



LIFE SCIENCES DIVISION E-NEWSLETTER

June 30, 2008

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DOE scientific focus area notes

Low Dose Radiation Research

RISC-RAD Meeting

Life scientist **Priscilla Cooper** attended the RISC-RAD Fourth Annual Meeting on Madeira, Portugal, May 28-31, 2008 as a member of their Advisory Scientific Committee. RISC-RAD, which stands for Radiosensitivity of Individuals and Susceptibility to Cancer induced by ionizing RADiations, is an EC consortium project involving 33 partners funded by Euratom. Like the DOE Low Dose Radiation Research Program, it addresses the issue of health risks from low-dose exposures to ionizing radiation. Cooper has been an adviser to RISC-RAD since its inception. In addition to sitting on their Project Board meetings, she gave an invited 45-minute lecture entitled "Mechanistic Studies of the Radiation Adaptive Response" that presented work from her own laboratory as well as from the laboratories of **Judith Campisi** and **Andrew Wyrobek**. [More info]

<http://www.riscrad.org/scripts/home/publigen/content/templates/show.asp?P=159&L=EN&ITEMID=14>

Priscilla Cooper, 6/08

ASA Conference on Radiation and Health

Amy Kronenberg was a member of the Organizing Committee for The American Statistical Association Conference on Radiation and Health held June 15-18, 2008. The conference, sponsored, in part, by the DOE Low Dose Program, reviewed recent advances in radiobiology, epidemiology, biodosimetry, and statistics. The radiobiology session, chaired and summarized by Kronenberg, included talks on the unique biology of telomeres and their response to individual DNA double-strand breaks, bystander signaling and the shape of the dose-response curve for carcinogenesis and adaptive responses and the risk of neoplastic conversion. The session concluded with a presentation on genetic variation and susceptibility to radiation-induced second breast cancers in the WECARE cohort. The conference highlighted advances in biodosimetry, updates on cancer and non-cancer late effects after diagnostic radiology procedures, updates on cancer incidence in cohorts with protracted exposures to radiation from occupational or environmental sources, and advanced statistical methods and their application to cancer and non-cancer late effects amongst individuals in the RERF study populations. [More info]

<http://www.amstat.org/meetings/radiation/2008/>

Andrew Wyrobek, 6/08

Low-Dose Exposures of Mouse Brain Tissue Affects Pathways Associated with Cognitive Function

A study from life scientists from the Department on Radiation Biosciences, led by **Andrew Wyrobek**, employed bioinformatics analyses of gene profiles of brain tissue of mice that received whole body radiation, and found that low-dose radiation exposures (10 cGy) induced changes of sets of genes that were not affected by high dose (2 Gy). The low-dose unique genes were associated with signaling pathways involving neural functions and neurotransmitters. Six of the molecular pathways that were downregulated after radiation exposures were previously found in other studies to also be downregulated in aging human brain tissue (unirradiated) and in brain tissue from patients with

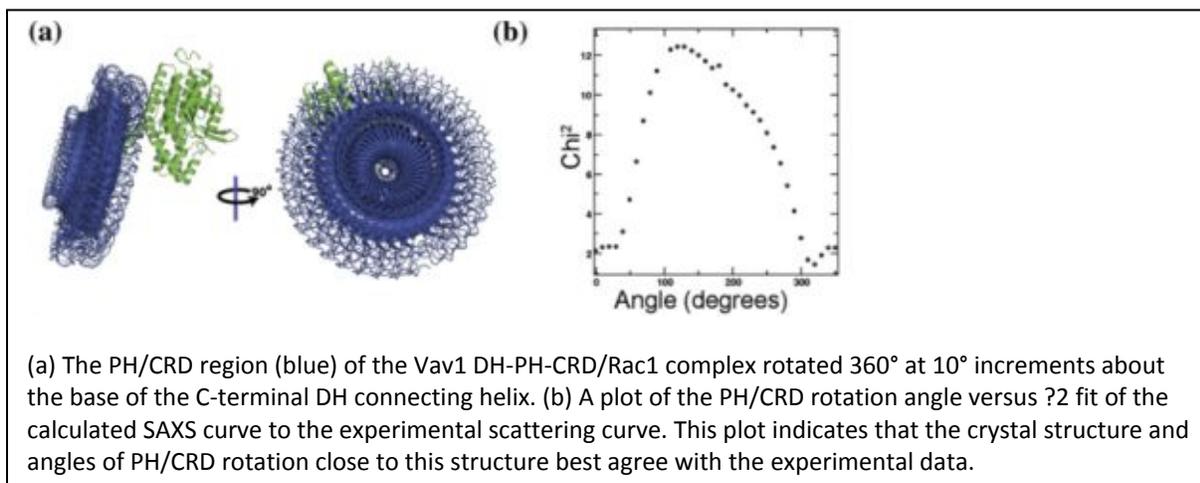
Alzheimer's disease. This finding indicates that the early molecular response of the mouse brain after exposure to low-dose irradiation involves the down regulation of sets of genes known to be associated with cognitive functions, but whether this is a protective response for brain tissue is not yet known. Other life scientists involved in this work sponsored by the DOE Low Dose Program include **Xiu Lowe**, **Sanchita Bhattacharya** and **Francesco Marchetti**.

Andrew Wyrobek, 6/08

GTL-Genomics

Structural Basis of Guanine Nucleotide Exchange Mediated by the T-Cell Essential Vav1 Protein Elucidated

In a joint collaboration between Scripps research Institute, and Novartis, **John Tainer** of Life Sciences and his group have elucidated the structural basis of guanine nucleotide exchange mediated by the T-Cell essential Vav1 protein. Their article is in press in the upcoming issue of the *Journal of Molecular Biology*. The guanine nucleotide exchange factor (GEF) Vav1 plays an important role in T-cell regulation and is also often over expressed in human cancers. In the GEF superfamily, Vav1 has the ability to interact with multiple families of Rho GTPases including Rac1. The structure of the Vav1/Rac1 complex to 2.6 Å resolution reveals a unique intramolecular network of contacts between the Vav1 cysteine-rich domain (CRD) and the C-terminal helix of the Vav1 Dbl homology (DH) domain. The identification of drugable protein-protein interaction interfaces represents an important avenue in drug discovery. Previous structural studies suggested no such interaction. To verify these observed interactions were relevant in solution the investigators used small angle x-ray scattering (SAXS) at the SIBYLS beamline at the ALS. These unique interactions stabilize the Vav1 DH domain for its intimate association with the Switch II region of Rac1 that is critical for the displacement of the guanine nucleotide. Further, mutational analyses confirms that the atypical CRD is critical for maintaining both optimal guanine nucleotide exchange activity and broader specificity of Vav family GEFs. Taken together, the data outline the detailed nature of Vav1's ability to contact a range of Rho GTPases using a novel protein-protein interaction network. The Tainer lab's effort in this project was supported by DOE Integrated Diffraction Analysis Technologies grant.



Gregory Hura, 6/08

Jill E. Chrencik, Alexei Brooun, Hui Zhang, Irimpan I. Mathews, Greg L. Hura, Scott A. Foster, J. Jefferson P. Perry, Markus Streiff, Paul Ramage, Hans Widmer, Gary M. Bokoch, **John A. Tainer**, Gisbert Weckbecker and Peter Kuhn. Structural Basis of Guanine Nucleotide Exchange Mediated by the T-Cell Essential Vav1. *Journal of Molecular Biology*, In press 2008.

Nuclear Medicine

SORMA Symposium Unqualified Success

The 12th Symposium on Radiation Measurements and Applications, held on the UC Berkeley campus June 2-5, 2008 and featured in the May issue of the LSD E-newsletter, was an unqualified success, **Stephen Derenzo** and **William Moses** (general chair and co-chair respectively) reported. There were 420 registered participants, 109 oral presentations, and over 200 posters. Traditionally held at the University of Michigan every four years, this was the first West coast meeting. The plan for the future is to interleave with the East and West coast meetings so that new developments in radiation measurements and applications can be presented every two years.



Members of the Department of Medical Imaging Technology authored eight presentations, describing recently discovered scintillation materials, advances in first-principles quantum calculations for predicting cerium activated scintillators, new measurements of scintillator non-proportionality, and new high-performance electronic circuits for time-of-flight positron tomography. Other papers presented at the Symposium described other novel concepts in X-ray, gamma-ray, and positron detection for medical imaging.

Stephen Derenzo, 6/08

Scientific news

Bay Area-Wide Workshop to Further Develop the Concept of a Multiscale Bioimaging Facility at Berkeley Lab: The Joint Center for Integrated Bioimaging (JCIB)

On June 18, 2008, one year after the Gulliver Multiscale Bioimaging Workshop, **Manfred Auer**, **Jan Liphardt** and **Joe Gray** invited over 50 scientists from the Bay Area and beyond to a day-long meeting at Berkeley Lab to further refine the concept of the multiscale bioimaging initiative. Most of the participants were from the different divisions at Berkeley Lab, UCSF, UC Davis, and Stanford University, but representatives from Microsoft, Google and General Electric also expressed their interest in multiscale imaging. The workshop was divided into four sections, starting with an overview on

multiscale biological problems, followed by an overview on local resources at Berkeley Lab and a section on possible JCIB technology concentrations, concluded with an "open mic" session that allowed workshop participants to provide feedback on the concept.

After welcoming the participants Joe Gray (LSD) laid out the current dilemma of cancer biology: while various "omics" have yielded an impressive list of components, we need to understand how the components work together, at the level of macromolecular machines, cells and tissues. **Priscilla Cooper** (LSD) illustrated how multiscale imaging can transform the field of DNA repair. Manfred Auer (LSD) described the need for integrated bioimaging in the context of bioenergy/biofuels, with a focus on the plant cell wall as well as microbial communities that are specialized to efficiently degrade lignocellulose. These three areas were considered to be of particular interest to DOE. Roger Falcone, Bruce Cohen and **Bill Jagust** (LSD) described the strong existing programs at the ALS, the Molecular Foundry as well as the Medical Imaging program, and their relationship to multiscale bioimaging. It is anticipated that JCIB will include components of these successful programs.

Four possible technology foci were proposed that include (1)integrated imaging, as showcased by Jan Liphardt (PBD), (2) further development of chemical probes, as illustrated by Gerard Marriott (University of Wisconsin), (3) computational sciences as presented by James Sethiam (CRHPM), and (4) engineering as described by Jian Jin (EGEE). These presentations concluded the formal part of the workshop and were followed by an "open mic" session that featured ad-hoc presentations by **Bob Glaeser** (LSD), **Paul Yaswen** (LSD) Andreas Ewald/Zena Werb (UCSF), Donna Albertson (UCSF), Alasdair MacDowell (ALS), Bahram Parvin (LSD), **Damir Sudar/Cynthia McMurray** (LSD), Jitendra Malik (UC Berkeley), **John Tainer** (LSD), Sabrina Rohnen (UCSF), and Gunther Weber (CRHPV).

The presentations and discussions held during the workshop were helpful in further refining the Whitepaper, which was sent to DOE shortly after the workshop.

Manfred Auer, 6/08

Work of Life Scientists among *Nature's* Top 10 Downloads

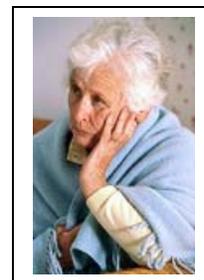
Nature reported the SATB1 article of **Yori Kohwi** and **Terumi Kohwi-Shigematsu** et al. (*Nature*, Mar 13, 2008) to be among the top ten articles that have been downloaded most often, in PDF format, from the *Nature* website in May, 2008. This article was highlighted in the March 2008 issue of the LSD E-newsletter. Linda Chin and **Joe Gray's** insight paper on Translating insights from genome into clinical practice (*Nature*, April 2008) made the top ten of most downloaded articles in June, 2008.

<http://www.nature.com/nature/topten/index.html>

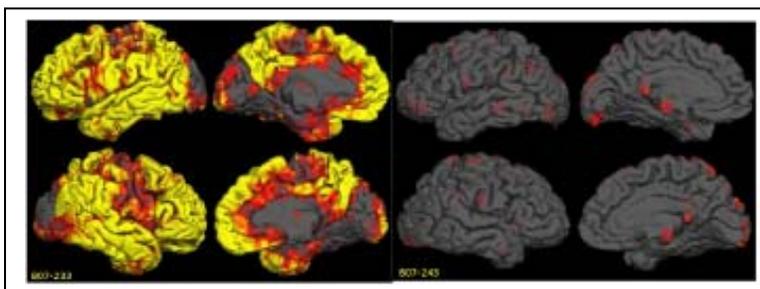
CG, 6/08

A Complex Approach to Curing Alzheimer's

Every 72 seconds, a new case of Alzheimer's is diagnosed. There is still no cure for this progressive and fatal brain disease, and the numbers are expected to rise as the baby boomer generation ages. Yet many of the fundamental questions about Alzheimer's remain unanswered. Researchers — including Berkeley Lab life scientists **Bing Jap** and **Bill Jagust** — are applying their particular skills and tools to address these questions.



A recent issue of the *Berkeley Science Review* featured a story on research about Alzheimer's Disease (AD) conducted at Berkeley in which Jap and Jagust were featured. The article, *Alzheimer's Unfolded; Taking a Complex Approach to Diagnosing a Complex Disease*, by James Walker, reviewed a number of approaches being taken to better understand brain abnormalities in patients with AD. These approaches include molecular biology approaches in the laboratories of Bing Jap and Randy Schekman in the department of Molecular and Cell biology at UC Berkeley, both of whom are studying the beta-amyloid protein that is deposited in plaques in the brains of AD patients. Jap and colleagues are looking at the production of amyloid beta 40, a small peptide that may contribute to the disease. Jagust's work uses PET scanning with the tracer C-11 PIB to visualize the beta-amyloid protein itself. This work could be important in early detection of AD so that new treatments could be applied before symptoms develop, as well as tracking the protein deposits to learn more about how beta-amyloid causes memory loss and cognitive failure.



The above scans were taken with the radiotracer C-11 PIB (Pittsburgh compound B). Both images show PIB retention with highest values in yellow, followed by red and they gray. The PIB uptake is superimposed on the subjects' MRI scan. The image on the left shows a patient with Alzheimer's disease, indicating beta- amyloid deposits throughout the brain. The image on the right shows a typical healthy older person with no PIB uptake, indicating no amyloid deposits. [More information]

http://sciencereview.berkeley.edu/articles.php?issue=14&article=features04_alzheimer

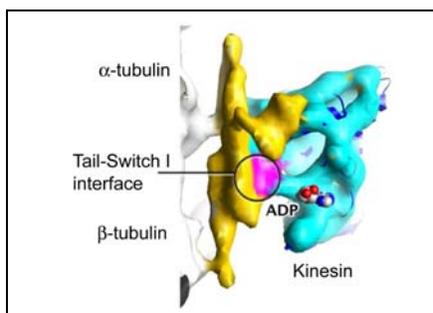
Bill Jagust, 6/08; also in Today at Berkeley Lab, 6/5/08

Research Update: Turning Kinesis-1 On and Off

Kenneth Downing and **Charles Sindelar** of the Life Sciences Division were members of a team led by Sarah Rice of Northwestern University that discovered how the cargo-carrying molecular motor protein kinesin-1 regulates its travels along microtubules, in order to conserve the cellular fuel ATP.

The microtubule cytoskeleton in eukaryotic cells serves a number of functions, including serving as tracks along which proteins known as motor molecules carry various cargoes. These motor proteins are fueled by ATP, which they hydrolyze to ADP in order to release energy. The energy is then used to haul cargo, which is attached to the motor by a long tether or tail. Kinesins are a family of proteins that share similar structures and generally carry cargo towards the end of a microtubule farthest from the cell center. For over a decade, cryo-electron microscopy has been extensively used in studies of how kinesins bind to microtubules. Recent advances in imaging and data processing made by scientists in the Life Sciences Division have allowed a substantial improvement in the resolution of these studies and in our understanding of how the motors work. In work published in 2007, Charles Sindelar and Kenneth Downing showed three-dimensional reconstructions of kinesin-decorated microtubules in which the resolution reached about 8 Å. At this resolution, elements of secondary structure such as alpha helices

are so clear that structures of individual molecules determined at very high resolution, for example by x-ray crystallography, can be docked together. This work led to hypotheses about conformational changes that occur when kinesin binds onto a microtubule. More recent work has extended these findings with studies of kinesin in a sequence of the nucleotide states that occur during ATP hydrolysis and release, and also with a motor that runs backwards on the microtubule, giving a much clearer picture of the set of conformational changes that produce motion through the ATP hydrolysis cycle. Work just recently published on line gives further insights into the regulation of this movement. In order to avoid wasting ATP when no cargo is attached to a kinesin molecule, the tail folds up in a way that inhibits movement. In collaboration with Kristen Dietrich and Sarah Rice at Northwestern University along with Paul Brewer and Christine Cremo at the University of Nevada, Sindelar and Downing have now shown how the tail binds to the kinesin in a way that affects ATP binding and hydrolysis.



The figure to the left shows a kinesin molecule in blue attached to a microtubule in grey at the left, as determined in the previous studies, and in yellow the extra density present when the tail is folded into the inactivating conformation. There is specific interaction between the tail and the "Switch I" region of kinesin, which is a control point in the nucleotide cycle. The report appears in Proceedings of the National Academy of Sciences. [Report]

<http://www.pnas.org/cgi/reprint/0803575105v1>

Kenneth Downing, 6/08; also in Today at Berkeley Lab, 6/30/08

Initiation of BioScience Microscopy Certificate Training Program

Life scientist **Damir Sudar** is serving as a founding member of the Advisory Board for the groundbreaking Bioscience Microscopy Certificate Training Program at Merritt College, a community college in Oakland, CA. Initiation of this successful program, which in its first semester has enrolled over 45 students from diverse backgrounds and will have a full degree program starting next year, was prompted by the increasing use of microscopy in modern biological research. Two of the program's students are currently doing their summer internship jointly in Sudar's microscopy lab at LBNL

(http://www.lbl.gov/lifesciences/labs/sudar_lab.html) and at UC Berkeley's Molecular Imaging Center (<http://imaging.berkeley.edu/>) to gain practical experience. [Program Information] [http://www.merritt.edu/apps/comm.asp?\\$1=40718](http://www.merritt.edu/apps/comm.asp?$1=40718)

Damir Sudar, 6/08



Launch Integrative Biology Journal

It was announced on 12 June, 2008 that a new journal, *Integrative Biology: Quantitative Biosciences from Nano to Macro*, will be launched in January 2009 by Royal Society of Chemistry Publishing. The Editorial Board Chair for this prestigious new journal will be **Mina Bissell**, and one of the two Science Editors will be **Mary Helen Barcellos-Hoff**, both of the Life Sciences Division, Berkeley Lab. *Integrative Biology* is a unique, highly interdisciplinary journal focused on quantitative multi-scale biology using

enabling technologies and tools to exploit the convergence of biology with physics, chemistry, engineering, imaging and informatics.

Monthly issues will include research articles including full papers, reviews (tutorial & critical), and perspectives. From launch, the latest issue of Integrative Biology will be made freely available to all readers via the website. Free institutional access to all 2009/2010 content is available following a simple registration process. [Registration]

http://www.rsc.org/Publishing/Journals/News/integrative_biology_announcement.asp

Mary Helen Barcellos-Hoff, 6/08

Gray Presents Work at Era of Hope Meeting

DOD Innovator Award recipient **Joe Gray** presented research aimed at improving early detection of breast cancer at the fifth Era of Hope meeting sponsored by the Department of Defense (DOD) Breast



Cancer Research Program (BCRP) held on June 25–28, 2008 in Baltimore, Maryland. Research participants in the work presented by Gray include **Matt Francis, Scott Taylor, Jim O'Neil, Frank Chen, Damir Sudar, Heidi Feiler, and Anna Lapuk.**

This international meeting is recognized as one of the premiere breast cancer research conferences in the United States and is a forum for research funded by the BCRP. It is unique in that it highlights the advancements made through the DOD BCRP and also provides a unique opportunity for investigators from different fields and research areas to share ideas, gain new insights, and forge collaborations that could lead to novel approaches to conquering breast cancer. More than 1,200 BCRP awardees, plus breast cancer survivors and advocates, policy makers, the general public and invited speakers attended. [More info] <http://cdmrp.army.mil/bcrp/era/>
CG, 6/08

Awards

Homeland Security Honors Life Scientist for Contributions

Stephen Derenzo, with Berkeley Lab's Life Sciences Division, has been honored by the Department of Homeland Security's Transformational and Applied Research Directorate and Domestic Nuclear Detection Office. Derenzo was recognized for his "superior contributions to the goals and mission" of the directorate, relating to his work with a program for the high-throughput discovery of scintillation materials at Berkeley Lab.

Today at Berkeley Lab, 6/12/08



Life Sciences Division to Sponsor Seaborg Postdoctoral Fellowship

The Life Sciences Division is welcoming postdoctoral fellow Cyrus Ghajar, a bioengineer from the University of California, Irvine, as a recipient of a 2008 Glenn Seaborg Postdoctoral Fellowship awarded by Berkeley Lab. The fellowship, named after the Nobel-winning pioneer of the atomic age, is one of

three Seaborg fellowships awarded by Berkeley Lab. The two other sponsoring divisions are Computing Sciences and Physics. Ghajar was selected from an applicant pool of outstanding recent Ph.D. recipients with no more than two years past their Ph.D. at the commencement of their fellowship. He will join the laboratory of **Mina Bissell** on July 14, 2008, where he will focus his research on building organotypic models of breast tumor angiogenesis. In addition to his salary, Ghajar receives a \$20,000 annual research supplement during his three-year appointment. [About Seaborg]

<https://isswprod2.lbl.gov/seaborg/start.asp>

CG, 6/08

Funded Proposal: Exploring Effect of Oxidative Stress on Development of Cardiovascular Disease

John Beliecki was awarded a grant funded through the Tobacco-Related Disease Research Program (TRDRP) of the State of California, administrated via the University of California. Duration of the award is three years, totaling approximately 680K. The project will explore how oxidative stress contributes to the development of cardiovascular disease. Specifically, the studies will define the molecular basic and biological relevance of protein oxidation motifs thought to impair anti-atherosclerosis activities of HDL. This will be modeled using synthetic biomimetic α -helical peptides. Impact of in vivo oxidative stress on the efficacy of HDL therapeutic interventions will be evaluated in mice exposed to environmental pollutants. The studies will be conducted in collaboration with Dr. Kent Pinkerton, Director, Center for Health and the Environment at UC Davis; and Dr. Stanley Hazen, Director, Center for Cardiovascular, Diagnostics and Prevention, Lerner Institute, at the Cleveland Clinic.

John Beliecki, 6/08

Recent publications (selected)

Auer M, Koster AJ, Ziese U, Bajaj C, Volkmann N, Wang da N, Hudspeth AJ. Three-dimensional Architecture of Hair-bundle Linkages Revealed by Electron-microscopic Tomography. *Journal of the Association for Research in Otolaryngology*, 2008 Jun;9(2):215-24. PMID: 18421501

The senses of hearing and balance rest upon mechano-electrical transduction by the hair bundles of hair cells in the inner ear. Located at the apical cellular surface, each hair bundle comprises several tens of stereocilia and a single kinocilium that are interconnected by extracellular proteinaceous links. Using electron-microscopic tomography of bullfrog saccular sensory epithelia, we examined the three-dimensional structures of basal links, kinociliary links, and tip links. We observed significant differences in the appearances and dimensions of these three structures and found two distinct populations of tip links suggestive of the involvement of different proteins, splice variants, or protein-protein interactions. We noted auxiliary links connecting the upper portions of tip links to the taller stereocilia. Tip links and auxiliary links show a tendency to adopt a globular conformation when disconnected from the membrane surface.

Salomao M, Zhang X, Yang Y, Lee S, Hartwig JH, **Chasis JA**, Mohandas N, An X. Protein 4.1R-dependent multiprotein complex: new insights into the structural organization of the red blood cell membrane. *Proceedings of the National Academy of Sciences U S A*, 2008 Jun 10;105(23):8026-31. PMID: 18524950

Protein 4.1R (4.1R) is a multifunctional component of the red cell membrane. It forms a ternary complex with actin and spectrin, which defines the nodal junctions of the membrane-skeletal network, and its attachment to the transmembrane protein glycophorin C creates a bridge between the protein network and the membrane bilayer. We now show that deletion of 4.1R in mouse red cells leads to a large diminution of actin accompanied by extensive loss of cytoskeletal lattice structure, with formation of bare areas of membrane. Whereas band 3, the preponderant transmembrane constituent, and proteins known to be associated with it are present in normal or increased amounts, glycophorin C is missing and XK, Duffy, and Rh are much reduced in the 4.1R-deficient cells. The inference that these are associated with 4.1R was borne out by the results of in vitro pull-down assays. Furthermore, whereas Western blot analysis showed normal levels of band 3 and Kell, flow cytometric analysis using an antibody against the extracellular region of band 3 or Kell revealed reduction of these two proteins, suggesting a conformational change of band 3 and Kell epitopes. Taken together, we suggest that 4.1R organizes a macromolecular complex of skeletal and transmembrane proteins at the junctional node and that perturbation of this macromolecular complex not only is responsible for the well characterized membrane instability but may also remodel the red cell surface.

Garrod MG, Green R, Allen LH, Mungas DM, **Jagust WJ**, Haan MN, Miller JW. Fraction of Total Plasma Vitamin B12 Bound to Transcobalamin Correlates with Cognitive Function in Elderly Latinos with Depressive Symptoms⁷. *Clinical Chemistry*, 2008 May 1. PMID: 18451312

BACKGROUND: The fraction of total plasma vitamin B12 bound to transcobalamin (holoTC/B12 ratio) may reflect tissue levels of the vitamin, but its clinical relevance is unclear. **METHODS:** We assessed associations between cognitive function and total B12, holoTC, and holoTC/B12 ratio in a cohort of elderly Latinos (n = 1089, age 60-101 years). We assessed cognitive function using the Modified Mini-Mental State Examination (3MSE) and a delayed recall test; we diagnosed clinical cognitive impairment by neuropsychological and clinical exam with expert adjudication; and we assessed depressive symptoms using the Center for Epidemiological Studies Depression Scale (CES-D). We measured total B12 and holoTC using radioassays. **RESULTS:** HoloTC/B12 ratio was directly associated with 3MSE score (P = 0.026) but not delayed recall score. Interactions between holoTC/B12 and CES-D score were observed for 3MSE (P = 0.026) and delayed recall scores (P = 0.013) such that associations between the ratio and cognitive function scores were confined to individuals with CES-D \geq 16. For individuals with CES-D \geq 16, the odds ratio for clinical cognitive impairment for the lowest holoTC/B12 tertile was 3.6 (95% CI 1.2-11.2) compared with the highest tertile (P = 0.03). We observed no associations between cognitive function and total B12 or holoTC alone, except between holoTC and 3MSE score (P = 0.021), and no interactions between holoTC or total B12 and CES-D score on cognitive function. **CONCLUSIONS:** HoloTC/B12 ratio is associated with cognitive function in elderly Latinos with depressive symptoms and may better reflect the adequacy of B12 for nervous system function than either holoTC or total B12 alone.

Labarge MA, Bissell MJ. Is CD133 a marker of metastatic colon cancer stem cells? *The Journal of Clinical Investigation*, 2008 May 22. PMID: 18497883

The concept of the so-called cancer stem cell (CSC) holds that only a minority of cells within a tumor have the ability to generate a new tumor. Over the last decade, a large body of literature has implicated the protein CD133 as a marker of organ-specific adult stem cells and in some cancers as a bona fide CSC marker. In this issue of the JCI, Shmelkov et al. challenge the view that CD133 is a marker of CSCs in colon cancer (see the related article, doi:10.1172/JCI34401). CD133 was thought previously to have a very restricted distribution within tissues; the authors have used genetic knock-in models to demonstrate that CD133 in fact is expressed on a wide range of differentiated epithelial cells in adult mouse tissues and on spontaneous primary colon tumors in mice. In primary human colon tumors, all of the epithelial cells also expressed CD133, whereas metastatic colon cancers isolated from liver had distinct CD133(+) and CD133(-)

) epithelial populations. Intriguingly, the authors demonstrate that the CD133(+) and CD133(-) populations were equally capable of tumor initiation in xenografts. In light of these new findings, the popular notion that CD133 is a marker of colon CSCs may need to be revised.

Young SS, Eskenazi B, **Marchetti FM**, Block G, **Wyrobek AJ**. The association of folate, zinc and antioxidant intake with sperm aneuploidy in healthy non-smoking men. *Human Reproduction*, 2008 May;23(5):1014-22.

A major finding of this study was that dietary deficiency of folate was associated with increases production of aneuploid sperm. This is a first demonstration of the impact of folate deficiency on chromosomally defective sperm in human males. This article was heavily cited in the scientific and lay press, as well as on the LBL website. **BACKGROUND:** Little is known about the effect of paternal nutrition on aneuploidy in sperm. We investigated the association of normal dietary and supplement intake of folate, zinc and antioxidants (vitamin C, vitamin E and beta-carotene) with the frequency of aneuploidy in human sperm. **METHODS:** Sperm samples from 89 healthy, non-smoking men from a non-clinical setting were analysed for aneuploidy using fluorescent in situ hybridization with probes for chromosomes X, Y and 21. Daily total intake (diet and supplements) for zinc, folate, vitamin C, vitamin E and beta-carotene was derived from a food frequency questionnaire. Potential confounders were obtained from a self-administered questionnaire. **RESULTS:** After adjusting for covariates, men with high folate intake (>75th percentile) had lower frequencies of sperm with disomies X, 21, sex nullisomy, and a lower aggregate measure of sperm aneuploidy ($P \leq 0.04$) compared with men with lower intake. In adjusted continuous analyses, total folate intake was inversely associated with aggregate sperm aneuploidy (-3.6% change/100 microg folate; 95% CI: -6.3, -0.8) and results were similar for disomies X, 21 and sex nullisomy. No consistent associations were found between antioxidant or zinc intakes and sperm aneuploidy. **CONCLUSIONS:** Men with high folate intake had lower overall frequencies of several types of aneuploid sperm.

Marchetti F, Wyrobek AJ. DNA repair decline during mouse spermiogenesis results in the accumulation of heritable DNA damage. *DNA Repair*, 2008 Apr 2;7(4):572-81.

The postmeiotic phase of mouse spermatogenesis (spermiogenesis) is very sensitive to the genomic effects of environmental mutagens because as male germ cells form mature sperm they progressively lose the ability to repair DNA damage. We hypothesized that repeated exposures to mutagens during this repair-deficient phase result in the accumulation of heritable genomic damage in mouse sperm that leads to chromosomal aberrations in zygotes after fertilization. We used a combination of single or fractionated exposures to diepoxybutane (DEB), a component of tobacco smoke, to investigate how differential DNA repair efficiencies during the 3 weeks of spermiogenesis affected the accumulation of DEB-induced heritable damage in early spermatids (21-15 days before fertilization (dbf)), late spermatids (14-8dbf) and sperm (7-1dbf). Analysis of chromosomal aberrations in zygotic metaphases using PAINT/DAPI showed that late spermatids and sperm are unable to repair DEB-induced DNA damage as demonstrated by significant increases ($P < 0.001$) in the frequencies of zygotes with chromosomal aberrations. Comparisons between single and fractionated exposures suggested that the DNA repair-deficient window during late spermiogenesis may be less than 2 weeks in the mouse and that during this repair-deficient window there is accumulation of DNA damage in sperm. Finally, the dose-response study in sperm indicated a linear response for both single and repeated exposures. These findings show that the differential DNA repair capacity of postmeiotic male germ cells has a major impact on the risk of paternally transmitted heritable damage and suggest that chronic exposures that may occur in the weeks prior to fertilization because of occupational or lifestyle factors (i.e., smoking) can lead to an accumulation of genetic damage in sperm and result in heritable chromosomal aberrations of paternal origin.

Bertin A, McMurray MA, Grob P, Park SS, Garcia G 3rd, Patanwala I, Ng HL, Alber T, Thorner J, **Nogales E**. *Saccharomyces cerevisiae* septins: supramolecular organization of heterooligomers and the mechanism of filament assembly. *Proceedings of the National Academy of Sciences U S A*, 2008 Jun 17;105(24):8274-9. PMID: 18550837

Mitotic yeast cells express five septins (Cdc3, Cdc10, Cdc11, Cdc12, and Shs1/Sep7). Only Shs1 is nonessential. The four essential septins form a complex containing two copies of each, but their arrangement was not known. Single-particle analysis by EM confirmed that the heterooligomer is octameric and revealed that the subunits are arrayed in a linear rod. Identity of each subunit was determined by examining complexes lacking a given septin, by antibody decoration, and by fusion to marker proteins (GFP or maltose binding protein). The rod has the order Cdc11-Cdc12-Cdc3-Cdc10-Cdc10-Cdc3-Cdc12-Cdc11 and, hence, lacks polarity. At low ionic strength, rods assemble end-to-end to form filaments but not when Cdc11 is absent or its N terminus is altered. Filaments invariably pair into long parallel "railroad tracks." Lateral association seems to be mediated by heterotetrameric coiled coils between the paired C-terminal extensions of Cdc3 and Cdc12 projecting orthogonally from each filament. Shs1 may be able to replace Cdc11 at the end of the rod. Our findings provide insights into the molecular mechanisms underlying the function and regulation of cellular septin structures.

Park CC, Zhang HJ, Yao ES, Park CJ, **Bissell MJ**. Beta1 integrin inhibition dramatically enhances radiotherapy efficacy in human breast cancer xenografts. *Cancer Research*, 2008 Jun 1;68(11):4398-405. PMID: 18519702

Beta(1) integrin signaling has been shown to mediate cellular resistance to apoptosis after exposure to ionizing radiation (IR). Other signaling molecules that increase resistance include Akt, which promotes cell survival downstream of beta(1) integrin signaling. We previously showed that beta(1) integrin inhibitory antibodies (e.g., A1B2) enhance apoptosis and decrease growth in human breast cancer cells in three-dimensional laminin-rich extracellular matrix (IrECM) cultures and in vivo. Here, we asked whether A1B2 could synergize with IR to modify Akt-mediated IR resistance. We used three-dimensional IrECM cultures to test the optimal combination of A1B2 with IR treatment of two breast cancer cell lines, MCF-7 and HMT3522-T4-2, as well as T4-2 myr-Akt breast cancer colonies or HMT3522-S-1, which form normal organotypic structures in three-dimensional IrECM. Colonies were assayed for apoptosis and beta(1) integrin/Akt signaling pathways were evaluated using Western blot. In addition, mice bearing MCF-7 xenografts were used to validate the findings in three-dimensional IrECM. We report that A1B2 increased apoptosis optimally post-IR by down-regulating Akt in breast cancer colonies in three-dimensional IrECM. In vivo, addition of A1B2 after IR significantly enhanced tumor growth inhibition and apoptosis compared with either treatment alone. Remarkably, the degree of tumor growth inhibition using A1B2 plus 2 Gy radiation was similar to that of 8 Gy alone. We previously showed that A1B2 had no discernible toxicity in mice; here, its addition allowed for a significant reduction in the IR dose that was necessary to achieve comparable growth inhibition and apoptosis in breast cancer xenografts in vivo.

Veress AI, Weiss JA, Huesman RH, Reutter BW, **Taylor SE**, Sitek A, Feng B, Yang Y, **Gullberg GT**. Measuring regional changes in the diastolic deformation of the left ventricle of SHR rats using microPET technology and hyperelastic warping. *Annals of Biomedical Engineering*, 2008 Jul;36(7):1104-17. PMID: 18437574

The objective of this research was to assess applicability of a technique known as hyperelastic warping for the measurement of local strains in the left ventricle (LV) directly from microPET image data sets. The technique uses differences in image intensities between template (reference) and target (loaded) image data sets to generate a body force that deforms a finite element (FE) representation of the template so that it registers with the target images. For validation, the template image was defined as the end-systolic

microPET image data set from a Wistar Kyoto (WKY) rat. The target image was created by mapping the template image using the deformation results obtained from a FE model of diastolic filling. Regression analysis revealed highly significant correlations between the simulated forward FE solution and image derived warping predictions for fiber stretch ($R^2 = 0.96$), circumferential strain ($R^2 = 0.96$), radial strain ($R^2 = 0.93$), and longitudinal strain ($R^2 = 0.76$) ($p < 0.001$ for all cases). The technology was applied to microPET image data of two spontaneously hypertensive rats (SHR) and a WKY control. Regional analysis revealed that, the lateral freewall in the SHR subjects showed the greatest deformation compared with the other wall segments. This work indicates that warping can accurately predict the strain distributions during diastole from the analysis of microPET data sets.