



LIFE SCIENCES DIVISION E-NEWSLETTER

May/June, 2009

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DOE scientific focus area notes

Low Dose Radiation Research

New Low Dose Project Funded

The DOE Low Dose Program will fund a new 3-year proposal entitled “Non-Invasive Early Detection and Molecular Analysis of Low X-ray Dose Effects in the Lens”. The principal investigator is Lee Goldstein, M.D., Ph.D., Associate Professor in Psychiatry, Neurology, Ophthalmology, Pathology and Laboratory Medicine, & Biomedical Engineering in Boston University’s School Medicine, College of Engineering, and Photonics Center. The project includes a new DOE FWP (~ \$400 K over 3 years) to Berkeley Lab with **Eleanor Blakely** as Project Leader. The work includes a subcontract to support the collaboration of Polly Chang of SRI, International, Menlo Park, CA and is scheduled to begin as early as August 2009.

This proposal was submitted in response to the joint DOE/NASA Research Announcement DE-PS02-08ER08-20 soliciting applications from Universities for new research to develop a better scientific basis for understanding health risks to humans from exposures to low doses or low fluences of ionizing radiation.

The goal of the project is to test the hypothesis that exposure to low dose ionizing radiation induces dose- and time dependent changes in the molecular organization of the lens that can be quantitatively detected and tracked by infrared quasi-elastic light scattering (OLS) technology. A novel non-invasive molecular biodosimetry instrument will be used as a rapid, sensitive tool for quantitative assessment of low dose exposures. The studies will be conducted longitudinally in mice irradiated at different ages with a range of acute gamma radiation doses. Serial OLS analyses will be evaluated for each mouse as a function of dose, post-exposure interval, and age. At the end of the study, lens tissues will be harvested, phenotyped by *ex vivo* stereophotomicroscopy, and undergo comprehensive molecular evaluation to identify candidate genes that are persistently and differentially expressed following radiation exposure. The study will allow a detailed clinicopathological analysis of pre-cataractous molecular changes in the lens and mapping of the natural history and molecular pathology following radiation exposure, with a baseline prior to, during, and after the onset of frank opacification. This work will contribute new data regarding basic radiobiology and potential health risks of low doses of radiation, and will provide important pre-clinical assessment of the potential use of this laser-based non-invasive technology for assessment of low dose exposures in humans. These studies will also complement ongoing NASA-funded research by Goldstein, Blakely and Chang establishing databases for additional comparative and cross-correlational analysis of quantitative measurements obtained with a range of radiation types and qualities, as encountered in space travel.

Eleanor Blakely, 6/09



GTL-Genomics

MAGGIE's Collaboration with the Institute for Systems Biology's Baliga Lab

Interaction with the environment is central to how information within DNA of an organism is decoded into observable phenotypes. Once delineated, the engineering principles governing environment-specified assembly of biological systems will help unlock potentials within diverse organisms. By responsibly using this information it will be possible to power spectacular solutions for problems in environment and medicine. Working with researchers at Berkeley Lab's GTL program **MAGGIE**, the

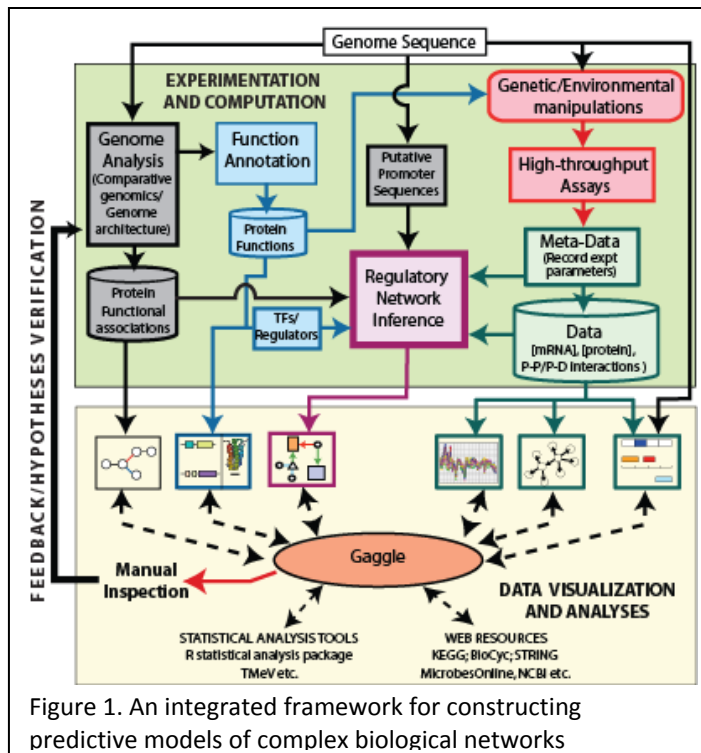


Figure 1. An integrated framework for constructing predictive models of complex biological networks

Baliga lab at the Institute for Systems Biology has developed an integrated multidisciplinary approach to decipher the process by which gene regulatory networks assemble through interactions among constituent parts (genes, RNAs, proteins, and metabolites) and external environmental factors (Figure 1).

In the last three years they have developed algorithms for data-driven discovery of conditionally co-regulated genes [Reiss, D. J., N. S. Baliga & R. Bonneau, (2006) Integrated biclustering of heterogeneous genome-wide datasets for the inference of global regulatory networks. *BMC Bioinformatics* 7: 280] and their associated regulatory sub-circuits [Bonneau, R., D. J. Reiss, P. Shannon, M. Facciotti, L. Hood, N. S. Baliga & V. Thorsson, (2006) The Inferelator: an algorithm for learning parsimonious regulatory networks from systems-biology

data sets de novo. *Genome Biology* 7: R36]. They have applied this approach to a wide array of measurements of stress-induced molecular changes including mRNA levels, protein levels, and interactions among protein. This has resulted in a model that can predict how 80% of all genes in *Halobacterium salinarum* NRC-1 are transcriptionally modulated in new and untested environmental conditions [Bonneau, R., M. T. Facciotti, D. J. Reiss, A. K. Schmid, M. Pan, A. Kaur, V. Thorsson, P. Shannon, M. H. Johnson, J. C. Bare, W. Longabaugh, M. Vuthoori, K. Whitehead, A. Madar, L. Suzuki, T. Mori, D. E. Chang, J. Diruggiero, C. H. Johnson, L. Hood & N. S. Baliga, (2007) A predictive model for transcriptional control of physiology in a free living cell. *Cell* 131: 1354-1365]. Analysis of this model and its predictive power has shed important insight into how biological circuits evolve and why these underlying principles of evolution make it possible to construct predictive models for these networks [Baliga, N. S., (2008) The scale of prediction. *Science* 320: 1297-1298].

In keeping with their mission, the Baliga Lab is working closely with researchers at Berkeley Lab and other collaborating institutions to apply this powerful methodology to other organisms including *Pyrococcus furiosus* and *Sulfolobus solfataricus*. Simultaneously, they are also developing new algorithms and technologies to make these models increasingly accurate so they can be precisely re-engineered for new desirable properties [Koide, T., W. Lee Pang & N. S. Baliga, (2009) The role of predictive modelling in rationally re-engineering biological systems. *Nat Rev Micro* 7: 297-305]. For instance, they have made a remarkable discovery that a significant fraction of transcriptional regulatory logic (i.e. promoters) are contained within protein coding sequences [Koide, T., Reiss, D.J., Bare, C.J., Pang, W.L. Facciotti, M.T., Schmid, A.K., Pan, M. Marzolf, B., Van, P.T. Lo, F.Y., Pratap, A., Deutsch, E.W., Peterson, A., Martin D., and Baliga, N.S. (2009); Prevalence of transcription promoters within archaeal operons and coding sequences. *Molecular Systems Biology* (in press)]. This new insight has significant implication on how we model the mechanistic aspects of gene regulation.

Finally, to enable the exploration of large regulatory network models and their underlying complex systems biology datasets the Baliga Lab has also developed a powerful framework (Gaggle and Firegoose) for rapid integration of software, algorithms and databases. Importantly, this framework enables integration across tools that are on a user's desktop or located remotely (via the internet) including tools written in a wide set of programming languages by diverse groups [Bare, J. C., P. T. Shannon, A. K. Schmid & N. S. Baliga, (2007) The Firegoose: two-way integration of diverse data from different bioinformatics web resources with desktop applications. *BMC Bioinformatics* 8: 456; Shannon, P., D. J. Reiss, R. Bonneau & N. S. Baliga, (2006) Gaggle: An open-source software system for integrating bioinformatics software and data sources. *BMC Bioinformatics* 7: 176] (Figure 2).
 Nitin Baliga, 5/09

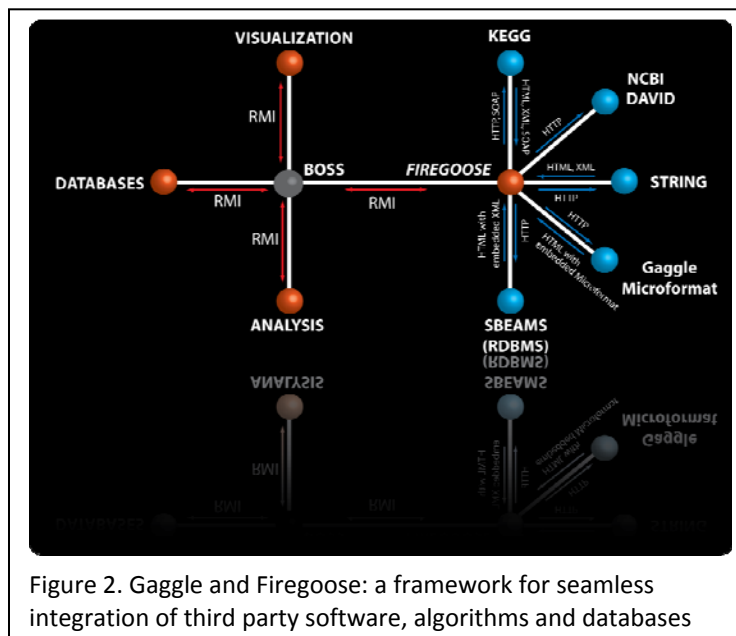


Figure 2. Gaggle and Firegoose: a framework for seamless integration of third party software, algorithms and databases

Nuclear Medicine

Research Published

Life Sciences **Anurag Chaudhry, Rostyslav Boutchko, Yetta Porter-Chapman, and Stephen Derenzo**, together with Materials Sciences Edith Bourret-Courchesne and Andrew Canning, and Niels Grønbech-Jensen of the Computational Research Division report on their research findings in the June, 2009 issue of *IEEE Transactions on Nuclear Science*.

From the authors: This work presents the results of first principles electronic structure calculations for Cerium (Ce) doped Yttrium (Y) and Lanthanum (La) oxyhalides performed using the pseudopotential

method based based on the local density approximation in the density functional theory. The relative position of the Ce 4f and 5d levels in the energy gap of the host are determined from the ground-state density of states for the Ce-doped material. Localization of the excited electron is determined from the calculations of the (Ce³⁺)*excited state. A qualitative prediction of Ce-activated scintillation is made based on these theoretical calculations. Our approach indicates that Ce-doped Y and La oxyhalides show progressively better luminescence as we move down the periodic table from oxyfluorides to oxyiodides. These families of materials have been synthesized and the experimental results agree qualitatively with our calculations.

Chaudhry A, Canning R, Boutchko Y, Porter E, Bourret-Courchesne E, Derenzo S, and Gronbeck-Jensen N. First principles calculations for scintillation in Ce-doped Y and La oxyhalides. *IEEE Transactions on Nuclear Science*, June 2009, vol. 56, No. 3, pp. 949-954

CG, 6/09

New Scintillator BaBrI:Eu Presented at Review

A quarterly Department of Homeland Security's review of the Berkeley Lab high-throughput scintillator discovery project was held in Washington, DC on April 10, 2009. The new scintillator BaBrI:Eu was presented there, which looks very promising in terms of cost, gamma-ray stopping power, and luminosity. Berkeley Lab filed a provisional patent in May, 2009. Several crystals have been grown at the Berkeley Lab crystal growth facility, and preliminary characterization will be presented by Edith Bourret-Courchesne (Materials Sciences Division) at the 10th International Conference on Inorganic Scintillators and their Applications (SCINT 2009), which will be held on Jeju island in South Korea from June 8 to 12, 2009.

At the same conference two Berkeley Lab scientists will be presenting invited talks: **Gregory Bizarri** (Life Sciences Division) on scintillator non-proportionality and Andrew Canning (Computational Research Division) on first-principles calculations for the discovery of new scintillators.

Stephen Derenzo, 5/09

Support for New Crystal Growth Facilities

Two funding agencies, DOE/NA 22 and DHS/DNDO (Domestic Nuclear Detection Office), recognize the need to accelerate the production of new detector crystals and to make them available to other researchers for evaluating their ability to detect and identify smuggled nuclear materials. New crystal growth facilities will be supported, and Berkeley Lab is in a good position to participate in this expansion.

Stephen Derenzo, 5/09

Society of Nuclear Medicine's 56th Annual Meeting

Several Life Sciences researchers of the Department of Radiotracer Development and Imaging Technology joined over 4,000 professional attendees and 200 companies at the Society of Nuclear Medicine's 56th Annual Meeting, June 13-17, 2009 in Toronto, Ontario, Canada. The Annual Meeting is the world's largest event focused exclusively on the latest developments in molecular imaging and therapy offering physicians, technologists and scientists' opportunities to earn valuable continuing

education credits, network with experts in the field, discover new technologies, and learn about the latest in medical products.

Oral presentations included: **Huang Q, Boutchko R, Reutter BW** and **Gullberg GT**. Dynamic imaging with a novel dedicated cardiac SPECT system; Huang Q, Seo Y, Boutchko R and Gullberg GT. A few planar detectors collimated by multiple pinholes for cardiac SPECT imaging; Reutter BW, Boutchko R, **Huesman RH, Hanrahan SM, Brennan KM**, Sauve AC and Gullberg GT. Quantitative dynamic SPECT imaging of the decline in fatty acid metabolism with age in the spontaneously hypertensive rat heart.

The following poster was also presented: Sauve A, Reutter BW and Gullberg GT. A Monte Carlo approach to estimating the system matrix for quantitative human cardiac SPECT.

More > <http://interactive.snm.org/index.cfm?PageID=7878&RPID=7878>

CG, 6/09

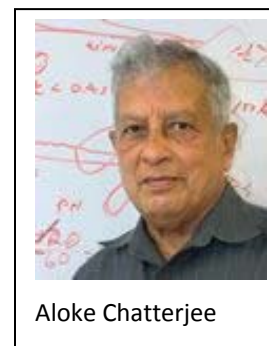
Scientific & Divisional news

In Memoriam: Alope Chatterjee (1940-2009)

Alope Chatterjee, an internationally known radiation biophysicist, former senior scientist and deputy director of the Life Sciences Division who gave this laboratory 36 years of exemplary service before retiring in 2006, passed away peacefully, surrounded by loved ones, on Saturday, June 20, 2009 at his home in Clayton, CA at the age of 68. The cause was heart failure. More >

[http://www.lbl.gov/lsc/News & Events/docs/Alope in memoriam.pdf](http://www.lbl.gov/lsc/News%20&%20Events/docs/Alope_in_memoriam.pdf)

Today at Berkeley Lab, CG, 6/24/09



Gray to Co-Lead Breast Cancer “Dream Team”

An \$16.5 million, three-year grant to develop new and more effective therapies to fight breast cancer was awarded on May 27, 2009 to a multi-institutional “Dream Team” of scientists and clinicians. **Joe Gray**, a renowned cancer researcher with Berkeley Lab, associate Lab Director, and Director of the Life Sciences Division, will co-lead the biological, genomic and computational study of breast cancer, with the goal of matching a tumor’s genetic and molecular profile with the therapy that has the best chance of treating it.

Press Release & Video > <http://newscenter.lbl.gov/press-releases/2009/05/27/breast-cancer-dream-team/>

Today at Berkeley Lab, CG, 5/27/09

New Cancer Grant Featured in KTVU Blog

KTVU’s chief science correspondent John Fowler included a post in his blog on the work of Berkeley Lab life scientist **Joe Gray**, who recently received a \$16.5 million grant for breast cancer research. “He is a quick-smiling bear of a man who started his professional life as a nuclear physicist. It was the death of his father from lung cancer that set him on the path to uncovering the mysteries of cancer cells,” writes Fowler. Go here to read the full post in the May 2009 archive section >

<http://www.ktvu.com/johnfowler/index.html>

Today at Berkeley Lab, 5/28/09

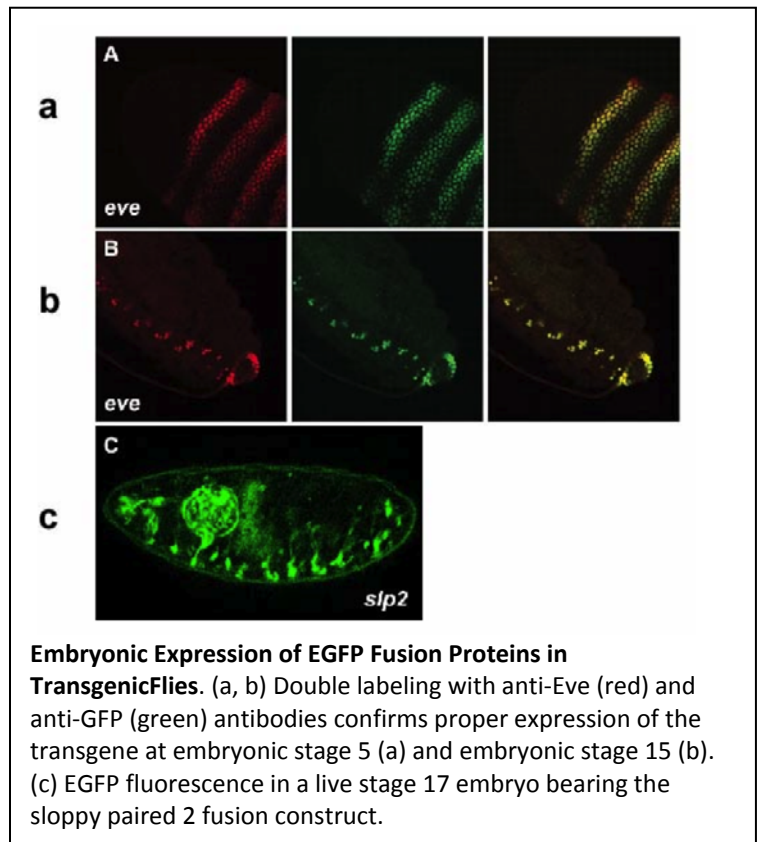
Library of Clones for Engineering the Fruit Fly's Genome Established

Using a specially adapted cloning vector called P[acman], a collaboration of researchers led by Baylor College of Medicine (BCM) and including Life Sciences **Roger Hoskins, Joseph Carlson and Kenneth Wan**, has established a library of clones that cover the genome of *Drosophila melanogaster* (fruit fly) and that will speed the pace of genetic research. In a report in the May online issue of the journal *Nature Methods*, Hugo Bellen, a professor of molecular and human genetics at BCM and a Howard Hughes Medical Institute investigator, and his colleagues describe the new libraries.

P[acman] - developed by Koen Venken in Bellen's laboratory - allows scientists to study large chunks of DNA in living flies. The vector - officially P/phiC31 artificial chromosome for manipulation - combines three different technologies: a bacterial artificial chromosome (BAC) that allows maintenance of large pieces of DNA in bacteria, recombineering that allows the manipulation of large pieces of DNA in bacteria to introduce specific mutations or tags at will, and the ability to insert the DNA into the genome of the fly at pre-determined sites using phiC31-mediated transgenesis.

Venken and Bellen adapted the P[acman] vector to create genomic libraries. Roger Hoskins and Joseph Carlson of Life Sciences, designed, mapped and annotated the genomic library. A researcher can now choose a gene in an on-line browser, find the corresponding clones in the library that covers that gene, and order them from a public repository.

"You can insert a single copy of a gene and rescue a mutation, or do a structure/function analysis of the gene," Bellen said. "If you don't know where the gene is expressed, you can tag it, put it back and locate where it is expressed."



The library is available at <http://pacmanfly.org/>; the report is available at <http://www.nature.com/nmeth/index.html> (subscribers only). Others who took part in this work include Karen L. Schulze, Hongling Pan and Yuchun He of BCM, Rebecca Spokony and Kevin P. White of the University of Chicago, and Maxim Koriabine and Pieter de Jong of Children's Hospital Oakland Research Institute in California. Funding for this work came from the Howard Hughes Medical Institute, the National Institutes of Health and the BCM Intellectual and Developmental Disabilities Research Center.

Venken KJ, Carlson JW, Schulze KL, Pan H, He Y, Spokony R, Wan KH, Koriabine M, de Jong PJ, White KP, Bellen HJ, Hoskins RA. Versatile P[acman] BAC libraries for transgenesis studies in *Drosophila melanogaster*. *Nature Methods*, 2009 May 24. [Epub ahead of print] PMID: 19465919

Abstract: We constructed *Drosophila melanogaster* bacterial artificial chromosome libraries with 21-kilobase and 83-kilobase inserts in the P[acman] system. We mapped clones representing 12-fold coverage and encompassing more than 95% of annotated genes onto the reference genome. These clones can be integrated into predetermined attP sites in the genome using PhiC31 integrase to rescue mutations. They can be modified through recombineering, for example, to incorporate protein tags and assess expression patterns.

Glenna Picton, BCM/Roger Hoskins, 6/09

World Renowned Radiation Cancer Specialist Joins Life Sciences Division

The Life Sciences Division welcomes **Mack Roach III** who joined the Cancer & DNA Damage Responses Department as a Medical Faculty Scientist per May 29, 2009. The appointment is consistent with his faculty appointment of Professor and Chair, Department of Radiation Oncology at the UCSF Hellen Diller Family Comprehensive Cancer Center. The Life Sciences Division Staff Committee unanimously



Mach Roach III

recommended the appointment, commenting that "his record of publications, presentations and grant funding attest to the breadth of his research interests and expertise and to the collaborative nature of his work. No doubt that the division and laboratory will be richer for the increased involvement in activities that this position should bring".

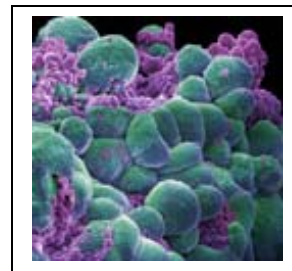
He was an outstanding candidate for this position since he is currently participating in the Carbon Therapy Working Group (CTWG) organized by AFRD Division Director Steve Gourlay. The position was created to provide a formal mechanism to promote UCSF/Berkeley Lab scientific interactions and joint research developments in the area of carbon ion therapy. Currently, implementation of particle radiotherapy for cancer is progressively advancing from proton therapy to consideration of heavy charged particle radiotherapy due to the recent demonstration of clinical successes in Japan and Germany with carbon ions. There are significant possibilities to develop novel accelerator technologies at Berkeley Lab that will revolutionize future particle therapy. The participation of a practicing radiation oncologist with prior particle radiotherapy experience will be very advantageous to the efforts of CTWG.

Roach has an MD from Stanford University School of Medicine. He has been a Chief Resident in Medicine at Highland General Hospital, a Resident in Radiation Therapy at the Stanford University School of Medicine and Chief Resident in Radiation Therapy at the Stanford University School of Medicine.

CG, 5/09

Novartis Licenses Technology for Breast Cancer Diagnosis

Berkeley Lab executed an exclusive license agreement with Novartis Vaccines and Diagnostics for patent-pending technology "SATB1: A Determinant of Morphogenesis and Tumor Metastasis." The SATB1 technology, developed by lead inventor **Terumi Kohwi-Shigematsu** in the Life Sciences Division at Berkeley Lab, showed that SATB1 protein can be down-regulated to prevent a tumor cell from becoming



malignant, rendering it to be an effective prognostic and diagnostic marker for detecting aggressive cancer cells. See a description of the technology > <http://www.lbl.gov/Tech-Transfer/techs/lbnl2186.html>

Today at Berkeley Lab, 6/23/09

Gray to Serve on Nuclear and Radiation Studies Board

Joe Gray has accepted an invitation to serve on the Nuclear and Radiation Studies Board (NRSB) at the National Academies. The Board's mission is to provide an open forum for discussion and to organize and oversee studies on safety, security, technical efficacy, and other policy and societal issues arising from the application of radiation-based technologies, including: Health effects, consequences, and amelioration of exposure to ionizing and non-ionizing radiation, including periodic assessments of the biological effects of ionizing radiation; Generation, use, remediation, and disposition of nuclear materials and radioactive (including mixed) wastes; Malevolent uses of nuclear and radiation-based technologies; Risks, benefits, and/or efficacies of nuclear and radiation-based technologies.



The board also has responsibility for the Academies' oversight of the Radiation Effects Research Foundation (RERF), a bi-national organization in Hiroshima, Japan, of which the Senior Review Panel on Future Planning Gray has served on since 2006. It also sponsors the annual Gilbert W. Beebe Symposium on radiation health effects which precedes the Board's winter meeting. The Board will meet next on July 8-9, 2009, Washington, DC at the National Academies Keck Center.

Gray was nominated because of his "distinguished career in radiation research and knowledge of radiation biology". He responded positively to the invitation, saying, "I appreciate the nomination and I am happy to participate. This is an important area now and I believe it will grow in importance as we reengage nuclear power."

CG, 6/09

Review Article: Mechanism by which the ECM Maintains Tissue Architecture and Function

Tissue architecture is critical for cell homeostasis and functional differentiation, and delineating the means by which context determines function in biology is paramount to our understanding of organ development and tissue differentiation. In a review of the June issue of *Cancer Metastasis*, **Ren Xu** and **Aaron Boudreau** of the **Bissell** Lab focus their discussion on the mechanism by which the ECM maintains tissue architecture and function. Engagement of ECM receptors induces a cascade of both physical and biochemical signals which transmit from the cell membrane to the nucleus, accompanied by changes in cell and tissue morphology and architecture. These alterations involve dramatic reorganization of both the cytoskeleton and chromatin structures, leading to changes in cellular and tissue architecture and gene expression which in turn affect ECM microenvironment. Using mammary gland as a model, the researchers discuss the following issues pertinent to the ECM-cytoskeleton-nucleus signaling axis: how coordinated ECM deposition and remodeling may be necessary for tissue morphogenesis during development; how the ECM acts as an organizing unit by which tissue architecture, polarity, and specificity are maintained; and lastly, how the cytoskeleton acts as a conduit mediating the dynamic and reciprocal signals between the ECM and the nucleus to maintain correct tissue form and function.

Xu R, Boudreau A, Bissell MJ. Tissue architecture and function: dynamic reciprocity via extra- and intra-cellular matrices. *Cancer Metastasis Rev.* 2009 Jun;28(1-2):167-76. PMID: 19160017

Ren Xu, 6/09

Nogales Presents at Berkeley Lab's Women Scientists' Council Event

Life Sciences **Eva Nogales**, a Howard Hughes Medical Institute Investigator, Professor of Biochemistry and Molecular Biology at UC Berkeley and a Senior Faculty Scientist in Life Sciences, presented as a guest speaker in the Luncheon and Networking Session of the Berkeley Lab's Women Scientists' Council Special Event on Friday, May 15, 2009. Nogales Lab researches the structural characterization of complex biological assemblies, their architecture, conformational flexibility, and their interactions with ligands and cellular partners with a major interest in structural basis of cytoskeletal self-assembly and regulation during cell division. More > http://www.lbl.gov/lsc/People_&_Organization/Scientific_Staff_Directory/Nogales_Lab.html
Today at Berkeley Lab, CG, 5/15/09



Eva Nogales

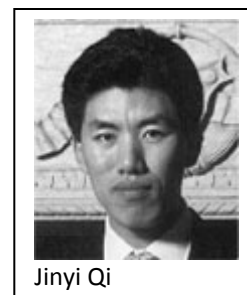
Campisi Contributes to Berkeley Lab Video Glossary

Life Sciences **Judith Campisi** was recently asked to define the term "cellular-senescence" in lay language on video, the recording to be included in the new Berkeley Lab on-line Video Glossary. She was one of the first Life Sciences researchers to participate. Each week, new entries are added to the glossary. And as science changes and entirely new terms arise, Berkeley Lab's video glossary offers a first stop for answers. Campisi's entry can be viewed here > <http://videoglossary.lbl.gov/2009/cellular-senescence/>
CG, 5/09

Awards

Early Achievement Award for Life Scientist Jinyi Qi

Jinyi Qi, a faculty scientist in Berkeley Lab's Life Sciences Division and associate professor of biomedical engineering at UC Davis, has been selected to receive the Early Achievement Award from the IEEE Nuclear and Plasma Sciences Society (<http://ewh.ieee.org/soc/nps/index.htm>). The selection committee cited Qi for his outstanding contributions to computational nuclear medical imaging, particularly his work on statistically based, three-dimensional image reconstruction.



Jinyi Qi

Qi has rapidly established himself as one of the leading research scientists in the field of computational imaging. He is particularly well known for his work to develop *maximum a posteriori* (MAP) 3D reconstruction algorithms for positron emission tomography (PET) that build on a Bayesian framework with accurate modeling of the imaging system and deliver stunning and quantitatively accurate images. Among other work, Qi collaborates with Life Sciences **William Moses** on the NIH R01 project "Exploring the Benefits of Time-of-Flight PET", aimed at developing a demonstration single-ring LSO PET camera with ultra-high timing resolution, and using it to measure the improvement in image quality afforded by time-of-flight as a function of timing resolution.

Today at Berkeley Lab, CG, 6/3/09

Recent publications (selected)

Venken KJ, **Carlson JW**, Schulze KL, Pan H, He Y, Spokony R, **Wan KH**, Koriabine M, de Jong PJ, White KP, Bellen HJ, **Hoskins RA**. Versatile P[acman] BAC libraries for transgenesis studies in *Drosophila melanogaster*. *Nature Methods*, 2009 May 24. [Epub ahead of print] PMID: 19465919

See Scientific Highlight, page 7.

Chaudhry A, Canning R, **Boutchko Y**, **Porter E**, Bourret-Courchesne E, **Derenzo S**, and Gronbech-Jensen N. First principles calculations for scintillation in Ce-doped Y and La oxyhalides. *IEEE Transactions on Nuclear Science*, June 2009, vol. 56, No. 3, pp. 949-954

See Nuclear Medicine Highlight, page 4.

Eberling JL, Kells AP, **Pivrotto P**, **Beyer J**, **Bringas J**, Federoff HJ, Forsayeth J, **Bankiewicz KS**. Functional effects of AAV2-GDNF on the dopaminergic nigrostriatal pathway in Parkinsonian Rhesus monkeys. *Human Gene Therapy*, 2009 May;20(5):511-8. PMID: 19254173

We investigated the safety and neuroregenerative potential of an adeno-associated virus (AAV2) containing human glial cell line-derived neurotrophic factor (GDNF) in an MPTP primate model of Parkinson's disease. Dopaminergic function was evaluated by positron emission tomography with 6-[(18)F]fluoro-l-m-tyrosine (FMT) before and after AAV2-GDNF or phosphate-buffered saline infusion bilaterally into the putamen. FMT uptake was significantly increased bilaterally in the putamen of AAV2-GDNF but not phosphate-buffered saline-treated animals 6 months after infusion, indicating increased dopaminergic activity in the nigrostriatal pathways. AAV2-GDNF-treated animals also showed clinical improvement without adverse effects. These findings are consistent with our previous report in aged nonhuman primates that showed evidence of enhanced use of striatal dopamine and dopaminergic nigrostriatal innervation. Clinical improvement and evidence of functional recovery in the nigrostriatal pathway, and the absence of adverse effects, support the safety of this approach for the delivery of GDNF over a 6-month period.

Novak P, Jensen TJ, **Garbe JC**, **Stampfer MR**, Futscher BW. Stepwise DNA methylation changes are linked to escape from defined proliferation barriers and mammary epithelial cell immortalization. *Cancer Research*, 2009 Jun 15;69(12):5251-8. PMID: 19509227

The timing and progression of DNA methylation changes during carcinogenesis are not completely understood. To develop a timeline of aberrant DNA methylation events during malignant transformation, we analyzed genome-wide DNA methylation patterns in an isogenic human mammary epithelial cell (HMEC) culture model of transformation. To acquire immortality and malignancy, the cultured finite lifespan HMEC must overcome two distinct proliferation barriers. The first barrier, stasis, is mediated by the retinoblastoma protein and can be overcome by loss of p16(INK4A) expression. HMEC that escape stasis and continue to proliferate become genomically unstable before encountering a second more stringent proliferation barrier, telomere dysfunction due to telomere attrition. Rare cells that acquire telomerase expression may escape this barrier, become immortal, and develop further malignant properties. Our analysis of HMEC transitioning from finite lifespan to malignantly transformed showed that aberrant DNA methylation changes occur in a stepwise fashion early in the transformation process. The first aberrant DNA methylation step coincides with overcoming stasis, and results in few to hundreds of changes, depending on how stasis was overcome. A second step coincides with immortalization and

results in hundreds of additional DNA methylation changes regardless of the immortalization pathway. A majority of these DNA methylation changes are also found in malignant breast cancer cells. These results show that large-scale epigenetic remodeling occurs in the earliest steps of mammary carcinogenesis, temporally links DNA methylation changes and overcoming cellular proliferation barriers, and provides a bank of potential epigenetic biomarkers that may prove useful in breast cancer risk assessment.

Zeng GL, **Gullberg GT**. Exact emission SPECT reconstruction with truncated transmission data. *Physics in Medicine and Biology*, 2009 May 8;54(11):3329-3340. [Epub ahead of print] PMID: 19430109

It is common, even with new SPECT/CT systems, that the transmission data are truncated. This paper develops a method that obtains exact attenuation correction with truncated transmission data. The emission object (e.g., the heart) is assumed to have a finite, convex support, whose emission projections are not truncated. The transmission measurements over the support are available, but may be truncated outside the support (within the torso). A novel emission data reconstruction technique combines emission projections from conjugate views; a modified version of the ML-EM algorithm is used to reconstruct emission data. The attenuation map outside the support is not needed during reconstruction. The transmission measurements through the support are used to pre-scale the emission data and to reconstruct the attenuation map within the support. The attenuation map reconstruction within the support is an interior problem in which only a biased solution can be obtained using an iterative algorithm. The bias is then corrected by identifying a soft tissue region within the support and the known attenuation coefficient values of these pixels for the soft tissue. Proof of convergence of the new algorithm is provided. Computer simulations verify the accuracy of the new method. Conclusions: an exact attenuation map within the support can be obtained provided the attenuation coefficient is known at 1 pixel within the support. The method, which requires emission data over 360 degrees, provides a means to perform attenuation correction in SPECT with truncated transmission data.

Weber GH, Rübél O, **Huang MY**, DePace AH, Fowlkes CC, Keränen SV, Luengo Hendriks CL, Hagen H, **Knowles DW**, Malik J, **Biggin MD**, Hamann B. Visual exploration of three-dimensional gene expression using physical views and linked abstract views. *IEEE/ACM transactions on computational biology and bioinformatics*, 2009 Apr-Jun;6(2):296-309. PMID: 19407353

During animal development, complex patterns of gene expression provide positional information within the embryo. To better understand the underlying gene regulatory networks, the Berkeley Drosophila Transcription Network Project (BDTNP) has developed methods that support quantitative computational analysis of three-dimensional (3D) gene expression in early Drosophila embryos at cellular resolution. We introduce PointCloudXplore (PCX), an interactive visualization tool that supports visual exploration of relationships between different genes' expression using a combination of established visualization techniques. Two aspects of gene expression are of particular interest: 1) gene expression patterns defined by the spatial locations of cells expressing a gene and 2) relationships between the expression levels of multiple genes. PCX provides users with two corresponding classes of data views: 1) Physical Views based on the spatial relationships of cells in the embryo and 2) Abstract Views that discard spatial information and plot expression levels of multiple genes with respect to each other. Cell Selectors highlight data associated with subsets of embryo cells within a View. Using linking, these selected cells can be viewed in multiple representations. We describe PCX as a 3D gene expression visualization tool and provide examples of how it has been used by BDTNP biologists to generate new hypotheses.

Jagust W. Mapping brain beta-amyloid. *Current Opinions in Neurology*, 2009 May 27. [Epub ahead of print] PMID: 19478666

PURPOSE OF REVIEW: This article reviews recent developments in the field of amyloid imaging using PET, specifically the ability to quantify the amount and distribution of brain beta-amyloid, the protein that occupies a central position in leading theories of the pathogenesis of Alzheimer's disease. **RECENT FINDINGS:** Several imaging-disorder correlations place the technique itself on a stronger footing by showing good agreement between in-vivo and histological measures of beta-amyloid deposition. Correlations between beta-amyloid and other measures of dementia - cognition, brain atrophy, and glucose metabolism - appear to support a view that beta-amyloid triggers a host of downstream alterations that are closely related to dementia severity and progression. However, associations between PET measures of beta-amyloid and cognition are generally fairly weak. The implications for clinical use are still uncertain. It seems likely that amyloid imaging will be useful for differentiating dementias associated with beta-amyloid from those that are not, but the utility of this approach will depend on the availability of effective beta-amyloid-directed treatments. Similarly, amyloid imaging offers the potential for predicting which nondemented individuals will eventually develop Alzheimer's disease, although here again the measurement of downstream beta-amyloid effects may be important. **SUMMARY:** The ability to quantify the onset and progression of beta-amyloid disorder in the brain offers the potential for investigating a host of questions concerning individual and neural vulnerability and the amyloid hypothesis of Alzheimer's disease itself. These findings will have important basic and clinical implications.

Agrelo R, Souabni A, Novatchkova M, Haslinger C, Leeb M, Komnenovic V, Kishimoto H, Gresh L, **Kohwi-Shigematsu T**, Kenner L, Wutz A. SATB1 defines the developmental context for gene silencing by Xist in lymphoma and embryonic cells. *Developmental Cell*, 2009 Apr;16(4):507-16. PMID: 19386260

The noncoding Xist RNA triggers silencing of one of the two female X chromosomes during X inactivation in mammals. Gene silencing by Xist is restricted to a special developmental context in early embryos and specific hematopoietic precursors. Here, we show that Xist can initiate silencing in a lymphoma model. We identify the special AT-rich binding protein SATB1 as an essential silencing factor. Loss of SATB1 in tumor cells abrogates the silencing function of Xist. In lymphocytes Xist localizes along SATB1-organized chromatin and SATB1 and Xist influence each other's pattern of localization. SATB1 and its homolog SATB2 are expressed during the initiation window for X inactivation in ES cells. Importantly, viral expression of SATB1 or SATB2 enables gene silencing by Xist in embryonic fibroblasts, which normally do not provide an initiation context. Thus, our data establish SATB1 as a crucial silencing factor contributing to the initiation of X inactivation.

Agarwal R, Gonzalez-Angulo AM, Myhre S, Carey M, Lee JS, Overgaard J, Alsner J, Stemke-Hale K, Lluch A, Neve RM, **Kuo WL**, Sorlie T, Sahin A, Valero V, Keyomarsi K, **Gray JW**, Borresen-Dale AL, Mills GB, Hennessy BT. Integrative analysis of cyclin protein levels identifies cyclin B1 as a classifier and predictor of outcomes in breast cancer. *Clinical Cancer Research*, 2009 May 26. [Epub ahead of print] PMID: 19470724

PURPOSE: We studied the expression levels of cyclins B1, D1, and E1 and the implications of cyclin overexpression for patient outcomes in distinct breast cancer subtypes defined by clinical variables and transcriptional profiling. **EXPERIMENTAL DESIGN:** The expression levels of cyclins B1, D1, and E1 were quantified in 779 breast tumors and 53 cell lines using reverse phase protein arrays and/or transcriptional profiling. **RESULTS:** Whereas cyclin E1 overexpression was a specific marker of triple-negative and basal-like tumors, cyclin B1 overexpression occurred in poor prognosis hormone receptor-positive, luminal B and basal-like breast cancers. Cyclin D1 overexpression occurred in luminal and normal-like cancers. Breast cancer subgroups defined by integrated expression of cyclins B1, D1, and E1 correlated significantly ($P < 0.000001$) with tumor subtypes defined by transcriptional profiling and clinical criteria. Across three hormone receptor-positive data sets, cyclin B1 was the dominant cyclin associated with poor prognosis in

univariate and multivariate analyses. Although CCNE1 was present in significantly higher copy numbers in basal-like versus other subtypes (ANOVA $P < 0.001$), CCNB1 gene copy number did not show gain in breast cancer. Instead, cyclin B1 expression was increased in tumors with co-occurrence of TP53 mutations and MYC amplification, a combination that seems to characterize basal-like and luminal B tumors. CCNB1 gene expression was significantly correlated with PLK, CENPE, and AURKB gene expression. CONCLUSION: Cyclins B1, D1, and E1 have distinct expressions in different breast cancer subtypes. Novel PLK, CENPE, and AURKB inhibitors should be assessed for therapeutic utility in poor prognosis cyclin B1-overexpressing breast cancers.

Lee E, Harris N, Mark G, Chetty R, Lewis S. Apollo: a community resource for genome annotation editing. *Bioinformatics*, 2009 May 13. [Epub ahead of print] PMID: 19439563

Apollo is a genome annotation-editing tool with an easy to use graphical interface. It is a component of the GMOD project, with ongoing development driven by the community. Recent additions to the software include support for GFF3, support for continuous transcriptome data, a full Chado database interface, integration with remote services for on-the-fly BLAST and Primer BLAST analyses, graphical interfaces for configuring user preferences, and full undo of all edit operations. Apollo's user community continues to grow, including its use as an educational tool for college and high school students.

Mellone BG, Zhang W, Karpen GH. Frosos found: behold the CENP-a "Ring" bearers. *Cell*, 2009 May 1;137(3):409-12. PMID: 19410539

CENP-A is a histone H3-like protein specific to centromeres that is essential for kinetochore formation and accurate chromosome segregation in eukaryotes. Recent studies (Dunleavy et al., 2009; Foltz et al., 2009; Perpelescu et al., 2009; Pidoux et al., 2009; Williams et al., 2009) analyze CENP-A binding proteins required for the recruitment of CENP-A to centromeres in humans and in fission yeast, bringing us closer to understanding how centromere identity is faithfully propagated.

Polyzos A, Ernst Schmid T, Piña-Guzmán B, Quintanilla-Vega B, Marchetti F. Differential sensitivity of male germ cells to mainstream and sidestream tobacco smoke in the mouse. *Toxicology and Applied Pharmacology*, 2009 Apr 5. [Epub ahead of print] PMID: 19345701

Cigarette smoking in men has been associated with increased chromosomal abnormalities in sperm and with increased risks for spontaneous abortions, birth defects and neonatal death. Little is known, however, about the reproductive consequences of paternal exposure to second-hand smoke. We used a mouse model to investigate the effects of paternal exposure to sidestream (SS) smoke, the main constituent of second-hand smoke, on the genetic integrity and function of sperm, and to determine whether male germ cells were equally sensitive to mainstream (MS) and SS smoke. A series of sperm DNA quality and reproductive endpoints were investigated after exposing male mice for two weeks to MS or SS smoke. Our results indicated that: (i) only SS smoke significantly affected sperm motility; (ii) only MS smoke induced DNA strand breaks in sperm; (iii) both MS and SS smoke increased sperm chromatin structure abnormalities; and (iv) MS smoke affected both fertilization and the rate of early embryonic development, while SS smoke affected fertilization only. These results show that MS and SS smoke have differential effects on the genetic integrity and function of sperm and provide further evidence that male exposure to second-hand smoke, as well as direct cigarette smoke, may diminish a couple's chance for a successful pregnancy and the birth of a healthy baby.

Ramey VH, Wang HW, Nogales E. Ab initio reconstruction of helical samples with heterogeneity, disorder and coexisting symmetries. *Journal of Structural Biology*, 2009 May 15. [Epub ahead of print] PMID: 19447181

We describe modifications of the single particle helical reconstruction approach devised for the analysis of a sample that could not be processed with existing methods due to its variable and short range helical order. The added steps of reference-free two-dimensional image classification and alignment, and automated microtubule removal from images, have particular application to proteins or protein complexes that assemble around microtubules. The method was successfully applied to the Dam1 complex, an essential component of the yeast kinetochore that couples replicated chromosomes to spindle microtubules during mitosis. Because of its novel mode of binding, which does not involve a footprint on the microtubule lattice, new steps to deal with the disorder and heterogeneity of the Dam1 complex assembly were required to gain structural information about this complex both routinely and efficiently.

Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee JS, Fridlyand J, Sahin A, Agarwal R, Joy C, Liu W, Stivers D, Baggerly K, Carey M, Lluch A, Monteagudo C, He X, Weigman V, Fan C, Palazzo J, Hortobagyi GN, Nolden LK, **Wang NJ**, Valero V, **Gray JW**, Perou CM, Mills GB. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. *Cancer Research*, May 12 2009;69(10):4116-24][Epub ahead of print] PMID: 19435916

Metaplastic breast cancers (MBC) are aggressive, chemoresistant tumors characterized by lineage plasticity. To advance understanding of their pathogenesis and relatedness to other breast cancer subtypes, 28 MBCs were compared with common breast cancers using comparative genomic hybridization, transcriptional profiling, and reverse-phase protein arrays and by sequencing for common breast cancer mutations. MBCs showed unique DNA copy number aberrations compared with common breast cancers. PIK3CA mutations were detected in 9 of 19 MBCs (47.4%) versus 80 of 232 hormone receptor-positive cancers (34.5%; $P = 0.32$), 17 of 75 HER-2-positive samples (22.7%; $P = 0.04$), 20 of 240 basal-like cancers (8.3%; $P < 0.0001$), and 0 of 14 claudin-low tumors ($P = 0.004$). Of 7 phosphatidylinositol 3-kinase/AKT pathway phosphorylation sites, 6 were more highly phosphorylated in MBCs than in other breast tumor subtypes. The majority of MBCs displayed mRNA profiles different from those of the most common, including basal-like cancers. By transcriptional profiling, MBCs and the recently identified claudin-low breast cancer subset constitute related receptor-negative subgroups characterized by low expression of GATA3-regulated genes and of genes responsible for cell-cell adhesion with enrichment for markers linked to stem cell function and epithelial-to-mesenchymal transition (EMT). In contrast to other breast cancers, claudin-low tumors and most MBCs showed a significant similarity to a "tumorigenic" signature defined using CD44(+)/CD24(-) breast tumor-initiating stem cell-like cells. MBCs and claudin-low tumors are thus enriched in EMT and stem cell-like features, and may arise from an earlier, more chemoresistant breast epithelial precursor than basal-like or luminal cancers. PIK3CA mutations, EMT, and stem cell-like characteristics likely contribute to the poor outcomes of MBC and suggest novel therapeutic targets.

Xu R, Boudreau A, Bissell MJ. Tissue architecture and function: dynamic reciprocity via extra- and intra-cellular matrices. *Cancer Metastasis Rev.* 2009 Jun;28(1-2):167-76. PMID: 19160017

See Scientific Highlight, page 9.

Fournier MV, Fata JE, Martin KJ, **Yaswen P, Bissell MJ.** Interaction of E-cadherin and PTEN regulates morphogenesis and growth arrest in human mammary epithelial cells. *Cancer Research*, May 5 2009;69(10):4545-52].[Epub ahead of print]PMID: 19417140

Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is a dual-function phosphatase with tumor suppressor function compromised in a wide spectrum of cancers. Because tissue polarity and architecture are crucial modulators of normal and malignant behavior, we postulated that PTEN may play a role in maintenance of tissue integrity. We used two nonmalignant human mammary epithelial cell lines that form polarized, growth-arrested structures (acini) when cultured in three-dimensional laminin-rich extracellular matrix gels (IrECM). As acini begin to form, PTEN accumulates both in the cytoplasm and at cell-cell contacts where it colocalizes with the E-cadherin/beta-catenin complex. Reduction of PTEN levels by shRNA in IrECM prevents formation of organized breast acini and disrupts growth arrest. Importantly, disruption of acinar polarity and cell-cell contact by E-cadherin function-blocking antibodies reduces endogenous PTEN protein levels and inhibits its accumulation at cell-cell contacts. Conversely, in Skbr-3 breast cancer cells lacking endogenous E-cadherin expression, exogenous introduction of E-cadherin gene causes induction of PTEN expression and its accumulation at sites of cell interactions. These studies provide evidence that E-cadherin regulates both the PTEN protein levels and its recruitment to cell-cell junctions in three-dimensional IrECM, indicating a dynamic reciprocity between architectural integrity and the levels and localization of PTEN. This interaction thus seems to be a critical integrator of proliferative and morphogenetic signaling in breast epithelial cells.