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The Genome Scientist

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Department Adds Three Faculty Members

Joshua Akey, Assistant Professor

Joshua Akey, Ph.D., joined Genome Sciences last fall from the Fred Hutchinson Cancer Research Center where he had been a postdoctoral fellow in the Kruglyak Lab. Dr. Akey commented that "there were many features that attracted me to Genome Sciences, including the strength, breadth, and collegiality of the faculty and a strong graduate program."

Well known in the fields of population genetics and molecular evolution, Dr. Akey has research interests that include understanding how evolutionary forces shape patterns of genetic variation within and between species and how we

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Michael MacCoss, Assistant Professor

Michael MacCoss, Ph.D., came to Genome Sciences in December 2003 from the Scripps Institute, where he had been a postdoctoral fellow in the Yates Lab. Commenting on his appointment, Dr. MacCoss observed that "for an analytical chemist interested in developing technology towards the analysis of complex protein mixtures, I felt I needed to be in an environment that complemented my own expertise. The choice of Genome Sciences and the University of Washington was simply a 'no brainer'….I can't think of a better opportunity."

A leader in the areas of proteomics and mass spectrometry, Dr. MacCoss and his lab focus on the development of stable isotope and mass spectrometry based approaches to improve understanding of

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Evan Eichler, Associate Professor

Evan Eichler, Ph.D., joined Genome Sciences in May 2004 from Case Western Reserve University, noting that "Genome Sciences combines the strengths of a more traditional genetics program while taking advantage of new developments in genome technology and computer science. I am excited by the prospects – genomics with a strong genetic backbone is poised to make some of the most significant contributions to a variety of fields including medicine and evolution." He comments as well that the University of Washington "is becoming a mecca for genome biologists. I consider myself fortunate to become a member of such a great faculty, and I am hopeful that interactions with these folks will spur my research in exciting new directions."

Dr. Eichler, a pioneer in the study of rapidly evolving portions of the genome, continues to study the organization, origin, and impact of recent segmental duplications within mammalian genomes. The general aims of his research

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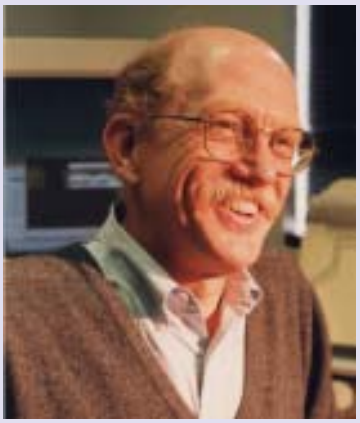
Notes from the Chair



Bob Waterston

This has been a busy year for everyone in Genome Sciences, with exciting activities to challenge all of us!

The most exciting part of my job continues to be leading the growth of the department. We are anticipating our move next year into our new building (see photos on pg. 3). Our new digs now have outside walls, and the inside walls are taking shape. The faculty had a chance to tour the building this spring, and we made sure our prospective new faculty had a tour as well. The building also now has a name – the William H. Foege Building – to honor a leader in eliminating smallpox from the planet. We hope the research carried out in this new space lives up to the name!

The department has been actively recruiting new faculty and students to put the new space to good use. Mike MacCoss, Evan Eichler and Josh Akey have all joined us in the past 18 months, and this spring we reviewed another group of excellent candidates. We are still in active negotiations, but have no firm news yet.

The department has also taken on the leadership in establishing a Center for Proteomics at the new South Lake Union Campus. The Washington State Legislature has generously provided $1.6M per year to the development of the program, and the Dean has allotted 6,890 square feet of space. The Center will be a joint effort with the departments of Biochemistry, Medicine and Immunology and perhaps others. We are currently recruiting two faculty to get the program off the ground.

Our excitement about our future must be contagious. We have recruited two excellent graduate classes, with 13 students joining us last fall and 13 more coming this fall. Thanks to Jim Thomas, Stan Fields, and our graduate program and grants managers, both the Genetics and Genomics Training Grants have been renewed. In fact, the latter received glowing praise from the reviewers as "a model of what a genomics training grant should be." The graduate students bring such energy and optimism!

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New Faculty

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can use this information to address fundamental questions in biology and evolution. His lab currently pursues projects in human population genomics, the genetic architecture of complex and quantitative traits using yeast as a model system, and canine evolution.

Originally from the Pittsburgh area, Josh and his wife, Dr. Dayna Akey, a postdoctoral fellow in the Swanson Lab at UW Genome Sciences, had their first child, Nicholas, in June.

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are to investigate the molecular mechanisms responsible for such duplications, to evaluate their role in the evolution of the primate genome, and to assess their impact in contributing to both normal and disease-causing variation in the human population. The Eichler Lab's approach has been to combine bioinformatics, comparative sequencing, phylogenetics, high-resolution FISH methods, and array comparative genomic hybridization to address these questions.

A native of Saskatchewan who earned his Ph.D. at the Baylor College of Medicine, Evan and his wife Marla have three children: Matt, Ehren, and Teresa.

MacCoss continued from page 1

biology on a molecular, cellular, and whole organism level. Individuals in the laboratory are working on technology for automating biochemical sample preparation methods for the analysis of protein mixtures; developing in vivo stable isotope methods for studying protein metabolism; increasing the dynamic range of liquid chromatography-mass spectrometry for the analysis of peptides; and developing computational tools for the automated conversion of mass spectrometry data into biologically meaningful results.

Originally from New Jersey, Mike earned his Ph.D. from the University of Vermont.

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Fangman Symposium: 40 Years of the Yeast Genome

Walt Fangman

A symposium to celebrate the career of Walton L. Fangman, Professor Emeritus in the Department of Genome Sciences, and his contributions to our understanding of DNA replication was held on September 3, 2004. Speakers and participants included past and present members of his laboratory.

Walt joined the Department of Genetics at the University of Washington in 1967. Originally interested in the initiation of DNA synthesis at the single origin of replication in prokaryotic chromosomes, Walt was quickly seduced by the small size of the budding yeast genome with its high density of replication origins. It is in this arena that Walt has spent most of his career, exploring the temporal program of chromosomal DNA replication and essentially creating the field along the way.

Besides serving as Chairman of the Department of Genetics (1985-1990), Walt has also served two stints as the Principal Investigator on the NIH Genetics Training Grant. Walt has been a Professor Emeritus at UW since 2000 and retired from active University life at the end of 2004.

A website featuring the symposium (including photos from the event) can be found at http://www.gs.washington.edu/~mraghu/wf/index.html

Foege Building

Construction continues on the new Bioengineering – Genome Sciences building. The $150 million structure, to be completed Spring 2006 and shared with the Department of Bioengineering, will provide 265,000 square feet of research space. The Bill and Melinda Gates Foundation contributed a record $70 million gift, $60 million of which will go toward construction costs. The remaining amount will be applied to collaborative global health programs at the UW. Additional funding for the building includes $12 million from the federal government, $10 million from the Whitaker Foundation, and gifts from other private sources.

Clockwise from upper right: east side view from Pacific street; west side along 15th ave; east side view from J-wing

Faculty Honors

King and Henikoff Elected to National Academy of Sciences

On May 3, 2005, The National Academy of Sciences announced the election of Dr. Mary-Claire King and Dr. Steven Henikoff as new members. Election to membership in the Academy is considered one of the highest honors that can be accorded a U.S. scientist or engineer.

Mary-Claire King

Steve Henikoff

Dr. King is the American Cancer Society Research Professor in the departments of Medicine and Genome Sciences. Her research interests include breast and ovarian cancer, inherited deafness, and systemic lupus erythematosus.

Dr. Henikoff is a member of the Fred Hutchinson Cancer Research Center, an Affiliate Professor of Genome Sciences, and Howard Hughes Medical Institute investigator. He studies chromatin inheritance and centromere evolution and develops tools for interpreting sequence information and predicting harmful mutations.

Waterston Awarded 2005 Gruber Genetics Prize

Dr. Robert Waterston, chair of the Department of Genome Sciences and the William Gates III Endowed Chair in Biomedical Sciences, has been awarded the 2005 Genetics Prize of the Gruber Foundation, to be presented in October at the meeting of the American Society of Human Genetics in Salt Lake City. Dr. Waterston was selected for his many accomplishments, including his pivotal role in the Human Genome Project.

Hall Honored as UW Inventor of the Year

Ben Hall

Dr. Benjamin Hall, Professor of Genome Sciences and of Biology, received the first annual Inventor of the Year award from the University of Washington on September 14, 2004.

Dr. Hall, a past chair of the former Department of Genetics, was honored for his many achievements, including his studies in yeast transcription. These studies led to two important inventions enabling the use of yeast cells for genetically engineered production of biopharmaceuticals, including hepatitis B vaccine, human insulin, and human serum albumin.

King Awarded 2004 Gruber Genetics Prize

Dr. Mary-Claire King, American Cancer Society Research Professor in Medicine and Genome Sciences, was awarded the 2004 Genetics Prize of the Gruber Foundation, which was presented at last year's meeting of the American Society of Human Genetics in Toronto. Dr. King was selected for her many accomplishments, including her pioneering work in the fields of breast and ovarian cancer genetics.

Dr. King was also recently awarded the University of California, San Francisco (UCSF) medal, and the Marion Spencer Fay Award from the Institute for Women's Health and Leadership of Drexel University's College of Medicine.

Waterston and Stamatoyannopoulos Elected to American Academy of Arts and Sciences

Dr. Robert Waterston and Dr. George Stamatoyannopoulos were elected in April 2005 as fellows of the American Academy of Arts and Sciences, one of the highest honors for scholars in the United States.

George Stamatoyannopoulos

Dr. Waterston, chair of the Department of Genome Sciences and the William Gates III Endowed Chair in Biomedical Sciences, led sequencing of the genome of the worm *C. elegans*, the first complete animal to be sequenced. His contributions to large-scale DNA sequencing were central to the success of the Human Genome Project.

Dr. Stamatoyannopoulos is Professor of Medicine and of Genome Sciences, Adjunct Professor of Pathology, Director of the Markey Molecular Medicine Center, and past head of the Division of Medical Genetics. He is known for his work on treatments for sickle cell disease and his studies of blood-forming stem cells and genetic controls for blood cells.

Faculty Honors

Eichler Selected as HHMI Investigator

Dr. Evan Eichler has been selected an investigator of the Howard Hughes Medical Institute. Dr. Eichler, a leader in the study of rapidly evolving portions of the genome, continues to study the organization, origin, and impact of recent segmental duplications within mammalian genomes. His selection brings the total number of HHMI investigators at the UW to 13, including Genome Sciences affiliated faculty members David Baker, Stan Fields, Phil Green, and Richard Palmiter.

The HHMI is the nation's largest private source of support for biomedical research and science education, with an annual research budget of approximately $400 million. The institute periodically selects new members from among the nation's top researchers in the ascending phase of their careers.

Faculty Receive Alvin J. Thompson Award

On May 20, 2005, a group of Seattle-area researchers, including Drs. Phil Green, Debbie Nickerson, Maynard Olson, and Robert Waterston of UW Genome Sciences, received the Northwest Association for Biomedical Research's Alvin J. Thompson Award for their breakthrough discoveries in genome sequencing, leading to the completion of the Human Genome Project.

The award was presented at the NWABR's Annual Fundraising Dinner by Francis Collins, M.D., Ph.D., Director of the National Human Genome Research Institute at the National Institutes of Health.

Baker Selected for AAAS Newcomb Cleveland Prize

David Baker

Dr. David Baker, Associate Professor of Biochemistry and Adjunct Associate Professor of Genome Sciences and of Bioengineering, was selected along with 5 colleagues at the UW and elsewhere to receive the 2003-2004 American Association for the Advancement of Science Newcomb Cleveland Prize.

Dr. Baker co-authored the article, Design of a Novel Globular Protein Fold with Atomic-Level Accuracy, which appeared in the Nov. 21, 2003, issue of Science. It details their work on a computational method for creating proteins not found in nature.

Dr. Baker was also recently awarded a Foresight Institute Feynman Prize in Nanotechnology.

Malik Named Searle Scholar

Harmit Malik

Dr. Harmit Malik, Assistant Member at the Fred Hutchinson Cancer Research Center and Affiliate Assistant Professor of Genome Sciences, was one of 15 scientists to receive a 2005 Searle Scholar Award, which provides $240,000 in research funding over three years. The Searle Scholars Program was established at The Chicago Community Trust in 1980 and is funded from the estates of Mr. and Mrs. John G. Searle.

Dr. Malik is interested in a variety of problems that could all be classified under the genetics of evolutionary conflict. He studies rapidly evolving proteins as a hallmark of this kind of conflict, hoping to better understand the molecular nature of the conflict, as well as uncover previously unrecognized sources of conflict. He has also recently received the Kimmel Scholar and Sloan Fellow awards.

Olson Elected to American Philosophical Society

Maynard Olson

Dr. Maynard Olson, Professor of Genome Sciences and of Medicine, Adjunct Professor of Computer Sciences, was recently elected to the American Philosophical Society. Dr. Olson's original concepts and technological and experimental innovations played a central role in laying the foundations for the Human Genome Project.

Founded by Benjamin Franklin in 1743, the APS honors extraordinary accomplishments in all fields. Membership is comprised of over 900 top scholars from Biological Sciences, Mathematics & Physical Sciences, Social Sciences, Humanities, and the Arts.

New Proteomics Center

The Washington State Legislature this year established an annual allocation of funds to the University to support a Proteomics Research Center, which will be administered by Genome Sciences and located at the new South Lake Union research campus. We are currently involved in recruiting two new faculty to occupy the 7000 sq. ft. space. Future plans call for further appointments, possibly in collaborating departments, as the Center expands into new space still on the drawing board.

Proteomics is the study of how proteins regulate activity throughout the body, such as muscle contraction, oxygen transport, and electron transport. Profiling the protein composition of cells and fluids like blood and cerebrospinal fluid will provide critical insights into prevention, diagnosis, and treatment of disease.

Focused proteomics studies through a center will combine interdisciplinary skills of biologists, computer scientists, and biochemists to identify the unique composition of specific proteins. Proteomics represents a major integration of life science research and informatics.

The discoveries the Center investigators make will lead initially to an increasingly sophisticated understanding of the way proteins carry out the tasks assigned them. This understanding will in turn lead to new possibilities in diagnosis, therapy, and monitoring therapy. Cancer diagnosis in the future will have proteomic analysis at its core for initial detection, for distinguishing subtle differences in cancer type and in evaluating therapy and progression of disease. We can expect a similar impact on infectious diseases and endocrine and metabolic imbalances such as diabetes. A deeper understanding of the biology associated with any disease will reveal potential drug targets and new modes of therapy.

Braun to Head Reproductive Research Center

Dr. Bob Braun has assumed leadership of the University of Washington's Specialized Cooperative Centers Program in Reproductive Research. The Center, funded by NICHD, is a multidisciplinary and cooperative effort among reproductive biologists and physician-scientists at the University of Washington. The Center has been in existence since 1979 and has a current direct budget of $1,300,000 per year. Dr. William Bremner, Chair of the Department of Medicine, is Co-Director of the Center. Other Center investigators include Drs. Bertil Hille, Professor of Physiology and Biophysics, Stanley McKnight, Professor of Pharmacology, and Robert Steiner, Professor of Physiology and Biophysics and Obstetrics and Gynecology.

The Center's research embraces both basic and clinical investigations relevant to reproductive medicine, infertility, and contraceptive development. Dr. Braun is also Co-Director of the University of Washington's Cooperative Center for Contraceptive Development. This Center, also funded by NICHD, has a current direct yearly budget of $1,500,000 and has been in existence since 2002. Other Center investigators include Drs. William Bremner, Co-Director of the Center, Joe Beavo, Professor of Pharmacology, and Michael Griswold, Dean of the College of Sciences at Washington State University and Professor of Biochemistry and Biophysics. The Center's goals are the development of a male contraceptive.

Motulsky & Gartler Birthday Celebration

A celebration was held on August 3, 2003, to honor Drs. Stanley Gartler and Arno Motulsky on the occasion of their 80th birthdays.

Drs. Gartler and Motulsky have created impressive legacies that have had far reaching effects in medicine and science. The celebration was a unique opportunity to honor their lifetimes of contributions.

In addition to the honorees, speakers included George Stamatoyannopoulos, M.D., Dr. Sci.; Paul Ramsey, M.D.; William Bremner, M.D., Ph.D.; Eloise Giblett, M.D.; Leland Hartwell, Ph.D.; Joseph Goldstein, M.D.; Gilbert Omenn, M.D., Ph.D.; R. Michael Liskay, Ph.D.; Phillip Chance, M.D.; Mary-Claire King, Ph.D.; and Stan Fields, Ph.D.

Stan Gartler

Arno Motulsky

Genome Training Grant Symposium: Genome Evolution

The first Genome Training Grant symposium was held at the University of Washington on April 5, 2005. Organized by doctoral students Laura Flinn and Joanna Kelley with assistance from other Genome Training Grant trainees, the theme was "Genome Evolution" and featured these speakers:

Dr. Hugh Robertson, University of Illinois
"Mode and tempo of gene loss in insects—is *Drosophila* unusual?"

Dr. Gary Litman, University of South Florida
"Reconstructing immune phylogeny: new bridges between innate and adaptive immunity"

Dr. Andrew Clark, Cornell University
"Inferring targets of natural selection from human-chimp comparative genomics"

Department Retreat Highlights

The Genome Sciences retreat, held just before the start of Autumn Quarter each year, provides an opportunity for faculty, students, and lab staff to learn more about the latest research developments in departmental labs. It also provides an introduction to the department for new Genome Sciences students and interested incoming students from the Molecular & Cellular Biology and Medical Scientist Training programs.

Highlights from the 2004 retreat included the joint session with UW Biochemistry, "New Technologies for the 21st Century," and the keynote address by Dr. Lee Silver, Professor of Molecular Biology and Public Affairs at Princeton University, "Biotechnology in a Spiritual World: Engagement between Science and Society." Graduate student Nathan Clark won the Alan Wade Parker travel award for best poster, which he used to attend the 2005 Biology of Genomes conference at Cold Spring Harbor Laboratories.

Highlights from the 2003 retreat included the keynote address by Dr. Gregory A. Petsko, Professor of Biochemistry and Chemistry at Brandeis University, "Structural Biology and Functional Genomics: A Marriage Made in Heaven, or in the Other Place?" Graduate students Jennifer Eklund and Ilona Holcomb won the Alan Wade Parker travel award for best poster.

Notes from the Chair continued from page 2

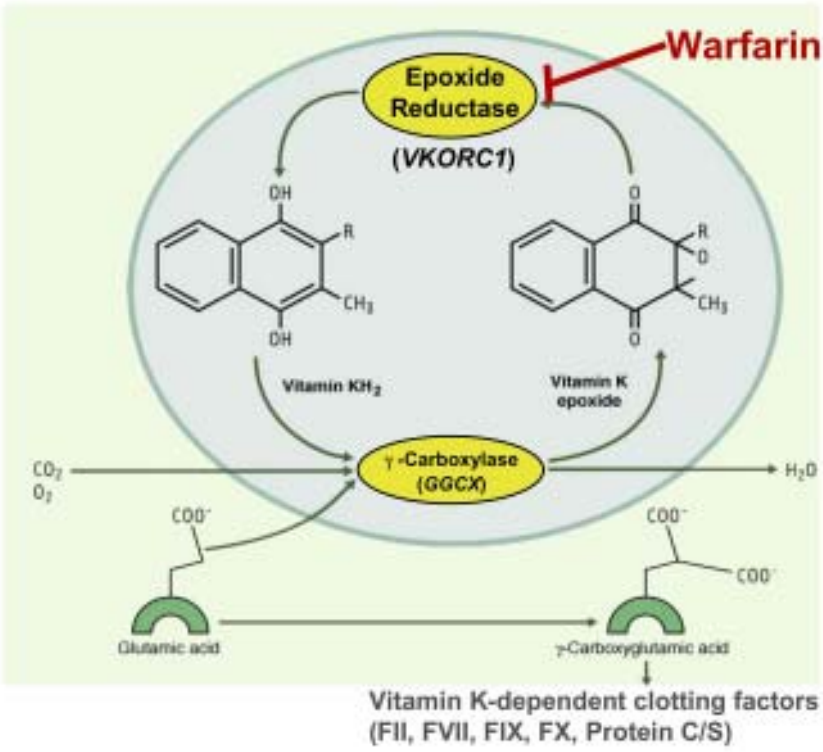
The current faculty continue to do outstanding work in both research and teaching. Perhaps you heard Mark Rieder describing his work on the role of the Vitamin K receptor in warfarin therapy on NPR a while ago. Stan Fields and Phil Green continue to be funded as Howard Hughes Medical Institute Investigators, and this fall Evan Eichler will join their ranks. Sam Miller and Bob Braun have taken on leadership of large research centers. And as you see elsewhere in this publication, awards accumulate for department members in all areas!

The Department has benefited greatly from outstanding financial gifts as well. Ben and Margaret Hall are providing an endowment for graduate students; IBM donated 25 nodes toward our growing computing capacity. AMGEN gave two gifts in support of our outreach program to area science teachers and underrepresented minorities.

So as you can tell, the Department is thriving and actively engaged in exciting work. Our thanks to all who have provided encouragement and support in the past, and we hope to see you in our new facilities sometime soon!

Identification of Genetic Variants Predictive for Warfarin Dosing

As reported in the *New England Journal of Medicine,* Vol **352**, pp 2285 – 2293 (2005), work carried out by SeattleSNPs, part of the National Heart Lung and Blood Institute's Programs for Genomic Applications, showed an association between single nucleotide polymorphisms (SNPs) in the gene VKORC1 (vitamin K epoxide reductase complex 1) and warfarin dose in clinical patients. Warfarin is the most commonly used oral anticoagulant, but it is difficult to manage. Dr. Mark Rieder in Genome Sciences and Dr. Allan Rettie in Medicinal Chemistry collaborated on this study using warfarin patient data that Dr. Rettie had collected for several years. The drug acts on the VKORC1 protein to inhibit the activation of vitamin K as a cofactor for several clotting factors. VKORC1 was an excellent candidate gene for the study of single SNPs in clinical patients on standard warfarin therapy. Even though no SNPs were identified that alter the protein coding of the gene, Rieder and colleagues could characterize the correlation between SNP sites and the haplotype structure. In these patients, and in a larger replication population at Washington University, they discovered a significant haplotype-warfarin dose association that allowed them to classify each patient into a low, intermediate or high dose group. This effect was found to explain a large portion (approximately 25%) of the variance in warfarin dose among all the patients. The mechanism of this SNP-dose correlation was due to the regulation of the gene at the mRNA level, presumably because the SNPs alter transcription factor binding sites. In addition, this study demonstrated that differences in the frequency of haplotypes in both Asian and African populations may account for inter-ethnic variability in warfarin dosing. These results may help doctors to establish a proper dose of warfarin for their patients.



Spontaneous Ribosome Bypassing in Growing Cells

Translating ribosomes can "bypass" a stretch of messenger RNA without translating it. The ribosome::peptidyl-tRNA stops elongating its peptide at a "takeoff" triplet, moves further along the message without translating until it arrives at a "landing site" triplet synonymous with the takeoff triplet, then resumes peptide chain elongation after the landing site. This bit of ribosome gymnastics was originally observed, by a group at the University of Utah, only at a very specialized site in gene 60 of bacteriophage T4, and it was subject to elaborate sequence rules. Subsequently, the Gallant lab found that bypassing could be stimulated artifically in *E. coli* cells on a variety of seemingly ordinary sequences. The artificial stimulus used was limitation for aminoacyl-tRNA so as to stall the ribosome at a "hungry codon" immediately following a takeoff site. Stalling at several different hungry codons had this effect, stimulating bypassing from virtually any takeoff triplet immediately upstream. The different takeoff triplets differed widely in this reponse.

In *The Journal of Molecular Biology,* Vol **349**, pp 261-272 (2005), Gallant and colleagues analyze the same phenomenon in normal, growing cells that were not subjected to aminoacyl-tRNA limitation. With the two takeoff triplets that showed the highest activity, they could use direct sequencing of the protein product to show that bypassing had occurred. With the other takeoff triplets, which yielded lower activities, indirect evidence pointed to the same conclu-

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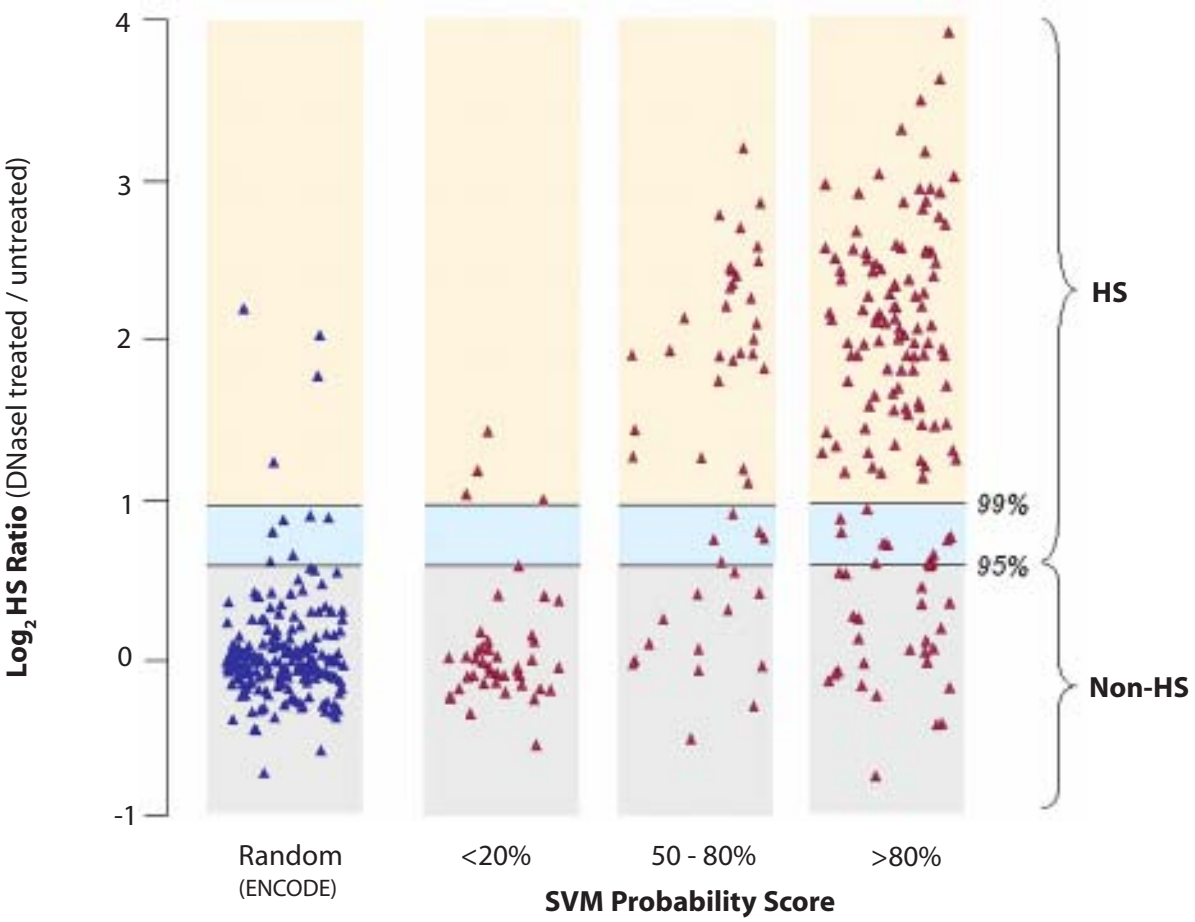
Computational Prediction of DNaseI Hypersensitive Sites

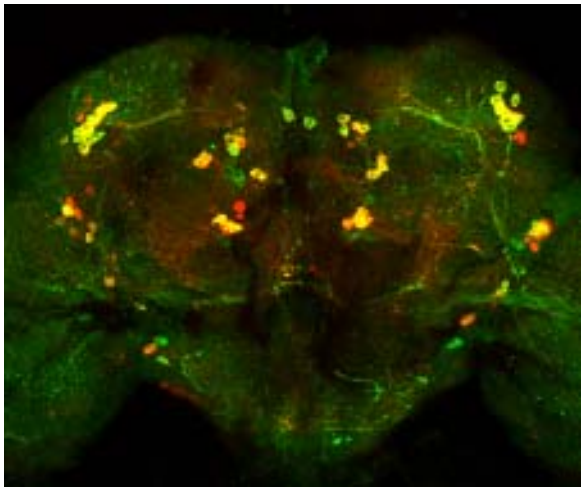
In the living cell nucleus, genomic DNA is packaged into chromatin. DNA sequences that regulate transcription and other chromosomal processes are associated with local disruptions, or "openings," in chromatin structure caused by the cooperative action of regulatory proteins. Such perturbations are extremely specific for regulatory elements found near genes and occur over short stretches of DNA (typically approximately 250 base pairs). They can be detected *in vivo* by experiments that identify DNA sites as hypersensitive to the enzyme DNaseI, although this process is extremely laborious and costly. The ability to discriminate DNaseI hypersensitive sites computationally would have a major impact on the annotation and utilization of the human genome. This computational challenge was successfully met by work from William Stafford Noble's group, in collaboration with John Stamatoyannopoulos of the Seattle-based biotechnology company Regulome, and published in *Bioinformatics* Vol **21**(Supplement 1), pp i338-i343 (2005). They found that a supervised pattern recognition algorithm, trained using a set of 280 DNaseI hypersensitive sites and 737 non-hypersensitive sites, was capable of *de novo* prediction of hypersensitive sites across the human genome with surprisingly high accuracy determined by prospective *in vivo* validation. Systematic application of this computational approach will greatly facilitate discovery and analysis of functional non-coding elements in the human and other complex genomes.



DNaseI hypersensitivity testing of computational predictions. The y-axis plots the log2 of the DNaseI sensitivity ratio assayed by real-time quantitative PCR. Results from the predictions are stratified into low (<20%), intermediate (50–80%), and high (>80%) probability groups. Results are classified as non-hypersensitive (gray shaded boxes) or hypersensitive [blue (95% confidence) and orange (99% confidence) shaded boxes] on the basis of quantitative DNaseI hypersensitivity measurements obtained with real-time PCR.

Fly Model of Parkinson's Disease

Parkinson's Disease (PD) is a common neurodegenerative disorder characterized by the loss of dopaminergic neurons in the midbrain. The molecular mechanisms responsible for PD pathogenesis are poorly understood, and there are currently no effective preventative treatments for this disorder. Leo Pallanck's laboratory has been using the fruit fly *Drosophila melanogaster* to study the functions of genes that have been implicated in heritable forms of PD in the hope that this knowledge will provide insight into the mechanisms of neuron death in PD and, ultimately, treatments for this disorder. Recent work published in the *Proceedings of the National Academy of Sciences U.S.A.,* Vol **102,** pp 8024-8029 (2005) focused on the *parkin* gene, mutations of which are a major cause of early onset parkinsonism. Analyzing mutations generated in a *Drosophila parkin* ortholog, they found that *Drosophila parkin* mutants display degeneration of a subset of dopaminergic (DA) neurons in the brain. The neurodegenerative phenotype of *parkin* mutants is enhanced by loss-of-function mutations of the *glutathione S-transferase S1* (*GstS1*) gene which were identified in an unbiased genetic screen for mutations that modify *parkin* phenotypes. Furthermore, overexpression of *GstS1* in DA neurons suppresses neurodegeneration in *parkin* mutants. Given that GstS1 is thought to be protective against the effects of oxidative stress and that altered glutathione metabolism and oxidative stress are features of PD, these data suggest that the mechanism of DA neuron loss in *Drosophila parkin* mutants is similar to the mechanisms underlying neuron death in PD. Because there are many compounds that are known to induce glutathione S-transferase activity in mammals, these findings identify a potential therapeutic approach in treating PD. More recent unpublished work from the Pallanck laboratory indicates that GstS1 induction also protects another distinct fly genetic model of PD from dopamine neuron loss. This finding further reinforces the conclusion that GstS1 induction may be a valuable preventative treatment for PD.



An adult Drosophila brain stained to reveal dopamine neurons. *Neurons in red are stained with an antiserum to tyrosine hydroxylase, an enzyme specific to dopamine neurons that is involved in the production of dopamine. Neurons in green express green fluorescent protein under the direction of a tyrosine hydroxylase promoter. Dopamine neuron clusters in the upper right and left of the image degenerate in Drosophila parkin mutants.*

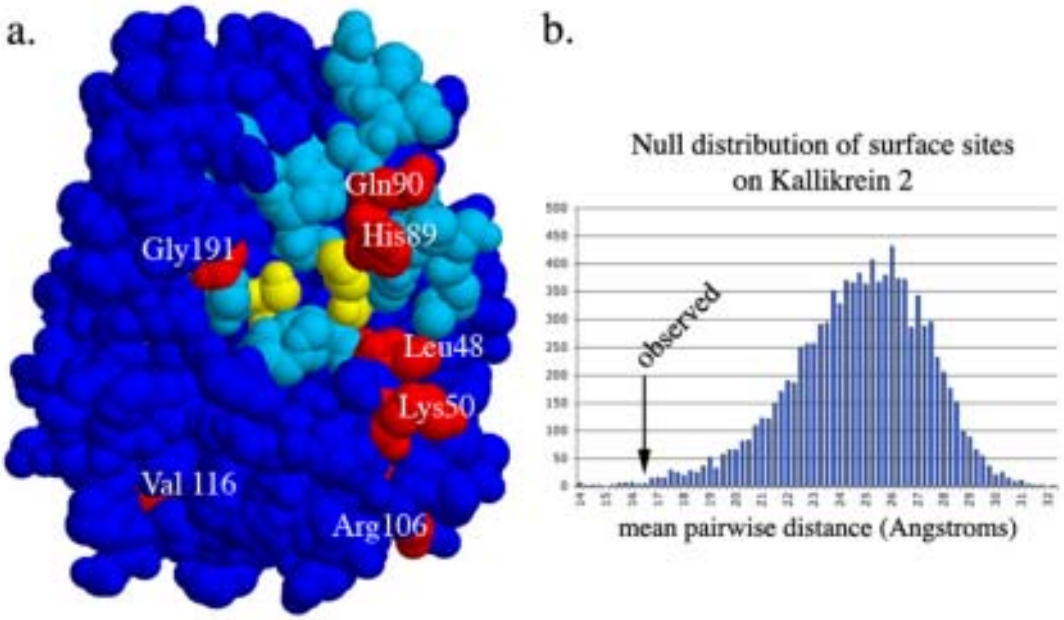
New Software Developed for Biologists

Mary Kuhner's group in Joe Felsenstein's lab has released a new version of their LAMARC software package, called LAMARC 2.0. This package is a suite of programs used by many biologists to estimate effective population sizes, population growth rates, past population migration rates, and recombination rates. In the first month since its release, there were over two hundred downloads of LAMARC 2.0. Users are applying it to study interesting problems including whale population sizes in the Pacific, flightless dung beetle populations, the genetic diversity of salmon populations, and insect/plant co-evolution. LAMARC is designed to be useful to a wide range of biological scientists. It is freely available, runs on all major operating systems, and accomodates DNA, SNP, microsatellite, and electrophoretic data. With LAMARC version 2.0, users can now perform either Bayesian or frequentist analyses, constrain parameter values to known ranges, analyze nuclear and mitochondrial data simultaneously and choose from several popular models of molecular evolution. More information and the LAMARC download can be found on the LAMARC home page at http://evolution.gs.washington.edu/lamarc.html

Fast Evolving Reproductive Proteins Identified

In a publication in press in *PLoS Genetics*, graduate student Nathan Clark and his mentor Willie Swanson have focused on the function and evolution of genes involved in reproduction. Proteins found in *Drosophila* seminal fluid accompanying sperm during reproduction show drastic effects on the mated female such as reducing her remating rate and inducing ovulation. Even in primates, these proteins participate in competition between sperm of different males and serve to protect sperm from infection by pathogens. These types of roles require the proteins to constantly adapt to stay ahead of the competition. Such adaptive pressures on proteins leave characteristic signatures in the DNA sequences that encode them. Clark and Swanson used these signatures to identify adaptive evolution in primate seminal proteins and found extensive signs of adaptation when comparing thousands of genes between human and chimpanzee that encode seminal fluid proteins. They further characterized genes showing rapid evolution between humans and chimpanzees in several additional primate species, including a diversity of apes and monkeys. Several of these proteins have no known function, yet by visualizing the sites undergoing adaptive evolution on their three-dimensional surfaces, they uncovered clues to what is driving their evolution. In addition, they found several cases in which certain species lost the functional copies of these genes. Interestingly, species that showed loss of function have mating systems in which little sperm competition would be expected. Their previous studies found widespread adaptation in genes encoding *Drosophila* seminal fluid proteins, and the current study reveals extensive adaptation in primate seminal proteins. Could this be a phenomenon common among animals?

i*mages courtesy of Nathan Clark*



Positive selection at sites involved in substrate binding in kallikrein 2 (KLK2).
(***a.***) *Several amino acid sites predicted to be under positive selection (red) are near the protease active site (yellow). Three selected sites are found in known structural components of kallikrein proteins (light blue residues): Residue Gly191 is part of the S1 substrate binding pocket, and residues His89 and Gln90 are part of the kallikrein loop (Laxmikanthan et al. 2005). Selected sites are labeled with the human residue on this threaded model.*
(***b.***) ***Positively selected sites are significantly clustered on the surface of KLK2***. *The observed mean pairwise distance between predicted positively selected sites is significantly lower than random sets of surface sites (P= 0.0043). This spatial clustering suggests that positive selection acted during KLK2 evolution to alter substrate binding.*

Research Highlights

Mathematical Analysis of Natural Mutation

Phil Green and graduate student Dick Hwang have developed a new mathematical approach to analyze the patterns of natural mutations in DNA, described in the *Proc. Natl. Acad. Sci. U.S.A.,* Vol **101**, pp13994-4001 (2004). Although mutations are the major drivers of evolution and genetic disease, little is known about their causes. Hwang and Green studied neutral DNA sequences, which are regions of the genome that lack genes or other important elements. Their approach, called "Bayesian Markov chain Monte Carlo sequence analysis," is a probabilistic method for distinguishing models of mutational mechanisms. An advantage of this approach is that it allowed them to take into account context effects, whereby flanking nucleotides influence the nature and rate of mutations. They analyzed a 1.7 million base pair segment, from 19 different mammals, that includes the gene whose mutation results in cystic fibrosis, although they examined only DNA sequences that did not encode genes. Hwang and Green found that in contrast to other substitution types, CpG transition substitutions have accumulated in a relatively clock-like fashion. More broadly, their results support the notion that context-dependent DNA replication errors, cytosine deamination, and biased gene conversion are major sources of naturally occurring mutations whose relative contributions have varied in mammalian evolution as a result of changes in generation times, effective population sizes, and recombination rates.

Spontaneous Ribosome Bypassing in Growing Cells continued from page 8

sion. They also made a library with a variety of triplets immediately following the takeoff site. The activity of these constructs varied inversely with the abundance of the tRNA encoded at this position, suggesting that the normal dwell-time affects bypassing in the same way as the artificially prolonged dwell time at a hungry codon. The overall implication of these results is that bypassing is a natural process that may occur, albeit at low frequencies, on many different messengers. This mechanism could permit individual messengers to generate multiple, related isoforms of their protein products, thus adding to the complexity of the proteome.

The paper, by Lindsley, Gallant, Doneanu, Bonthuis, Caldwell, and Fontalera, included results of Genome Science 499 projects by students Seth Caldwell and Ashley Fontalera. Mass spectrometry was carried out by Catalin Doneanu of the Department of Medicinal Chemistry mass spec center.

Postdoctoral Fellows Highlights

Crawford Wins Cotterman Award

Dr. Dana Crawford won the C. W. Cotterman award for the best paper published in The American Journal of Human Genetics during the previous year on which the first author was either a pre- or postdoctoral trainee. Dr. Crawford, a postdoctoral fellow in the Nickerson Lab, received the award at last year's American Society of Human Genetics conference in Toronto.

Sharp, She Awarded Rosetta Fellowships

Dr. Andrew Sharp and Dr. Xinwei She of the Eichler Lab have each been awarded Rosetta Inpharmatics Fellowships in Molecular Profiling. The fellowships, funded by Merck Research Laboratories, provide $45,000 in funding for one year beginning September 2005.

Dr. Sharp has also given several recent conference presentations, including the May 2005 Biology of Genomes conference, Cold Spring Harbor Labs ("Segmental duplications and copy number variation in the human genome assessed by array comparative genomic hybridization") and the October 2004 American Society of Human Genetics conference in Toronto ("X/autosome translocations: Spreading of silencing and implications for outcome").

Outreach

Genome Sciences Education Outreach

The Genome Sciences Education Outreach group, founded in 1993, was originally part of the Department of Molecular Biotechnology. Housed in both Genome Sciences and the UW Genome Center, the outreach group develops innovative programs that bring leading-edge science to teachers and students in K-12 schools. These programs provide interdisciplinary, hands-on science curricula, teacher training, equipment, and support to promote excellence in K-12 science education. Staff members include Maureen Munn, Ph.D., Megan Brown, Ph.D., and Kristi Martinez. The Outreach Group is funded by national agencies, including the National Institute on Drug Abuse and the Department of Energy; private foundations including the Howard Hughes Medical Institute and the Amgen Foundation; and private donations.

The StarNet Project (and its predecessor, the High School Human Genome Program) provides opportunities for high school students and their teachers to participate in authentic research. Past participants sequenced genes implicated in an autosomal deafness disorder (Drs. Mary-Claire King and Eric Lynch) and in nicotine addiction (Dr. Carl Ton). Our latest research project, which will be carried out by teachers, students, and outreach scientists, is a multi-year case control study investigating the association of genetic and environmental factors with smoking behavior. Scientists, ethicists, and teachers provide guidance in project design and implementation, particularly project PIs Maynard Olson, Debbie Nickerson, and Gail Jarvik.

Other past and current projects include the GENETICS Project (PI: Maynard Olson), which focused on teaching basic genetic concepts in grades 4-12; the Genomics Teacher Workshop (PI: Robert Waterston), professional development and preparation for attending *DNA, Health, and Social Justice: A Community Forum on Genetics*; and Bringing Biotechnology to King County Teachers (PI: Robert Waterston), a teacher education program that will support the integration of biotechnology and bioinformatics into our local high schools.

The outreach group also collaborates with department faculty and other UW programs on their outreach efforts. For more information, please visit our web site at http://chroma.gs.washington.edu/outreach.

Science Education Partnership

More than two dozen science teachers from Washington – and two all the way from Singapore – are spending part of their vacation at "summer school". The Science Education Partnership is a professional development program for teachers offered by the Fred Hutchinson Cancer Research Center and partner institutions, including UW Genome Sciences, providing teachers the opportunity to work beside scientists in research laboratories at sites throughout Seattle. The summer workshop, which runs through July 27, will host teachers from more than two dozen communities throughout the state and abroad. Genome Sciences' contributions to this program are coordinated by Dr. Carol Sibley and graduate student Tobias Mann.

Participating institutions this year include the Fred Hutchinson Cancer Research Center, UW Genome Sciences, the corporate biotechnology firms Amgen and Zymogenetics, the Pacific Northwest Research Institute, the Seattle Biomedical Research Institute, and the joint UW/Hutchinson Center Molecular and Cellular Biology doctoral research program.

After a jumpstart session to learn laboratory basics, the teachers will spend about half of their time working one-on-one with a scientist-mentor in a research laboratory on projects tailored to their interests. Lab work over the past several years has focused on such topics as protein structure, DNA sequencing, oncogenes, yeast genetics, and fruit-fly development. This mentorship often leads to lasting partnerships that extend beyond the summer session to include classroom visits by scientists during the school year. For more information, please see the SEP website: http://www.fhcrc.org/science/education/educators/sep/

Graduate Student News

Congratulations to 2004-2005 graduates!

Michael Babcock (Ph.D. in Genetics)
"Forward and Reverse Genetic Approaches to Studying Synaptic Transmission in *Drosophila melanogaster*."

Michael Bonham (Ph.D. in Molecular Biotechnology)
"Identification of tumor cell growth inhibitory compounds within the herbal extract PC-SPES"

Jennifer Eklund (Ph.D. in Genetics)
" Design and characterization of homing endonuclease I-*Ppo*I variants with novel DNA sequence specificity"

Michele Hastings (Ph.D. in Genetics)
"Analysis of Dihydrofolate Reductase Variations in Relation to Antifolate Resistance in *Plasmodium vivax*"

Dick Hwang (Ph.D. in Molecular Biotechnology)
"Bayesian Markov Chain Monte Carlo Phylogenetic Analysis of Mammalian Evolution Reveals Varying Substitution Patterns Along the Sequence and Across Lineages"

Mara Jeffress (Ph.D. in Molecular & Cellular Biology)
"Identification of Putative *Plasmodium falciparum* Mefloquine Resistance Genes"

Heather McCune (Ph.D. in Genetics)
"Microarray-Based Analysis of DNA Replication Dynamics in Saccharomyces cerevisiae lacking the B-type cyclin CLB5"

Josh McElwee (Ph.D. in Molecular & Cellular Biology)
"A comparative analysis of transcriptional alterations in long-lived insulin/IGF-1-like signaling mutants in *Caenorhabditis elegans* and *Drosophila melanogaster*."

John Miller (Ph.D. in Genetics)
"Interactions Among Integral Membrane Proteins of Yeast"

Tera Newman (Ph.D. in Molecular Biotechnology)
"Complex Evolution of the 7E Olfactory Receptor Genes and 7E Segmental Duplications"

Max Robinson (Ph.D. in Molecular Biotechnology)
"Splicing Signals in *Caenorhabditis elegans*: Candidate Exonic Splicing Enhancer Motifs"

Elaine Round (Ph.D. in Genetics)
"Identification and Analysis of G-Protein Pathway Control in the *Caenorhabditis elegans* defecation motor program"

Terrence Satterfield (Ph.D. in Genetics)
"Genetics and Biochemical Analysis of the *Drosophila melanogaster* Homolog of the Human SCA2 Gene

Audrey Seamons (Ph.D. in Molecular Biotechnology)
"Implications of Myelin Basic Protein Processing and Presentation on T Cell Activation and Tolerance"

James Sherman (Ph.D. in Molecular Biotechnology)
"Proteome Scale Decay Kinetic Discovery: Methodologies and Applications"

Monika Tzoneva (Ph.D. in Genetics)
"UNC-58 is an unusual member of the *C. elegans* TWIK potassium channel family"

Jessica Greene Zuniga (Ph.D. in Genetics)
"Investigation of parkin function in a *Drosophila* model of Parkinson's Disease"

Recent Conference Presentations

Nathan Clark: "Pervasive Adaptive Evolution of Primate Seminal Fluid Proteins"; Evolution 2005, University of Alaska.

Greg Finney: "Protein False Discovery Rates from MS/MS experiments : Decoy Databases and Normalized Cross-Correlation"; 53rd ASMS Conference on Mass Spectrometry.

Joanna Kelley: "A genome-wide scan for signatures of adaptive evolution using SNP data"; Biology of Genomes, Cold Spring Harbor Laboratory.

Aaron Klammer: "Peptide charge state determination for low-resolution tandem mass spectra"; 53rd ASMS Conference on Mass Spectrometry.

Tobias Mann: "Automated validation of polymerase chain reactions using amplicon melting curves"; IEEE Computational Systems Bioinformatics conference and Conference on Intelligent Systems for Molecular Biology, Stanford University.

Chris Saunders: "Maximum likelihood phylogenetic estimation of selection on amino acid substitution and context-dependent mutation in protein coding sequence"; Penn State Summer Symposium in Molecular Biology: Comparative and Functional Genomics.

Selected Publications

Analysis of xbx genes in C. Elegans. Efimenko E, **Bubb K**, et al. *Development* **132**:1923-34 (2005).

High Genetic Diversity in the Chemoreceptor Superfamily of Caenorhabditis elegans. Stewart MK, **Clark NL**, et al. *Genetics* **169**:1985-96 (2005).

Differential Regulation of KiSS-1 mRNA Expression by Sex Steroids in the Brain of the Male Mouse. Smith JT, Dungan HM, Stoll EA, Gottsch ML, Braun RE, **Eacker SM**, et al. *Endocrinology* **146**: 2976-84 (2005).

Array comparative genomic hybridization analysis of genomic alterations in breast cancer subtypes. Loo LW, Grove DI, Williams EM, Neal CL, Cousens LA, Schubert EL, **Holcomb IN**, et al. *Cancer Res*. **64**: 8541-9 (2004).

Lineage-specific expansions of retroviral insertions within the genomes of African great apes but not humans and orangutans. Yohn CT, **Jiang Z**, et al. *PLoS Biol.* **3**: e110 (2005).

Adaptive evolution in the SRZ chemoreceptor families of Caenorhabditis elegans and Caenorhabditis briggsae. Thomas JH, **Kelley JL**, et al. *Proc. Natl .Acad. Sci. U.S.A.***102**: 4476-81 (2005).

Genetic structure of the purebread domestic dog. Parker HG, **Kim LV**, et al. *Science* **304**: 1160-4 (2004).

Increased measurement accuracy for sequence-verified microarray probes.
Mecham BH, Wetmore DZ, Szallasi Z, Sadovsky Y, Kohane I, Mariani TJ. *Physiol. Genomics* **18**: 308-15 (2004).

Redefinition of Affymetrix probe sets by sequence overlap with cDNA microarray probes reduces cross-platform inconsistencies in cancer-associated gene expression measurements. Carter SL, Eklund AC, **Mecham BH**, et al. *BMC Bioinformatics* **6**: 107 (2005).

Simultaneous genotyping, gene-expression measurement, and detection of allele-specific expression with oligonucleotide arrays. **Ronald J**, Akey JM, et al. *Genome Res*. **15**: 284-91 (2005).

Recapitulation of protein family divergence using flexible backbone protein design. **Saunders CT**, Baker D. *J. Mol. Biol*. **346**: 631-44 (2005).

Evidence for diversifying selection at the pyoverdine locus of Pseudomonas aeruginosa. **Smith EE**, Sims EH, **Spencer DH**, et al. *J. Bacteriol*. **187**: 2138-47 (2005).

2004 Incoming Class

Carlos Araya, Washington State University
Divya Bhat, Massachusetts Institute of Technology
Shameek Biswas, Columbia University
Jonathan Bleyhl, UW Applied Math
Ross Centers, University of California, Santa Cruz
Michael Hoopmann, College of New Jersey
Zhaoshi Jiang, Case Western Reserve University
Brigham Mecham, Washington University
Angela Poole, California Institute of Technology
James Ronald, UW Medical Scientist Training Program
William Sheffler, Brown University
Benjamin Smith, University of Southern Maine
David Spencer, UW Medical Scientist Training Program

2005 Incoming Class

Max Boeck, Reed College
Diane Dickel, University of Chicago
Geoffrey Findlay, Carleton College
Marianna Ivanov, University of California, Berkeley
Jeffrey Kidd, Case Western Reserve University
Kristen Lewis, Virginia Commonwealth University
Graham McVicker, University of British Columbia
Richard Meraz, California State University, Long Beach
Thomas Nicholas, University of Utah
Matthew Sandel, UW Medical Scientist Training Program
Rorianne Rohlfs, Carnegie-Mellon University
James Thompson, Rochester Institute of Technology
Troy Zerr, University of Washington

Comparative Genomic Analysis

The 2005 Symposium, "Comparative Genomic Analysis", held May 18 at the University of Washington, featured these speakers and topics:

Dr. Russell Doolittle, UC San Diego
"The Tree of Life Remains Mysterious"

Dr. Kenneth Wolfe, University of Dublin
"Comparative Genomics and Genome Evolution in Yeasts"

Dr. Wen-Hsiung Li, University of Chicago,
"Determinants of Gene Duplicability"

Dr. Joachim Messing, Rutgers, The State University of New Jersey
"Analysis of Polyploidization and Hybrid Vigor in Maize by Comparative Genomics"

Dr. David Kingsley, HHMI and Stanford University
"Fishing for the Secrets of Vertebrate Evolution"

Dr. Molly Przeworski, Brown University
"Insights into Recombination from Patterns of Genetic Variation in Humans and Chimpanzees"

Dr. Richard Durbin, The Wellcome Trust Sanger Institute
"Finding all the Genes in all the Genomes"

The Future of Human and Medical Genetics

The 2004 Symposium, "The Future of Human and Medical Genetics", was held May 19 at the University of Washington and honored the contributions of Dr. Arno Motulsky with the following speakers and topics:

Dr. Joseph Goldstein, University of Texas Southwestern Medical Center
"A Century of Research in Atherosclerosis: From the Cholesterol-Fed Rabbit to the Statin-Treated Patient"

Dr. Ernest Beutler, Scripps Research Institute
"Phenotypic Variability of Single Gene Disorders: G6PD Deficiency, Gaucher Disease and Hemochromatosis"

Dr. Jeremy Nathans, Johns Hopkins University
"Visual Pigments and the Evolution of Primate Color Vision"

Dr. Sarah Tishkoff, University of Maryland
"Genetic Diversity in Africa: Implications for Human Origins and Evolution of Malarial Resistance and Color Vision"

Dr. David Weatherall, University of Oxford
"Genomics and Global Health"

Dr. Neil Risch, Stanford University
"Genetics of Complex Diseases"

Dr. Charles Epstein, UC San Francisco
"The Future of Human and Medical Genetics in the World of Genomic Medicine"

Coming May 24, 2006: The fifth annual Genome Sciences Symposium
"What have we learned from model organisms -- yeast, worms, flies?"