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Aab Institute of Biomedical Sciences

Lowell A. Goldsmith, M.D.
Dean, School of Medicine and Dentistry

Lawrence A. Tabak, D.D.S., Ph.D.,
Senior Associate Dean for Research

Jay H. Stein, M.D.
Senior Vice President and Vice Provost for Health Affairs

Introduction

The University of Rochester's Aab Institute of Biomedical Sciences was created in 1998 and consists of six centers with interdisciplinary research foci (Table 1). Institutional research foci were identified after an intensive 22-month strategic planning process with the entire Medical Center community and the University of Rochester College of Arts, Sciences and Engineering. Factors considered in choices of centers were the current strengths within our institution, long-term directions of the biomedical sciences, future disease trends, and our overarching goal of making the city of Rochester, NY the healthiest community in America by the year 2020.

After heated debate about the institutional strengths and weaknesses, virtually everyone agreed that our most significant institutional strength was the highly collaborative nature of our faculty. We felt it imperative to create an Institute structure that would not harm this attribute, but rather, enhance it. There was universal understanding that new advances will likely be made at the interfaces of traditional disciplines in the future. Accordingly, a major objective was to ensure that institute members became fully integrated within the traditional fabric our Medical Center and that individuals with diverse scientific backgrounds would be brought together in contiguous space to work on the broad common theme of the Center.

To accomplish this objective, and in recognition of the need to enhance interdisciplinary programs throughout the Medical Center, we created a dual-appointment procedure whereby all Institute members would have their academic appointments within a traditional department of the university. This allows for a rather interesting and diverse mix of individuals within a center; for example, within the Center for Oral Biology, Institute members are appointed to the Departments of Biochemistry and Biophysics, Biology, Dentistry, Microbiology and Immunology, Neurobiology and Anatomy, and Pharmacology and Physiology.

Address correspondence and reprint requests to Dr. Lowell A. Goldsmith, Dean's Office Box 706, School of Medicine and Dentistry, University of Rochester, 601 Elmwood Avenue, Rochester, NY 14642, U.S.A. Phone: 716-275-0017; Fax: 716-256-1131; E-mail: lowell_goldsmith@urmc.rochester.edu

Arthur Kornberg Medical Research Building

The availability of research laboratory space was a critical factor in developing these new initiatives and recruiting the new center directors and faculty to Rochester. The strategic planning process included an evaluation of the general condition and capacity of our current facilities and a master facilities plan was developed that suggested a way for the campus to evolve and support the research, education, and patient care missions of the medical center. A basic zoning plan was agreed upon to develop future research and education facilities on the west campus with patient care services to continue to be clustered on the east. Maintaining physical building connections facilitates access to all corners of the

Table 1. Centers and Their Directors at Aab Institute

Center	Director
Aging and Developmental Biology	Howard Federoff, M.D., Ph.D.
Cancer Biology	Hartmut Land, Ph.D.
Cardiovascular Research	Bradford Berk, M.D., Ph.D.
Human Genetics and Molecular Pediatric Disease	To be named
Oral Biology	Lawrence Tabak, D.D.S., Ph.D.
Vaccine Biology and Immunology	Tim Mosmann, Ph.D.

campus and supports the collaborative environment of the Medical Center.

Planning for a new medical research laboratory building began upon approval by the University's Board of Trustees in October 1996. By December, the architect and construction firm were hired and ground-breaking took place in June of 1997. A "fast-track" planning process was employed so that decisions on the size and shape of the building were made before interior floor design details were finalized. This allowed the exterior construction to get underway in time to enclose the building for the winter and continue the interior construction.

The 240,000–gross square foot (gsf) lab building (Fig. 1) consists of four floors of wet bench space and one floor of vivarium support. The sixth floor is an enclosed roof that contains the building mechanical systems. By building new research labs, the opportunity existed to implement fundamental changes to the lab design that were not physically or financially possible by renovating existing space, such as increasing the distance between floors to allow adequate room for state-of-the-art heating and air-cooling system distribution, telecommuni-

Fig. 1. Aab Institute of Biomedical Sciences at the University of Rochester, School of Medicine and Dentistry, Rochester, New York.

cations network infrastructure, and higher ceilings to complement a very open and large lab design.

Each floor adheres to basic design principles developed by a team of existing scientists from the Medical Center. Labs are along three sides of the building with large windows for daylight (Fig. 2). Faculty, administrative offices, and conference rooms are close to, but outside of, the labs and along the "public" corridor to foster communication among faculty.

Other features of the medical research building include the following:

- Adjustable and movable oak lab benches and casework, to adapt to needs of the various lab teams
- Linear equipment rooms, which are internal corridors to labs, accommodate large equipment
- Alcoves within the labs for tissue culture work, fume hoods, equipment, microscopy, additional benches, and other special needs
- Shared glass wash, darkroom, and cold room facilities on each floor

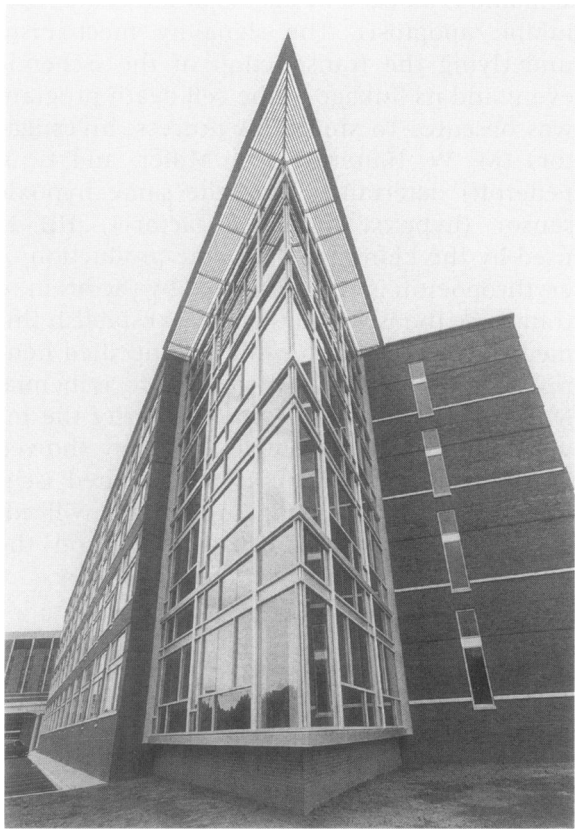

Fig. 2. Large windows were incorporated into the building design to bring daylight into the labs.

- Shared common rooms on each floor for library or food service

The research building is connected to the existing Medical Center by a 55,000 gsf pavilion building made up of new medical education facilities and additional conference center rooms (three auditoria and smaller seminar rooms) and lobby. The pavilion also serves as the new main entrance to the Medical School.

Five of the centers are new, and one, the Center for Oral Biology, is built upon the existing Department of Dental Research.

Center for Aging and Developmental Biology, Howard Federoff, M.D., Ph.D., Director

The Center for Aging and Developmental Biology, occupying the first floor of the medical research building, will comprise faculty with interests in the development, maturation, senescence, and dysfunction of the nervous system. Center investigators will exploit multiple organisms, classical and molecular genetics, and diverse experimental preparations to elucidate the function of genes involved in these processes. Among the themes to be represented are the following.

Neuronal Differentiations and Pathfinding

Newly postmitotic neurons in the central and peripheral nervous systems must be capable of utilizing guidance cues to direct axons to appropriate targets. This pathfinding process involves the proper coordination and orchestration of gene expression to achieve normal innervation. Lin Gan, Ph.D., a newly recruited investigator, uses the mouse to study genes that are vital for eye development. The mammalian retina serves as an excellent model for studies of central nervous system (CNS) development and degenerative diseases because of its relative simplicity and exceptional accessibility for experimental manipulation. The retina contains only five neuron groups: photoreceptor cells, bipolar cells, horizontal cells, amacrine cells, and ganglion cells. Dr. Gan's work focuses on how a specific group of POU-domain transcriptional factor genes, called *brn-3a, -3b* and *-3c,* function in directing retinal ganglion cell (RGC) formation and survival. The *brn-3* genes are expressed in distinct but overlapping patterns in the developing and adult CNS, including retinal ganglion cells. This localized expression pattern suggests an impor-

tant role in the development and survival of particular sets of neurons. Using a gene-targeting approach, each of the three *brn-3* genes have been disrupted. Mutation of each *brn-3* gene affects unique sets of neurons in the CNS. The mutation in the *brn-3b* gene results in the loss of 70% of RGCs and subsequent loss of other retinal neurons. The mutation of the *brn-3c* gene causes deafness due to the loss of vestibular and cochlear hair cells. The *brn-3a* mutant mice show ataxia and impaired facial movement ability due to a decrease or absence of neurons in the trigeminal ganglia and selected brainstem nuclei. Further cell lineage and functional studies using *brn-3b/lacZ* (β-galactosidase) and *brn-3b/AP* (human placenta alkaline phosphatase) reporter genes showed that mutation of the *brn-3b* gene does not affect the initial cell differentiation and migration of RGCs. However, mutation of *brn-3b* causes the absence of RGC axons and consequently, a massive degeneration of postmigration RGCs by programmed cell death (apoptosis). These results led to the hypothesis that the *brn-3b* gene is essential for the differentiation, maturation, and survival of RGCs. The testing of this hypothesis, currently under investigation, will not only advance our basic understanding of retinal neuron formation and degeneration but may also have relevance for disease mechanisms underlying some of the retinal degeneration syndromes.

Experience-driven Plasticity

Behavioral experience impacts learning circuitry. The role of pathway-specific behavioral experience on the anatomic pathway itself has been held as a principle underlying learning. To test this concept in the intact mouse, Center scientists (A. I. Brooks and H. J. Federoff) developed somatic mosaic analyses. The approach allows investigative control of genes in the intact brain; the experimentalist determines the temporal and spatial characteristics of gene addition or removal. Thus the approach is well suited to making perturbations in one part of the neural network or pathway and studying its impact on the system's output, e.g., a change in learning. The septohippocampal pathway defines a critical cholinergic tract required for spatial learning. Using adult somatic mosaics that have gain of additional nerve growth factor (NGF) function within the hippocampus, Center scientists are showing that behavioral experience involving use of the pathway stimulates its reorganization. These studies underscore the neural plasticity in the adult and the relevance of experience in its modulation.

Mechanisms of Neurological Disease

The familial neurodegenerative diseases appear to cause selective neuronal death by toxic gain of function mechanisms. The recent description of two kindreds with familial Parkinson's disease and the identification of the disease gene α-synuclein has led to the exploration of these novel pathogenic mechanisms. In studies by Dr. Eric Richfield, in collaboration with Dr. Federoff, the actions of mutant synnucleins in cultured cells and mice are being examined. These studies should reveal information relevant to the intrinsic vulnerability of substantia nigra neurons, those consistently lost in Parkinson's disease.

Role of Hypoxic Sensor in Ischemic Cell Death

Stroke produces rapid and delayed death of CNS neurons. Delayed death proceeds through a mechanism requiring de novo gene expression and is blocked by agents or molecules that inhibit apoptosis. The signaling mechanism underlying the transduction of the ischemic event and its linkage to the cell death program was obscure. To study this process, investigators (M. W. Halterman, C. Miller, and H. J. Federoff) determined that the same hypoxic sensor (hypoxia inducible factor-1, HIF-1) used by the kidney to stimulate production of erythropoeitin is also employed by the brain to transduce the ischemic signal. To establish this mechanism the group examined purified neuronal cultures subjected to in vitro ischemia. Not only did these experiments verify the involvement of HIF-1 complex but they showed that its molecular disruption prevented ischemic neuron death. Ongoing studies will address the proximate regulators of and the downstream effectors of the HIF complex.

Gene–Environment Interactions in Nonfamilial Parkinson's Disease

Epidemiologic data suggest that nonfamilial cases of Parkinson's disease may be explained by exposure to environmental toxicants. Center scientists (H. J. Federoff and E. Richfield) are testing the hypothesis that genetic vulnerability synergizes with neurotoxicants to comprise dopaminergic neurons. Using the somatic

mosaic approach whereby single genes can be turned on and off within defined groups of neurons within the intact brain, Center investigators are exploring specific gene–environment interactions as a plausible mechanism for Parkinson's disease.

Gene Therapy for Parkinson's Disease

The stereotypical movement disorder of Parkinson's disease results largely from degeneration of the nigrostriatal pathway. One challenge confronting the successful implementation of gene therapy is the ability to selectively target a gene to be expressed within the dopamine neurons at risk. A second challenge is to have therapeutic expression be sustained at levels appropriate for the clinical disease state. Using herpes simplex virus (HSV) as a platform, Center scientists (W. Bowers and H. J. Federoff) have developed vectors capable of specifically targeting gene expression to substantia nigra dopamine neurons, as the vectors are regulated by administered pharmaceuticals and resistant to transcriptional repression. These vectors configured to carry therapeutic genes are under investigation in models of Parkinson's disease.

Alzheimer's Disease

Loss of cholinergic input to the hippocampus and cortex is one of the cardinal features of this disease. The cognitive decline and, in particular, memory impairment are related to loss of cholinergic innervation. Since many of the cholinergic neurons of interest are responsive to NGF, Center investigators (A. Brooks and H. J. Federoff) have developed HSV vectors to transduce the NGF gene. In an animal model in which memory impairment is linked to reduced NGF, the neurosurgical delivery of NGF virus to the hippocampus reverses the spatial memory impairment. Further studies are underway to extend these observations.

Center for Cancer Biology, Hartmut Land, Ph.D., Director

The Center for Cancer Biology occupies 21,000 square feet of research space and is a significant extension to the existing National Cancer Institute (NCI)-designated Comprehensive Cancer Center at the University of Rochester School for Medicine and Dentistry. The Center Director has just arrived after 8 years at the Imperial Cancer Research Fund in London.

Cancer is caused by multiple genetic defects resulting in loss of cell proliferation control, de novo angiogenesis, tumor cell invasion, and ultimately, metastasis. Understanding how signaling networks control this multitude of cellular responses is one of the fundamental challenges in cancer biology and is critical for the design of novel therapeutic strategies targeting specific cancer cell characteristics.

Building on the existing strong programs in biochemistry, molecular biology, and genetics at the University of Rochester, the Center for Cancer Biology will have a highly interactive environment and will focus on basic research in molecular cell biology designed to explore the molecular architecture, function, and genetics of signaling networks.

Eight to ten faculty members are being recruited at all levels of experience. Areas of research emphasis include signal transduction, cell cycle control, apoptosis, gene expression, intercellular communication, cell adhesion, migration, cell homing, and epithelial and endothelial biology. These areas find common ground in the field of cell signaling, providing a strong base for synergistic interdisciplinary interactions among the various groups in the Center.

An understanding of the complex nature of signaling networks requires the integration of biochemical, biophysical, genetic, and genomic approaches. This will be achieved by bringing together investigators with the appropriate complementary expertise. The laboratory of H. Land has long-standing experience in the investigation of the molecular mechanisms of oncogene cooperation. The group has demonstrated the importance of signal quantity and cross-talk in the definition of signal specificity at the signal–cell cycle interface and the relevance of these integration processes for multistep tumorigenesis.

Comprehensive analysis of signal integration mechanisms requires access to genetic screening systems. Given the high conservation of signaling pathways in vertebrates and insects, *Drosophila melanogaster* and the mouse are the main genetically tractable organisms. With the rapid progress of genome sequencing projects, the increasing availability of DNA sequence information, and the development of DNA microarray and proteomics technologies, it has become possible to comprehensively monitor cellular gene expression profiles. Re-

cording the alterations of such profiles in response to specific signals and signal combinations will provide important insights into the complexity of genetic programs that control specific cellular responses.

Center for Cardiovascular Research, Bradford Berk, M.D., Ph.D., Director

Four areas of research will be developed in the Center for Cardiovascular Research vascular and developmental biology: ischemic injury, molecular pharmacology and signal transduction, and genetics of cardiovascular disease. The overall goal is to understand how the cardiovascular system develops and responds to physiological and pathological changes.

Vascular and Developmental Biology

To understand what makes blood vessels grow where needed and how tissues "know" the number of vessels they require, researchers will try a number of tactics, including manipulation of genes that regulate vessel growth and blood flow. Studies looking at how the vascular system develops may enable us to control blood flow to tumors or to circumvent blood clots with new vessels. Current projects include analysis of the role of retinoids in treating vascular diseases. Joe Miano, Ph.D., has found that all-*trans* retinoic acid favorably remodels the vessel wall following experimental angioplasty. He hypothesizes that the changes in vessel wall geometry are related to the induction (or suppression) of retinoid-responsive genes. Expression profiling of human coronary artery smooth muscle cells is a major focus for uncovering such genes. A second project tests the hypothesis that a smooth muscle–restricted promoter (SM22) can direct the expression of therapeutic genes exclusively to arterial smooth muscle cells of the vessel wall as a means of preventing or possibly reversing vascular diseases. To this end, Dr. Miano has generated a panel of adenoviral constructs containing the SM22 promoter driving expression of various candidate therapeutic genes. Finally, Dr. Miano is exploring the transcriptional regulation of SM-calponin, a differentiation gene whose expression is compromised during vascular diseases. Here, he is using a bacterial artificial chromosome to uncover distal elements and their binding factors whose functional activity may be subverted during vascular diseases.

A recent recruit, Wang Min, Ph.D., studies the relation between inflammation and angiogenesis. Inhibition of angiogenesis by production of angiostatic factors should be a viable approach for cancer gene therapy. When endostatin, a potent angiostatic factor, was expressed in mouse muscle and secreted into the bloodstream for up to 2 weeks after a single intramuscular administration of the endostatin gene, the expressed endostatin inhibited systemic angiogenesis. Moreover, the sustained production of endostatin by this intramuscular gene therapy inhibited both the growth of primary tumors and the development of metastatic lesions. Through similar studies the role of various inflammatory mediators in the initiation of angiogenesis may be determined.

Ischemic Injury

Researchers will study the role of free radicals to understand how a tissue deprived of oxygen, or exposed to oxygen after being deprived of it, incurs damage. With this new knowledge, researchers could reverse or prevent the damage done to the heart muscle with infarction. Dr. Jun-ichi Abe, M.D., Ph.D., studies how reactive oxygen species (ROS) respond to ischemia and reperfusion in the heart. Using dominant negative cell transfection and cells isolated from transgenic knockout mice that lack the tyrosine kinases c-Src or Fyn, Dr. Abe has delineated the signal pathways activated by ischemia. A related project is investigating the role of ROS in the ability of blood vessels to remodel in response to alterations in blood flow as may occur during coronary stenoses. Using vitamin E–deficient rats, researchers in Dr. Berk's lab have studied vascular remodeling induced by increased flow. Chen Yan, Ph.D., in collaboration with Dr. Abe, has been analyzing the mechanisms by which a particular kinase, big MAP kinase 1 (BMK1), is activated by ischemia.

Molecular Pharmacology and Signal Transduction

Precise blocking or stimulation of these signals can lead to better treatments for a variety of diseases and injuries, including stresses created by angioplasty. Dr. Berk's lab has several signal transduction projects, including an analysis of mechanisms by which endothelial cells respond to fluid shear stress and regulate gene expression and cell function, and study of the control of smooth muscle cell growth by angiotensin II,

focusing on the activation of intracellular kinases and phosphatases by the angiotensin II receptor. Site-directed mutations in the angiotensin II receptor are being used to study the binding and activation of receptor-associated signaling molecules. Downstream events of signaling include regulation of the mitogen-activated protein kinases and potential substrates such as the Na^+/H^+ exchanger. Jane Sottile, Ph.D., another recent recruit, is focusing on the mechanisms by which fibronectin regulates cell growth. She has cloned a fibronectin null cell from transgenic knockout mice and is using these cells to study the mechanisms by which cells organize extracellular matrix and the role of fibronectin–integrin interactions in cell growth.

Genetics of Cardiovascular Disease

A genetic model of vascular remodeling in the rat has been established in Dr. Berk's lab. A carotid flow reduction model has been characterized and is being used to identify genes responsible for impaired flow-dependent remodeling by positional cloning in inbred strains of rats. Ming Qi, Ph.D., is studying the role of collagen in bone and cardiovascular development by creating transgenic knockout mice with specific dominant mutations of collagen genes.

Center for Oral Biology, Lawrence Tabak, D.D.S., Ph.D., Director

The Center for Oral Biology is a multidisciplinary unit that conducts biomedical research related to microbial biofilms, cell and molecular physiology of exocrine glands, and development of the craniofacial complex. Currently, within the Center are eight tenure-stream faculty, 10 research-track faculty and some 40 postdocs, graduate students and research technicians, all of whom are supported by a dedicated administrative support staff. The Center is an outgrowth of a previous Medical School department, the Department of Dental Research.

Microbial Biofilms

The microbial biofilm that forms on the surface of the human dentition is termed the dental plaque. It consists of microorganisms embedded in a polysaccharide matrix. Glucosyltransferases, produced by oral streptococci, form most of this polysaccharide, using dietary sucrose as a substrate. Work conducted by Center investigators William Bowen, B.D.S., Ph.D., and Robert Burne, Ph.D., has shown that streptococci that lack glucosyltransferases are far less virulent than wild-type counterparts and are thus less efficient at producing dental decay. Remarkably, the enzymatic properties of the glucosyltransferases are altered when they are adsorbed to the solid surface of the biofilm; surface-bound enzymes elaborate polymers, which are more sticky and support increased adhesion of selected microorganisms.

Life on a tooth surface can be quite harsh, particularly in face of wide fluctuations in pH. Center investigator Robert Quivey, Ph.D., has focused on the mechanisms by which oral bacteria adapt to the highly acidic conditions in dental plaque. He has found that *Streptococcus mutans* increase the expression level of a molecular pump, termed the F-ATPase, which efficiently removes offending acid from the bacteria during periods of low pH. Low pH also enhances the expression of a DNA repair enzyme. The ultimate goal will be to understand the patterns and mechanisms by which disease-producing bacteria protect themselves from harm. In that way, we will begin to understand ways in which we might circumvent those protective mechanisms to provide protection to humans from bacterial disease.

Most work related to dental decay focuses on acid production by tooth-borne bacteria. However, Center investigator Robert Burne, Ph.D. has been studying the enzymatic machinery used by some bacteria to produce ammonia from urea, which can rapidly neutralize microbial acids. His work has focused on the urease genes of a prominent ureolytic bacteria, *S. salivarius.* These genes are activated when the bacteria are grown at low pH. The long-term goal of the Burne lab is to dissect the gene network controlling induction or repression of gene expression specifically in response to cytoplasmic pH.

Dental caries (decay) remains the most prevalent of human infections. Remarkably, an increasingly smaller segment of the population accounts for a greater proportion of disease. Work conducted in the Bowen laboratory has suggested that this may be due in part to presence of heavy metals such as lead in the environment. Lead, once incorporated in tooth mineral, renders the tooth more susceptible to demineralization and hence decay. One of the Center goals is to develop rapid, diagnostic tests to determine which children are at greatest risk to develop future decay. This goal has spawned interactions with clinicians, toxicologists, and epidemiolo-

gists. In this manner, health care can be distributed in the most cost-efficient manner.

Cell and Molecular Physiology of Exocrine Glands

The salivary secretions that bathe the mouth are one of our most precious natural defense system. Salivary glands are often damaged in patients undergoing radiation therapy for head and neck cancer, by autoimmune diseases, such as Sjögren's syndrome, or drugs, including antidepressants, antihistaminics, and antihypertensives. Center investigators David Culp, Ph.D., and James Melvin, D.D.S., Ph.D., are delineating the pathways that water, salts, and proteins take during the formation of saliva and the regulatory circuits controlling saliva production.

Secretion is driven by the activation of K^+ and Cl^- channels. In secretory epithelium there are at least four distinct Cl^- channels, classified according to their mode of activation; these include cAMP-activated, volume-regulated, voltage-regulated, or Ca^{2+}-activated channels. Ongoing work in the Melvin laboratory seeks to delineate the specific contribution of each of these channels. With expression cloning, site-directed mutagenesis mouse models in which the expression of specific channels or exchangers has been ablated.

For those individuals who lack all functional salivary gland tissue, Center investigator Lawrence Tabak, D.D.S., Ph.D., and his colleagues are attempting to create a suitable "artificial" saliva. Much of the unique physicochemical properties of saliva can be attributed to the presence of mucin glycoproteins. These high-molecular-weight species are heavily decorated with carbohydrate side chains, making it impractical to produce mucins by standard recombinant DNA methods (e.g., *E. coli* is incapable of producing this post-translational modification). The Tabak group is attempting to exploit the phenomenon of "molecular mimicry" to create peptidomimetics of carbohydrates that will be useful in producing low-cost mucin surrogates.

Craniofacial Development

The Notch signaling pathway is an evolutionarily conserved intercellular communication mechanism that controls cell fate specification and organ morphogenesis in numerous metazoan organisms. Center investigator Rulang Jiang, Ph.D., has generated mice carrying a mutation in one of the Notch ligands, Jagged2, and found that these mutant mice exhibit cleft palate, digit fusions, and defects in inner ear development. These mutant phenotypes correlate with the tissue-specific expression pattern of Jagged2 during embryogenesis and indicate that Jagged2-Notch signaling is essential for craniofacial, limb, and inner ear development. The current effort in the Jiang laboratory focuses on understanding how Jagged2-Notch signaling regulates craniofacial development. These will be a combination of molecular, genetic, and embryological approaches to dissect the molecular cascade and cell differentiation steps from expression of the Jagged2 gene to formation of the normal palate structure.

Compelling evidence demonstrates that carbohydrate side chains (oligosaccharides) carry specific information involved in cell recognition. During differentiation and development, cell surface carbohydrates undergo remarkable alterations. Since carbohydrates cannot be mutated directly, center investigators Fred Hagen, Ph.D., and Lawrence Tabak, D.D.S., Ph.D., are performing loss-of-function experiments with the glycosyltransferases that are necessary to synthesize the oligosaccharides. Both groups are focusing on O-linked oligosaccharides. Because these sugar chains are synthesized step-wise, inhibition of the enzyme responsible for the initial step of synthesis (UDP-GalNAc:polypeptide *N*-acetylgalactosaminyltransferase [ppGaNTase]) effectively blocks the formation of the entire chain.

Within the Hagen laboratory, these studies are being conducted on a simple model organism, *C. elegans*. The use of this small round worm will enable Hagen and colleagues to study the role of cell surface sugars in developmental processes such as axon migration, epithelial cell interactions, and head formation at single-cell resolution in a defined genetic background. The Tabak group is using the mouse as a model system. Recent work has demonstrated that ppGaNTases are expressed in a spatially and temporally specific manner during mouse development. Each group is systematically ablating the expression of each form of the ppGaNTases and determining the effect on development.

Center for Vaccine Biology and Immunology, Tim Mosmann, Ph.D., Director

Vaccines have had remarkable success in reducing many infectious diseases to low levels, and in the case of smallpox, the disease has actually been eradicated by an effective vaccine program. Basic

immunology has allowed the design of vaccines that induce strong immune responses against the correct antigens, detailed knowledge of microbial pathogens has made it possible to produce attenuated strains that are effective vaccine organisms, and the organization of large vaccine campaigns has brought several critical vaccines to most of the world's children. Because vaccines prevent rather than cure diseases, they are cost-effective because of reductions in treatment costs and sickness-related productivity losses.

Alongside the spectacular successes of vaccination programs, several infectious diseases have remained intractable. Although large amounts of information on the infectious agents have been obtained, we still do not have effective vaccines for tuberculosis, AIDS, malaria, and other infections. In many cases, the antigens of the microorganisms are known in considerable detail, but the "correct" immune response, i.e., the type of response that kills the pathogen or prevents initial infection, is not understood.

The immune system acts by initially recognizing the antigens on pathogens as foreign, and then mounting an attack on the pathogen using one or more of a wide variety of effector functions. These range from antibody responses that are effective at neutralizing toxins and preventing initial viral entry into cells to cytotoxic T cells that recognize and kill infected cells. The choice of the correct effector function(s) is crucial to ensure that the immune response will destroy a pathogen, as many microorganisms can circumvent several immune effector mechanisms, and an ineffective immune response may cause a great deal of damage to host tissues. A better understanding of immunoregulation, the way that the host chooses the correct immune effector functions, will be central to designing more effective vaccines. It will also be crucial to determine the effector functions that can prevent infections by the difficult pathogens mentioned above. Together with recent advances in manipulation of immune responses, such as recombinant DNA vaccines, this knowledge should enable the rational design of more effective vaccine strategies.

The University of Rochester is an exceptional location in which to establish a new center in vaccine research. The University already has a well-established core of investigators in immunology, microbiology, and infectious diseases, and Rochester is a major center for clinical trials of vaccines for HIV, human papillomavirus, influenza, and other infections. The current successful vaccine for hemophilus influenzae b (Hib) was developed in Rochester, and this vaccine is a good example of the strength of applying basic immunology to design a better vaccine. The *Hemophilus* bacteria are covered by a polysaccharide capsule, and it is difficult to induce a strong, long-lasting immune response by immunizing with carbohydrate alone. By taking advantage of knowledge of the requirement for T lymphocytes to help B lymphocytes to produce antibodies, David Smith and Porter Anderson developed a protein–carbohydrate conjugate to induce a much stronger response. This strategy led to the production of the Hib vaccine, and in recognition of this groundbreaking work, the Lasker prize was awarded to Smith and Anderson in 1996.

Future vaccines may be targeted at a much wider spectrum of diseases than just those caused by microorganisms. Modern advances in our understanding of basic immunoregulation have opened up the possibility of making vaccines that would prevent or cure allergy, autoimmunity, or cancer. For autoimmunity and allergy, it would be desirable to prevent or turn off the immune response, whereas for cancer it will be important to activate those immune functions that can effectively attack cancer cells. A clear understanding of the regulation of immune effector functions, as well as the ability of each to cause damage, should enable the design of vaccines that adjust the immune response into the appropriate mixture of effector functions.

The Center for Vaccine Biology and Immunology is focusing on recruiting exceptional basic scientists working on immunoregulation, disease models, and clinical research. This combination of skills should provide the best chance of discovering new ways to tailor immune responses, leading to the design of the next generation of vaccines.

The Future

The first investigators moved into the new building in June 1999 and with a diverse multidisciplinary team, we face the exciting, new millenium. Recruitment for the Human Genetics and Molecular Medicine Disease Center Director is ongoing.