References

Abdala, A. P., Bissonnette, J. M., & Newman-Tancredi, A. (2014). Pinpointing brainstem mechanisms responsible for autonomic dysfunction in rett syndrome: Therapeutic perspectives for 5-HT1A agonists. *Frontiers in Physiology, 5*, 205.

Rett syndrome is a neurological disorder caused by loss of function of methyl-CpG-binding protein 2 (MeCP2). Reduced function of this ubiquitous transcriptional regulator has a devastating effect on the central nervous system. One of the most severe and life-threatening presentations of this syndrome is brainstem dysfunction, which results in autonomic disturbances such as breathing deficits, typified by episodes of breathing cessation intercalated with episodes of hyperventilation or irregular breathing. Defects in numerous neurotransmitter systems have been observed in Rett syndrome both in animal models and patients. Here we dedicate special attention to serotonin due to its role in promoting regular breathing, increasing vagal tone, regulating mood, alleviating Parkinsonian-like symptoms and potential for therapeutic translation. A promising new symptomatic strategy currently focuses on regulation of serotonergic function using highly selective serotonin type 1A (5-HT1A) "biased agonists." We address this newly emerging therapy for respiratory brainstem dysfunction and challenges for translation with a holistic perspective of Rett syndrome, considering potential mood and motor effects.

Abdala, A. P., Lioy, D. T., Garg, S. K., Knopp, S. J., Paton, J. F. R., & Bissonnette, J. M. (2014). Effect of sarizotan, a 5-HT1a and D2-like receptor agonist, on respiration in three mouse models of rett syndrome. *American Journal of Respiratory Cell and Molecular Biology, 50*(6), 1031-1039.

Disturbances in respiration are common and debilitating features of Rett syndrome (RTT). A previous study showed that the 5-HT1a receptor agonist (R)-(+)-8-hydroxy-dipropyl-2-aminotetralin hydrobromide (8-OH-DPAT) significantly reduced the incidence of apnea and the irregular breathing pattern in amouse model of the disorder. 8-OH-DPAT, however, is not available for clinical practice. Sarizotan, a full 5- HT1a agonist and a dopamine D2 -like agonist/partial agonist, has been used in clinical trials for the treatment of L-dopa- induced dyskinesia. The purpose of this study was to evaluate the effects of sarizotan on respiration and locomotion in mouse models of RTT. Studies were performed in Bird and Jaenisch strains of methyl-CpG- binding protein 2- - deficient heterozygous female and Jaenisch strain Mecp2 null

male mice and in knock-in heterozygous female mice of a common nonsense mutation (R168X). Respiratory pattern was determined with body plethysmography, and locomotion was determined with open-field recording. Sarizotan or vehicle was administered 20 minutes before a 30-minute recording of respiratory pattern or motor behavior. In separate studies, a crossover design was used to administer the drug for 7 and for 14 days. Sarizotan reduced the incidence of apnea in all three RTTmousemodels to approximately 15% of their pretreatment levels. The irregular breathing pattern was corrected to that of wild-type littermates. When administered for 7 or 14 days, apnea decreased to 25 to 33% of the incidence seen with vehicle. This study indicates that the clinically approved drug sarizotan is an effective treatment for respiratory disorders in mouse models of RTT. 

Abdel-Jabbar, N., Baptista, A. M., Karna, T., Turner, P., & Sen, G. (2013). *US experience will advance gulf ecosystem research* (Wuhan ed.) Springer Verlag.

This paper addresses the vision and early steps of the cooperation between the Center for Coastal Margin Observation and Prediction (CMOP) in Oregon, United States and the emerging Gulf Ecosystems Research Center (GERC) at the American University of Sharjah, UAE. The cooperation focuses on a better understanding and ability to predict the Arabian Gulf as a complex ecosystem, and involves science, technology and training components. An ultimate goal is the development for the Gulf of a "collaboratory" inspired on the concepts of integration of observations, simulations and stakeholder needs developed by CMOP for the Columbia River coastal margin, in the Eastern North Pacific. An early phase of the cooperation addresses the development of a 3D numerical model for the Arabian Gulf water circulation. A very preliminary forecasting system has been developed at CMOP, and its skill will be systematically assessed and improved by GERC and CMOP over the next several years, with the progressive deployment of a targeted observation network. Preliminary products include the visualization of the salinity fields associated with various river plumes. The model used was SELFE (a Semiimplicit Eulerian-Lagrangian Finite-Element model for cross-scale ocean circulation), the same that is being used for the Gulf predictions. Exploratory simulations were made to assess the ability of simple grid refinement strategies and/or use of higher order numerical schemes in improving the representation of the complex dynamics of plumes, filaments (eddies) and upwelling in the

continental shelf of the Eastern North Pacific, off the Columbia River. Results suggested the need for automated grid optimization strategies, which are currently in progress. © Springer-Verlag Berlin Heidelberg 2013.

Affara, N. I., Ruffell, B., Medler, T. R., Gunderson, A. J., Johansson, M., Bornstein, S., et al. (2014). B cells regulate macrophage phenotype and response to chemotherapy in squamous carcinomas. *Cancer Cell, 25*(6), 809-821.

B cells foster squamous cell carcinoma (SCC) development through deposition of immunoglobulin-containing immune complexes in premalignant tissue and Fcgamma receptor-dependent activation of myeloid cells. Because human SCCs of the vulva and head and neck exhibited hallmarks of B cell infiltration, we examined B cell-deficient mice and found reduced support for SCC growth. Although ineffective as a single agent, treatment of mice bearing preexisting SCCs with B cell-depleting alphaCD20 monoclonal antibodies improved response to platinum- and Taxol-based chemotherapy. Improved chemoresponsiveness was dependent on altered chemokine expression by macrophages that promoted tumor infiltration of activated CD8(+) lymphocytes via CCR5-dependent mechanisms. These data reveal that B cells, and the downstream myeloid-based pathways they regulate, represent tractable targets for anticancer therapy in select tumors.

Ahani, A., Wahbeh, H., Nezamfar, H., Miller, M., Erdogmus, D., & Oken, B. (2014). Quantitative change of EEG and respiration signals during mindfulness meditation. *Journal of Neuroengineering and Rehabilitation, 11*(1), 87-0003-11-87.

BACKGROUND: This study investigates measures of mindfulness meditation (MM) as a mental practice, in which a resting but alert state of mind is maintained. A population of older people with high stress level participated in this study, while electroencephalographic (EEG) and respiration signals were recorded during a MM intervention. The physiological signals during meditation and control conditions were analyzed with signal processing. METHODS: EEG and respiration data were collected and analyzed on 34 novice meditators after a 6-week meditation intervention. Collected data were analyzed with spectral analysis, phase analysis and classification to evaluate an objective marker for meditation. RESULTS: Different frequency bands

showed differences in meditation and control conditions. Furthermore, we established a classifier using EEG and respiration signals with a higher accuracy (85%) at discriminating between meditation and control conditions than a classifier using the EEG signal only (78%). CONCLUSION: Support vector machine (SVM) classifier with EEG and respiration feature vector is a viable objective marker for meditation ability. This classifier should be able to quantify different levels of meditation depth and meditation experience in future studies.

Alfadhli, A., & Barklis, E. (2014). The roles of lipids and nucleic acids in HIV-1 assembly. *Frontiers in Microbiology, 5*, 253.

During HIV-1 assembly, precursor Gag (PrGag) proteins are delivered to plasma membrane (PM) assembly sites, where they are triggered to oligomerize and bud from cells as immature virus particles. The delivery and triggering processes are coordinated by the PrGag matrix (MA) and nucleocapsid (NC) domains. Targeting of PrGag proteins to membranes enriched in cholesterol and phosphatidylinositol-4,5-bisphosphate (PI[4,5]P2) is mediated by the MA domain, which also has been shown to bind both RNA and DNA. Evidence suggests that the nucleic-acid-binding function of MA serves to inhibit PrGag binding to inappropriate intracellular membranes, prior to delivery to the PM. At the PM, MA domains putatively trade RNA ligands for PI(4,5)P2 ligands, fostering high-affinity membrane binding. Triggering of oligomerization, budding, and virus particle release results when NC domains on adjacent PrGag proteins bind to viral RNA, leading to capsid (CA) domain oligomerization. This process leads to the assembly of immature virus shells in which hexamers of membrane-bound MA trimers appear to organize above interlinked CA hexamers. Here, we review the functions of retroviral MA proteins, with an emphasis on the nucleic-acid-binding capability of the HIV-1 MA protein, and its effects on membrane binding.

Ali, A., & Rosenbaum, J. T. (2014). TINU (tubulointerstitial nephritis uveitis) can be associated with chorioretinal scars. *Ocular Immunology and Inflammation, 22*(3), 213-217.

Purpose: To report a case series of patients with chorioretinal lesions secondary to tubulointerstitial nephritis and uveitis (TINU). Methods: Retrospective chart review of patients with TINU. Results: We found 4 patients (3 with a possible or probable diagnosis of TINU and 1 with a definite diagnosis of TINU) and multiple chorioretinal lesions. Conclusion: Tubulointerstitial

nephritis and uveitis usually presents with anterior uveitis, but chorioretinal lesions do occur and may facilitate the diagnosis. © 2014 Informa Healthcare USA, Inc. All rights reserved: reproduction in whole or part not permitted.

Amara, S. G., Underhill, S. M., Wheeler, D. S., Hong, C. W., Murdoch, G. H., Romero, G., et al. (2013). *A new take on uptake: Dopamine transporters and the cellular mechanisms of amphetamine action* Elsevier Inc.

Anacker, A. M., Smith, M. L., & Ryabinin, A. E. (2014). Establishment of stable dominance interactions in prairie vole peers: Relationships with alcohol drinking and activation of the paraventricular nucleus of the hypothalamus. *Social Neuroscience,* , 1-11.

Dominance hierarchies are an important aspect of group-living as they determine individual access to resources. The existence of dominance ranks in access to space has not been described in socially monogamous, communally nesting prairie voles (Microtus ochrogaster). Here, we tested whether dominance could be assessed using the tube test. We also tested whether dominance related to alcohol intake, similar to what has been demonstrated in nonmonogamous species. Same-sex pairs of unfamiliar peers were tested in a series of three trials of the tube test, then paired and allowed individual access to alcohol and water for 4 days, and then tested again in the tube test. For all pairs, the same subjects won the majority of trials before and after alcohol drinking. The number of wins negatively correlated with alcohol intake on the first day of drinking and positively correlated with levels of Fos in the paraventricular nucleus of the hypothalamus following the tube test in a separate group of voles. Dominance was not related to Fos levels in other brain regions examined. Together, these results indicate that prairie voles quickly establish stable dominance ranks through a process possibly involving the hypothalamus and suggest that dominance is linked to alcohol drinking.

Angier, H., DeVoe, J. E., Tillotson, C., Wallace, L., & Gold, R. (2013). Trends in health insurance status of US children and their parents, 1998-2008. *Maternal and Child Health Journal, 17*(9), 1550-1558.

In the United States (US), a parent's health insurance status affects their children's access to health care making it critically important to examine trends in coverage for both children and

parents. To gain a better understanding of these health insurance trends, we assessed the coverage status for both children and their parents over an 11-year time period (1998-2008). We conducted secondary analysis of data from the nationally-representative Medical Expenditure Panel Survey. We examined frequency distributions for full-year child/parent insurance coverage status by family income, conducted Chi-square tests of association to assess significant differences over time, and explored factors associated with full-year insurance coverage status in 1998 and in 2008 using logistic regression. When considering all income groups together, the group with both child and parent insured decreased from 72.4 % in 1998 to 67.2 % in 2008. When stratified by income, the percentage of families with an insured child, but an uninsured parent increased for low-income families from 12.4 to 25.1 % and from 3.8 to 7.1 % for middle-income families when comparing 1998-2008. In regression analyses, family income remained the strongest characteristic associated with a lack of full-year health insurance. As future policy reforms take shape, it will be important to look beyond children's coverage patterns to assess whether gains have been made in overall family coverage.

Apostolides, P. F., & Trussell, L. O. (2014). Superficial stellate cells of the dorsal cochlear nucleus. *Frontiers in Neural Circuits, 8*, 63.

The dorsal cochlear nucleus (DCN) integrates auditory and multisensory signals at the earliest levels of auditory processing. Proposed roles for this region include sound localization in the vertical plane, head orientation to sounds of interest, and suppression of sensitivity to expected sounds. Auditory and non-auditory information streams to the DCN are refined by a remarkably complex array of inhibitory and excitatory interneurons, and the role of each cell type is gaining increasing attention. One inhibitory neuron that has been poorly appreciated to date is the superficial stellate cell. Here we review previous studies and describe new results that reveal the surprisingly rich interactions that this tiny interneuron has with its neighbors, interactions which enable it to respond to both multisensory and auditory afferents.

Armsby, L., Beekman, R. H.,3rd, Benson, L., Fagan, T., Hagler, D. J., Hijazi, Z. M., et al. (2014). SCAI expert consensus statement for advanced training programs in pediatric and congenital interventional cardiac catheterization. *Catheterization and Cardiovascular Interventions : Official*

*Journal of the Society for Cardiac Angiography & Interventions,*

Pediatric and Congenital Interventional Cardiology is the practice of catheter-based techniques that improve cardiac physiology and circulation through the treatment of heart disease in children and adults with congenital or acquired heart defects. Over the last decade, and since last published training guidelines for pediatric cardiac catheterization and interventional cardiology were published in 2005 [1] the field of Pediatric and Congenital Cardiac Catheterization has evolved into a predominantly interventional discipline. As there is no sub-specialty certification for interventional cardiac catheterization in pediatrics, the Congenital Heart Disease Committee of the Society of Cardiovascular Angiography and Interventions has put together this consensus statement for advanced training in pediatric and congenital interventional cardiac catheterization. The statement puts forth recommendations for program infrastructure in terms of teaching, personnel, equipment, facilities, conferences, patient volume and trainee assessment. This is meant to set a standard for training programs as well as giving applicants a basis on which to judge and compare programs. (c) 2014 Wiley Periodicals, Inc.

Ash, J. S., & Hartzog, T. H. (2014). *Organizational and cultural change* Elsevier Inc.

This chapter addresses organizational and cultural change issues related to clinical decision support (CDS). It describes how different types of settings and users may influence acceptance and therefore change strategies concerning decision support, how issues of organizational and personal control and professional autonomy are associated with decision support, how different stakeholder groups view decision support, and how an analysis can be done to assist in the development of change strategies. 

Backeljauw, P. F., Dattani, M. T., Cohen, P., & Rosenfeld, R. G. (2014). *Disorders of growth hormone/insulin-like growth factor secretion and action* Elsevier Inc.

Banta-Wright, S. A., Kodadek, S. M., Steiner, R. D., & Houck, G. M. (2014). Challenges to breastfeeding infants with phenylketonuria. *Journal of Pediatric Nursing,*

Breastfeeding duration for infants with phenylketonuria (PKU) is less than other full-term infants. However, no study has examined the challenges encountered by mothers' breastfeeding infants with PKU. In 75 mothers of a child with PKU, three categories of breastfeeding challenges were

identified: common breastfeeding issues, breastfeeding and PKU, and no challenges. The common breastfeeding issues can be identified in the literature but for these mothers, the issues are heightened due to frequent phenylalanine (Phe) monitoring. Even so, many mothers adapt breastfeeding to maintain desired Phe levels. A few mothers had no issues and were the exception, not the norm.

Barbati, A. C., Fang, C., Banker, G., & Kirby, B. J. (2009). Microfluidic device and culture platform for the observation and control of axonal growth and axonal organelle transport of rat hippocampal neurons. *13th International Conference on Miniaturized Systems for Chemistry and Life Sciences, MicroTAS 2009,* Jeju. pp. 481-483.

We report the design, fabrication, and implementation of a device to culture rat hippocampal neurons guided by arrays of cell-adhesive biopolymers on traditional cell culture substrates. These guided arrays of cells are shown to permit live-imaging of mitochondrial transport through the cell axon. We further report the development of a microfluidic device to deliver solutes to discrete sections of rat hippocampal neurons with spatial and temporal resolution. © 2009 CBMS.

Bennett, T. A., Szatmari, P., Georgiades, K., Hanna, S., Janus, M., Georgiades, S., et al. (2014). Language impairment and early social competence in preschoolers with autism spectrum disorders: A comparison of DSM-5 profiles. *Journal of Autism and Developmental Disorders,*

Children with autism spectrum disorder (ASD) and structural language impairment (LI) may be at risk of more adverse social-developmental outcomes. We examined trajectories of early social competence (using the Vineland-II) in 330 children aged 2-4 years recently diagnosed with ASD, and compared 3 subgroups classified by: language impairment (ASD/LI); intellectual disability (ASD/ID) and ASD without LI or ID (ASD/alone). Children with ASD/LI were significantly more socially impaired at baseline than the ASD/alone subgroup, and less impaired than those with ASD/ID. Growth in social competence was significantly slower for the ASD/ID group. Many preschool-aged children with ASD/LI at time of diagnosis resembled "late talkers" who appeared to catch up linguistically. Children with ASD/ID were more severely impaired and continued to lag further behind. © 2014 Springer Science+Business Media New York.

Bethea, C. L., Coleman, K., Phu, K., Reddy, A. P., & Phu, A. (2014). Relationships between androgens, serotonin gene expression and innervation in male macaques. *Neuroscience, 274C*, 341-356.

Androgen administration to castrated individuals was purported to decrease activity in the serotonin system. However, we found that androgen administration to castrated male macaques increased fenfluramine-induced serotonin release as reflected by increased prolactin secretion. In this study, we sought to define the effects of androgens and aromatase inhibition on serotonin-related gene expression in the dorsal raphe, as well as serotonergic innervation of the LC. Male Japanese macaques (Macaca fuscata) were castrated for 5-7months and then treated for 3months with (1) placebo, (2) testosterone (T), (3) dihydrotestosterone (DHT; non-aromatizable androgen) and ATD (steroidal aromatase inhibitor), or (4) Flutamide (FLUT; androgen antagonist) and ATD (n=5/group). This study reports the expression of serotonin-related genes: tryptophan hydroxylase 2 (TPH2), serotonin reuptake transporter (SERT) and the serotonin 1A autoreceptor (5HT1A) using digoxigenin-ISH and image analysis. To examine the production of serotonin and the serotonergic innervation of a target area underlying arousal and vigilance, we measured the serotonin axon density entering the LC with ICC and image analysis. TPH2 and SERT expression were significantly elevated in T- and DHT+ATD-treated groups over placebo- and FLUT+ATD-treated groups in the dorsal raphe (pplacebo>DHT+ATD=FLUT+ATD treatments. Comparatively, T- and DHT+ATD-treated groups had elevated TPH2 and SERT gene expression, but the DHT+ATD group had markedly suppressed serotonin axon density relative to the T-treated group. Further comparison with previously published data indicated that TPH2 and SERT expression reflected yawning and basal prolactin secretion. The serotonin axon density in the LC agreed with the area under the fenfluramine-stimulated prolactin curve, providing a morphological basis for the pharmacological results. This suggested that androgen activity increased TPH2 and SERT gene expression but, aromatase activity, and neural production of estradiol (E), may subserve axonal serotonin and determination of the compartment acted upon by fenfluramine. In summary, androgens stimulated serotonin-related gene expression, but aromatase inhibition dissociated gene expression from the serotonin innervation of the LC terminal field and fenfluramine-stimulated prolactin secretion.

Bian, F., Simon, R. P., Li, Y., David, L., Wainwright, J., Hall, C. L., et al. (2014). Nascent proteomes in peripheral blood mononuclear cells as a novel source for biomarker discovery in human stroke. *Stroke; a Journal of Cerebral Circulation, 45*(4), 1177-1179.

BACKGROUND AND PURPOSE: The proteome of newly synthesized proteins (nascent proteome) in peripheral blood mononuclear cells (PBMCs) can be a novel source of stroke biomarkers. Changes in the PBMC nascent proteome after stroke reflect the dynamic response-in-action not detectable in the total proteome (all existing proteins) in blood. Here, we test the application of nascent proteomics as a novel approach for stroke biomarker discovery. METHODS: The PBMC nascent proteome in human blood was determined by metabolic labeling of fresh PBMC cultures with azidohomoalanine (an azide-containing methionine surrogate), followed by mass spectrometry detection and quantification of azidohomoalanine-labeled proteins. The PBMC nascent and total proteomes were compared between patients with stroke and matched controls. RESULTS: Both PBMC nascent and total proteomes showed differences between stroke patients and controls. Results of hierarchical clustering analysis of proteomic data revealed greater changes in the nascent than in the total PBMC proteomes, supporting the usefulness of the PBMC nascent proteome as a novel source of stroke biomarkers. CONCLUSIONS: Nascent proteomes in PBMC can be a novel source for biomarker discovery in human stroke.

Bianco, K., Norton, R., Schwab, F., Smith, J. S., Klineberg, E., Obeid, I., et al. (2014). Complications and intercenter variability of three-column osteotomies for spinal deformity surgery: A retrospective review of 423 patients. *Neurosurgical Focus, 36*(5)

Object: Three-column resection osteotomies (3COs) are commonly performed for sagittal deformity but have high rates of reported complications. Authors of this study aimed to examine the incidence of and intercenter variability in major intraoperative complications (IOCs), major postoperative complications (POCs) up to 6 weeks postsurgery, and overall complications (that is, both IOCs and POCs). They also aimed to investigate the incidence of and intercenter variability in blood loss during 3CO procedures. Methods: The incidence of IOCs, POCs, and overall complications associated with 3COs were retrospectively determined for the study population and for each of 8 participating surgical centers. The incidence of major blood loss (MBL) over 4 L and the percentage of total blood volume lost were also determined for the study population and each

surgical center. Complication rates and blood loss were compared between patients with one and those with two osteotomies, as well as between patients with one thoracic osteotomy (ThO) and those with one lumbar or sacral osteotomy (LSO). Risk factors for developing complications were determined. Results: Retrospective review of prospectively acquired data for 423 consecutive patients who had undergone 3CO at 8 surgical centers was performed. The incidence of major IOCs, POCs, and overall complications was 7%, 39%, and 42%, respectively, for the study population overall. The most common IOC was spinal cord deficit (2.6%) and the most common POC was unplanned return to the operating room (19.4%). Patients with two osteotomies had more POCs (56% vs 38%, p = 0.04) than the patients with one osteotomy. Those with ThO had more IOCs (16% vs 6%, p = 0.03), POCs (58% vs 34%, p 60 years), two osteotomies, ThO, and MBL © AANS, 2014.

Bishop, C. V., Molskness, T. A., Xu, F., Belcik, J. T., Lindner, J. R., Slayden, O. D., et al. (2014). Quantification of dynamic changes to blood volume and vascular flow in the primate corpus luteum during the menstrual cycle. *Journal of Medical Primatology,*

BACKGROUND: The objective of the current study was to determine changes to vascular parameters of nonhuman primate dominant ovarian structures by dynamic contrast-enhanced ultrasound (DCE-US). MATERIALS AND METHODS: Dynamic contrast-enhanced ultrasound with intravenous microbubble infusion was performed on the rhesus macaque ovary bearing the pre-ovulatory follicle and corpus luteum (CL) sequentially during the natural luteal phase (n = 8) and GnRH antagonist (antide)-induced luteal regression (n = 6). RESULTS: Changes in luteal blood volume (BV) and vascular flow (VF) were observed between stages of the luteal phase Luteal BV was highest in early stage CL, before decreasing 2.5-fold in late stage CL (P < 0.06); in contrast, luteal VF peaked at mid luteal stage (P < 0.01). Two females identified with luteal insufficiency trended toward lower peak BV, compared to typical CLs. Another female was identified with a luteal cyst on the contralateral ovary, and a CL that regressed before P levels declined. After 72 hours of antide exposure, BV was reduced 2.3-fold (P = 0.03). CONCLUSIONS: DCE-US provides a sensitive, non-invasive measurement of the dynamics of blood volume and flow in dominant ovarian structures.

Bittel, A. M., Nickerson, A. K., Lin, L. -., Nan, X., & Gibbs, S. L. (2014). Design and development of BODIPY-based photoswitchable fluorophores to visualize cell signaling with multispectral super resolution microscopy. *Single Molecule Spectroscopy and Superresolution Imaging VII,* San Francisco, CA. *, 8950.*

Super resolution microscopy (SRM) has overcome the historic spatial resolution limit of light microscopy, enabling fluorescence visualization of cellular structures and multi-protein complexes at the nanometer scale. Using singlemolecule localization microscopy, the precise location of a stochastically activated population of photoswitchable fluorophores is determined during the collection of many images to form a single image with resolution of ~10-20 nm, an order of magnitude improvement over conventional microscopy. However, the spectral resolution of current SRM techniques are limited by existing fluorophores with only up to four colors imaged simultaneously, limiting the number of intracellular components that can be studied in a single sample. In the current work, a library of novel BODIPY-based fluorophores was synthesized using a solid phase synthetic platform with the goal of creating a set of photoswitchable fluorophores that can be excited by 5 distinct laser lines but emit throughout the spectral range (450-850 nm) enabling multispectral super resolution microscopy (MSSRM). The photoswitching properties of all new fluorophores were quantified for the following key photoswitching characteristics: (1) the number of photons per on cycle (2) the number of on cycles (switching events), (3) the percentage of time the fluorophore spends in the fluorescent on and off states, and (4) the susceptibility of the fluorophore to photobleaching (time of last event). To ensure the accuracy of our photoswitching measurements, our methodology to detect and quantitate the photoswitching properties of individual fluorophore molecules was validated by comparing measured photoswitching properties of three commercial dyes to published results.1 We also identified two efficient methods to positionally isolate fluorophores on coverglass for screening of the BODIPY-based library. © 2014 SPIE.

Bodhankar, S., Chen, Y., Vandenbark, A. A., Murphy, S. J., & Offner, H. (2013). PD-L1 enhances CNS inflammation and infarct volume following experimental stroke in mice in opposition to PD-1. *Journal of Neuroinflammation, 10*, 111-2094-10-111.

BACKGROUND: Stroke severity is worsened by recruitment of inflammatory immune cells into the

brain. This process depends in part on T cell activation, in which the B7 family of co-stimulatory molecules plays a pivotal role. Previous studies demonstrated more severe infarcts in mice lacking programmed death-1 (PD-1), a member of the B7 family, thus implicating PD-1 as a key factor in limiting stroke severity. The purpose of this study was to determine if this protective effect of PD-1 involves either of its ligands, PD-L1 or PD-L2. METHODS: Central nervous system (CNS) inflammation and infarct volume were evaluated in male PD-L1 and PD-L2 knockout (-/-) mice undergoing 60 minutes of middle cerebral artery occlusion (MCAO) followed by 96 hours of reperfusion and compared to wild-type (WT) C57BL/6J mice. RESULTS: PD-L1-/- and PD-L2-/- mice had smaller total infarct volumes compared to WT mice. The PD-L1-/- and to a lesser extent PD-L2-/- mice had reduced levels of proinflammatory activated microglia and/or infiltrating monocytes and CD4+ T cells in the ischemic hemispheres. There was a reduction in ischemia-related splenic atrophy accompanied by lower activation status of splenic T cells and monocytes in the absence of PD-L1, suggesting a pathogenic rather than a regulatory role for both PD-1 ligands (PD-Ls). Suppressor T cells (IL-10-producing CD8+CD122+ T cells) trafficked to the brain in PD-L1-/- mice and there was decreased expression of CD80 on splenic antigen-presenting cells (APCs) as compared to the WT and PD-L2-/- mice. CONCLUSIONS: Our novel observations are the first to implicate PD-L1 involvement in worsening outcome of experimental stroke. The presence of suppressor T cells in the right MCAO-inflicted hemisphere in mice lacking PD-L1 implicates these cells as possible key contributors for controlling adverse effects of ischemia. Increased expression of CD80 on APCs in WT and PD-L2-/- mice suggests an overriding interaction leading to T cell activation. Conversely, low CD80 expression by APCs, along with increased PD-1 and PD-L2 expression in PD-L1-/- mice suggests alternative T cell signaling pathways, leading to a suppressor phenotype. These results suggest that agents (for example antibodies) that can target and neutralize PD-L1/2 may have therapeutic potential for treatment of human stroke.

Bohlen, M., Hayes, E. R., Bohlen, B., Bailoo, J., Crabbe, J. C., & Wahlsten, D. (2014). Experimenter effects on behavioral test scores of eight inbred mouse strains under the influence of ethanol. *Behavioural Brain Research,*

Eight standard inbred mouse strains were evaluated for ethanol effects on a refined battery of

behavioral tests in a study that was originally designed to assess the influence of rat odors in the colony on mouse behaviors. As part of the design of the study, two experimenters conducted the tests, and the study was carefully balanced so that equal numbers of mice in all groups and times of day were tested by each experimenter. A defect in airflow in the facility compromised the odor manipulation, and in fact the different odor exposure groups did not differ in their behaviors. The two experimenters, however, obtained markedly different results for three of the tests. Certain of the experimenter effects arose from the way they judged behaviors that were not automated and had to be rated by the experimenter, such as slips on the balance beam. Others were not evident prior to ethanol injection but had a major influence after the injection. For several measures, the experimenter effects were notably different for different inbred strains. Methods to evaluate and reduce the impact of experimenter effects in future research are discussed.

Bolkan, B. J., & Kretzschmar, D. (2014). Loss of tau results in defects in photoreceptor development and progressive neuronal degeneration in drosophila. *Developmental Neurobiology,* Accumulations of Tau, a microtubule-associated protein (MAP), into neurofibrillary tangles is a hallmark of Alzheimer's disease and other tauopathies. However, the mechanisms leading to this pathology are still unclear: the aggregates themselves could be toxic or the sequestration of Tau into tangles might prevent Tau from fulfilling its normal functions, thereby inducing a loss of function defect. Surprisingly, the consequences of losing normal Tau expression in vivo are still not well understood, in part due to the fact that Tau knockout mice show only subtle phenotypes, presumably due to the fact that mammals express several MAPs with partially overlapping functions. In contrast, flies express fewer MAP, with Tau being the only member of the Tau/MAP2/MAP4 family. Therefore, we used Drosophila to address the physiological consequences caused by the loss of Tau. Reducing the levels of fly Tau (dTau) ubiquitously resulted in developmental lethality, whereas deleting Tau specifically in neurons or the eye caused progressive neurodegeneration. Similarly, chromosomal mutations affecting dTau also caused progressive degeneration in both the eye and brain. Although photoreceptor cells initially developed normally in dTau knockdown animals, they subsequently degenerated during late pupal stages whereas weaker dTau alleles caused an age-dependent defect in rhabdomere structure. Expression of wild type human Tau partially rescued the neurodegenerative phenotype

caused by the loss of endogenous dTau, suggesting that the functions of Tau proteins are functionally conserved from flies to humans. (c) 2014 Wiley Periodicals, Inc. Develop Neurobiol, 2014.

Bourdette, D. (2014). Alemtuzumab and multiple sclerosis: Is it safe? *Neurology,*

Bowman, A. B., Kwakye, G. F., Hernandez, E. H., & Aschner, M. (2014). The role of manganese in neurodegenerative diseases. [Die Rolle von Mangan bei neurodegenerativen Erkrankungen] *Perspectives in Medicine, 2*(1-4), 91-108.

Brambrink, A. M., & Hagberg, C. A. (2012). *The ASA difficult airway algorithm: Analysis and presentation of a new algorithm* Elsevier Inc.

Brickman, D., & Gross, N. D. (2014). Robotic approaches to the pharynx: Tonsil cancer. *Otolaryngologic Clinics of North America, 47*(3), 359-372.

Treatment of squamous cell carcinoma of the oropharynx is challenging because of its effects on speech and swallowing, which may affect quality of life. Transoral robotic surgery may be an effective alternative to open surgery. Robotic lateral oropharyngectomy is best suited for early stage oropharyngeal squamous cell carcinoma, with the goal of avoiding or reducing the use or dose of adjuvant therapies. Successful robotic lateral oropharyngectomy requires appropriate training, detailed preoperative planning, organized operating room setup to obtain exposure, an understanding of the pertinent surgical anatomy, and knowledge of the postoperative care of the oncologic patient.

Broberg, C. S., Prasad, S. K., Carr, C., Babu-Narayan, S. V., Dimopoulos, K., & Gatzoulis, M. A. (2014). Myocardial fibrosis in eisenmenger syndrome: A descriptive cohort study exploring associations of late gadolinium enhancement with clinical status and survival. *Journal of Cardiovascular Magnetic Resonance : Official Journal of the Society for Cardiovascular Magnetic Resonance, 16*(1), 32-429X-16-32.

BACKGROUND: A relationship between myocardial fibrosis and ventricular dysfunction has been demonstrated using late gadolinium enhancement (LGE) in the pressure-loaded right ventricle

from congenital heart defects. In patients with Eisenmenger syndrome (ES), the presence of LGE has not been investigated. The aims of this study were to detect any myocardial fibrosis in ES and describe major clinical variables associated with the finding. METHODS: From 45 subjects screened, 30 subjects (age 43 +/- 13 years, 20 female) underwent prospective cardiovascular magnetic resonance with LGE to quantify biventricular volume and function as well as maximal and submaximal exercise during a single visit. Standard cine acquisitions were obtained for ventricular volume and function. Further imaging was performed after administration of 0.1 mmol/kg gadolinium contrast. Regions of LGE were evaluated qualitatively and quantitatively by manual contouring of identified areas, with total area expressed as a percentage of mass. Patients were followed prospectively (mean follow up 7.4 +/- 0.4 years) and any deaths recorded. Patients with LGE findings were compared to those without. RESULTS: LGE was present in 22/30 (73%) patients, specifically in RV myocardium (70%), RV trabeculae (60%), LV myocardium (33%) or LV papillary muscles (30%), though in small amounts (mean 1.4% of total ventricular mass, range 0.16 - 6.0%). Those with any LGE were not different in age, history of arrhythmia, desaturation, nor hemoglobin, nor ventricular size, mass, or function. Exercise capacity was low, but also not different between those with and without LGE. Similarly no significant associations were found with amount of fibrosis. There were five deaths among patients with LGE, versus two in patients without, but no difference in survival (log rank =0.03, P = 0.85). CONCLUSIONS: Myocardial fibrosis by LGE is common in ES, though not extensive. The presence and quantity of LGE did not correlate with ventricular size, function, degree of cyanosis, exercise capacity, or survival in this pilot study. More data are clearly required before recommendations for routine use of LGE in these patients can be made.

Brown, J. R., Byrd, J. C., Coutre, S. E., Benson, D. M., Flinn, I. W., Wagner-Johnston, N. D., et al. (2014). Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood, 123*(22), 3390-3397.

In a phase 1 trial, idelalisib (GS-1101, CAL-101), a selective inhibitor of the lipid kinase PI3Kd, was evaluated in 54 patients with relapsed/refractory chronic lymphocytic leukemia (CLL) with adverse characteristics including bulky lymphadenopathy (80%), extensive prior therapy (median 5 [range 2-14] prior regimens), treatment-refractory disease (70%), unmutated IGHV (91%),

and del17p and/or TP53 mutations (24%). Patients were treated at 6 dose levels of oral idelalisib (range 50-350 mg once or twice daily) and remained on continuous therapy while deriving clinical benefit. Idelalisib-mediated inhibition of PI3Kd led to abrogation of Akt phosphorylation in patient CLL cells and significantly reduced serum levels of CLL-related chemokines. The most commonly observed grade ≥3 adverse events were pneumonia (20%), neutropenic fever (11%), and diarrhea (6%). Idelalisib treatment resulted in nodal responses in 81% of patients. The overall response rate was 72%, with 39% of patients meeting the criteria for partial response per IWCLL 2008 and 33% meeting the recently updated criteria of PR with treatment-induced lymphocytosis.1,2 The median progression-free survival for all patients was 15.8 months. This study demonstrates the clinical utility of inhibiting the PI3Kd pathway with idelalisib. Our findings support the further development of idelalisib in patients with CLL. These trials were registered at clinicaltrials.gov as #NCT00710528 and #NCT01090414. © 2014 by The American Society of Hematology.

Bruckner, T. A., Cheng, Y. W., Singh, A., & Caughey, A. B. (2014). Economic downturns and male cesarean deliveries: A time-series test of the economic stress hypothesis. *BMC Pregnancy and Childbirth, 14*(1)

Background: In light of the recent Great Recession, increasing attention has focused on the health consequences of economic downturns. The perinatal literature does not converge on whether ambient economic declines threaten the health of cohorts in gestation. We set out to test the economic stress hypothesis that the monthly count of cesarean deliveries (CD), which may gauge the level of fetal distress in a population, rises after the economy declines. We focus on male CD since the literature reports that male more than female fetuses appear sensitive to stressors in utero.Methods: We tested our ecological hypothesis in California for 228 months from January 1989 to December 2007, the most recent data available to us at the time of our tests. We used as the independent variable the Bureau of Labor Statistics unadjusted total state employment series. Time-series methods controlled for patterns of male CD over time. We also adjusted for the monthly count of female CD, which controls for well-characterized factors (e.g., medical-legal environment, changing risk profile of births) that affect CD but are shared across infant sex.Results: Findings support the economic stress hypothesis in that male CD increases

above its expected value one month after employment declines (employment coefficient = -24.09, standard error = 11.88, p = .04). Additional exploratory analyses at the metropolitan level indicate that findings in Los Angeles and Orange Counties appear to drive the State-level relation.Conclusions: Contracting economies may perturb the health of male more than female fetuses sufficiently enough to warrant more CD. Male relative to female CD may sensitively gauge the cohort health of gestations. 

Bubier, J. A., Jay, J. J., Baker, C. L., Bergeson, S. E., Ohno, H., Metten, P., et al. (2014). Identification of a QTL in mus musculus for alcohol preference, withdrawal and Ap3m2 expression using integrative functional genomics and precision genetics. *Genetics,*

Extensive genetic and genomic studies of the relationship between alcohol drinking preference and withdrawal severity have been performed using animal models. Data from multiple such publications and public data resources have been incorporated in GeneWeaver's database of over 60,000 gene sets including 285 alcohol withdrawal and preference related gene sets. Among these are evidence for positional candidates regulating these behaviors in overlapping quantitative trait loci (QTL) mapped in distinct mouse populations. Combinatorial integration of functional genomics experimental results revealed a single QTL positional candidate gene in one of the loci common to both preference and withdrawal. Functional validation studies in Ap3m2 knock-out mice confirmed these relationships. Genetic validation involves confirming the existence of segregating polymorphisms that could account for the phenotypic effect. By exploiting recent advances in mouse genotyping, sequence and phylogeny resources we confirmed that Ap3m2 resides in an appropriately segregating genomic region. We have demonstrated genetic and alcohol induced regulation of Ap3m2 expression. Although sequence analysis revealed no polymorphisms in the Ap3m2 coding region that could account for all phenotypic differences, there are several upstream SNPs that could. We have identified one of these to be an H3K4me3 site that exhibits strain differences in methylation. Thus, by making cross-species functional genomics readily computable we identified a common QTL candidate for two related bio-behavioral processes via functional evidence and demonstrate sufficiency of the genetic locus as a source of variation underlying two traits.

Buchanan, N. D., Block, R., Smith, A. W., & Tai, E. (2014). Psychosocial barriers and facilitators to clinical trial enrollment and adherence for adolescents with cancer. *Pediatrics, 133 Suppl 3*, S123-30.

Adolescents (aged 15-19 years) have not experienced the same survival gains as children and older adults diagnosed with cancer. Poor clinical trial enrollment and adherence rates among adolescents may account for some of this disparity. Although biological, regulatory, systemic, and practice-related challenges to clinical trial enrollment and adherence have been examined, studies of psychosocial factors, which can serve as barriers or facilitators to enrollment and adherence, are limited. To bring attention to these psychological factors, we reviewed existing literature on psychosocial barriers and facilitators that can affect an adolescent's decision to enroll and adhere to a clinical trial. We also provide potential strategies to address psychosocial factors affecting clinical trial accrual and adherence.

Buist, D. S., Anderson, M. L., Smith, R. A., Carney, P. A., Miglioretti, D. L., Monsees, B. S., et al. (2014). Effect of radiologists' diagnostic work-up volume on interpretive performance. *Radiology,* , 132806.

Purpose To examine radiologists' screening performance in relation to the number of diagnostic work-ups performed after abnormal findings are discovered at screening mammography by the same radiologist or by different radiologists. Materials and Methods In an institutional review board-approved HIPAA-compliant study, the authors linked 651 671 screening mammograms interpreted from 2002 to 2006 by 96 radiologists in the Breast Cancer Surveillance Consortium to cancer registries (standard of reference) to evaluate the performance of screening mammography (sensitivity, false-positive rate [FPR], and cancer detection rate [CDR]). Logistic regression was used to assess the association between the volume of recalled screening mammograms ("own" mammograms, where the radiologist who interpreted the diagnostic image was the same radiologist who had interpreted the screening image, and "any" mammograms, where the radiologist who interpreted the diagnostic image may or may not have been the radiologist who interpreted the screening image) and screening performance and whether the association between total annual volume and performance differed according to the volume of diagnostic work-up. Results Annually, 38% of radiologists performed the diagnostic work-up for

25 or fewer of their own recalled screening mammograms, 24% performed the work-up for 0-50, and 39% performed the work-up for more than 50. For the work-up of recalled screening mammograms from any radiologist, 24% of radiologists performed the work-up for 0-50 mammograms, 32% performed the work-up for 51-125, and 44% performed the work-up for more than 125. With increasing numbers of radiologist work-ups for their own recalled mammograms, the sensitivity (P = .039), FPR (P = .004), and CDR (P < .001) of screening mammography increased, yielding a stepped increase in women recalled per cancer detected from 17.4 for 25 or fewer mammograms to 24.6 for more than 50 mammograms. Increases in work-ups for any radiologist yielded significant increases in FPR (P = .011) and CDR (P = .001) and a nonsignificant increase in sensitivity (P = .15). Radiologists with a lower annual volume of any work-ups had consistently lower FPR, sensitivity, and CDR at all annual interpretive volumes. Conclusion These findings support the hypothesis that radiologists may improve their screening performance by performing the diagnostic work-up for their own recalled screening mammograms and directly receiving feedback afforded by means of the outcomes associated with their initial decision to recall. Arranging for radiologists to work up a minimum number of their own recalled cases could improve screening performance but would need systems to facilitate this workflow. (c) RSNA, 2014 Online supplemental material is available for this article.

Burke, W., Appelbaum, P., Dame, L., Marshall, P., Press, N., Pyeritz, R., et al. (2014). The translational potential of research on the ethical, legal, and social implications of genomics. *Genetics in Medicine : Official Journal of the American College of Medical Genetics,*
Federally funded research on the ethical, legal, and social implications (ELSI) of genomics includes a programmatic charge to consider policy-relevant questions and to communicate findings in venues that help inform the policy-making process. In addressing this goal, investigators must consider the range of policies that are relevant to human genetics; how foundational research in bioethics, law, and the social sciences might inform those policies; and the potential professional issues that this translational imperative raises for ELSI investigators. We review these questions in light of experiences from a consortium of federally funded Centers of Excellence in ELSI Research, and offer a set of policy recommendations for program design and evaluation of ELSI research. We conclude that it would be a mistake to require that ELSI

research programs demonstrate a direct impact on science or health policy; however, ELSI researchers can take steps to increase the relevance of their work to policy makers. Similarly, funders of ELSI research who are concerned with facilitating policy development can help by building cross-disciplinary translational research capacities, and universities can take steps to make policy-relevant research more rewarding for scholars in the humanities, social sciences, and law.Genet Med advance online publication 19 June 2014Genetics in Medicine (2014); doi:10.1038/gim.2014.74.

Burwick, R. M., Easter, S. R., Dawood, H. Y., Yamamoto, H. S., Fichorova, R. N., & Feinberg, B. B. (2014). Complement activation and kidney injury molecule-1-associated proximal tubule injury in severe preeclampsia. *Hypertension,*

Kidney injury with proteinuria is a characteristic feature of preeclampsia, yet the nature of injury in specific regions of the nephron is incompletely understood. Our study aimed to use existing urinary biomarkers to describe the pattern of kidney injury and proteinuria in pregnancies affected by severe preeclampsia. We performed a case-control study of pregnant women from Brigham and Women's Hospital from 2012 to 2013. We matched cases of severe preeclampsia (n=25) 1:1 by parity and gestational age to 2 control groups with and without chronic hypertension. Urinary levels of kidney injury molecule-1 and complement components (C3a, C5a, and C5b-9) were measured by enzyme-linked immunosorbent assay, and other markers (albumin, beta2 microglobulin, cystatin C, epithelial growth factor, neutrophil gelatinase-associated lipocalin, osteopontin, and uromodulin) were measured simultaneously with a multiplex electrochemiluminescence assay. Median values between groups were compared with the Wilcoxon signed-rank test and correlations with Spearman correlation coefficient. Analysis of urinary markers revealed higher excretion of albumin and kidney injury molecule-1 and lower excretion of neutrophil gelatinase-associated lipocalin and epithelial growth factor in severe preeclampsia compared with chronic hypertension and healthy controls. Among subjects with severe preeclampsia, urinary excretion of complement activation products correlated most closely with kidney injury molecule-1, a specific marker of proximal tubule injury (C5a: r=0.60; P=0.001; and C5b-9: r=0.75; P<0.0001). Taken together, we describe a pattern of kidney injury in severe preeclampsia that is characterized by glomerular impairment and complement-

mediated inflammation and injury, possibly localized to the proximal tubule in association with kidney injury molecule-1.

Cameron, M. H., Bethoux, F., Davis, N., & Frederick, M. (2014). Botulinum toxin for symptomatic therapy in multiple sclerosis. *Current Neurology and Neuroscience Reports, 14*(8), 463-014-0463-7.

Botulinum toxin (BT) is a neurotoxin that paralyzes muscles by inhibiting release of acetylcholine from presynaptic vesicles at the neuromuscular junction. In people with multiple sclerosis (MS), clinical experience and research studies show that local injection of minute quantities of BT can temporarily control skeletal muscle spasticity, bladder detrusor hyperreflexia, and tremor. Specifically, BT injections have been shown to reduce muscle tone and improve passive function, and possibly improve active function, in patients with spasticity. Injection of BT into the bladder wall is a uniquely effective, safe, and durable treatment in patients with neurogenic detrusor hyperreflexia due to MS who have insufficient response or who do not tolerate oral antimuscarinic medications. This procedure has markedly reduced the need for indwelling catheters and bladder surgery. In addition, a recent study suggests BT may be effective for select patients with MS-associated upper extremity tremor. Appropriate use of BT can improve quality of life for many patients with MS.

Caputo, N., Jackson, M. A., Castle, J. R., El Youssef, J., Bakhtiani, P. A., Bergstrom, C. P., et al. (2014). Biochemical stabilization of glucagon at alkaline pH. *Diabetes Technology & Therapeutics,*

Abstract Background: For patients with type 1 diabetes mellitus, a bihormonal artificial endocrine pancreas system utilizing glucagon and insulin has been found to stabilize glycemic control. However, commercially available formulations of glucagon cannot currently be used in such systems because of physical instability characterized by aggregation and chemical degradation. Storing glucagon at pH 10 blocks protein aggregation but results in chemical degradation. Reductions in pH minimize chemical degradation, but even small reductions increase protein aggregation. We hypothesized that common pharmaceutical excipients accompanied by a new excipient would inhibit glucagon aggregation at an alkaline pH. Methods and Results: As measured by tryptophan intrinsic fluorescence shift and optical density at 630 nm, protein

aggregation was indeed minimized when glucagon was formulated with curcumin and albumin. This formulation also reduced chemical degradation, measured by liquid chromatography with mass spectrometry. Biological activity was retained after aging for 7 days in an in vitro cell-based bioassay and also in Yorkshire swine. Conclusions: Based on these findings, a formulation of glucagon stabilized with curcumin, polysorbate-80, l-methionine, and albumin at alkaline pH in glycine buffer may be suitable for extended use in a portable pump in the setting of a bihormonal artificial endocrine pancreas.

Carek, P. J., Simpson, D., & Yarris, L. M. (2014). Comments: Authors' response to letters regarding "defining the scholarly and scholarship common program requirements". *Journal of Graduate Medical Education, 6*(2), 392-D-14-00173.1.

Carpenter, K. M., Stoner, S. A., Schmitz, K., McGregor, B. A., & Doorenbos, A. Z. (2014). An online stress management workbook for breast cancer. *Journal of Behavioral Medicine, 37*(3), 458-468. Cognitive behavioral stress management groups have been shown to be decrease psychological symptoms and increase adaptive coping in breast cancer patients, but dissemination of this effective intervention has been challenging. The goal of the present project was to develop an online cognitive behavioral stress management intervention for early stage breast cancer survivors and evaluate its effectiveness using a 2 group × 3 time randomized, waitlist-controlled design. Intervention and waitlist control group participants were assessed at three time points: at baseline; at 10 weeks, after which only intervention participants had used the workbook; and at 20 weeks, after which both groups had used the workbook. Results indicate that at 10 weeks intervention participants showed improved self-efficacy for coping with their cancer and for regulating negative mood and lower levels of cancer-related post-traumatic symptoms as compared to the control group, suggesting that an internet stress management intervention could be effective for helping breast cancer patients increase their confidence in their ability to cope with stress. 

Carraro, M., Giorgio, V., Sileikyte, J., Sartori, G., Forte, M., Lippe, G., et al. (2014). Channel formation by yeast F-ATP synthase and the role of dimerization in the mitochondrial permeability transition. *Journal of Biological Chemistry, 289*(23), 15980-15985.

Purified F-ATP synthase dimers of yeast mitochondria display Ca 2+-dependent channel activity with properties resembling those of the permeability transition pore (PTP) of mammals. After treatment with the Ca 2+ ionophore ETH129, which allows electrophoretic Ca2+ uptake, isolated yeast mitochondria undergo inner membrane permeabilization due to PTP opening. Yeast mutant strains ATIM11 and AATP20 (lacking the e and g F-ATP synthase subunits, respectively, which are necessary for dimer formation) display a striking resistance to PTP opening. These results show that the yeast PTP originates from F-ATP synthase and indicate that dimerization is required for pore formation in situ. 

Chan, C. M., Hahn, E., & Zuber, P. (2014). Adaptor bypass mutations of bacillus subtilis spx suggest a mechanism for YjbH-enhanced proteolysis of the regulator spx by ClpXP. *Molecular Microbiology,* The global regulator, Spx, is under proteolytic control exerted by the adaptor YjbH and ATP-dependent protease ClpXP in Bacillus subtilis. While YjbH is observed to bind the Spx C-terminus, YjbH shows little affinity for ClpXP, indicating adaptor activity that does not operate by tethering. Chimeric proteins derived from B. subtilis AbrB and the Spx C-terminus showed that a 28 residue C-terminal section of Spx (AbrB28), but not the last 12 or 16 residues (AbrB12, AbrB16), was required for YjbH interaction and for ClpXP proteolysis, although the rate of AbrB28 proteolysis was not affected by YjbH addition. The result suggested that the YjbH-targeted 28 residue segment of the Spx C-terminus bears a ClpXP-recognition element(s) that is hidden in the intact Spx protein. Residue substitutions in the conserved helix alpha6 of the C-terminal region generated Spx substrates that were degraded by ClpXP at accelerated rates compared to wild type Spx, and showed reduced dependency on the YjbH activity. The residue substitutions also weakened the interaction between Spx and YjbH. The results suggest a model in which YjbH, through interaction with residues of alpha6 helix, exposes the C-terminus of Spx for recognition and proteolysis by ClpXP.

Chang, A. M., Leung, A. C., Saynisch, O., Griffis, H., Hill, S., Hershey, J. C., et al. (2014). Using a mobile app and mobile workforce to validate data about emergency public health resources. *Emergency Medicine Journal, 31*(7), 545-548.

Background: Social media and mobile applications that allow people to work anywhere are

changing the way people can contribute and collaborate. Objective: We sought to determine the feasibility of using mobile workforce technology to validate the locations of automated external defibrillators (AEDs), an emergency public health resource. Methods: We piloted the use of a mobile workforce application, to verify the location of 40 AEDs in Philadelphia county. AEDs were pre-identified in public locations for baseline data. The task of locating AEDs was posted online for a mobile workforce from October 2011 to January 2012. Participants were required to submit a mobile phone photo of AEDs and descriptions of the location. Results: Thirty- five of the 40 AEDs were identified within the study period. Most, 91% (32/35) of the submitted AED photo information was confirmed project baseline data. Participants also provided additional data such as business hours and other nearby AEDs. Conclusions: It is feasible to engage a mobile workforce to complete health research-related tasks. Participants were able to validate information about emergency public health resources.

Chang, H., Fontenay, G. V., Bilgin, C. C., Borowsky, A., Spellman, P., & Parvin, B. (2013). *Molecular correlates of morphometric subtypes in glioblastoma multiforme* Elsevier Inc.

Integrated analysis of tissue histology with the genome-wide array and clinical data has the potential to generate hypotheses as well as be prognostic. However, due to the inherent technical and biological variations, automated analysis of whole mount tissue sections is impeded in very large datasets, such as The Cancer Genome Atlas (TCGA), where tissue sections are collected from different laboratories. We aim to characterize tumor architecture from hematoxylin and eosin (H&E) stained tissue sections, through the delineation of nuclear regions on a cell-by-cell basis. Such a representation can then be utilized to derive intrinsic morphometric subtypes across a large cohort for prediction and molecular association. Our approach has been validated on manually annotated samples, and then applied to a Glioblastoma Multiforme (GBM) cohort of 377 whole slide images from 146 patients. Further bioinformatics analysis, based on the multidimensional representation of the nuclear features and their organization, has identified (i) statistically significant morphometric sub types; (ii) whether each subtype can be predictive or not and (iii) that the molecular correlates of predictive subtypes are consistent with the literature. The net result is the realization of the concept of pathway pathology through analysis of a large cohort of whole slide images. 

Chen, M., Kretzschmar, D., Verdile, G., & Lardelli, M. (2013). *Models of alzheimer's disease* Elsevier Inc.

Alzheimer's disease (AD) is a major and increasing burden on families, communities, and national health budgets. Despite intensive and extended research, there is still widespread debate about its cause(s), and no effective treatments exist. Familial (inherited, mainly early onset) and sporadic (mainly late onset) forms of the disease exist, and it is uncertain to what extent they are related. Transgenic mouse models have dominated the investigation of this disease, but their validity can be questioned. Numerous alternative models exist that can provide valuable information on the molecular and cellular basis of AD. In this chapter, we review the various invertebrate, nonmammalian vertebrate, and mammalian models and how these have been used to investigate this disease. We examine the strengths and weaknesses of these various model systems. Of course, animal models never completely reflect the true nature of a human disease, but progress in understanding and finding preventative and ameliorative treatments for AD is hindered by the lack of a convincing hypothesis for the cause of this complex condition. © 2013 Elsevier Inc. All rights reserved.

Cheng, A., & Bui, T. (2014). Submental island flap. *Oral and Maxillofacial Surgery Clinics of North America,*

The submental island flap is a local flap that is simple to raise and is useful for oral and lower face reconstruction of soft tissue defects. It is based on the submental artery and the facial vein. Using a retrograde flow design allows for reconstruction of forehead, temporal, and periorbital defects. Raising the flap with the ipsilateral digastric and a portion of the mylohyoid muscle is helpful in protecting the vascular pedicle. Extra care is required when raising the flap when performing an elective or therapeutic neck dissection, because Level I lymph-node-bearing tissue may be harvested with the flap.

Cherkin, D. C., Sherman, K. J., Balderson, B. H., Turner, J. A., Cook, A. J., Stoelb, B., et al. (2014). Comparison of complementary and alternative medicine with conventional mind-body therapies for chronic back pain: Protocol for the mind-body approaches to pain (MAP) randomized controlled trial. *Trials, 15*(1)

Background: The self-reported health and functional status of persons with back pain in the United States have declined in recent years, despite greatly increased medical expenditures due to this problem. Although patient psychosocial factors such as pain-related beliefs, thoughts and coping behaviors have been demonstrated to affect how well patients respond to treatments for back pain, few patients receive treatments that address these factors. Cognitive-behavioral therapy (CBT), which addresses psychosocial factors, has been found to be effective for back pain, but access to qualified therapists is limited. Another treatment option with potential for addressing psychosocial issues, mindfulness-based stress reduction (MBSR), is increasingly available. MBSR has been found to be helpful for various mental and physical conditions, but it has not been well-studied for application with chronic back pain patients. In this trial, we will seek to determine whether MBSR is an effective and cost-effective treatment option for persons with chronic back pain, compare its effectiveness and cost-effectiveness compared with CBT and explore the psychosocial variables that may mediate the effects of MBSR and CBT on patient outcomes. Methods/Design: In this trial, we will randomize 397 adults with nonspecific chronic back pain to CBT, MBSR or usual care arms (99 per group). Both interventions will consist of eight weekly 2-hour group sessions supplemented by home practice. The MBSR protocol also includes an optional 6-hour retreat. Interviewers masked to treatment assignments will assess outcomes 5, 10, 26 and 52 weeks postrandomization. The primary outcomes will be pain-related functional limitations (based on the Roland Disability Questionnaire) and symptom bothersomeness (rated on a 0 to 10 numerical rating scale) at 26 weeks. Discussion: If MBSR is found to be an effective and cost-effective treatment option for patients with chronic back pain, it will become a valuable addition to the limited treatment options available to patients with significant psychosocial contributors to their pain. Trial registration: Clinicaltrials.gov Identifier: NCT01467843. 

Cheung, C. Y., Beardall, M. K., Anderson, D. F., & Brace, R. A. (2014). Prostaglandin E2 regulation of amnion cell vascular endothelial growth factor expression: Relationship with intramembranous absorption rate in fetal sheep. *American Journal of Physiology.Regulatory, Integrative and Comparative Physiology,*

Introduction: We hypothesized that prostaglandin E2 (PGE2) stimulates amniotic fluid transport

across the amnion by upregulating vascular endothelial growth factor (VEGF) expression in amnion cells and that amniotic PGE2 concentration correlates positively with intramembranous (IM) absorption rate in fetal sheep. Methods: The effects of PGE2 at a range of concentrations on VEGF164 and caveolin-1 gene expressions were analyzed in cultured ovine amnion cells. IM absorption rate, amniotic fluid (AF) volume and PGE2 concentration in AF were determined in late gestation fetal sheep during control conditions, isovolumic fetal urine replacement (low IM absorption rate) or intra-amniotic fluid infusion (high IM absorption rate). Results: In ovine amnion cells, PGE2 induced dose and time dependent increases in VEGF164 mRNA levels and reduced caveolin-1 mRNA and protein levels. VEGF receptor blockade abolished the caveolin-1 response while minimally affecting the VEGF response to PGE2. In sheep fetuses, urine replacement reduced amniotic PGE2 concentration by 58%, decreased IM absorption rate by half and doubled AF volume ($P<0.01$). Intra-amniotic fluid infusion increased IM absorption rate and AF volume ($P<0.01$) while amniotic PGE2 concentration was unchanged. Neither IM absorption rate nor AF volume correlated with amniotic PGE2 concentration under each experimental condition. Conclusion: Although PGE2 at micromolar concentrations induced dose dependent responses in VEGF and caveolin-1 gene expression in cultured amnion cells consistent with a role of PGE2 in activating VEGF to mediate AF transport across the amnion, amniotic PGE2 at physiologic nanomolar concentrations does not appear to regulate IM absorption rate or AF volume.

Chinsongkram, B., Chaikeeree, N., Saengsirisuwan, V., Viriyatharakij, N., Horak, F. B., & Boonsinsukh, R. (2014). Reliability and validity of the balance evaluation systems test (BESTest) in people with subacute stroke. *Physical Therapy,*

BACKGROUND: The Balance Evaluation Systems Test (BESTest) is new clinical balance assessment tool but it has never been validated in patients with subacute stroke. OBJECTIVE: To examine the reliability and validity of the BESTest in patients with subacute stroke. DESIGN: An observational reliability and validity study. METHODS: Twelve patients participated in the interrater and intrarater reliability study. The convergent validity was studied in seventy patients using the Berg Balance Scale (BBS), Postural Assessment Scale for Stroke (PASS), Community Balance and Mobility Scale (CB&M) and Mini-BESTest as the references. The Receiver Operating

Characteristics curve was used to calculate the sensitivity, specificity and accuracy of the scale in classifying patients into low (LFA) and high functional ability level (HFA) based on the Fugl- Meyer Assessment motor subscale. RESULTS: The BESTest showed excellent intrarater reliability and interrater reliability (ICC = 0.99) and was highly correlated with the BBS (Spearman Rank r=0.96), PASS (r=0.96), CB&M (r=0.91) and Mini-BESTest (r=0.96), indicating excellent convergent validity. No floor and ceiling effects were observed with the BESTest. In contrast, the Mini-BESTest and CB&M had a floor effect in the LFA group, and the BBS and PASS demonstrated responsive ceiling effects in HFA. In addition, the BESTest showed high accuracy as the BBS and Mini-BESTest in separating patients into HFA and LFA group. LIMITATION: Unknown generalization to patients with chronic stroke. CONCLUSION: The BESTest is reliable, valid, and sensitive and specific in assessing balance in persons with subacute stroke across all levels of functional disability.

Chiovaro, J. C., & Gaggar, A. (2014). Crystalline bone marrow in systemic oxalosis. *Journal of General Internal Medicine, 29*(6), 961.

Chou, R., & Nuckols, T. J. (2014). Letters. *Annals of Internal Medicine, 160*(10), 737-738.

Chou, S., Ercolani, R. J., Sahoo, M. K., Lefterova, M. I., Strasfeld, L. M., & Pinsky, B. A. (2014). Improved detection of emerging drug-resistant mutant cytomegalovirus subpopulations by deep sequencing. *Antimicrobial Agents and Chemotherapy,*

In immunosuppressed hosts, development of multi-drug resistance complicates the treatment of cytomegalovirus (CMV) infection. Improved genotypic detection of impending drug resistance may follow from recent technical advances. A severely T-cell depleted patient with chronic lymphocytic leukemia developed CMV pneumonia and high plasma viral loads poorly responsive to antiviral therapy. Serial plasma specimens were analyzed for mutant viral populations by conventional and high throughput deep sequencing methods. Uncharacterized mutations were phenotyped for drug resistance using recombinant viruses. Conventional genotyping detected viral UL97 kinase substitution C607Y after ganciclovir treatment, a transient subpopulation of UL54 polymerase L773V first detected 8 weeks after starting foscarnet, and a subpopulation of UL54 codon 981-2 deletion 2 months after adding cidofovir. Deep sequencing of the same serial

specimens revealed the same UL54 mutants sooner, along with a more complex evolution of known and newly recognized mutant subpopulations missed by conventional sequencing. UL54 exonuclease substitutions D413N, K513R and C539G were newly shown to confer ganciclovir-cidofovir resistance, while L773V was shown to confer foscarnet resistance and add to the ganciclovir resistance conferred by UL97 C607Y. Increased sequencing depth provided a more timely and detailed diagnosis of mutant viral subpopulations that evolved with changing anti-CMV therapy.

Coleman, K., Weed, J. L., & Schapiro, S. J. (2013). *Environmental enrichment for animals used in research* Elsevier Inc.

Environmental enrichment is an integral part of animal care practices. Enrichment generally refers to items we provide to the animals to support their behavioral needs. It provides a way to functionally simulate the natural environment of captive animals, in an effort to increase opportunities for the expression of species-specific behaviors and decrease the occurrence of abnormal behaviors. Further, enrichment can also be a tool in the study of basic science questions, such as how environmental factors may affect disease etiology or progression. In this chapter, we will examine the use of enrichment in both applied and basic science contexts; as a welfare tool and as an experimental model. 

Conley, A. J., Christenson, L. K., Ford, S. P., & Christenson, R. K. (1994). Immunocytochemical localization of cytochromes P450 17α-hydroxylase and aromatase in embryonic cell layers of elongating porcine blastocysts. *Endocrinology, 135*(5), 2248-2254.

Localized expression of cytochromes P450 17α-hydroxylase (P450(c17)) and aromatase (P450(arom)) was investigated in embryonic cell layers of elongating porcine blastocysts by immunocytochemistry. Blastocysts were flushed from the uterus on day 12 of pregnancy, fixed in paraformaldehyde, embedded in paraffin, sectioned, and stained using immunogold- and peroxidase-based techniques. Staining for both P450(c17) and P450(arom) was intense in spherical 7- to 10-mm blastocysts, but was absent in earlier stage 2- to 4-mm blastocysts and less intense or absent in later stage 20-mm and filamentous embryos. Cytochrome P450(c17) was limited to the trophoblast of all blastocysts expressing the enzyme, and in spherical 7- to 10-

mm blastocysts, essentially all cells of the trophoblast layer stained positively for P450(c17). However, as elongation became apparent in 10-mm blastocysts, the cells of the trophoblast became flattened, and the expression of P450(c17) declined particularly in those trophoblast cells adjacent to the embryonic disc where mesoderm outgrowth was occurring. In fact, two distinct populations of trophoblast cells became obvious: one that maintained P450(c17) expression, and one that did not. Moreover, those trophoblast cells expressing P450(c17) were less flattened than neighboring cells in which P450(c17) expression was absent. These two morphologically and functionally distinct trophoblastic cell populations were most obvious in areas furthest from the embryonic disc. Cytochrome P450(arom) was expressed in the trophoblast as well as the hypoblast under the embryonic disc. Neither P450(c17) nor P450(arom) appeared to be expressed in the embryonic disc or the mesoderm of the expanding blastocyst. These functional and structural changes in the embryonic cell layers of the elongating conceptus may be associated with the transient synthesis and secretion of estrogen that occur at the time of maternal recognition of pregnancy in the pig.

Coronado, G. D., Vollmer, W. M., Petrik, A., Taplin, S. H., Burdick, T. E., Meenan, R. T., et al. (2014). Strategies and opportunities to STOP colon cancer in priority populations: Design of a cluster-randomized pragmatic trial. *Contemporary Clinical Trials,*

BACKGROUND: Colorectal cancer is the second-leading cause of cancer deaths in the United States. The Strategies and Opportunities to Stop Colorectal Cancer (STOP CRC) in Priority Populations study is a pragmatic trial and a collaboration between two research institutions and a network of more than 200 safety net clinics. The study will assess the effectiveness of a system-based intervention designed to improve the rates of colorectal-cancer screening using fecal immunochemical testing (FIT) in federally qualified health centers in Oregon and Northern California. MATERIAL AND METHODS: STOP CRC is a cluster-randomized comparative-effectiveness pragmatic trial enrolling 26 clinics. Clinics will be randomized to one of two arms. Clinics in the intervention arm (1) will use an automated, data-driven, electronic health record-embedded program to identify patients due for colorectal screening and mail FIT kits (with pictographic instructions) to them; (2) will conduct an improvement process (e.g. Plan-Do-Study-Act) to enhance the adoption, reach, and effectiveness of the program. Clinics in the control arm

will provide opportunistic colorectal-cancer screening to patients at clinic visits. The primary outcomes are: proportion of age- and screening-eligible patients completing a FIT within 12months; and cost, cost-effectiveness, and return on investment of the intervention. CONCLUSIONS: This large-scale pragmatic trial will leverage electronic health record information and existing clinic staff to enroll a broad range of patients, including many with historically low colorectal-cancer screening rates. If successful, the program will provide a model for a cost-effective and scalable method to raise colorectal-cancer screening rates.

Costello, J. C., Heiser, L. M., Georgii, E., Gonen, M., Menden, M. P., Wang, N. J., et al. (2014). A community effort to assess and improve drug sensitivity prediction algorithms. *Nature Biotechnology,*

Predicting the best treatment strategy from genomic information is a core goal of precision medicine. Here we focus on predicting drug response based on a cohort of genomic, epigenomic and proteomic profiling data sets measured in human breast cancer cell lines. Through a collaborative effort between the National Cancer Institute (NCI) and the Dialogue on Reverse Engineering Assessment and Methods (DREAM) project, we analyzed a total of 44 drug sensitivity prediction algorithms. The top-performing approaches modeled nonlinear relationships and incorporated biological pathway information. We found that gene expression microarrays consistently provided the best predictive power of the individual profiling data sets; however, performance was increased by including multiple, independent data sets. We discuss the innovations underlying the top-performing methodology, Bayesian multitask MKL, and we provide detailed descriptions of all methods. This study establishes benchmarks for drug sensitivity prediction and identifies approaches that can be leveraged for the development of new methods.

Cowan, N. G., Chen, Y., Downs, T. M., Bochner, B. H., Apolo, A. B., Porter, M. P., et al. (2014). Neoadjuvant chemotherapy use in bladder cancer: A survey of current practice and opinions. *Advances in Urology,*

Objectives. Level 1 evidence supports the use of neoadjuvant chemotherapy (NAC) to improve overall survival in muscle invasive bladder cancer; however utilization rates remain low. The aims of our study were to determine factors associated with NAC use, to more clearly define reasons

for low utilization, and to determine the current rate of NAC use among urologic oncologists. Materials and Methods. Active members of the Society for Urologic Oncology were provided a 20-question survey. Descriptive statistical analysis was conducted for each question and univariate analysis was performed. Results. We achieved a response rate of 21%. Clinical T3/T4 disease was the most often selected reason for recommending NAC (87%). Concerns with recommending NAC were age and comorbidities (54%) followed by delay in surgery (35%). An association was identified between urologic oncologists who discussed NAC with >90% of their patients and medical oncologists "always" recommending NAC (P=0.0009). NAC utilization rate was between 30 and 57%. Conclusions. Amongst this highly specialized group of respondents, clinical T3-T4 disease was the most common reason for implementation of NAC. Respondents who frequently discussed NAC were more likely to report their medical oncologist always recommending NAC. Reported NAC use was higher in this surveyed group (30-57%) compared with recently published rates. 

Crabbe, J. C. (2014). *The genetic complexity of alcohol drinking in rodents* Elsevier Inc.

This chapter first discusses the alcohol-drinking phenotypes most commonly used in rodent genetic studies. The emphasis is on the complexity of the phenotypic spaces encompassed by the drinking assays (many of which are amalgamations of multiple approaches). It then reviews the evidence for genetic contributions to those drinking traits. For several of them, there is unequivocal evidence for genetic contributions to individual differences in drinking, and for one of them, two-bottle preference drinking, there are voluminous data. Finally, it discusses the genetic singularity of each trait versus what appear to be pleiotropic genetic influences (those in which one or more genes influence multiple traits related to drinking). Sorting out this genetic complexity is difficult because genetic information is sparse for many drinking-related behaviors, and many procedures are used in combination with others. 

Cservenka, A., Fair, D. A., & Nagel, B. J. (2014). Emotional processing and brain activity in youth at high risk for alcoholism. *Alcoholism, Clinical and Experimental Research,*

BACKGROUND: Even in the absence of heavy alcohol use, youth with familial alcoholism (family

history positive [FHP]) exhibit atypical brain functioning and behavior. Although emotional and cognitive systems are affected in alcohol use disorders (AUDs), little attention has focused on whether brain and behavior phenotypes related to the interplay between affective and executive functioning may be a premorbid risk factor for the development of AUDs in FHP youth. METHODS: Twenty-four FHP and 22 family history negative (FHN) 12- to 16-year-old adolescents completed study procedures. After exclusion of participants with clinically significant depressive symptoms and those who did not meet performance criteria during an Emotional Go-NoGo task, 19 FHP and 17 FHN youth were included in functional magnetic resonance imaging (fMRI) analyses. Resting state functional connectivity MRI, using amygdalar seed regions, was analyzed in 16 FHP and 18 FHN youth, after exclusion of participants with excessive head movement. RESULTS: fMRI showed that brain activity in FHP youth, compared with FHN peers, was reduced during emotional processing in the superior temporal cortex, as well as during cognitive control within emotional contexts in frontal and striatal regions. Group differences in resting state amygdalar connectivity were seen bilaterally between FHP and FHN youth. In FHP youth, reduced resting state synchrony between the left amygdala and left superior frontal gyrus was related to poorer response inhibition, as measured during the fMRI task. CONCLUSIONS: To our knowledge, this is the first study to examine emotion-cognition interactions and resting state functional connectivity in FHP youth. Findings from this research provide insight into neural and behavioral phenotypes associated with emotional processing in familial alcoholism, which may relate to increased risk of developing AUDs.

Cuevas-Ramos, D., & Fleseriu, M. (2014). Somatostatin receptor ligands and resistance to treatment in pituitary adenomas. *Journal of Molecular Endocrinology, 52*(3), R223-R240.

Somatostatin (SST), an inhibitory polypeptide with two biologically active forms SST14 and SST28, inhibits GH, prolactin (PRL), TSH, and ACTH secretion in the anterior pituitary gland. SST also has an antiproliferative effect inducing cell cycle arrest and apoptosis. Such actions are mediated through five G-protein-coupled somatostatin receptors (SSTR): SSTR1-SSTR5. In GH-secreting adenomas, SSTR2 expression predominates, and somatostatin receptor ligands (SRLs; octreotide and lanreotide) directed to SSTR2 are presently the mainstays of medical therapy. However, about half of patients show incomplete biochemical remission, but the definition of

resistance per se remains controversial. We summarize here the determinants of SRL resistance in acromegaly patients, including clinical, imaging features as well as molecular (mutations, SSTR variants, and polymorphisms), and histopathological (granulation pattern, and proteins and receptor expression) predictors. The role of SSTR5 may explain the partial responsiveness to SRLs in patients with adequate SSTR2 density in the cell membrane. In patients with ACTH-secreting pituitary adenomas, i.e. Cushing's disease (CD), SSTR5 is the most abundant receptor expressed and tumors show low SSTR2 density due to hypercortisolism-induced SSTR2 down-regulation. Clinical studies with pasireotide, a multireceptor-targeted SRL with increased SSTR5 activity, lead to approval of pasireotide for treatment of patients with CD. Other SRL delivery modes (oral octreotide), multireceptortargeted SRL (somatoprim) or chimeric compounds targeting dopamine D2 receptors and SSTR2 (dopastatin), are briefly discussed. © 2014 Society for Endocrinology.

Daunais, J. B., Davenport, A. T., Helms, C. M., Gonzales, S. W., Hemby, S. E., Friedman, D. P., et al. (2014). Monkey alcohol tissue research resource: Banking tissues for alcohol research. *Alcoholism: Clinical and Experimental Research,*

Background: An estimated 18 million adults in the United States meet the clinical criteria for diagnosis of alcohol abuse or alcoholism, a disorder ranked as the third leading cause of preventable death. In addition to brain pathology, heavy alcohol consumption is comorbid with damage to major organs including heart, lungs, liver, pancreas, and kidneys. Much of what is known about risk for and consequences of heavy consumption derive from rodent or retrospective human studies. The neurobiological effects of chronic intake in rodent studies may not easily translate to humans due to key differences in brain structure and organization between species, including a lack of higher-order cognitive functions, and differences in underlying prefrontal cortical neural structures that characterize the primate brain. Further, rodents do not voluntarily consume large quantities of ethanol (EtOH) and they metabolize it more rapidly than primates. Methods: The basis of the Monkey Alcohol Tissue Research Resource (MATRR) is that nonhuman primates, specifically monkeys, show a range of drinking excessive amounts of alcohol (>3.0 g/kg or a 12 drink equivalent per day) over long periods of time (12 to 30 months) with concomitant pathological changes in endocrine, hepatic, and central nervous system (CNS)

processes. The patterns and range of alcohol intake that monkeys voluntarily consume parallel what is observed in humans with alcohol use disorders and the longitudinal experimental design spans stages of drinking from the EtOH-naïve state to early exposure through chronic abuse. Age- and sex-matched control animals self-administer an isocaloric solution under identical operant procedures. Results: The MATRR is a unique postmortem tissue bank that provides CNS and peripheral tissues, and associated bioinformatics from monkeys that self-administer EtOH using a standardized experimental paradigm to the broader alcohol research community. Conclusions: This resource provides a translational platform from which we can better understand the disease processes associated with alcoholism. © 2014 by the Research Society on Alcoholism.

Davare, M. A., Lal, S., Peckham, J. L., Prajapati, S. I., Gultekin, S. H., Rubin, B. P., et al. (2014). Secreted meningeal chemokines, but not VEGFA, modulate the migratory properties of medulloblastoma cells. *Biochemical and Biophysical Research Communications,*
Leptomeningeal metastasis is a cause of morbidity and mortality in medulloblastoma, but the understanding of molecular mechanisms driving this process is nascent. In this study, we examined the secretory chemokine profile of medulloblastoma cells (DAOY) and a meningothelial cell line (BMEN1). Conditioned media (CM) of meningothelial cells increased adhesion, spreading and migration of medulloblastoma. VEGFA was identified at elevated levels in the CM from BMEN1 cells (as compared to DAOY CM); however, recombinant VEGFA alone was insufficient to enhance medulloblastoma cell migration. In addition, bevacizumab, the VEGFA scavenging monoclonal antibody, did not block the migratory phenotype induced by the CM. These results reveal that paracrine factors secreted by meningothelial cells can influence migration and adherence of medulloblastoma tumor cells, but VEGFA may not be a specific target for therapeutic intervention in this context.

de Godoy Fróes-Salgado, N. R., Gajewski, V., Ornaghi, B. P., Pfeifer, C. S. C., Meier, M. M., Xavier, T. A., et al. (2014). Influence of the base and diluent monomer on network characteristics and mechanical properties of neat resin and composite materials. *Odontology,*
This study evaluated the effect of the combination of two dimethacrylate-based monomers [bisphenol A diglycidyl dimethacrylate (BisGMA) or bisphenol A ethoxylated dimethacrylate

(BisEMA)] with diluents either derived from ethylene glycol dimethacrylate (ethylene glycol dimethacrylate, diethylene glycol dimethacrylate, triethylene glycol dimethacrylate, tetraethylene glycol dimethacrylate) or 1,10-decanediol dimethacrylate (D3MA) on network characteristics and mechanical properties of neat resin and composite materials. The degree of conversion, maximum rate of polymerization and water sorption/solubility of unfilled resins and the flexural strength and microhardness of composites (after 24 h storage in water and 3 months storage in a 75 vol% ethanol aqueous solution) were evaluated. Data were analyzed with two-way ANOVA and Tukey's test (α = 0.05). The higher conversion and lower water sorption presented by BisEMA co-polymers resulted in greater resistance to degradation in ethanol compared with BisGMA-based materials. In general, conversion and mechanical properties were optimized with the use of long-chain dimethacrylate derivatives of ethylene glycol. D3MA rendered more hydrophobic materials, but with relatively low conversion and mechanical properties. © 2014 The Society of The Nippon Dental University.

Deloughery, T. G. (2013). *Anticoagulation for atrial fibrillation and prosthetic cardiac valves* Elsevier Inc.

Derose, S. F., Gabayan, G. Z., Chiu, V. Y., Yiu, S. C., & Sun, B. C. (2014). Emergency department crowding predicts admission length-of-stay but not mortality in a large health system. *Medical Care, 52*(7), 602-611.

BACKGROUND: Emergency department (ED) crowding has been identified as a major threat to public health. OBJECTIVES: We assessed patient transit times and ED system crowding measures based on their associations with outcomes. RESEARCH DESIGN: Retrospective cohort study. SUBJECTS: We accessed electronic health record data on 136,740 adults with a visit to any of 13 health system EDs from January 2008 to December 2010. MEASURES: Patient transit times (waiting, evaluation and treatment, boarding) and ED system crowding [nonindex patient length-of-stay (LOS) and boarding, bed occupancy] were determined. Outcomes included individual inpatient mortality and admission LOS. Covariates included demographic characteristics, past comorbidities, severity of illness, arrival time, and admission diagnoses. RESULTS: No patient transit time or ED system crowding measure predicted increased mortality after control for

patient characteristics. Index patient boarding time and lower bed occupancy were associated with admission LOS (based on nonoverlapping 95% CI vs. the median value). As boarding time increased from none to 14 hours, admission LOS increased an additional 6 hours. As mean occupancy decreased below the median (80% occupancy), admission LOS decreased as much as 9 hours. CONCLUSIONS: Measures indicating crowded ED conditions were not predictive of mortality after case-mix adjustment. The first half-day of boarding added to admission LOS rather than substituted for it. Our findings support the use of boarding time as a measure of ED crowding based on robust prediction of admission LOS. Interpretation of measures based on other patient ED transit times may be limited to the timeliness of care.

Doggett, J. S., Ojo, K. K., Fan, E., Maly, D. J., & Van Voorhis, W. C. (2014). Bumped kinase inhibitor 1294 treats established toxoplasma gondii infection. *Antimicrobial Agents and Chemotherapy, 58*(6), 3547-3549.

Toxoplasma gondii is a unicellular parasite that causes severe brain and eye disease. Current drugs for T. gondii are limited by toxicity. Bumped kinase inhibitors (BKIs) selectively inhibit calcium-dependent protein kinases of the apicomplexan pathogens T. gondii, cryptosporidia, and plasmodia. A lead anti-Toxoplasma BKI, 1294, has been developed to be metabolically stable and orally bioavailable. Herein, we demonstrate the oral efficacy of 1294 against toxoplasmosis in vivo. 

Dorfman, M. D., Garcia-Rudaz, C., Alderman, Z., Kerr, B., Lomniczi, A., Dissen, G. A., et al. (2014). Loss of Ntrk2/Kiss1r signaling in oocytes causes premature ovarian failure. *Endocrinology,* , en20141111.

Neurotrophins (NTs), once believed to be neural-specific trophic factors, are now known to also provide developmental cues to non-neural cells. In the ovary, NTs contribute to both the formation and development of follicles. Here we show that oocyte-specific deletion of the Ntrk2 gene, which encodes the NTRK2 receptor (NTRK2) for neurotrophin-4/5 and brain-derived neurotrophic factor (BDNF), results in post-pubertal oocyte death, loss of follicular organization, and early adulthood infertility. Oocytes lacking NTRK2 do not respond to gonadotropins with activation of phosphatidylinositol 3-kinase (PI3K)-AKT-mediated signaling. Before puberty,

oocytes only express a truncated NTRK2 form (NTRK2.T1), but at puberty full-length (NTRK2.FL) receptors are rapidly induced by the preovulatory gonadotropin surge. A cell line expressing both NTRK2.T1 and the kisspeptin receptor (KISS1R) responds to BDNF stimulation with activation of Ntrk2 expression only if kisspeptin is present. This suggests that BDNF and kisspeptin, which are produced by granulosa cells (GCs) of periovulatory follicles, act in concert to mediate the effect of gonadotropins on Ntrk2 expression in oocytes. In keeping with this finding, the oocytes of NTRK2-intact mice fail to respond to gonadotropins with increased Ntrk2 expression in the absence of KISS1R. Our results demonstrate that the preovulatory gonadotropin surge promotes oocyte survival at the onset of reproductive cyclicity by inducing oocyte expression of NTRK2.FL receptors, which set in motion an AKT-mediated survival pathway. They also suggest that gonadotropins activate NTRK2.FL expression via a dual communication pathway involving BDNF and kisspeptin produced in GCs and their respective receptors NTRK2.T1 and KISS1R expressed in oocytes.

Draz, M. S., Fang, B. A., Zhang, P., Hu, Z., Gu, S., Weng, K. C., et al. (2014). Nanoparticle-mediated systemic delivery of siRNA for treatment of cancers and viral infections. *Theranostics, 4*(9), 872-892.

RNA interference (RNAi) is an endogenous post-transcriptional gene regulatory mechanism, where non-coding, double-stranded RNA molecules interfere with the expression of certain genes in order to silence it. Since its discovery, this phenomenon has evolved as powerful technology to diagnose and treat diseases at cellular and molecular levels. With a lot of attention, short interfering RNA (siRNA) therapeutics has brought a great hope for treatment of various undruggable diseases, including genetic diseases, cancer, and resistant viral infections. However, the challenge of their systemic delivery and on how they are integrated to exhibit the desired properties and functions remains a key bottleneck for realizing its full potential. Nanoparticles are currently well known to exhibit a number of unique properties that could be strategically tailored into new advanced siRNA delivery systems. This review summarizes the various nanoparticulate systems developed so far in the literature for systemic delivery of siRNA, which include silica and silicon- based nanoparticles, metal and metal oxides nanoparticles, carbon nanotubes, graphene, dendrimers, polymers, cyclodextrins, lipids, hydrogels, and semiconductor nanocrystals.

Challenges and barriers to the delivery of siRNA and the role of different nanoparticles to surmount these challenges are also included in the review. © Ivyspring International Publisher.

Duell, P. B., Dubuc, G., Seidah, N. G., & Davignon, J. (2014). Clearance of plasma proprotein convertase subtilisin/kexin 9 by low-density lipoprotein apheresis. *Circulation Research, 115*(1), e3-4.

Duyn, J. H., & Barbara, T. M. (2014). Sphere of lorentz and demagnetization factors in white matter. *Magnetic Resonance in Medicine, 72*(1), 1-3.

Elbogen, E. B., Johnson, S. C., Newton, V. M., Timko, C., Vasterling, J. J., Van Male, L. M., et al. (2014). Protective mechanisms and prevention of violence and aggression in veterans. *Psychological Services, 11*(2), 220-228.

Although a subset of Iraq and Afghanistan Veterans show aggression toward others after they return home from military service, little is known about protective mechanisms that could be bolstered to prevent violence. A national longitudinal survey was conducted between 2009 and 2011 using a random sample of veterans who served in Operation Iraqi Freedom or Operation Enduring Freedom. One thousand and ninety veterans, from 50 states representing all military branches, completed 2 waves of data collection, 1 year apart (retention rate = 79%). The final sample resembled the U.S. military post 9/11 in terms of age, sex, ethnicity, geography, and service branch. Protective mechanisms in socioeconomic (money to cover basic needs, stable employment), psychosocial (resilience, perceiving control over one's life, social support), and physical (healthy sleep, no physical pain) domains were examined. We found these protective mechanisms predicted decreased aggression and violence at follow-up, particularly among higher risk veterans. Multivariable analyses confirmed that protective mechanisms lowered violence through their interaction with risk factors. This study identifies protective mechanisms related to decreased community violence in veterans and indicates that rehabilitation aimed at improving socioeconomic, psychosocial, and physical well-being has potential promise to reduce aggression and violence among veterans after returning home from military service.

Englander, H., Michaels, L., Chan, B., & Kansagara, D. (2014). The care transitions innovation (C-TraIn) for socioeconomically disadvantaged adults: Results of a cluster randomized controlled trial. *Journal of General Internal Medicine,*

BACKGROUND: Despite growing emphasis on transitional care to reduce costs and improve quality, few studies have examined transitional care improvements in socioeconomically disadvantaged adults. It is important to consider these patients separately as many are high-utilizers, have different needs, and may have different responses to interventions. OBJECTIVE: To evaluate the impact of a multicomponent transitional care improvement program on 30-day readmissions, emergency department (ED) use, transitional care quality, and mortality. DESIGN: Clustered randomized controlled trial conducted at a single urban academic medical center in Portland, Oregon. PARTICIPANTS: Three hundred eighty-two hospitalized low-income adults admitted to general medicine or cardiology who were uninsured or had public insurance. INTERVENTION: Multicomponent intervention including (1) transitional nurse coaching and education, including home visits for highest risk patients; (2) pharmacy care, including provision of 30 days of medications after discharge for those without prescription drug coverage; (3) post-hospital primary care linkages; (4) systems integration and continuous quality improvement. MEASUREMENTS: Primary outcomes included 30-day inpatient readmission and ED use. Readmission data were obtained using state-wide administrative data for all participants (insured and uninsured). Secondary outcomes included quality (3-item Care Transitions Measure) and mortality. Research staff administering questionnaires and assessing outcomes were blinded. RESULTS: There was no significant difference in 30-day readmission between C-TraIn (30/209, 14.4 %) and control patients (27/173, 16.1 %), p = 0.644, or in ED visits between C-TraIn (51/209, 24.4 %) and control (33/173, 19.6 %), p = 0.271. C-TraIn was associated with improved transitional care quality; 47.3 % (71/150) of C-TraIn patients reported a high quality transition compared to 30.3 % (36/119) control patients, odds ratio 2.17 (95 % CI 1.30-3.64). Zero C-TraIn patients died in the 30-day post-discharge period compared with five in the control group (unadjusted p = 0.02). CONCLUSIONS: C-TraIn did not reduce 30-day inpatient readmissions or ED use; however, it improved transitional care quality.

Evans, D. S., Cailotto, F., Parimi, N., Valdes, A. M., Castano-Betancourt, M. C., Liu, Y., et al. (2014). Genome-wide association and functional studies identify a role for IGFBP3 in hip osteoarthritis. *Annals of the Rheumatic Diseases,*

OBJECTIVES: To identify genetic associations with hip osteoarthritis (HOA), we performed a meta-analysis of genome-wide association studies (GWAS) of HOA. METHODS: The GWAS meta-analysis included approximately 2.5 million imputed HapMap single nucleotide polymorphisms (SNPs). HOA cases and controls defined radiographically and by total hip replacement were selected from the Osteoporotic Fractures in Men (MrOS) Study and the Study of Osteoporotic Fractures (SOF) (654 cases and 4697 controls, combined). Replication of genome-wide significant SNP associations (p </=5x10-8) was examined in five studies (3243 cases and 6891 controls, combined). Functional studies were performed using in vitro models of chondrogenesis and osteogenesis. RESULTS: The A allele of rs788748, located 65 kb upstream of the IGFBP3 gene, was associated with lower HOA odds at the genome-wide significance level in the discovery stage (OR 0.71, p=2x10-8). The association replicated in five studies (OR 0.92, p=0.020), but the joint analysis of discovery and replication results was not genome-wide significant (p=1x10-6). In separate study populations, the rs788748 A allele was also associated with lower circulating IGFBP3 protein levels (p=4x10-13), suggesting that this SNP or a variant in linkage disequilibrium could be an IGFBP3 regulatory variant. Results from functional studies were consistent with association results. Chondrocyte hypertrophy, a deleterious event in OA pathogenesis, was largely prevented upon IGFBP3 knockdown in chondrocytes. Furthermore, IGFBP3 overexpression induced cartilage catabolism and osteogenic differentiation. CONCLUSIONS: Results from GWAS and functional studies provided suggestive links between IGFBP3 and HOA.

Fabricant, L., Ham, B., Mullins, R., & Mayberry, J. (2014). Prospective clinical trial of surgical intervention for painful rib fracture nonunion. *The American Surgeon, 80*(6), 580-586.

We performed a prospective clinical trial of resection with or without plate fixation for symptomatic rib fracture nonunion three or more months postinjury with 6-month postoperative followup. The McGill Pain Questionnaire (MPQ) and RAND 36 Health Survey were administered and activity level (sedentary, ambulatory, moderately active, vigorous), functional status

(disabled, nonphysical labor, physical labor), and work status (employed, unemployed, retired, student) were queried pre- and postoperatively. Twenty-four patients 4 to 197 months (median, 16 months) postinjury underwent surgical intervention for one to four rib fracture nonunions (median, two nonunions). Evidence of intercostal nerve entrapment was present in nine patients (38%). MPQ Present Pain Intensity and Pain Rating Index and RAND 36 Physical Functioning, Role Physical, Social Functioning, Role Social, Bodily Pain, Vitality, Mental Health, and General Health were significantly improved at six months compared with study entry ($P < 0.05$). Activity levels significantly improved ($P < 0.0001$) but functional and work status did not change. Twenty-four-hour morphine equivalent dosage of opioids at study entry was 20.3 +/- 30.8 (mean +/- standard deviation) and at study completion was 9.4 +/- 17.5 ($P = 0.054$). Complications included one wound infection, two partial screw backouts, and one chest wall hernia at one year after resection of adjacent nonunions with significant gaps repaired with absorbable plates. Surgical intervention for rib fracture nonunion may improve chronic pain and disability but without change in functional or work status. Resection of adjacent nonunions with significant gaps may lead to chest wall hernia.

Fagin, A. P., Howell, T. H., Da Silva, J., & Park, S. E. (2014). The impact on dental students of changes to the national board dental examination grading system. *Journal of Dental Education, 78*(6), 813-822.

The purpose of this study was to assess how the change to pass/fail grading of the National Board Dental Examination (NBDE) Part I has impacted dental students' study habits and their perspectives on pursuit of postdoctoral specialty education. This cross-sectional survey-based study included over 75 percent of U.S. dental schools and a total of 1,843 responses. This sample was 18.5 percent of all potentially eligible U.S. dental students. Participating schools distributed the electronic survey to their last class to take the NBDE Part I for a numerical score and the first class to take the NBDE Part I pass/fail. Respondents who took the exam for a numerical score and were interested in a specialty reported studying the most (average 167 hours) compared to respondents who took the exam pass/fail (average 114 hours). Respondents who took the exam pass/fail and reported feeling that this change decreased their chances of getting into a specialty program outnumbered those who thought the change increased their chances (3:1). This study

observed a correlation between the recent grading changes to the NBDE Part I and decreased reported study time. Eighty percent of the respondents preferred a standardized, objective measure to help differentiate them when applying to specialty programs, and the majority reported feeling that the change in grading practices negatively affected their chances of pursuing a specialty.

Fan, D., Anitori, R. P., Tebo, B. M., Tratnyek, P. G., Lezama Pacheco, J. S., Kukkadapu, R. K., et al. (2014). Oxidative remobilization of technetium sequestered by sulfide-transformed nano zerovalent iron. *Environmental Science & Technology,*

Our previous study showed that formation of TcS2-like phases is favored over TcO2 under sulfidic conditions stimulated by nano zerovalent iron. This study further investigates the stability of Tc(IV) sulfide upon reoxidation by solution chemistry, solid phase characterization, and X-ray absorption spectroscopy. Tc dissolution data showed that Tc(VII) reduced by sulfide-transformed nZVI has substantially slower reoxidation kinetics than Tc(VII) reduced by nZVI only. The initial inhibition of Tc(IV) dissolution at S/Fe = 0.112 is due to the redox buffer capacity of FeS, which is evidenced by the parallel trends in oxidation-reduction potentials (ORP) and Tc dissolution kinetics. The role of FeS in inhibiting Tc oxidation is further supported by the Mossbauer spectroscopy and micro X-ray diffraction data at S/Fe = 0.112, showing persistence of FeS after 24-h oxidation but complete oxidation after 120-h oxidation. X-ray absorption spectroscopy data for S/Fe = 0.011 showed significantly increasing percentages of TcS2 in the solid phase after 24-h oxidation, indicating stronger resistance of TcS2 to oxidation. At S/Fe = 0.112, the XAS results revealed significant transformation of Tc speciation from TcS2 to TcO2 after 120-h oxidation. Given that no apparent Tc dissolution occurred during this period, the speciation transformation might play a secondary role in hindering Tc oxidation. Collectively, the results indicate that sequestrating Tc as TcS2 under stimulated sulfate reduction is a promising strategy to improve the long-term stability of reduced Tc in subsurface remediation.

Fawley, J. A., Hofmann, M. E., & Andresen, M. C. (2014). Cannabinoid 1 and transient receptor potential vanilloid 1 receptors discretely modulate evoked glutamate separately from spontaneous glutamate transmission. *The Journal of Neuroscience : The Official Journal of the*

*Society for Neuroscience, 34*(24), 8324-8332.

Action potentials trigger synaptic terminals to synchronously release vesicles, but some vesicles release spontaneously. G-protein-coupled receptors (GPCRs) can modulate both of these processes. At cranial primary afferent terminals, the GPCR cannabinoid 1 (CB1) is often coexpressed with transient receptor potential vanilloid 1 (TRPV1), a nonselective cation channel present on most afferents. Here we tested whether CB1 activation modulates synchronous, action potential-evoked (eEPSCs) and/or spontaneous (sEPSCs) EPSCs at solitary tract nucleus neurons. In rat horizontal brainstem slices, activation of solitary tract (ST) primary afferents generated ST-eEPSCs that were rapidly and reversibly inhibited from most afferents by activation of CB1 with arachidonyl-2'-chloroethylamide (ACEA) or WIN 55,212-2 [R-(+)-(2,3-dihydro-5-methyl-3-[(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzo xazin-6-yl)(1-naphthalenyl) methanone monomethanesulfonate]. The CB1 antagonist/inverse agonist AM251 [N-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl-1H-pyrazole-3 -carboxamide] blocked these responses. Despite profound depression of ST-eEPSCs during CB1 activation, sEPSCs in these same neurons were unaltered. Changes in temperature changed sEPSC frequency only from TRPV1(+) afferents (i.e., thermal sEPSC responses only occurred in TRPV1(+) afferents). CB1 activation failed to alter these thermal sEPSC responses. However, the endogenous arachidonate metabolite N-arachidonyldopamine (NADA) promiscuously activated both CB1 and TRPV1 receptors. NADA inhibited ST-eEPSCs while simultaneously increasing sEPSC frequency, and thermally triggered sEPSC increases in neurons with TRPV1(+) afferents. We found no evidence for CB1/TRPV1 interactions suggesting independent regulation of two separate vesicle pools. Together, these data demonstrate that action potential-evoked synchronous glutamate release is modulated separately from TRPV1-mediated glutamate release despite coexistence in the same central terminations. This two-pool arrangement allows independent and opposite modulation of glutamate release by single lipid metabolites.

Ferracane, J. L., & Palin, W. M. (2012). *Effects of particulate filler systems on the properties and performance of dental polymer composites* Elsevier Inc.

The filler component is the main determinant of the mechanical and wear properties of a dental composite. The filler also significantly influences curing shrinkage, thermal properties, optical

properties, water uptake, handling and other physical properties. In general, maximizing filler reinforcement, specifically by using a high concentration of relatively small particulate fillers that have been coated with a silane agent to enhance the interfacial adhesion between the filler and resin matrix, is desirable to maximize the mechanical properties. It is generally believed that the result of this filler optimization will be superior clinical performance. But the specific manner in which the filler characteristics affect clinical outcomes of composites is not well understood or well described in the literature. However, there have been numerous studies and investigations into the role of the filler formulation on the properties and performance of dental composites, many of which will be reviewed in this chapter. 

Findholt, N. E., Izumi, B. T., Nguyen, T., Pickus, H., & Chen, Z. (2014). Availability of healthy snack foods and beverages in stores near high-income urban, low-income urban, and rural elementary and middle schools in oregon. *Childhood Obesity (Print),*

Abstract Background: Food stores near schools are an important source of snacks for children. However, few studies have assessed availability of healthy snacks in these settings. The aim of this study was to assess availability of healthy snack foods and beverages in stores near schools and examine how availability of healthy items varied by poverty level of the school and rural-urban location. Methods: Food stores were selected based on their proximity to elementary/middle schools in three categories: high-income urban, low-income urban, and rural. Audits were conducted within the stores to assess the presence or absence of 48 items in single-serving sizes, including healthy beverages, healthy snacks, fresh fruits, and fresh vegetables. Results: Overall, availability of healthy snack foods and beverages was low in all stores. However, there was significant cross-site variability in availability of several snack and fruit items, with stores near high-income urban schools having higher availability, compared to stores near low-income urban and/or rural schools. Stores near rural schools generally had the lowest availability, although several fruits were found more often in rural stores than in urban stores. There were no significant differences in availability of healthy beverages and fresh vegetables across sites. Conclusions: Availability of healthy snack foods and beverages was limited in stores near schools, but these limitations were more severe in stores proximal to rural and low-income schools. Given

that children frequent these stores to purchase snacks, efforts to increase the availability of healthy products, especially in stores near rural and low-income schools, should be a priority.

Fleischhauer, K., Fernandez-Vina, M. A., Wang, T., Haagenson, M., Battiwalla, M., Baxter-Lowe, L. A., et al. (2014). Risk associations between HLA-DPB1 T-cell epitope matching and outcome of unrelated hematopoietic cell transplantation are independent of HLA-DPA1. *Bone Marrow Transplantation,*

HLA-DP antigens are beta-alpha heterodimers encoded by polymorphic HLA-DPB1 and -DPA1 alleles, respectively, in strong linkage disequilibrium (LD) with each other. Non-permissive unrelated donor (UD)-recipient HLA-DPB1 mismatches across three different T-cell epitope (TCE) groups are associated with increased mortality after hematopoietic SCT (HCT), but the role of HLA-DPA1 is unclear. We studied 1281 onco-hematologic patients after 10/10 HLA-matched UD-HCT facilitated by the National Marrow Donor Program. Non-permissive mismatches defined solely by HLA-DPB1 TCE groups were associated with significantly higher risks of TRM compared to permissive mismatches (hazard ratio (HR) 1.30, confidence interval (CI) 1.06-1.53; P=0.009) or allele matches. Moreover, non-permissive HLA-DPB1 TCE group mismatches in the graft versus host (GvH) direction significantly decreased the risk of relapse compared to permissive mismatches (HR 0.55, CI 0.37-0.80; P=0.002) or allele matches. Splitting each group into HLA-DPA1*02:01 positive or negative, in frequent LD with HLA-DPB1 alleles from two of the three TCE groups, or into HLA-DPA1 matched or mismatched, did not significantly alter the observed risk associations. Our findings suggest that the effects of clinically non-permissive HLA-DPB1 TCE group mismatches are independent of HLA-DPA1, and that selection of donors with non-permissive DPB1 TCE mismatches in GvH direction might provide some protection from disease recurrence.Bone Marrow Transplantation advance online publication, 23 June 2014; doi:10.1038/bmt.2014.122.

Fling, B. W., Cohen, R. G., Mancini, M., Carpenter, S. D., Fair, D. A., Nutt, J. G., et al. (2014). Functional reorganization of the locomotor network in parkinson patients with freezing of gait. *PloS One, 9*(6), e100291.

Freezing of gait (FoG) is a transient inability to initiate or maintain stepping that often

accompanies advanced Parkinson's disease (PD) and significantly impairs mobility. The current study uses a multimodal neuroimaging approach to assess differences in the functional and structural locomotor neural network in PD patients with and without FoG and relates these findings to measures of FoG severity. Twenty-six PD patients and fifteen age-matched controls underwent resting-state functional magnetic resonance imaging and diffusion tensor imaging along with self-reported and clinical assessments of FoG. After stringent movement correction, fifteen PD patients and fourteen control participants were available for analysis. We assessed functional connectivity strength between the supplementary motor area (SMA) and the following locomotor hubs: 1) subthalamic nucleus (STN), 2) mesencephalic and 3) cerebellar locomotor region (MLR and CLR, respectively) within each hemisphere. Additionally, we quantified structural connectivity strength between locomotor hubs and assessed relationships with metrics of FoG. FoG+ patients showed greater functional connectivity between the SMA and bilateral MLR and between the SMA and left CLR compared to both FoG- and controls. Importantly, greater functional connectivity between the SMA and MLR was positively correlated with i) clinical, ii) self-reported and iii) objective ratings of freezing severity in FoG+, potentially reflecting a maladaptive neural compensation. The current findings demonstrate a re-organization of functional communication within the locomotor network in FoG+ patients whereby the higher-order motor cortex (SMA) responsible for gait initiation communicates with the MLR and CLR to a greater extent than in FoG- patients and controls. The observed pattern of altered connectivity in FoG+ may indicate a failed attempt by the CNS to compensate for the loss of connectivity between the STN and SMA and may reflect a loss of lower-order, automatic control of gait by the basal ganglia.

Flinn, I. W., Kahl, B. S., Leonard, J. P., Furman, R. R., Brown, J. R., Byrd, J. C., et al. (2014). Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-δ, as therapy for previously treated indolent non-hodgkin lymphoma. *Blood, 123*(22), 3406-3413.

Idelalisib (GS-1101, CAL-101), an oral inhibitor of phosphatidylinositol 3-kinase-δ, was evaluated in a phase I study in 64 patients with relapsed indolent non-Hodgkin lymphoma (iNHL). Patients had a median (range) age of 64 (32-91) years, 34 (53%) had bulky disease (≥1 lymph nodes ≥5 cm), and 37 (58%) had refractory disease. Patients had received a median (range) of 4 (1-10)

prior therapies. Eight dose regimens of idelalisib were evaluated; idelalisib was taken once or twice daily continuously at doses ranging from 50 to 350 mg.After 48 weeks, patients still benefitting (n519; 30%) enrolled into an extension study. Adverse events (AEs) occurring in 20% or more patients (total%/grade ≥3%) included diarrhea (36/8), fatigue (36/3), nausea (25/3), rash (25/3), pyrexia (20/3), and chills (20/0). Laboratory abnormalities included neutropenia (44/23), anemia (31/5), thrombocytopenia (25/11), and serum transaminase elevations (48/25). Twelve (19%) patients discontinued therapy due to AEs. Idelalisib induced disease regression in 46/54 (85%) of evaluable patients achieving an overall response rate of 30/64 (47%), with 1 patient having a complete response (1.6%). Median duration of response was 18.4 months, median progression-free survival was 7.6 months. Idelalisib is well tolerated and active in heavily pretreated, relapsed/refractory patients with iNHL. These trials were registered at clinicaltrials.gov as NCT00710528 and NCT01090414. © 2014 by The American Society of Hematology.

Forthofer, R. N., Lee, E. S., & Hernandez, M. (2006). *Biostatistics: A guide to design, analysis and discovery* Elsevier Inc.

Today, mathematics, biology, medicine, and statistics are closing the interdisciplinary gap in an unprecedented way and many of the important unanswered questions now emerge at the interface of these disciplines. Now in its Second Edition, this user-friendly guide on biostatistics focuses on the proper use and interpretation of statistical methods. This textbook does not require extensive background in mathematics, making it user-friendly for all students in the public health sciences field. Instead of highlighting derivations of formulas, the authors provide rationales for the formulas, allowing students to grasp a better understanding of the link between biology and statistics. The material on life tables and survival analysis allows students to better understand the recent literature in the health field, particularly in the study of chronic disease treatment. Biostatistics now includes a companion website to demonstrate the different applications of computer packages for performing the various analyses presented in this text. Includes access to a companion website with further examples and a full explanation of computer packages. Over 40% new material with modern real-life examples, exercises and references. New chapters on Logistic Regression; Analysis of Survey Data; and Study Designs. Introduces

strategies for analyzing complex sample survey data. Written in a conversational style more accessible to students with real data. 

Fraunfelder, F. W., & Fraunfelder, F. T. (2014). Conjunctival and corneal ulceration associated with nicorandil. *Cutaneous and Ocular Toxicology, 33*(2), 120-121.

Context/Objective: To report an association between conjunctival and corneal ulceration and nicorandil therapy for angina. Methods: Review of the literature and spontaneous reports collected at the National Registry of Drug-Induced Ocular Side Effects (Portland, Oregon), the FDA Spontaneous Reporting System (Bethesda, Maryland) and the World Health Organization's Uppsala Monitoring Center (Uppsala, Sweden). Results: Thirteen case reports of adverse ocular reactions were collected. Abnormal vision (5 reports), corneal ulcer (4 reports) and conjunctival ulcer (4 reports) were associated with nicorandil. Eight subjects were male and 5 female with an average age of 75.4± 8.3 years. The average duration of therapy to development of the ADR was 30.4 days ±3 days. Eleven case reports had positive dechallenge and the patients fully recovered. The average dose was 21.6mg daily. Conclusion: Using WHO classification for adverse drug reactions, the association between nicorandil and conjunctival and corneal ulceration is "possible". The case reports indicate that, if recognized, withdrawing nicorandil will lead to resolution of the conjunctival or corneal ulceration. Advanced age and accumulation of nicotinic acid in tissues may be contributory to the risk of developing ocular ulcerations from nicorandil. 

Freeman, K. A., Riley, A., Duke, D. C., & Fu, R. (2014). Systematic review (and meta-analysis) of behavioral interventions for fecal incontinence with constipation. *Journal of Pediatric Psychology,*

BACKGROUND: Multiple treatments exist for fecal incontinence. However, the relative and additive influence of commonly used behavioral approaches remains unclear. OBJECTIVE: We conducted a systematic review of randomized controlled trials to synthesize the effects of behavioral treatment of fecal incontinence with constipation in children aged 4-18 years. Mixed treatment comparisons (MTCs) and random effects models were used to analyze outcomes. Risk of bias and quality of evidence were rated. RESULTS: Although 10 studies were identified for MTCs, results did not yield reliable or valid estimates. Four studies were retained for random

effects pooled outcome analysis. Results indicated that behavioral intervention was more effective than control conditions for author-defined success and soiling frequency. CONCLUSION: Although evidence supports behavioral treatments for fecal incontinence with constipation in children, available evidence is limited. More and higher-quality trials are needed to better understand the relative effects of different treatments, including behavioral strategies.

Friesen, C. R., Kerns, A. R., & Mason, R. T. (2014). Factors influencing paternity in multiply mated female red-sided garter snakes and the persistent use of sperm stored over winter. *Behavioral Ecology and Sociobiology,*

In some species, sperm is stored within the female reproductive tract for months to years, and yet remains viable to fertilize eggs and produce offspring. Female red-sided garter snakes store sperm for over 7 months of winter dormancy. In previous work, we demonstrated that these stored sperm account for an average of 25 % paternity of a litter when the female mates with a male at spring emergence. Here, we tested whether last-male sperm precedence was prevalent when a female mates with two males during the spring. On average, paternity was shared equally among the first (P1 proportion of paternity of the first male to mate) and second males (P2) to mate in the spring, and stored sperm (Pss), but the variance in paternity was high. Thus, last male sperm precedence may diminish when a female has more than two mates. Male size did not affect paternity, but, as the interval between matings increased, P1 increased at the expense of Pss. Interestingly, as the second spring male's copulation duration increased, P1 also increased at the expense of P2. This result suggests that female influence over sperm and/or copulatory plug transfer during matings may also affect which male fathers her offspring in response to coercive matings as we assisted females to mate for their second mating. Finally, all females were spring "virgins"; consequently, sperm stored from autumn matings (and/or previous spring matings) remain competitive even when faced with two rivals in sperm competition and is likely the driver of the evolution of sperm longevity. 

Fromme, E. K., Zive, D., Schmidt, T. A., Cook, J. N., & Tolle, S. W. (2014). Association between physician orders for life-sustaining treatment for scope of treatment and in-hospital death in oregon. *Journal of the American Geriatrics Society,*

OBJECTIVES: To examine the relationship between Physician Orders for Life-Sustaining Treatment (POLST) for Scope of Treatment and setting of care at time of death. DESIGN: Cross-sectional. SETTING: Oregon in 2010 and 2011. PARTICIPANTS: People who died of natural causes. MEASUREMENTS: Oregon death records containing cause and location of death were matched with POLST orders for people with a POLST form in the Oregon POLST registry. Logistic regression was used to measure the association between POLST orders and location of death. RESULTS: Of 58,000 decedents, 17,902 (30.9%) had a POLST form in the registry. Their orders for Scope of Treatment were comfort measure only, 11,836 (66.1%); limited interventions, 4,787 (26.7%); and full treatment, 1,153 (6.4%). Comfort measures only (CMO) orders advise avoiding hospitalization unless comfort cannot be achieved in the current setting; 6.4% of participants with POLST CMO orders died in the hospital, compared with 44.2% of those with orders for full treatment and 34.2% for those with no POLST form in the registry. In the logistic regression, the odds of dying in the hospital of those with an order for limited interventions was 3.97 times as great (95% CI = 3.59-4.39) as of those with a CMO order, and the odds of those with an order for full treatment was 9.66 times as great (95% CI = 8.39-11.13). CONCLUSIONS: The association with numbers of deaths in the hospital suggests that end-of-life preferences of people who wish to avoid hospitalization as documented in POLST orders are honored.

Gallagher, E. R., Hing, A. V., & Cunningham, M. L. (2013). Evaluating fontanels in the newborn skull. *Contemporary Pediatrics, 30*(11)

Palpating an infant's anterior and posterior fontanels provides a window into what may be occurring in the newborn brain, but also examining skull shape and size will identify underlying problems that require further evaluation or intervention. 

Gao, B., Pollock, J. A., & Hinson, H. E. (2014). Paroxysmal sympathetic hyperactivity in hemispheric intraparenchymal hemorrhage. *Annals of Clinical and Translational Neurology, 1*(3), 215-219.

INTRODUCTION: Paroxysmal sympathetic hyperactivity (PSH) is a hyperadrenergic syndrome that may follow acute brain injury characterized by episodic, hyperadrenergic alterations in vital signs. Identifying commonality in lesion localization in patients with PSH is challenging, but intraparenchymal hemorrhage (IPH) represents a focal injury that might provide insight. We

describe a series of patients with IPH that developed PSH, and review the literature. METHODS: Patients with IPH who developed PSH were identified from OHSU hospital records. A literature review was conducted to identify similar cases through PUBMED, OVID, and Google Scholar. RESULTS: Three cases meeting criteria for PSH were identified. Hemorrhage volume ranged from 70 to 128 mL, and intracranial hemorrhage score ranged from 2 to 3. The laterality of the hemorrhage and significant volume of hemorrhage was similar in each of the patients, specifically all hemorrhages were large, subcortical, and right-sided. A literature search identified six additional cases, half of whom reported a right hemisphere hemorrhage and the majority also had subcortical localization. CONCLUSIONS: Our literature review identified six cases of IPH associated with PSH with five cases having subcortical lesion locations, echoing the areas of disruption in our three cases. On the basis of these observations, we hypothesize that injuries along the pathway from the insular cortex to downstream sympathetic centers may remove tonic inhibition leading to unchecked sympathetic outflow. Prospective investigations of lesion location in patients with IPH and PSH are warranted to test this hypothesis, especially with advanced neuroimaging techniques.

Geltzeiler, C. B., Nabavizadeh, N., Kim, J., Lu, K. C., Billingsley, K. G., Thomas, C. R., et al. (2014). Chemoradiotherapy with a radiation boost for anal cancer decreases the risk for salvage abdominoperineal resection: Analysis from the national cancer data base. *Annals of Surgical Oncology,*

BACKGROUND: Chemoradiotherapy (CRT), the primary treatment for anal cancer, achieves complete tumor regression in most patients. Abdominoperineal resection (APR) is reserved for persistent or recurrent disease. An additional boost dose of radiation after CRT often is used to improve the response rate for advanced local disease (T3, 4, and N+). This study examines the need for salvage APR after radiation boost. METHODS: Patients with de novo anal cancer in the National Cancer Data Base from the years 2004-2010 were analyzed. Patients with missing data points or who did not receive standard CRT were excluded. Variables included age, gender, race, primary tumor size, clinical nodal status, TNM stage, radiation boost, and APR. A logistic regression model assessing the relationship between boost radiation and APR was developed. RESULTS: Of 1,025 patients meeting inclusion criteria, 450 patients received CRT without a

radiation boost and 575 patients received CRT with a radiation boost. The two groups were similar in age, gender, race, tumor size, nodal status, and TNM stage (p values all >0.05). Significant multivariate predictors of salvage APR were tumor size, negative nodal status, and boost RT (all p 0.05). When controlling for age, tumor size, and nodal status, salvage APR is less likely to occur after boost RT (odds ratio 0.63; 95 % confidence interval 0.47, 0.85; p = 0.003). CONCLUSIONS: When controlling for age, tumor size, and nodal status, those who received boost radiation for anal cancer were less likely to require salvage APR.

Gerolamo, A. M., Overcash, A., McGovern, J., Roemer, G., & Bakewell-Sachs, S. (2014). Who will educate our nurses? A strategy to address the nurse faculty shortage in new jersey. *Nursing Outlook,*

BACKGROUND: The nurse faculty shortage hampers the capacity of the nursing workforce to respond to the demands of the evolving health care system. As a strategy to address the shortage in New Jersey, the Robert Wood Johnson Foundation implemented the New Jersey Nursing Initiative Faculty Preparation Program to prepare nurses for the faculty role. This article highlights program implementation successes and challenges, scholar and faculty perceptions of the program, and provides recommendations for others interested in preparing nurse faculty. METHODS: This evaluation uses data from scholar surveys and focus groups, interviews with grantees, and grantee reports. RESULTS: Findings suggest that a program that includes generous monetary support, socialization to the nurse faculty role, and formal education courses produces graduates who readily assume a faculty position and are committed to at least a part-time career in nursing education. CONCLUSIONS: This evaluation emphasizes the need to carefully design programs that integrate faculty preparation and advanced clinical training.

Gilbert, D. N. (2014). Treatment of infections caused by multidrug resistant gram-negative bacilli. *Therapeutic Research, 35*(4), 339-344.

Glynn, J. J., & Hinds, M. T. (2014). Endothelial outgrowth cells regulate coagulation, platelet accumulation and respond to tumor necrosis factor similar to carotid endothelial cells. *Tissue Engineering.Part A,*

Endothelial cells (ECs) are central regulators of hemostasis, inflammation, and other vascular

processes. ECs have been used to cover vascular graft materials in an attempt to improve the biologic integration of the grafts with the surrounding tissue. Although EC-seeded grafts demonstrated improved patency, the invasive nature of EC harvest has limited the clinical translation of this technique. Endothelial outgrowth cells (EOCs) can be derived from circulating endothelial progenitor cells, which are non-invasively isolated from a peripheral blood draw. Although EOCs have been presumed to regulate hemostasis and inflammation similarly to arterial ECs, there has been limited research that directly compares EOCs to arterial ECs, particularly using pairs of donor-matched cells. This study provides a multifaceted characterization of hemostasis regulation by baboon EOCs and carotid ECs, both in the presence and absence of tumor necrosis factor alpha (TNFalpha). The expression of genes involved in thrombosis and inflammation was highly similar between ECs and EOCs at a basal state and following TNFalpha stimulation. ECs and EOCs activated similar levels of protein C and Factor X (FX) at a basal state. Following TNFalpha treatment, EOCs had less of an increase in tissue factor activity than ECs. Cell-seeded ePTFE vascular grafts connected to a baboon femoral arteriovenous shunt loop demonstrated no significant differences between ECs and EOCs in platelet accumulation or fibrinogen incorporation. This work demonstrates that EOCs regulate thrombus formation and respond to an inflammatory stimulus similar to ECs, and supports utilizing EOCs as an autologous endothelium in tissue engineering applications.

Gonzales, D., Hajek, P., Pliamm, L., Nackaerts, K., Tseng, L. J., McRae, T. D., et al. (2014). Re-treatment with varenicline for smoking cessation in smokers who have previously taken varenicline: A randomized, placebo-controlled trial. *Clinical Pharmacology and Therapeutics,* The efficacy and safety of re-treatment with varenicline in smokers attempting to quit was evaluated in this randomized, double-blind, placebo-controlled, multicenter trial (Australia, Belgium, Canada, Czech Republic, France, Germany, UK and US). Participants were generally-healthy adult smokers (>/=10 cigs/day); >/=1 prior quit attempt (>/=2 weeks) using varenicline; no quit attempts in </=3 months; and randomly-assigned (1:1) to 12 weeks' varenicline (N=251) or placebo (N=247) treatment, with individual counseling, plus 40 weeks non-treatment follow-up. Primary efficacy endpoint was carbon monoxide confirmed (</=10 ppm) continuous abstinence rate (CAR) for weeks 9-12, which were 45.0% (varenicline; N=249)

versus 11.8% (placebo; N=245; OR=7.08; 95% CI: 4.34, 11.55; P<0.0001). Common varenicline-group adverse events were nausea, abnormal dreams, and headache, with no reported suicidal behavior. Varenicline is effective and well-tolerated in smokers who have previously taken varenicline. Abstinence rates are comparable with rates reported for varenicline-naive smokers. Trial registration: www.clinicaltrials.gov (NCT01244061). Funding source: Pfizer Inc.Clinical Pharmacology & Therapeutics (2014); Accepted article preview online 09 June 2014; doi:10.1038/clpt.2014.124.

Gonzalez, M. A., VanBooven, D., Hulme, W., Ulloa, R. H., Lebrigio, R. F. A., Osterloh, J., et al. (2012). Whole genome sequencing and a new bioinformatics platform allow for rapid gene identification in d. melanogaster EMS screens. *Biology, 1*(3), 766-777.

Forward genetic screens in Drosophila melanogaster using ethyl methanesulfonate (EMS) mutagenesis are a powerful approach for identifying genes that modulate specific biological processes in an in vivo setting. The mapping of genes that contain randomly-induced point mutations has become more efficient in Drosophila thanks to the maturation and availability of many types of genetic tools. However, classic approaches to gene mapping are relatively slow and ultimately require extensive Sanger sequencing of candidate chromosomal loci. With the advent of new high-throughput sequencing techniques, it is increasingly efficient to directly re-sequence the whole genome of model organisms. This approach, in combination with traditional chromosomal mapping, has the potential to greatly simplify and accelerate mutation identification in mutants generated in EMS screens. Here we show that next-generation sequencing (NGS) is an accurate and efficient tool for high-throughput sequencing and mutation discovery in Drosophila melanogaster. As a test case, mutant strains of Drosophila that exhibited longterm survival of severed peripheral axons were identified in a forward EMS mutagenesis. All mutants were recessive and fell into a single lethal complementation group, which suggested that a single gene was responsible for the protective axon degenerative phenotype. Whole genome sequencing of these genomes identified the underlying gene ect4. To improve the process of genome wide mutation identification, we developed Genomes Management Application (GEM.app, https://genomics.med.miami.edu), a graphical online user interface to a custom query framework. Using a custom GEM.app query, we were able to identify that each mutant carried a

unique non-sense mutation in the gene ect4 (dSarm), which was recently shown by Osterloh et al. to be essential for the activation of axonal degeneration. Our results demonstrate the current advantages and limitations of NGS in Drosophila and we introduce GEM.app as a simple yet powerful genomics analysis tool for the Drosophila community. At a current cost of <$1,000 per genome, NGS should thus become a standard gene discovery tool in EMS induced genetic forward screens. © 2012 by the authors; licensee MDPI, Basel, Switzerland.

Gorman, M. C., Orme, K. S., Nguyen, N. T., Kent, E. J.,3rd, & Caughey, A. B. (2014). Outcomes in pregnancies complicated by methamphetamine use. *American Journal of Obstetrics and Gynecology,*

OBJECTIVES: Methamphetamine use is widespread. Our goal was to examine the effects of methamphetamine use on various maternal and neonatal outcomes. STUDY DESIGN: We conducted a retrospective cohort study looking at all pregnancies between 2005 and 2008 in the state of California associated with a diagnosis of methamphetamine use. Outcomes examined included: gestational hypertension, preeclampsia, preterm birth, small for gestational age, birth weight, abruption, IUFD, neonatal death, infant death, jaundice, and gestational diabetes. Statistical analysis included chi squared tests and multivariable logistic regression analyses. RESULTS: After adjusting for multiple confounding variables on multivariable regression analysis, results indicated that compared with controls, methamphetamine users had greater odds of: gestational hypertension (OR 1.8, 95% CI 1.6-2.0), preeclampsia (OR 2.7, 95% CI 2.4-3.0), IUFD (OR 5.1, 95% CI 3.7-7.2), and abruption (OR 5.5, 95% CI 4.9-6.3). Additionally, these patients had a higher odds of preterm birth (OR 2.9, 95% CI 2.7-3.1), , neonatal death (OR 3.1, 95% CI 2.3-4.2, and infant death (OR 2.5, 95% CI 1.7-3.7). CONCLUSION: Methamphetamine use in pregnancy was found to be associated with specific patterns of increased maternal and fetal morbidity and mortality. With these results in mind, further work can be done to improve the care of pregnancies complicated by methamphetamine use in hopes of reducing these complications.

Grandy, D. K. (2014). TAAR1 transforms thinking about a plant alkaloid that transformed the practice of medicine. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP),* , 1-3.

Grant, K. A., Ferguson, B., Helms, C., & McClintick, M. (2014). *Drinking to dependence risk factors in nonhuman primates* Elsevier Inc.

Nonhuman primates (NHPs), in particular old-world monkeys, are excellent human surrogates for understanding putative risk factors, including genetic and epigenetic factors, behavioral traits, and stress and hormonal interactions. NHPs have been very informative in alcohol research because they will repeatedly drink intoxicating doses of ethanol, including drinking until signs of physical dependence upon alcohol appear. Perhaps even more informative is that NHPs show a wide distribution in the daily intake of alcohol (with resultant blood ethanol concentrations) when they have nearly constant access to alcohol (22. hrs/day). Given the individual differences in drinking alcohol repeatedly to intoxication, this chapter will address several main risk factors for developing alcohol dependence that have been documented in humans and can be studied in monkeys. These main factors include genetic mechanisms, stress and the HPA axis, age of onset of drinking alcohol, and temperament. © 2014 Elsevier Inc. All rights reserved.

Graydon, C. W., Cho, S., Diamond, J. S., Kachar, B., von Gersdorff, H., & Grimes, W. N. (2014). Specialized postsynaptic morphology enhances neurotransmitter dilution and high-frequency signaling at an auditory synapse. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34*(24), 8358-8372.

Sensory processing in the auditory system requires that synapses, neurons, and circuits encode information with particularly high temporal and spectral precision. In the amphibian papillia, sound frequencies up to 1 kHz are encoded along a tonotopic array of hair cells and transmitted to afferent fibers via fast, repetitive synaptic transmission, thereby promoting phase locking between the presynaptic and postsynaptic cells. Here, we have combined serial section electron microscopy, paired electrophysiological recordings, and Monte Carlo diffusion simulations to examine novel mechanisms that facilitate fast synaptic transmission in the inner ear of frogs (Rana catesbeiana and Rana pipiens). Three-dimensional anatomical reconstructions reveal

specialized spine-like contacts between individual afferent fibers and hair cells that are surrounded by large, open regions of extracellular space. Morphologically realistic diffusion simulations suggest that these local enlargements in extracellular space speed transmitter clearance and reduce spillover between neighboring synapses, thereby minimizing postsynaptic receptor desensitization and improving sensitivity during prolonged signal transmission. Additionally, evoked EPSCs in afferent fibers are unaffected by glutamate transporter blockade, suggesting that transmitter diffusion and dilution, and not uptake, play a primary role in speeding neurotransmission and ensuring fidelity at these synapses.

Grnøseth, R., Vollmer, W. M., Hardie, J. A., Ólafsdóttir, I. S., Lamprecht, B., Buist, A. S., et al. (2014). Predictors of dyspnoea prevalence: Results from the BOLD study. *European Respiratory Journal, 43*(6), 1610-1620.

Dyspnoea is a cardinal symptom for cardiorespiratory diseases. No study has assessed worldwide variation in dyspnoea prevalence or predictors of dyspnoea. We used cross-sectional data from population-based samples in 15 countries of the Burden of Obstructive Lung Disease (BOLD) study to estimate prevalence of dyspnoea in the full sample, as well as in an a priori defined low-risk group (few risk factors or dyspnoea-associated diseases). Dyspnoea was defined by the modified Medical Research Council questions. We used ordered logistic regression analysis to study the association of dyspnoea with site, sex, age, education, smoking habits, low/high body mass index, self-reported disease and spirometry results. Of the 9484 participants, 27% reported any dyspnoea. In the low-risk subsample (n=4329), 16% reported some dyspnoea. In multivariate analyses, all covariates were correlated to dyspnoea, but only 13% of dyspnoea variation was explained. Females reported more dyspnoea than males (odds ratio ~2.1). When forced vital capacity fell below 60% of predicted, dyspnoea was much more likely. There was considerable geographical variation in dyspnoea, even when we adjusted for known risk factors and spirometry results. We were only able to explain 13% of dyspnoea variation. Copyright ©ERS 2014.

Haley, K. M., Recht, M., & McCarty, O. J. (2014). Neonatal platelets: Mediators of primary hemostasis in the developing hemostatic system. *Pediatric Research,*

The human hemostatic system is developmentally regulated, resulting in qualitative and quantitative differences in the mediators of primary and secondary hemostasis as well as fibrinolysis in neonates and infants. Although gestational and age related differences in coagulation factor levels occur, the existence of a unique neonatal platelet phenotype remains controversial. Complicated by difficulties in obtaining adequate neonatal blood volumes with which to perform functional assays, ambiguity surrounds the characterization of neonatal platelets. Thus, much of the current knowledge of neonatal platelet function has been based on studies from cord blood samples. Studies suggest that cord blood-derived platelets, as a surrogate for neonatal platelets, are hypo-functional when compared to adult platelets. This relative platelet dysfunction combined with a propensity toward thrombocytopenia in the Neonatal Intensive Care Unit population, creates a clinical conundrum regarding the appropriate administration of platelet transfusions. This review provides an appraisal of the distinct functional phenotype of neonatal platelets. Neonatal platelet transfusion practices and the impact of the relatively hypo-functional neonatal platelet on those practices will be considered.Pediatric Research (2014); doi:10.1038/pr.2014.87.

Hamilton, B., Liu, S., Simon, J. H., & Bourdette, D. (2014). Response to comment on letter for: Prevalence of brain magnetic resonance imaging meeting barkhof and McDonald criteria for dissemination in space among headache patients. *Multiple Sclerosis, 20*(7), 899.

Hansen, K. E., Blank, R. D., Palermo, L., Fink, H. A., & Orwoll, E. S. (2014). What analytic method should clinicians use to derive spine T-scores and predict incident fractures in men? results from the MrOS study. *Osteoporosis International,*

Summary In this study, the area under the curve was highest when using the lowest vertebral body T-score to diagnose osteoporosis. In men for whom hip imaging is not possible, the lowest vertebral body T-score improves the ability to diagnose osteoporosis in men who are likely to have an incident fragility fracture. Introduction Spine T-scores have limited ability to predict fragility fracture. We hypothesized that using lowest vertebral body T-score to diagnose osteoporosis would better predict fracture. Methods Among men enrolled in the Osteoporotic Fractures in Men Study, we identified cases with incident clinical fracture (n = 484) and controls

without fracture (n = 1,516). We analyzed the lumbar spine bone mineral density (BMD) in cases and controls (n = 2,000) to record the L1-L4 (referent), the lowest vertebral body, and International Society for Clinical Densitometry (ISCD)-determined T-scores using a male normative database and the L1-L4 T-score using a female normative database. We compared the ability of method to diagnose osteoporosis and, therefore, to predict incident clinical fragility fracture, using area under the receiver operator curves (AUCs) and the net reclassification index (NCI) as measures of diagnostic accuracy. ISCD-determined T-scores were determined in only 60 % of participants (n = 1,205). Results Among 1,205 men, the AUC to predict incident clinical fracture was 0.546 for L1-L4 male, 0.542 for the L1-L4 female, 0.585 for lowest vertebral body, and 0.559 for ISCD-determined T-score. The lowest vertebral body AUC was the only method significantly different from the referent method (p = 0.002). Likewise, a diagnosis of osteoporosis based on the lowest vertebral body T-score demonstrated a significantly better net reclassification index (NRI) than the referent method (net NRI +0.077, p = 0.005). By contrast, the net NRI for other methods of analysis did not differ from the referent method. Conclusion Our study suggests that in men, the lowest vertebral body T-score is an acceptable method by which to estimate fracture risk. 

Harding, M. J., McGraw, H. F., & Nechiporuk, A. (2014). The roles and regulation of multicellular rosette structures during morphogenesis. *Development (Cambridge, England), 141*(13), 2549-2558.

Multicellular rosettes have recently been appreciated as important cellular intermediates that are observed during the formation of diverse organ systems. These rosettes are polarized, transient epithelial structures that sometimes recapitulate the form of the adult organ. Rosette formation has been studied in various developmental contexts, such as in the zebrafish lateral line primordium, the vertebrate pancreas, the Drosophila epithelium and retina, as well as in the adult neural stem cell niche. These studies have revealed that the cytoskeletal rearrangements responsible for rosette formation appear to be conserved. By contrast, the extracellular cues that trigger these rearrangements in vivo are less well understood and are more diverse. Here, we review recent studies of the genetic regulation and cellular transitions involved in rosette

formation. We discuss and compare specific models for rosette formation and highlight outstanding questions in the field.

Haus, T., Ferguson, B., Rogers, J., Doxiadis, G., Certa, U., Rose, N. J., et al. (2014). Genome typing of nonhuman primate models: Implications for biomedical research. *Trends in Genetics : TIG,*

The success of personalized medicine rests on understanding the genetic variation between individuals. Thus, as medical practice evolves and variation among individuals becomes a fundamental aspect of clinical medicine, a thorough consideration of the genetic and genomic information concerning the animals used as models in biomedical research also becomes critical. In particular, nonhuman primates (NHPs) offer great promise as models for many aspects of human health and disease. These are outbred species exhibiting substantial levels of genetic variation; however, understanding of the contribution of this variation to phenotypes is lagging behind in NHP species. Thus, there is a pivotal need to address this gap and define strategies for characterizing both genomic content and variability within primate models of human disease. Here, we discuss the current state of genomics of NHP models and offer guidelines for future work to ensure continued improvement and utility of this line of biomedical research.

Hawkins, S. C., Caudell, M. J., Deloughery, T., & Murray, W. (2014). Reply to: Novel anticoagulants should NOT be recommended for high-risk activity. *Wilderness & Environmental Medicine,*

Hayes, T. L., Riley, T., Mattek, N., Pavel, M., & Kaye, J. A. (2014). Sleep habits in mild cognitive impairment. *Alzheimer Disease and Associated Disorders, 28*(2), 145-150.

We explored the relationship between sleep disturbances and mild cognitive impairment (MCI) in community-dwelling seniors. Recent evidence suggests that sleep habits are differentially compromised in different subtypes of MCI, but the relationship between sleep disruption and MCI remains poorly understood. We gathered daily objective measures of sleep disturbance from 45 seniors, including 16 with MCI (mean age, 86.9±4.3 y), over a 6-month period. We also collected self-report measures of sleep disturbance. Although there were no differences between groups in any of our self-report measures, we found that amnestic MCI (aMCI) volunteers had less disturbed sleep than both nonamnestic MCI (naMCI) and cognitively intact volunteers, as measured objectively by movement in bed at night ($F_{2,1078}=4.30$, $P=0.05$), wake after sleep

onset (F2,1078=41.6, P<0.001), and number of times up at night (F2,1078=26.7, P<0.001). The groups did not differ in total sleep time. In addition, the aMCI group had less day-to-day variability in these measures than the intact and naMCI volunteers. In general, the naMCI volunteers showed a level of disturbed sleep that was intermediate to that of aMCI and intact volunteers. These differences in sleep disruption between aMCI and naMCI may be related to differences in the pathology underlying these MCI subtypes. 

Hedditch, E. L., Gao, B., Russell, A. J., Lu, Y., Emmanuel, C., Beesley, J., et al. (2014). ABCA transporter gene expression and poor outcome in epithelial ovarian cancer. *Journal of the National Cancer Institute, 106*(7), 10.1093/jnci/dju149. Print 2014 Jul.

BACKGROUND: ATP-binding cassette (ABC) transporters play various roles in cancer biology and drug resistance, but their association with outcomes in serous epithelial ovarian cancer (EOC) is unknown. METHODS: The relationship between clinical outcomes and ABC transporter gene expression in two independent cohorts of high-grade serous EOC tumors was assessed with real-time quantitative polymerase chain reaction, analysis of expression microarray data, and immunohistochemistry. Associations between clinical outcomes and ABCA transporter gene single nucleotide polymorphisms were tested in a genome-wide association study. Impact of short interfering RNA-mediated gene suppression was determined by colony forming and migration assays. Association with survival was assessed with Kaplan-Meier analysis and log-rank tests. All statistical tests were two-sided. RESULTS: Associations with outcome were observed with ABC transporters of the "A" subfamily, but not with multidrug transporters. High-level expression of ABCA1, ABCA6, ABCA8, and ABCA9 in primary tumors was statistically significantly associated with reduced survival in serous ovarian cancer patients. Low levels of ABCA5 and the C-allele of rs536009 were associated with shorter overall survival (hazard ratio for death = 1.50; 95% confidence interval [CI] =1.26 to 1.79; P = 6.5e-6). The combined expression pattern of ABCA1, ABCA5, and either ABCA8 or ABCA9 was associated with particularly poor outcome (mean overall survival in group with adverse ABCA1, ABCA5 and ABCA9 gene expression = 33.2 months, 95% CI = 26.4 to 40.1; vs 55.3 months in the group with favorable ABCA gene expression, 95% CI = 49.8 to 60.8; P = .001), independently of tumor stage or surgical debulking status. Suppression

of cholesterol transporter ABCA1 inhibited ovarian cancer cell growth and migration in vitro, and statin treatment reduced ovarian cancer cell migration. CONCLUSIONS: Expression of ABCA transporters was associated with poor outcome in serous ovarian cancer, implicating lipid trafficking as a potentially important process in EOC.

Heffner, J. E. (2012). *Tracheotomy and upper airway obstruction* Elsevier Inc.

Heitzeg, M. M., Nigg, J. T., Hardee, J. E., Soules, M., Steinberg, D., Zubieta, J. K., et al. (2014). Left middle frontal gyrus response to inhibitory errors in children prospectively predicts early problem substance use. *Drug and Alcohol Dependence, 141C*, 51-57.

BACKGROUND: A core vulnerability trait for substance use disorder (SUD) is behavioral disinhibition. Error processing is a central aspect of inhibitory control that determines adaptive adjustment of performance; yet it is a largely overlooked aspect of disinhibition as it relates to risk for SUD. We investigated whether differences in brain activation during both successful and failed inhibition predicts early problem substance use. METHOD: Forty-five 9-12 year olds underwent a functional MRI scan during a go/no-go task. They were then followed over approximately 4 years, completing assessments of substance use. Externalizing behavior was measured at ages 3-8, 9-12 and 11-13. Participants with drug use or problem alcohol use by ages 13-16 (n=13; problem-user group) were individually matched by gender, age, and family history of alcoholism with non-substance-using children (n=13; non-user group). The remaining 19 participants provided an independent sample from which to generate unbiased regions-of-interest for hypothesis testing in the problem-user and non-user groups. RESULTS: No differences were observed between groups in activation during correct inhibition compared with baseline. A significant difference arose in left middle frontal gyrus (LMFG) activation during failed inhibition compared with correct inhibition, with the problem-user group demonstrating blunted activation. The problem-user group also had more externalizing problems at ages 11-13. Logistic regression found that activation of LMFG significantly predicted group membership over and above externalizing problems. CONCLUSIONS: Blunted LMFG activation during performance errors may underlie problems adapting behavior appropriately, leading to undercontrolled behavior, early problem substance use and increased risk for SUD.

Hickey, R. D., Mao, S. A., Glorioso, J., Lillegard, J. B., Fisher, J. E., Amiot, B., et al. (2014). Fumarylacetoacetate hydrolase deficient pigs are a novel large animal model of metabolic liver disease. *Stem Cell Research, 13*(1), 144-153.

Hereditary tyrosinemia type I (HT1) is caused by deficiency in fumarylacetoacetate hydrolase (FAH), an enzyme that catalyzes the last step of tyrosine metabolism. The most severe form of the disease presents acutely during infancy, and is characterized by severe liver involvement, most commonly resulting in death if untreated. Generation of FAH+/- pigs was previously accomplished by adeno-associated virus-mediated gene knockout in fibroblasts and somatic cell nuclear transfer. Subsequently, these animals were outbred and crossed to produce the first FAH-/- pigs. FAH-deficiency produced a lethal defect in utero that was corrected by administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC) throughout pregnancy. Animals on NTBC were phenotypically normal at birth; however, the animals were euthanized approximately four weeks after withdrawal of NTBC due to clinical decline and physical examination findings of severe liver injury and encephalopathy consistent with acute liver failure. Biochemical and histological analyses, characterized by diffuse and severe hepatocellular damage, confirmed the diagnosis of severe liver injury. FAH-/- pigs provide the first genetically engineered large animal model of a metabolic liver disorder. Future applications of FAH-/- pigs include discovery research as a large animal model of HT1 and spontaneous acute liver failure, and preclinical testing of the efficacy of liver cell therapies, including transplantation of hepatocytes, liver stem cells, and pluripotent stem cell-derived hepatocytes.

Hoberman, A., Greenfield, S. P., Mattoo, T. K., Keren, R., Mathews, R., Pohl, H. G., et al. (2014). Antimicrobial prophylaxis for children with vesicoureteral reflux. *New England Journal of Medicine, 370*(25), 2367-2376.

BACKGROUND: Children with febrile urinary tract infection commonly have vesicoureteral reflux. Because trial results have been limited and inconsistent, the use of antimicrobial prophylaxis to prevent recurrences in children with reflux remains controversial. METHODS: In this 2-year, multisite, randomized, placebo-controlled trial involving 607 children with vesicoureteral reflux that was diagnosed after a first or second febrile or symptomatic urinary tract infection, we evaluated the efficacy of trimethoprim-sulfamethoxazole prophylaxis in preventing recurrences

(primary outcome). Secondary outcomes were renal scarring, treatment failure (a composite of recurrences and scarring), and antimicrobial resistance. RESULTS: Recurrent urinary tract infection developed in 39 of 302 children who received prophylaxis as compared with 72 of 305 children who received placebo (relative risk, 0.55; 95% confidence interval [CI], 0.38 to 0.78). Prophylaxis reduced the risk of recurrences by 50% (hazard ratio, 0.50; 95% CI, 0.34 to 0.74) and was particularly effective in children whose index infection was febrile (hazard ratio, 0.41; 95% CI, 0.26 to 0.64) and in those with baseline bladder and bowel dysfunction (hazard ratio, 0.21; 95% CI, 0.08 to 0.58). The occurrence of renal scarring did not differ significantly between the prophylaxis and placebo groups (11.9% and 10.2%, respectively). Among 87 children with a first recurrence caused by Escherichia coli, the proportion of isolates that were resistant to trimethoprim-sulfamethoxazole was 63% in the prophylaxis group and 19% in the placebo group. CONCLUSIONS: Among children with vesicoureteral reflux after urinary tract infection, antimicrobial prophylaxis was associated with a substantially reduced risk of recurrence but not of renal scarring. Copyright © 2014 Massachusetts Medical Society.

Holley, A. L. (2014). Commentary: Routh early career award: The "not-so" painful journey of a pediatric pain researcher. *Journal of Pediatric Psychology,*

Horner-Johnson, W., Dobbertin, K., Lee, J. C., Andresen, E. M., & the Expert Panel on Disability and Health Disparities. (2014). Disparities in health care access and receipt of preventive services by disability type: Analysis of the medical expenditure panel survey. *Health Services Research,* OBJECTIVE: To examine differences in access to health care and receipt of clinical preventive services by type of disability among working-age adults with disabilities. DATA SOURCE: Secondary analysis of Medical Expenditure Panel Survey (MEPS) data from 2002 to 2008. STUDY DESIGN: We conducted cross-sectional logistic regression analyses comparing people with different types of disabilities on health insurance status and type; presence of a usual source of health care; delayed or forgone care; and receipt of dental checkups and cancer screening. DATA COLLECTION: We pooled annualized MEPS data files across years. Our analytic sample consisted of adults (18-64 years) with physical, sensory, or cognitive disabilities and nonmissing data for all variables of interest. PRINCIPAL FINDINGS: Individuals with hearing impairment had better

health care access and receipt than people with other disability types. People with multiple types of limitations were especially likely to have health care access problems and unmet health care needs. CONCLUSIONS: There are differences in health care access and receipt of preventive care depending on what type of disability people have. More in-depth research is needed to identify specific causes of these disparities and assess interventions to address health care barriers for particular disability groups.

Hussain, M., Corn, P. G., Michaelson, M. D., Hammers, H., Alumkal, J. J., Ryan, C. J., et al. (2014). Phase II study of single agent orteronel (TAK-700) in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research,*

Purpose: Orteronel (TAK-700) is an investigational, non-steroidal, oral, inhibitor of androgen synthesis with greater specificity for 17,20-lyase than for 17alpha-hydroxylase. We investigated orteronel without steroids in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC; M0). Experimental Design: Patients with nmCRPC and rising prostate-specific antigen (PSA) received orteronel 300 mg twice daily until PSA progression, metastases, or unacceptable toxicity. The primary endpoint was percentage of patients achieving PSA 30% in 35 patients and 6 (16%) achieved PSA /=3/4 adverse events occurred in 22 patients. Most frequent all-cause adverse events included fatigue (64%), hypertension (44%), diarrhea (38%), and nausea (33%), which were primarily grade 1/2. Conclusions: Single-agent orteronel produced marked and durable declines in PSA in patients with nmCRPC. Orteronel has moderate but manageable toxicities and its chronic administration without steroids appears feasible.

Hutchens, M. P., Kosaka, Y., Zhang, W., Fujiyoshi, T., Murphy, S., Alkayed, N., et al. (2014). Estrogen-mediated renoprotection following cardiac arrest and cardiopulmonary resuscitation is robust to GPR30 gene deletion. *PloS One, 9*(6), e99910.

INTRODUCTION: Acute kidney injury is a serious,sexually dimorphic perioperative complication, primarily attributed to hypoperfusion. We previously found that estradiol is renoprotective after cardiac arrest and cardiopulmonary resuscitation in ovariectomized female mice. Additionally, we found that neither estrogen receptor alpha nor beta mediated this effect. We hypothesized that

the G protein estrogen receptor (GPR30) mediates the renoprotective effect of estrogen. METHODS: Ovariectomized female and gonadally intact male wild-type and GPR30 gene-deleted mice were treated with either vehicle or 17beta-estradiol for 7 days, then subjected to cardiac arrest and cardiopulmonary resuscitation. Twenty four hours later, serum creatinine and urea nitrogen were measured, and histologic renal injury was evaluated by unbiased stereology. RESULTS: In both males and females, GPR30 gene deletion was associated with reduced serum creatinine regardless of treatment. Estrogen treatment of GPR30 gene-deleted males and females was associated with increased preprocedural weight. In ovariectomized female mice, estrogen treatment did not alter resuscitation, but was renoprotective regardless of GPR30 gene deletion. In males, estrogen reduced the time-to-resuscitate and epinephrine required. In wild-type male mice, serum creatinine was reduced, but neither serum urea nitrogen nor histologic outcomes were affected by estrogen treatment. In GPR30 gene-deleted males, estrogen did not alter renal outcomes. Similarly, renal injury was not affected by G1 therapy of ovariectomized female wild-type mice. CONCLUSION: Treatment with 17beta-estradiol is renoprotective after whole-body ischemia-reperfusion in ovariectomized female mice irrespective of GPR30 gene deletion. Treatment with the GPR30 agonist G1 did not alter renal outcome in females. We conclude GPR30 does not mediate the renoprotective effect of estrogen in ovariectomized female mice. In males, estrogen therapy was not renoprotective. Estrogen treatment of GPR30 gene-deleted mice was associated with increased preprocedural weight in both sexes. Of significance to further investigation, GPR30 gene deletion was associated with reduced serum creatinine, regardless of treatment.

Izumi, B. T., Findholt, N. E., Pickus, H. A., Nguyen, T., & Cuneo, M. K. (2014). Inter-rater reliability of a food store checklist to assess availability of healthier alternatives to the energy-dense snacks and beverages commonly consumed by children. *Childhood Obesity, 10*(3), 266-271. Background: Food stores have gained attention as potential intervention targets for improving children's eating habits. There is a need for valid and reliable instruments to evaluate changes in food store snack and beverage availability secondary to intervention. The aim of this study was to develop a valid, reliable, and resource-efficient instrument to evaluate the healthfulness of food store environments faced by children. Methods: The SNACZ food store checklist was developed to

assess availability of healthier alternatives to the energy-dense snacks and beverages commonly consumed by children. After pretesting, two trained observers independently assessed the availability of 48 snack and beverage items in 50 food stores located near elementary and middle schools in Portland, Oregon, over a 2-week period in summer 2012. Inter-rater reliability was calculated using the kappa statistic. Results: Overall, the instrument had mostly high inter-rater reliability. Seventy-three percent of items assessed had almost perfect or substantial reliability. Two items had moderate reliability (0.41-0.60), and no items had a reliability score less than 0.41. Eleven items occurred too infrequently to generate a kappa score. Conclusion: The SNACZ food store checklist is a first-step toward developing a valid and reliable tool to evaluate the healthfulness of food store environments faced by children. The tool can be used to compare availability of healthier snack and beverage alternatives across communities and measure change secondary to intervention. As a wider variety of healthier snack and beverage alternatives become available in food stores, the checklist should be updated. © 2014, Mary Ann Liebert, Inc. 2014.

Jacobsen, P. B., Le-Rademacher, J., Jim, H., Syrjala, K., Wingard, J. R., Logan, B., et al. (2014). Exercise and stress management training prior to hematopoietic cell transplantation: Blood and marrow transplant clinical trials network (BMT CTN) 0902. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation,* Studies show that engaging patients in exercise and/or stress management techniques during hematopoietic cell transplantation (HCT) improves quality of life. The Blood and Marrow Transplant Clinical Trials Network tested the efficacy of training patients to engage in self-directed exercise and stress management during HCT. The study randomized 711 patients at 21 centers to receive 1 of 4 training interventions before HCT: a self-directed exercise program, a self-administered stress management program, both, or neither. Participants completed self-reported assessments at enrollment and up to 180 days after HCT. Randomization was stratified by center and transplant type. There were no differences in the primary endpoints of the Physical Component Summary and Mental Component Summary scales of the Medical Outcomes Study Short Form 36 at day +100 among the groups, based on an intention-to-treat analysis. There also were no differences in overall survival, days of hospitalization through day +100 post-HCT,

or in other patient-reported outcomes, including treatment-related distress, sleep quality, pain, and nausea. Patients randomized to training in stress management reported more use of those techniques, but patients randomized to training in exercise did not report more physical activity. Although other studies have reported efficacy of more intensive interventions, brief training in an easy-to-disseminate format for either self-directed exercise or stress management was not effective in our trial.

Janghorban, M., Farrell, A. S., Allen-Petersen, B. L., Pelz, C., Daniel, C. J., Oddo, J., et al. (2014). Targeting c-MYC by antagonizing PP2A inhibitors in breast cancer. *Proceedings of the National Academy of Sciences of the United States of America, 111*(25), 9157-9162.

The transcription factor c-MYC is stabilized and activated by phosphorylation at serine 62 (S62) in breast cancer. Protein phosphatase 2A (PP2A) is a critical negative regulator of c-MYC through its ability to dephosphorylate S62. By inactivating c-MYC and other key signaling pathways, PP2A plays an important tumor suppressor function. Two endogenous inhibitors of PP2A, I2PP2A, Inhibitor-2 of PP2A (SET oncoprotein) and cancerous inhibitor of PP2A (CIP2A), inactivate PP2A and are overexpressed in several tumor types. Here we show that SET is overexpressed in about 50-60% and CIP2A in about 90% of breast cancers. Knockdown of SET or CIP2A reduces the tumorigenic potential of breast cancer cell lines both in vitro and in vivo. Treatment of breast cancer cells in vitro or in vivo with OP449, a novel SET antagonist, also decreases the tumorigenic potential of breast cancer cells and induces apoptosis. We show that this is, at least in part, due to decreased S62 phosphorylation of c-MYC and reduced c-MYC activity and target gene expression. Because of the ubiquitous expression and tumor suppressor activity of PP2A in cells, as well as the critical role of c-MYC in human cancer, we propose that activation of PP2A (here accomplished through antagonizing endogenous inhibitors) could be a novel antitumor strategy to posttranslationally target c-MYC in breast cancer.

Kahl, B. S., Spurgeon, S. E., Furman, R. R., Flinn, I. W., Coutre, S. E., Brown, J. R., et al. (2014). A phase 1 study of the PI3Kd inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). *Blood, 123*(22), 3398-3405.

Idelalisib, an oral inhibitor of phosphatidylinositol-3-kinase d (PI3Kd), was evaluated in a 48-

week phase 1 study (50-350 mg daily or twice daily) enrolling 40 patients with relapsed or refractory mantle cell lymphoma (MCL). Primary outcome was safety and dose-limiting toxicity (DLT). Secondary outcomes were pharmacokinetic parameters, pharmacodynamic effects, overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR). Patients without DLT and no evidence of disease progression after 48 weeks enrolled in the extension study. Patients had median age of 69 years (range, 52-83) and receivedmedian of 4 prior therapies (1-14); 17 of 40 patients (43%) were refractory to their most recent treatment. Median duration of idelalisib treatment was 3.5 months (range, 0.7-30.7), with 6 (15%) continuing extension treatment. Commongrade ≥3 adverse events (AEs) included (total%/grade ≥3%) diarrhea (40/18), nausea (33/5), pyrexia (28/0), fatigue (25/3), rash (23/3), decreased appetite (20/15), upper respiratory infection (20/0), pneumonia (13/10), and alanine transaminase or aspartate transaminase elevations (60/20). ORR was 16 of 40 patients (40%), with CR in 2 of 40 patients (5%). Median DOR was 2.7 months, median PFS was 3.7 months, and 1-year PFS was 22%. These data provide proof of concept that targeting PI3Kd is a viable strategy and worthy of additional study in MCL. This trial was registered at www.clinicaltrials.gov as #NCT00710528. © 2014 by The American Society of Hematology.

Kalinichev, M., Le Poul, E., Bolea, C., Girard, F., Campo, B., Fonsi, M., et al. (2014). Characterization of the novel positive allosteric modulator of mGlu4 receptor characterization of the novel positive allosteric modulator of mGlu4 receptor ADX88178 in rodent models of neuropsychiatric disorders. *The Journal of Pharmacology and Experimental Therapeutics,*

There is growing evidence that activation of the mGlu4 receptor leads to anxiolytic- and antipsychotic-like efficacy in rodent models, yet its relevance to depression-like reactivity remains unclear. Here, we present the pharmacological evaluation of ADX88178, a novel potent, selective and brain-penetrant positive allosteric modulator (PAM) of mGlu4 receptor in rodent models of anxiety, obsessive compulsive disorder (OCD), fear, depression and psychosis. ADX88178 dose-dependently reduced the number of buried marbles in the marble burying test and increased open-arm exploration in the elevated plus maze (EPM) test, indicative of anxiolytic-like efficacy. Target specificity of the effect in the EPM test was confirmed using male and female mGlu4 receptor knock-out mice. In mice, ADX88178 reduced the likelihood of

conditioned freezing in the acquisition phase of the fear conditioning test, yet had no carry-over effect in the expression phase. Also, ADX88178 dose-dependently reduced duration of immobility in the forced swim test, indicative of anti-depressant like efficacy. ADX88178 reduced DOI-mediated head twitches (albeit with no dose-dependency) and MK-801-induced locomotor hyperactivity in mice, but was inactive in the conditioned avoidance response test in rats. The compound showed good specificity as it had no effect on locomotor activity in mice and rats at efficacious doses. Thus, allosteric activation of mGlu4 receptors can be a promising new therapeutic approach for treatment of anxiety, OCD, fear-related disorders and psychosis.

Kaplan, M. S., Huguet, N., McFarland, B. H., Caetano, R., Conner, K. R., Giesbrecht, N., et al. (2014). Use of alcohol before suicide in the united states. *Annals of Epidemiology,*

PURPOSE: Few studies have compared acute use of alcohol in suicide decedents with that in a nonsuicide group. This study provides the first national analysis of acute use of alcohol before suicide compared with an estimate of acute use of alcohol in a living sample. METHODS: Pooled 2003-2011 National Violent Death Reporting System data were used to estimate the prevalence of postmortem blood alcohol content positivity (blood alcohol content >0.0 g/dL) and intoxication (blood alcohol content >/=0.08 g/dL). Population estimates of comparable use of alcohol (within the past 48 hours) were based on the National Epidemiologic Survey on Alcohol and Related Conditions. RESULTS: Compared with the living sample, male and female suicide decedents showed, respectively, a 1.83-fold (95% confidence interval [CI], 1.73-1.93) and 2.40-fold (95% CI, 2.24-2.57) increased risk of alcohol ingestion before their death after age, race/ethnicity, and chronic alcohol problems were controlled. Furthermore, male and female decedents exhibited, respectively, a 6.18-fold (95% CI, 5.57-6.86) and a 10.04-fold (95% CI, 8.67-11.64) increased risk of being intoxicated before their death after confounders were considered. CONCLUSIONS: The findings underscore the crucial need to include among the essential components of suicide prevention policies programs that minimize the use of alcohol, particularly drinking to intoxication.

Kardos, G. R., Dai, M. -., & Robertson, G. P. (2014). Growth inhibitory effects of large subunit ribosomal proteins in melanoma. *Pigment Cell and Melanoma Research,*

Ribosome biogenesis can modulate protein synthesis, a process heavily relied upon for cancer cell proliferation. In this study, involvement of large subunit ribosomal proteins (RPLs) in melanoma has been dissected and RPLs categorized based on modulation of cell proliferation and therapeutic targeting potential. Based on these results, two categories of RPLs were identified: the first causing negligible effects on cell viability, p53 expression, and protein translation, while the second category decreased cell viability and inhibited protein synthesis mediated with or without p53 protein stabilization. RPL13 represents the second category, where siRNA-mediated targeting inhibited tumor development through decreased cellular proliferation. Mechanistically, decreased RPL13 levels increased p53 stability mediated by RPL5 and RPL11 binding to and preventing MDM2 from targeting p53 for degradation. The consequence was p53-dependent cell cycle arrest and decreased protein translation. Thus, targeting certain category 2 RPL proteins can inhibit melanoma tumor development mediated through the MDM2-p53 pathway. 

Kennecke, H., Yu, J., Gill, S., Cheung, W. Y., Blanke, C. D., Speers, C., et al. (2014). Effect of M1a and M1b category in metastatic colorectal cancer. *The Oncologist,*

BACKGROUND: In 2009, the American Joint Committee on Cancer version 7 staging system introduced the M1 subclassifications M1a (single metastatic site) and M1b (peritoneal or multiple metastatic sites). The study objectives were to evaluate the prognostic effect of site of metastasis and M1a/b category among patients with newly diagnosed colorectal cancer and synchronous metastasis.PATIENTS AND METHODS: Patients with newly diagnosed pathologic or clinical category M1 colorectal cancer referred to the British Columbia Cancer Agency between 1999 and 2007 were included. Demographic, tumor, treatment, and outcome data were prospectively collected, and prognostic factors were identified. Univariate Cox models were used to assess the prognostic impact of individual sites of metastasis and to determine the effect of M1a/b category on overall survival (OS).RESULTS: Among 2,049 eligible patients, 70% had M1a and 30% M1b category disease. The most common sites of common single sites of metastasis included liver (56%), lung (5.3%), and peritoneum (3.6%). Metastasis to a single organ or site, including peritoneum, was associated with improved OS compared with multiple sites of metastasis. In multivariate analysis, M1b category conferred inferior survival and hazard ratio (HR) 1.38 (95%

confidence interval [CI]: 1.22, 1.55), along with age >70 and Eastern Cooperative Oncology Group performance status of 3-4. Resection of primary tumor was associated with improved survival, HR 0.46 (95% CI: 0.41, 0.52). Results were similar in subgroup analysis of patients undergoing resection of their primary tumor when histology, tumor, and node category were included.CONCLUSION: The results lend support to the introduction of M1a/b colorectal cancer categories. Consideration may be given to classifying patients with solitary peritoneal metastasis only as M1a rather than M1b category. Further refinement of category M1a to reflect resectability of metastasis at initial diagnosis may improve prognostication.

Khan, A., Morgenthaler, T. I., & Ramar, K. (2014). Sleep disordered breathing in isolated unilateral and bilateral diaphragmatic dysfunction. *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine, 10*(5), 509-515.
INTRODUCTION: The effect of isolated unilateral or bilateral diaphragmatic dysfunction (DD), in the absence of a generalized neuromuscular disorder, on sleep disordered breathing (SDB) is not well understood. The type of positive airway pressure (PAP) device needed to treat SDB in patients with isolated DD is also not well established. METHODS: We retrospectively analyzed data on patients with isolated unilateral or bilateral DD who were referred for polysomnography (PSG) for clinical symptoms or abnormal oximetry between 1994 and 2006. RESULTS: We found 66 patients who met criteria, of whom 74.2% were males with an average age of 58.8 +/- 10.9 years. 56 had isolated unilateral DD, and 10 had isolated bilateral DD. All had significant SDB with an apnea-hypopnea index (AHI) of 26.6 +/- 28.4. There were no significant differences in PSG measures, arterial blood gas analysis, pulmonary function tests, or echocardiographic data, except for lower maximal inspiratory pressure in patients with bilateral DD compared to unilateral DD (40.2% +/- 17.8% vs. 57.7% +/- 20.5%, p = 0.02). Control of SDB with continuous PAP (CPAP) was possible in only 37.9% of patients with the rest requiring bilevel PAP (BPAP). Patients with isolated bilateral DD and SDB were 6.8 times more likely to fail CPAP than those with unilateral DD (p = 0.03). CONCLUSIONS: Most patients with isolated DD failed CPAP and required BPAP. Patients with bilateral DD were more likely to require BPAP than those with unilateral DD. Patients with isolated DD should be considered for in-lab titration to determine adequacy of therapy.

Kim, M. S., Zhong, Y., Yachida, S., Rajeshkumar, N. V., Abel, M. L., Marimuthu, A., et al. (2014). Heterogeneity of pancreatic cancer metastases in a single patient revealed by quantitative proteomics. *Molecular & Cellular Proteomics : MCP,*

Many patients with pancreatic cancer have metastases to distant organs at the time of initial presentation. Recent studies examining the evolution of pancreatic cancer at the genetic level have shown that clonal complexity of metastatic pancreatic cancer is already initiated within primary tumors, and organ-specific metastases are derived from different subclones. However, we do not yet understand to what extent the evolution of pancreatic cancer contributes to proteomic and signaling alterations. We hypothesized that genetic heterogeneity of metastatic pancreatic cancer results in heterogeneity at the proteome level. To address this, we employed a model system in which cells isolated from three sites of metastasis (liver, lung and peritoneum) from a single patient were compared. We used a SILAC-based accurate quantitative proteomic strategy combined with a high resolution mass spectrometry to analyze the total proteome and tyrosine phosphoproteome of each of the distal metastases. Our data reveal distinct patterns of both overall proteome expression as well as tyrosine kinase activities across the three different metastatic lesions. This heterogeneity is significant because it led to differential sensitivity of the neoplastic cells to small molecule inhibitors targeting various kinases and other pathways. For example, R428, a tyrosine kinase inhibitor that targets Axl receptor tyrosine kinase, was able to inhibit cells derived from lung and liver metastases much more effectively than cells from the peritoneal metastasis. Finally, we confirmed that administration of R428 in mice bearing xenografts of cells derived from the three different metastatic sites significantly diminished tumors formed from liver and lung metastasis-derived cell lines as compared to tumors derived from the peritoneal metastasis cell line. Overall, our data provide proof-of-principle support that personalized therapy of multiple organ metastases in a single patient should involve administration of a combination of agents with each agent targeted to the features of different subclones.

Kim, R. J., Choi, N. S., Ferracane, J., & Lee, I. B. (2014). Acoustic emission analysis of the effect of simulated pulpal pressure and cavity type on the tooth-composite interfacial de-bonding. *Dental Materials : Official Publication of the Academy of Dental Materials,*

OBJECTIVE: The aim of this study was to evaluate the influence of in vitro pulpal pressure and cavity type on the tooth-composite bonding interface by means of acoustic emission (AE) analysis. METHODS: Classes I and II cavities on extracted third molars were prepared and assigned to four groups of seven teeth each: (1) direct composite restoration without simulated pulpal pressure (SPP) in class I cavity, (2) direct composite restoration with SPP in class I cavity, (3) direct composite restoration without SPP in class II cavity, (4) direct composite restoration with SPP in class II cavity. The teeth were restored with Filtek Z250 composite and Adper Scotchbond Multi-Purpose adhesive system (3M ESPE, St. Paul, MN, USA). AE events were recorded for 2000s during light-curing. Groups 2 and 4 were subjected to 20cm H2O hydrostatic pressure throughout the procedures. The data were analyzed with two-way ANOVA. After the AE test, teeth were sectioned longitudinally in mesio-distal direction, the tooth-composite interface was examined using SEM. RESULTS: SPP in Groups 2 (4.57+/-1.40) and 4 (3.43+/-1.13) yielded significantly higher AE events number than those of Groups 1 (3.43+/-1.51) and 3 (1.71+/-0.95) where the SPP was not applied ($p<0.05$). The number of AE events of class I cavity in Groups 1 and 2 were significantly higher than those of class II cavity in Groups 3 and 4 ($p<0.05$). SEM examination showed that all groups had intact enamel-composite interface, while micro-gaps were observed at the dentin-composite interface, mainly at the pulpal floor of the cavity. The class I cavities with SPP in Group 2 showed wider gaps more frequently than class II cavities without SPP in Group 3. SIGNIFICANCE: The SPP and class I cavity with high C-factor triggered more AE events, confirming its negative impact on the bonding interface.

Kim, Y. D., Kim, S. -., Hwang, S. -., Choi, H. -., Bae, J. -., Song, D. -., et al. (2014). B-cell translocation gene 2 regulates hepatic glucose homeostasis via induction of orphan nuclear receptor Nur77 in diabetic mouse model. *Diabetes, 63*(6), 1870-1880.

β-cell translocation gene 2 (BTG2) is a member of an emerging gene family that is involved in cellular functions. In this study, we demonstrate that BTG2 regulates glucose homeostasis via upregulation of Nur77 in diabetic mice. Hepatic BTG2 gene expression was elevated by fasting and forskolin. Overexpression of Btg2 increased the expression of hepatic gluconeogenic genes and blood glucose output and subsequently impaired glucose and insulin tolerance. Upregulation of the transcriptional activity of Nur77, gluconeogenic genes, and glucose production by forskolin

was observed by Btg2 transduction, but not in Btg2 knockdown. BTG2-stimulated glucose production and glucose-6- phosphatase promoter activity were attenuated by dominant-negative Nur77. Coimmunoprecipitation and chromatin immunoprecipitation assays showed that BTG2 induced Nur77 occupancy on the glucose-6- phosphatase promoter via a physical interaction. Btg2 gene expression was increased in streptozotocintreated and db/db mice. Finally, impairment of glucose homeostasis, such as the increase of blood glucose, glucose intolerance, and insulin intolerance, was elevated in diabetic mice, whereas this phenomenon was abolished in knockdown of Btg2. Together, these data suggest that BTG2 participates in the regulation of hepatic glucose homeostasis, which means that BTG2 might serve as a potential therapeutic target for combating metabolic dysfunction. 

Krishnan, B., Vlachos, I., Faith, A., Mullane, S., Williams, K., Alexopoulos, A., et al. (2014). A novel spatiotemporal analysis of peri-ictal spiking to probe the relation of spikes and seizures in epilepsy. *Annals of Biomedical Engineering,*

The relation between epileptic spikes and seizures is an important but still unresolved question in epilepsy research. Preclinical and clinical studies have produced inconclusive results on the causality or even on the existence of such a relation. We set to investigate this relation taking in consideration seizure severity and spatial extent of spike rate. We developed a novel automated spike detection algorithm based on morphological filtering techniques and then tested the hypothesis that there is a pre-ictal increase and post-ictal decrease of the spatial extent of spike rate. Peri-ictal (around seizures) spikes were detected from intracranial EEG recordings in 5 patients with temporal lobe epilepsy. The 94 recorded seizures were classified into two classes, based on the percentage of brain sites having higher or lower rate of spikes in the pre-ictal compared to post-ictal periods, with a classification accuracy of 87.4%. This seizure classification showed that seizures with increased pre-ictal spike rate and spatial extent compared to the post-ictal period were mostly (83%) clinical seizures, whereas no such statistically significant ($\alpha$ = 0.05) increase was observed peri-ictally in 93% of sub-clinical seizures. These consistent across patients results show the existence of a causal relation between spikes and clinical seizures, and imply resetting of the preceding spiking process by clinical seizures. 

Kunio, N. R., & Schreiber, M. A. (2013). *Topical hemostatic agents* Elsevier Inc.

Lädermann, A., Stimec, B. V., Denard, P. J., Cunningham, G., Collin, P., & Fasel, J. H. D. (2014). Erratum to "injury to the axillary nerve after reverse shoulder arthroplasty: An anatomic study" [orthop. traumatol. surg. res. 2014;100:105-8]. *Orthopaedics and Traumatology: Surgery and Research,*

Lamy, C. J. (2012). *Digital medical photography* Elsevier Ltd.

Lancet, J. E., Cortes, J. E., Hogge, D. E., Tallman, M. S., Kovacsovics, T. J., Damon, L. E., et al. (2014). Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/ daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood, 123*(21), 3239-3246.
CPX-351 is a liposomal formulation of cytarabine:daunorubicin designed to deliver synergistic drug ratios to leukemia cells. In this phase 2 study, newly diagnosed older acute myeloid leukemia (AML) patients were randomized 2:1 to first-line CPX-351 or 7+3 treatment. The goal was to determine efficacy and identify patient subgroups that may benefit from CPX-351 treatment. Response rate (complete remission + incomplete remission) was the primary end point, with event-free survival (EFS) and overall survival (OS) as secondary end points. The 126 patients entered were balanced for disease and patient-specific risk factors. Overall, CPX-351 produced higher response rates (66.7% vs 51.2%,P=.07), meeting predefined criteria for success (P100 000: 37 vs 28) with more grade 3-4 infections but without increase in infection-related deaths (3.5% vs 7.3%) or 60-day mortality (4.7% vs 14.6%), indicating acceptable safety. These results suggest a clinical benefit with CPX-351, particularly among patients with secondary AML, and provide the rationale for a phase 3 trial currently underway in newly diagnosed secondary AML patients. This study is registered at Clinicaltrials. gov as #NCT00788892. © 2014 by The American Society of Hematology.

Lanekoff, I., Stevens, S. L., Stenzel-Poore, M. P., & Laskin, J. (2014). *Matrix effects in biological mass spectrometry imaging: Identification and compensation* Royal Society of Chemistry.
Matrix effects in mass spectrometry imaging (MSI) may affect the observed molecular distribution in chemical and biological systems. In this study, we use mouse brain tissue of a middle cerebral

artery occlusion (MCAO) stroke model to examine matrix effects in nanospray desorption electrospray ionization MSI (nano-DESI MSI). This is achieved by normalizing the intensity of the sodium and potassium adducts of endogenous phosphatidylcholine (PC) species to the intensity of the corresponding adduct of the PC standard supplied at a constant rate with the nano-DESI solvent. The use of MCAO model with an ischemic region localized to one hemisphere of the brain enables immediate comparison of matrix effects within one ion image. Furthermore, significant differences in sodium and potassium concentrations in the ischemic region in comparison with the healthy tissue allowed us to distinguish between two types of matrix effects. Specifically, we discuss matrix effects originating from variations in alkali metal concentrations and matrix effects originating from variations in the molecular composition of the tissue. Compensation for both types of matrix effects was achieved by normalizing the signals corresponding to endogenous PC to the signals of the standards. This approach, which does not introduce any complexity in sample preparation, efficiently compensates for signal variations resulting from differences in the local concentrations of sodium and potassium in tissue sections and from the complexity of the extracted analyte mixture derived from local variations in molecular composition. This journal is 

Lasater, K., Johnson, E. A., Ravert, P., & Rink, D. (2014). Role modeling clinical judgment for an unfolding older adult simulation. *Journal of Nursing Education, 53*(5), 257-264.

Nurse educators must foster development of clinical judgment in students to help them provide the best care for the increasing population of older adult patients. This article reports qualitative findings from a mixed-methods study that focused on clinical judgment in the simulated perioperative care of an older adult. The sample was composed of treatment and control groups of prelicensure students (N = 275) at five sites. The treatment group watched a video of an expert nurse role model caring for a patient similar to the simulation patient, whereas the control group did not watch the video. Four weeks after simulation, participants cared for real-life, older adult perioperative patients. After the simulated and real-life care experiences, participants completed questionnaires related to clinical judgment dimensions. These two data sets revealed rich findings about the students' simulation learning, affirming the value of expert role models. Transferability of simulation learning to practice was also explored. 

Lee, C. S., Chien, C. V., Bidwell, J. T., Gelow, J. M., Denfeld, Q. E., Masterson Creber, R., et al. (2014). Comorbidity profiles and inpatient outcomes during hospitalization for heart failure: An analysis of the U.S. nationwide inpatient sample. *BMC Cardiovascular Disorders, 14*(1), 73-2261-14-73.

BACKGROUND: Treatment of heart failure (HF) is particularly complex in the presence of comorbidities. We sought to identify and associate comorbidity profiles with inpatient outcomes during HF hospitalizations. METHODS: Latent mixture modeling was used to identify common profiles of comorbidities during adult hospitalizations for HF from the 2009 Nationwide Inpatient Sample (n = 192,327). RESULTS: Most discharges were characterized by "common" comorbidities. A "lifestyle" profile was characterized by a high prevalence of uncomplicated diabetes, hypertension, chronic pulmonary disorders and obesity. A "renal" profile had the highest prevalence of renal disease, complicated diabetes, and fluid and electrolyte imbalances. A "neurovascular" profile represented the highest prevalence of cerebrovascular disease, paralysis, myocardial infarction and peripheral vascular disease. Relative to the common profile, the lifestyle profile was associated with a 15% longer length of stay (LOS) and 12% greater cost, the renal profile was associated with a 30% higher risk of death, 27% longer LOS and 24% greater cost, and the neurovascular profile was associated with a 45% higher risk of death, 34% longer LOS and 37% greater cost (all $p < 0.001$). CONCLUSIONS: Comorbidity profiles are helpful in identifying adults at higher risk of death, longer length of stay, and accumulating greater costs during hospitalizations for HF.

Lee, C. S., Gelow, J. M., Bidwell, J. T., Mudd, J. O., Green, J. K., Jurgens, C. Y., et al. (2013). Blunted responses to heart failure symptoms in adults with mild cognitive dysfunction. *The Journal of Cardiovascular Nursing, 28*(6), 534-540.

INTRODUCTION: Mild cognitive dysfunction is common among adults with heart failure (HF). We hypothesized that mild cognitive dysfunction would be associated with poor HF self-care behaviors, particularly patients' ability to respond to symptoms. METHODS: We analyzed data on 148 participants in an observational study of symptoms in adults with moderate-to-advanced HF. Mild cognitive dysfunction was measured with the Montreal Cognitive Assessment (MoCA; range, 0-30), using cutoff scores for the general population (26) and for adults with cardiovascular

disease (24). Heart failure self-care management (evaluation and response to HF symptoms) was measured with the Self-care of HF Index, and consulting behaviors (calling a provider when symptoms occur) were measured using the European HF Self-care Behavior Scale-9. Generalized linear modeling and hierarchical linear modeling were used to quantify the relationship between MoCA cutoff scores and indices of HF self-care. RESULTS: The mean age of the sample was 57 +/- 12 years, 61.5% were men, and 58.8% had class III/IV HF; the mean left ventricular ejection fraction was 28% +/- 12%. Using MoCA scores of 26 and 24, respectively, 33.1% and 14.2% of the sample had mild cognitive dysfunction. Controlling for common confounders, participants with MoCA scores lower than 26 reported self-care comparable with that of participants with MoCA scores of 26 or higher. Participants with MoCA scores lower than 24, however, reported 21.5% worse self-care management (P = 0.014) and 51% worse consulting behaviors (P < 0.001) compared with participants with MoCA scores of 24 or higher. CONCLUSIONS: A disease-specific cutoff for mild cognitive dysfunction reveals marked differences patients' ability to recognize and respond to HF symptoms when they occur. Adults with HF and mild cognitive dysfunction are a vulnerable patient group in great need of interventions that complement HF self-care.

Lee, C. S., Gelow, J. M., Denfeld, Q. E., Mudd, J. O., Burgess, D., Green, J. K., et al. (2014). Physical and psychological symptom profiling and event-free survival in adults with moderate to advanced heart failure. *Journal of Cardiovascular Nursing, 29*(4), 315-323.

: Heart failure (HF) is a heterogeneous symptomatic disorder. The goal of this study was to identify and link common profiles of physical and psychological symptoms to 1-year event-free survival in adults with moderate to advanced HF. Methods: Multiple valid, reliable, and domain-specific measures were used to assess physical and psychological symptoms. Latent class mixture modeling was used to identify distinct symptom profiles. Associations between observed symptom profiles and 1-year event-free survival were quantified using Cox proportional hazards modeling. Results: The mean age of the participants (n = 202) was 57 ± 13 years, 50% were men, and 60% had class III/IV HF. Three distinct profiles, mild (41.7%), moderate (30.2%), and severe (28.1%), that captured a gradient of both physical and psychological symptom burden were identified (P < .001 for all comparisons). Controlling for the Seattle HF Score, adults with

the moderate symptom profile were 82% more likely (hazard ratio, 1.82; 95% confidence interval, 1.07-3.11; P = .028) and adults with the severe symptom profile were more than twice as likely (hazard ratio, 2.06; 95% confidence interval, 1.21-3.52; P = .001) to have a clinical event within 1 year than patients with the mild symptom profile. Conclusions: Profiling patterns among physical and psychological symptoms identifies HF patient subgroups with significantly worse 1-year event-free survival independent of prognostication based on objective clinical HF data. 

Lee, D. S., Markwardt, S., Goeres, L., Lee, C. G., Eckstrom, E., Williams, C., et al. (2014). Statins and physical activity in older men: The osteoporotic fractures in men study. *JAMA Internal Medicine,* IMPORTANCE Muscle pain, fatigue, and weakness are common adverse effects of statin medications and may decrease physical activity in older men. OBJECTIVE To determine whether statin use is associated with physical activity, longitudinally and cross-sectionally. DESIGN, SETTING, AND PARTICIPANTS Men participating in the Osteoporotic Fractures in Men Study (N = 5994), a multicenter prospective cohort study of community-living men 65 years and older, enrolled between March 2000 and April 2002. Follow-up was conducted through 2009. EXPOSURES Statin use as determined by an inventory of medications (taken within the last 30 days). In cross-sectional analyses (n = 4137), statin use categories were users and nonusers. In longitudinal analyses (n = 3039), categories were prevalent users (baseline use and throughout the study), new users (initiated use during the study), and nonusers (never used). MAIN OUTCOMES AND MEASURES Self-reported physical activity at baseline and 2 follow-up visits using the Physical Activity Scale for the Elderly (PASE). At the third visit, an accelerometer measured metabolic equivalents (METs [kilocalories per kilogram per hour]) and minutes of moderate activity (METs >/=3.0), vigorous activity (METs >/=6.0), and sedentary behavior (METs </=1.5). RESULTS At baseline, 989 men (24%) were users and 3148 (76%) were nonusers. The adjusted difference in baseline PASE between users and nonusers was -5.8 points (95% CI, -10.9 to -0.7 points). A total of 3039 men met the inclusion criteria for longitudinal analysis: 727 (24%) prevalent users, 845 (28%) new users, and 1467 (48%) nonusers. PASE score declined by a mean (95% CI) of 2.5 (2.0 to 3.0) points per year for nonusers and 2.8 (2.1 to 3.5) points per year for prevalent users, a nonstatistical difference (0.3 [-0.5 to 1.0] points).

For new users, annual PASE score declined at a faster rate than nonusers (difference of 0.9 [95% CI, 0.1 to 1.7] points). A total of 3071 men had adequate accelerometry data, 1542 (50%) were statin users. Statin users expended less METs (0.03 [95% CI, 0.02-0.04] METs less) and engaged in less moderate physical activity (5.4 [95% CI, 1.9-8.8] fewer minutes per day), less vigorous activity (0.6 [95% CI, 0.1-1.1] fewer minutes per day), and more sedentary behavior (7.6 [95% CI, 2.6-12.4] greater minutes per day). CONCLUSIONS AND RELEVANCE Statin use was associated with modestly lower physical activity among community-living men, even after accounting for medical history and other potentially confounding factors. The clinical significance of these findings deserves further investigation.

Lee-Lin, F., Domenico, L. J., Ogden, L. A., Fromwiller, V., Magathan, N., Vail, S., et al. (2014). Academic-community partnership development lessons learned: Evidence-based interventions to increase screening mammography in rural communities. *Journal of Nursing Care Quality,*

Early detection of breast cancer leads to higher survival; yet, women who live in rural areas have lower screening rates and receive diagnosis at later stages. Effective screening approaches have been published in scientific journals but are not easily available to and understandable by community members. This article describes the development of an academic-community collaboration to implement evidence-based interventions to increase screening.

Liang, L., Guan, X., Shi, Z., Li, J., Wu, Y., & Tratnyek, P. G. (2014). Coupled effects of aging and weak magnetic fields on sequestration of selenite by zero-valent iron. *Environmental Science and Technology, 48*(11), 6326-6334.

The sequestration of Se(IV) by zero-valent iron (ZVI) is strongly influenced by the coupled effects of aging ZVI and the presence of a weak magnetic field (WMF). ZVI aged at pH 6.0 with MES as buffer between 6 and 60 h gave nearly constant rates of Se(IV) removal with WMF but with rate constants that are 10- to 100-fold greater than without. XANES analysis showed that applying WMF changes the mechanism of Se(IV) removal by ZVI aged for 6-60 h from adsorption followed by reduction to direct reduction. The strong correlation between Se(IV) removal and Fe2+ release suggests direct reduction of Se(IV) to Se(0) by Fe0, in agreement with the XANES analysis. The numerical simulation of ZVI magnetization revealed that the WMF influence on

Se(IV) sequestration is associated mainly with the ferromagnetism of ZVI and the paramagnetism of Fe2+. In the presence of the WMF, the Lorentz force gives rise to convection in the solution, which narrows the diffusion layer, and the field gradient force, which tends to move paramagnetic ions (esp. Fe2+) along the higher field gradient at the ZVI particle surface, thereby inducing nonuniform depassivation and eventually localized corrosion of the ZVI surface. 

Lin, Z., Zachariah, M. M., Marett, L., Hughen, R. W., Teichert, R. W., Concepcion, G. P., et al. (2014). Griseorhodins D-F, neuroactive intermediates and end products of post-PKS tailoring modification in griseorhodin biosynthesis. *Journal of Natural Products, 77*(5), 1224-1230.

The griseorhodins belong to a family of extensively modified aromatic polyketides that exhibit activities such as inhibition of HIV reverse transcriptase and human telomerase. The vast structural diversity of this group of polyketides is largely introduced by enzymatic oxidations, which can significantly influence the bioactivity profile. Four new compounds, griseorhodins D-F, were isolated from a griseorhodin producer, Streptomyces sp. CN48+, based upon their enhancement of calcium uptake in a mouse dorsal root ganglion primary cell culture assay. Two of these compounds, griseorhodins D1 and D2, were shown to be identical to the major, previously uncharacterized products of a grhM mutant in an earlier griseorhodin biosynthesis study. Their structures enabled the establishment of a more complete hypothesis for the biosynthesis of griseorhodins and related compounds. The other two compounds, griseorhodins E and F, represent new products of post-polyketide synthase tailoring in griseorhodin biosynthesis and showed significant binding activity in a human dopamine active transporter assay. 

Lindau, R. H., Su, Y. B., Kobayashi, R., & Smith, R. B. (2013). Immunoglobulin G4-related sclerosing disease of the paranasal sinus. *Head & Neck, 35*(10), E321-4.

BACKGROUND: Immunoglobulin G4 (IgG4)-related sclerosing disease is a systemic disease characterized by extensive IgG4-positive plasma cells and T-lymphocyte infiltration of various organs. We present a case of a 69-year-old man with maxillary sinus IgG4 sclerosing disease, with orbital invasion treated with rituximab and dexamethasone pulse therapy. Surgery was used

as well to debulk the disease and to obtain tissue for diagnosis. METHODS: A PubMed search using the key phrase "IgG4-related Sclerosing Disease" was performed. There were 304 different articles regarding the disease for a multitude of different organ sites. Of the 304 articles, there were 3 articles that reported this disease in the paranasal sinuses. CONCLUSIONS: IgG4-related sclerosing disease is a rare entity in the head and neck. There are documented reports of steroid therapy for this disease, but the patient presented here demonstrated clinical progression of disease with steroids alone. The use of combination therapy of surgery, dexamethasone, and rituximab provided clinical improvement and stable disease determined by radiographic means.

Margolis, K. L., O'Connor, P. J., Morgan, T. M., Buse, J. B., Cohen, R. M., Cushman, W. C., et al. (2014). Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: The accord randomized trial. *Diabetes Care, 37*(6), 1721-1728.

OBJECTIVE To compare effects of combinations of standard and intensive treatment of glycemia and either blood pressure (BP) or lipids in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. RESEARCH DESIGN AND METHODS ACCORD enrolled 10,251 type 2 diabetes patients aged 40-79 years at high risk for cardiovascular disease (CVD) events. Participants were randomly assigned to hemoglobin A1c goals of >6.0% (>42mmol/mol; intensive glycemia) or 7.0-7.9% (53- 63mmol/mol; standard glycemia) and then randomized a second time to either 1) systolic BP goals of >120 mmHg (intensive BP) or >140 mmHg (standard BP) or 2) simvastatin plus fenofibrate (intensive lipid) or simvastatin plus placebo (standard lipid). Proportional hazards models were used to assess combinations of treatment assignments on the composite primary (deaths due to CVD, nonfatal myocardial infarction [MI], and nonfatal stroke) and secondary outcomes. RESULTS In the BP trial, risk of the primary outcome was lower in the groups intensively treated for glycemia (hazard ratio [HR] 0.67; 95% CI 0.50-0.91), BP (HR 0.74; 95%CI 0.55-1.00), or both (HR 0.71; 95%CI 0.52-0.96) comparedwith combined standard BP and glycemia treatment. For secondary outcomes,MIwas significantly reduced by intensive glycemia treatment and stroke by intensive BP treatment; most other HRs were neutral or favored intensive treatment groups. In the lipid trial, the general pattern of results showed no evidence of benefit of intensive regimens (whether single or combined) compared with combined standard lipid and glycemia treatment. Themortality HRwas 1.33 (95%CI 1.02-1.74) in the

standard lipid/ intensive glycemia group compared with the standard lipid/standard glycemia group. CONCLUSIONS In the ACCORD BP trial, compared with combined standard treatment, intensive BP or intensive glycemia treatment alone improvedmajor CVD outcomes, without additional benefit from combining the two. In the ACCORD lipid trial, neither intensive lipid nor glycemia treatment produced an overall benefit, but intensive glycemia treatment increased mortality. 

Maric, M., Haugo, A. C., Dauer, W., Johnson, D., & Roller, R. J. (2014). Nuclear envelope breakdown induced by herpes simplex virus type 1 involves the activity of viral fusion proteins. *Virology, 460-461*(1), 128-137.

Herpesvirus infection reorganizes components of the nuclear lamina usually without loss of integrity of the nuclear membranes. We report that wild-type HSV infection can cause dissolution of the nuclear envelope in transformed mouse embryonic fibroblasts that do not express torsinA. Nuclear envelope breakdown is accompanied by an eight-fold inhibition of virus replication. Breakdown of the membrane is much more limited during infection with viruses that lack the gB and gH genes, suggesting that breakdown involves factors that promote fusion at the nuclear membrane. Nuclear envelope breakdown is also inhibited during infection with virus that does not express UL34, but is enhanced when the US3 gene is deleted, suggesting that envelope breakdown may be enhanced by nuclear lamina disruption. Nuclear envelope breakdown cannot compensate for deletion of the UL34 gene suggesting that mixing of nuclear and cytoplasmic contents is insufficient to bypass loss of the normal nuclear egress pathway. 

Marino, M., Li, Y., Pencina, M. J., D'Agostino RB, S., Berkman, L. F., & Buxton, O. M. (2014). Quantifying cardiometabolic risk using modifiable non-self-reported risk factors. *American Journal of Preventive Medicine,*

BACKGROUND: Sensitive general cardiometabolic risk assessment tools of modifiable risk factors would be helpful and practical in a range of primary prevention interventions or for preventive health maintenance. PURPOSE: To develop and validate a cumulative general cardiometabolic risk score that focuses on non-self-reported modifiable risk factors such as glycosylated hemoglobin (HbA1c) and BMI so as to be sensitive to small changes across a span of major

modifiable risk factors, which may not individually cross clinical cut-off points for risk categories. METHODS: We prospectively followed 2,359 cardiovascular disease (CVD)-free subjects from the Framingham offspring cohort over a 14-year follow-up. Baseline (fifth offspring examination cycle) included HbA1c and cholesterol measurements. Gender-specific Cox proportional hazards models were considered to evaluate the effects of non-self-reported modifiable risk factors (blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, BMI, and HbA1c) on general CVD risk. We constructed 10-year general cardiometabolic risk score functions and evaluated its predictive performance in 2012-2013. RESULTS: HbA1c was significantly related to general CVD risk. The proposed cardiometabolic general CVD risk model showed good predictive performance as determined by cross-validated discrimination (male C-index=0.703, 95% CI=0.668, 0.734; female C-index=0.762, 95% CI=0.726, 0.801) and calibration (lack-of-fit chi-square=9.05 [p=0.338] and 12.54 [p=0.128] for men and women, respectively). CONCLUSIONS: This study presents a risk factor algorithm that provides a convenient and informative way to quantify cardiometabolic risk on the basis of modifiable risk factors that can motivate an individual's commitment to prevention and intervention.

Martin, D. T., & Schreiber, M. A. (2014). Modern resuscitation of hemorrhagic shock: What is on the horizon? *European Journal of Trauma and Emergency Surgery,*

Purpose Mortality rates among the severely injured remain high. The successful treatment of hemorrhagic shock relies on expeditious control of bleeding through surgical ligation, packing, or endovascular techniques. An important secondary concern in hemorrhaging patients is how to respond to the lost blood volume. A single method that is able to adequately address all needs of the exsanguinating patient has not yet been agreed upon, despite a large growth of knowledge regarding the causative factors of traumatic shock. Methods A review of relevent literature was performed. Conclusions Many different trials are currently underway to discriminate ways to improve outcomes in the severely injured and bleeding patient. This paper will review: (1) recent advances in our understanding of the effects hemorrhagic shock has on the coagulation cascade and vascular endothelium, (2) recent research findings that have changed resuscitation, and (3) resuscitation strategies that are not widely used but under active investigation. 

Martindale, R. G., Enomoto, T. M., & McCarthy, M. (2013). *Nutritional and metabolic therapy* Elsevier Inc.

McCarthy-Jones, S., Thomas, N., Strauss, C., Dodgson, G., Jones, N., Woods, A., et al. (2014). Better than mermaids and stray dogs? subtyping auditory verbal hallucinations and its implications for research and practice. *Schizophrenia Bulletin, 40 Suppl 4*, S275-84.

The phenomenological diversity of auditory verbal hallucinations (AVH) is not currently accounted for by any model based around a single mechanism. This has led to the proposal that there may be distinct AVH subtypes, which each possess unique (as well as shared) underpinning mechanisms. This could have important implications both for research design and clinical interventions because different subtypes may be responsive to different types of treatment. This article explores how AVH subtypes may be identified at the levels of phenomenology, cognition, neurology, etiology, treatment response, diagnosis, and voice hearer's own interpretations. Five subtypes are proposed; hypervigilance, autobiographical memory (subdivided into dissociative and nondissociative), inner speech (subdivided into obsessional, own thought, and novel), epileptic and deafferentation. We suggest other facets of AVH, including negative content and form (eg, commands), may be best treated as dimensional constructs that vary across subtypes. After considering the limitations and challenges of AVH subtyping, we highlight future research directions, including the need for a subtype assessment tool.

McCarty, D., Braude, L., Lyman, D. R., Dougherty, R. H., Daniels, A. S., Ghose, S. S., et al. (2014). Substance abuse intensive outpatient programs: Assessing the evidence. *Psychiatric Services, 65*(6), 718-726.

Objective: Substance abuse intensive outpatient programs (IOPs) are direct services for people with substance use disorders or co-occurring mental and substance use disorders who do not require medical detoxification or 24-hour supervision. IOPs are alternatives to inpatient and residential treatment. They are designed to establish psychosocial supports and facilitate relapse management and coping strategies. This review assessed the evidence base for IOPs. Methods: Authors searched major databases: PubMed, PsycINFO, Applied Social Sciences Index and Abstracts, Sociological Abstracts, Social Services Abstracts, Published International Literature on

Traumatic Stress, ERIC, and CINAHL. They identified 12 individual studies and one review published between 1995 and 2012. They chose from three levels of research evidence (high, moderate, and low) based on benchmarks for the number of studies and quality of their methodology. They also described evidence of service effectiveness. Results: Based on the quality of trials, diversity of settings, and consistency of outcomes, the level of evidence for IOPs was rated high. Multiple randomized trials and naturalistic analyses that compared IOPs with inpatient or residential care found comparable outcomes. All studies reported reductions in alcohol and drug use. However, substantial variability in the operationalization of IOPs and outcome measures was apparent. Conclusions: IOPs are an important part of the continuum of care for substance use disorders. They are as effective as inpatient treatment for most individuals. Public and commercial health plans should consider IOP services as a covered health benefit. Standardization of the elements included in IOPs may improve their quality and effectiveness.

McGee, W. K., Bishop, C. V., Pohl, C. R., Chang, R. J., Marshall, J. C., Pau, F. K., et al. (2014). Effects of hyperandrogenemia and increased adiposity on reproductive and metabolic parameters in young adult female monkeys. *American Journal of Physiology - Endocrinology and Metabolism, 306*(11), E1292-E1304.

Many patients with hyperandrogenemia are overweight or obese, which exacerbates morbidities associated with polycystic ovary syndrome (PCOS). To examine the ability of testosterone (T) to generate PCOS-like symptoms, monkeys received T or cholesterol (control) implants (n = 6/group) beginning prepubertally. As previously reported, T-treated animals had increased neuroendocrine drive to the reproductive axis [increased luteinizing hormone (LH) pulse frequency] at 5 yr, without remarkable changes in ovarian or metabolic features. To examine the combined effects of T and obesity, at 5.5 yr (human equivalent age: 17 yr), monkeys were placed on a high-calorie, high-fat diet typical of Western cultures [Western style diet (WSD)], which increased body fat from <2% (pre-WSD) to 15-19% (14 mo WSD). By 6 mo on WSD, LH pulse frequency in the controls increased to that of T-treated animals, whereas LH pulse amplitude decreased in both groups and remained low. The numbers of antral follicles present during the early follicular phase increased in both groups on the WSD, but maximal follicular size

decreased by 50%. During the late follicular phase, T-treated females had greater numbers of small antral follicles than controls. T-treated monkeys also had lower progesterone during the luteal phase of the menstrual cycle. Although fasting insulin did not vary between groups, T-treated animals had decreased insulin sensitivity after 1 yr on WSD. Thus, while WSD consumption alone led to some features characteristic of PCOS, T + WSD caused a more severe phenotype with regard to insulin insensitivity, increased numbers of antral follicles at midcycle, and decreased circulating luteal phase progesterone levels. © 2014 the American Physiological Society.

Mease, P. J., Genovese, M. C., Greenwald, M. W., Ritchlin, C. T., Beaulieu, A. D., Deodhar, A., et al. (2014). Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *The New England Journal of Medicine, 370*(24), 2295-2306.

BACKGROUND: We assessed the efficacy and safety of brodalumab, a human monoclonal antibody against interleukin-17 receptor A (IL17RA), in a phase 2, randomized, double-blind, placebo-controlled study involving patients with psoriatic arthritis. METHODS: We randomly assigned patients with active psoriatic arthritis to receive brodalumab (140 or 280 mg subcutaneously) or placebo on day 1 and at weeks 1, 2, 4, 6, 8, and 10. At week 12, patients who had not discontinued their participation in the study were offered open-label brodalumab (280 mg) every 2 weeks. The primary end point was 20% improvement in American College of Rheumatology response criteria (ACR 20) at week 12. RESULTS: Of the 168 patients who underwent randomization (57 in the brodalumab 140-mg group, 56 in the brodalumab 280-mg group, and 55 in the placebo group), 159 completed the double-blind phase and 134 completed 40 weeks of the open-label extension. At week 12, the brodalumab 140-mg and 280-mg groups had higher rates of ACR 20 than the placebo group (37% [P=0.03] and 39% [P=0.02], respectively, vs. 18%); they also had higher rates of 50% improvement (ACR 50) (14% [P=0.05] and 14% [P=0.05] vs. 4%). Rates of 70% improvement were not significantly higher in the brodalumab groups. Similar degrees of improvement were noted among patients who had received previous biologic therapy and those who had not received such therapy. At week 24, ACR 20 response rates in the brodalumab 140-mg and 280-mg groups were 51% and 64%, respectively, as compared with 44% among patients who switched from placebo to open-label

brodalumab; responses were sustained through week 52. At week 12, serious adverse events had occurred in 3% of patients in the brodalumab groups and in 2% of those in the placebo group. CONCLUSIONS: Brodalumab significantly improved response rates among patients with psoriatic arthritis. Larger studies of longer duration are necessary to assess adverse events. (Funded by Amgen; ClinicalTrials.gov number, NCT01516957 .).

Merte, J. L., Kroll, C. M., Collins, A. S., & Melnick, A. L. (2014). An epidemiologic investigation of occupational transmission of mycobacterium tuberculosis infection to dental health care personnel : Infection prevention and control implications. *Journal of the American Dental Association, 145*(5), 464-471.

Background. The authors describe an investigation of a dental hygienist who developed active pulmonary tuberculosis (TB), worked for several months while infectious and likely transmitted Mycobacterium tuberculosis in a dental setting in Washington state. Methods. Clark County Public Health (CCPH) conducted an epidemiologic investigation of 20 potentially exposed close contacts and 734 direct-care dental patients in 2010. Results. Of 20 close contacts, one family member and two coworkers, all of whom were from countries in which TB is endemic, had latent TB infection (LTBI). One U.S.-born coworker experienced a tuberculin skin test (TST) conversion from 0 to 8 millimeters. Of the 305 of 731 (41.7 percent) potentially exposed patients who received a single TST, 23 (7.5 percent) had a positive TST result of at least 5 mm. Among the subset of 157 patients tested by CCPH staff, 16 (10.2 percent) had a positive TST result. The dental office did not have infection prevention and control policies related to TB identification, prevention or education. Conclusions. The coworker's TST conversion indicated a recent infection, likely owed to occupational transmission. The proportion of dental patients with positive TST results was greater than the 1999-2000 National Health and Nutrition Examination Survey prevalence estimate in the general population, and it may reflect transmission from the hygienist with active TB or a prevalence of LTBI in the community. Practical Implications. All dental practices should implement administrative procedures for TB identification and control as described in this article, even if none of their patients are known to have TB. 

Messaoudi, I., Pasala, S., & Grant, K. (2014). Could moderate alcohol intake be recommended to improve vaccine responses? *Expert Review of Vaccines, 13*(7), 817-819.

The impact of alcohol consumption on human health is complex and modulated by several factors such as patterns and amount of drinking, genetics, the organ system studied, as well as the sex and age of the user. There is strong evidence that chronic ethanol abuse is associated with increased morbidity and mortality, immunosuppression and increased susceptibility to both bacterial and viral infections. In contrast, moderate alcohol consumption exerts positive effects including decreased mortality, and improved cardiovascular disease and insulin sensitivity. Interestingly, accumulating evidence also supports an immune-boosting effect of moderate alcohol. In this editorial, we summarize the findings that support a positive effect of moderate alcohol on host immunity. We also discuss the limitations of the previous data and emphasize the importance of additional studies to uncover mechanisms for these immune-stimulating effects in order to extend these benefits to vulnerable segments of the population who cannot consume alcohol. © 2014 Informa UK, Ltd.

Miller, J. A., Teel, D. J., Peterson, W. T., & Baptista, A. M. (2014). Assessing the relative importance of local and regional processes on the survival of a threatened salmon population. *PloS One, 9*(6), e99814.

Research on regulatory mechanisms in biological populations often focuses on environmental covariates. An integrated approach that combines environmental indices with organismal-level information can provide additional insight on regulatory mechanisms. Survival of spring/summer Snake River Chinook salmon (Oncorhynchus tshawytscha) is consistently low whereas some adjacent populations with similar life histories experience greater survival. It is not known if populations with differential survival respond similarly during early marine residence, a critical period in the life history. Ocean collections, genetic stock identification, and otolith analyses were combined to evaluate the growth-mortality and match-mismatch hypotheses during early marine residence of spring/summer Snake River Chinook salmon. Interannual variation in juvenile attributes, including size at marine entry and marine growth rate, was compared with estimates of survival and physical and biological metrics. Multiple linear regression and multi-model inference were used to evaluate the relative importance of biological and physical metrics in

explaining interannual variation in survival. There was relatively weak support for the match-mismatch hypothesis and stronger evidence for the growth-mortality hypothesis. Marine growth and size at capture were strongly, positively related to survival, a finding similar to spring Chinook salmon from the Mid-Upper Columbia River. In hindcast models, basin-scale indices (Pacific Decadal Oscillation (PDO) and the North Pacific Gyre Oscillation (NPGO)) and biological indices (juvenile salmon catch-per-unit-effort (CPUE) and a copepod community index (CCI)) accounted for substantial and similar portions of variation in survival for juvenile emigration years 1998-2008 (R2>0.70). However, in forecast models for emigration years 2009-2011, there was an increasing discrepancy between predictions based on the PDO (50-448% of observed value) compared with those based on the NPGO (68-212%) or biological indices (CPUE and CCI: 83-172%). Overall, the PDO index was remarkably informative in earlier years but other basin-scale and biological indices provided more accurate indications of survival in recent years.

Minko, I. G., Earley, L. F., Larlee, K. E., Lin, Y. C., & Lloyd, R. S. (2014). Pyrosequencing: Applicability for studying DNA damage-induced mutagenesis. *Environmental and Molecular Mutagenesis,* Site-specifically modified DNAs are routinely used in the study of DNA damage-induced mutagenesis. These analyses involve the creation of DNA vectors containing a lesion at a pre-determined position, DNA replication, and detection of mutations at the target site. The final step has previously required the isolation of individual DNA clones, hybridization with radioactively labeled probes, and verification of mutations by Sanger sequencing. In the search for an alternative procedure that would allow direct quantification of sequence variants in a mixed population of DNA molecules, we evaluated the applicability of pyrosequencing to site-specific mutagenesis assays. The progeny DNAs were analyzed that originated from replication of N6 -(deoxy-D-erythro-pentofuranosyl)-2,6-diamino-3,4-dihydro-4-oxo-5-N-methylformami dopyrimidine (MeFapy-dG)-containing vectors in primate cells, with the lesion being positioned in the 5'-GCNGG-3' sequence context. Pyrosequencing detected approximately 8% G to T transversions and approximately 3.5% G to A transitions, a result that was in excellent agreement with frequencies previously measured by the standard procedure (Earley LF et al. [2013]: Chem Res Toxicol 26:1108-1114). However, approximately 3.5% G to C transversions and approximately 2.0% deletions could not be detected by pyrosequencing. Consistent with

these observations, the sensitivity of pyrosequencing for measuring the single deoxynucleotide variants differed depending on the deoxynucleotide identity, and in the given sequence contexts, was determined to be approximately 1-2% for A and T and approximately 5% for C. Pyrosequencing of other DNA isolates that were obtained following replication of MeFapy-dG-containing vectors in primate cells or Escherichia coli, identified several additional limitations. Collectively, our data demonstrated that pyrosequencing can be used for studying DNA damage-induced mutagenesis as an effective complementary experimental approach to current protocols. Environ. Mol. Mutagen., 2014. (c) 2014 Wiley Periodicals, Inc.

Mohan, V., Abbott, P., Acteson, S., Berner, E. S., Devlin, C., Hammond, W. E., et al. (2014). Design and evaluation of the ONC health information technology curriculum. *Journal of the American Medical Informatics Association : JAMIA, 21*(3), 509-516.

OBJECTIVE: As part of the Heath Information Technology for Economic and Clinical Health (HITECH) Act, the Office of the National Coordinator for Health Information Technology (ONC) implemented its Workforce Development Program, which included initiatives to train health information technology (HIT) professionals in 12 workforce roles, half of them in community colleges. To achieve this, the ONC tasked five universities with established informatics programs with creating curricular materials that could be used by community colleges. The five universities created 20 components that were made available for downloading from the National Training and Dissemination Center (NTDC) website. This paper describes an evaluation of the curricular materials by its intended audience of educators. METHODS: We measured the quantity of downloads from the NTDC site and administered a survey about the curricular materials to its registered users to determine use patterns and user characteristics. The survey was evaluated using mixed methods. Registered users downloaded nearly half a million units or components from the NTDC website. We surveyed these 9835 registered users. RESULTS: 1269 individuals completed all or part of the survey, of whom 339 identified themselves as educators (26.7% of all respondents). This paper addresses the survey responses of educators. DISCUSSION: Successful aspects of the curriculum included its breadth, convenience, hands-on and course planning capabilities. Several areas were identified for potential improvement. CONCLUSIONS:

The ONC HIT curriculum met its goals for community college programs and will likely continue to be a valuable resource for the larger informatics community in the future.

Moldt, B., & Hessell, A. J. (2013). *FcγRs across species* Elsevier Inc.

Mood, L. C., Neunzert, C., & Tadesse, R. (2014). Centering the concept of transitional care: A teaching-learning innovation. *Journal of Nursing Education, 53*(5), 287-290.

Coordination of care, including the provision of safe and effective transitions, is a core professional standard for nurses. However, as currently designed, prelicensure nursing education prepares nurses to function in discrete settings rather than across settings. A teaching-learning innovation focusing on transitional care was implemented as an educational pilot project with 20 senior-level baccalaureate students in their leadership course. Students in the educational pilot immersed in the subject of transitional care via concept-based learning activities and performance improvement projects. During the course, students were assigned to designated clinical sites representative of a continuum of care. An integrated clinical postconference offered students the opportunity to discover the role of the nurse in transitional care from a systems perspective and facilitated a deeper understanding of the subject that extended beyond the walls of students' discrete clinical sites. © SLACK Incorporated.

Morasco, B. J., O'Hearn, D., Turk, D. C., & Dobscha, S. K. (2014). Associations between prescription opioid use and sleep impairment among veterans with chronic pain. *Pain Medicine (Malden, Mass.),*

OBJECTIVE: Chronic pain is associated with impairments in sleep; however, the relationship between prescription opioid status and sleep is unclear. The primary aim of this study was to examine differences in self-reported sleep quality between groups of patients who varied based on chronic pain and prescription opioid status. DESIGN: This is a cross-sectional study with retrospective review of patient medical records. SETTING: The study was performed in a single VA medical center located in the Pacific Northwest. SUBJECTS: Participants with chronic pain and a current prescription for opioid medications (N = 72), chronic pain and no opioid prescription (N = 104), or who did not report current chronic pain or opioid prescription (N = 91) were included. METHODS: All participants completed self-report questionnaires assessing demographic

characteristics, sleep parameters, pain-related variables, and psychiatric symptoms. Data on prescription opioid use were extracted from patients' medical records. RESULTS: In unadjusted analyses, patients with chronic pain who were prescribed opioids were more likely to have sleep apnea diagnoses in their medical record and reported more impairment on sleep global score and across four sleep parameter subscales (subjective sleep quality, sleep latency, sleep disturbance, and use of sleeping medications). In linear regression analyses controlling for demographic and clinical covariates, prescription opioid status was associated with sleep latency, and opioid dose was significantly associated with sleep latency and sleep global score. CONCLUSIONS: Prescription opioid status and dose were associated with impairment in self-reported sleep. For patients with chronic pain, consideration should be given to use of nonpharmacological interventions to improve sleep.

Morton, J. M., & Wolfe, B. (2013). Letter to the editor. *Surgery for Obesity and Related Diseases : Official Journal of the American Society for Bariatric Surgery, 9*(5), 831-832.

Muramoto, O. (2014). Retrospective diagnosis of a famous historical figure: Ontological, epistemic, and ethical considerations. *Philosophy, Ethics, and Humanities in Medicine : PEHM, 9*(1), 10-5341-9-10.

The aim of this essay is to elaborate philosophical and ethical underpinnings of posthumous diagnosis of famous historical figures based on literary and artistic products, or commonly called retrospective diagnosis. It discusses ontological and epistemic challenges raised in the humanities and social sciences, and attempts to systematically reply to their criticisms from the viewpoint of clinical medicine, philosophy of medicine, particularly the ontology of disease and the epistemology of diagnosis, and medical ethics. The ontological challenge focuses on the doubt about the persistence of a disease over historical time, whereas the epistemic challenge disputes the inaccessibility of scientific verification of a diagnosis in the past. I argue that the critics are in error in conflating the taxonomy of disease (nosology) and the act of diagnosing a patient. Medical diagnosis is fundamentally a hypothesis-construction and an explanatory device that can be generated under various degrees of uncertainty and limited amount of information. It is not an apodictic judgment (true or false) as the critics presuppose, but a probabilistic (Bayesian)

judgment with varying degrees of plausibility under uncertainty. In order to avoid this confusion, I propose that retrospective diagnosis of a historical figure be syndromic without identifying underlying disease, unless there is justifiable reason for such specification. Moreover it should be evaluated not only from the viewpoint of medical science but also in a larger context of the scholarship of the humanities and social sciences by its overall plausibility and consistency. On the other hand, I will endorse their concerns regarding the ethics and professionalism of retrospective diagnosis, and call for the need for situating such a diagnosis in an interdisciplinary scope and the context of the scholarship of the historical figure. I will then enumerate several important caveats for interdisciplinary retrospective diagnosis using an example of the retrospective diagnosis of Socrates for his life-long intermittent neurologic symptoms. Finally, I will situate the present argument in a larger context of the major debate among the historians of medicine and paleopathologists, and discuss the similarities and differences.

Murphy, E. V. (2014). Clinical decision support: Effectiveness in improving quality processes and clinical outcomes and factors that may influence success. *The Yale Journal of Biology and Medicine, 87*(2), 187-197.

The use of electronic health records has skyrocketed following the 2009 HITECH Act, which provides financial incentives to health care providers for the "meaningful use" of electronic medical record systems. An important component of the "Meaningful Use" legislation is the integration of Clinical Decision Support Systems (CDSS) into the computerized record, providing up-to-date medical knowledge and evidence-based guidance to the physician at the point of care. As reimbursement is increasingly tied to process and clinical outcomes, CDSS will be integral to future medical practice. Studies of CDSS indicate improvement in preventive services, appropriate care, and clinical and cost outcomes with strong evidence for CDSS effectiveness in process measures. Increasing provider adherence to CDSS recommendations is essential in improving CDSS effectiveness, and factors that influence adherence are currently under study.

Nakajima, T., Hirata, M., Shearer, T. R., & Azuma, M. (2014). Mechanism for laser-induced neovascularization in rat choroid: Accumulation of integrin alpha chain-positive cells and their ligands. *Molecular Vision, 20*, 864-871.

PURPOSE: Inhibitors binding to integrins alpha5 and alphav are antiangiogenic in models of choroidal neovascularization (CNV). However, a comprehensive understanding of the accumulation of integrin alpha isoform-positive cells, their ligands, and associations is limited. The purpose of the present study was to examine the localization of integrin alpha chain-positive cells and their extracellular matrix (ECM) ligands in the RPE/choroid after laser injury. METHODS: CNV, observed with fluorescein isothiocyanate (FITC)-labeled isolectin, was produced in Brown Norway rats with a 532 nm green laser. Localization of alpha5 and alphav integrins and their ligands was performed with immunohistochemistry in consecutive cryosections. To test the binding specificity between the integrin alpha chains and ECM ligands, an in vitro cell adhesion assay was performed using retinal endothelial cells and specific antibodies. RESULTS: Angiogenesis was observed on day 7 after laser injury in choroidal flat mounts and cryosections. The number of integrin alpha5- and alphav-positive cells markedly increased at day 3 and then gradually decreased, but was still elevated on day 14. One day after laser treatment, alpha integrin ligands fibronectin (FN) and vitronectin (VN) were markedly increased, and localized closely to integrins in the laser-injured regions. FN decreased on day 7, but was still retained until 14 days. In contrast, VN disappeared. Cell adhesion assays showed specific association of integrin alpha5 to FN, and integrin alphav to VN. CONCLUSIONS: Laser-induced choroidal injury increased FN and VN, followed by accumulation of integrin alpha5- and alphav-positive cells. The interaction between integrin alpha chain-positive cells and their specific ligands FN and VN may be important steps leading to CNV.

Nanji, K. C., Rothschild, J. M., Boehne, J. J., Keohane, C. A., Ash, J. S., & Poon, E. G. (2014). Unrealized potential and residual consequences of electronic prescribing on pharmacy workflow in the outpatient pharmacy. *Journal of the American Medical Informatics Association, 21*(3), 481-486.

Introduction: Electronic prescribing systems have often been promoted as a tool for reducing medication errors and adverse drug events. Recent evidence has revealed that adoption of electronic prescribing systems can lead to unintended consequences such as the introduction of new errors. The purpose of this study is to identify and characterize the unrealized potential and residual consequences of electronic prescribing on pharmacy workflow in an outpatient pharmacy.

Methods: A multidisciplinary team conducted direct observations of workflow in an independent pharmacy and semi-structured interviews with pharmacy staff members about their perceptions of the unrealized potential and residual consequences of electronic prescribing systems. We used qualitative methods to iteratively analyze text data using a grounded theory approach, and derive a list of major themes and subthemes related to the unrealized potential and residual consequences of electronic prescribing. Results: We identified the following five themes: Communication, workflow disruption, cost, technology, and opportunity for new errors. These contained 26 unique subthemes representing different facets of our observations and the pharmacy staff's perceptions of the unrealized potential and residual consequences of electronic prescribing. Discussion: We offer targeted solutions to improve electronic prescribing systems by addressing the unrealized potential and residual consequences that we identified. These recommendations may be applied not only to improve staff perceptions of electronic prescribing systems but also to improve the design and/or selection of these systems in order to optimize communication and workflow within pharmacies while minimizing both cost and the potential for the introduction of new errors.

Napoli, N., Strotmeyer, E. S., Ensrud, K. E., Sellmeyer, D. E., Bauer, D. C., Hoffman, A. R., et al. (2014). Fracture risk in diabetic elderly men: The MrOS study. *Diabetologia,*

Aims/hypothesis Diabetes mellitus is associated with increased fracture risk in women but few studies are available in men. To evaluate the relationship between diabetes and prospective non-vertebral fractures in elderly men, we used data from the Osteoporotic Fractures in Men (MrOS) study. Methods The MrOS enrolled 5,994 men (aged ≥65 years). Diabetes (ascertained by self-report, the use of medication for diabetes or an elevated fasting glucose level) was reported in 881 individuals, 80 of whom were using insulin. Hip and spine bone mineral density (BMD) was measured using dual x-ray absorptiometry (DXA). After recruitment, the men were followed for incident non-vertebral fractures using a triannual (3 yearly) questionnaire for an average of 9.1 (SD 2.7) years. The Cox proportional hazards model was used to assess the incident risk of fractures. Results In models adjusted for age, race, clinic site and total hip BMD, the risk of non-vertebral fracture was higher in men with diabetes compared with normoglycaemic men (HR 1.30, 95% CI 1.09, 1.54) and was elevated in men using insulin (HR 2.46, 95% CI 1.69, 3.59).

Men with impaired fasting glucose did not have a higher risk of fracture compared with normoglycaemic men (HR 1.04, 95% CI 0.89, 1.21). After multivariable adjustment, the risk of non-vertebral fracture remained higher only among men with diabetes who were using insulin (HR 1.74, 95% CI 1.13, 2.69). Conclusions/interpretation Men with diabetes who are using insulin have an increased risk of non-vertebral fracture for a given age and BMD. © 2014 Springer-Verlag Berlin Heidelberg.

Naugler, W. E., Alsina, A. E., Frenette, C. T., Rossaro, L., & Sellers, M. T. (2014). Building the multidisciplinary team for management of patients with hepatocellular carcinoma. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association,*

Optimal care of the patient with hepatocellular carcinoma (HCC) necessitates the involvement of multiple providers. Because the patient with HCC often carries two conditions with competing mortality risks (cancer and underlying cirrhosis), no one provider is equipped to adequately deal with all of these patients' needs. Multidisciplinary teams (MDT) have evolved to facilitate care coordination, reassessments of clinical course, and nimble changes in treatment plans required for this complex group of patients. Providers or sites that elect to manage patients with HCC are thus increasingly aware of the need to build their own MDT or communicate with an established one. The availability of new communication technologies, such as teleconferencing or teleconsultation, offers the possibility of MDT expansion into underserved or rural areas, as well as areas such as correctional facilities. Although the availability of resources for HCC patient care varies from site to site, construction of an MDT is possible in a wide spectrum of clinical practices, and this article suggests a blueprint for assembly of such collaboration. Research strategies are needed to explain how MDTs improve clinical outcomes so that MDTs themselves can be improved.

Nelson, P. T., Estus, S., Abner, E. L., Parikh, I., Malik, M., Neltner, J. H., et al. (2014). ABCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology. *Acta Neuropathologica, 127*(6), 825-843.

Hippocampal sclerosis of aging (HS-Aging) is a high-morbidity brain disease in the elderly but risk

factors are largely unknown. We report the first genome-wide association study (GWAS) with HS-Aging pathology as an endophenotype. In collaboration with the Alzheimer's Disease Genetics Consortium, data were analyzed from large autopsy cohorts: (#1) National Alzheimer's Coordinating Center (NACC); (#2) Rush University Religious Orders Study and Memory and Aging Project; (#3) Group Health Research Institute Adult Changes in Thought study; (#4) University of California at Irvine 90+ Study; and (#5) University of Kentucky Alzheimer's Disease Center. Altogether, 363 HS-Aging cases and 2,303 controls, all pathologically confirmed, provided statistical power to test for risk alleles with large effect size. A two-tier study design included GWAS from cohorts #1-3 (Stage I) to identify promising SNP candidates, followed by focused evaluation of particular SNPs in cohorts #4-5 (Stage II). Polymorphism in the ATP-binding cassette, sub-family C member 9 (ABCC9) gene, also known as sulfonylurea receptor 2, was associated with HS-Aging pathology. In the meta-analyzed Stage I GWAS, ABCC9 polymorphisms yielded the lowest p values, and factoring in the Stage II results, the meta-analyzed risk SNP (rs704178:G) attained genome-wide statistical significance ($p = 1.4 \times 10\text{-}9$), with odds ratio (OR) of 2.13 (recessive mode of inheritance). For SNPs previously linked to hippocampal sclerosis, meta-analyses of Stage I results show OR = 1.16 for rs5848 (GRN) and OR = 1.22 rs1990622 (TMEM106B), with the risk alleles as previously described. Sulfonylureas, a widely prescribed drug class used to treat diabetes, also modify human ABCC9 protein function. A subsample of patients from the NACC database (n = 624) were identified who were older than age 85 at death with known drug history. Controlling for important confounders such as diabetes itself, exposure to a sulfonylurea drug was associated with risk for HS-Aging pathology ($p = 0.03$). Thus, we describe a novel and targetable dementia risk factor. 

Nickerson, A., Huang, T., Lin, L. J., & Nan, X. (2014). Photoactivated localization microscopy with bimolecular fluorescence complementation (BiFC-PALM) for nanoscale imaging of protein-protein interactions in cells. *PloS One, 9*(6), e100589.

Bimolecular fluorescence complementation (BiFC) has been widely used to visualize protein-protein interactions (PPIs) in cells. Until now, however, the resolution of BiFC has been limited by the diffraction of light to approximately 250 nm, much larger than the nanometer scale at which PPIs occur or are regulated. Cellular imaging at the nanometer scale has recently been realized

with single molecule superresolution imaging techniques such as photoactivated localization microscopy (PALM). Here we have combined BiFC with PALM to visualize PPIs inside cells with nanometer spatial resolution and single molecule sensitivity. We demonstrated that PAmCherry1, a photoactivatable fluorescent protein commonly used for PALM, can be used as a BiFC probe when split between residues 159 and 160 into two fragments. PAmCherry1 BiFC exhibits high specificity and high efficiency even at 37 degrees C in detecting PPIs with virtually no background from spontaneous reconstitution. Moreover, the reconstituted protein maintains the fast photoconversion, high contrast ratio, and single molecule brightness of the parent PAmCherry1, which enables selective PALM localization of PPIs with approximately 18 nm spatial precision. With BiFC-PALM, we studied the interactions between the small GTPase Ras and its downstream effector Raf, and clearly observed nanoscale clustering and diffusion of individual KRas G12D/CRaf RBD (Ras-binding domain) complexes on the cell membrane. These observations provided novel insights into the regulation of Ras/Raf interaction at the molecular scale, which would be difficult with other techniques such as conventional BiFC, fluorescence co-localization or FRET.

Nilsagard, Y., Gunn, H., Freeman, J., Hoang, P., Lord, S., Mazumder, R., et al. (2014). Falls in people with MS-an individual data meta-analysis from studies from australia, sweden, united kingdom and the united states. *Multiple Sclerosis (Houndmills, Basingstoke, England),*

BACKGROUND: Falls are common in people with multiple sclerosis (PwMS). Previous studies have generally included small samples and had varied methods. OBJECTIVES: The objectives of this paper are to compile fall rates across a broad range of ages and disease severity and to definitively assess the extent to which MS-associated and demographic factors influence fall rates. METHODS: Individual data from studies in four countries that prospectively measured falls for three months were analyzed. We determined fall rates, prevalence of fallers (>/=1 falls) and frequent fallers (>/=2 falls), location and timing of falls, and fall-related demographic factors. RESULTS: A total of 537 participants reported 1721 falls: 56% were fallers and 37% frequent fallers. Most falls occurred indoors (65%) between 6 a.m. and 6 p.m. (75%). Primary progressive MS was associated with significantly increased odds of being a faller (odds ratio (OR) 2.02; CI 1.08-3.78). Fall risk peaked at EDSS levels of 4.0 and 6.0 with significant ORs between 5.30

(2.23-12.64) and 5.10 (2.08-12.47). The fall rate was lower in women than men (relative risk (RR) 0.80; CI 0.67-0.94) and decreased with increasing age (RR 0.97 for each year, CI 0.95-0.98). CONCLUSION: PwMS are at high risk of falls and there are important associations between falls and MS-associated disability, gender and age.

Niu, B., Lee, V. R., Cheng, Y. W., Frias, A. E., Nicholson, J. M., & Caughey, A. B. (2014). What is the optimal gestational age for women with gestational diabetes type A1 to deliver? *American Journal of Obstetrics and Gynecology,*

OBJECTIVE: Gestational diabetes type A1 (A1GDM), also known as diet-controlled gestational diabetes, is associated with an increase in adverse perinatal outcomes such as macrosomia and Erb's palsy. However, it remains unclear when to deliver these women because optimal timing of delivery requires balancing neonatal morbidities from early term delivery against the risk of IUFD. We sought to determine the optimal gestational age (GA) for women with A1GDM to deliver. STUDY DESIGN: A decision-analytic model was built to compare the outcomes of delivery at 37 through 41 weeks in a theoretical cohort of 100,000 women with A1GDM. Strategies involving expectant management until a later GA accounted for probabilities of spontaneous delivery, indicated delivery, and IUFD during each week. GA associated risks of neonatal complications included cerebral palsy, infant death, and Erb's palsy. Probabilities were derived from the literature, and total quality-adjusted life years (QALYs) were calculated. Sensitivity analyses were used to investigate the robustness of the baseline assumptions. RESULTS: Our model showed that induction at 38 weeks maximized QALYs. Within our cohort, delivery at 38 weeks would prevent 48 stillbirths but lead to 12 more infant deaths compared to 39 weeks. Sensitivity analysis revealed that 38 weeks remains the optimal timing of delivery until IUFD rates fall below 0.3-fold of our baseline assumption at which expectant management until 39 weeks is optimal. CONCLUSION: By weighing the risks of IUFD against infant deaths and neonatal morbidities from early term delivery, the ideal GA for women with A1GDM to deliver is 38 weeks.

Noronha, A., Cui, C., Harris, R. A., & Crabbe, J. C. (2014). *Neurobiology of alcohol dependence* Elsevier Inc.

Recent scientific advances have provided substantial information on the brain circuits and

pathways relevant to various aspects of dependence. Neurobiology of Alcohol Dependence highlights the most recent data at the molecular, cellular, neurocircuitry, and behavioral levels, fostering an understanding how neuroplasticity and neuroadaptation occur, and how different neural pathways and neurocircuits contribute to dependence. Highlights recent advances in understanding alcohol addiction from molecular, cellular, neurocircuitry, and behavioral levels Integrates several emerging areas of research and discusses the application of novel research techniques to the understanding of alcohol dependence. 

Norton, W. E., Funkhouser, E., Makhija, S. K., Gordan, V. V., Bader, J. D., Brad Rindal, D., et al. (2014). Concordance between clinical practice and published evidence findings from the national dental practice-based research network. *Journal of the American Dental Association, 145*(1), 22-31.

Background. Documenting the gap between what is occurring in clinical practice and what published research findings suggest should be happening is an important step toward improving care. The authors conducted a study to quantify the concordance between clinical practice and published evidence across preventive, diagnostic and treatment procedures among a sample of dentists in The National Dental Practice-Based Research Network (the network). Methods. Network dentists completed one questionnaire about their demographic characteristics and another about how they treat patients across 12 scenarios/clinical practice behaviors. The authors coded responses to each scenario/clinical practice behavior as consistent (1) or inconsistent (0) with published evidence, summed the coded responses and divided the sum by the number of total responses to create an overall concordance score. The overall concordance score was calculated as the mean percentage of responses that were consistent with published evidence. Results. The authors limited analyses to participants in the United States (N = 591). The study results show a mean concordance at the practitioner level of 62 percent (SD = 18 percent); procedure-specific concordance ranged from 8 to 100 percent. Affiliation with a large group practice, being a female practitioner and having received a dental degree before 1990 were independently associated with high concordance (≥75 percent). Conclusion. Dentists reported a medium-range concordance between practice and published evidence. Practical Implications.

Efforts to bring research findings into routine practice are needed. 

Oh, C. C., Nguy, M. Q., C Schwenke, D., Migrino, R. Q., Thornburg, K., & Reaven, P. (2014). P38alpha mitogen-activated kinase mediates cardiomyocyte apoptosis induced by palmitate. *Biochemical and Biophysical Research Communications,*

RATIONALE: The mechanisms underlying lipotoxic/diabetic cardiomyopathy remain poorly understood. Saturated fatty acid (SFA) levels, elevated in obesity and type 2 diabetes, induce apoptosis in many cell types including cardiomyocytes. Signaling pathways, including the p38alpha mitogen-activated kinase (MAPK)-dependent pathway, have been implicated in apoptosis due to a diverse range of insults. OBJECTIVE: We tested the hypothesis that SFA-induced cardiomyocyte apoptosis is dependent on p38alpha activation. METHODS AND RESULTS: Human adult ventricular cardiomyocytes (AC16 cells) were exposed to high physiological levels of palmitate (PA), a SFA. The apoptotic response was measured using annexin-V by flow cytometry, and the p38alpha-dependent pathway was evaluated using a p38 inhibitor PD169316, and by p38alpha small interfering RNA (siRNA) knockdown. PA exposure for 16h dose-dependently increased apoptosis in AC16 cardiomyocytes (control: 2.6+/-0.6%, 150muM PA: 3.5+/-0.9%, 300muM PA: 11.5+/-1.6%, n=4, p<0.01). PA did not change total p38alpha protein levels, but increased p38alpha phosphorylation dose-dependently (n=5, p<0.01). PD169316 tended to reduce PA-induced apoptosis (n=4, p=0.05). Specific p38alpha siRNA markedly reduced the expression of p38alpha but not p38beta (n=3, p<0.0001), and dose-dependently attenuated PA-induced apoptosis (control siRNA: 7.7+/-1.0%, 300muM PA: 34.4+/-5.0%, 300muM PA+30pmol siRNA: 23.7+/-4.4%, 300muM PA+60pmol siRNA: 19.7+/-2.6%, 300muM PA+120pmol siRNA: 17.3+/-2.8%, n=4, p<0.0001). CONCLUSIONS: These results demonstrate that PA induces p38alpha activation, and reducing p38alpha expression attenuates PA-induced cardiomyocyte apoptosis. Our results support a potential mechanism by which high plasma SFA levels through p38alpha activation may lead to the development of lipotoxic/diabetic cardiomyopathy.

Orlandi, R. R., Smith, T. L., Marple, B. F., Harvey, R. J., Hwang, P. H., Kern, R. C., et al. (2014). Update on evidence-based reviews with recommendations in adult chronic rhinosinusitis.

*International Forum of Allergy and Rhinology,*

Chronic rhinosinusitis (CRS) has a significant impact not only on individuals who are afflicted but also on society as a whole. An increasing emphasis is being placed on incorporating the best available evidence into the care of patients, in association with an individual clinician's expertise and the patient's values. Recent evidence-based reviews with recommendations (EBRRs) have distilled our knowledge of CRS treatment options and have also pointed out continued gaps in this knowledge. This review synthesizes the findings of 8 EBRRs regarding CRS published in the International Forum of Allergy and Rhinology between 2011 and 2014. The recommendations in this review are based on the best available evidence and are meant to be incorporated into each patient's individual care, along with the practitioner's expertise and the individual patient's values and expectations. It is hoped that the EBRRs, and the process that spawned them, can provide the foundation for future guidelines in the diagnosis and management of CRS. © 2014 ARS-AAOA, LLC.

O'Rourke, R. W. (2013). Inflammation, obesity, and the promise of immunotherapy for metabolic disease. *Surgery for Obesity and Related Diseases : Official Journal of the American Society for Bariatric Surgery, 9*(5), 609-616.

Orwoll, E. S., & Martin, E. (2013). *Pharmacologic treatment of osteogenesis imperfecta: New agents and their potential implications for osteogenesis imperfecta* Elsevier Inc.

Current pharmacologic treatment of osteogenesis imperfecta (OI) consists of agents studied in and developed for use in osteoporosis. New agents under study for use in osteoporosis may also benefit patients with OI. In this chapter we review recommendations for current dietary supplements and the potential of several new anabolic and anti-resorptive agents for use in OI, including recombinant parathyroid hormone, sclerostin antibodies, strontium ranelate, RANK-ligand inhibitors, and cathepsin K inhibitors. While many of these agents may prove beneficial to patients with OI, optimal therapies for the future will target the specific collagen mutations underlying the disorder. © 2014 Elsevier Inc. All rights reserved.

Palmer, V. S., Mazumder, R., & Spencer, P. S. (2014). Interprofessional global health education at oregon health & science university: The interprofessional community health and education

exchange (iCHEE) experience. *Academic Medicine : Journal of the Association of American Medical Colleges,*

PROBLEM: The rapidly diversifying population of North America has disparate health needs that are addressed by creative, community-based training of health professions students. APPROACH: The authors report five years (2008-2012) of experience implementing a novel interprofessional Community Health and Education Exchange (iCHEE) elective course for dental, medical, nursing, nutrition, pharmacy, physician assistant, and public health students at Oregon Health & Science University (OHSU). This pioneering interprofessional course was created by the OHSU Global Health Center and is offered in fall, winter, and spring quarters. Students interact with individual clients drawn from community centers supporting refugees, recent immigrants, and other underserved people. In addition to health concerns, clients are encouraged to share backgrounds and experiences with student teams. Clients receive guidance on nutrition, exercise, pharmaceuticals, and accessible health services. Student teams perform a noninvasive health check on clients with the assistance of faculty mentors who, on finding a physical or mental health issue, refer the client from the educational setting to an appropriate health care facility. OUTCOMES: In addition to supporting health promotion and early intervention for medically underserved people, students reported gaining valuable cross-cultural knowledge, understanding, and experience from clients. Students also appreciated the value of diverse skills and knowledge available in their multidisciplinary teams. Through the end of 2012, over 300 health professions students worked with approximately 1,200 clients to complete the iCHEE course. NEXT STEPS: The iCHEE model should prove helpful in preparing health professions students at other institutions to understand and serve diverse populations.

Pan, J., Palmateer, J., Schallert, T., Hart, M., Pandya, A., Vandenbark, A. A., et al. (2014). Novel humanized recombinant T cell receptor ligands protect the female brain after experimental stroke. *Translational Stroke Research,*

Transmigration of peripheral leukocytes to the brain is a major contributor to cerebral ischemic cell death mechanisms. Humanized partial major histocompatibility complex class II constructs (pMHC), covalently linked to myelin peptides, are effective for treating experimental stroke in males, but new evidence suggests that some inflammatory cell death mechanisms after brain

injury are sex-specific. We here demonstrate that treatment with pMHC constructs also improves outcomes in female mice with middle cerebral artery occlusion (MCAO). HLA-DR2 transgenic female mice with MCAO were treated with RTL1000 (HLA-DR2 moiety linked to human MOG-35-55 peptide), HLA-DRa1-MOG-35-55, or vehicle (VEH) at 3, 24, 48, and 72 h after reperfusion and were recovered for 96 h or 2 weeks post-injury for measurement of histology (TTC staining) or behavioral testing. RTL1000- and DRa1-MOG-treated mice had profoundly reduced infarct volumes as compared to the VEH group, although higher doses of DRa1-MOG were needed for females vs. males evaluated previously. RTL1000-treated females also exhibited strongly improved functional recovery in a standard cylinder test. In novel studies of post-ischemic ultrasonic vocalization (USV), as measured by animal calls to their cage mates, we modeled in mice the post-stroke speech deficits common in human stroke survivors. The number of calls was reduced in injured animals relative to pre-MCAO baseline regardless of RTL1000 treatment status. However, call duration was significantly improved by RTL1000 treatment, suggesting benefit to the animal's recovery of vocalization capability. We conclude that both the parent RTL1000 molecule and the novel non-polymorphic DRα1-MOG-35-55 construct were highly effective immunotherapies for treatment of transient cerebral ischemia in females. 

Papadopoulos, M., Edmunds, B., Fenerty, C., & Khaw, P. T. (2014). Childhood glaucoma surgery in the 21st century. *Eye (London, England),*

Most children with glaucoma will require surgery in their lifetime, often in their childhood years. The surgical management of childhood glaucoma is however challenging, largely because of its greater potential for failure and complications as compared with surgery in adults. The available surgical repertoire for childhood glaucoma has remained relatively unchanged for many years with most progress owing to modifications to existing surgery. Although the surgical approach to childhood glaucoma varies around the world, angle surgery remains the preferred initial surgery for primary congenital glaucoma and a major advance has been the concept of incising the whole of the angle (circumferential trabeculotomy). Simple modifications to the trabeculectomy technique have been shown to considerably minimise complications. Glaucoma drainage devices maintain a vital role for certain types of glaucoma including those refractory to other surgery.

Cyclodestruction continues to have a role mainly for patients following failed drainage/filtering surgery. Although the prognosis for childhood glaucoma has improved significantly since the introduction of angle surgery, there is still considerable progress to be made to ensure a sighted lifetime for children with glaucoma all over the world. Collaborative approaches to researching and delivering this care are required, and this paper highlights the need for more high-quality prospective surgical trials in the management of the childhood glaucoma.Eye advance online publication, 13 June 2014; doi:10.1038/eye.2014.140.

Patel, R. M., Nagamani, S. C. S., Cuthbertson, D., Campeau, P. M., Krischer, J. P., Shapiro, J. R., et al. (2014). A cross-sectional multicenter study of osteogenesis imperfecta in north america - results from the linked clinical research centers. *Clinical Genetics,*

Osteogenesis imperfecta (OI) is the most common skeletal dysplasia that predisposes to recurrent fractures and bone deformities. In spite of significant advances in understanding the genetic basis of OI, there have been no large-scale natural history studies. To better understand the natural history and improve the care of patients, a network of Linked Clinical Research Centers (LCRC) was established. Subjects with OI were enrolled in a longitudinal study, and in this report, we present cross-sectional data on the largest cohort of OI subjects (n=544). OI type III subjects had higher prevalence of dentinogenesis imperfecta, severe scoliosis, and long bone deformities as compared to those with OI types I and IV. Whereas the mean lumbar spine area bone mineral density (LS aBMD) was low across all OI subtypes, those with more severe forms had lower bone mass. Molecular testing may help predict the subtype in type I collagen-related OI. Analysis of such well-collected and unbiased data in OI can not only help answering questions that are relevant to patient care but also foster hypothesis-driven research, especially in the context of 'phenotypic expansion' driven by next-generation sequencing. © 2014 John Wiley & Sons A/S.

Patton, P. E., Samuels, M. H., Trinidad, R., & Caughey, A. B. (2014). Controversies in the management of hypothyroidism during pregnancy. *Obstetrical and Gynecological Survey, 69*(6), 346-358.

IMPORTANCE: In the last 3 years, we have witnessed the publication of multiple but conflicting

guidelines on the management of hypothyroidism during pregnancy. Hypothyroidism is one of the most common endocrinopathies in reproductive-age and pregnant women. Given the prevalence of thyroid disease, it is highly likely that obstetricians will encounter and provide care for pregnant women with thyroid disease. Therefore, a review of current guidelines and management options is clinically relevant. OBJECTIVES: Our goals are to review the changes in thyroid function during pregnancy, the options for testing for thyroid disease, the different categories of thyroid dysfunction and surveillance strategies among subspecialty societies, and the obstetric hazards associated with thyroid dysfunction and review the evidence for benefit of treatment options for thyroid disease. EVIDENCE ACQUISITION: We reviewed key subspecialty guidelines, as well as current and ongoing studies focused on the treatment of hypothyroidism during pregnancy. RESULTS: There are significant differences in the identification and management of thyroid disease during pregnancy among subspecialists. We present our recommendations based on the available evidence. RELEVANCE: Evidence exists that obstetricians struggle with the diagnosis and treatment of hypothyroidism. According to recent surveys, the management of hypothyroidism during pregnancy is the number 1 endocrine topic of interest for obstetricians. A synopsis of recently published subspecialty guidelines is timely. CONCLUSIONS: Recent, evidence-based findings indicate that obstetricians should consider modifying their approach to the identification and treatment of thyroid disease during pregnancy. TARGET AUDIENCE: Obstetricians and gynecologists, family physicians LEARNING OBJECTIVES: After completing this CME activity, physicians should be better able to identify the changes in thyroid function testing during pregnancy; choose the appropriate methods of testing thyroid function during the first, second, and third trimesters; and compare treatment options of the various forms of thyroid dysfunction and the evidence behind treatment recommendations. 

Perry, L. M., Winthrop, K. L., & Curtis, J. R. (2014). Vaccinations for rheumatoid arthritis. *Current Rheumatology Reports, 16*(8), 431-014-0431-x.

Patients with rheumatoid arthritis (RA) suffer an increased burden of infectious disease-related morbidity and mortality and have twice the risk of acquiring a severe infection compared to the general population. This increased risk is not only a result of the autoimmune disease but is also

attributed to the immunosuppressive therapies that are commonly used in this patient population. Given the increase in infection-related risks in RA, there is great interest in mitigating such risk. A number of vaccines are available to the rheumatologist, with a handful that are of importance for RA patients in the United States. The goal of this paper is to highlight the most recent literature on the key vaccines and the specific considerations for the rheumatologist and their RA patients, with a particular focus on influenza, pneumococcal, and herpes zoster vaccines. It is important for rheumatologist to understand and be aware of which vaccines are live and what potential contraindications exist for giving vaccines to RA patients.

Pina, M. M., & Cunningham, C. L. (2014). Effects of the novel cannabinoid CB1 receptor antagonist PF 514273 on the acquisition and expression of ethanol conditioned place preference. *Alcohol (Fayetteville, N.Y.),*

The centrally expressed cannabinoid receptor (CB1) has been considered a potential therapeutic target in treating alcoholism. Though CB1 receptors have been shown to modulate primary and conditioned ethanol reward, much of this research employed animal models that require ethanol ingestion or oral routes of administration. This is problematic considering CB1 antagonist drugs have high anorectic liability and have been used clinically in the treatment of obesity. Therefore, the present study examined CB1 antagonism in DBA/2J mice using an unbiased ethanol-induced conditioned place preference (CPP) procedure, a paradigm that does not require ethanol ingestion. To evaluate the role of CB1 receptors in primary ethanol reward, the highly potent and selective novel CB1 antagonist 2-(2-chlorophenyl)-3-(4-chlorophenyl)-7-(2,2-difluoropropyl)-6,7-dihydro-2H-pyraz olo[3,4-f][1,4]oxazepin-8(5H)-one (PF 514273) was administered 30 min before place preference conditioning with a fixed dose of ethanol (acquisition). To evaluate the role of CB1 receptors in ethanol-conditioned reward, PF 514273 was administered 30 min before place preference testing (expression). Although PF 514273 reduced ethanol-stimulated and basal locomotor activity, it did not perturb the acquisition or expression of ethanol-induced CPP. Results from the present study appear inconsistent with other studies that have demonstrated a role for CB1 antagonism in ethanol reward using oral administration paradigms. Our findings suggest that CB1 antagonism may have greater involvement in consummatory behavior than ethanol reward.

Pokidysheva, E., Mizuno, K., & Bächinger, H. P. (2013). *The collagen folding machinery: Biosynthesis and post-translational modifications of collagens* Elsevier Inc.

The complex biosynthesis of type I procollagen involves a large number of post-translational modifications and a highly choreographed folding mechanism. This folding machinery resides primarily in the rough endoplasmic reticulum and consists of many enzymes and molecular chaperones which act as interacting cogs in this process. The importance of this machinery for normal bone formation has recently been demonstrated by the discovery of recessive forms of osteogenesis imperfecta that are due to mutations in the proteins that are part of this machinery. In this chapter we present the current knowledge of the folding machinery and the consequences of the absence of some of these cogs on the structure and function of type I procollagen. © 2014 Elsevier Inc. All rights reserved.

Pommerening, M. J., Schwartz, D. A., Cohen, M. J., Schreiber, M. A., Del Junco, D. J., Camp, E. A., et al. (2014). Hypercoagulability after injury in premenopausal females: A prospective, multicenter study. *Surgery,*

BACKGROUND: Recent studies suggest there are gender-specific differences in injury response that may be related to coagulation. The objective of this study was to test the hypothesis that rapid thrombelastography (rTEG) coagulation profiles differ by gender. METHODS: Adult trauma patients were prospectively followed at 3 level 1 trauma centers over a 14-month period. rTEG was obtained upon arrival and serially at several time points during the hospital stay. Female patients were stratified into premenopausal (50 years) age groups with age-matched male cohorts. Values were analyzed using a repeated-measures multilevel linear model to evaluate the effect of gender on coagulation. RESULTS: A total of 795 patients had serial rTEG data (24% female and 76% male). Compared with age-matched males, premenopausal females were more hypercoagulable by rTEG on admission (P 4-fold increased risk of hypercoagulable complications than premenopausal females (odds ratio, 4.7; P = .038). CONCLUSION: This prospective, multicenter study demonstrates that premenopausal females are relatively hypercoagulable compared with age-matched males early after injury. However, this did not translate into higher thromboembolic complications.

Powers, R. J., Kulason, S., Atilgan, E., Brownell, W. E., Sun, S. X., Barr-Gillespie, P. G., et al. (2014). The local forces acting on the mechanotransduction channel in hair cell stereocilia. *Biophysical Journal, 106*(11), 2519-2528.

In hair cells, mechanotransduction channels are located in the membrane of stereocilia tips, where the base of the tip link is attached. The tip-link force determines the system of other forces in the immediate channel environment, which change the channel open probability. This system of forces includes components that are out of plane and in plane relative to the membrane; the magnitude and direction of these components depend on the channel environment and arrangement. Using a computational model, we obtained the major forces involved as functions of the force applied via the tip link at the center of the membrane. We simulated factors related to channels and the membrane, including finite-sized channels located centrally or acentrally, stiffness of the hypothesized channel-cytoskeleton tether, and bending modulus of the membrane. Membrane forces are perpendicular to the directions of the principal curvatures of the deformed membrane. Our approach allows for a fine vectorial picture of the local forces gating the channel; membrane forces change with the membrane curvature and are themselves sufficient to affect the open probability of the channel.

Rabinowitz, A., Cohen, S. J., Finn, D. A., & Stackman, R. W.,Jr. (2014). The neurosteroid allopregnanolone impairs object memory and contextual fear memory in male C57BL/6J mice. *Hormones and Behavior, 66*(2), 238-246.

Allopregnanolone (ALLO, or 3alpha-hydroxy-5alpha-pregnan-20-one) is a steroid metabolite of progesterone and a potent endogenous positive allosteric modulator of GABA-A receptors. Systemic ALLO has been reported to impair spatial, but not nonspatial learning in the Morris water maze (MWM) and contextual memory in rodents. These cognitive effects suggest an influence of ALLO on hippocampal-dependent memory, although the specific nature of the neurosteroid's effects on learning, memory or performance is unclear. The present studies aimed to determine: (i) the memory process(es) affected by systemic ALLO using a nonspatial object memory task; and (ii) whether ALLO affects object memory via an influence within the dorsal hippocampus. Male C57BL/6J mice received systemic ALLO either before or immediately after the sample session of a novel object recognition (NOR) task. Results demonstrated that systemic

ALLO impaired the encoding and consolidation of object memory. A subsequent study revealed that bilateral microinfusion of ALLO into the CA1 region of dorsal hippocampus immediately following the NOR sample session also impaired object memory consolidation. In light of debate over the hippocampal-dependence of object recognition memory, we also tested systemic ALLO-treated mice on a contextual and cued fear-conditioning task. Systemic ALLO impaired the encoding of contextual memory when administered prior to the context pre-exposure session. Together, these results indicate that ALLO exhibits primary effects on memory encoding and consolidation, and extend previous findings by demonstrating a sensitivity of nonspatial memory to ALLO, likely by disrupting dorsal hippocampal function.

Radhakrishnan, A., Kumar, N., Wright, C. C., Chou, T. -., Tringides, M. L., Bolla, J. R., et al. (2014). Crystal structure of the transcriptional regulator Rv0678 of mycobacterium tuberculosis. *Journal of Biological Chemistry, 289*(23), 16526-16540.

Recent work demonstrates that the MmpL(mycobacterial membrane protein large) transporters are dedicated to the export of mycobacterial lipids for cell wall biosynthesis. An MmpL transporter frequently works with an accessory protein, belonging to the MmpS (mycobacterial membrane protein small) family, to transport these key virulence factors. One such efflux system in Mycobacterium tuberculosis is the MmpS5-MmpL5 transporter. The expression of MmpS5-MmpL5is controlled by the MarR-like transcriptional regulator Rv0678, whose open reading frame is located down stream of the mmpS5-mmpL5operon. To elucidate the structural basis of Rv0678 regulation, we have determined the crystal structure of this regulator, to 1.64Å resolution, revealing a dimeric two-domain molecule with an architecture similar to members of the MarR family of transcriptional regulators. Rv0678 is distinct from other MarR regulators in that its DNA-binding and dimerization domains are clustered together. These two domains seemingly cooperate to bind an inducing ligand that we identified as 2-stearoylglycerol, which is a fatty acid glycerol ester. The structure also suggests that the conformational change leading to substrate mediated derepression is primarily caused by a rigid body rotational motion of the entire DNA-binding domain of the regulator toward the dimerization domain. This movement results in a conformational state that is incompatible with DNA binding. We demonstrate using electrophoretic mobility shift assays that Rv0678 binds to the mmpS5-mmpL5, mmpS4-mmpL4,

and the mmpS2-mmpL2 promoters. Binding by Rv0678 was reversed upon the addition of the ligand. These findings provide new insight into the mechanisms of gene regulation in the MarR family of regulators. © 2014 by The American Society for Biochemistry and Molecular Biology, Inc.

Ragel, B. T., Piedra, M., Klimo, P., Burchiel, K. J., Waldo, H., McCartney, S., et al. (2014). An ACGME duty hour compliant 3-person night float system for neurological surgery residency programs. *Journal of Graduate Medical Education, 6*(2), 315-319.

BACKGROUND: In 2003, the Accreditation Council for Graduate Medical Education (ACGME) instituted the 24+6-hour work schedule and 80-hour workweek, and in 2011, it enhanced work hour and supervision standards. INNOVATION: In response, Oregon Health & Science University's (OHSU) neurological surgery residency instituted a 3-person night float system. METHODS: We analyzed work hour records and operative experience for 1 year before and after night float implementation in a model that shortened a combined introductory research and basic clinical neurosciences rotation from 12 to 6 months. We analyzed residents' perception of the system using a confidential survey. The ACGME 2011 work hour standards were applied to both time periods. RESULTS: AFTER NIGHT FLOAT IMPLEMENTATION, THE NUMBER OF DUTY HOUR VIOLATIONS WAS REDUCED: 28-hour shift (11 versus 235), 8 hours off between shifts (2 versus 20), 80 hours per week (0 versus 17), and total violations (23 versus 275). Violations increased only for the less than 4 days off per 4-week interval rule (10 versus 3). No meaningful difference was seen in the number of operative cases performed per year at any postgraduate year (PGY) training level: PGY-2 (336 versus 351), PGY-3 (394 versus 354), PGY-4 (803 versus 802), PGY-5 (1075 versus 1040), PGY-7 (947 versus 913), and total (3555 versus 3460). Residents rated the new system favorably. CONCLUSIONS: To meet 2011 ACGME duty hour standards, the OHSU neurological surgery residency instituted a 3-person night float system. A nearly complete elimination of work hour violations did not affect overall resident operative experience.

Raney, L., Pollack, D., Parks, J., & Katon, W. (2014). The american psychiatric association response to the "joint principles: Integrating behavioral health care into the patient-centered medical home". *Families, Systems & Health : The Journal of Collaborative Family Healthcare, 32*(2), 147-148.

Comments on the article "Joint principles: Integrating behavioral health care into the patient-centered medical home" (see record 2014-24217-011). The American Psychiatric Association Workgroup on Integrated Care supports the recommendations made in these Joint Principles and recognizes the significant benefit of treating behavioral and general medical conditions concurrently. The workgroup offers comments on this effort as it pertains to health care in general and psychiatric practice. (PsycINFO Database Record (c) 2014 APA, all rights reserved).

Rantala, J. K. (2014). Converting imaging-based cell biology to high-throughput biology. *European Pharmaceutical Review, 19*(1), 62-66.

The last 10 years in biomedical research marks the period of deepening our understanding of the human genome. In the context of cancer research, The Cancer Genome Atlas (TCGA) and related international genomics efforts have now revealed the full complexity of genomic aberrations in human cancers that are postulated to contribute to the aspects of cancer pathophysiology. It is plausible that an ensemble of the numerous aberrations in each individual tumour collaborate at various strengths to deregulate master signalling pathways of cells, thereby enabling the established cancer 'hallmarks'1.

Ratnapriya, R., Zhan, X., Fariss, R. N., Branham, K. E., Zipprer, D., Chakarova, C. F., et al. (2014). Rare and common variants in extracellular matrix gene fibrillin 2 (FBN2) are associated with macular degeneration. *Human Molecular Genetics,*

Neurodegenerative diseases affecting the macula constitute a major cause of incurable vision loss and exhibit considerable clinical and genetic heterogeneity, from early-onset monogenic disease to multifactorial late-onset age-related macular degeneration (AMD). As part of our continued efforts to define genetic causes of macular degeneration, we performed whole exome sequencing in four individuals of a two-generation family with autosomal dominant maculopathy and identified a rare variant p.Glu1144Lys in Fibrillin 2 (FBN2), a glycoprotein of the elastin-rich extracellular matrix (ECM). Sanger sequencing validated the segregation of this variant in the complete pedigree, including two additional affected and one unaffected individual. Sequencing of 192 maculopathy patients revealed additional rare variants, predicted to disrupt FBN2 function. We then undertook additional studies to explore the relationship of FBN2 to macular disease. We

show that FBN2 localizes to Bruch's membrane and its expression appears to be reduced in aging and AMD eyes, prompting us to examine its relationship with AMD. We detect suggestive association of a common FBN2 non-synonymous variant, rs154001 (p.Val965Ile) with AMD in 10 337 cases and 11 174 controls (OR = 1.10; P-value = 3.79 x 10-5). Thus, it appears that rare and common variants in a single gene-FBN2-can contribute to Mendelian and complex forms of macular degeneration. Our studies provide genetic evidence for a key role of elastin microfibers and Bruch's membrane in maintaining blood-retina homeostasis and establish the importance of studying orphan diseases for understanding more common clinical phenotypes.

Raymond, J., Klink, R., Chagnon, M., Barnwell, S. L., Evans, A. J., Mocco, J., et al. (2014). Patients prone to recurrence after endovascular treatment: Periprocedural results of the PRET randomized trial on large and recurrent aneurysms. *AJNR.American Journal of Neuroradiology,* BACKGROUND AND PURPOSE: Some patients with large or recurrent aneurysms may be at increased risk of recurrence postcoiling. The Patients Prone to Recurrence after Endovascular Treatment (PRET) trial was designed to assess whether hydrogel coils were superior to platinum coils in these high-risk patients. This article reports periprocedural safety and operator-assessed angiographic results from the PRET trial. MATERIALS AND METHODS: PRET was a pragmatic, multicenter, randomized controlled trial. Patients had >/=10-mm aneurysms (PRET-1) or a major recurrence after coiling of an aneurysm of any size (PRET-2). Patients were randomly allocated to hydrogel or control arms (any platinum coil) by using concealed allocation with minimization. Assist devices could be used as clinically required. Aneurysms could be unruptured or recently ruptured. Analyses were on an intent-to-treat basis. RESULTS: Four hundred forty-seven patients were recruited (250 PRET-1; 197 PRET-2). Aneurysms were recently ruptured in 29% of PRET-1 and 4% of PRET-2 patients. Aneurysms were >/=10 mm in all PRET-1 and in 50% of PRET-2 patients. They were wide-neck (>/=4 mm) in 70% and in the posterior circulation in 24% of patients. Stents were used in 28% of patients (35% in PRET-2). Coiling was successful in 98%. Adverse events occurred in 28 patients with hydrogel and 23 with platinum coils. Mortality (n = 2, unrelated to treatment) and morbidity (defined as mRS >2 at 1 month) occurred in 25 patients (5.6%; 12 hydrogel, 13 platinum), related to treatment in 10 (4 hydrogel; 6 platinum) (or 2.3% of 444 treated patients). No difference was seen between hydrogel and platinum for any of the

indices used to assess safety up to at least 30 days after treatment. At 1 month, 95% of patients were home with a good outcome (mRS </=2 or unchanged). Operator-assessed angiographic outcomes were satisfactory (complete occlusion or residual neck) in 339 of 447 or 76.4% of patients, with no significant difference between groups. CONCLUSIONS: Endovascular treatment of large and recurrent aneurysms can be performed safely with platinum or hydrogel coils.

Rodriguez, S. A. (2014). Response. *Gastrointestinal Endoscopy, 80*(1), 192.

Rohlman, D. S., Ismail, A. A., Abdel-Rasoul, G., Lasarev, M., Hendy, O., & Olson, J. R. (2014). Characterizing exposures and neurobehavioral performance in egyptian adolescent pesticide applicators. *Metabolic Brain Disease,*

Children and adolescents may have occupational exposure to pesticides. Although previous studies examining prenatal pesticide exposure have identified neurobehavioral deficits in children, there are limited studies examining the impact of occupational exposure in children. The objectives of this study are to estimate exposures to the organophosphorus pesticide, chlorpyrifos (CPF), by measuring urinary levels of 3,5,6-trichloro-2-pyridinol (TCPy), a specific CPF metabolite, and blood cholinesterase (ChE) activities and to characterize neurobehavioral performance in adolescents working as seasonal pesticide applicators and non-applicator controls. A neurobehavioral test battery, consisting of 14 tests, was used to assess a broad range of functions. Applicators performed worse than controls on the majority of tests. Principal component analysis was used to reduce the number of outcome variables and two components, focused on reasoning-short-term memory and attention-executive functioning, showed significant deficits in applicators compared to non-applicators. Elevated metabolite levels were found in the applicators compared to the non-applicators, confirming CPF exposure in the applicators. Although this study is limited by a small sample size, it provides preliminary evidence of moderate CPF exposures, decreased blood ChE in some applicators and decreased neurobehavioral performance in an adolescent working population. © 2014 Springer Science+Business Media New York.

Rosenbaum, B. P., Silkin, N., & Miller, R. A. (2014). Easily configured real-time CPOE pick off tool supporting focused clinical research and quality improvement. *Journal of the American Medical*

*Informatics Association, 21*(3), 564-568.

Real-time alerting systems typically warn providers about abnormal laboratory results or medication interactions. For more complex tasks, institutions create site-wide 'data warehouses' to support quality audits and longitudinal research. Sophisticated systems like i2b2 or Stanford's STRIDE utilize data warehouses to identify cohorts for research and quality monitoring. However, substantial resources are required to install and maintain such systems. For more modest goals, an organization desiring merely to identify patients with 'isolation' orders, or to determine patients' eligibility for clinical trials, may adopt a simpler, limited approach based on processing the output of one clinical system, and not a data warehouse. We describe a limited, order-entrybased, real-time 'pick off' tool, utilizing public domain software (PHP, MySQL). Through a web interface the tool assists users in constructing complex order-related queries and auto-generates corresponding database queries that can be executed at recurring intervals. We describe successful application of the tool for research and quality monitoring.

Rosenstein, M. G., Snowden, J. M., Cheng, Y. W., & Caughey, A. B. (2014). The mortality risk of expectant management compared with delivery stratified by gestational age and race and ethnicity. *American Journal of Obstetrics and Gynecology,*

OBJECTIVE: The objective of the study was to compare the mortality risk of expectant management with the risk of delivery at each week of term pregnancy in 4 racial/ethnic groups. STUDY DESIGN: This was a retrospective cohort study of all nonanomalous, term deliveries in California from 1997 to 2006 among white, black, Hispanic, and Asian women. In each racial/ethnic group, we compared the risk of infant death at each week with a composite risk representing the mortality risk of 1 week of expectant management. RESULTS: The risk of stillbirth and infant death is highest in black women (stillbirth risk: 18.0 per 10,000, infant death: 24.4 per 10,000, compared with 9.4 per 10,000 and 10.8 per 10,000 in white women, respectively; $P < .001$). Although absolute risks differ by race/ethnicity, the composite risk of expectant management does not surpass the risk of delivery until 39 weeks in any group. At 39 weeks these absolute risk differences are low, however, with a number needed to deliver to prevent 1 death ranging from 751 (among black women) to 2587 (among Asian women).

CONCLUSION: The mortality risk of expectant management exceeds the risk of delivery at 39 weeks in all racial/ethnic groups, despite variation in absolute risks.

Ross, A. M., Lee, C. S., & Brewer, M. (2014). Peripheral immune response and infection in first-time and recurrent ischemic stroke or transient ischemic attack. *The Journal of Neuroscience Nursing : Journal of the American Association of Neuroscience Nurses,*

Goals: The aims of this study were to determine if the infection rate differs between the first and recurrent ischemic stroke/transient ischemic attack (TIA), if the pattern of the peripheral immune response (PIR) differs between the first and recurrent ischemic stroke/TIA and if infection further influenced the pattern of the PIR. Methods: Retrospective review of 500 stroke cases with strict exclusion criteria (e.g., hemorrhagic stroke, subarachnoid hemorrhage, or spontaneous intracerebral hemorrhage; history of cancer; on steroids or immune suppressive drugs; recent invasive procedure) resulted in inclusion of 198 cases. Independent variables were first stroke or recurrent stroke and not infected or infected cases. Main-effect dependent variables were the white blood cell (WBC) and differential leukocyte counts (percentages of 100 cell counts for neutrophils, lymphocytes, and monocytes and absolute counts of neutrophils, lymphocytes, and monocytes). Findings: Infection rate was not different between the first versus recurrent stroke ($p = .279$). The pattern of WBC and differential counts were not different between groups, but addition of the covariate of infection showed group differences ($p = .05$). A four-group comparison of the dependent variables with the laboratory normal ranges showed lymphocyte percentages below the lower range limit in all four groups. Generalized linear modeling showed a modest rise (15%) in WBC counts in both groups with concomitant infection, a modestly low (-18%) lymphocyte percentage in recurrent stroke with infection, and a more substantial rise (22%-26%) in absolute neutrophil count in both groups with concomitant infection. Conclusions: Infection influences the pattern of the PIR in the first and recurrent stroke/TIA, and this difference can be quantified.

Rothberg, D. L., & Yoo, B. J. (2014). Posterior facet cartilage injury in operatively treated intra-articular calcaneus fractures. *Foot & Ankle International./ American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society,*

BACKGROUND: Direct visualization of the posterior facet in displaced intra-articular calcaneus fractures (DIACF) frequently shows partial or full thickness cartilage delamination. This is felt to be secondary to the depression of an osteoarticular segment of the posterior facet within the calcaneal body and the subsequent contact with fracture edges as it impacts caudally. The purpose of this study was to determine the frequency of cartilage injury and if it correlates with fracture classification. METHODS: A single surgeon prospective, observational series of 28 patients with 28 DIACFs was reviewed for patient demographic and injury data, radiographic fracture characterization, and intraoperative observation of articular injury size, depth, and location over the time period of February 2010 to December 2012. Observations were correlated with the OTA and Sanders classification systems. RESULTS: Age, sex, mechanism of injury, and depth and location of cartilage injury were not significantly different between the 13 OTA/Sanders type 2 and 15 type 3 DIACFs evaluated in this study. Posterior facet articular cartilage delamination was found in 77% of type 2 and 100% of type 3 fractures ($P = .09$). Location of cartilage injury was common (56%) along the distal, lateral aspect of the posterior facet ($P < .05$). The percentage area of cartilage injury was significantly larger in type 3 fractures (3.1%) then type 2 (1.3%) ($P < .02$). CONCLUSIONS: DIACFs had a consistent location of posterior facet articular cartilage delamination along the distal lateral aspect of the osteoarticular fragment. This lesion was larger in OTA/Sanders classification type 3 fractures compared to type 2 fractures. LEVEL OF EVIDENCE: Level IV, prospective, observational series.

Saint-Martin, C., Zhou, Q., Martin, G. M., Vaury, C., Leroy, G., Arnoux, J. -., et al. (2014). Monoallelic ABCC8 mutations are a common cause of diazoxide-unresponsive diffuse form of congenital hyperinsulinism. *Clinical Genetics,*

ABCC8 encodes a subunit of the β-cell potassium channel (KATP) whose loss of function is responsible for congenital hyperinsulinism (CHI). Patients with two recessive mutations of ABCC8 typically have severe diffuse forms of CHI unresponsive to diazoxide. Some dominant ABCC8 mutations are responsible for a subset of diffuse diazoxide-unresponsive forms of CHI. We report the analysis of 21 different ABCC8 mutations identified in 25 probands with diazoxide-unresponsive diffuse CHI and carrying a single mutation in ABCC8. Nine missense ABCC8 mutations were subjected to in vitro expression studies testing traffic efficiency and responses of

mutant channels to activation by MgADP and diazoxide. Eight of the 9 missense mutations exhibited normal trafficking. Seven of the 8 mutants reaching the plasma membrane had dramatically reduced response to MgADP or to diazoxide (<10% of wild-type response). In our cohort, dominant KATP mutations account for 22% of the children with diffuse unresponsive-diazoxide CHI. Their clinical phenotype being indistinguishable from that of children with focal CHI and diffuse CHI forms due to two recessive KATP mutations, we show that functional testing is essential to make the most reliable diagnosis and offer appropriate genetic counseling. © 2014 John Wiley & Sons A/S.

Salinsky, M., Storzbach, D., Goy, E., & Evrard, C. (2014). Traumatic brain injury and psychogenic seizures in veterans. *The Journal of Head Trauma Rehabilitation,*

OBJECTIVE:: To evaluate a proposed seizure etiology of traumatic brain injury (TBI) as a risk factor for psychogenic nonepileptic seizures (PNESs), the effect of reported TBI severity on the diagnosis of PNES versus epileptic seizures (ESs), and the potential moderating role of posttraumatic stress disorder (PTSD). PARTICIPANTS, SETTING:: Veterans with a diagnosis of PNES or ES during epilepsy monitoring at a Veterans Affairs Medical Center. DESIGN:: Retrospective review of seizure type, proposed seizure etiology, TBI severity, and PTSD. MAIN OUTCOMES:: Both PNES and ES groups were compared for TBI history and severity, and prior diagnosis of PTSD. RESULTS:: Traumatic brain injury was the proposed seizure etiology for 57% of 67 PNES patients versus 35% of 54 ES patients ($P < .05$). It was mild in 87% of PNES patients and 37% of ES patients ($P < .001$). Posttraumatic stress disorder increased the likelihood of diagnosing PNES versus ES in Veterans with mild TBI as the proposed seizure etiology. CONCLUSIONS:: Veterans with PNES commonly cite a TBI as the cause for seizures. Mild TBI was strongly associated with PNES versus ES. Posttraumatic stress disorder may moderate the development of PNES in Veterans with a history of mild TBI. Clinicians caring for Veterans with seizures may use these results in selecting patients for early diagnostic evaluation.

Samuels, M. H. (2013). *Cushing syndrome* Elsevier Inc.

Samuels, M. H. (2013). *Growth hormone-secreting pituitary tumors* Elsevier Inc.

Samuels, M. H. (2014). Thyroid disease and cognition. *Endocrinology and Metabolism Clinics of North America, 43*(2), 529-543.

Overt hypothyroidism and thyrotoxicosis are associated with significant decrements in mood and cognitive function, and therapy usually leads to improvement in these symptoms. In contrast, major affective or cognitive dysfunction is not typical of subclinical thyroid disease. Subtle deficits in specific cognitive domains (primarily working memory and executive function) likely exist in subclinical hypothyroidism and thyrotoxicosis, but these are unlikely to cause major problems in most patients. Patients with mild thyroid disease and significant distress related to mood or cognition most likely have independent diagnoses that should be evaluated and treated separately.

Saultz, J. (2014). Short and sweet. *Family Medicine, 46*(5), 333-334.

Saultz, J. (2014). Today's family medicine clerkship. *Family Medicine, 46*(6), 417-418.

Saver, J. L., Jahan, R., Levy, E. I., Jovin, T. G., Baxter, B., Nogueira, R., et al. (2014). SOLITAIRE™ with the intention for thrombectomy (SWIFT) trial: Design of a randomized, controlled, multicenter study comparing the SOLITAIRE™ flow restoration device and the MERCI retriever in acute ischaemic stroke. *International Journal of Stroke, 9*(5), 658-668.

Rationale: Self-expanding stent retrievers are a promising new device class designed for rapid flow restoration in acute cerebral ischaemia. The SOLITAIRE™ Flow Restoration device (SOLITAIRE) has shown high rates of recanalization in preclinical models and in uncontrolled clinical series. Aims: (1) To demonstrate non-inferiority of SOLITAIRE compared with a legally marketed device, the MERCI Retrieval System®, (2) To demonstrate safety, feasibility, and efficacy of SOLITAIRE in subjects requiring mechanical thrombectomy diagnosed with acute ischaemic stroke. Design: Multicenter, randomized, prospective, controlled trial with blinded primary end-point ascertainment. Study Procedures: Key entry criteria include: age 22-85; National Institute of Health Stroke Scale (NIHSS) ≥8 and <30; clinical and imaging findings consistent with acute ischaemic stroke; patient ineligible or failed intravenous tissue plasminogen activator; accessible occlusion in M1 or M2 middle cerebral artery, internal carotid artery, basilar artery, or vertebral artery; and patient able to be treated within 8h of onset. Sites first

participate in a roll-in phase, treating two patients with the SOLITAIRE device, before proceeding to the randomized phase. In patients unresponsive to the initially assigned therapy, after the angiographic component of the primary end-point is ascertained (reperfusion with the initial assigned device), rescue therapy with other reperfusion techniques is permitted. Outcomes: The primary efficacy end-point is successful recanalization with the assigned study device (no use of rescue therapy) and with no symptomatic intracranial haemorrhage. Successful recanalization is defined as achieving Thrombolysis In Myocardial Ischemia 2 or 3 flow in all treatable vessels. The primary safety end-point is the incidence of device-related and procedure-related serious adverse events. A major secondary efficacy end-point is time to achieve initial recanalization. Additional secondary end-points include clinical outcomes at 90 days and radiologic haemorrhagic transformation. 

Sayer, N. A., Orazem, R. J., Noorbaloochi, S., Gravely, A., Frazier, P., Carlson, K. F., et al. (2014). Iraq and afghanistan war veterans with reintegration problems: Differences by veterans affairs healthcare user status. *Administration and Policy in Mental Health and Mental Health Services Research,*

We studied 1,292 Iraq and Afghanistan War veterans who participated in a clinical trial of expressive writing to estimate the prevalence of perceived reintegration difficulty and compare Veterans Affairs (VA) healthcare users to nonusers in terms of demographic and clinical characteristics. About half of participants perceived reintegration difficulty. VA users and nonusers differed in age and military background. Levels of mental and physical problems were higher in VA users. In multivariate analysis, military service variables and probable traumatic brain injury independently predicted VA use. Findings demonstrate the importance of research comparing VA users to nonusers to understand veteran healthcare needs. 

Schapiro, S. J., Coleman, K., Akinyi, M., Koenig, P., Hau, J., & Domaingue, M. C. (2013). *Nonhuman primate welfare in the research environment* Elsevier Inc.

Nonhuman primates in research environments provide special challenges for discussions of animal welfare. Captive nonhuman primates are extremely intelligent and capable animals, and few, if any, research environments can duplicate their natural conditions. However, there are

numerous ways to functionally simulate critical aspects of the natural environment in captivity, thereby stimulating species-typical behavior patterns in captive primates. Evidence suggests that primate subjects that display many species-typical behavior patterns have enhanced welfare. Behavioral management techniques, including socialization strategies, environmental enrichment, and positive reinforcement training are used to provide primates in research environments with opportunities to control aspects of their environments and to make meaningful choices, in some cases, even facilitating participation in their own care. Such techniques typically not only enhance the primates' welfare, but also improve the quality and utility of the animals as research models by minimizing confounding influences. 

Schepman, K., Fombonne, E., Collishaw, S., & Taylor, E. (2014). Cognitive styles in depressed children with and without comorbid conduct disorder. *Journal of Adolescence, 37*(5), 622-631.

Little is known about patterns of cognitive impairment in depression comorbid with conduct disorder. The study included clinically depressed children with (N = 23) or without conduct disorder (N = 29), and controls without psychiatric disorder (N = 37). Cognitive biases typical of depression and patterns of social information processing were assessed. Both depressed groups had substantially higher rates of negative cognitive distortions, attributional biases and ruminative responses than non-depressed children. Children in the comorbid group made more hostile attributions and suggested more aggressive responses for dealing with threatening social situations, whilst children with depression only were more likely to be unassertive. Depression has a number of similar depressotypic cognitive biases whether or not complicated by conduct disorder, and may be potentially susceptible to similar interventions. The results also highlight the importance of recognising social information processing deficits when they occur and targeting those too, especially in comorbid presentations.

Schilaty, N. D., Hedges, D. M., Jang, E. Y., Folsom, R. J., Yorgason, J. T., McIntosh, J. M., et al. (2014). Acute ethanol inhibits dopamine release in the nucleus accumbens via α6 nicotinic acetylcholine receptors. *Journal of Pharmacology and Experimental Therapeutics, 349*(3), 559-567.

Electrophysiology and microdialysis studies have provided compelling evidence that moderate to

high ethanol concentrations enhance dopamine (DA) neurotransmission in the nucleus accumbens (NAc) through the mesolimbic DA system. However, with fast-scan cyclic voltammetry, short-term exposure to moderate to high doses of ethanol decreases evoked DA release at terminals in the NAc. The aim of this study was to evaluate the involvement of nicotinic acetylcholine receptors (nAChRs) in modulating the effects of ethanol on DA release in the NAc of C57BL/6 mice ex vivo and in vivo. Local stimulation evoked robust, frequency-dependent DA release in the NAc slice preparation, with maximal release at 40 Hz in the shell and 20 Hz in the core. Nicotine decreased DA release in a concentration-dependent (0.01-10 μM) manner in the shell and core, with an IC50 of 0.1 μM ex vivo and 0.5 mg/kg in vivo. Nicotine and ethanol inhibition of DA release was blocked by the α6 *-nAChR antagonist α-conotoxins CtxMII and a-CtxMII [H9A; L15A] ex vivo (100 nM) in the core but not the shell. Furthermore, the nonspecific nAChR antagonist mecamylamine (2 mg/kg) blocked the effects of ethanol in the core in vivo. These findings suggest that DA release is inhibited by ethanol via nAChRs in the NAc and that DA modulation by nAChRs differs in the core versus the shell, with α6*-nAChRs affecting DA release in the core but not in the shell. 

Sehgal, R., Hardman, J., & Haney, E. (2014). Observing trainee encounters using a one-way mirror. *Clinical Teacher, 11*(4), 247-250.

Background: Direct observation of patient encounters is a key component of evaluating residents during training, but there are scarce data on the various methods of observation. Aim: To implement a novel method for direct observation of out-patient encounters via a one-way mirror in an internal medicine resident practice, and to assess the feasibility and acceptance of this method. Methods: Each selected resident-patient encounter was directly observed by a preceptor through a one-way mirror. The preceptor provided feedback to the resident at the conclusion of each encounter. A post-visit survey assessed resident satisfaction and comfort with this method of observation. Results: Using a one-way mirror was a feasible method of observation. Fifty residents had a clinic visit that was directly observed, and 42 (84%) completed the post-visit survey. Residents reported that they preferred direct observation through a one-way mirror compared with other methods, including videotaped encounters or having a preceptor physically

present in the room. They also felt that having a preceptor observing through the one-way mirror had no negative effect on the clinic visit. Direct observation of patient encounters is a key component of evaluating residents Conclusions: Direct observation through a one-way mirror is a viable method in the out-patient setting, and might be preferable for evaluating certain skills. © 2014 John Wiley & Sons Ltd.

Seil, F. J. (2014). The changeable nervous system: Studies on neuroplasticity in cerebellar cultures. *Neuroscience and Biobehavioral Reviews,*

Circuit reorganization after injury was studied in a cerebellar culture model. When cerebellar cultures derived from newborn mice were exposed at explantation to a preparation of cytosine arabinoside that destroyed granule cells and oligodendrocytes and compromised astrocytes, Purkinje cells surviving in greater than usual numbers were unensheathed by astrocytic processes and received twice the control number of inhibitory axosomatic synapses. Purkinje cell axon collaterals sprouted and many of their terminals formed heterotypical synapses with other Purkinje cell dendritic spines. The resulting circuit reorganization preserved inhibition in the cerebellar cortex. Following this reorganization, replacement of the missing granule cells and glia was followed by a restitution of the normal circuitry. Most of these developmental and reconstructive changes were not dependent on neuronal activity, the major exception being inhibitory synaptogenesis. The full complement of inhibitory synapses did not develop in the absence of neuronal activity, which could be mitigated by application of exogenous TrkB receptor ligands. Inhibitory synaptogenesis could also be promoted by activity-induced release of endogenous TrkB receptor ligands or by antibody activation of the TrkB receptor.

Selby Jr., J. B., Darcy, M. D., Smith, T. P., Kaufman, J. A., & Kim, H. S. (2014). Evolution of a specialty: The case for the association of chiefs of interventional radiology. *Seminars in Interventional Radiology, 31*(2), 107-109.

Senestraro, S. V., Crowe, J., Vo, A., Covell Jr., D., Ferracane, J., Wang, M., et al. (2013). Authors' response. *Journal of the American Dental Association, 144*(12), 1334.

Sharp, A. L., Cobb, E. M., Dresden, S. M., Richardson, D. K., Sabbatini, A. K., Sauser, K., et al. (2014). Understanding the value of emergency care: A framework incorporating stakeholder perspectives. *The Journal of Emergency Medicine,*

BACKGROUND: In the face of escalating spending, measuring and maximizing the value of health services has become an important focus of health reform. Recent initiatives aim to incentivize high-value care through provider and hospital payment reform, but the role of the emergency department (ED) remains poorly defined. OBJECTIVES: To achieve an improved understanding of the value of emergency care, we have developed a framework that incorporates the perspectives of stakeholders in the delivery of health services. METHODS: A pragmatic review of the literature informed the design of this framework to standardize the definition of value in emergency care and discuss outcomes and costs from different stakeholder perspectives. The viewpoint of patient, provider, payer, health system, and society is each used to assess value for emergency medical conditions. RESULTS: We found that the value attributed to emergency care differs substantially by stakeholder perspective. Potential targets to improve ED value may be aimed at improving outcomes or controlling costs, depending on the acuity of the clinical condition. CONCLUSION: The value of emergency care varies by perspective, and a better understanding is achieved when specific outcomes and costs can be identified, quantified, and measured. Using this framework can help stakeholders find common ground to prioritize which costs and outcomes to target for research, quality improvement efforts, and future health policy impacting emergency care.

Shaw, P. H., Hayes-Lattin, B., Johnson, R., & Bleyer, A. (2014). Improving enrollment in clinical trials for adolescents with cancer. *Pediatrics, 133 Suppl 3*, S109-13.

Overall cancer cure rates have risen over the last 30 years. Adolescent and young adult (AYA) oncology patients aged 15 to 39 have not shared in these successes as an age group, including those who fall into the younger age group of 15 to 19 years. The reasons for this deficit in survival improvement are manifold, but research has shown that an important factor is decreased enrollment in therapeutic clinical trials in this population versus younger patients. The paucity of adolescents treated in clinical trials is itself the result of several elements of the health care landscape in the United States. On the local level, these factors include referral patterns and

facilities available; on the national level, related factors include the number of clinical trials available for this age group and health care provider education in the care of these patients. We examine the data available that have contributed to this deficit in the United States and offer broad strategies to address these shortcomings with the goal of improving outcomes in this underserved population.

Shen, K. Z., Yakhnitsa, V., Munhall, A. C., & Johnson, S. W. (2014). AMP kinase regulates K-ATP currents evoked by NMDA receptor stimulation in rat subthalamic nucleus neurons. *Neuroscience, 274C*, 138-152.

Our lab recently showed that N-methyl-d-aspartate (NMDA) evokes ATP-sensitive K+ (K-ATP) currents in subthalamic nucleus (STN) neurons in slices of the rat brain. Both K-ATP channels and 5'-adenosine monophosphate-activated protein kinase (AMPK) are considered cellular energy sensors because their activities are influenced by the phosphorylation state of adenosine nucleotides. Moreover, AMPK has been shown to regulate K-ATP function in a variety of tissues including pancreas, cardiac myocytes, and hypothalamus. We used whole-cell patch clamp recordings to study the effect of AMPK activation on K-ATP channel function in STN neurons in slices of the rat brain. We found that bath or intracellular application of the AMPK activators A769662 and PT1 augmented tolbutamide-sensitive K-ATP currents evoked by NMDA receptor stimulation. The effect of AMPK activators was blocked by the AMPK inhibitor dorsomorphin (compound C), and by STO609, an inhibitor of the upstream AMPK activator CaMKKbeta. AMPK augmentation of NMDA-induced K-ATP current was also blocked by intracellular BAPTA and by inhibitors of nitric oxide synthase and guanylyl cyclase. However, A769662 did not augment currents evoked by the K-ATP channel opener diazoxide. In the presence of NMDA, A769662 inhibited depolarizing plateau potentials and burst firing, both of which could be antagonized by tolbutamide or dorsomorphin. These studies show that AMPK augments NMDA-induced K-ATP currents by a Ca2+-dependent process that involves nitric oxide and cGMP. By augmenting K-ATP currents, AMPK activation would be expected to dampen the excitatory effect of glutamate-mediated transmission in the STN.

Shi, Z. S., Liebeskind, D. S., Xiang, B., Ge, S. G., Feng, L., Albers, G. W., et al. (2014). Predictors of functional dependence despite successful revascularization in large-vessel occlusion strokes. *Stroke; a Journal of Cerebral Circulation, 45*(7), 1977-1984.

BACKGROUND AND PURPOSE: High revascularization rates in large-vessel occlusion strokes treated by mechanical thrombectomy are not always associated with good clinical outcomes. We evaluated predictors of functional dependence despite successful revascularization among patients with acute ischemic stroke treated with thrombectomy. METHODS: We analyzed the pooled data from the Multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI), Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO), and TREVO 2 trials. Successful revascularization was defined as thrombolysis in cerebral infarction score 2b or 3. Functional dependence was defined as a score of 3 to 6 on the modified Rankin Scale at 3 months. We assessed relationship of demographic, clinical, angiographic characteristics, and hemorrhage with functional dependence despite successful revascularization. RESULTS: Two hundred and twenty-eight patients with successful revascularization had clinical outcome follow-up. The rates of functional dependence with endovascular success were 48.6% for Trevo thrombectomy and 58.0% for Merci thrombectomy. Age (odds ratio, 1.04; 95% confidence interval, 1.02-1.06 per 1-year increase), National Institutes of Health Stroke Scale score (odds ratio, 1.08; 95% confidence interval, 1.02-1.15 per 1-point increase), and symptom onset to endovascular treatment time (odds ratio, 1.11; 95% confidence interval, 1.01-1.22 per 30-minute delay) were predictors of functional dependence despite successful revascularization. Symptom onset to reperfusion time beyond 5 hours was associated with functional dependence. All subjects with symptomatic intracranial hemorrhage had functional dependence. CONCLUSIONS: One half of patients with successful mechanical thrombectomy do not have good outcomes. Age, severe neurological deficits, and delayed endovascular treatment were associated with functional dependence despite successful revascularization. Our data support efforts to minimize delays to endovascular therapy in patients with acute ischemic stroke to improve outcomes. CLINICAL TRIAL REGISTRATION URL: http://www.clinicaltrials.gov. Unique identifier: NCT00318071, NCT01088672, and NCT01270867.

Sibley, C., Yazici, Y., Tascilar, K., Khan, N., Bata, Y., Yazici, H., et al. (2014). Behcet syndrome manifestations and activity in the united states versus turkey - A cross-sectional cohort comparison. *The Journal of Rheumatology,*

OBJECTIVE: To compare clinical manifestations and activity of Behcet syndrome (BS) in the United States versus Turkey using validated outcome measures. METHODS: Consecutive patients with BS from the US National Institutes of Health (NIH), New York University, and the University of Istanbul were evaluated. Disease activity was measured using the Behcet's Syndrome Activity Scale (BSAS) and the Behcet's Disease Current Activity Form (BDCAF) with quality of life measured by the Behcet Disease Quality of Life (BDQOL) form. One-way ANOVA, t-tests, and multivariate regression analyses were performed. RESULTS: Mean age did not differ between sites; however, more women were seen in the United States versus in Turkey ($p < 0.001$), and disease duration was longer in the United States ($p = 0.02$). Organ manifestations were similar for oral and genital ulcers, skin disease, arthralgia, eye disease, and thrombosis. However, more gastrointestinal ($p < 0.001$) and neurologic disease ($p = 0.003$) was seen in the United States. BSAS and BDCAF scores were worse in the United States compared to Turkey ($p = 0.013$ and $< 0.001$, respectively). Worse mean BDQOL scores were observed at the NIH compared to Istanbul (not significant). Multivariable regression models showed worse scores in ethnically atypical patients for BSAS and BDCAF ($p = 0.04$ and $p = 0.001$), American patients for BDCAF ($p = 0.01$), older age for BDCAF ($p = 0.005$), and women for BDQOL ($p = 0.01$). CONCLUSION: Demographic and clinical manifestations of BS differ between sites with higher disease activity in the United States compared to Turkey. Referral patterns, age, sex, ethnicity, and country of origin may be important in these differences. These observations raise the question of whether pathogenic mechanisms differ in Turkish and American patients.

Siefkes, H. M., Hogan, W. J., Flood, S. M., Ramsey, K. L., Reller, M. D., Starmer, A. J., et al. (2014). Impact of educational video on critical congenital heart disease screening. *Clinical Pediatrics, 53*(8), 733-741.

Objective: To assess the status of pulse oximetry screening and barriers to implementing screening programs. Methods: This was a prospective pre-post intervention survey of nurse managers and medical directors of hospital-based birthing centers in Oregon, Idaho, and

Southern Washington. The intervention was a 7-minute video demonstrating and discussing pulse oximetry screening for critical congenital heart disease. Results: Analysis of matched pairs showed a significant increase in the use of pulse oximetry screening during the study period from 52% to 73% (P <.0001). Following implementation of the video, the perception of all queried potential barriers decreased significantly among individuals from hospitals self-identified as nonscreening at baseline. Viewing the educational video was associated with an increase in the percentage of individuals from nonscreening hospitals that rated screening as "very beneficial" (45% vs 90%, P =.0001). Conclusions: An educational video was associated with improved opinions of pulse oximetry screening among hospitals not currently screening. © The Author(s) 2014.

Sikma, S. K., Young, H. M., Reinhard, S. C., Munroe, D. J., Cartwright, J., & McKenzie, G. (2014). Madication management roles in assisted living. *Journal of Gerontological Nursing, 40*(6), 42-53. Residents in assisted living (AL) frequently need assistance with medication management. Rooted in a social model, AL serves people facing increasing health management challenges as they "age in place."This study explored roles in AL medication management and satisfaction with unlicensed assistive personnel (UAP) as medication aides, a cost-effective staffing approach that is used frequently. The sample included 112 participants representing all parties involved in medication administration (residents, medication aides, administrators, RNs and licensed practical nurses, pharmacists, and primary care providers) in 15 AL settings in four states. Results include description of medication management roles; empirical validation of existing AL nursing professional standards; and satisfaction with the role of UAP as medication aide from all perspectives. Clinical implications include creating a supportive environment for medication aides (i.e., UAPs); the importance of the RN role as facilitator of AL medication management; and the need for collaboration and interprofessional team development across disparate settings. © SLACK Incorporated.

Sinha, A., Jones Brunette, A. M., Fay, J. F., Schafer, C. T., & Farrens, D. L. (2014). Rhodopsin TM6 can interact with two separate and distinct sites on arrestin: Evidence for structural plasticity and multiple docking modes in arrestin-rhodopsin binding. *Biochemistry, 53*(20), 3294-3307.

Various studies have implicated the concave surface of arrestin in the binding of the cytosolic surface of rhodopsin. However, specific sites of contact between the two proteins have not previously been defined in detail. Here, we report that arrestin shares part of the same binding site on rhodopsin as does the transducin Gα subunit C-terminal tail, suggesting binding of both proteins to rhodopsin may share some similar underlying mechanisms. We also identify two areas of contact between the proteins near this region. Both sites lie in the arrestin N-domain, one in the so-called "finger" loop (residues 67-79) and the other in the 160 loop (residues 155-165). We mapped these sites using a novel tryptophan-induced quenching method, in which we introduced Trp residues into arrestin and measured their ability to quench the fluorescence of bimane probes attached to cysteine residues on TM6 of rhodopsin (T242C and T243C). The involvement of finger loop binding to rhodopsin was expected, but the evidence of the arrestin 160 loop contacting rhodopsin was not. Remarkably, our data indicate one site on rhodopsin can interact with multiple structurally separate sites on arrestin that are almost 30 Å apart. Although this observation at first seems paradoxical, in fact, it provides strong support for recent hypotheses that structural plasticity and conformational changes are involved in the arrestin-rhodopsin binding interface and that the two proteins may be able to interact through multiple docking modes, with arrestin binding to both monomeric and dimeric rhodopsin. 

Slatore, C. G., Sullivan, D. R., Pappas, M., & Humphrey, L. L. (2014). Patient-centered outcomes among lung cancer screening recipients with computed tomography: A systematic review. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 9*(7), 927-934.

INTRODUCTION: Lung cancer screening using low-dose computed tomography (LDCT) is now widely recommended for adults who are current or former heavy smokers. It is important to evaluate the impact of screening on patient-centered outcomes. Among current and former smokers eligible for lung cancer screening, we sought to determine the consequences of screening with LDCT, and subsequent results, on patient-centered outcomes such as quality of life, distress, and anxiety. METHODS: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the fourth Quarter 2012),

MEDLINE (2000 to May 31, 2013), reference lists of articles, and Scopus for relevant English-language studies and systematic reviews. To evaluate the effect of LDCT screening on patient-centered outcomes, we included only randomized controlled trials (RCTs) involving asymptomatic adults. To evaluate the association of particular results and/or recommendations from a screening LDCT with patient-centered outcomes, we included results from RCTs as well as from cohort studies. RESULTS: A total of 8215 abstracts were reviewed. Five publications from two European RCTs and one publication from a cohort study conducted in the United States met inclusion criteria. The process of LDCT lung cancer screening was associated with short-term psychologic discomfort in many people but did not affect distress, worry, or health-related quality of life. False-positive results were associated with short-term increases in distress that returned to levels that were similar to those among people with negative results. Negative results were associated with short-term decreases in distress. CONCLUSIONS: As lung cancer screening is implemented in the general population, it will be important to evaluate its association with patient-centered outcomes. People considering lung cancer screening should be aware of the possibility of distress caused by false-positive results. Clinicians may want to consider tailoring communication strategies that can decrease the distress associated with these results.

Slayden, O. D. (2014). Cyclic remodeling of the nonhuman primate endometrium: A model for understanding endometrial receptivity. *Seminars in Reproductive Medicine, 32*(5), 385-391.
Old World monkeys display physiological responses to steroid hormones that are similar to those of women. In this review, we describe cyclic morphological changes that take place within the uterus of Old World primates during the menstrual cycle. In primates, estrogen stimulates endometrial growth in the follicular phase of the menstrual cycle. Progesterone secreted in the luteal phase acts to induce secretory differentiation, which is required for successful embryo implantation. During the differentiation process, endometrial estrogen receptor-1 (ESR-1) is suppressed, and reduced staining for ESR-1 is a definitive marker of the onset of uterine receptivity. Downregulation of ESR-1 is topographically limited to the functionalis (upper) zones of the endometrium, the zones in which embryo implantation occurs, indicating that zone-specific factors play a role in the differentiation process. Future genomic and proteomic studies are expected to reveal additional markers for diagnosing endometrial receptivity. Due to the distinct

zonal response of the endometrium to ovarian steroids, accurate histological characterization will remain necessary to interpret novel targets in the assessment of fertility.

Smolen, J. S., Landewé, R., Breedveld, F. C., Buch, M., Burmester, G., Dougados, M., et al. (2014). EULAR recommendations for the managements of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. [Odporúčania EULAR pre manažment reumatoidnej artritídy syntetickými a biologickými ochorenie modifikujúcimi antireumatickými liekmi: Aktualizácia 2013] *Rheumatologia, 28*(1), 1-25.

In this article, the 2010 European League against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis (RA) with synthetic and biological disease-modifying antirheumatic drugs (sDMARDs and bDMARDs, respectively) have been updated. The 2013 update has been developed by an international task force, which based its decisions mostly on evidence from three systematic literature reviews (one each on sDMARDs, including glucocorticoids, bDMARDs and safety aspects of DMARD therapy); treatment strategies were also covered by the searches. The evidence presented was discussed and summarised by the experts in the course of a consensus finding and voting process. Levels of evidence and grades of recommendations were derived and levels of agreement (strengths of recommendations) were determined. Fourteen recommendations were developed (instead of 15 in 2010). Some of the 2010 recommendations were deleted, and others were amended or split. The recommendations cover general aspects, such as attainment of remission or low disease activity using a treat-to-target approach, and the need for shared decision-making between rheumatologists and patients. The more specific items relate to starting DMARD therapy using a conventional sDMARD (csDMARD) strategy in combination with glucocorticoids, followed by the addition of a bDMARD or another csDMARD strategy (after stratification by presence or absence of adverse risk factors) if the treatment target is not reached within 6 months (or improvement not seen at 3 months). Tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars), abatacept, tocilizumab and, under certain circumstances rituximab are essentially considered to have similar efficacy and safety. If the first bDMARD strategy fails, any other bDMARD may be used. The recommendations also address tofacitinib as a targeted sDMARD (tsDMARD), which is recommended, where licensed, after use of at least one bDMARD.

Biosimilars are also addressed. These recommendations are intended to inform rheumatologists, patients, national rheumatology societies and other stakeholders about EULAR's most recent consensus on the management of RA with sDMARDs, glucocorticoids and bDMARDs. They are based on evidence and expert opinion and intended to improve outcome in patients with RA.

Sobecks, R. M., Leis, J. F., Gale, R. P., Ahn, K. W., Zhu, X., Sabloff, M., et al. (2014). Outcomes of human leukocyte antigen-matched sibling donor hematopoietic cell transplantation in chronic lymphocytic leukemia: Myeloablative versus reduced-intensity conditioning regimens. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation,*

Allogeneic hematopoietic cell transplantation (HCT) can cure some chronic lymphocytic leukemia (CLL) subjects. This study compared outcomes of myeloablative (MA) and reduced-intensity conditioning (RIC) transplantations from HLA-matched sibling donors (MSD) for CLL. From 1995 to 2007, information regarding 297 CLL subjects was reported to the Center of International Blood and Marrow Transplant Research; of these, 163 underwent MA and 134 underwent RIC MSD HCT. The MA subjects underwent transplantation less often after 2000 and less commonly received antithymocyte globulin (4% versus 13%, P = .004) or prior antibody therapy (14% versus 53%; P < .001). RIC was associated with a greater likelihood of platelet recovery and less grade 2 to 4 acute graft-versus-host disease compared with MA conditioning. One- and 5-year treatment-related mortality (TRM) were 24% (95% confidence intervals [CI], 16% to 33%) versus 37% (95% CI, 30% to 45%; P = .023), and 40% (95% CI, 29% to 51%) versus 54% (95% CI, 46% to 62%; P = .036), respectively, and the relapse/progression rates at 1 and 5 years were 21% (95% CI, 14% to 29%) versus 10% (95% CI, 6% to 15%; P = .020), and 35% (95% CI, 26% to 46%) versus 17% (95% CI, 12% to 24%; P = .003), respectively. MA conditioning was associated with better progression-free (PFS) (relative risk, .60; 95% CI, .37 to .97; P = .038) and 3-year survival in transplantations before 2001, but for subsequent years, RIC was associated with better PFS and survival (relative risk, 1.49 [95% CI, .92 to 2.42]; P = .10; and relative risk, 1.86 [95% CI, 1.11 to 3.13]; P = .019). Pretransplantation disease status was the most important predictor of relapse (P = .003) and PFS (P = .0007) for both forms of

transplantation conditioning. MA and RIC MSD transplantations are effective for CLL. Future strategies to decrease TRM and reduce relapses are warranted.

Sonnenberg, A. (2014). Timing of endoscopy in gastrointestinal bleeding. *United European Gastroenterology Journal, 2*(1), 5-9.

BACKGROUND: In gastrointestinal bleeding, a physician often has to make a decision between two possible choices. Endoscopic management of the bleeding could be initiated immediately, or it could be delayed until the patient has become haemodynamically stable or the conditions for a successful endoscopy have otherwise improved. OBJECTIVE: The present article serves to present such situations and highlights their characteristic features. METHODS: The choice between immediate and delayed endoscopy is analysed in terms of a decision tree, comparing the expected results of the two management alternatives. The decision tree is applied to three different clinical scenarios associated with gastrointestinal bleeding, where performing endoscopy later rather than sooner represents the preferred management option. RESULTS: The work up of chronic iron-deficient anaemia in patients with serious cardiac problems should be deferred until resolution of their reduced cardiovascular status. It is also recommended that, even in acute bleeding, endoscopy is deferred until the patient has become haemodynamically stable. Lastly, for nonemergency treatment of oesophageal varices bleeding, a long rather than short interval between consecutive banding sessions appears more beneficial. CONCLUSIONS: The results illustrate how to use threshold analysis as a simple bedside tool to solve seemingly complex decisions associated with management of gastrointestinal bleeding.

Soysa, R., Carter, N. S., & Yates, P. A. (2014). A dual luciferase system for analysis of post-transcriptional regulation of gene expression in leishmania. *Molecular and Biochemical Parasitology, 195*(1), 1-5.

Gene expression in kinetoplastid parasites is regulated via post-transcriptional mechanisms that modulate mRNA turnover, translation rate, and/or post-translational protein stability. To facilitate the analysis of post-transcriptional regulation, a dual luciferase system was developed in which firefly and Renilla luciferase reporters genetically fused to compatible drug resistance genes are integrated in place of one allele of the gene of interest and of an internal control gene,

respectively, in a manner that preserves the cognate pre-mRNA processing signals. The sensitivity and reproducibility of the assay coupled with the ability to rapidly assemble reporter integration constructs render the dual luciferase system suitable for analysis of multiple candidates derived from global expression analysis platforms. To demonstrate the utility of the system, regulation of three genes in response to purine starvation was examined in Leishmania donovani promastigotes. This dual luciferase system should be directly applicable to the analysis of post-transcriptional regulation in other kinetoplastids.

Spector, N. D., Cull, W., Daniels, S. R., Gilhooly, J., Hall, J., Horn, I., et al. (2014). Gender and generational influences on the pediatric workforce and practice. *Pediatrics, 133*(6), 1112-1121. In response to demographic and other trends that may affect the future of the field of pediatrics, the Federation of Pediatric Organizations formed 4 working groups to participate in a year 's worth of research and discussion preliminary to a Visioning Summit focusing on pediatric practice, research, and training over the next 2 decades. This article, prepared by members of the Gender and Generations Working Group, summarizes findings relevant to the 2 broad categories of demographic trends represented in the name of the group and explores the interface of these trends with advances in technology and social media and the impact this is likely to have on the field of pediatrics. Available data suggest that the trends in the proportions of men and women entering pediatrics are similar to those over the past few decades and that changes in the overall ratio of men and women will not substantially affect pediatric practice. However, although women may be as likely to succeed in academic medicine and research, fewer women than men enter research, thereby potentially decreasing the number of pediatric researchers as the proportion of women increases. Complex generational differences affect both the workforce and interactions in the workplace. Differences between the 4 generational groups comprising the pediatric workforce are likely to result in an evolution of the role of the pediatrician, particularly as it relates to aspects of work-life balance and the use of technology and social media. 

Stecker, E. C. (2014). How does the heart heal? *Science Translational Medicine, 6*(237)

Stevens, S. L., Vartanian, K. B., & Stenzel-Poore, M. P. (2014). Reprogramming the response to stroke by preconditioning. *Stroke; a Journal of Cerebral Circulation,*

Streiff, C., Zhu, M., Panosian, J., Sahn, D. J., & Ashraf, M. (2014). Comprehensive evaluation of cardiac function and detection of myocardial infarction based on a semi-automated analysis using full-volume real time three-dimensional echocardiography. *Echocardiography (Mount Kisco, N.Y.),* OBJECTIVE: Quantitative left ventricular mass (LVM) as well as regional strain values may be obtained from full-volume real time 3D echocardiography data via semi-automated feature tracking and represent indices of heart function, both in health and disease. METHODS: Fresh adult porcine and ovine hearts were passively pumped to simulate normal cardiac motion at stroke volumes (SVs) varying from 30 to 70 mL. A 3V-D Matrix probe, interfaced with a GE Vivid E9 ultrasound system, was used to image each heart at baseline conditions and after simulated myocardial infarction (MI). The 4D LV quantification function of EchoPAC PC was used to quantify the LVM and longitudinal and circumferential strain (LS & CS) of LV segments at each SV prior and subsequent to simulated MI. LVM was validated by volumetric displacement, while LS and CS values were compared to sonomicrometry-based strain. RESULTS: Linear regression analyses show excellent correlations in LVM, LS, and CS between the 4D echo and volumetric/sonomicrometric displacement with R2 values of 0.99, 0.88, and 0.67, respectively. Bland-Altman analyses for all variables validate the compatibility of both methods. It was also determined that EchoPAC PC was able to detect a decrease in LS and CS in the relevant segments between pre- and post-MI at all SVs ($P < 0.05$). CONCLUSIONS: EchoPAC PC is a robust utility with the ability to accurately obtain quantitative LVM, LS, and CS values from 4D echo volumes and has the potential to improve the yield of clinical studies in cases of suspected MI.

Sun, B. C., Costantino, G., Barbic, F., Bossi, I., Casazza, G., Dipaola, F., et al. (2014). Priorities for emergency department syncope research. *Annals of Emergency Medicine,*
STUDY OBJECTIVES: There is limited evidence to guide the emergency department (ED) evaluation and management of syncope. The First International Workshop on Syncope Risk Stratification in the Emergency Department identified key research questions and methodological

standards essential to advancing the science of ED-based syncope research. METHODS: We recruited a multinational panel of syncope experts. A preconference survey identified research priorities, which were refined during and after the conference through an iterative review process. RESULTS: There were 31 participants from 7 countries who represented 10 clinical and methodological specialties. High-priority research recommendations were organized around a conceptual model of ED decisionmaking for syncope, and they address definition, cohort selection, risk stratification, and management. CONCLUSION: We convened a multispecialty group of syncope experts to identify the most pressing knowledge gaps and defined a high-priority research agenda to improve the care of patients with syncope in the ED.

Sun, X. X., & Dai, M. S. (2014). Deubiquitinating enzyme regulation of the p53 pathway: A lesson from Otub1. *World Journal of Biological Chemistry, 5*(2), 75-84.
Deubiquitination has emerged as an important mechanism of p53 regulation. A number of deubiquitinating enzymes (DUBs) from the ubiquitin-specific protease family have been shown to regulate the p53-MDM2-MDMX networks. We recently reported that Otub1, a DUB from the OTU-domain containing protease family, is a novel p53 regulator. Interestingly, Otub1 abrogates p53 ubiquitination and stabilizes and activates p53 in cells independently of its deubiquitinating enzyme activity. Instead, it does so by inhibiting the MDM2 cognate ubiquitin-conjugating enzyme (E2) UbcH5. Otub1 also regulates other biological signaling through this non-canonical mechanism, suppression of E2, including the inhibition of DNA-damage-induced chromatin ubiquitination. Thus, Otub1 evolves as a unique DUB that mainly suppresses E2 to regulate substrates. Here we review the current progress made towards the understanding of the complex regulation of the p53 tumor suppressor pathway by DUBs, the biological function of Otub1 including its positive regulation of p53, and the mechanistic insights into how Otub1 suppresses E2.

Suriano, F., Conlin, M. J., & Buscarini, M. (2014). Feasibility of felt application for renorrhaphy after laparoscopic partial nephrectomy. *Minerva Urologica e Nefrologica, 66*(1), 83-85.
Aim. Laparoscopic partial nephrectomy (LPN) has become a well-established treatment for selected renal malignancies. Aim of the study was to explore feasibility of the application of

haemostatic felt pledgets during renorrhaphy after Laparoscopic Partial Nephrectomy (LPN) and evaluate its efficacy. Methods. Between May 2008 and December 2011, 42 patients underwent LPN as a treatment for renal tumors by a single surgeon. Tumor size and location were assessed by contrast enhanced computed tomography (CT) scan. A rolled Tabotamp was placed on the tumor bed; 2/0 Vycril sutures, secured with 5mm Hem-o-lok clips, were used to perform the renorrhaphy. 7.9x7.9 mm (5/16"x5/16") felt pledgets were placed between the hem-o-lok clips and the renal parenchyma on both needle entrance sites. W.i.t., EBL, OR time, post-operative complications and hospital stay were recorded. Results. Mean w.i.t. was 21±5 min, mean OR time 151±52 min, while EBL was 162±56 cc. Surgical complications were recorded in 11/42 (26%; Clavien-Dindo classification: II-III). Three patients experienced postoperative ileus, 3 had a urinary leakage, 1 a wound infection and 4 tumor bed bleeding: of these, 2 required blood transfusions, 1 was managed by embolization and 1 underwent nephrectomy. Mean LOS was 2 days. Conclusion. The application of hemostatic felt pledgets during renorrhaphy after LPN is feasible and safe. This technique may reduce cortical bleeding, and could ameliorate surgical outcomes.

Suzuki, R., Oka, T., Tamada, Y., Shearer, T. R., & Azuma, M. (2014). Degeneration and dysfunction of retinal neurons in acute ocular hypertensive rats: Involvement of calpains. *Journal of Ocular Pharmacology and Therapeutics, 30*(5), 419-428.

Purpose: Retinal ischemic diseases primarily lead to damage of the inner retinal neurons. Electrophysiological studies also suggest impairment of the inner retinal neurons. Our recent studies with acute ocular hypertensive rats confirmed damage predominantly in the inner retinal layer along with the ganglion cell layer, changes that are ameliorated by the calpain inhibitor SNJ-1945. However, we do not know which specific neuronal cells in the inner retinal layer are damaged by calpains. Thus, the purpose of the present study was to identify specific calpain-damaged neuronal cells in the inner retina from acute ocular hypertensive rats. Methods: Intraocular pressure was elevated to 110mm Hg for 40min. One hour after ocular hypertension (OH), SNJ-1945 was administrated as a single oral dose of 50mg/kg. Retinal function was assessed by scotopic electroretinography (ERG). Histological degeneration was evaluated by hematoxylin and eosin, terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick-end-

labeling (TUNEL), and immunostaining in thin sections and flat mounts of the retina. Calpain activation was determined by proteolysis of the calpain substrate α-spectrin. Results: OH caused calpain activation, increased TUNEL-positive staining, decreased thickness of the inner nuclear layer (INL), and decreased amplitudes of the ERG a- and b-waves and oscillatory potentials (OPs). SNJ-1945 significantly inhibited calpain activation and the decrease in ERG values. Interestingly, the changes in the b-wave and OPs amplitudes were significantly correlated to changes in the thickness of the INL. In the inner retinal layer, the numbers of rod bipolar, cone-ON bipolar, and amacrine cells were decreased after OH. SNJ-1945 suppressed the loss of cone-ON bipolar and amacrine cells, but did not inhibit the loss of rod bipolar cells. We also observed increased glial fibrillary acid protein-positive staining in the Müller cells after OH and the treatment with SNJ-1945. Conclusions: Calpains may contribute to ischemic retinal dysfunction by causing the loss of cone-ON bipolar and amacrine cells and causing the activation of Müller cells. Calpain inhibitor SNJ-1945 may be a candidate compound for treatment of retinal ischemic disease. © Mary Ann Liebert, Inc. 2014.

Tandon, A., Tehrani, S., Greiner, M. A., Fingert, J. H., & Alward, W. L. (2014). Thin central corneal thickness and early-onset glaucoma in lacrimo-auriculo-dento-digital syndrome. *JAMA Ophthalmology, 132*(6), 782-784.

Tarpley, M. J., Van Way, C.,3rd, Friedell, M., Deveney, K., Farley, D., Mellinger, J., et al. (2014). The role of a preliminary PGY-3 in general surgery training. *Journal of Surgical Education,* INTRODUCTION: Even before the preliminary postgraduate year (PGY)-3 was eliminated from surgical residency, it had become increasingly difficult to fill general surgery PGY-4 vacancies. This ongoing need prompted the Association of Program Directors in Surgery (APDS) leadership to form a task force to study the possibility of requesting the restoration of the preliminary PGY-3 to Accreditation Council for Graduate Medical Education-approved general surgery residency programs. METHODS: The task force conducted a 10-year review of the APDS list serve to ascertain the number of advertised PGY-4 open positions. Following the review of the list serve, the task force sent IRB-approved electronic REDCap surveys to 249 program directors (PDs) in general surgery. RESULTS: The list serve review revealed more than 230 requests for fourth-year

residents, a number that most likely underestimates the need, as such, vacancies are not always advertised through the APDS. A total of 119 PDs (~48%) responded. In the last 10 years, these 119 programs needed an average of 2 PGY-4 residents (range: 0-8), filled 1.3 positions (range: 0-7), and left a position unfilled 1.3 times (range: 0-7). Methods for finding PGY-4 residents included making personal contacts with other PDs (52), posting on the APDS Topica List Serve (47), and using the APDS Web site for interested candidates on residency and fellowship job listings (52). Reasons for needing a PGY-4 resident included residents leaving the program (82), extra laboratory years (39), remediation (31), and approved program expansion (21), as well as other issues. Satisfaction scores for the added PGY-4 residents were more negative (43) than positive (30). Problems ranged from lack of preparation to professionalism. When queried as to an optimal number of preliminary residents needed nationally at the PGY-3 level, responses varied from 0 to 50 (34 suggested 10). CONCLUSIONS: The survey of PDs supports the need for the reintroduction of a limited number of Accreditation Council for Graduate Medical Education-approved preliminary PGY-3 positions in general surgery residency programs.

Tippens, K. M., Purnell, J. Q., Gregory, W. L., Connelly, E., Hanes, D., Oken, B., et al. (2014). Expectancy, self-efficacy, and placebo effect of a sham supplement for weight loss in obese adults. *Journal of Evidence-Based Complementary and Alternative Medicine, 19*(3), 181-188. This study examined the role of expectancy in the placebo effect of a sham dietary supplement for weight loss in 114 obese adults with metabolic syndrome. All participants received lifestyle education and were randomized to 1 of 3 conditions: (1) a daily placebo capsule and told that they were taking an active weight loss supplement, (2) daily placebo and told they had a 50% random chance of receiving either the active or placebo, or (3) no capsules. At 12 weeks, weight loss and metabolic outcomes were similar among the 3 groups. Participants in both groups that took capsules showed decreased weight loss self-efficacy and increased expectations of benefit from dietary supplements. Participants not taking capsules showed the opposite. Adverse events were more frequently reported in groups taking capsules than those who were not. These findings suggest that supplements without weight loss effects may have nocebo effects through diminished self-efficacy. 

Triplett, W. T., Baligand, C., Forbes, S. C., Willcocks, R. J., Lott, D. J., DeVos, S., et al. (2014). Chemical shift-based MRI to measure fat fractions in dystrophic skeletal muscle. *Magnetic Resonance in Medicine, 72*(1), 8-19.

Purpose The relationship between fat fractions (FFs) determined based on multiple TE, unipolar gradient echo images and 1H magnetic resonance spectroscopy (MRS) was evaluated using different models for fat-water decomposition, signal-to-noise ratios, and excitation flip angles. Methods A combination of single-voxel proton spectroscopy (1H-MRS) and gradient echo imaging was used to determine muscle FFs in both normal and dystrophic muscles. In order to cover a large range of FFs, the soleus and vastus lateralis muscles of 22 unaffected control subjects, 16 subjects with collagen VI deficiency (COL6), and 71 subjects with Duchenne muscular dystrophy (DMD) were studied. 1H-MRS-based FF were corrected for the increased muscle 1H2O T1 and T2 values observed in dystrophic muscles. Results Excellent agreement was found between coregistered FFs derived from gradient echo images fit to a multipeak model with noise bias correction and the relaxation-corrected 1H-MRS FFs ($y = 0.93x + 0.003$; $R2 = 0.96$) across the full range of FFs. Relaxation-corrected 1H-MRS FFs and imaging-based FFs were significantly elevated ($P < 0.01$) in the muscles of COL6 and DMD subjects. Conclusion FFs, T2, and T1 were all sensitive to muscle involvement in dystrophic muscle. MRI offered an additional advantage over single-voxel spectroscopy in that the tissue heterogeneity in FFs could be readily determined. © 2013 Wiley Periodicals, Inc.

Tsikitis, V. L., Larson, D. W., Huebner, M., Lohse, C. M., & Thompson, P. A. (2014). Predictors of recurrence free survival for patients with stage II and III colon cancer. *BMC Cancer, 14*(1), 336-2407-14-336.

BACKGROUND: The aim of this study was to evaluate clinico-pathologic specific predictors of recurrence for stage II/III disease. Improving recurrence prediction for resected stage II/III colon cancer patients could alter surveillance strategies, providing opportunities for more informed use of chemotherapy for high risk individuals. METHODS: 871 stage II and 265 stage III patients with colon cancers were included. Features studied included surgery date, age, gender, chemotherapy, tumor location, number of positive lymph nodes, tumor differentiation, and lymphovascular and perineural invasion. Time to recurrence was evaluated, using Cox's proportional hazards models.

The predictive ability of the multivariable models was evaluated using the concordance (c) index. RESULTS: For stage II cancer patients, estimated recurrence-free survival rates at one, three, five, and seven years following surgery were 98%, 92%, 90%, and 89%. Only T stage was significantly associated with recurrence. Estimated recurrence-free survival rates for stage III patients at one, three, five, and seven years following surgery were 94%, 78%, 70%, and 66%. Higher recurrence rates were seen in patients who didn't receive chemotherapy ($p = 0.023$), with a higher number of positive nodes ($p < 0.001$). The c-index for the stage II model was 0.55 and 0.68 for stage III. CONCLUSIONS: Current clinic-pathologic information is inadequate for prediction of colon cancer recurrence after resection for stage II and IIII patients. Identification and clinical use of molecular markers to identify the earlier stage II and III colon cancer patients at elevated risk of recurrence are needed to improve prognostication of early stage colon cancers.

Turvey, C. L., Klein, D., Fix, G., Hogan, T. P., Woods, S., Simon, S. R., et al. (2014). Blue button use by patients to access and share health record information using the department of veterans affairs' online patient portal. *Journal of the American Medical Informatics Association, 21*(4), 657-663.

Objective: The Blue Button feature of online patient portals promotes patient engagement by allowing patients to easily download their personal health information. This study examines the adoption and use of the Blue Button feature in the Department of Veterans Affairs' (VA) personal health record portal, My HealtheVet. Materials and methods: An online survey presented to a 4% random sample of My HealtheVet users between March and May 2012. Questions were designed to determine characteristics associated with Blue Button use, perceived value of use, and how Veterans with non-VA providers use the Blue Button to share information with their non-VA providers. Results: Of the survey participants (N=18 398), 33% were current Blue Button users. The most highly endorsed benefit was that it helped patients understand their health history better because all the information was in one place (73%). Twenty-one percent of Blue Button users with a non-VA provider shared their VA health information, and 87% reported that the non-VA provider found the information somewhat or very helpful. Veterans' self-rated computer ability was the strongest factor contributing to both Blue Button use and to sharing information with non-VA providers. When comparing Blue Button users and non-users, barriers to adoption were

low awareness of the feature and difficulty using the Blue Button. Conclusions: This study contributes to the understanding of early Blue Button adoption and use of this feature for patient-initiated sharing of health information. Educational efforts are needed to raise awareness of the Blue Button and to address usability issues that hinder adoption.

Tuuli, M. G., Odibo, A. O., Caughey, A. B., Roehl, K., Macones, G. A., & Cahill, A. G. (2014). Are there differences in the first stage of labor between black and white women? *American Journal of Perinatology,*

Objective The objective of this study was to determine whether the duration and progress of the first stage of labor are different in black compared with white women. Study Design Retrospective cohort study of labor progress among consecutive black (n = 3,924) and white (n = 921) women with singleton term pregnancies (>/= 37 weeks) who completed the first stage of labor. Duration of labor and progression from 1 cm to the next was estimated using interval-censored regression. Labor duration and progress among black and white women in the entire cohort, and stratified by parity, were compared in multivariable interval-censored regression models. Repeated-measures analysis with 9th-degree polynomial modeling was used to construct average labor curves. Results There were no significant differences in duration of the first stage of labor in black compared with white women (median, 4-10 cm: 5.1 vs. 4.9 hours [p = 0.43] for nulliparous and 3.5 vs. 3.9 hours [p = 0.84] for multiparous women). Similarly, there were no significant differences in progression in increments of 1 cm. Average labor curves were also not significantly different. Conclusion Duration and progress of the first stage of labor are identical in black and white women. This suggests similar standards may be applied in the first stage of labor.

Vaaga, C. E., Tovar, K. R., & Westbrook, G. L. (2014). The IGF-derived tripeptide gly-pro-glu is a weak NMDA receptor agonist. *Journal of Neurophysiology,*

Glutamate acts as the universal agonist at ionotropic glutamate receptors in part because of its high degree of conformational flexibility. Other amino acids and small peptides, however, can activate N-methyl -aspartate (NMDA) receptors, albeit usually with lower affinity and efficacy. Here we examined the action of GPE (glycine-proline-glutamate), a naturally occurring tripeptide formed in the brain following cleavage of insulin-like growth factor 1 (IGF-1). GPE is thought to

have biological activity in the brain but its mechanism of action remains unclear. With its flanking glutamate and glycine residues, GPE could bind to either the agonist or co-agonist sites on NMDA receptors, however this has not been directly tested. Using whole cell patch clamp recordings in combination with rapid solution exchange, we examined both steady state currents induced by GPE as well as the effects of GPE on synaptically-evoked currents. High concentrations of GPE evoked inward currents, which were blocked either by NMDA receptor competitive antagonists or the voltage-dependent channel blocker, Mg2+. GPE also produced a slight attenuation in the NMDA- and AMPA-mediated EPSCs, without altering the paired pulse ratio. Our results suggest that GPE can activate NMDA receptors, but at concentrations well above the expected concentration of GPE in the brain. Therefore, it is unlikely that endogenous GPE interacts with glutamate receptors under normal conditions.

Varlamov, O. (2014). Real-time detection of SNARE complex assembly with FRET using the tetracysteine system. *Methods in Molecular Biology (Clifton, N.J.), 1174*, 49-55.

Small tetracysteine insertions are more suitable for fluorescence resonance energy transfer (FRET) studies of protein folding and small complex assembly than bulky GFP-based fluorophores. Here, we describe a procedure for expression, purification, and fluorescent labeling of a FRET-based probe, called CSNAC that can track the conformational changes undergone by SNAP-25 as it folds in the exocytic complex. The fluorescent protein Cerulean was attached to the N-terminus and served as a FRET donor. The biarsenical dye FlAsH, served as a FRET acceptor, was bound to a short tetracysteine motif positioned in the linker domain of SNAP-25. CSNAC can report real-time FRET changes when the Syntaxin soluble domain is added in vitro.

Varner, M. W., Marshall, N. E., Rouse, D. J., Jablonski, K. A., Leveno, K. J., Reddy, U. M., et al. (2014). The association of cord serum cytokines with neurodevelopmental outcomes. *American Journal of Perinatology,*

Objective To test whether elevated umbilical cord serum inflammatory cytokine levels predicted subsequent cerebral palsy (CP) or neurodevelopmental delay (NDD). Study Design Nested case-control analysis within a clinical trial of antenatal magnesium sulfate (MgSO4) before anticipated preterm birth (PTB) for prevention of CP, with evaluation of surviving children at the age of 2.

NDD was defined as a Bayley psychomotor developmental index (PDI) and/or mental developmental index (MDI) /= 85, were matched by race and gestational age. Cord serum was analyzed for interleukin-8 (IL-8) interleukin-1 beta (IL-1beta), and tumor necrosis factor-alpha (TNF-alpha) levels. Elevated cytokine levels were defined as >/= 75th percentile in placebo-exposed controls. Analyses compared case/control cytokine levels, adjusting for MgSO4 exposure, gestational age, race/ethnicity, and sociodemographic differences. Results Logistic regression analysis with 339 cases and 276 controls showed that elevated IL-8 and IL-1beta were more common in cord blood serum from infants with subsequent low MDI as compared with controls. After adjusting for additional confounders, the significant differences were no longer evident. Cytokine levels (IL-8, IL-1beta, and TNF-alpha) were not elevated with CP or low PDI. Conclusion Cord serum IL-8, IL-1beta, and TNF-alpha levels in preterm infants are not associated with subsequent CP or NDD.

Verner-Cole, E. A., Campbell, J. P., Hwang, T. S., Klein, M. L., Lauer, A. K., Choi, D., et al. (2014). Retinal and choroidal imaging with 870-nm spectral-domain OCT compared with 1050-nm spectral-domain OCT, with and without enhanced depth imaging. *Translational Vision Science & Technology, 3*(3), 3.

PURPOSE: The purpose of this study was to compare images of the retina and choroid obtained with Spectralis 1050-nm spectral-domain optical coherence tomography (SD-OCT) with and without enhanced depth imaging (EDI) to the commercially available 870-nm SD-OCT with and without EDI. METHODS: Full-length 30 degrees line scans were obtained with both 870- and 1050-nm Spectralis OCT instruments, with and without EDI. Two trained retina physicians masked to wavelength and EDI status assessed the ability to visualize the vitreoretinal interface and full-thickness choroid, and subfoveal choroidal thickness (SFCT) was measured. RESULTS: Included in the study were 21 eyes. The vitreoretinal interface was visualized best with 870-nm OCT without EDI and was diminished with 1050-nm OCT. Graders preferred 1050 nm with EDI over 870 nm with EDI in qualitative comparisons of the choroid; 1050 nm without EDI was slightly preferred over 870 nm with EDI but was not statistically significant. SFCT measurements correlated well among the imaging modalities except for 870 nm without EDI. CONCLUSIONS: SD-OCT with EDI at 870 nm provides good visualization of both the vitreoretinal interface and

choroid, whereas 1050-nm SD-OCT with or without EDI provides more choroidal detail at the expense of visualization of the vitreoretinal interface. TRANSLATIONAL RELEVANCE: Use of longer wavelength 1050-nm SD-OCT provides greater choroidal detail compared with 870-nm SD-OCT, but has reduced detail of the vitreoretinal interface. The significance of this trade-off for clinical management of retinal disease needs further evaluation.

Wahab, S., Trimble, J., Mejia, A., Mitchell, S. R., Thomas, M. J., Timmons, V., et al. (2014). Motivational interviewing at the intersections of depression and intimate partner violence among african american women. *Journal of Evidence-Based Social Work, 11*(3), 291-303.
This article focuses on design, training, and delivery of a culturally tailored, multi-faceted intervention that used motivational interviewing (MI) and case management to reduce depression severity among African American survivors of intimate partner violence (IPV). We present the details of the intervention and discuss its implementation as a means of creating and providing culturally appropriate depression and violence services to African American women. We used a community-based participatory research approach to develop and evaluate the multi-faceted intervention. As part of the evaluation, we collected process measures about the use of MI, assessed MI fidelity, and interviewed participants about their experiences with the program. Copyright Taylor & Francis.

Weaver, T. S., Wester, J. L., Gleysteen, J. P., Peck, J. J., & Wax, M. K. (2014). Surgical outcomes in the elderly patient after osteocutaneous free flap transfer. *The Laryngoscope,*
OBJECTIVES/HYPOTHESIS: Morbidity of free tissue transfer in the elderly patient is controversial. Recent studies have shown no significant difference in elderly fasciocutaneous free-flap donor site morbidity. The purpose of this study is to assess surgical outcomes in elderly patients receiving osteocutaneous free-tissue transfer. STUDY DESIGN: Retrospective chart review of patients 70 years and older undergoing osteocutaneous free flaps from 2000 to 2013. METHODS: Fibular, radial forearm, and scapular flaps were reviewed. Younger patients randomly selected from the same time period served as controls. Data collected included donor site morbidity, flap complications, feeding tube and tracheostomy dependence, and hospital stay. RESULTS: Forty-four osteocutaneous free flaps were performed in elderly patients. Overall, there was no

significant difference in donor site morbidity between older and younger patients (P = 0.50) (tendon exposure, P = 1.00; split-thickness skin graft loss, P = 0.36; infections, P = 0.52; dehiscence, P = 1.00; and seroma, P = 1.00). There was no significant difference between older and younger patients being decannulated (P = 0.61) or the time to decannulation (P = 0.24). There was no difference in those who returned to baseline diet (P = 0.67). All patients returned to baseline ambulatory and shoulder status. Length of postoperative hospitalization (P = 0.78) and intensive care unit stay (P = 0.94) were also equal. The only significant difference was that more elderly patients were discharged to skilled nursing facilities (SNF) (40.9% vs. 15.9%, P < 0.01). CONCLUSION: Elderly patients undergoing free tissue transfer have similar flap and donor site outcomes, feeding tube and tracheostomy outcomes, ambulatory status, and hospital stays compared to younger patients. They are, however, more likely to require SNF care posthospitalization. LEVEL OF EVIDENCE: 4. Laryngoscope, 2014.

Wei, K., Shah, S., Jaber, W. A., & DeMaria, A. (2014). An observational study of the occurrence of serious adverse reactions among patients who receive optison in routine medical practice. *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography,*

BACKGROUND: Reports of ultrasound contrast agent safety have been derived mainly from retrospective databases rather than from studies specifically designed to assess safety. The purpose of this study was to prospectively determine the safety of Optison in routine medical practice. METHODS: Patients referred for routine rest or stress two-dimensional echocardiography who had indications for contrast were enrolled. Vital signs were obtained at baseline and at intervals up to 1 hour after dosing of Optison. Patients were followed for the development of any serious adverse event (SAE), defined as an event that causes death, is life threatening, requires or prolongs hospitalization, or causes another important event, for 24 hours after Optison administration. RESULTS: A total of 1,039 patients were enrolled, and 76% had 24-hour follow-up. The median age was 60 years (range, 20-97 years), and 62% were men. The mean body mass index was 33 +/- 9 kg/m2. Patient comorbidities included hypertension (73%), hyperlipidemia (64%), smoking (52%), and diabetes (37%). There were significant increases in systolic blood pressure, heart rate, and respiratory rate between the baseline, 5- to 15-min, 30-

min, and 60-min time points after the administration of Optison in patients undergoing stress studies but none in those undergoing rest studies. There was a total of six SAEs during the study, which were felt to be related not to Optison but rather to the stress test itself or to the patient's underlying pathology. Although two events were classified as SAEs because of hospitalization, the hospitalizations were appropriate for pathology that would have been missed without Optison use. CONCLUSIONS: In this large, prospective safety study of Optison during routine resting and stress echocardiography, no SAEs related to Optison developed. Optison helped define abnormalities that required appropriate hospitalization for further management.

Whitworth, L. A., & Burchiel, K. J. (2012). *Deep brain stimulation in movement disorders: Parkinson's disease, essential tremor, and dystonia* Elsevier Inc.

Wiener, R. S., Ouellette, D. R., Diamond, E., Fan, V. S., Maurer, J. R., Mularski, R. A., et al. (2014). An official american thoracic Society/American college of chest physicians policy statement: The choosing wisely top five list in adult pulmonary medicine. *Chest, 145*(6), 1383-1391.
The American Board of Internal Medicine Foundation's Choosing Wisely campaign aims to curb health-care costs and improve patient care by soliciting lists from medical societies of the top five tests or treatments in their specialty that are used too frequently and inappropriately. The American Thoracic Society (ATS) and American College of Chest Physicians created a joint task force, which produced a top five list for adult pulmonary medicine. Our top five recommendations, which were approved by the executive committees of the ATS and American College of Chest Physicians and published by Choosing Wisely in October 2013, are as follows: (1) Do not perform CT scan surveillance for evaluation of indeterminate pulmonary nodules at more frequent intervals or for a longer period of time than recommended by established guidelines; (2) do not routinely offer pharmacologic treatment with advanced vasoactive agents approved only for the management of pulmonary arterial hypertension to patients with pulmonary hypertension resulting from left heart disease or hypoxemic lung diseases (groups II or III pulmonary hypertension); (3) for patients recently discharged on supplemental home oxygen following hospitalization for an acute illness, do not renew the prescription without assessing the patient for ongoing hypoxemia; (4) do not perform chest CT angiography to

evaluate for possible pulmonary embolism in patients with a low clinical probability and negative results of a highly sensitive D-dimer assay; (5) do not perform CT scan screening for lung cancer among patients at low risk for lung cancer. We hope pulmonologists will use these recommendations to stimulate frank discussions with patients about when these tests and treatments are indicated - and when they are not. © 2014 American College of Chest Physicians.

Willis, D. L., Flaig, T. W., Hansel, D. E., Milowsky, M. I., Grubb, R. L., Al-Ahmadie, H. A., et al. (2014). Micropapillary bladder cancer: Current treatment patterns and review of the literature. *Urologic Oncology,*

OBJECTIVES: No guidelines exist for the management of micropapillary bladder cancer (MPBC) and most reports of this variant of urothelial carcinoma are case series comprising small numbers of patients. We sought to determine current practice patterns for MPBC using a survey sent to the Society of Urologic Oncology (SUO) and to present those results in the setting of a comprehensive review of the existing literature. MATERIALS AND METHODS: A survey developed by the Translational Science Working Group of the Bladder Cancer Advocacy Network-sponsored Think Tank meeting was distributed to members of the SUO. The results from 118 respondents were analyzed and presented with a literature review. RESULTS: Most survey respondents were urologists, with 80% considering bladder cancer their primary area of interest. Although 78% of the respondents reported a dedicated genitourinary pathologist at their institution, there were discrepant opinions on how a pathologic diagnosis of MPBC is determined as well as variability on the proportion of MPBC that is clinically significant. Among them, 78% treat MPBC differently than conventional urothelial carcinoma, with 81% reporting that they would treat cT1 MPBC with upfront radical cystectomy. However, the respondents had split opinions regarding the sensitivity of MPBC to cisplatin-based chemotherapy, which affected utilization of neoadjuvant chemotherapy in muscle-invasive disease. CONCLUSIONS: The management of MPBC is diverse among members of the SUO. Although most favors early cystectomy for cT1 MPBC, there is no consensus on the use of neoadjuvant chemotherapy for muscle-invasive MPBC.

Winters-Stone, K. M., Neil, S. E., & Campbell, K. L. (2014). Attention to principles of exercise training: A review of exercise studies for survivors of cancers other than breast. *British Journal of Sports*

*Medicine, 48*(12), 987-995.

Objectives: Randomised controlled trials (RCTs) can evaluate how well a particular exercise programme reduces cancer treatment-related side effects. Adequate design and reporting of the exercise prescription employed in RCTs is central to interpreting study findings and translating effective interventions into practice. Our previous review on the quality and reporting of exercise prescriptions in RCTs in breast cancer survivors revealed several inadequacies. This review similarly evaluates exercise prescriptions used in RCTs in patients with cancers other than the breast. Methods: The literature was searched for RCTs in persons diagnosed with a cancer other than breast. Data were extracted to evaluate the attention to the principles of exercise training in the study design and the reporting of and adherence to the exercise prescription used for the intervention. Results: Of the 33 studies reviewed, none attended to all of the exercise training principles. Specificity was applied by 89%, progression by 26%, overload by 37%, initial values by 26%, diminishing returns by 9% and reversibility by 3%. Only 2 of 33 studies (6%) reported both the exercise prescription in full and adherence to each individual component of the prescription. Conclusions: Application of the principles of training in exercise RCTs of non-breast cancer survivors was incomplete and inconsistent. Given these observations, interpretation of findings from the reviewed studies should consider potential shortcomings in intervention design. Though the prescribed exercise programme was often described, adherence to the entire prescription was rarely reported providing a less accurate picture of dose-response and challenges in translating programmes to community settings.

Winthrop, K. L., Yamanaka, H., Valdez, H., Mortensen, E., Chew, R., Krishnaswami, S., et al. (2014). Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. *Arthritis & Rheumatology (Hoboken, N.J.),*

Objective. Patients with rheumatoid arthritis (RA) are at increased risk for herpes zoster (HZ) (i.e., "shingles"). It is unknown if tofacitinib increases HZ risk. Methods. We identified HZ cases, reported by trial investigators, from Phase 2, 3, and long-term extension (LTE) clinical trial databases of the tofacitinib RA development program. We calculated HZ crude incidence rates (IRs) per 100 patient-years (pt-yrs) (95% CI) by exposure group and used logistic regression to evaluate potential risk factors for HZ (e.g., age, prednisone use). Results. Among 4789

participants, 239 tofacitinib-associated HZ cases were identified during Phases 2, 3, and LTE, of which 208 (87%) were female with median age 57 years (range, 21-75 years). One (0.4%) case was multi-dermatomal; none involved visceral dissemination or death. Twenty-four (10%) patients with HZ permanently discontinued tofacitinib and 16 (7%) were either hospitalized or received intravenous anti-viral drugs. The crude HZ IR across the development program was 4.4/100 pt-yrs (95% CI 3.8-4.9), but was substantially higher within Asia (7.7/100 pt-yrs [95% CI 6.4-9.3]). Older age was associated with HZ (OR 1.9 [95% CI 1.5-2.6]), and IRs were similar between 5 mg (4.4/100 pt-yrs [95% CI 3.2-6.0]) and 10 mg BID groups (4.2/100 pt-yrs [95% CI 3.1-5.8]). In Phase 3 trials among placebo recipients, HZ incidence was 1.5/100 pt-yrs (95% CI 0.5-4.6). Conclusions. In the tofacitinib RA development program, increased HZ rates were observed with tofacitinib compared with placebo, particularly among patients within Asia. Complicated HZ among tofacitinib-treated patients was rare. (c) 2014 American College of Rheumatology.

Woodham, M., Woodham, A., Skeate, J. G., & Freeman, M. (2014). Long-term lumbar multifidus muscle atrophy changes documented with magnetic resonance imaging: A case series. *Journal of Radiology Case Reports, 8*(5), 27-34.

A retrospective case series of three patients with chronic low back pain who received baseline MRI scans revealing multifidus muscle atrophy with fatty replacement is provided. Each patient received spinal manipulative therapy, and two were compliant with low back exercises targeting the multifidus. A follow-up scan performed >1 year later was compared to the baseline scan revealing a decrease in atrophy with fatty replacement in the two patients who performed multifidus-focused low back exercises (15% and 39% on the left and 7% and 32% on the right respectively), and an increase in the patient who underwent spinal manipulation alone (41% and 53%). Interestingly, the decrease in atrophy in the two patients that performed the exercises correlated to functional improvements. Though limited, these results highlight the utility of MRI in quantifying positive and negative long-term changes in multifidus atrophy, which may be an indicator of recovery in chronic low back pain patients.

Wright, A., Ash, J. S., Erickson, J. L., Wasserman, J., Bunce, A., Stanescu, A., et al. (2014). A qualitative study of the activities performed by people involved in clinical decision support: Recommended practices for success. *Journal of the American Medical Informatics Association, 21*(3), 464-472.

Objective: To describe the activities performed by people involved in clinical decision support (CDS) at leading sites. Materials and methods: We conducted ethnographic observations at seven diverse sites with a history of excellence in CDS using the Rapid Assessment Process and analyzed the data using a series of card sorts, informed by Linstone's Multiple Perspectives Model. Results: We identified 18 activities and grouped them into four areas. Area 1: Fostering relationships across the organization, with activities (a) training and support, (b) visibility/presence on the floor, (c) liaising between people, (d) administration and leadership, (e) project management, (f ) cheerleading/buy-in/sponsorship, (g) preparing for CDS implementation. Area 2: Assembling the system with activities (a) providing technical support, (b) CDS content development, (c) purchasing products from vendors (d) knowledge management, (e) system integration. Area 3: Using CDS to achieve the organization's goals with activities (a) reporting, (b) requirements-gathering/specifications, (c) monitoring CDS, (d) linking CDS to goals, (e) managing data. Area 4: Participation in external policy and standards activities (this area consists of only a single activity). We also identified a set of recommendations associated with these 18 activities. Discussion: All 18 activities we identified were performed at all sites, although the way they were organized into roles differed substantially. We consider these activities critical to the success of a CDS program. Conclusions: A series of activities are performed by sites strong in CDS, and sites adopting CDS should ensure they incorporate these activities into their efforts.

Xu, T., Stephane, M., & Parhi, K. K. (2013). Schizophrenia classification with single-trial MEG during language processing. *2013 47th Asilomar Conference on Signals, Systems and Computers,* Pacific Grove, CA. pp. 354-357.

Language disorder is a core symptom associated with schizophrenia. This study investigates schizophrenia classification based on brain activity during language processing. 6 healthy controls and 6 schizophrenia patients were instructed to read words and sentences silently while 248

channel magnetoencephalography (MEG) signals were recorded. For each trial, power spectral features were extracted in 8 frequency bands from all channels which form a spectral-spatial feature set. Top features ranked by F-score were fed into machine learning based classifiers for patient and control classification. Following cross validation procedure, 98.94% and 99.78% accuracies were achieved in classifying 470 word trials and 450 sentence trials, respectively. The high accuracy indicates abnormalities of brain activity during language processing in patient group and show that MEG patterns reflecting such abnormalities can be used to discriminate schizophrenia patients from healthy subjects. The proposed scheme may have potential application in schizophrenia diagnosis and classifying other mental diseases. © 2013 IEEE.

Ying, G. S., Kim, B. J., Maguire, M. G., Huang, J., Daniel, E., Jaffe, G. J., et al. (2014). Sustained visual acuity loss in the comparison of age-related macular degeneration treatments trials. *JAMA Ophthalmology,*

IMPORTANCE Although anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration (AMD) results in improved vision overall, loss of substantial vision can occur. Understanding the processes that lead to loss of vision may lead to preventive strategies. OBJECTIVE To determine the incidence, characteristics, causes, and baseline predictors of sustained visual acuity loss after 2 years of treatment with ranibizumab or bevacizumab for neovascular AMD. DESIGN, SETTING, AND PARTICIPANTS A cohort study within a randomized clinical trial of participants in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). INTERVENTIONS Participants were randomly assigned to treatment with ranibizumab or bevacizumab and to 2 years of monthly or as needed injections or monthly injections for 1 year and as needed injections the following year. MAIN OUTCOMES AND MEASURES Sustained visual acuity loss, defined as loss of 15 or more letters from baseline at weeks 88 and 104. RESULTS Among 1030 participants, 61 eyes (5.9%) developed sustained visual acuity loss in 2 years. Within this group, visual acuity decreased gradually over time, with a mean decrease of 2, 19, and 33 letters from baseline at 4 weeks, 1 year, and 2 years, respectively. At 2 years, eyes with sustained visual acuity loss had more scarring (60.0% vs 41.4%, P = .007), more geographic atrophy (GA) (31.6% vs 20.7%, P = .004), larger lesions (16 vs 8 mm2, P 4-disc area vs </=1-disc area, 3.91; 95% CI, 1.70-9.03; P = .007), and

bevacizumab treatment (OR, 1.83; 95% CI, 1.07-3.14; P = .03). CONCLUSIONS AND RELEVANCE Sustained visual acuity loss was relatively rare in CATT. The development of foveal scar, pigmentary abnormalities, or GA contributed to most of the sustained visual acuity loss. Risk was 3% higher among eyes treated with bevacizumab. Treatment that targeted the prevention of scarring or GA may improve vision outcomes. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00593450.

Zackowski, K. M., Cameron, M., & Wagner, J. M. (2014). 2nd international symposium on gait and balance in multiple sclerosis: Interventions for gait and balance in MS. *Disability and Rehabilitation, 36*(13), 1128-1132.

Purpose: To provide a review of the 2nd International Symposium on Gait and Balance in Multiple Sclerosis (MS), emphasizing interventions in gait and balance for people with MS. Method: Review of current research on interventions used with people having MS and with people having other disorders that may provide novel insights into improving gait and balance and preventing falls in people with MS (pwMS). Results: Nine speakers provided evidence-based recommendations for interventions aimed at improving gait and balance dysfunction. Speaker recommendations covered the following areas: balance rehabilitation, self-management, medications, functional electrical stimulation, robotics, sensory augmentation, gait training with error feedback and fall prevention. Conclusions: The causes of gait and balance dysfunction in pwMS are multifactorial and therefore may benefit from a wide range of interventions. The symposium provides avenues for exchange of evidence and clinical experience that is critical in furthering physical rehabilitation including gait and balance dysfunction in MS.Implications for RehabilitationApproaches to improve Gait and Balance dysfunction in Multiple Sclerosis.Balance exercises that include training of sensory strategies.Self-management and self-management support.Pharmacologic intervention, such as Dalfampradine.Functional electrical stimulation that may provide the extra stimulation to influence coordinated leg movements needed for walking. 

Zebrack, B., Kwak, M., Salsman, J., Cousino, M., Meeske, K., Aguilar, C., et al. (2014). The relationship between posttraumatic stress and posttraumatic growth among adolescent and

young adult (AYA) cancer patients. *Psycho-Oncology,*

Objective: Theories of posttraumatic growth suggest that some degree of distress is necessary to stimulate growth; yet, investigations of the relationship between stress and growth following trauma are mixed. This study aims to understand the relationship between posttraumatic stress symptoms and posttraumatic growth in adolescent and young adult (AYA) cancer patients. Method: 165 AYA patients aged 14-39 years at diagnosis completed standardized measures of posttraumatic stress and posttraumatic growth at 12months following diagnosis. Locally weighted scatterplot smoothing and regression were used to examine linear and curvilinear relationships between posttraumatic stress and posttraumatic growth. Results: No significant relationships between overall posttraumatic stress severity and posttraumatic growth were observed at 12-month follow-up. However, curvilinear relationships between re-experiencing (a posttraumatic stress symptom) and two of five posttraumatic growth indicators (New Possibilities, Personal Strengths) were observed. Conclusion: Findings suggest that re-experiencing is associated with some aspects of posttraumatic growth but not others. Although re-experiencing is considered a symptom of posttraumatic stress disorder, it also may represent a cognitive process necessary to achieve personal growth for AYAs. Findings call into question the supposed psychopathological nature of re-experiencing and suggest that re-experiencing, as a cognitive process, may be psychologically adaptive. Opportunities to engage family, friends, cancer survivors, or health care professionals in frank discussions about fears, worries, or concerns may help AYAs re-experience cancer in a way that enhances their understanding of what happened to them and contributes to positive adaptation to life after cancer. © 2014 John Wiley & Sons, Ltd.

Zelnick, L. R., Morrison, L. J., Devlin, S. M., Bulger, E. M., Brasel, K. J., Sheehan, K., et al. (2014). Addressing the challenges of obtaining functional outcomes in traumatic brain injury research: Missing data patterns, timing of follow-up, and three prognostic models. *Journal of Neurotrauma, 31*(11), 1029-1038.

Traumatic brain injury (TBI) is common and debilitating. Randomized trials of interventions for TBI ideally assess effectiveness by using long-term functional neurological outcomes, but such outcomes are difficult to obtain and costly. If there is little change between functional status at hospital discharge versus 6 months, then shorter-term outcomes may be adequate for use in

future clinical trials. Using data from a previously published multi-center, randomized, placebo-controlled TBI clinical trial, we evaluated patterns of missing outcome data, changes in functional status between hospital discharge and 6 months, and three prognostic models to predict long-term functional outcome from covariates available at hospital discharge (functional measures, demographics, and injury characteristics). The Resuscitation Outcomes Consortium Hypertonic Saline trial enrolled 1282 TBI patients, obtaining the primary outcome of 6-month Glasgow Outcome Score Extended (GOSE) for 85% of patients, but missing the primary outcome for the remaining 15%. Patients with missing outcomes had less-severe injuries, higher neurological function at discharge (GOSE), and shorter hospital stays than patients whose GOSE was obtained. Of 1066 (83%) patients whose GOSE was obtained both at hospital discharge and at 6-months, 71% of patients had the same dichotomized functional status (severe disability/death vs. moderate/no disability) after 6 months as at discharge, 28% had an improved functional status, and 1% had worsened. Performance was excellent (C-statistic between 0.88 and 0.91) for all three prognostic models and calibration adequate for two models (p values, 0.22 and 0.85). Our results suggest that multiple imputation of the standard 6-month GOSE may be reasonable in TBI research when the primary outcome cannot be obtained through other means. 

Zhao, N., Zhang, A. S., Worthen, C., Knutson, M. D., & Enns, C. A. (2014). An iron-regulated and glycosylation-dependent proteasomal degradation pathway for the plasma membrane metal transporter ZIP14. *Proceedings of the National Academy of Sciences of the United States of America, 111*(25), 9175-9180.

Protein degradation is instrumental in regulating cellular function. Plasma membrane proteins targeted for degradation are internalized and sorted to multivesicular bodies, which fuse with lysosomes, where they are degraded. ZIP14 is a newly identified iron transporter with multitransmembrane domains. In an attempt to dissect the molecular mechanisms by which iron regulates ZIP14 levels, we found that ZIP14 is endocytosed, extracted from membranes, deglycosylated, and degraded by proteasomes. This pathway did not depend on the retrograde trafficking to the endoplasmic reticulum and thus did not involve the well-defined endoplasmic reticulum-associated protein degradation pathway. Iron inhibited membrane extraction of

internalized ZIP14, resulting in higher steady-state levels of ZIP14. Asparagine-linked (N-linked) glycosylation of ZIP14, particularly the glycosylation at N102, was required for efficient membrane extraction of ZIP14 and therefore is necessary for its iron sensitivity. These findings highlight the importance of proteasomes in the degradation of endocytosed plasma membrane proteins.

Zhu, W., Libal, N. L., Casper, A., Bodhankar, S., Offner, H., & Alkayed, N. J. (2014). Recombinant T cell receptor ligand treatment improves neurological outcome in the presence of tissue plasminogen activator in experimental ischemic stroke. *Translational Stroke Research,* RTL1000 is a partial human MHC molecule coupled to a human myelin peptide. We previously demonstrated that RTL1000 was protective against experimental ischemic stroke in HLA-DR2 transgenic (DR2-Tg) mice. Since thrombolysis with recombinant tissue plasminogen activator (t-PA) is a standard therapy for stroke, we determined if RTL1000 efficacy is altered when combined with t-PA in experimental stroke. Male DR2-Tg mice underwent 60 min of intraluminal middle cerebral artery occlusion (MCAO). t-PA or vehicle was infused intravenously followed by either a single or four daily subcutaneous injections of RTL1000 or vehicle. Infarct size was measured by 2, 3, 5-triphenyltetrazolium chloride staining at 24 or 96 h of reperfusion. Our data showed that t-PA alone reduced infarct size when measured at 24 h but not at 96 h after MCAO. RTL1000 alone reduced infarct size both at 24 and 96 h after MCAO. Combining RTL1000 with t-PA did not alter its ability to reduce infarct size at either 24 or 96 h after MCAO and provides additional protection in t-PA treated mice at 24 h after ischemic stroke. Taken together, RTL1000 treatment alone improves outcome and provides additional protection in t-PA-treated mice in experimental ischemic stroke.