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OUTLOOK

NEWS FROM THE CENTER ON HUMAN DEVELOPMENT AND DISABILITY AT THE UNIVERSITY OF WASHINGTON HEALTH SCIENCES CENTER

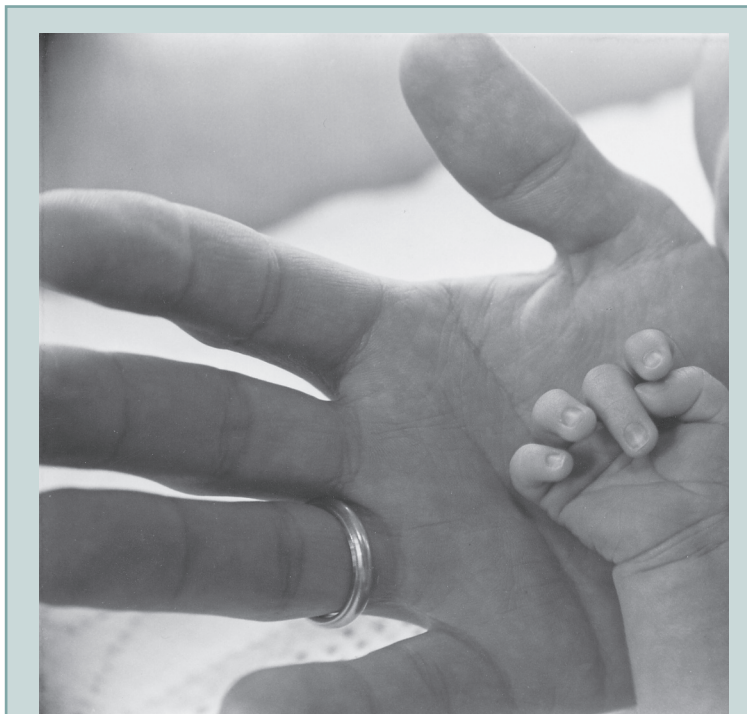
Preventing Infections, Protecting the Developing Brain

INFECTIONS BEFORE AND after birth are a major cause of developmental disabilities. Take herpes simplex. In adults, this virus causes cold sores and genital herpes, conditions that can be uncomfortable, but not life threatening. However, herpes simplex can kill newborns. It can also cause brain lesions that may result in a wide range of developmental disabilities, depending on which parts of the brain are damaged.

Infants are more vulnerable to infection than adults because their immune systems are still maturing. “Infants are slower to develop an effective immune response to infection and their response may be less robust,” said Christopher Wilson, M.D., research affiliate at the Center on Human Development and Disability (CHDD), chair of immunology, and professor of pediatrics. “Newborns also don’t respond as efficiently to most vaccines as adults,” said Wilson.

Wilson studies the development of the immune system to find ways to protect very young children from herpes simplex and other pathogens. His goal is to identify adjuvants, compounds that boost the immune system, and use these to make vaccines more effective in young infants.

Specifically, Wilson researches how the immune response in infants may reflect reduced or qualitatively different responses to signals received by Toll-like receptors (TLRs). TLRs detect structures



Illnesses that cause only minor symptoms in adults can lead to developmental disabilities in unborn and newborn children. CHDD researcher Chris Wilson is studying ways to protect newborns by boosting their immune systems.

Innate immune cells also initiate a cascade of chemical signals, including cytokines, needed to activate the acquired immune system, which includes T cells, antibodies, and other defenses against specific pathogens. If the acquired immune system has already encountered the pathogen in question, an effective response develops in just a matter of hours or days. However, if the acquired immune system is encountering a pathogen for the first time, it requires much more time to provide protection: one to two weeks in adults and up to several weeks in infants. Similar delays occur in developing acquired immunity in response to vaccines.

on pathogens and are found in cells of the innate immune system, which serve as the body’s first responder to infection. When a TLR alerts an innate immune cell to the presence of a pathogen, it triggers a general attack on all potential pathogens

“Our goal is to . . . improve vaccine efficacy early in life.”

- Christopher Wilson

in a matter of hours. The innate immune response can include the redness, swelling, and fevers associated with infection.

Unlike the acquired immune system, which “learns,” expanding its capabilities as it is exposed to new infectious agents and vaccines, the innate immune system is genetically hard-wired to recognize a fixed, limited number of signals mediated by TLRs. So far researchers have identified ten TLRs in humans. For example, one TLR detects lipopolysaccharides, large molecules found only in the membranes of gram-negative bacteria. Other TLRs detect structures from viruses, fungi, and parasites. Many of the TLRs in humans are very similar to TLRs found in other mammals, as well as in birds, reptiles, and insects.

See ‘Immune Boost’ on page 2



CHDD OUTLOOK is published by the Center on Human Development and Disability (CHDD) at the University of Washington Health Sciences Center. An online version can be downloaded from <http://www.chdd.washington.edu/gjst/outlook.html>

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Mental Retardation and Developmental Disabilities Research Center.

Address correspondence to:
CHDD OUTLOOK
Center on Human Development and Disability
University of Washington
Box 357920
Seattle, Washington 98195-7920

chdd@u.washington.edu
<http://www.chdd.washington.edu>

Writer, editor, and photographer: Kris Freeman

Center on Human Development and Disability



Michael J. Guralnick, Ph.D., Director
Christene James, Administrator

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES RESEARCH CENTER (MRDDRC)

Donald F. Farrell, M.D.,
Associate Director,
Interdisciplinary Research

Albert R. La Spada, M.D., Ph.D.,
Associate Director,
Research Development

MRDDRC CORE SERVICES

Behavioral Science Core
Susan Spieker, Ph.D.,
Director

Genetics Core

Albert R. La Spada, M.D., Ph.D.,
Director

Infant Primate Research Laboratory

Thomas M. Burbacher, Ph.D.,
Director

Instrument Development Laboratory

Kirk Beach, M.D., Ph.D.,
Director

Neuroscience Core

Kenneth Maravilla, M.D.,

UNIVERSITY CENTER FOR EXCELLENCE IN DEVELOPMENTAL DISABILITIES (UCEDD)

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Director

Autism Center

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Center on Infant Mental Health and Development

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Immune Boost . . . from pg. 1

All infants are born with TLRs. However, the signaling system initiated by TLRs appears not to be fully functional at birth. Some researchers theorize that an infant's immune system has to be primed by environmental exposures. "The idea is that the only difference between the immune systems of infants and adults is that newborns have been living in a sterile environment, and then they're dropped into a dirty world and it takes a while for things to kick in," said Wilson. Another theory is that the pace of immune system development is genetically determined.

"Our goal is to try to understand the extent to which these differences are fixed and immutable, that is hard-wired in development, or are in fact subject to modification by appropriate environmental cues," said Wilson. These cues could include agonists, compounds that bind to and stimulate TLRs. "The immune system of infants may require different kinds of signals or more robust signals to achieve immunity than the immune systems of older children," said Wilson.

Wilson's research program has three primary goals. The first is to determine in detail the immune responses of newborns as compared to adults. He and colleagues at the UCLA Center for Vaccine Research are studying a group of infants by measuring immune function at birth, age seven months, and age sixteen months.

His second goal is to define the molecular mechanisms responsible for the differences in immune function observed between infants and adults. For example, Wilson and colleagues, including Samuel Miller, M.D., professor of medicine, of microbiology, and of genome sciences, have identified the structure that allows *Pseudomonas aeruginosa* to evade detection by TLR4 in the immune systems of infants and ill adults. *P. aeruginosa*, a common bacterium found in the human intestine, can cause swimmer's ear and hot tub rash in healthy adults and extremely serious infections in infants, persons with cystic fibrosis, and cancer and burn patients. Wilson also studies the immune response to the bacterium *Listeria monocytogenes*, which can cause severe developmental disabilities.

Wilson's third research goal is to identify TLR agonists that might serve as adjuvants, compounds that can boost or trigger the immune system, including the activity of vaccines. "Our number one goal is to develop ways to improve vaccine efficacy early in life," said Wilson. A hepatitis B vaccine that uses a TLR adjuvant was recently approved for use in Europe.

To test adjuvants for their possible use in human infants, Wilson and his colleagues are developing mouse models that respond to TLR agonists the same way that humans do. "The TLRs in mice and humans differ in some important ways and one of these differences affects responses to neonatal pathogens and adjuvants," said Wilson. "So what we're doing is creating mice that have human receptors rather than mouse receptors." These animal models will be used to test the ability of different adjuvants to improve protection when they are administered together with vaccines, with the expectation that their responses will more closely predict what would occur in humans. A goal would be "to provide children with immediate protection at the same time they're developing a protective immune response to the vaccine," said Wilson. ♦



Christopher Wilson



Expanding Medical Care for Children with Autism Spectrum Disorders



In addition to expanding the variety of services available to children with autism spectrum disorders, the CHDD Autism Center has also increased its capacity by opening a satellite clinic at the UW Tacoma campus. Allison Brookes (above, left) directs the new satellite clinic.

HOW CAN YOU EXPLAIN THAT YOUR stomach aches if you can't talk? Or what if you can talk, but don't understand what or where the hurt is? Because of communication challenges, medical concerns of children with autism spectrum disorders (ASD) have often been unrecognized and untreated. In addition, health care providers have tended to focus on the behaviors of children with ASD rather than their possible medical problems.

To better meet the needs of children with ASD, the Autism Center at the Center on Human Development and Disability (CHDD) is expanding its clinical services, which have emphasized behavioral and educational interventions, to provide a more comprehensive assessment of medical issues. As part of this effort, the Autism Center has joined the Autism Treatment Network, a national nonprofit organization founded in January 2005 to develop a uniform "gold standard" of care for persons with autism, with an

emphasis on medical care.

ASD are among the most common developmental disorders in the U.S. These neurological disorders disrupt connections in the brain critical to communication, resulting in impairments that can range from an inability to speak, to difficulties

Because of communication challenges, medical concerns of children with ASD have often been unrecognized and untreated.

interpreting facial expressions and other problems with non-verbal communication.

Health issues reported by parents of children with ASD include sleep difficulties and problems related to gastrointestinal (GI) function. Both types of problems may affect behavior. "We think that, in some cases, behaviors that we attribute to autism, such as self-injurious behavior and

some ritualistic behaviors and aggression, can be associated with the underlying pain and stress associated with these medical conditions," said Geraldine Dawson, Ph.D., director of the Autism Center, CHDD research affiliate, and professor of psychology.

Some researchers hypothesize that some episodes of self-injurious behaviors, such as biting or head banging, may cause the body to release beta-endorphins that dampen pain. Or such behaviors may "gate" or serve as a distraction from discomfort caused by medical problems, or may simply be an individual's way of expressing distress or pain.

GI-related issues reported among children with ASD include acid reflux, constipation, and abdominal pain. Reported sleep disorders are equally varied. "Some children have trouble falling asleep," said Dawson. "Others might fall asleep but waken early or in the middle of the night. There are some children whose sleep cycle is completely reversed so they are literally awake all night long. As you can imagine, this is not only very disruptive for the family, but a sleep-deprived child is not able to optimally benefit from the educational and other behavioral interventions that we offer."

Addressing the medical needs of children with ASD is not intended to replace the Center's emphasis on behavioral and educational interventions, said Dawson. Instead, the goal is to augment those programs by helping children become more responsive to them.

The Autism Center has established a monthly clinic focused on medical assessment of children with ASD. The assessment team includes Yemiserach Kifle, M.D., medical director of the Sleep Disorders Program at Children's Hospital and Regional Medical Center (CHRMC) and assistant professor of pediatrics; Dennis Christie, M.D., professor of pediatrics, head of gastroenterology, and chief of CHRMC gastroenterology; Felice Orlich,

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Pediatric Neurogenetics Team: Diagnosing Rare Disorders

FAMILIES OF CHILDREN WITH RARE, genetically based neurological disorders often endure long rounds of medical appointments while seeking a diagnosis. First, get the referral to the neurologist. Next, see the neurologist, who will refer you to a geneticist, who, after ordering tests, will send you back to the neurologist.

To streamline the diagnostic process, the Center on Human Development and Disability (CHDD) has established the Pediatric Neurogenetics Clinic, a new consulting service that brings together providers with expertise in neurology, medical genetics, pediatrics, and genetic counseling. “We try to save the family time by having them meet with several specialists at once,” said Mercy Laurino, M.S., a genetic counselor, and clinic coordinator. The new clinic focuses on children, while the existing CHDD Neurogenetics Clinic primarily serves adults.

“The diagnostic process for patients with rare neurogenetic disorders can be so challenging and problematic that it requires specialists with expertise in multiple disciplines,” said Ian Glass, M.D., a CHDD research affiliate and the clinic director. Therefore, during patient visits, clinic specialists work as a team to maximize communication and collaboration, said Glass, who is also an associate professor of pediatrics and chief of the Genetics Clinic at Children’s Hospital and Regional Medical Center (CHRMC).

Children who are eligible for the clinic may have dysmorphic, or atypical, facial features, as well as severe neurological symptoms, such as mental retardation, seizures, movement disorders, unexplained muscle weakness, or abnormal brain scans or muscle biopsies. They may have had atypical development from birth or may have developed typically and then experienced a regression in development.

Other CHDD clinics provide services for persons with several other types of genetic disorders, notably inborn errors of metabolism, including severe congenital



Ian Glass (left), Katelyn Lawrenz, and Anthony Bouldin discuss Katelyn’s symptoms at the Pediatric Neurogenetics Clinic. The clinic team is trying to determine if Katelyn’s nerve damage has a genetic cause.

hypothyroidism (a deficiency of thyroid hormone) and PKU (phenylketonuria, a genetic disorder in which a child is born without the ability to break down the amino acid phenylalanine).

The Pediatric Neurogenetics Clinic, which was formed in November 2005, currently sees only a small number of patients. Potential patients are screened. “Even if we determine that an appointment at this clinic wouldn’t be appropriate, we hope that we may be able to direct families to other services that would meet their needs,” said Laurino.

Once an appointment is made, the clinic’s team of physicians and genetic counselors reviews a patient’s personal and family medical history and help the family make informed choices about genetic testing. “There are a lot of tests available for genetic disorders and knowing how to apply them well is important because they are potentially expensive,” said Robin Bennett, M.S., a genetic counselor. “You can waste a lot of money if you order them willy-nilly.”

Reaching a diagnosis, if one is possible, may require several appointments. In addition to analyzing test results, team

members may also need time to think over the case, discuss it among themselves, and do additional research in the medical literature. Some children may require long-term follow-up, so the team members can observe how the disorder unfolds, information that may lead to a diagnosis. In others cases, the disorder may not yet be described or known to doctors. “Again, follow-up is important because new reports in the scientific and medical literature appear regularly,” said Glass.

If the clinicians are able to reach a diagnosis, they can provide information about the child’s prognosis, for example, if the diagnosed disorder is degenerative. They can also determine the mode of inheritance and recurrence risks. The team members can then direct the family to resources such as peer support groups or state-funded resources and special services. One of the most important benefits of a diagnosis may be one of the least tangible for families, what Glass calls, “relief from the burden of not knowing.”

While a diagnosis may provide families with valuable information, it may also dash hopes. Cures do not yet exist for many of the disorders diagnosed in the

clinic. "In the meantime, until cures are developed, many valuable managements and interventions are available for children with neurogenetic disorders to maximize their developmental potential," said Glass.

Because understanding the cause of a disorder is critical to treatment and, more important, prevention, Glass and other clinic specialists are working to isolate the genes responsible for several types of inherited neurological disorders.

Glass researches disorders of the cerebellum, the portion of the brain that controls balance, coordination, and some cognitive functions. For example, he studies Joubert syndrome, a rare autosomal recessive disorder with a distinctive hindbrain-midbrain malformation. His group identified the first gene responsible for this group of disorders.

Thomas Bird, M.D., a CHDD research affiliate and professor of medicine, medical genetics, and neurology, has helped locate genes implicated in Charcot-Marie-Tooth neuropathy type 1B, which causes muscle weakness and other symptoms, and familial Alzheimer's disease, a rare, early-onset form of the disease that affects people in their forties and fifties.

Glass and Bird are regular attending physicians at the clinic along with Anthony Bouldin, M.D., clinical instructor of pediatric neurology. Other clinical staff members include Suman Jayadev, M.D., a neurology fellow, and Sara Michelson, M.S., a genetic counselor.

Several CHDD affiliates were instrumental in helping to form the Pediatric Neurogenetics clinic, including Sidney Gospe, Jr., M.D., Ph.D., professor of neurology and pediatrics; and Phillip Chance, M.D., professor of neurology and pediatrics, director of the University of Washington Joubert Center, and chief of the CHRMC Division of Genetics and Development.

To contact the Pediatric Neurogenetics Clinic, call Mercy Laurino at (206) 598-8771. More information about CHDD clinics is available online at <http://chdd.washington.edu/families.html#clinics>. ♦

Thousands of Genes at a Time: Microarray Core Component Helps Design Microarray Experiments



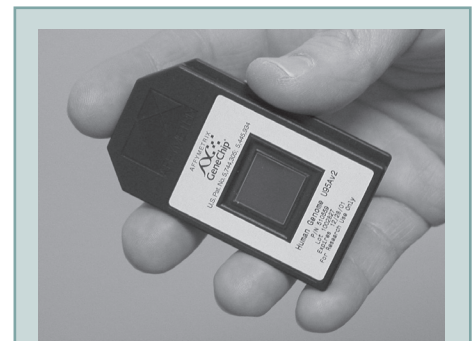
Sandra Juul, left, discusses her microarray data with Dick Beyer, bioinformaticist for the Microarray component of the CHDD Genetics Core. Juul's microarray data were essential to the success of one of her recent grant applications.

TEN YEARS AGO, ANALYZING A single variation in a gene could take up to two days. Now, with microarray technology, an investigator can analyze the expression of thousands of genes or characterize thousands of genetic variants in one day. The team at the Microarray component of the Center on Human Development and Disability (CHDD) Genetics Core can help CHDD investigators with all aspects of microarray experiments, from experimental design to data analysis.

Microarray experiments are often used for exploratory research and hypothesis generation. "Microarray technology allows you to go into a project with very little preconception," said Al La Spada, M.D., Ph.D., a CHDD research affiliate, associate professor of laboratory medicine, and director of CHDD Genetics Core. "A researcher starts with a notion that environmental stress or disease must cause a difference in the way genes are being turned on and off. Microarray research can provide data about the

pathways that might be affected by a given condition," said La Spada, who is also director of the Center for Neurogenetics and Neurotherapeutics and an associate director of the CHDD. The Microarray component of the Genetics Core provides services in collaboration with the Center for Ecogenetics and Environmental Health.

Typical experiments might analyze differences in gene activity between cell lines that have been exposed to neurotoxic



A single microarray can collect hundreds of thousands of pieces of genetic data.

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substances and those that have not, or samples from persons with and without a specific neurodevelopmental disorder. Data from the microarray experiment can then provide a basis for more targeted, hypothesis-driven experiments.

Measuring Gene Expression and Characterizing the Genome

Microarrays have typically been used to analyze the activity, or expression, of genes. Genes code for a protein or a related group of proteins. When a gene is expressed, molecules known as messenger RNA (mRNA) copy the relevant code from the DNA and carry it to the cell's protein-building machinery. The Microarray component offers arrays that can detect mRNAs or variations in DNA.

Expression microarrays measure gene expression by detecting the presence and relative abundance of mRNAs. Arrays are available for multiple genomes, including human, mouse, and rat as well as many other species, such as pigs, dogs, and zebrafish.

Tiling microarrays cover a complete section of a genome, including areas between genes once referred to as "junk." These arrays are used to discover or detect the presence of RNA and other molecules with unknown or regulatory functions.

SNP (single nucleotide polymorphism) microarrays detect variations, or polymorphisms, in DNA consisting of a change in a single base pair of nucleotides. "SNP microarrays allow us to look at polymorphisms in a much more cost-effective, time-efficient manner than previous methods," said Fred Farin, M.D., coordinator of microarray services.

Sequencing microarrays can sequence up to 600,000 base pairs of DNA at one time. "These newly available arrays can do DNA sequencing at a very low cost," said Farin.

Researchers may use several types of standard or custom arrays in succession. For example, a team might begin with a full genome scan of two populations using a standard, off-the-shelf array. "The expression results might point activity to a

specific area of a particular chromosome, so now you design a very specific SNP array that only looks at this region," said Farin. If a microarray with known SNPs doesn't catch the hypothesized variation, the team may switch to sequencing arrays in an attempt to discover new SNPs relevant to their research.

Experimental Design and Data Analysis

"Before investigators raise their pipette to aliquot an RNA sample, they can meet Core members to discuss the best way to design a microarray experiment, including issues such as the number of samples needed for statistically significant results," said La Spada. As few as three to four samples per category may be acceptable. For example, Sandra Juul, M.D., Ph.D., a CHDD research affiliate and associate professor of pediatrics, used microarrays in her research on the hormone erythropoietin (EPO), which stimulates the body to produce red blood cells. She is exploring the potential use of EPO to decrease brain cell death caused by oxygen deprivation (hypoxia). Her experiment required 27 arrays (one for each of three groups of experimental animals, three parts of the brain, and three time points).

Richard Beyer, Ph.D., Core bioinformaticist, and Theo Bammler, Ph.D., bioinformatics coordinator, can also help investigators anticipate how microarray data may be used in follow-up experiments. For example, gene expression doesn't always translate into protein creation because regulatory RNAs, such as "silencing" RNAs, can disable mRNAs. Identifying and quantifying the proteins that result from gene expression requires mass spectrometry and other technologies available through the Proteomics component of the Genetics Core. Juul has used services from both Core components in her EPO research. "We did real-time PCR to confirm key findings from the microarrays and backed that up with protein data," said Juul.

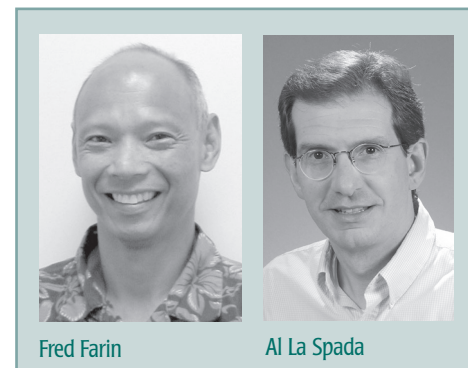
Analysis of the data resulting from microarray experiments is an especially

important service. "When you do this type of high-throughput study, you get smacked by a tidal wave of data," said La Spada. The biological signals of interest are often subtle, and easily overlooked against a noisy background of signals from thousands of other genes. Teasing statistically significant results from such data requires the use of sophisticated bioinformatics software.

"Fred Farin and Theo Bammler have provided excellent service for the design and completion of microarray experiments, and they along with Dick Beyer have been instrumental in data analysis," said Robert Rostomily, M.D., CHDD research affiliate and associate professor of neurological surgery. Rostomily has used arrays to analyze gene function in brain tumor cell lines and compare expression profiles of genetically inherited tumors compared with tumors that arise sporadically. Currently, Beyer is compiling array data from public databases to complement Rostomily's and La Spada's experimental findings.

The Microarray component team also sees student and resident training as part of its mission. Students can be involved in every level of the component's service, including experimental design, sample processing, processing and scanning of microarrays, analysis and visualization of data, and production of posters and manuscripts.

"Working with the Microarray component is much more than just dropping off the data and getting the analysis," said Farin. "It is a very creative, collaborative process." ♦



Fred Farin

Al La Spada



Robin Talley of the CHDD Autism Center works with a client. While expanding its medical services, the Center continues to focus on behavioral interventions to help children with ASD improve their communication and social skills.

Ph.D., associate director of the Autism Center, a clinical neuropsychologist, and assistant clinical professor of psychiatry and behavioral sciences; Sam Zinner, M.D., a developmental pediatrician and assistant professor of pediatrics; Hower Kwon, M.D., a child psychiatrist and assistant professor of psychiatry and behavioral sciences; and Robert Devney, M.D., a child and adolescent psychiatrist. Team members collaborate with psychologists, speech and language pathologists, and an occupational therapist.

In addition to expanding treatment options for individual children, the Autism Center is working with other institutions affiliated with the Autism Treatment Network to improve overall standards of medical care for children with ASD. One project is the development of a shared database of the results of ASD treatments and research studies. A similar approach—pooling knowledge among regional research centers—has been effective in enhancing care for other childhood diseases, such as cystic fibrosis and childhood leukemia.

“One of our goals is to try to develop more consistent care guidelines for autism,” said Dawson. “Although there

the expertise available there.

While expanding treatment to include medical care, the Autism Center continues to offer all its previously existing services, as part of the CHDD’s University Center for Excellence in Developmental Disabilities. Coordinated services include diagnosis and intervention for children as young as 18 months. Early diagnosis is crucial because intensive early intervention can alleviate many long-term effects of the disorder, such as delays in cognitive and emotional development. The Center’s team of early childhood autism consultants uses a variety of research-based techniques to help toddlers improve their play, communication, and social skills.

The Center also provides a wide variety of services for older children, including diagnosis, behavioral intervention, social skills groups, and speech-language and occupational therapies. New programs include a teen mentoring program in which typically developing college students mentor adolescents with ASD

are now good guidelines for assessment, there still aren’t well established guidelines for treatment, especially for some of these underlying medical issues.” As a result, children may receive different assessments and treatment plans at different centers, depending on each institution’s philosophy and

who, in turn, mentor younger children with ASD by serving as teacher aids at the CHDD Experimental Education Unit. “You’re teaching the kids how to be a contributing member of society, how to give back,” said Orlich.

The Autism Center has also increased services by establishing a satellite clinic on the UW campus in Tacoma. “It has allowed us to expand our clinical and training reach down to the South Sound and Tri-Cities area,” said Orlich. “The new clinic has basically doubled our ability to offer diagnostic services.” Allison Brooks, Ph.D., directs the Tacoma clinic.

Despite recent increases in capacity, the Autism Center is far from meeting the needs of the population of children with ASD in Washington State. In late 2005 about 240 families were on waiting lists for Center services. Therefore, professional training is a critical component of the Center’s work. Recent efforts include partnerships with school districts, to help develop their educational and intervention programs, and the expansion of web-based professional training programs for health care providers. The Center is also fine-tuning a social skills curriculum for children with ASD that is scheduled for release to teachers and clinicians in the spring of 2006. The curriculum differs from others currently available by tying social skills to developmental levels.

More information on the Autism Center is available online on the CHDD web site at <http://depts.washington.edu/uwautism/services/index.html>. ♦



Felice Orlich



Geraldine Dawson



Faculty members appointed as new CHDD research affiliates

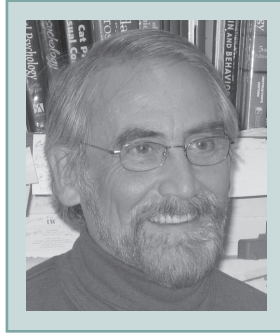
David Kimelman, Ph.D., is a professor of biochemistry. Using animal models (primarily zebrafish and frogs) he studies signaling pathways within and among cells that are critical to the development of vertebrate embryos. Results from his research may lead to a better understanding of developmental disorders caused by errors



in embryonic development. A major research focus is the Wnt signaling pathway, which is of critical importance in a wide array of biological

processes, from the regulation of early embryonic development to the control of stem cell growth. His team has determined several of the key intracellular interactions that regulate this pathway, including the kinase GSK3 and an inhibitor of this enzyme. Kimelman earned his doctoral degree at Harvard University.

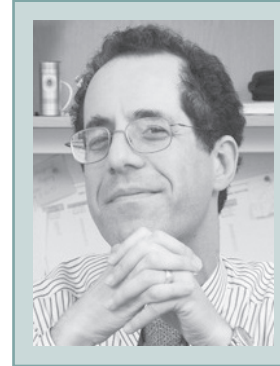
Jaime Olavarria, M.D., Ph.D., is an associate professor of psychology. He studies the development of organized neural circuits (topographic maps) in the visual cortex. He has shown that normal map development requires retinal input during a well-defined critical period. His goal is to understand the nature of



the retinal influences (neural activity or chemical cues) that specify the topography of maps, as well as the cellular and molecular processes that regulate the

timing and duration of this critical period. He is also interested in studying how anomalous factors, such as epilepsy, can affect map development. Olavarria earned his medical degree at the University of Chile in Santiago, Chile, and his Ph.D. in neurobiology at the University of California, Berkeley.

Jay T. Rubinstein, M.D., Ph.D., is a professor of otolaryngology–head and neck surgery, as well as bioengineering. He is also the director of the Virginia Merrill Bloedel Hearing Research Center. His primary research focus is to improve hearing in persons with cochlear implants, surgically implanted devices used by



persons with severe hearing impairments. In particular, his goal is to improve perception of music and speech in noisy environments. Toward this end he focuses on

the patterns of electronic signals the implant sends to the brain, with the aim of finding ways to optimize signals for speech and music, while de-emphasizing signals for competing sounds. Rubinstein earned his medical degree and a Ph.D. in bioengineering from the University of Washington.



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University of Washington
Center on Human Development and Disability
Box 357920
Seattle, Washington 98195-7920

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