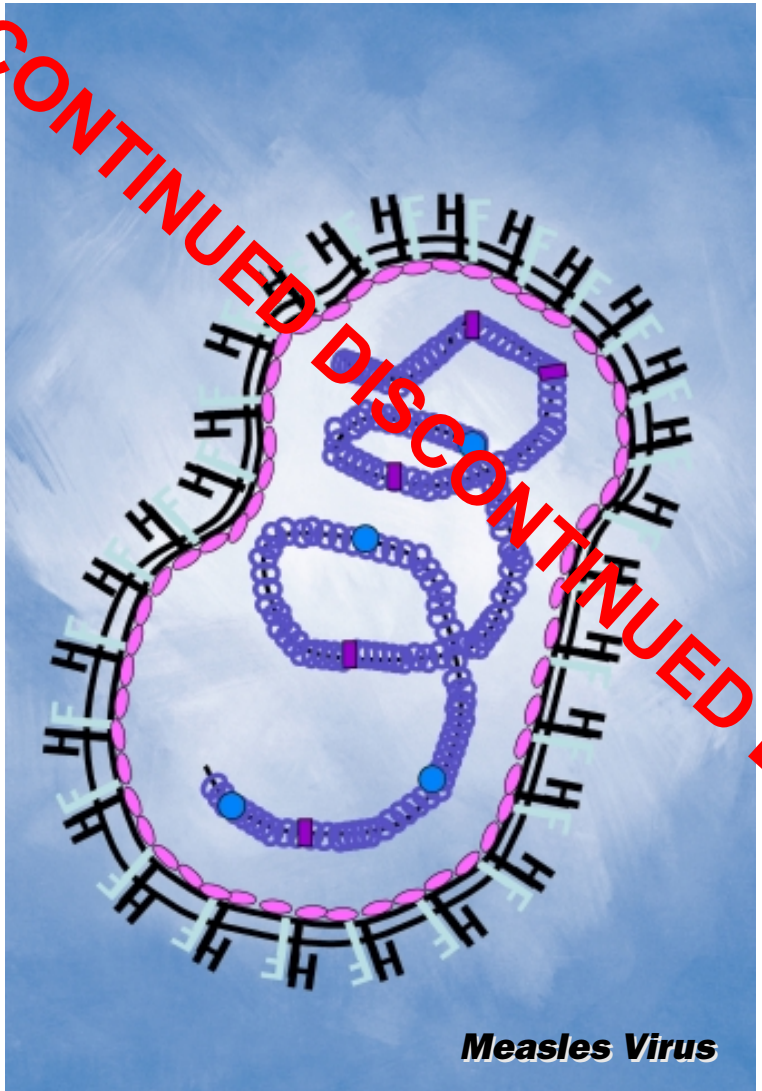




MAYO CLINIC

21st Century Medicine
Celebration of Research
February 6, 2003



Measles Virus

Welcome

On behalf of Mayo Clinic Rochester and the Celebration of Research Committee, I welcome you to the 2003 Celebration of Research. The purpose of this biennial event is to provide an opportunity for high school science students and their teachers from southeastern Minnesota to experience the ongoing variety of research at Mayo Clinic.

Medical research is dynamic; the constant change is part of the excitement of a career in research. Since our first Celebration of Research program in 1987, there have been major advances in medical research—some by investigators at Mayo, in such areas as gene therapy, cancer research, AIDS research and imaging technology. With the completion of the human genome project, we are at the beginning of a new and revolutionary era of genomics and proteomics. These are truly exhilarating times for medical research.

Researchers who are making advances in science and medicine today are individuals much like you. Their careers in medical research started with an interest in science during high school. With appropriate training and career choices, these individuals are now expanding the research frontier as lab directors, physicians, lab technicians or in other positions within the research endeavor.

Today, each of you will be able to visit several research laboratories at Mayo. Throughout the day, we hope to introduce you to the broad range of career opportunities available in research. We want you to sense the satisfaction that can be achieved by

gaining new knowledge that can benefit society. We hope to share the scientific community's enthusiasm for shaping a vision of tomorrow's world while demonstrating the ways that we work to make that vision come true.

Thank you for spending the day with us. We are very pleased to have you here.

David I. Smith, Ph.D.
Chair, Celebration of Research Committee

2003 Celebration of Research Committee

David I. Smith, Ph.D., chair
Michael J. Ackerman, M.D., Ph.D.
Gregory J. Ahmann
Glenda L. Evans
Alice J. Golla
Sharri L. Hackbarth
Karen E. Hedin, Ph.D.
Amy J. Knutson
L. James Maher, III, Ph.D.
Richard McGee, Ph.D.
Gary C. Sieck, Ph.D.

Research at Mayo

Early in his medical practice, Dr. William Worrall Mayo acquired the habit of reviewing the histories of patients following their treatment. When there was no satisfactory outcome, he would add a note at the end: "Left open for further thought and research." His sons, William and Charles, learned this habit from their father and looked upon medicine as always needing new ideas derived from practice and research.

Formal research at Mayo can be traced to the turn of the century when Dr. Louis B. Wilson built a small laboratory behind his home and began to develop Mayo's laboratory techniques on a scientific basis. Since those pioneering days, the annals of research at Mayo have included many important contributions.

Probably the best known success story is Dr. Edward C. Kendall's investigations of the hormones of the thyroid and adrenal cortex. His research, underwritten by Mayo for over 40 years, led in 1914 to the discovery of thyroxin and in 1949, to cortisone. The latter discovery, in collaboration with Dr. Philip Hench, was honored with a Nobel Prize.

Other significant contributions by Mayo scientists include a method of analyzing surgical tissue for quick diagnosis; a system for grading the severity of cancers; the first reliable test of the activity of the thyroid gland; the first use of tuberculosis drugs; and pioneering work in the development of open heart surgery, hip replacement surgery and CT scanning.

Research Statistics

Personnel..... 1,981

Protocols..... 5,895

Funding \$258 million

42% Mayo funds

58% other sources

For more information, visit:

<http://www.mayo.edu/research>

and

<http://www.mayo.edu/research/celebration>

Program

Celebration of Research

Thursday, February 6, 2003
Phillips Hall, Siebens Building

- 9:00 - 9:10 a.m. **Introduction/Welcome**
David I. Smith, Ph.D.
Department of Laboratory
Medicine and Pathology
Chair, Celebration of Research
Committee
- 9:10 - 9:40 a.m. **Keynote Address**
21st Century Medicine
Stephen J. Russell, M.D., Ph.D.
Molecular Medicine Program
- 9:45 - 10:30 a.m. **Tour of Mayo Research**
Laboratories
- 10:30 - 11:15 a.m. **Tour of Mayo Research**
Laboratories
- 11:30 a.m. - 12:45 p.m. **Lunch**
- Getting Started in a Research**
Career
Richard McGee, Ph.D.
Associate Dean for Student
Affairs
Mayo Graduate School

Career Paths in Research

Sara Van Driest,

*M.D., Ph.D., Student in
Molecular Pharmacology and
Experimental Therapeutics*

Jeffrey Bailey,

*Senior Research Technologist I
in Physiology and Biophysics*

Nisha Charkoudian, Ph.D.,

*Postdoctoral Research
Fellow in Anesthesiology
Research*

Karen Hedin, Ph.D.,

*Senior Associate Consultant
in Transplant Biology*

1:00 - 1:45 p.m.

**Tour of Mayo Research
Laboratories**

1:45 - 2:30 p.m.

**Tour of Mayo Research
Laboratories**

2:30 - 3:00 p.m.

Refreshments and Departure

Educational Opportunities at Mayo Foundation

Mayo Graduate School

Offers Ph.D. degree in seven different areas.
Graduate students pay no tuition and receive \$19,800 to offset their living expenses while in school.
Fantastic laboratory facilities. Summer research for college students. \$4,000 stipend.
Graduate students: 132

Mayo Medical School

Small (42 students per class). Very personalized medical education with outstanding, accessible faculty. Much lower tuition than other private medical schools. Also has a combined M.D./Ph.D. program.
Medical Students: 177

Mayo School of Health Sciences

Trains students in 24 allied health programs, including physical therapy, laboratory technology, radiography, respiratory therapy, physician assistant and nurse practitioner.
Students: 224

Mayo Graduate School of Medicine

One of the world's largest graduate medical education centers, training physicians in more than 100 specialties and subspecialties.
Residents and clinical fellows: 1,055
Living alumni: 12,500

Mayo School of Continuing Medical Education
Courses for physicians, nurses and other medical
professionals.

Courses: 148

Attendees: 32,800

For more information on Mayo Education Programs,
see www.mayo.edu/education/education.html

Career Pathways in Biomedical Research

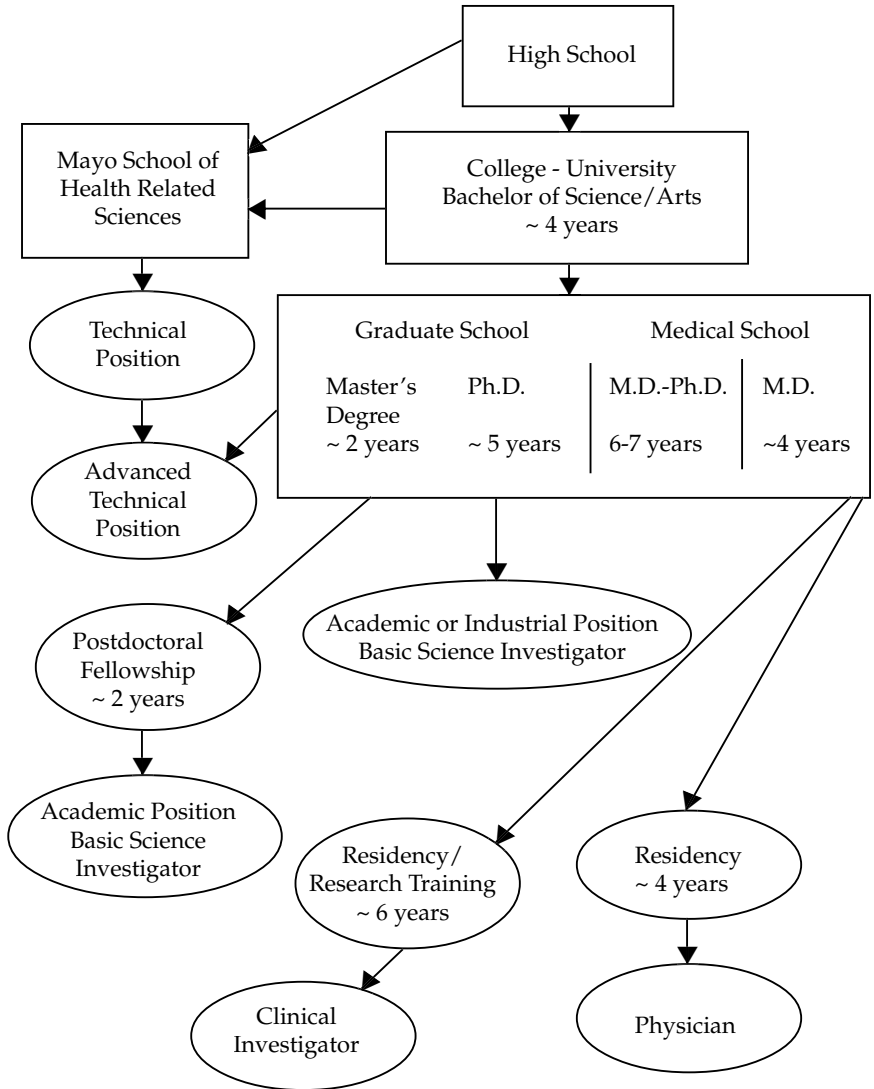


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Sudden Death Genomics Laboratory – It's in the Genes

Michael J. Ackerman, M.D., Ph.D.

Over 1,000 sudden deaths occur each day in the United States. Most cases of sudden death are related to coronary artery disease. However, sudden death involving infants, children, adolescents, and young adults is often due to genetic defects in the heart.

Our laboratory is interested in the molecular basis underlying two primary cardiac syndromes: long QT syndrome (a “channelopathy”) and hypertrophic cardiomyopathy. Our laboratory uses various techniques in mutational analysis to discover new genes responsible for these conditions and to identify a patient’s disease-causing mutation. In addition, we perform a “molecular autopsy” to probe for genetic causes of sudden death in cases of sudden infant death syndrome (SIDS) and unexplained drownings.

A visit to our lab will allow you to explore the fascinating world of molecular sleuthing with the search for an individual’s sudden-death-causing genetic defect.

*How do YOU respond to medicines:
why is it sometimes different than
expected? (It's in the genes!)*

Matthew M. Ames, Ph.D.

Every day, millions of people take the same drugs — pain relievers, medicines for high blood pressure or high cholesterol, anticancer agents, or any of the thousands of drugs available for the treatment of disease. We have known for decades that while most people respond as expected, both in terms of the desired effects and undesired side effects, some people do not. For those individuals, certain drugs may not be effective (for example, some people fail to achieve pain relief from several very potent agents) or drugs may cause severe side effects (as for several potent anticancer agents). We now know that for many individuals who do not respond as expected to specific medicines, the key factor is variation in the DNA sequence of certain genes (and therefore the protein products of those genes) when compared to the common DNA sequence for those genes in the general population. The protein products of these specific genes are responsible for determining how we all respond to many drugs.

During your visit to our laboratory, we will briefly discuss how these genes differ in their DNA (and the possible results in functional proteins in the body). You will see the methods and experiments in use to detect these genetic differences in patients, and we will discuss analysis of data from those experiments.

Graves' Disease – An Autoimmune Disease of the Thyroid Gland

Rebecca S. Bahn, M.D.

In my lab, we are studying various aspects of thyroid gland over activity. In particular, we are interested in determining why some people mount an autoimmune reaction directed against the thyrotropin receptor on their thyroid cells. This results in the overproduction of thyroid hormone and a condition known as Graves' disease. People with this disease develop eye problems, which may begin with bulging and painful eyes and progress to blindness. As one possible explanation for these eye problems, we discovered that besides being found on thyroid cells, the thyrotropin receptor is present on fat cells in the orbit behind the eyes. It appears that the autoimmune reaction against the thyrotropin receptors near the eye may be causing the eye problems. We wish to better understand the mechanisms responsible for this reaction directed against eye and thyroid cells in order to ultimately devise better treatments for patients with Graves' and other autoimmune diseases.

Microvascular Research Laboratory

Allen T. Bishop, M.D.

Our laboratory is interested in the development of new applications of microsurgery for reconstruction of missing bone and joints. These problems occur as a result of tumors, infections and traumatic loss, and present a difficult challenge for surgeons at present. Specifically, we are studying the possible transplant of living bone grafts from donors including other people (allograft) and animals (xenograft). The grafts will have their circulation restored by microscopic repair of nutrient blood vessels. This is analogous to the transplantation of hearts and other organs that is commonly performed. We are searching for ways to perform these procedures without the risks of lifelong immunosuppressive drugs currently required for these critical organ transplants.

Cardiorenal Research Laboratory

John C. Burnett, M.D.

The Cardiorenal Research Laboratory (CRRL) is a major research unit in the Division of Cardiovascular Diseases. Founded in 1982, the focus of the CRRL is on the integration and coordination of the heart, kidneys and blood vessels by the endocrine system and other local chemical mediators.

Our lab is interested in the role of the natriuretic peptides, endothelin, angiotensin and adrenomedullin, in cardiovascular-renal homeostasis. We are investigating the role of pathophysiology, therapeutics and diagnostics in human congestive heart failure and atherosclerosis. And we design and synthesize unique peptides that mimic the actions of endogenous hormones and provide novel therapeutic strategies in cardiorenal disease states.

The CRRL also determines the amount of various hormones in blood samples from clinical trials in cardiovascular medicine.

Enteric Physiology - The Long and Winding Road

Michael Camilleri, M.D.

It is estimated that over 35 million people within the United States suffer from functional gastrointestinal (GI) disorders. These disorders are defined as, “variable combinations of chronic or recurrent GI symptoms not explained by structural or biochemical abnormalities.” As many as 25 such disorders affect approximately one out of every five people in the U.S. and are the second leading cause for absenteeism in the workplace.

Our lab conducts various research studies investigating the multiple causes and possible treatments associated with functional GI disorders.

A visit to our lab will allow you to learn about the various research and diagnostic tools used in our investigations. Components you will see are endoscopy, nuclear imaging with radioisotopes and enteric motility recording apparatus.

Recombinant Viruses Targeting Deleterious Cells

Roberto Cattaneo, Ph.D.

The study of microbes has allowed the development of vaccines and disease therapies while contributing to our understanding of life. A new frontier in the field of microbiology involves the transformation of available vaccine strains into therapeutic agents.

Our research group focuses on developing the safe and effective measles virus (MV) vaccine strain Edmonston into a vector for targeting and eliminating deleterious (cancerous or HIV-infected) cells. Based on our knowledge of the structure, intracellular transport, assembly and functional regulation of the viral components, we have designed and produced recombinant viruses efficiently entering host cells through tumor-associated antigens. To test the efficacy of these viruses, we are developing model animal systems. These systems include transgenic mice expressing human MV receptors with humanlike tissue specificity and immunosuppressed mice bearing human tumors.

Immune-based Therapies for Cancer

Esteban Celis, M.D., Ph.D.

Our program is interested in the recognition and destruction of tumor cells by a class of white blood cells, known as T-lymphocytes (T cells). T cells can recognize molecules on the surface of tumor cells. This recognition then causes an immune response to the “foreign” cells. The T cells involved in this response can be either cytotoxic T cells or helper T cells. Both types are required for an effective response to the tumor cells. Some of the molecules on the surface of tumor cells are also found in small quantities on normal cells. This may cause the T cells to no longer recognize this molecule as a marker for a “foreign” tumor cell. This is referred to as immune tolerance. The research interests in our lab focus on using these principles to develop immune-based therapies for cancer.

Four areas of research currently investigated in our laboratory are: (1) identifying the molecules on the surface of tumor cells that are recognized by T cells so that vaccines for certain cancers can be developed, (2) overcoming tolerance so that the therapy used will cause a strong and effective anticancer immunity, (3) regulating and enhancing the T cell response to tumors, and (4) studying the role of helper T cells and regulating the activity of cytotoxic T cells to tumor cells. Any vaccines developed will need to activate both of these cell types.

We also use specialized mice to evaluate the responses to vaccines against surface molecules found on tumors. These responses will allow development of therapeutic vaccines to treat cancer.

Cancer Genetics

Fergus J. Couch, Ph.D.

Our laboratory studies breast and ovarian cancer and specializes in analysis of inherited forms of these diseases. Genetic studies in the laboratory are aimed at identifying novel oncogenes that contribute to the development of breast and ovarian cancer. Initially, we select genes that have extra copies in precancerous cells due to widespread DNA damage. These genes are then studied in tumors to determine if the extra gene copies result in production of abnormal amounts of protein and if these proteins lead to tumor formation.

One such gene that we are studying is the BRCA2 familial breast cancer gene. BRCA2 is associated with regulation of cell division and cell death. By studying the underlying mechanisms for this regulation, we hope to better understand how BRCA2 contributes to cancer formation. Genetic epidemiology studies in the laboratory are aimed at identifying the environmental factors that increase or decrease the risk of breast cancer in members of families with inherited breast and ovarian cancer.

Mouse Genetics Core Facility

Chella S. David, Ph.D.

The Mouse Genetics Core Facility utilizes state-of-the-art serological, molecular and genetic techniques for determining the role of individual genes and gene products in health and disease. It comprises two laboratories: the Hybridoma Laboratory and the Gene Targeting Laboratory.

The Hybridoma Laboratory produces monoclonal antibodies, meaning they are derived from a single clone of B cells. These antibodies are reactive to very specific proteins and have applications in basic research, diagnostics and immunotherapies.

The Gene Targeting Laboratory produces transgenic mice. Transgenic mice are mice expressing cloned DNA that has been introduced into fertilized mouse embryos. Adult transgenic mice are frequently constructed to express a single human gene thought to be disease-associated. Many of the transgenic mice developed by the Gene Targeting Laboratory express human genes implicated in the pathogenesis of arthritis, allergy and diabetes. In addition, the Gene Targeting Laboratory produces transgenic mice that express specifically altered or mutated genes. Transgenic mice expressing these “gene constructs” are used in research to determine the role of the protein produced by the mutated gene in disease process.

Veterinary Medicine Research

Craig S. Frisk, D.V.M.,

Michael C. Blanco, D.V.M.

The Section of Veterinary Medicine supports the research effort at Mayo Clinic by providing care for the animals that are used in biomedical research projects. Nearly every major medical advance of the last 100 years has depended upon research involving animals. Animal studies have provided the knowledge that allows Mayo Clinic to improve and lengthen the life of people by preventing and treating diseases.

Cardiovascular Health Clinic
– Testing the reserves of heart
Gerald T. Gau, M.D.

Good cardiac function is essential to enjoying many aspects of life. Many disease entities that can influence the heart are relatively inactive at rest; however with the increased demands of exercise, a heart with limited reserves (either for blood flow or muscle function) will begin to influence the normal cardiopulmonary responses to exercise.

Our laboratory examines the limits of human performance in athletes as well as in patients with various heart-related abnormalities. This is done through a progressive treadmill exercise test while monitoring the electrocardiogram ratings of perceived exertion and through measurements of expired gases.

A visit to our cardiopulmonary laboratories will help you begin to understand how the body adapts to the increasing metabolic demands of exercise.

Rheumatoid Arthritis and the Immune System

*Jörg J. Goronzy, M.D., and
Cornelia M. Weyand, M.D.*

We are interested in the disease mechanisms that are involved in rheumatoid arthritis. Rheumatoid arthritis is a chronic inflammatory disease that is caused by a dysfunction of the immune system. The immune system is composed of many different types of cells, including T lymphocytes, B lymphocytes and natural killer cells. In order for the immune system to function properly, there must be a balance between each of the different populations of cells. These immune cells express particular receptors on their surface that regulate their function.

We have found that individuals with rheumatoid arthritis have an expanded population of T lymphocytes that lack an important regulatory receptor. We are interested in understanding how these particular cells are involved in rheumatoid arthritis. We hope that our research will one day help in the treatment of rheumatoid arthritis as well as increase our knowledge about the regulation of the human immune system.

Use of Ultrasound for Diagnosis and Treatment

James F. Greenleaf, Ph.D.

Ultrasonic energy interacts sensitively and differentially with soft tissues. It can be used for diagnostic purposes or for therapy.

In our research work, we are studying both uses. We are developing diagnostic methods for imaging the beating heart in three dimensions using specialized scanners and advanced computer software and hardware. Characteristics of the tissue are deduced from the scattering attributes of the ultrasound and displayed in multidimensional formats on computer workstation monitors. Computerized pattern recognition of ultrasound images using artificial neural networks and artificial intelligence is being used to diagnose breast cancer. Ultrasound is being investigated for its therapeutic value in fracture healing. Ultrasonic methods of activating drugs anywhere in the body are being investigated for therapies such as tumor killing.

Myeloma Tumor Biology Laboratory

*Philip R. Greipp, M.D., Rafael Fonseca, M.D.,
Thomas E. Witzig, M.D.,
Vincent Rajkumar, M.D.*

Multiple myeloma is a disease of bone marrow plasma cells primarily confined to the bone marrow. Multiple myeloma causes 14,000 deaths each year and appears to be on the increase.

Normal plasma cells belong to the B cell family of white blood cells. B cells normally go through several stages of development to become antibody-secreting plasma cells. During this maturation process, some event(s) may cause these cells to become cancerous. If these events happen in the final stages of maturation, the cancerous cells are plasma cells and are characterized by the production of a monoclonal protein (antibody). Levels of the monoclonal protein in the serum and urine are used by physicians to “track” responses to treatment.

The research goals in this lab are to identify and understand genetic changes that turn normally non-growing plasma cells into abnormally growing malignant plasma cells. Additionally, we study changes in the bone marrow microenvironment that support malignant plasma cell growth. These changes include angiogenesis (blood vessel formation) and uncoupling of the normal bone remodeling mechanisms. Within this lab, we perform assays that include both cellular and molecular techniques. Some of the techniques employed in this area include: cell culture, fluorescent in situ hybridization (FISH), polymerase chain reaction, real-time PCR, flow cytometry, immunohistochemistry, proliferation and apoptotic (cell death) assays.

Mechanical Properties and Deformation Responses of Lung Tissue

Rolf D. Hubmayr, M.D.

Mechanical ventilation is a lifesaving intervention but it carries the risk of damaging the lungs by overdistending them. When this happens blood, plasma and inflammatory cells accumulate in the airsacks and produce, in effect, a pneumonia. For this reason, we want to know: (1) how should the physician set a mechanical ventilator to avoid this problem? and (2) how do cultured lung cells respond to deforming stresses?

We image the lungs of experimental animals during mechanical ventilation and describe the patterns of deformation of different parts of the lung. We culture lung cells on malleable membranes, stretch the membranes, and measure gene expression and release of those signaling proteins known to be involved in inflammation. We image the cells in an undeformed and a deformed state with laser confocal microscopy and measure the changes in cell volume, shape and surface area. By attaching iron beads to the cell surface and moving the beads with a magnet, we can estimate cell stiffness and manipulate it with drugs. Changes in cell stiffness can then be correlated with changes in deformation responses. For example, we can test if a “floppy” cell is less likely to be damaged than a “stiff” cell. This holds the promise of preventing ventilator induced lung injury with drugs that alter the resistance of lung cells to a shape change.

Use of Yeast and Mouse Genetics to Understand Mitochondrial Disease

Grazia Isaya, M.D., Ph.D.

Mitochondria represent the main source of energy for the cell. In a process known as *oxidative phosphorylation* (OXPHOS), the energy derived from oxidation of foods is channeled into formation of ATP, a high-energy compound that is used by the cell in the synthesis of all types of essential molecules. More than 1,000 genes are required for OXPHOS maintenance, and mutations in these genes can lead to OXPHOS defects, which are a frequent and important cause of disease.

Our lab is interested in the identification and characterization of new OXPHOS genes. In our research, we use the yeast *Saccharomyces cerevisiae* and the mouse as our working models. In these organisms, we can mutate OXPHOS genes and create yeast or mouse mutants with OXPHOS defects. The analysis of these mutants helps us understand the normal function of OXPHOS genes and their roles in disease. Our goal is to provide information that can be useful for the diagnosis and treatment of patients with OXPHOS defects.

Genetic Studies of Brain Tumors

Charles D. James, Ph.D.

The major interest of my laboratory is the identification of mutations that frequently occur in brain tumors, and understanding how these mutations affect the various biologic properties of the tumor. Of particular interest are mutations affecting the epidermal growth factor receptor (EGFR) gene, which is an important protein for transmitting extracellular signals to numerous signaling pathways inside the cell. We are currently investigating the relationship between EGFR mutations and tumor invasion, the process by which cancer cells spread into normal tissue.

Molecular Studies of B Cell Cancers

Diane F. Jelinek, Ph.D.

Our laboratory is studying B cells, which are white blood cells dedicated to making antibodies that provide protection from circulating bacteria and viruses.

To become an antibody-secreting cell, the B cell goes through several stages of development. During this development, B cells may become cancerous, causing diseases such as B cell chronic lymphocytic leukemia (B-CLL) and multiple myeloma (MM). Each type of B cell cancer has unique features that are important to understand. With B-CLL, very large numbers of cancerous B cells accumulate in the blood of patients. These cells are long-lived and do not develop further. With MM, a B cell at the antibody-producing stage becomes cancerous; in these patients, very large numbers of cancerous B cells accumulate in the bone marrow. These tumor cells are capable of growing and dividing, whereas normal B cells at this stage cannot divide.

We are trying to understand the abnormal behavior of B cells in both diseases by studying the role of growth factors and receptors, as well as genetic differences. These studies will provide new basic information that may lead to therapeutic interventions for patients suffering from B-CLL and MM.

Genetics of Cancer

Robert B. Jenkins, M.D., Ph.D.

My laboratory is generally interested in the genetic causes of cancer. It is now generally thought that most, if not all, cancer is caused by genetic alterations. We are interested in defining and understanding these alterations in some specific cancers. For example, we know that alterations of human chromosomes 1 and 19 are associated with oligodendrogliomas (a kind of brain tumor). Importantly, when a tumor has such an alteration, it responds (gets smaller) to specific chemo- and radiation therapies. My laboratory is trying to find the genes on chromosomes 1 and 19. Once we find the genes, we plan to study their normal function and the means by which they cause cancer. We are also studying genetic alterations that have similar relevance for prostate cancer and breast cancer.

Daily Activity and the Cardiovascular System

*Michael J. Joyner, M.D., and
Niki M. Dietz, M.D*

Our research focuses on how the human cardiovascular system adapts and responds to exercise and other stresses encountered during everyday life. In particular, we are trying to identify what hormonal, neural or metabolic factors are responsible for changes in blood flow in various regions of the body during exposure to various stresses. Examples of stresses we have investigated include exposure to a hot environment (thermal stress), altitude (hypoxic stress) and adjustments in response to changes in body position (gravitational stress). Many of these responses are related to issues of human health and disease.

Motion Analysis Laboratory

Kenton R. Kaufman, Ph.D.

The Motion Analysis Laboratory provides state-of-the-art, dynamic musculoskeletal testing for patient evaluation. This includes upper and lower extremity strength and motion measurements, balance evaluation, dynamic foot pressure measurements, and real-time muscle activity monitoring (electromyography). The laboratory is staffed by kinesiologists, physical therapists, engineers and postdoctoral researchers with training in engineering and medicine. Current projects include: (1) evaluation of the effects of aerobic exercise on osteoarthritis of the knee; (2) development and testing of a miniaturized pressure measurement system to study pressures inside tissues and organs; (3) design and testing of a “smart” knee brace; (4) analysis of wheelchair propulsion; and (5) effects of different types of ankle braces on walking.

Understanding Age-Related Bone Loss in Humans

Sundeep Khosla, M.D.

Our research focuses on the role of the sex steroids, estrogen and testosterone, on bone cell growth and differentiation. Both estrogen and testosterone have been shown to play an important role in maintaining the balance between bone growth and bone loss during the life long process of bone remodeling.

To address the questions of how these hormones affect bone density, we use epidemiological and clinical research studies. In addition, at the cellular level, we use in vitro osteoblast (bone-making cells) and osteoclast (bone-degrading cells) tissue culture models to study effects on different cell types in the bone. Finally, we address the molecular mechanisms of estrogen and testosterone in bone using state-of-the-art molecular biology techniques such as real-time quantitative polymerase chain reaction (PCR) technology to understand how different genes are regulated when exposed to these compounds.

Studying Asthma – Just Breathe!

Hirohito Kita, M.D.

Rates of asthma worldwide are rising 50% on average every decade and nobody really knows why. Today, asthma affects 10 to 12 million Americans and accounts for a loss of more than 10 million school days annually due to shortness of breath, chest tightness, coughing and wheezing. Our laboratory is devoted to understanding asthma and discovering new ways to interfere with the disease process.

Our lab is particularly interested in a white blood cell, called an eosinophil, and its role in asthma. Everyone has eosinophils in their blood and in their gut. However, eosinophils are also found in the lungs of people who have asthma, and the presence of these cells is associated with asthma symptoms. Eosinophils produce many chemicals in the lungs that can cause narrowing of the airways; this is why people with asthma have difficulty breathing. In our lab, you will learn how we can separate this one type of white blood cell from all the others, how individuals could spend their whole life unlocking the secrets of just one cell, and how studying this cell is helping us understand asthma and how to treat it.

Immunochemical Core Laboratory

George G. Klee, M.D.

The Immunochemical Core Laboratory (ICL) provides laboratory testing at minimal cost to Mayo researchers. When capacity is available, testing is also provided for investigators outside of Mayo on a collaborative basis and for Mayo Medical Laboratories' clinical trials clients.

The ICL staff is actively involved in new assay development and improvement of current assay methodologies. The ICL will analyze research samples from animals or humans for a wide variety of immunochemicals. The current menu of 97 tests includes assays for hormones, vitamins, growth factors and other peptides as well as tests for various lipids and apolipoproteins. The ICL is fully equipped with state-of-the-art instruments including robotics for conducting large or repetitive assays.

Prostate Cancer Research

Eugene D. Kwon, M.D.

Prostate cancer is the most commonly diagnosed malignancy in U.S. men. Prostate cancer is also the second-most common cause of cancer-related death for men in the United States.

A primary focus of our laboratory is to develop new methods to treat prostate cancer using host immune responses. We have developed various strategies to stimulate T lymphocyte immune cells in mice as well as patients so that such T cells can attack prostate tissues to cause prostate tumor regression. Specifically, we have developed a method to stimulate T cells so that these cells can recognize prostate tissues and tumors.

We have also developed a method to keep T cells from turning off again so that these cells can persistently attack prostate tumor tissues. This method involves the administration of an antibody that can block the T cell CTLA-4 receptor that then prevents T cells from shutting down again. By administering this antibody, we have successfully treated prostate tumors in TRAMP mice (mice that have been engineered to spontaneously develop prostate cancer). We have also shown that we can enhance the effectiveness of immune responses by depriving the male host of testosterone.

Based on these observations, our lab will be testing a strategy to treat advanced prostate cancer in patients who come to Mayo Clinic for treatment.

Gastroenterology Basic Research Center

Nicholas F. LaRusso, M.D.

My laboratory studies liver epithelial cells, called hepatocytes or cholangiocytes. In addition to our interest in the normal function of these cells, we are also interested in the mechanisms that account for their dysfunction in disease states. We hope to develop new treatments for cholangiopathies, a group of malignant, developmental, genetic, infectious and immunological liver diseases in which biliary epithelia are the principal targets of diverse and destructive processes.

In our studies, we utilize an array of complementary and sophisticated cell and molecular biological techniques to define regulatory and mechanistic aspects of hepatic epithelial cell function. Our current attention is focused on questions related to the cell cycle (programmed cell death and proliferation), cholangiocyte and biliary ductal architecture, cholangiocyte interactions with microbes (how cholangiocytes resist microbial invasion), regulation of selected gene expression, and solute and water transport in cholangiocytes.

TGF β - A Protein with Many Functions

Edward B. Leof, Ph.D.

Thousands of proteins are involved in the essential regulation of our growth and development. Transforming growth factor β (TGF β) is one such protein, which has multiple important roles in determining the fate of growing cells in our bodies. Being such an important protein, alterations in TGF β functions can have dramatic effects on our bodies leading to diseases such as cancer, fibroses and immune system disorders.

Our laboratory is studying how TGF β interacts with cells and how these interactions change the life processes which occur within the cells. Understanding how TGF β signals these cellular effects will greatly help us to understand the concepts of fibrosis and cancer growth and their spread through our bodies, and to find effective treatments for the diseases.

A visit to our laboratory will introduce you to how we study these cellular communications from visualization of the physical effects TGF β has on cells viewed through a microscope, to how we extract the cellular signaling machinery and decipher the messages being sent.

Flow Cytometry and Optical Morphology Research

Paul J. Leibson, M.D., Ph.D.

This research core facility uses sophisticated electronics, optics, lasers and computer technology to answer biological questions. A flow cytometer is an instrument that measures properties of cells or other particles. The cells are suspended in liquid and passed at high speeds through one or more laser beams. About 20,000 cells per second can be measured in this way. The flow cytometer provides information on relative size, shape and fluorescence intensity of the cells. The fluorescence intensity, or color, usually comes from dyes that have been used to stain the cells. The dyes are used to look at particular characteristics of the cell such as DNA, RNA or other molecules found on the surface or inside the cell. The flow cytometer can also sort out a mixture of cells based on whether or not they bind a fluorescent-tagged molecule (antibody). The cells of interest are deflected by an electric field to their own collection tube, leaving the unwanted cells in a separate tube.

The Optical Morphology area provides instruments for microscopy and analysis of the microscopic images. Fluorescent and confocal microscopes are available for general use. The confocal microscope allows for high-resolution viewing of cells or tissues. Fluorescent dyes are used to label structures or molecules of interest. Laser beams are then used to excite the dyes and multiple slices or views are

collected. Software programs then create three-dimensional images from these optical slices. Additional software determines differences in dye intensity or the area stained by the dye. The instruments are shared by a variety of investigators involved in many fields of biomedical research.

Nerve Microenvironment

Phillip A. Low, M.D.

Each of us has millions of nerve fibers of all sizes. Each fiber is extremely thin (measuring as small as one-millionth of a meter in diameter) and exists a long distance from its parent cell body. Thus, nerve fibers are very dependent on their microenvironment for nourishment, growth and survival. Our particular focus is how normal and diabetic nerves survive disturbances to their environment. The main disturbance we study is nerve ischemia and the molecular mechanisms that result in damage to nerves. Upon determining the mechanisms responsible for nerve damage, we can proceed to studying mechanisms of neuroprotection (or how we can rescue nerves from dying).

Nuclear Magnetic Resonance

Core Facility

Slobodan I. Macura, Ph.D.

Nuclear magnetic resonance is a well-established analytical procedure for studying molecular structure. It can be used in biomedical research to identify various biomolecules in solution, cell cultures, tissues and in the human body. The method is based on the fact that many stable and naturally occurring atomic nuclei act as small magnets. In other words, most matter, including our bodies, possesses macroscopic nuclear magnetism. All of us are magnetic. However, this magnetism is so tiny that only very sensitive instruments can observe it. Even then, the most sensitive technique, resonance detection, must be applied to observe this magnetism. Hence, the name nuclear magnetic resonance or NMR. The definition comes from “nuclear magnetic” because magnetism comes from the atomic nuclei, and “resonance” because of the way magnetism is detected. Nuclear magnetic resonance has nothing to do with radioactivity.

Dozens of stable nuclei (a few of which are natural parts of our bodies) are suitable for NMR studies. In NMR, the sample to be studied is positioned in the static magnetic field and exposed to weak radio-frequency waves. The signal that we subsequently detect depends on the physicochemical properties of the immediate environment of the nuclear magnet (i.e., it depends on the structure and dynamics of the molecules). Analyzing such signals can reveal what molecules are present in a sample, their concentrations, spatial structure, mobility, etc. The method is nondestructive and, therefore, particularly convenient for long-term studies of biological systems.

Studying DNA — The Longest Molecule in the Cell

Jim Maher, Ph.D.

Each of the trillions of cells in your body contains about six feet of DNA — the “hard disk” of digital information needed to make a new copy of you.

Our lab is interested in how this information is physically managed (how do you fold up a six-foot molecule to fit into a microscopic cell?) and whether we can learn to artificially turn genetic recipes off and on (what kinds of molecules might block the use of particular DNA instructions, but not others?).

Our laboratory uses recombinant DNA techniques, DNA and RNA molecules, bacteria and yeast to help us answer these questions.

A visit to our lab will allow you to learn how we study molecules that are too small to see, how microorganisms help teach us about human molecular biology, and how we are imagining the drugs of the future.

Growth Control in Cancer Cells

Nita J. Mairle, Ph.D.

Cancer is in fact multiple different diseases, with each distinct tumor arising from altered cells from various tissues.

What causes normal cells to become cancer cells? It is generally accepted that damage to DNA, especially to certain critical genes, causes normal cells to grow abnormally and result in tumor growth.

My research hopes to discover which genes are damaged and how the products of these mutated genes behave differently in tumor cells. The results of these studies may allow us to detect cancer at an early stage and also to design drugs to selectively target tumor cells.

We are studying a critical cancer gene called the epidermal growth factor receptor gene (EGFR). The EGFR regulates many functions of the cell including the ability to grow, move, attach to other cells and tissues, and even to survive. The EGFR has been found to be both mutated and overexpressed in many different types of tumors. Mutation and overexpression of EGFR somehow allows the cell to become cancerous. We are currently working to determine what other molecules the EGFR interacts with and the nature of these interactions. In future studies, specific drugs may be designed to either stop or modify these communications between EGFR and other molecules, thus inhibiting the signals that cause unregulated growth and halting cancer.

*Expression Proteomics and Protein
Chemistry Group of the Mayo
Proteomics Research Center*

Daniel J. McCormick, Ph.D.

The word proteomics is used to describe the focus on the role of all proteins in living organisms. In diseases like cancer, arthritis, or glaucoma, there are proteins that are uniquely expressed and may be found in or on the surface of the cells in diseased tissues. These proteins may also be excreted into blood, urine or other body fluids. Detection and identification of these unique proteins will provide the potential for using them as markers in detection and diagnosis of the disease and as therapeutic targets used in the treatments of the disease. The challenge to researchers lies in the fact that a human cell contains tens of thousands of different proteins varying in abundance from a few copies per cell to millions of copies per cell.

The Expression Proteomics and Protein Chemistry Group provides the entire Mayo research community with methods and techniques for reducing this complexity and identifying proteins that may be unique to a disease state. The strategy we use is termed differential proteomics, where we compare the proteins present in a normal state to the proteins present in an abnormal or disease state.

Cytoskeleton and Membrane Dynamics During Vesicle Trafficking and Cell Migration

Mark A. McNiven, Ph.D.

Mammalian cells are composed of an outer plasma membrane and multiple internal membrane-bound organelles and vesicles. In order for the cell to maintain its structure and for vesicles to be transported from one organelle to another, the cell contains rigid filamentous structures known as the cytoskeleton. However, even though this cellular cytoskeleton is rigid and provides support for the cell, it is also very dynamic. Interactions between the cytoskeleton and cellular membranes allow the cell to take up nutrients, transport vesicles, change shape and migrate.

Our laboratory is interested in studying the molecular mechanisms underlying these cytoskeletons and membrane dynamics as they relate to vesicle trafficking and cell migration. The uptake of nutrients and transport of them to the proper location within the cell is important for cell survival; whereas migration of cells from one area to another is important for processes such as development of an organism and wound healing. When processes of vesicle trafficking and migration become altered, they can lead to disease or metastasis, as in the case of tumor cells. Much of the work in our laboratory focuses on the dynamics of the cytoskeleton and vesicles within cells or the migration of cells from one place to another. We routinely use video-computer microscopy to visualize these processes as they occur as well as confocal and immunofluorescence microscopy to capture still images of these processes within the cell.

Blood Vessel Lining

Virginia M. Miller, Ph.D.

Blood vessels are lined with a single layer of cells called the endothelium. These cells provide an interface between the blood and the muscle layer of the blood vessel. An important function of these cells is to produce chemicals, which help prevent the formation of blood clots and cause the muscle of the blood vessel to contract or relax. This latter function contributes to maintaining blood pressure and to distributing the blood throughout the body.

Research in our laboratory is directed toward determining what regulates release of these substances from endothelial cells. Studies are ongoing to examine how estrogen and hormone replacement therapy affects endothelial function including the regulation of specific protein receptors and release of certain chemicals such as nitric oxide.

Changes in endothelial cells can lead to heart attacks, strokes and high blood pressure. Increased understanding of which chemicals and hormones alter endothelial cells may lead to development of therapies and the prevention of some vascular diseases.

Protein Synthesis in Body Tissue

K. Sreekumaran Nair, M.D., Ph.D.

The main focus of our research is to understand how protein synthesis and breakdown are regulated. Proteins in the body are distributed in various tissues and they perform vital functions. The body constantly maintains the quality of proteins by removing old and damaged or defective proteins by the protein breakdown process. The proteins are then replaced by new proteins in the process called protein synthesis. When protein synthesis lags behind protein breakdown in a tissue, the protein content of that tissue declines.

We measure protein synthesis and breakdown using labeled amino acids, which are the building blocks of protein. Amino acids are labeled with non radioactive stable isotopes. Mass spectrometers are used to detect the abundance of these amino acids in various tissues of the body. State-of-the-art technology allows us to understand the mechanism of many diseases such as muscle-wasting conditions including normal aging. Other diseases we investigate include diabetes, thyroid diseases, cancer and obesity.

Development of a Bioartificial Liver (BAL) to Support Patients With Acute and Chronic Liver Failure

Scott L. Nyberg, M.D., Ph.D.

We plan to develop a bioartificial liver to help patients with acute and chronic liver failure. This device will use liver cell, or hepatocytes, obtained from pig livers or from human livers not suitable for liver transplantation. The current set of experiments is designed to test this device in dogs with liver failure due to drug toxicity (acute) or cirrhosis (chronic). If the device proves successful in these preclinical animal studies, we plan to proceed with clinical testing of the bioartificial liver.

The three specific aims of our project include (1) first evaluating the device in acute and chronic liver failure. We are addressing both the immune and nonimmune mechanisms of cell death within the device since cell death in the device appears to affect performance of the bioartificial liver. In order to improve baseline performance of the device, we are (2) also testing co-culture techniques to improve cell function. In order to utilize cells from human livers, the techniques of isolation and cryopreservation of human hepatocytes from discarded human livers must be improved. Therefore, we will (3) test cytoprotective agents during the isolation and cryopreservation of hepatocytes from allogeneic (dog) livers.

*Mayo Clinic Cancer Center
Microarray/Molecular
Epidemiology Shared Resource
Dennis J. O'Kane, Ph.D.*

The completion of the human genome sequence is resulting in revolutionary changes in medical research and thinking. Diagnoses, treatments and responses to therapy are now being considered based upon the genetic make up of an individual. This may result in improved patient care, treatment and quality of life.

This Mayo Clinic Cancer Center Shared Resource investigates means of correlating individual patient differences with tests that may improve patient care. Two different approaches are used.

One approach is to investigate which genes are changed in levels of expression between diseased and normal tissue. Changes in the expression levels of genes may reveal candidate genes that are markers of disease and its progression, or genes that are potential new therapeutic targets.

A second approach is to discover and investigate small genetic differences (single nucleotide polymorphisms or SNPs) that occur in populations of people (molecular epidemiology) and correlate these changes with disease processes. These small differences may affect the level of activity of the enzymes encoded by these genes, disposing an individual to adverse drug reactions. A variety of different technologies are utilized to determine individual genetic differences, including DNA-microarray chips that are designed from computer chips, SNP detection arrays and DNA sequencing.

Infectious Diseases Investigation

Robin Patel, M.D.

In our research, we conduct innovative investigations into several different areas of infectious diseases and teach research techniques to medical students, visiting scientists, doctors in residency training and postdoctoral fellows.

We are currently studying the genetic basis of new patterns of antibiotic resistance to better understand how antibiotic resistance is spread among bacteria.

We are working with a newly described virus found in joint tissue to determine what role this virus may play in degenerative joint disease.

We have projects in progress studying new chemical compounds that may be useful as antibiotics for humans.

We are studying biodegradable polymers that may be useful as antibiotic delivery systems in humans.

We use in vitro bacteriology techniques, animal models for in vivo experiments, and sophisticated molecular biology methods to study bacterial genetics.

Transplantation Biology

Jeffrey L. Platt, M.D.

The Mayo Clinic Transplantation Biology program seeks to understand fundamental aspects of the biological and immunological hurdles to transplantation and to develop novel approaches to overcoming these hurdles.

Currently comprised of four closely integrated research laboratories and core facilities, the Transplantation Biology program pursues cutting-edge investigation in the following areas: (1) transplantation immunology, (2) signal transduction, (3) B lymphocyte biology and (4) developmental genetics.

Members of the program work in a highly innovative and collaborative environment that extends far beyond the walls of the program and provides a valuable partnership with the greater basic science and clinical communities at Mayo Clinic. The program offers world-class resources to graduate students, postdoctoral fellows and clinical trainees.

When Proteins Misbehave and Mis-shape: Protein Misfolding Research Program

Marina Ramirez-Alvarado, Ph.D.

Our laboratory is interested in a process called protein misfolding in which the proteins for some reason do not adopt their “shape” (tertiary structure) that is required for their function and this “mis-shape” causes the protein to clump together. These clumps are found in diseases like Alzheimer’s and mad cow disease (transmissible spongiform encephalopathies). We study the proteins from patients who have a disease that causes clumps in different organs (heart, liver, kidneys are the most common organs affected). The protein that clumps in these patients is part of an antibody; we think the reason it is clumping is that it contains mutations that normally would help the immune system to be able to generate immune response against antigens (proteins from bacteria, for example).

We use biochemical and biophysical techniques to characterize the “mis-shape” of the proteins and recombinant DNA technology to generate the protein material we need for our studies. A visit to our lab will allow you to learn how we study the changes that occur between a protein with the right shape (fold) and a protein that lost its ability to find the right shape to do its normal function.

Fast-Scan Magnetic Resonance Imaging

Stephen J. Riederer, Ph.D.

Magnetic resonance imaging (MRI) has been used for over two decades for the imaging of the brain and spine. Although MRI works effectively to detect diseases in these areas, the application to the heart and abdomen has been more limited. The principal reason is that the motion of the heart and abdomen over the several-minute-long acquisition time causes false or “artifactual” signals. This interferes with the interpretation of the primary desired image.

We are developing several techniques for effective imaging of the heart and abdomen. First, modeling of the physics of MR image acquisition has enabled the development of signal-acquisition techniques, which can reduce scan time into the 10-second range. Second, high-speed signal processing methods have permitted high-speed reconstruction, which facilitates observation of the structures of interest. Finally, the integration of the fast-signal acquisition and image reconstruction has allowed for the development of real-time imaging which permits capturing of images effectively devoid of motion artifact. These methods have recently been further adapted to imaging of the major blood vessels of the abdomen and other regions.

Role of the Invisible Blood Vessels and Micro "Architecture" Within Organs and Bones

Erik L. Ritman, M.D., Ph.D.

We have developed a micro-computed tomography technique to directly visualize and measure small blood vessels and structures within organs and bones of small animals such as rats and mice as well as in small "biopsy" samples in human and large-animal organs.

Our particular interest is in the imaging and structural analysis of the networks formed by the small arteries that convey blood flow to the heart, kidney, liver and lung, and by the small bone "trabeculations."

The 3-D imaging method involves computer-based image analysis and display techniques. This image information tells us about mechanisms resulting in uneven blood flow distribution in organs as well as in locally weakened mechanical strength of bone. Using the information obtained from these studies, we hope to better understand the effect of various common diseases such as atherosclerosis, hypertension, diabetes, liver disease and osteoporosis.

Pathophysiology of Type II Diabetes Mellitus

Robert A. Rizza, M.D.

Our laboratory is studying the various aspects of the pathophysiology of Type II diabetes mellitus. We are looking at the mechanisms of fasting and post-meal high blood sugars in people with Type II diabetes. We are also looking at how various hormones such as insulin and glucagon play a role in this disease. We are also studying the effects of aging on glucose tolerance and how replacement of testosterone (a male hormone) in elderly men deficient in this hormone may help delay the changes (muscle wasting, osteoporosis, diabetes, etc.) associated with aging. We use various isotopic substances and mass-spectroscopic, liquid scintillation counting and chromatographic techniques to make these measurements and calculations.

Biomedical Imaging Core Facility

Richard A. Robb, Ph.D.

Our laboratory is involved in the development and application of computer systems for processing, analyzing and displaying biomedical images. We provide expertise and advanced technology related to biomedical imaging and scientific visualization. This includes: image display, processing and analysis; image data storage and database management; virtual reality applications; computer programming; computer graphics; computer workstations; and networking.

The comprehensive software programs developed by our laboratory, which provide advanced capabilities for multidimensional biomedical image visualization and analysis, are used by over 300 institutions around the world.

There are several specific clinical applications of these biomedical imaging techniques, including: 3-D image-guided neurosurgery for brain cancer and epilepsy; prostate cancer diagnosis and treatment; quantification and treatment of coronary artery disease; catheter-based myocardial ablation; radiation therapy planning; craniofacial reconstructive surgery and computerized histological analysis.

The laboratory's virtual reality and advanced simulation section is developing leading-edge applications for virtual surgery and virtual endoscopy. Other interests include design and evaluation of new-generation paradigms for biomedical visualization systems of the future.

Virotherapy: Engineering viruses to attack cancer

Stephen J. Russell M.D., Ph.D.

Viruses are tiny submicroscopic particles that have been responsible for some of the greatest scourges of mankind (e.g., smallpox, AIDS, influenza and measles). They inject their genetic material into cells in the body of their victim, and turn those cells into virus reproduction centers that release thousands of progeny viruses before they are killed.

Our lab is interested in changing the genetic codes of viruses to eliminate their formidable destructive power against normal cells and to redirect it against cancer cells.

We have a particular interest in the attenuated vaccine strain of measles virus, which can eradicate several different types of cancer grown in mice. We have inserted a variety of therapeutic genes into the measles virus genome to enhance its potency and its specificity for human cancer, and we will soon be testing our first engineered measles virus in the clinic.

A visit to the lab will allow you to learn how we make and study genetically engineered viruses.

Physiology of the Transplanted Gut

Michael G. Sarr, M.D.

The new frontier in human transplantation is transplantation of the intestine. Our laboratory is not so much interested in the rejection or acceptance of the transplant by the body, but is more interested in how the intestine works once it has been transplanted.

When the intestine is removed, all connections between the brain and the intestine are severed, and the brain definitely affects how the intestines work (imagine the crampy feeling in your stomach and the discomfort you suffer just before a big test!).

We are interested in how the nerves control the movement of the intestine and how the intestine absorbs the nutrients we eat.

Cardiac Surgical Research: Much More Than Just Blocked Arteries.
Hartzell V. Schaff, M.D.

Our research team is dedicated to expanding the surgical arsenal to combat cardiac disease.

A large amount of our work aims to improve outcomes of coronary artery bypass surgery by understanding and manipulating processes leading to stenosis of both arterial and venous grafts and through development of new anastomotic technologies, facilitating off-pump techniques and reducing the need for aortic cross-clamping.

We also have several projects investigating the following: utility of radiofrequency ablation and cryoblation devices for producing electrically insulating scars in the Maze procedure for atrial fibrillation; utility of new anticoagulant therapies to inhibit clotting on prosthetic heart valve surfaces; effectiveness of MRI to quantify myocardial stress and strain; and gene sequences in cells comprising aortic aneurysms.

We are also in the process of designing new studies to develop percutaneous approaches to prosthetic mitral valve replacement, evaluating the operation of a new ventricular assist device, and developing strategies to improve cardiac mechanics in congestive heart failure.

As you can see, research in our laboratory involves much more than just studying blocked arteries.

Muscle Remodeling in Health and Disease

Gary C. Sieck, Ph.D.

Our laboratory studies muscles and how they adapt to normal activities of everyday living as well as to disease conditions and other abnormal circumstances.

We study all three basic types of muscle: *skeletal* muscle, connected to bones and responsible for movements such as walking and running; *cardiac* or heart muscle; and *smooth* muscle, which lines blood vessels and airways.

Each of these muscle types adapts or remodels in response to changes in the lifestyle of its owner, whether someone is physically active or a couch potato. Additional changes normally occur during early development and with aging. Furthermore, muscles adapt under abnormal circumstances such as disease, stress or a prolonged period of medication or forced inactivity.

We hope that the results of our basic studies will eventually lead to a better understanding of muscle remodeling under these various conditions and possibly to new treatments for human disease.

Molecular Vascular Biology

Robert D. Simari, M.D.

Injury to the arterial wall results in immediate and long-term changes to the vessel. The immediate changes include blood clotting and vessel contraction. The chronic changes include the development of atherosclerosis and re-closure of the vessel following coronary angioplasty (stretching).

The main interest in my laboratory is to understand the molecular mechanisms for these immediate and chronic changes and to develop strategies to prevent them from using direct gene transfer. Direct vascular gene transfer is the introduction of native or foreign genes into cells lining the arterial wall. Our primary targets are cells of the vessels themselves and one type of immune cell macrophages, which may harm the vessels.

Both viruses and lipid vesicles are used to transfer genes into target cells. Direct gene transfer can be used to understand the role of gene products in the development of disease. Transfer of genes encoding for growth factors clarified their role in vessels closing back up again (restenosis) after being opened by angioplasty. It has also been shown that direct gene transfer can introduce biologically active and potentially therapeutic genes to the arterial wall in animal models, including atherosclerotic arteries.

Our goal is to use gene transfer to understand and to develop treatments for vascular disease.

Cancer Genetics

David I. Smith, Ph.D.

It is well known that cancer is the result of mutations and alterations to a number of key genes that control cell growth, division and DNA repair. However, little is known about precisely which genes are altered during the early stages of cancer development. My laboratory is working primarily on two types of cancer that affect women: ovarian cancer and cervical cancer.

Ovarian cancer is one of the most lethal cancers specific to women and little is known about the early genetic events that give rise to this lethal disease. Cervical cancer is caused primarily by long-term infection with human papillomaviruses. When these viruses integrate into the host genome in cervical epithelial cells, they cause generalized genomic instability that eventually leads to invasive cervical cancer.

We have been using molecular biology techniques to understand the earliest genetic changes that occur during the development of these two cancers. These tools include measuring gene-expression levels in cancer cells, as compared to normal cells, with chips containing thousands of human genes. The resulting “profiles” of gene expression help us to determine markers for the early detection of these cancers, and also enable us to classify different cancers.

We have also been studying the integration of human papillomaviruses into cervical epithelial cells, as this gives important information about the resulting cervical cancers that develop.

By beginning to understand more about the genetic changes that give rise to ovarian and cervical cancer, we can better design strategies to detect these cancers at an earlier, more treatable stage and develop therapies to target and destroy these cancers.

Cardiovascular Human Physiology Lab

Virend K. Somers, M.D., D.Phil.

The Cardiovascular Human Physiology Lab is involved in measurements of blood pressure, heart rate, breathing and sympathetic nerve activity. The sympathetic nerve activity measurements are obtained by an electrode placed into a nerve either in the arm or the leg and essentially measure the message point from the brain to the peripheral blood vessels telling these blood vessels to tighten. This sympathetic signal is very important in blood pressure control. Obtaining simultaneous measurements of the above variables in humans provides a very important and comprehensive picture of how the body functions at rest and how the cardiovascular system responds to stress.

Examples of stressors used in our studies include isometric handgrip, mental arithmetic and the cold pressor test. We are able to quantify the magnitude of the cardiovascular responses both in healthy conditions and in patients with cardiovascular diseases such as high blood pressure and heart failure.

Our other major area of investigation is in patients who have obstructive sleep apnea or who are obese. In patients with obstructive sleep apnea, the upper airway collapses temporarily during sleep resulting in marked reductions in the blood oxygen level. This can be a very stressful phenomenon with dramatic cardiovascular responses. Blood pressure in particular can increase significantly because of

increased sympathetic activation in response to the low oxygen levels. We are interested in the mechanisms by which these repeated episodes of obstructive apnea that occur during the night may lead to sustained daytime cardiovascular diseases.

In addition, we are interested in how obesity may affect the cardiovascular system and may predispose to cardiovascular disease conditions. We believe that the precursors of cardiovascular disease may have different effects depending on the genotype of the person at risk. We are therefore evaluating whether individuals with certain genetic backgrounds may respond differently to stress and may be at different degrees of risk for developing cardiovascular disease.

Polycystic Kidney Disease

Vincent E. Torres, M.D., Ph.D.

This research program has focused on the study of the pathogenesis of renal cystic disease. Our research examines: (1) the control of tubule epithelial cell proliferation and cyst development in autosomal dominant, autosomal recessive, and acquired renal cystic diseases, (2) the pathogenesis of neoplastic proliferation associated with renal cystic disease, (3) the mechanisms of progression of renal insufficiency, (4) the pathogenesis of hypertension in polycystic kidney disease, and (5) the pathogenesis of extrarenal manifestations associated with autosomal dominant polycystic kidney disease (ADPKD). Experimental models employed include chemically induced models of renal cystic disease (diphenylthiazole), inherited models of renal cystic disease, Eker rats, *in vitro* cultures of normal kidney and cyst-derived cells, established renal tubule epithelial cell lines, and aortic vascular smooth muscle cell lines from wild-type mice and Pkd1 and Pkd2 knock-outs.

A priority of this program is to make a transition from the knowledge gained in experimental animals to clinical trials of promising therapies for patients with ADPKD. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) is an NIH-sponsored study with the aim to identify surrogate markers for progression of ADPKD that can be used in the design of future clinical trials. The HALT-PKD study is a recently

initiated NIH-sponsored clinical trial in ADPKD patients. Another interest of this research program includes the genetics of the renal cystic disease. In particular, we research the ascertainment of genotype/phenotype correlations in ADPKD and ARPKD (in collaboration with Dr. Peter C. Harris) and the phenotypic characterization and identification by positional cloning of the gene responsible for isolated autosomal dominant polycystic liver disease (in collaboration with Dr. Stefan Somlo).

Hypertension Research Laboratory

Stephen T. Turner, M.D.

Hypertension, or high blood pressure, affects approximately 50 million people in the United States. If left untreated, hypertension can cause serious medical conditions including heart attack, stroke and kidney damage.

The Hypertension Research Laboratory conducts population studies to identify genetic and biochemical differences between people who have hypertension and those who do not. The research conducted may help to prevent and treat hypertension in the future.

Cancer Research: The Molecular Basis of Human Cancer

Jan M.A. van Deursen, Ph.D.

Our laboratory is interested in the molecular basis of human cancer. Our approach is to study the normal and malignant functions of genes known to be involved in human cancer at the level of the cell and the entire organism. We are interested in some of the basic molecular mechanisms that regulate chromosome number stability in mammalian cells. Our understanding of these mechanisms is relevant as abnormalities of chromosome number are a hallmark of the vast majority of human cancers. The major objective of our work is to understand the role of distinct mitotic checkpoint proteins in normal and neoplastic growth. Much of our work utilizes genetically engineered mice in which individual mitotic checkpoint genes have been mutated, but we also address several basic questions of mitotic checkpoint regulation using somatic tissue culture cells.

Another major objective of our work is to understand the role of CBP and p300 in normal and malignant cell growth. CBP and p300 are highly related transcriptional coactivators that seem to modulate the functions of a wide variety of transcription factors. Recent studies have provided genetic evidence that CBP and p300 could act as tumor-suppressor genes in a variety of human tissues, including breast, colon and lung. One idea is that loss of CBP or p300 function could simply lead to derailment of factors that are required for the proper control of cell growth, differentiation and death. The

simplest way to demonstrate the tumor-suppressor activity of CBP and p300 would be to genetically disrupt their genetic loci in the mouse and monitor the resulting animals for tumor formation. However, both CBP and p300 are essential for growth and development, and cause similar embryonically lethal phenotypes when completely disrupted in the mouse. We are trying to bypass this problem using CBP and p300 conditional knockout mice. Our emphasis is to test whether disruption of CBP and p300 in intestinal and mammary gland epithelium leads to tumor formation.

Bioinformatics

George Vasmatazis, Ph.D.

Research in the genomics era requires multi disciplinary knowledge. One of the primary goals in our laboratory is to train investigators in diverse disciplines, including bioinformatics, molecular biology, and computational biology.

Our research program consists of a bioinformatics laboratory and a molecular biology laboratory where we combine computational and experimental techniques to facilitate discovery of genes that can be used as diagnostic markers or targets for therapy of different cancers. We analyze genomic information to identify such genes and then we verify their utility using molecular biology techniques and the rich patient sample resources at Mayo Clinic. We develop novel electronic expression-profiling algorithms to search expression databases for genes that show high and/or differential expression in cancer compared to normal tissue. The predictions associated with electronic profiling are experimentally verified for candidate genes using real-time RT-PCR, laser capture microdissection (LCM), in situ hybridization, immunohistochemistry, etc. We analyze gene expression patterns in cancers, including prostate, ovarian, kidney, head and neck, and pancreatic cancers.

Genetic Disorders of Metabolism and Gene Therapy

Jerry Vockley, M.D., Ph.D.

Patients with altered function of enzymes in fatty acid breakdown present with many varied symptoms — from muscle weakness to sudden death. How can we diagnose them correctly? Sometimes we can't. In this lab, we attempt to diagnose specifically which enzyme (or group of enzymes) is affected in patients with disorders of fatty acid metabolism. For this, we use genetic analysis, enzyme function analysis, and (in mice only, so far) gene expression analysis.

Fatty acid catabolism (breakdown) is carried out in the mitochondria of the cell by many different enzymes. Some of them have only recently been discovered. What happens when someone is born with an alteration (for example, a mutation) in one or more of the genes for these enzymes? What does it do to the function of the enzyme and how can we fix it? In order to learn how the enzyme works *abnormally*, we must also study how the enzyme works normally.

In our lab, we study not only how the alteration affects the patient, but more specifically, how it affects the function and the structure of the enzyme itself. Since we can't see enzymes, we use many different instruments to indirectly measure their characteristics. In the future, we hope that with this information, a treatment can be developed that will interfere with the dysfunction of an enzyme.

Another form of treatment, or perhaps a cure, for alterations in genes of fatty acid metabolism, involves gene therapy. How can we get a normal gene into cells that carry an alteration in an enzyme for fatty acid metabolism? How can we make sure the new normal enzyme is made in the correct *cell type* in the body? How can we make sure the enzyme gets into the correct *part of the cell* where fatty acids are degraded? In this lab, we attempt to answer some of these questions using cells in culture. Later, mice may be used to test the results.

Investigating Multiple Sclerosis by Analysis of Candidate Genes using Association-Based Genetic Epidemiologic Methods

Brian G. Weinshenker, M.D.

Multiple Sclerosis (MS) is an inflammatory, likely autoimmune disease of the brain and spinal cord. Axons of neurons in the brain are unable to send messages as the protective coating (myelin) is damaged. The culprits are the body's immune cells that are triggered by a process of antigen-induced activation. Certain individuals are at higher risk of developing multiple sclerosis if they have a certain change in their DNA sequence. Only a single genetic variation that affects immune system function is definitely established as being involved in MS, but many studies document that there are likely several others that are involved. Uncovering these genes will help us to understand how MS begins and may point to therapies for MS.

Our laboratory uses a new technology to type the DNA variations in cases and controls for association studies (comparison of the genetic code in cases compared to controls for differences). SBE (single base extension) is a method that extends a piece of DNA called a primer by a single DNA base (building block of DNA) that is specific to the DNA variation. These genetic variations have been identified either by us using DNA sequencing methods, or are obtained through databases resulting from the Human Genome Project. This extended

dideoxynucleotide is tagged with a specific fluorescein probe and is read by a fluorescent polarization reader. If a difference is detected in multiple DNA variations in a given gene, it is a good indicator that the gene predisposes individuals to develop MS. These same techniques can be applied to a broad variety of rare and common genetic diseases.

Molecular Pharmacogenetics

Richard M. Weinshilboum, M.D.

Pharmacogenetics studies the role of inheritance in differences among patients in their response to drugs. We now know that variation among patients in either the occurrence of side effects, or in the desired therapeutic response to medications, can occur because of genetic differences in the enzymes that metabolize drugs in the body.

This research program uses the techniques of molecular biology and genomics to study the role of inheritance in variations in drug response. These studies have resulted in the development of clinical laboratory tests that help protect patients from drug toxicity or, equally dangerous, if the drug is being used to treat a life-threatening illness, from inadequate treatment and inadequate drug response.

Peripheral Nerve Injury and Repair

Anthony J. Windebank, M.D.

Our laboratory studies the effects of various neurotoxins on the peripheral nervous system, especially chemotherapeutic drugs used to treat cancer.

Several cancer drugs cause damage to the nervous system, which limits how much of the drug patients can receive to treat their cancer. It is not understood why these drugs, which are designed to kill rapidly dividing cancer cells, also damage nerve cells that are non-dividing.

We are studying an agent called Cisplatin that is used in treating ovarian and testicular cancer. Many patients who receive this drug develop a peripheral neuropathy. Symptoms include tingling in the hands and feet and loss of balance. This condition is caused by Cisplatin damaging the nerve cells called dorsal root ganglion (DRG) neurons. We are interested in understanding how Cisplatin damages and kills DRG neurons. To study this question, we harvest DRG neurons and place them into a tissue culture incubator. We can then perform biochemical and molecular biological studies under highly controlled conditions. Using this system, we hope to understand how the drugs damage nerve cells and how this can be prevented. If we can prevent this side effect, patients will be able to receive full therapeutic doses of the drug needed to treat their cancer.

We also study spinal cord injury. We are developing tissue-engineering approaches to try to repair the paralysis resulting from spinal cord injury.

Orthopedics and Tissue Engineering

Michael J. Yaszemski, M.D., Ph.D.

Synthetic graft substitutes are typically biocompatible, biodegradable materials that provide support for a new tissue (i.e., bone, cartilage, nerve tissue) to grow. These synthetic biomaterials may be used alone, as scaffold or as carrier for bioactive agents (proteins, antibiotics, blood- or bone marrow-derived agents, and cells).

The overall goal of our research is to develop materials that will promote healing of various tissue defects. This new orthobiologic field is evolving rapidly as new materials are being constantly developed. This also requires a symbiosis of several professionals: polymer chemists, molecular biologists, engineers and physicians.

A visit to our lab will allow you to meet with our multi-specialty team and learn about various aspects of tissue engineering and challenges that we face.

From Molecular Mechanisms to Vaccination and Chemo-Prevention of Prostate Cancer

Charles Y.F. Young , Ph.D.

Prostate cancer now exceeds lung cancer as the most commonly diagnosed cancer in males and is the second leading cause of male cancer death in this country. Each year, 190,000 new cases of prostate cancer are diagnosed in the United States. This laboratory has been focusing on several aspects of fighting this disease: 1) understanding fundamental biology of the cancer, 2) early cancer detection, 3) cancer prevention and 4) development of cancer vaccines.

Male hormones or androgens play an important role in development and progression of prostate cancer, and the hormones action are mediated through androgen receptor (AR). We are studying how androgens via AR influence the proliferation of prostate cancer cells and the molecular mechanisms involved in AR-mediated gene regulation. In addition, microarray technology has been used to identify genes whose expression is associated with cancer development and progression (prostate cancer biology). Such studies have provided opportunities for identifying unique genes and products in the cancer that allow us to develop new reagents for detecting the cancer at its early stage as well as for developing potent cancer vaccines.

A variety of naturally occurring or synthetic chemicals are used in our studies to determine whether they can lessen androgen's "bad effects" on prostate cancer development (prostate cancer prevention). Effort is also being made to understand how these chemicals work at molecular levels, so that more effective chemo-preventive drugs can be designed.





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