologically active protein is detectable by immunocytochemical and Western blot analysis of tissues of these mice.

How precisely HIV infection causes immune system disorders remains a mystery. The group found that the Tat transgenic mice display reduced cell-mediated immunity as measured by cytotoxic T cell and natural killer cell activities. Both cytotoxic T cell and natural killer cells function in controlling viral infection. These mice also showed aberrant regulation of a number of cytokines, suggesting that Tat can affect immune cell function in the absence of other viral gene products. While Tat is known to exert immunosuppressive effects, alcohol is also an immunosuppressive agent. Since alcohol use is common in society, both factors may interact in an additive or synergistic fashion to further impair the host defenses of these patients. In vivo studies in mice indicate that ethanol intoxication suppresses neutrophil functional activity. This impairment of neutrophil function is more severe in mice that express the HIV-1 Tat protein, suggesting that alcohol consumption in HIV-infected

individuals might further increase host susceptibility to opportunistic infections. Studies also indicate that Tat can significantly contribute to toxicity in bone marrow progenitor cells, and it could be one of the contributory factors in AZT-induced hematopoietic toxicities during AZT therapy for the clinical management of HIV infection.

Laboratory of Molecular Immunogenetics

This unit (Sonia Montenegro-James, D.V.M., Ph.D.) utilizes polymerase chain reaction (PCR) and other amplification techniques in the diagnosis of human disease. The laboratory develops and standardizes molecular assays that assist in the clinical evaluation of patients suffering from infectious and oncological diseases and in the evaluation of the large organ transplantation population seen at Ochsner. In addition, the laboratory monitors the efficacy of antiretroviral therapy by performing HIV-1 viral load testing. The Molecular Immunogenetics Laboratory is certified by the College of American Pathologists in molecular diagnostics and immunology and is a member of the Association for Molecular Pathology. The laboratory has an active research and training program in the immunology and molecular diagnosis of infectious diseases, especially diseases caused by emerging/re-emerging pathogens (malaria, tuberculosis, Lyme disease). This group works at the interface between basic and applied clinical science using molecular technologies to aid in timely diagnosis and treatment. It is an attempt to focus some of the scientific expertise resident in the organization on problems of day-to-day concern to Ochsner patients.

Conclusions

The Ochsner molecular medicine initiative is approximately 10 years old and has already proven its worth to the organization. It has provided intellectual insights to scientists and physicians alike and has contributed to the literature in important ways. It has also directly and indirectly improved the quality of care provided to patients at Ochsner and elsewhere.