

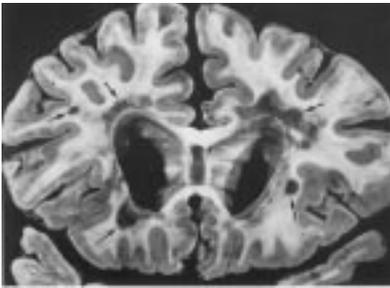


Center for
Molecular Medicine
& Genetics

Advances

Center's Neurogenetics Program Brings New Discoveries — and Hope

Hereditary neurological disorders affect millions of people every year. In fact, about 2-3% of the population have a genetic disorder primarily affecting the nervous system and muscles. And of the 7,500 described genetic disorders in general, about one-third to one-half affect the nervous or muscular systems.



That's why the Center for Molecular Medicine and Genetics has made the study and treatment of neurodegenerative and neuro-

muscular diseases one of its major focus areas. For the past several years, the Center has recruited several nationally known experts in neurogenetics.

The goal is to establish a comprehensive basic science and clinical program to offer new hope for such crippling diseases as multiple sclerosis, Charcot-Marie-Tooth disease, Pelizaeus-Merzbacher disease, Huntington's disease and diabetic neuropathy.

The Center's four lead neuroscience faculty members, who also have joint appointments in the Department of Neurology, include John Kamholz, M.D., Ph.D.;

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Message From the Director



George Grunberger, M.D.
Director

Neuroscience: An Important Focus

Researchers around the world are unraveling the human genome, identifying genes so rapidly that the identification and sequencing of all genes is expected to be complete by the year 2003.

These discoveries pave the way for the next even more important step — understanding at the genetic and molecular levels many of the devastating diseases that plague the people of our society, from cancer and cardiovascular disease to multiple sclerosis and Alzheimer's.

At the Center for Molecular Medicine and Genetics, we are well positioned to use this unfolding information and to conduct the novel research that may bring cures and better health to people worldwide. We already have developed several key research strengths, including our focus on neurodegenerative and neuromuscular diseases.

Neurodegenerative illness encompasses such diseases of the central nervous system and peripheral nervous system as multiple sclerosis and diabetic neuropathy, both of which afflict millions of people. This is an

continued on page 7

Michael Shy, M.D.; James Garbern, M.D., Ph.D.; and Jeffrey Loeb, M.D., Ph.D., who just recently arrived at Wayne State.

The program fosters a close working partnership among basic science and clinician-investigators.

Other faculty members associated with the program include Jack Lilien, Ph.D., chairman, Department of Biological Sciences; Anders Sima, M.D., Ph.D., Department of Pathology;

George Grunberger, M.D., the Center's director; William Lyman, Ph.D., director of the Children's Hospital Research Center; Greg Moore, Ph.D., Department of Psychiatry; Richard Lewis, M.D., vice chairman, Department of Neurology; and Karen Krajewski, M.S., genetic counselor, Department of Neurology.

The Center's neurogenetics program fosters a close working partnership among basic science and clinician-investigators to increase the understanding of these complex diseases. Together they are seeking novel discoveries while offering patients and their families evaluation, diagnosis, education and support.

Demyelinating Disease Research Focus

The Center's current neurogenetic research (see story about Dr. Kamholz

on page 4) focuses on conditions affecting myelin, the fatty layer insulating nerve cells and the molecular and cellular processes regulated by interactions between oligodendrocytes and axons in the central nervous system and Schwann cells and axons in the peripheral nervous system.

Both Charcot-Marie-Tooth (CMT) disease and Pelizaeus-Merzbacher disease (PMD) are caused by mutations in glial-specific proteins which lead to axonal degeneration—which then produces the clinical signs and symptoms of the disease. The axonal degeneration in CMT and PMD is similar to that also found in multiple sclerosis and diabetic neuropathy, two common demyelinating diseases with a more complex etiology. The molecular basis of axonal degeneration in CMT and PMD and its treatment will also be relevant to these common disorders.

Becoming a National Leader in Charcot-Marie-Tooth Disease

In addition to its basic research activities, the Center has several clinical and research activities available to patients with CMT. More than 150 patients from around the U.S. and the world have taken part in a clinical research project to determine the natural history of CMT. The program allows the Center to see and follow patients with unusual forms of CMT, which may lead to studies in

new mechanisms of demyelination or axonal loss. The Center is also developing a comprehensive database for all CMT patients.

As part of the large longitudinal study on patients with CMT, the Center provides patients neurological services, genetic counseling (see story on page 5) and psychiatry assistance as well as other neurophysiologic tests for research purposes.

The Center also sees many patients with PMD. It is in the process of developing a national PMD consortium to be centered at Wayne State University.

Neurogenetics Clinic

The Center's Neurogenetics Clinic, also at Harper Hospital, is one of only two adult clinics devoted to genetic disorders at the Detroit Medical Center. The clinic, under the direction of Dr. Garbern, offers patients and their families evaluation, diagnosis, education, genetic counseling and support. It is one of only a few clinics in the U.S. that specializes in the area of adults with, or at risk for, inherited neurologic conditions.

For more information about the Center's comprehensive neurogenetic disease program, please contact (313) 577-8317 or e-mail J_garbern@wayne.edu or visit the web site: www.med.wayne.edu/Neurology/neurogenetics.html.

Center Holds First Scientific Retreat

Students, faculty members, research scientists and invited guests of the Center for Molecular Medicine and Genetics presented summaries of their key research on posters or in 30-minute invited talks at the Center's first annual Scientific Retreat on November 13 and 14 at the Maumee Bay Resort and Conference Center near Toledo, Ohio.



David A. Jackson, Ph.D., executive vice president and chief scientific officer of VIMRX Pharmaceuticals, Inc., presented the keynote address.

The retreat offered the opportunity for all those affiliated with the Center to discuss state-of-the-art science with their colleagues in a friendly and inviting environment. In a judged competition, Mr. Mikhail G. Kolonin, a Ph.D. candidate in the Molecular Biology and Genetics training program, was awarded first prize for the best poster presented by a graduate student.

The Center extends gratitude and congratulations to the hardworking organizing committee headed by Mark Hughes, M.D., Ph.D., the Center's director of basic research, with special assistance from Ms. Barbara Knoth, administrator. Because the retreat was widely acclaimed to be a success by its participants, Dr. Hughes has been asked to organize additional Center scientific retreats in the future, in addition to next year's retreat in October at the same site. Breaking developments in the planning for the retreat will be posted at the Center's web site at: <http://cmmg.biosci.wayne.edu>

Center's First Summer Internship Program a Success

Seven students from across the United States and Canada took part in the first summer undergraduate research program sponsored by the Center for Molecular Medicine and Genetics.



Undergraduate students at the sophomore and junior level from such institutions as Duke University, University of Windsor and University of Guelph attended the 12-week, hands-on research experience designed to expose students to careers in biomedical research as well as the Center and Wayne State University.

"It was a hands-down success," says Stephen A. Krawetz, Ph.D., associate professor and director of the program. "We had more than 50 applicants and participation from several Center faculty. The students had a very good experience, which will help us spread the word about the Center and WSU as they return to their universities."

During the program, each student worked in the laboratory of a Center faculty member and attended regular departmental research and other seminars. They also were exposed to laboratory safety techniques. Their summer culminated by participating in the Howard Hughes Summer Program Poster Day on campus.



The seven outstanding students studied with these mentors: Michelle Castelli (University of Detroit, Mercy) with Jeffrey Moshier, Ph.D.; Esther Farkas (Duke University) with Mark Hughes, M.D., Ph.D.; Bobbi Gronemeyer (Ferris State University) with John Tomkiel, Ph.D.; Kory Lavine (University of Rochester) and Susan Pearson (University of Guelph) with Russell Finley, Ph.D.; David Ouellette (University of Windsor) with Li Li, Ph.D.; and Cheryl Turansky (Michigan State University) with James Garbern, M.D., Ph.D.

For more information, please contact Dr. Krawetz at (313) 577-6770 or e-mail steve@compbio.med.wayne.edu.

While great strides have been made in finding treatments for multiple sclerosis, finding a cure for this complex, devastating disease has remained elusive.



Until now, according to John Kamholz, M.D., Ph.D., who believes he and his team of physicians, researchers and students — including Michael Shy, M.D., and James Garbern, M.D., Ph.D. — may have found a way to unlock the mystery of this disease.

Dr. Kamholz, who has a joint appointment with the Center for Molecular Medicine and Genetics and Department of Neurology, spends much of his clinical time seeing patients with multiple sclerosis. But his research efforts have focused on two demyelinating diseases, Pelizeaus-Merzbacher disease (PMD), which primarily affects the central nervous system, and Charcot-Marie-Tooth (CMT) disease, which affects the peripheral nervous system.

Dr. Kamholz believes understanding the molecular mechanisms of PMD and CMT may hold the key

“Now maybe we are onto something that will make a difference.”

—John Kamholz, M.D., Ph.D.

to a possible cure for multiple sclerosis, linking his work in neurodegenerative diseases to other Center initiatives in human genetics and developmental biology.

Dr. Kamholz’s glial-axonal interactions program — which includes basic molecular biology, clinical and translational studies — focuses on myelin, the fatty layer insulating

nerve cells, and the molecular and cellular processes regulated by interactions between oligodendrocytes and axons in the central nervous system and Schwann cells and axons in the peripheral nervous system. Both PMD and CMT are caused by mutations in glial-specific proteins which lead to axonal degeneration — which then produces the clinical signs and symptoms of the disease.

While most multiple sclerosis research has focused on studying the immunomodulation of the disease, for the first time, recent studies have also shown that patients with multiple sclerosis also exhibit axonal injury and damage. Dr. Kamholz hopes that data obtained from his disease models can be applied to both multiple sclerosis and diabetic neuropathy, diseases in which it is now known glial-axonal interactions are disrupted but for which defined molecular causes are not yet known.

When Dr. Kamholz began studying PMD and CMT patients, he didn’t know it would lead to a connection with multiple sclerosis, but he is



excited about the possible outcome. “I have been taking care of multiple sclerosis patients for a long time. It is very frustrating to see them get worse and worse and not be able to offer them effective treatments or any real hope. Now maybe we are onto something that will make a difference.”

Dr. Kamholz joined the faculty of the Center in 1994, after serving on faculty in the Department of Neurology at the University of Pennsylvania, where he also completed his medical degree, doctorate in Genetics and residency in Internal Medicine and Neurology. He also served as a medical staff fellow in the Laboratory of Medical Genetics at the National Institutes of Health.

In addition to his clinical and research responsibilities, Dr. Kamholz is also co-director of the Center’s Viral Vector Core Facility, which is integral to the development of gene therapy programs throughout the Center and Wayne State University. The facility makes several recombinant viral vectors, including adenoviral vectors, available to WSU scientists.

To reach Dr. Kamholz, please contact him by phone at (313) 577-0925 or e-mail at jkamholz@cmb.biosci.wayne.edu.

Genetic Counselor Karen Krajewski: Patients Need Information and Support

When the uncle of genetic counselor Karen Krajewski was born with Down Syndrome, the family doctor didn't tell her grandmother because he didn't want to upset her.



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One patient found out that Huntington disease was in her husband's family seven years after she was married and had a child. His aunt knew she had the disease but other family members had described away her early symptoms as nervousness.

Krajewski, a genetic counselor in Wayne State University's Department of Neurology since January 1998, is one of only a handful of full-time genetic counselors in the country specializing in neurogenetic diseases.

"I have seen too many people hurt by not knowing the full truths about their medical conditions," says Krajewski. "People need to know about their diseases and genetic history so they can make informed decisions about their health."

Krajewski's responsibilities include assisting patients in WSU's Neurogenetics Clinic and Charcot-Marie-Tooth (CMT) Disease Clinic, both at Harper Hospital. She also works with and follows patients with Pelizeaus-Merzbacher disease (PMD) who are participating in a major research study at WSU.

While her role changes from patient to patient, she generally provides information and support to patients and their families. She gives them in-depth education about their disease, collects family histories, reviews the pros and cons of genetic testing, helps them make decisions about their future and connects them with the resources they need. When needed, she also gets involved with helping family members cope with the realities of the patient's disease.

Krajewski received her Master of Science in Genetic Counseling from Indiana University. A volunteer experience at Children's Hospital of Michigan while she was an undergraduate led her back to WSU and her hometown of Detroit.

"People are very grateful to get information about their diseases," says Krajewski, who maintains strong ties to the Center for Molecular Medicine and Genetics. "Many people have heard or read a lot about their disease—from doctors, nurses, the Internet—but often, no one has sat down with them and given them the whole picture. When I do this, they are very appreciative and can make better, more informed decisions."

To reach Krajewski, please contact her by phone at (313) 577-8317 or by e-mail: kwalkowicz@wayne.edu.

Center Welcomes New Faculty Member

A warm welcome to Jeffrey A. Loeb, M.D., Ph.D., who joined the Center faculty this fall as assistant professor, with a joint appointment with the Department of Neurology.



Dr. Loeb most recently served as an instructor in neurobiology in the Department of Neurobiology at Harvard Medical School. He received his medical degree and doctorate degree in Biochemistry and Molecular Biology from the University of Chicago. He completed his internship in Internal Medicine and residency in Neurology at Massachusetts General Hospital. He completed postdoctoral research in the Department of Neurobiology at the Harvard Medical School and a fellowship in the Comprehensive Epilepsy Program at Beth Israel Hospital in Boston.

As director of the new Developmental and Molecular Neurobiology Laboratory at Wayne State University, Loeb is studying the fundamental question of how synapses form during embryonic development using the neuromuscular synapse as one of the primary models. His research interests extend beyond this simple model synapse to the central nervous system and to diseases of the nervous system in humans.

The opportunity to conduct collaborative research in the neurosciences and developmental neurosciences among investigators

in the Center for Molecular Medicine and Genetics, Department of Neurology and Children's Hospital of Michigan helped attract Dr. Loeb to Wayne State University. "Bringing basic and clinical interests together in this kind of communal, close-knit environment is very important to successful investigation. You don't often see these kinds of interactions and multi-department commitments at larger universities."

Dr. Loeb may be reached at (313) 577-1265 or by e-mail at jloeb@med.wayne.edu.

Multiple sclerosis (MS) is a demyelinating disorder of the central nervous system (CNS) affecting one in every 1,000 individuals. The clinical presentation of MS is variable, but can include difficulty walking, abnormal sensations such as numbness or “pins and needles,” loss of vision, spasticity, difficulty urinating and fatigue. There are more females than males affected and the average age of onset is between 28-30.

The natural history of MS varies and may follow a “relapsing-remitting” course with episodes of neurological dysfunction followed by symptom-free periods. In more than half of all MS patients, the relapsing-remitting course is eventually followed by a relentlessly progressive phase referred to as “secondary progressive MS.” Only the relapsing-remitting form has been shown to respond to therapy, mainly immunomodulatory agents.

The pathogenesis of MS is complex. The primary pathological finding in the brain is the “plaque,” a localized area of CNS myelin destruction associated with white cell infiltration with relative sparing of neurons and their axons. The amount of myelin destruction and remyelination probably determines the severity of clinical symptoms during exacerbation and the extent of recovery during remission. Brain demyelination studies of MS patients using magnetic resonance imaging (MRI) do not correlate with clinical disability. In contrast, clinical disability does correlate with neuronal and axonal injury, as measured by magnetic resonance spectroscopy (MRS) of the neuronal marker N-acetyl-aspartate (NAA). This suggests that axonal injury is the major cause of permanent neurologic dysfunction in patients with MS.

Although the etiology of MS is complicated, it is clear that the susceptibility to this disease follows a multifactorial pattern of inheritance. Population, twin and adoption studies demonstrate a familial aggregation of MS. Also suggest-

ing a genetic susceptibility is that certain ethnic groups are “resistant” to MS even though they reside in high-risk regions of the world. In addition, various major histocompatibility complex (MHC) antigens, such as HLA-Dw2, are associated with MS in some families. Finally, the risk of developing MS for individuals with an affected first-degree relative is approximately four percent which is much greater than the general population risk of one in 1,000.

Although population data clearly supports a genetic susceptibility to develop MS, molecular genetic data, or the identification of specific susceptibility genes, has been slow to emerge. Despite considerable opinion that HLA antigens are involved in MS susceptibility, linkage analysis to HLA loci has been weak. This is perhaps because HLA genes account for a relatively small portion of overall disease susceptibility. Several other genes involved in immunologic function, such as tumor necrosis factor (TNF) and T-cell receptors, have been studied and may be candidates for MS susceptibility genes.

Genes involved in myelin formation and function may also play a causative role in the inherited susceptibility of MS. One of these genes, the myelin basic protein gene (MBP) which encodes a major structural myelin protein, is linked with MS susceptibility in an inbred Finnish population. The linked marker, a VNTR (variable number of tandem repeats), may itself directly affect regulation of MBP expression since it is located

within the regulatory region of the gene. In this way, the VNTR could alter expression of MBP, acting as one of the many susceptibility genes leading to MS. A similar genetic mechanism has been found to affect expression of the insulin gene in type-1 diabetes.

Additional insight into the pathogenesis of MS may come from studying a rare X-linked genetic disorder of myelination called Pelizaeus-Merzbacher disease (PMD). PMD is caused by mutations in the proteolipid protein (PLP) gene that makes a membrane protein involved in stabilizing CNS myelin. PMD is similar to MS because it has similar neurological signs and symptoms and demyelination is the primary pathological process.

The cause of demyelination is not known in MS, but is well understood in PMD. Researchers at Wayne State University are studying the effect of different PLP mutations on myelination in the brains of individuals with PMD. In a family with a null mutation, they discovered that myelin is made normally even though no PLP is produced. By further studying one affected family member using magnetic resonance spectroscopy (MRS), researchers found decreased levels of NAA in the brain, suggesting axonal damage. Since a similar process of axonal injury is correlated with disability in secondary progressive MS, further understanding of how mutations in a myelin protein gene can lead to axonal damage will provide valuable insight into the pathogenesis of MS.

Faculty News

Mark Evans, M.D., is a section editor of a new textbook, *Principles & Practice of Medical Therapy in Pregnancy*. Several chapters in the book were authored by Center members, including Dr. Evans, Mark P. Johnson, M.D., and Anne Greb, M.S.

Anne Greb, M.S., has authored a chapter for the first textbook devoted to the process of genetic counseling. Her chapter, "Multiculturalism and the Practice of Genetic Counseling," is in the textbook, *A Guide to Genetic Counseling* (Wiley & Sons).

Stephen A. Krawetz, Ph.D., was an invited speaker at the 18th International Congress of Genetics in Beijing, China in August. He presented "Structuring the Male Genome During Spermatogenesis" in the Gene Expression symposia.

At a recent Gordon Conference on Mammalian Gametogenesis and Embryogenesis, **Mary Murray, Ph.D.**, presented "Analysis of an Evolutionarily Conserved Germ Cell Translation Masking Mechanism," which was selected for an oral presentation.

In addition to **Jeffrey A. Loeb, M.D., Ph.D.**, (see story page 5) the Center is pleased to welcome

three other new joint appointees to its faculty: **Erawati V. Bawle, M.D.** (also with Pediatrics), **Li Li, Ph.D.**, (also with Internal Medicine), and **Anjan Kowluru, Ph.D.**, (also with Pharmaceutical Sciences). The Center is also pleased to announce the appointments of **Robin Gold, M.S.**, (Michigan Teratogen Information Service), and **Karen Krajewski, M.S.** (neurology), as associate members.

Student News

The Center welcomed four new students into the Ph.D. training program in Molecular Biology and Genetics this fall. They are: **Ms. Ke Zhou, Mr. Dawei Wang, Mr. Zhan Yin, and Ms. Qunfang Li.**

Four Center students recently completed their Ph.D. degree requirements in the Molecular Biology and Genetics training program. Hearty congratulations are extended to **Drs. Hairong Geng, Saied Jaradat, Elizabeth Ruhl Quinn, and Chongsuk Ryou.**

Rolland Reinbold, a Ph.D. candidate in the Molecular Biology and Genetics training program, presented his work, "*In vitro* Assembly of Masked mRNPs" at the Third International Meeting of the RNA Society in Madison, Wisconsin, in May. He received a full fellowship from the Society to support his participation.

Message From the Director

Continued from the cover

exciting time of discovery in the field of neuroscience and the Center stands poised to make significant contributions through interdisciplinary, collaborative research. We believe new understanding of these cruel diseases is very near.

This issue of *Advances* takes a close look at the Center's involve-

ment in the study of neurodegenerative disease. The cover story gives an overview of the innovative research and clinical activities at the Center. On page 4, meet John Kamholz, M.D., Ph.D., who is leading our team of investigators seeking new insight into multiple sclerosis, Charcot-Marie-Tooth disease and Pelizaeus-Merzbacher disease.

On page 6, learn more about the complexities of multiple sclerosis. And on page 5, find out about the unique role of our neuroscience genetic counselor, Karen Krajewski.

As always, I welcome your feedback and comments.

Seminar Series: "Molecular Medicine, Genetics, and Gene Therapy"

The Center's seminar series, "Molecular Medicine, Genetics, and Gene Therapy" is held Thursdays at noon in Room 2268 Scott Hall. The schedule for the second semester follows. For the most up-to-date information on the series, please visit our web site at: <http://cmmg.biosci.wayne.edu>.

January

- 7 Mikhail Kolonin, WSU graduate student
- 14 Jouni Uitto, Thomas Jefferson University:
"Molecular Genetics of the Cutaneous Basement Membrane Zone"
- 21 Wenbo Xu, WSU graduate student
- 28 Daniel Djakiew, Georgetown University:
"The Role of Neurotrophins/Receptors in the Growth and Malignant Progression of the Human Prostate"

February

- 4 Wendy Walter, WSU graduate student
- 11 Robert Braun, University of Washington - Seattle: "Proteins that Mediate RNA Function in Mammalian Germ Cells"
- 18 Sungpil Yoon, WSU graduate student
- 25 Cristina Rondinone, Abbott Laboratories:
"Molecular Basis of Insulin Resistance"

March

- 4 Xiaoju Wang, WSU graduate student
- 11 Alan Wolffe, National Institute of Child Health and Human Development:
"Regulatory Roles of Chromatin"
- 25 Charles Little, Medical University of South Carolina: "The Morphogenesis of Blood Vessels, De Novo"

April

- 8 Nahum Sonenberg, McGill University:
"Translation Initiation Factors in Control of Gene Expression, Cell Growth and Tumorigenesis"
- 15 Fatimah Nahhas, WSU graduate student
- 22 John Blenis, Harvard Medical School:
"Signaling Processes Regulating Cell Proliferation and Death"
- 29 Maria Stamboulova, WSU graduate student

May

- 6 Hayes M. Dansky, The Rockefeller University:
"Using Genomics to Search for Genetic Factors Affecting Atherosclerosis Susceptibility and HDL Metabolism"
- 13 Stanley Forfa, WSU graduate student
- 20 R. Keith Humphries, British Columbia Cancer Agency: "From Hox Genes to Globin Genes: Genetic Control and Manipulation of Hematopoiesis"
- 27 Susan Wykes, WSU graduate student

June

- 3 Li Yang, WSU graduate student
- 10 Poongyeon Lee, WSU graduate student

Advances is published by the Center for Molecular Medicine & Genetics

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The online version of the newsletter and other information about the CMMG are available at the CMMG web site: <http://cmmg.biosci.wayne.edu>



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Enhancing Research and Training in Molecular Medicine and Genetics

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