

## References

Adamus, G., Bonnah, R., Brown, L., & David, L. (2013). Detection of autoantibodies against heat shock proteins and collapsin response mediator proteins in autoimmune retinopathy. *BMC Ophthalmology*, 13(1) doi:10.1186/1471-2415-13-48

Background: Autoimmune retinopathy (AR) and Cancer-Associated Retinopathy (CAR) are associated with a diverse repertoire of anti-retinal autoantibodies (AABs) but not all antigenic targets have been characterized. Identification of new AABs may help with clinical diagnosis and prognosis of retinal dysfunction in AR. The goal was to identify frequently targeted retinal autoantigens within the 60-70-kDa molecular weight range. Methods. Human retinal proteins were separated by SDS-PAGE and 2D gel electrophoresis (2-DE) and sera from AR patients with and without cancer were used to identify immunoreactive proteins by Western blotting. Proteins were identified following separation by electrophoresis, Coomassie staining using in-gel trypsin digestion and mass spectrometric analysis. Circulating serum hsp60 and anti-hsp60 antibody levels were determined by quantitative ELISA. Results: Retrospective evaluation of 819 patients with anti-retinal AABs showed that 29% patients had AABs targeted proteins between 60-70-kDa. Shotgun mass spectrometry of human retinal proteins present in 1D-gel found 66 species within this range. To identify the immunoreactive proteins, we performed Western blots of 2-DE gels and showed a group of heat shock proteins (hsps), including hsp60 and CRMP proteins that were frequently recognized by AR patient AABs, irrespective of cancer status. These results were validated by immunostaining of purified hsp60 and CRMP2 proteins. ELISA results revealed that patients with AR and CAR had significantly increased levels of serum anti-hsp60 antibodies compared to control healthy subjects ( $p < 0.0001$ ). However, circulating hsp60 protein was not significantly elevated in sera of either patient group. Conclusions: Different anti-retinal antibodies frequently co-exist in a single patient, creating antibody-arrays related to the syndrome. Hsps and CRMP-2 are newly identified autoantigens in AR. A frequent co-association of anti-hsp antibodies with other anti-retinal AABs may augment pathogenic processes, leading to retinal degeneration. © 2013 Adamus et al.; licensee BioMed Central Ltd.

Adamus, G., & Wilson, D. J. (2013). Detection of antiretinal autoantibodies in serum by Western blotting. *JAMA Ophthalmology*, *131*(10), 1371. doi:10.1001/jamaophthalmol.2013.4588; 10.1001/jamaophthalmol.2013.4588

Al-Bustani, S. S., & Bell, R. B. (2013). *Scar Revision* John Wiley & Sons, Inc. doi:10.1002/9781118704677.ch11

Ali, A., & Rosenbaum, J. T. (2013). TINU (Tubulointerstitial Nephritis Uveitis) Can Be Associated with Chorioretinal Scars. *Ocular Immunology and Inflammation*, doi:10.3109/09273948.2013.841624  
Abstract 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.

Allott, E. H., Abern, M. R., Gerber, L., Keto, C. J., Aronson, W. J., Terris, M. K., . . . Freedland, S. J. (2013). Metformin does not affect risk of biochemical recurrence following radical prostatectomy: results from the SEARCH database. *Prostate Cancer and Prostatic Diseases*, doi:10.1038/pcan.2013.48  
Background: While epidemiologic studies suggest that metformin use among diabetics may decrease prostate cancer (PC) incidence, the effect of metformin use on PC outcome is unclear. We investigated the association between pre-operative metformin use, dose and duration of use and biochemical recurrence (BCR) in PC patients with diabetes who underwent radical prostatectomy (RP). Methods: We conducted a retrospective cohort analysis within the Shared Equal Access Regional Cancer Hospital (SEARCH) database of 371 PC patients with diabetes who underwent RP. Time to BCR between metformin users and non-users, and by metformin dose and duration of use was assessed using multivariable Cox proportional analysis adjusted for demographic, clinical and/or pathologic features. Time to castrate-resistant PC (CRPC), metastases and PC-specific mortality were explored as secondary outcomes using unadjusted analyses. Results: Of 371 diabetic men, 156 (42%) were using metformin before RP. Metformin

use was associated with more recent year of surgery ( $P < 0.0001$ ) but no clinical or pathologic characteristics. After adjustment for year of surgery, clinical and pathologic features, there were no associations between metformin use (hazard ratio (HR) 0.93; 95% confidence interval (CI) 0.61-1.41), high metformin dose (HR 0.96; 95% CI 0.57-1.61) or duration of use (HR 1.00; 95% CI 0.99-1.02) and time to BCR. A total of 14 patients (3.8%) developed CRPC, 10 (2.7%) distant metastases and 8 (2.2%) died from PC. Unadjusted analysis suggested that high metformin dose vs non-use was associated with increased risk of CRPC (HR 5.1; 95% CI 1.6-16.5), metastases (HR 4.8; 95% CI 1.2-18.5) and PC-specific mortality (HR 5.0; 95% CI 1.1-22.5).

Conclusions: Metformin use, dose or duration of use was not associated with BCR in this cohort of diabetic PC patients treated with RP. The suggestion that higher metformin dose was associated with increased risk of CRPC, metastases and PC-specific mortality merits testing in large prospective studies with longer follow-up. Prostate Cancer and Prostatic Disease advance online publication, 8 October 2013; doi:10.1038/pcan.2013.48.

Alt, J. A., Sautter, N. B., Mace, J. C., Detwiller, K. Y., & Smith, T. L. (2013). Antisomnogenic cytokines, quality of life, and chronic rhinosinusitis: A pilot study. *The Laryngoscope*, doi:10.1002/lary.24412; 10.1002/lary.24412

OBJECTIVES/HYPOTHESIS: Sleep disturbance, reduced quality of life (QOL), and other components of "sickness behavior" in patients with chronic rhinosinusitis (CRS) are poorly understood. These complex changes in central behavior are due to the effects of immune mediators acting in the brain. We hypothesized that immune mediators that have been associated with CRS are also associated with sickness behavior, somnifacient complaints, and CRS disease-specific QOL. STUDY DESIGN: Pilot study. METHODS: Twenty patients with CRS were prospectively enrolled and completed the Pittsburgh Sleep Quality Index (PSQI), disease-specific QOL, and olfactory instruments. Ethmoid mucosa was obtained and reverse transcription-polymerase chain reaction was performed for the cytokines interleukin (IL)-4, -13, and transforming growth factor-beta (TGF-beta). Average change in crossover threshold was calculated, and differences in gene expression were correlated with sleep quality, CRS-specific QOL, and disease severity. RESULTS: Patients with CRS reported overall poor sleep quality and poor CRS-specific QOL with significant correlations between them. Increased expression of TGF-

beta ( $r = -0.443$ ;  $P = .050$ ) and IL-4 ( $r = -0.548$ ;  $P = .012$ ) correlated with sleep dysfunction, whereas IL-13 expression was linearly associated with worse sleep quality (PSQI scores  $r = -0.417$ ;  $P = .075$ ). IL-4 and TGF-beta expression was not associated with CRS disease severity or QOL, whereas significantly higher levels of IL-13 expression correlated with worse CRS disease severity and QOL. CONCLUSIONS: Patients with CRS exhibited behavioral changes commonly referred to as sickness behavior, which include poor sleep quality and reduced QOL. The upregulation of IL-4 and TGF-beta may contribute to inflammatory brain-mediated effects on sleep quality, whereas IL-13 may be a pleiotropic signaling molecule influencing sleep, QOL, and CRS disease severity. LEVEL OF EVIDENCE: 2b Laryngoscope, 2013.

Ames, C. P., Smith, J. S., Scheer, J. K., Shaffrey, C. I., Lafage, V., Deviren, V., . . . Schwab, F. J. (2013). A standardized nomenclature for cervical spine soft-tissue release and osteotomy for deformity correction. *Journal of Neurosurgery: Spine*, 19(3), 269-278.

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Object. Cervical spine osteotomies are powerful techniques to correct rigid cervical spine deformity. Many variations exist, however, and there is no current standardized system with which to describe and classify cervical osteotomies. This complicates the ability to compare outcomes across procedures and studies. The authors' objective was to establish a universal nomenclature for cervical spine osteotomies to provide a common language among spine surgeons. Methods. A proposed nomenclature with 7 anatomical grades of increasing extent of bone/soft tissue resection and de-stabilization was designed. The highest grade of resection is termed the major osteotomy, and an approach modifier is used to denote the surgical approach(es), including anterior (A), posterior (P), anterior-posterior (AP), posterior-anterior (PA), anterior-posterior-anterior (APA), and posterior-anterior-posterior (PAP). For cases in which multiple grades of osteotomies were performed, the highest grade is termed the major osteotomy, and lower-grade osteotomies are termed minor osteotomies. The nomenclature was evaluated by 11 reviewers through 25 different radiographic clinical cases. The review was performed twice, separated by a minimum 1-week interval. Reliability was assessed using Fleiss kappa coefficients. Results. The average intrarater reliability was classified as "almost perfect agreement" for the major osteotomy (0.89 [range 0.60-1.00]) and approach modifier (0.99

[0.95-1.00]); it was classified as "moderate agreement" for the minor osteotomy (0.73 [range 0.41-1.00]). The average interrater reliability for the 2 readings was the following: major osteotomy, 0.87 ("almost perfect agreement"); approach modifier, 0.99 ("almost perfect agreement"); and minor osteotomy, 0.55 ("moderate agreement"). Analysis of only major osteotomy plus approach modifier yielded a classification that was "almost perfect" with an average intrarater reliability of 0.90 (0.63-1.00) and an interrater reliability of 0.88 and 0.86 for the two reviews. Conclusions. The proposed cervical spine osteotomy nomenclature provides the surgeon with a simple, standard description of the various cervical osteotomies. The reliability analysis demonstrated that this system is consistent and directly applicable. Future work will evaluate the relationship between this system and health-related quality of life metrics. © AANS, 2013.

Anderson, E. D., Horak, F. B., Lasarev, M. R., & Nutt, J. G. (2013). Performance of a motor task learned on levodopa deteriorates when subsequently practiced off. *Movement Disorders : Official Journal of the Movement Disorder Society*, doi:10.1002/mds.25702; 10.1002/mds.25702

Studies in animals and in people with Parkinson's disease (PD) demonstrate complex effects of dopamine on learning motor tasks; its effect on retention of motor learning has received little attention. Recent animal studies demonstrate that practicing a task in the off state, when initially learned in the on state, leads to progressive deterioration in performance. We measured the acquisition and retention of 3 different motor tasks in the presence and absence of levodopa. Twenty individuals with Hoehn and Yahr Stage 1.5 to 3 PD practiced the tasks daily for two 4-day weeks, one half practicing on l-dopa the first week and off the second week. The other half practiced off l-dopa both weeks. The tasks were (1) alternate tapping of 2 keys, (2) moving the body toward 2 targets on a posturography device, and (3) mirror drawing of a star. For the tapping and body movement tests, those who practiced on the first week had a progressive decline in performance with practice during week 2, while subjects off during week 1 maintained or improved. In contrast, for the mirror task, subjects on l-dopa initially had much more difficulty completing the task compared to subjects who practiced off. Both groups improved with practice the first week and had flat performance the second week. These data suggest that performance of speed-accuracy tasks learned in the on state may progressively worsen if subsequently

practiced in the off state. In addition, performance, but not learning, of some tasks may be impeded by l-dopa. (c) 2013 International Parkinson and Movement Disorder Society.

Antonio, T., Childers, S. R., Rothman, R. B., Dersch, C. M., King, C., Kuehne, M., . . . Alper, K. (2013).

Effect of Iboga Alkaloids on  $\mu$ -Opioid Receptor-Coupled G Protein Activation. *Plos One*, 8(10)

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**Objective:**The iboga alkaloids are a class of small molecules defined structurally on the basis of a common ibogamine skeleton, some of which modify opioid withdrawal and drug self-administration in humans and preclinical models. These compounds may represent an innovative approach to neurobiological investigation and development of addiction pharmacotherapy. In particular, the use of the prototypic iboga alkaloid ibogaine for opioid detoxification in humans raises the question of whether its effect is mediated by an opioid agonist action, or if it represents alternative and possibly novel mechanism of action. The aim of this study was to independently replicate and extend evidence regarding the activation of  $\mu$ -opioid receptor (MOR)-related G proteins by iboga alkaloids.**Methods:**Ibogaine, its major metabolite noribogaine, and 18-methoxycoronaridine (18-MC), a synthetic congener, were evaluated by agonist-stimulated guanosine-5-O-( $\gamma$ -thio)-triphosphate ([<sup>35</sup>S]GTP $\gamma$ S) binding in cells overexpressing the recombinant MOR, in rat thalamic membranes, and autoradiography in rat brain slices.**Results And Significance:**In rat thalamic membranes ibogaine, noribogaine and 18-MC were MOR antagonists with functional  $K_e$  values ranging from 3  $\mu$ M (ibogaine) to 13  $\mu$ M (noribogaine and 18MC). Noribogaine and 18-MC did not stimulate [<sup>35</sup>S]GTP $\gamma$ S binding in Chinese hamster ovary cells expressing human or rat MORs, and had only limited partial agonist effects in human embryonic kidney cells expressing mouse MORs. Ibogaine did not did not stimulate [<sup>35</sup>S]GTP $\gamma$ S binding in any MOR expressing cells. Noribogaine did not stimulate [<sup>35</sup>S]GTP $\gamma$ S binding in brain slices using autoradiography. An MOR agonist action does not appear to account for the effect of these iboga alkaloids on opioid withdrawal. Taken together with existing evidence that their mechanism of action also differs from that of other non-opioids with clinical effects on opioid tolerance and withdrawal, these findings suggest a novel mechanism of action, and further justify the search for alternative targets of iboga alkaloids. © 2013 Antonio et al.

Banerjee, A., Wang, J., Bodhankar, S., Vandembark, A. A., Murphy, S. J., & Offner, H. (2013).

Phenotypic Changes in Immune Cell Subsets Reflect Increased Infarct Volume in Male vs. Female Mice. *Translational Stroke Research*, 4(5), 554-563. doi:10.1007/s12975-013-0268-z

Inflammatory responses in the brain after cerebral ischemia have been studied extensively in male mice, but not female mice, thus potentially giving a less-than-accurate view of gender associated pathological processes. In humans, cerebral infarcts are typically smaller in premenopausal females than in age-matched males. In the current study, we confirmed smaller infarcts in female vs. male mice after middle cerebral artery occlusion and 96 h of reperfusion. Moreover, we explored immunological alterations related to this difference and found that the percentage of CD4+ T lymphocytes was significantly higher in spleens in males than females, with increased expression of the activation markers, CD69 and CD44. In contrast, the percentage of CD8+ T lymphocytes was significantly higher in spleens of females than males, leading to the identification of a small but distinct population of IL-10-secreting CD8+CD122+ suppressor T cells that were also increased in females. Finally, we observed that males have a greater percentage of activated macrophages/microglia in the brain than females, as well as increased expression of the VLA-4 adhesion molecule in both brain and spleen. This new information suggesting gender-dependent immunological mechanisms in stroke implies that effective treatments for human stroke may also be gender specific. © 2013 Springer Science+Business Media New York.

Baomin, L., Yongbing, S., & Xiangyu, C. (2013). Angioplasty and Stenting for Intractable Pulsatile Tinnitus Caused by Dural Venous Sinus Stenosis: A Case Series Report. *Otology & Neurotology : Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology*, doi:10.1097/MAO.0b013e3182990d52

OBJECTIVE: Pulsatile tinnitus caused by dural venous sinus (DVS) stenosis is a newly identified form of tinnitus. Its persistent nature can severely affect patients' sleep and quality of life, leading to depression in severe cases. The aim of this report is to investigate the efficacy and safety of angioplasty and stenting in treating this form of tinnitus. STUDY DESIGN: Retrospective review. SETTING: Chinese PLA General Hospital. METHODS: Clinical data of 46 cases of pulsatile tinnitus caused by DVS stenosis treated between December 2009 and October 2012 using

angioplasty and stenting were reviewed. Diagnosis of DVS abnormality was confirmed in all cases using digital subtraction angiography (DSA). Among these cases, stenosis was located in the transverse-sigmoid sinuses junction area ipsilateral to tinnitus in 44 cases and on both sides in the remaining 2 cases. Stenosis was treated with angioplasty and stenting in all cases. RESULTS: Pulsatile tinnitus disappeared immediately after the procedure in all 46 cases. There was no procedure-related complication. During the 2 to 36 months' follow-up, there was no recurrence. CONCLUSION: These results indicate that DVS stenosis is the cause of pulsatile tinnitus in these cases and that angioplasty and stenting are an effective and safe treatment for intractable pulsatile tinnitus caused by DVS stenosis.

Barbati, A. C., Fang, C., Banker, G. A., & Kirby, B. J. (2010). Directed growth of rat hippocampal neurons in microfluidic culture without surface patterning or chemical gradients. *14th International Conference on Miniaturized Systems for Chemistry and Life Sciences 2010, MicroTAS 2010, Groningen. , 1* 40-42.

We present a microfluidic device that controls rat hippocampal neurons without chemical surface patterning or chemical gradients and is capable of solute delivery to discrete sections of neurons with spatial and temporal resolution. Through the use of analytical expressions and computational models, we select device geometry based upon injection time, ability to confine solutes, and shear stress considerations. Preliminary results show guidance of rat hippocampal neurons within channels, response of mitochondrial transport to toxins, and theoretical solute distributions as a function of device parameters.

Barr-Gillespie, P. G., & Nicolson, T. (2013). Who needs tip links? Backwards transduction by hair cells. *The Journal of General Physiology, 142*(5), 481-486. doi:10.1085/jgp.201311111; 10.1085/jgp.201311111

Bayer, M. L., Frommelt, P. C., Blei, F., Breur, J. M. P. J., Cordisco, M. R., Frieden, I. J., . . . Drolet, B. A. (2013). Congenital Cardiac, Aortic Arch, and Vascular Bed Anomalies in PHACE Syndrome (from the International PHACE Syndrome Registry). *American Journal of Cardiology*, doi:10.1016/j.amjcard.2013.08.025

PHACE syndrome represents the association of large infantile hemangiomas of the head and neck

with brain, cerebrovascular, cardiac, ocular, and ventral or midline defects. Cardiac and cerebrovascular anomalies are the most common extracutaneous features of PHACE, and they also constitute the greatest source of potential morbidity. Congenital heart disease in PHACE is incompletely described, and this study was conducted to better characterize its features. This study of the International PHACE Syndrome Registry represents the largest central review of clinical, radiologic, and histopathologic data for cardiovascular anomalies in patients with PHACE to date. Sixty-two (41%) of 150 subjects had intracardiac, aortic arch, or brachiocephalic vessel anomalies. Aberrant origin of a subclavian artery was the most common cardiovascular anomaly (present in 31 (21%) of 150 subjects). Coarctation was the second most common anomaly, identified in 28 (19%) of 150 subjects, and can be missed clinically in patients with PHACE because of the frequent association of arch obstruction with aberrant subclavian origin. Twenty-three (37%) of 62 subjects with cardiovascular anomalies required procedural intervention. A greater percentage of hemangiomas were located on the left side of the head and neck in patients with coarctation (46% vs 39%); however, hemangioma distribution did not predict the presence of cardiovascular anomalies overall. In conclusion, PHACE is associated with a high risk of congenital heart disease. Cardiac and aortic arch imaging with detailed assessment of arch patency and brachiocephalic origins is essential for any patient suspected of having PHACE. Longitudinal investigation is needed to determine the long-term outcomes of cardiovascular anomalies in PHACE. © 2013 Elsevier Inc. All rights reserved.

Beadling, C., Patterson, J., Justusson, E., Nelson, D., Pantaleo, M. A., Hornick, J. L., . . . Heinrich, M. C. (2013). Gene expression of the IGF pathway family distinguishes subsets of gastrointestinal stromal tumors wild type for KIT and PDGFRA. *Cancer Medicine*, 2(1), 21-31.

doi:10.1002/cam4.57; 10.1002/cam4.57

Gastrointestinal stromal tumors (GISTs) arise from the interstitial cells of Cajal (ICCs) and are the most common mesenchymal neoplasm of the gastrointestinal tract. While the majority of GISTs harbor activating mutations in either the v-kit Hardy-Zuckerman feline sarcoma viral oncogene homolog (KIT) or platelet-derived growth factor receptor alpha (PDGFRA) tyrosine kinases, approximately 10-15% of adult GISTs and 85% of pediatric GISTs lack such mutations. These "wild-type" GISTs have been reported to express high levels of the insulin-like growth

factor 1 receptor (IGF1R), and IGF1R-targeted therapy of wild-type GISTs is being evaluated in clinical trials. However, it is not clear that all wild-type GISTs express IGF1R, because studies to date have predominantly focused on a particular subtype of gastric wild-type GIST that is deficient in the mitochondrial succinate dehydrogenase (SDH) complex. This study of a series of 136 GISTs, including 72 wild-type specimens, was therefore undertaken to further characterize wild-type GIST subtypes based on the relative expression of transcripts encoding IGF1R. Additional transcripts relevant to GIST biology were also evaluated, including members of the IGF-signaling pathway (IGF1, IGF2, and insulin receptor [INSR]), neural markers (CDH2[CDH: Cadherin], neurofilament, light polypeptide, LHX2 [LHX: LIM homeobox], and KIRREL3 [KIRREL: kin of IRRE like]), KIT, PDGFRA, CD34, and HIF1A. Succinate dehydrogenase complex, subunit B protein expression was also assessed as a measure of SDH complex integrity. In addition to the previously described SDH-deficient, IGF1R(high) wild-type GISTs, other SDH-intact wild-type subpopulations were defined by high relative expression of IGF1R, neural markers, IGF1 and INSR, or low IGF1R coupled with high IGF2. These results underscore the complexity and heterogeneity of wild-type GISTs that will need to be factored into molecularly-targeted therapeutic strategies.

Bednarek, P. H., & Edelman, A. B. (2011). *Contraception Following Ectopic Pregnancy, and Induced or Spontaneous Abortion* Wiley-Blackwell. doi:10.1002/9781444342642.ch24

Berry, S. A., Fleishman, J. A., Yehia, B. R., Korthuis, P. T., Agwu, A. L., Moore, R. D., & Gebo, K. A. (2013). Thirty-day hospital readmission rate among adults living with HIV. *Aids*, 27(13), 2059-2068. doi:10.1097/QAD.0b013e3283623d5f

Objective: Thirty-day hospital readmission rate is receiving increasing attention as a quality-of-care indicator. The objective of this study was to determine readmission rates and to identify factors associated with readmission among persons living with HIV. Design: Prospective multicenter observational cohort. Setting: Nine US HIV clinics affiliated through the HIV Research Network. Participants: Patients engaged in HIV care during 2005-2010. Main outcome measure(s): Readmission rate was defined as the proportion of hospitalizations followed by a readmission within 30 days. Factors in multivariate analyses included diagnostic categories,

patient demographic and clinical characteristics, and having an outpatient follow-up visit. Results: Among 11 651 total index hospitalizations, the 30-day readmission rate was 19.3%. AIDS-defining illnesses (ADIs, 9.6% of index hospitalizations) and non-AIDSdefining infections (26.4% of index hospitalizations) had readmission rates of 26.2 and 16.6%, respectively. Factors independently associated with readmission included lower CD4+ cell count [adjusted odds ratio 1.80 (1.53-2.11) for CD4+ cell count <50 vs. ≥351 cells/μl], longer length of stay [1.77 (1.53-2.04) for ≥9 days vs. 1-3 days], and several diagnostic categories including ADI. Having an outpatient follow-up clinic visit was not associated with lower readmission risk [adjusted hazard ratio 0.98 (0.88-1.08)]. Conclusion: The 19.3% readmission rate exceeds the 13.3% rate reported for the general population of 18-64-year-olds. HIV providers may use the 19.3% rate as a basis of comparison. Policymakers may consider the impact of HIV when estimating expected readmissions for a hospital or region. Preventing or recovering from severe immune dysfunction may be the most important factor to reducing readmissions. © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Bethell, C., Kemper, K. J., Gombojav, N., & Koch, T. K. (2013). Complementary and conventional medicine use among youth with recurrent headaches. *Pediatrics*, *132*(5), e1173-83.

doi:10.1542/peds.2013-1816; 10.1542/peds.2013-1816

OBJECTIVE: To identify prevalence and patterns of complementary and alternative medicine (CAM) use among youth with recurrent headaches (HA) and evaluate associations with co-occurring health problems and limitations as well as with the use and expenditures for conventional medical care. METHODS: Variables were constructed for youth aged 10 to 17 by using linked data from the 2007 National Health Interview Survey and the 2008 Medical Expenditures Panel Survey. Bivariate, logistic, and 2-part regression analyses were used. RESULTS: Of the 10.6% of youth experiencing HA, 29.6% used CAM, rising to 41% for the many HA sufferers who also experienced difficulties with emotions, concentration, behavior, school attendance, or daily activities. Biologically based products (16.2%) and mind-body therapies (13.3%) were most commonly used, especially by the 86.4% of youth with HA experiencing at least 1 other chronic condition. Compared with non-CAM users, youth with HA who used CAM also had higher expenditures for and use of most types of conventional care. CONCLUSIONS: CAM use

is most common among youth with HA experiencing multiple chronic conditions and difficulties in daily functioning. Associations among CAM use, multiple chronic conditions, and higher use of conventional care highlight the need for medical providers to routinely ask about CAM use to meet the complex health needs of their patients and facilitate the optimal integration of care. Research is needed to identify models for coordinating complementary and conventional care within a medical home and to understand the health benefits or risks associated with CAM use in conjunction with conventional treatments for patients with HA.

Bethell, C. D., Newacheck, P. W., Fine, A., Strickland, B. B., Antonelli, R. C., Wilhelm, C. L., . . . Wells, N. (2013). Optimizing Health and Health Care Systems for Children with Special Health Care Needs Using the Life Course Perspective. *Maternal and Child Health Journal*, doi:10.1007/s10995-013-1371-1

To date, life course research in maternal and child health has largely focused on elucidating fetal and early life influences on adult health and less on promoting the health of children with special health care needs (CSHCN). Consideration of life course theory (LCT) for CSHCN is especially important given their increasing prevalence and comorbidity, their disproportionate vulnerability to weaknesses or instability in the health care system, and the growing evidence linking child and adult health and quality of life. In this commentary we seek to advance the consideration of LCT for CSHCN. We (1) briefly summarize key issues and the importance of a life course approach for CSHCN; (2) present illustrative findings from population-based cross-sectional data that serve to generate hypotheses that can be more rigorously examined when population-based longitudinal data become available; and (3) discuss the application of life course principles as a driving force in the continued implementation and improvement of integrated systems of care for CSHCN.

Brennan, C. W., Verhaak, R. G. W., McKenna, A., Campos, B., Nounmehr, H., Salama, S. R., . . . Chin, L. (2013). The somatic genomic landscape of glioblastoma. *Cell*, *155*(2), 462-477. doi:10.1016/j.cell.2013.09.034

We describe the landscape of somatic genomic alterations based on multidimensional and comprehensive characterization of more than 500 glioblastoma tumors (GBMs). We identify several novel mutated genes as well as complex rearrangements of signature receptors, including

EGFR and PDGFRA. TERT promoter mutations are shown to correlate with elevated mRNA expression, supporting a role in telomerase reactivation. Correlative analyses confirm that the survival advantage of the proneural subtype is conferred by the G-CIMP phenotype, and MGMT DNA methylation may be a predictive biomarker for treatment response only in classical subtype GBM. Integrative analysis of genomic and proteomic profiles challenges the notion of therapeutic inhibition of a pathway as an alternative to inhibition of the target itself. These data will facilitate the discovery of therapeutic and diagnostic target candidates, the validation of research and clinical observations and the generation of unanticipated hypotheses that can advance our molecular understanding of this lethal cancer. © 2013 Elsevier Inc.

Brown, K. K., Viana, L. M., Helwig, C. C., Artunduaga, M. A., Quintanilla-Dieck, L., Jarrin, P., . . . Seidman, C. E. (2013). HOXA2 haploinsufficiency in dominant bilateral microtia and hearing loss. *Human Mutation, 34*(10), 1347-1351. doi:10.1002/humu.22367

Microtia is a rare, congenital malformation of the external ear that in some cases has a genetic etiology. We ascertained a three-generation family with bilateral microtia and hearing loss segregating as an autosomal dominant trait. Exome sequencing of affected family members detected only seven shared, rare, heterozygous, nonsynonymous variants, including one protein truncating variant, a HOXA2 nonsense change (c.703C>T, p.Q235\*). The HOXA2 variant was segregated with microtia and hearing loss in the family and was not seen in 6,500 individuals sequenced by the NHLBI Exome Sequencing Project or in 218 control individuals sequenced in this study. HOXA2 has been shown to be critical for outer and middle ear development through mouse models and has previously been associated with autosomal recessive bilateral microtia. Our data extend these conclusions and define HOXA2 haploinsufficiency as the first genetic cause for autosomal-dominant nonsyndromic microtia. © 2013 WILEY PERIODICALS, INC.

Brunt, V. E., Miner, J. A., Kaplan, P. F., Halliwill, J. R., Strycker, L. A., & Minson, C. T. (2013). Short-term administration of progesterone and estradiol independently alter carotid-vasomotor, but not carotid-cardiac, baroreflex function in young women. *American Journal of Physiology - Heart and Circulatory Physiology, 305*(7), H1041-H1049. doi:10.1152/ajpheart.00194.2013

The individual effects of estrogen and progesterone on baroreflex function remain poorly

understood. We sought to determine how estradiol (E2) and progesterone (P4) independently alter the carotid-cardiac and carotid-vasomotor baroreflexes in young women by using a hormone suppression and exogenous add-back design. Thirty-two young women were divided into two groups and studied under three conditions: 1) after 4 days of endogenous hormone suppression with a gonadotropin releasing hormone antagonist (control condition), 2) after continued suppression and 3 to 4 days of supplementation with either 200 mg/day oral progesterone (N = 16) or 0.1 to 0.2 mg/day transdermal 17 $\beta$ -estradiol (N = 16), and 3) after continued suppression and 3 to 4 days of supplementation with both hormones. Changes in heart rate (HR), mean arterial pressure (MAP), and femoral vascular conductance (FVC) were measured in response to 5 s of +50 mmHg external neck pressure to unload the carotid baroreceptors. Significant hormone effects on the change in HR, MAP, and FVC from baseline at the onset of neck pressure were determined using mixed model covariate analyses accounting for P4 and E2 plasma concentrations. Neither P4 (P = 0.95) nor E2 (P = 0.95) affected the HR response to neck pressure. Higher P4 concentrations were associated with an attenuated fall in FVC (P = 0.01), whereas higher E2 concentrations were associated with an augmented fall in FVC (P = 0.02). Higher E2 was also associated with an augmented rise in MAP (P = 0.01). We conclude that progesterone blunts whereas estradiol enhances carotidvasomotor baroreflex sensitivity, perhaps explaining why no differences in sympathetic baroreflex sensitivity are commonly reported between low and high combined hormone phases of the menstrual cycle. © 2013 the American Physiological Society.

Buck, K. J., Walter, N. A., & Denmark, D. L. (2013). Genetic variability of respiratory complex abundance, organization, and activity in mouse brain. *Genes, Brain, and Behavior*, doi:10.1111/gbb.12101; 10.1111/gbb.12101

Mitochondrial dysfunction is implicated in the etiology and pathogenesis of numerous human disorders involving tissues with high energy demand. Murine models are widely used to elucidate genetic determinants of phenotypes relevant to human disease, with recent studies of C57BL/6J (B6), DBA/2J (D2) and B6xD2 populations implicating naturally occurring genetic variation in mitochondrial function/dysfunction. Using blue native polyacrylamide gel electrophoresis, immunoblots, and in-gel activity analyses of complexes I, II, IV and V, our studies are the first to

assess abundance, organization, and catalytic activity of mitochondrial respiratory complexes and supercomplexes in mouse brain. Remarkable strain differences in supercomplex assembly and associated activity are evident, without differences in individual complexes I, II, III, or IV. Supercomplexes I1 III2 IV2 -3 exhibit robust complex III immunoreactivity and complex I and IV activities in D2, but with little detected in B6 for I1 III2 IV2 , and I1 III2 IV3 is not detected in B6. I1 III2 IV1 and I1 III2 are abundant and catalytically active in both strains, but significantly more so in B6. Furthermore, while supercomplex III2 IV1 is abundant in D2, none is detected in B6. In aggregate, these results indicate a shift toward more highly assembled supercomplexes in D2. Respiratory supercomplexes are thought to increase electron flow efficiency and individual complex stability, and to reduce electron leak and generation of reactive oxygen species. Our results provide a framework to begin assessing the role of respiratory complex suprastructure in genetic vulnerability and treatment for a wide variety of mitochondrial-related disorders.

Burrows, G. G., Van't Hof, W., Newell, L. F., Reddy, A., Wilmarth, P. A., David, L. L., . . . Maziarz, R. T. (2013). Dissection of the human multipotent adult progenitor cell secretome by proteomic analysis. *Stem Cells Translational Medicine*, 2(10), 745-757. doi:10.5966/sctm.2013-0031

Multipotent adult progenitor cells (MAPCs) are adult adherent stromal stem cells currently being assessed in acute graft versus host disease clinical trials with demonstrated immunomodulatory capabilities and the potential to ameliorate detrimental autoimmune and inflammation-related processes. Our previous studies documented that MAPCs secrete factors that play a role in regulating T-cell activity. Here we expand our studies using a proteomics approach to characterize and quantify MAPC secretome components secreted over 72 hours in vitro under steady-state conditions and in the presence of the inflammatory triggers interferon- $\gamma$  and lipopolysaccharide, or a tolerogenic CD74 ligand, RTL1000. MAPCs differentially responded to each of the tested stimuli, secreting molecules that regulate the biological activity of the extracellular matrix (ECM), including proteins that make up the ECM itself, proteins that regulate its construction/deconstruction, and proteins that serve to attach and detach growth factors from ECM components for redistribution upon appropriate stimulation. MAPCs secreted a wide array of proteases, some detectable in their zymogen forms. MAPCs also secreted protease inhibitors that would regulate protease activity. MAPCs secreted chemokines and cytokines that could provide

molecular guidance cues to various cell types, including neutrophils, macrophages, and T cells. In addition, MAPCs secreted factors involved in maintenance of a homeostatic environment, regulating such diverse programs as innate immunity, angiogenesis/angiostasis, targeted delivery of growth factors, and the matrix-metalloprotease cascade. © AlphaMed Press 2013.

Bykerk, V. P., Cush, J., Winthrop, K., Calabrese, L., Lortholary, O., de Longueville, M., . . . Mariette, X. (2013). Update on the safety profile of certolizumab pegol in rheumatoid arthritis: An integrated analysis from clinical trials. *Annals of the Rheumatic Diseases*, doi:10.1136/annrheumdis-2013-203660

Objective: To report the long-term safety data of certolizumab pegol (CZP) in rheumatoid arthritis (RA) accumulated as of 30 November 2011. Design: Data from 10 completed randomised controlled trials (RCT) of CZP in RA and several open-label extensions (OLE) were pooled across all doses. Reported adverse events (AE) occurred between the first dose and 84 days after the last dose. All deaths, serious infectious events (SIE) and malignancies were reviewed by external experts, classified according to predefined rules, and validated by an external steering committee. Incidence rates (IR) and event rates (ER) per 100 patient-years (PY) are presented. Results: 4049 RA patients who received CZP were included in the safety pooling; total exposure 9277 PY, mean exposure 2.1 years (range 0.04-7.6). SIE, most frequently pneumonia (IR 0.73/100 PY), were the most common serious AE, occurring more frequently in CZP compared to placebo-treated patients in RCT (IR 5.61/100 PY vs 1.35/100 PY, odds ratio (OR) 4.35, 95% CI 0.65 to 29.30). SIE rates were lower in the CZP-treated population including OLE (ER 4.33/100 PY). 44 patients developed tuberculosis (IR 0.47/100 PY), 39 from high endemic regions. 58 deaths occurred in CZP-exposed patients (IR 0.63/100 PY) and 70 developed malignancies excluding non-melanoma skin cancer (IR 0.76/100 PY), including five lymphomas (IR 0.05/100 PY). Conclusions: No new or unexpected safety signals associated with CZP emerged in this updated long-term safety analysis. While SIE rates were higher for CZP than for placebo in RCT, the rate decreased with continued exposure to CZP. These rates are consistent with data previously reported for CZP and other tumour necrosis factor inhibitors. © 2013 BMJ Publishing Group Ltd & European League Against Rheumatism.

Cahill, A. G., Caughey, A. B., Roehl, K. A., Odibo, A. O., & Macones, G. A. (2013). Terminal fetal heart decelerations and neonatal outcomes. *Obstetrics and Gynecology*, 122(5), 1070-1076.

doi:10.1097/AOG.0b013e3182a8d0b0; 10.1097/AOG.0b013e3182a8d0b0

OBJECTIVE: To describe the incidence and characteristics of terminal fetal heart rate decelerations and to estimate their association with acidemia. METHODS: A 5-year retrospective cohort study of all women with singleton, nonanomalous gestations who labored and reached complete dilation at or after 37 weeks of gestation. The 30 minutes of electronic fetal monitoring before delivery were interpreted by two formally trained research nurses, blind to clinical data, using American College of Obstetricians and Gynecologists guidelines. Terminal decelerations (decelerations without recovery of 120 seconds or more) defined the exposure. Terminal bradycardia (10 minutes or more) was secondarily explored. Univariable and multivariable analyses were performed to estimate risk of acidemia (umbilical cord gas arterial pH level 7.10 or less). RESULTS: Of 5,388 women meeting inclusion criteria, 951 (17.7%) experienced a terminal deceleration whereas 4,437 (82.3%) did not. The incidence of acidemia among the 951 women with a terminal deceleration was low (1.3%; n=12). However, acidemia (adjusted odds ratio [OR] 18.6; 95% confidence [CI] 5.0-68.9) and higher-level nursery admission (adjusted OR 5.4; 95% CI 1.9-15.3) were more likely if the terminal deceleration was 10 minutes or more. Terminal decelerations were longer among neonates with acidemia (6.7 minutes compared with 3.2 minutes;  $P < .01$ ). For every additional 120 seconds of duration beyond the first 120 seconds, there was a corresponding decrease in umbilical cord gas pH level by 0.042 (95% CI 0.040-0.048;  $P < .01$ ). CONCLUSIONS: More than 98% of term fetuses with terminal decelerations deliver with normal umbilical cord gas pH levels. However, bradycardia is associated with increased risk of acidemia and higher-level nursery admission. This information can be incorporated into clinical decision-making regarding urgency of delivery. LEVEL OF EVIDENCE: : II.

Cai, Q., Whitcomb, C., Eggleston, J., Sun, W., Salvi, R., & Hu, B. H. (2013). Round window closure affects cochlear responses to suprathreshold stimuli. *Laryngoscope*, doi:10.1002/lary.24394

Objectives/Hypothesis: The round window acts as a vent for releasing inner ear pressure and facilitating basilar membrane vibration. Loss of this venting function affects cochlear function,

which leads to hearing impairment. In an effort to identify functional changes that might be used in clinical diagnosis of round window atresia, the current investigation was designed to examine how the cochlea responds to suprathreshold stimuli following round window closure. Study Design: Prospective, controlled, animal study. Methods: A rat model of round window occlusion (RWO) was established. With this model, the thresholds of auditory brainstem responses (ABR) and the input/output (IO) functions of distortion product otoacoustic emissions (DPOAEs) and acoustic startle responses were examined. Results: Round window closure caused a mild shift in the thresholds of the auditory brainstem response ( $13.5 \pm 9.1$  dB). It also reduced the amplitudes of the distortion product otoacoustic emissions and the slope of the input/output functions. This peripheral change was accompanied by a significant reduction in the amplitude, but not the threshold, of the acoustic startle reflex, a motor response to suprathreshold sounds. Conclusions: In addition to causing mild increase in the threshold of the auditory brainstem response, round window occlusion reduced the slopes of both distortion product otoacoustic emissions and startle reflex input/output functions. These changes differ from those observed for typical conductive or sensory hearing loss, and could be present in patients with round window atresia. However, future clinical observations in patients are needed to confirm these findings. © 2013 The American Laryngological, Rhinological and Otological Society, Inc.

Cameron, M. H., Overs, S., Murchison, C., Whitham, R., Fitzpatrick, M., & Manning, J. (2013).

Dalfampridine improves walking speed, walking endurance, and community participation in veterans with multiple sclerosis: a longitudinal cohort study. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, doi:10.1177/1352458513507356

BACKGROUND: In short-term trials, dalfampridine extended release (ER) improves walking in people with multiple sclerosis (MS). The tolerability and effects of dalfampridine-ER in clinical practice have not been reported. OBJECTIVES: The objective of this paper is to determine the clinical tolerability and effects of dalfampridine on walking and community participation.

METHODS: All patients at the Portland VA Medical Center prescribed dalfampridine-ER over one year completed the Timed 25-Foot Walk (T25FW), Multiple Sclerosis Walking Scale-12 (MSWS-12), Two-Minute Timed Walk (2MTW), and Community Integration Questionnaire (CIQ) at baseline and follow-up clinic visits. Ongoing use and measures over one year were analyzed.

RESULTS: A total of 39 patients (mean age 56.5 years, mean disease duration 19.5 years, 82% male, 38% relapsing-remitting MS, 62% progressive MS) were prescribed dalfampridine-ER. Twenty-four (62%) continued to take dalfampridine-ER. At initial follow-up, all measures improved significantly from baseline (T25FW: -2.7 s,  $p = 0.004$ ; 2MTW: 41 feet (ft),  $p = 0.002$ ; MSWS12: -11,  $p < 0.001$ ; CIQ: 1.2,  $p = 0.003$ ). At one year, walking endurance and self-perceived walking were still significantly improved (2MTW: 33 ft,  $p = 0.03$ ; MSWS-12: 5.9,  $p = 0.007$ ). CONCLUSIONS: Dalfampridine-ER was associated with short-term improvements in walking speed and community participation, and sustained improvements in walking endurance and self-perceived impact of MS on walking for one year. Our study supports the utility of this medication in late MS.

Carlson, K. F., Taylor, B. C., Hagel, E. M., Cutting, A., Kerns, R., & Sayer, N. A. (2013). Headache Diagnoses Among Iraq and Afghanistan War Veterans Enrolled in VA: A Gender Comparison. *Headache*, doi:10.1111/head.12216; 10.1111/head.12216

OBJECTIVE: To examine the prevalence and correlates of headache diagnoses, by gender, among Iraq and Afghanistan War Veterans who use Department of Veterans Affairs (VA) health care. BACKGROUND: Understanding the health care needs of recent Veterans, and how these needs differ between women and men, is a priority for the VA. The potential for a large burden of headache disorders among Veterans seeking VA services exists but has not been examined in a representative sample. METHODS: We conducted a historical cohort study using national VA inpatient and outpatient data from fiscal year 2011. Participants were all ( $n = 470,215$ ) Iraq and Afghanistan War Veteran VA users in 2011; nearly 13% were women. We identified headache diagnoses using International Classification of Diseases (ICD-9) diagnosis codes assigned during one or more VA inpatient or outpatient encounters. Descriptive analyses included frequencies of patient characteristics, prevalence and types of headache diagnoses, and prevalence of comorbid diagnoses. Prevalence ratios (PR) with 95% confidence intervals (CI) were used to estimate associations between gender and headache diagnoses. Multivariate models adjusted for age and race. Additional models also adjusted for comorbid diagnoses. RESULTS: In 2011, 56,300 (11.9%) Veterans received a headache-related diagnosis. While controlling for age and race, headache diagnoses were 1.61 times more prevalent (95% CI = 1.58-1.64) among women

(18%) than men (11%). Most of this difference was associated with migraine diagnoses, which were 2.66 times more prevalent (95% CI = 2.59-2.73) among women. Cluster and post-traumatic headache diagnoses were less prevalent in women than in men. These patterns remained the same when also controlling for comorbid diagnoses, which were common among both women and men with headache diagnoses. The most prevalent comorbid diagnoses examined were depression (46% of women with headache diagnoses vs 40% of men), post-traumatic stress disorder (38% vs 58%), and back pain (38% vs 46%). CONCLUSIONS: Results of this study have implications for the delivery of post-deployment health services to Iraq and Afghanistan War Veterans. Migraine and other headache diagnoses are common among Veterans, particularly women, and tend to occur in combination with other post-deployment health conditions for which patients are being treated.

Carney, P. A., Bogart, A., Sickles, E. A., Smith, R., Buist, D. S., Kerlikowske, K., . . . Geller, B. M. (2013). Feasibility and acceptability of conducting a randomized clinical trial designed to improve interpretation of screening mammography. *Academic Radiology, 20*(11), 1389-1398. doi:10.1016/j.acra.2013.08.017; 10.1016/j.acra.2013.08.017

PURPOSE: To describe recruitment, enrollment, and participation in a study of US radiologists invited to participate in a randomized controlled trial of two continuing medical education (CME) interventions designed to improve interpretation of screening mammography. METHODS: We collected recruitment, consent, and intervention-completion information as part of a large study involving radiologists in California, Oregon, Washington, New Mexico, New Hampshire, North Carolina, and Vermont. Consenting radiologists were randomized to receive either a 1-day live, expert-led educational session; to receive a self-paced DVD with similar content; or to a control group (delayed intervention). The impact of the interventions was assessed using a preintervention-postintervention test set design. All activities were institutional review board approved and HIPAA compliant. RESULTS: Of 403 eligible radiologists, 151 of 403 (37.5%) consented to participate in the trial and 119 of 151 (78.8%) completed the preintervention test set, leaving 119 available for randomization to one of the two intervention groups or to controls. Female radiologists were more likely than male radiologists to consent to and complete the study (P = .03). Consenting radiologists who completed all study activities were more likely to have

been interpreting mammography for 10 years or less compared to radiologists who consented and did not complete all study activities or did not consent at all. The live intervention group was more likely to report their intent to change their clinical practice as a result of the intervention compared to those who received the DVD (50% versus 17.6%,  $P = .02$ ). The majority of participants in both interventions groups felt the interventions were a useful way to receive CME mammography credits. CONCLUSIONS: Community radiologists found interactive interventions designed to improve interpretative mammography performance acceptable and useful for clinical practice. This suggests CME credits for radiologists should, in part, be for examining practice skills.

Carney, P. A., Tucker, E. K., Newby, T. A., & Beer, T. M. (2013). Feasibility, Acceptability and Findings from a Pilot Randomized Controlled Intervention Study on the Impact of a Book Designed to Inform Patients about Cancer Clinical Trials. *Journal of Cancer Education : The Official Journal of the American Association for Cancer Education*, doi:10.1007/s13187-013-0567-9

This study was conducted to assess the feasibility, acceptability, and changes in knowledge among cancer patients assigned to receive a 160-page book on experimental cancer therapies and clinical trials. We enrolled 20 patients with cancer who had never participated in a clinical trial and randomly assigned them to receive the book either during week 1 or week 4 of the study. We collected baseline patient demographic and cancer-related information as well as knowledge about cancer clinical trials at week 0. Follow-up surveys were administered at weeks 3 and 6 for both study groups. Comparisons were made within and between groups randomized to receive the book early (at week 1) to those who received it later (at week 4). One hundred percent of data were captured in both groups at baseline, which decreased to 77.8 % by week 6. The vast majority of participants found the book moderately or very useful (89 % in the Early Group at week 3 and 95.5 % in the Late Group at week 6). Within group pairwise comparisons found significant difference between baseline and week 6 in content-specific knowledge scores among participants in the Late Group [79 % versus 92.1 %,  $p = 0.01$ ]. Global knowledge scores increased significantly for variables reflecting knowledge that promotes decisions to participate in clinical trials. Providing published reading material to patients with cancer is both feasible and

acceptable. Offering information to patients about cancer clinical trials, using a book designed for patients with cancer may influence knowledge related to decision to participate in clinical trials.

Caughey, A. B. (2012). *Post-Term Pregnancy* Wiley-Blackwell. doi:10.1002/9781119979449.ch23

Post-term pregnancy is one that progresses to 42 weeks' gestation. A key in making the proper diagnosis of post-term pregnancy is accurate pregnancy dating, best done with confirmational first-trimester ultrasound. The epidemiology is the opposite to preterm birth, with higher rates in obese women and those of white race/ethnicity. Such prolonged pregnancy is also seen more commonly with fetal complications such as anencephaly and placental sulphatase deficiency, pointing towards a fetal contribution to the initiation of labour. Complications of post-term pregnancy include higher rates of stillbirth, Caesarean delivery, meconium-stained amniotic fluid, neonatal acidaemia and neonatal death. One advantage of post-term pregnancy is that it is easily preventable with induction of labour. However, the timing of such induction during the term period is costly and understudied. © 2012 John Wiley and Sons, Ltd.

Chadderdon, S. M., Belcik, J. T., Bader, L., Kirigiti, M. A., Peters, D. M., Kievit, P., . . . Lindner, J. R.

(2013). Pro-Inflammatory Endothelial Activation Detected by Molecular Imaging in Obese Non-Human Primates Coincides with the Onset of Insulin Resistance and Progressively Increases with Duration of Insulin Resistance. *Circulation*, doi:10.1161/CIRCULATIONAHA.113.003645

BACKGROUND: Inflammation and insulin resistance (IR) are associated processes that potentiate risk for cardiovascular disease in obesity. The temporal relation between IR and inflammation is not completely characterized. We hypothesized that endothelial cell adhesion molecule (ECAM) expression in large arteries is an early event that coincides with diet-induced obesity and IR in primates. METHODS AND RESULTS: Ten adult male rhesus macaques were studied at baseline and every 4-6 months on high-fat diet (HFD) for 2 years. Truncal fat, carotid intima-media thickness (IMT), plasma inflammatory biomarkers, and carotid P-selectin and VCAM-1 expression by contrast-enhanced ultrasound molecular imaging were assessed. Intravenous glucose tolerance test (IVGTT) was performed at baseline, 4 and 18 months. HFD produced a rapid increase ( $p < 0.01$ ) in weight, truncal fat, and degree of IR indicated by the insulin area-under-the-curve and glucose disappearance rate on IVGTT; all of which worsened minimally thereafter.

Molecular imaging detected a progressive increase in ECAM expression over time (5-7-fold greater than control agent signal at 2 yrs,  $p < 0.01$ ). Changes in IMT were not detected until 2 years and, while there was a trend toward an increase in plasma markers of inflammation (MCP-1, CRP), the pattern of increase varied considerably over time. CONCLUSIONS: In primates with diet-induced obesity, endothelial inflammatory activation is an early event that occurs coincident with the development of IR and long before any measurable change carotid IMT. Endothelial activation is more related to the duration rather than severity of IR and is not mirrored by changes in plasma biomarkers.

Chai, S., Cambronne, X. A., Eichhorn, S. W., & Goodman, R. H. (2013). MicroRNA-134 activity in somatostatin interneurons regulates H-Ras localization by repressing the palmitoylation enzyme, DHHC9. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(44), 17898-17903. doi:10.1073/pnas.1317528110; 10.1073/pnas.1317528110

MicroRNA-134 (miR-134) serves as a widely accepted model for microRNA function in synaptic plasticity. In this model, synaptic activity stimulates miR-134 expression, which then regulates dendrite growth and spine formation. By using a ratiometric microRNA sensor, we found, unexpectedly, that miR-134 activity in cortical neurons was restricted to interneurons. Using an assay designed to trap microRNA-mRNA complexes, we determined that miR-134 interacted directly with the mRNA encoding the palmitoylation enzyme, DHHC9. This enzyme is known to palmitoylate H-Ras, a modification required for proper membrane trafficking. Treatment with bicuculline, a GABAA receptor antagonist, decreased DHHC9 expression in somatostatin-positive interneurons and membrane localization of an H-Ras reporter in a manner that depended on miR-134. Thus, although miR-134 has been proposed to affect all types of neurons, we showed that functionally active miR-134 is produced in only a selected population of neurons where it influences the expression of targets, such as DHHC9, that regulate membrane targeting of critical signaling molecules.

Chen, E. Y., Dobrinski, K. P., Brown, K. H., Clagg, R., Edelman, E., Ignatius, M. S., . . . Langenau, D. M. (2013). Cross-Species Array Comparative Genomic Hybridization Identifies Novel Oncogenic Events in Zebrafish and Human Embryonal Rhabdomyosarcoma. *PLoS Genetics*, *9*(8)

doi:10.1371/journal.pgen.1003727

Human cancer genomes are highly complex, making it challenging to identify specific drivers of cancer growth, progression, and tumor maintenance. To bypass this obstacle, we have applied array comparative genomic hybridization (array CGH) to zebrafish embryonal rhabdomyosarcoma (ERMS) and utilized cross-species comparison to rapidly identify genomic copy number aberrations and novel candidate oncogenes in human disease. Zebrafish ERMS contain small, focal regions of low-copy amplification. These same regions were commonly amplified in human disease. For example, 16 of 19 chromosomal gains identified in zebrafish ERMS also exhibited focal, low-copy gains in human disease. Genes found in amplified genomic regions were assessed for functional roles in promoting continued tumor growth in human and zebrafish ERMS - identifying critical genes associated with tumor maintenance. Knockdown studies identified important roles for Cyclin D2 (CCND2), Homeobox Protein C6 (HOXC6) and PlexinA1 (PLXNA1) in human ERMS cell proliferation. PLXNA1 knockdown also enhanced differentiation, reduced migration, and altered anchorage-independent growth. By contrast, chemical inhibition of vascular endothelial growth factor (VEGF) signaling reduced angiogenesis and tumor size in ERMS-bearing zebrafish. Importantly, VEGFA expression correlated with poor clinical outcome in patients with ERMS, implicating inhibitors of the VEGF pathway as a promising therapy for improving patient survival. Our results demonstrate the utility of array CGH and cross-species comparisons to identify candidate oncogenes essential for the pathogenesis of human cancer. © 2013 Chen et al.

Chen, P. C., Kryukova, Y. N., & Shyng, S. L. (2013). Leptin Regulates KATP Channel Trafficking in Pancreatic beta-cells by a Signaling Mechanism Involving AMPK and PKA. *The Journal of Biological Chemistry*, doi:10.1074/jbc.M113.516880

Pancreatic beta-cells secrete insulin in response to metabolic and hormonal signals to maintain glucose homeostasis. Insulin secretion is under the control of ATP-sensitive potassium (KATP) channels which play key roles in setting beta-cell membrane potential. Leptin, a hormone secreted by adipocytes, inhibits insulin secretion by increasing KATP channel conductance in beta-cells. We investigated the mechanism by which leptin increases KATP channel conductance. We show that leptin causes a transient increase in surface expression of KATP channels without

affecting channel gating properties. This increase results primarily from increased channel trafficking to the plasma membrane rather than reduced endocytosis of surface channels. The effect of leptin on KATP channels is dependent on the protein kinases AMPK and PKA. Activation of AMPK or PKA mimics, whereas inhibition of AMPK or PKA abrogates the effect of leptin. Leptin activates AMPK directly by increasing AMPK phosphorylation at Threonine 172. Activation of PKA leads to increased channel surface expression even in the presence of AMPK inhibitors, suggesting AMPK lies upstream of PKA in the leptin signaling pathway. Leptin signaling also leads to F-actin depolymerization. Stabilization of F-actin pharmacologically occludes, whereas destabilization of F-actin simulates, the effect of leptin on KATP channel trafficking, indicating that leptin-induced actin reorganization underlies enhanced channel trafficking to the plasma membrane. Our study uncovers the signaling and cellular mechanism by which leptin regulates KATP channel trafficking to modulate beta-cell function and insulin secretion.

Cheng, Y. W., Snowden, J. M., King, T. L., & Caughey, A. B. (2013). Selected perinatal outcomes associated with planned home births in the United States. *American Journal of Obstetrics and Gynecology*, 209(4), 325.e1-325.e8. doi:10.1016/j.ajog.2013.06.022

Objective More women are planning home birth in the United States, although safety remains unclear. We examined outcomes that were associated with planned home compared with hospital births. Study Design We conducted a retrospective cohort study of term singleton live births in 2008 in the United States. Deliveries were categorized by location: hospitals or intended home births. Neonatal outcomes were compared with the use of the  $\chi^2$  test and multivariable logistic regression. Results There were 2,081,753 births that met the study criteria. Of these, 12,039 births (0.58%) were planned home births. More planned home births had 5-minute Apgar score <4 (0.37%) compared with hospital births (0.24%; adjusted odds ratio, 1.87; 95% confidence interval, 1.36-2.58) and neonatal seizure (0.06% vs 0.02%, respectively; adjusted odds ratio, 3.08; 95% confidence interval, 1.44-6.58). Women with planned home birth had fewer interventions, including operative vaginal delivery and labor induction/augmentation. Conclusion Planned home births were associated with increased neonatal complications but fewer obstetric interventions. The trade-off between maternal preferences and neonatal outcomes should be weighed thoughtfully. © 2013 Mosby, Inc. All rights reserved.

Cheong, F. Y., Sharma, V., Blagoveshchenskaya, A., Oorschot, V. M., Brankatschk, B., Klumperman, J., . . . Mayinger, P. (2010). Spatial regulation of Golgi phosphatidylinositol-4-phosphate is required for enzyme localization and glycosylation fidelity. *Traffic (Copenhagen, Denmark)*, *11*(9), 1180-1190. doi:10.1111/j.1600-0854.2010.01092.x; 10.1111/j.1600-0854.2010.01092.x

The enrichment of phosphatidylinositol-4-phosphate (PI(4)P) at the trans Golgi network (TGN) is instrumental for proper protein and lipid sorting, yet how the restricted distribution of PI(4)P is achieved remains unknown. Here, we show that lipid phosphatase Suppressor of actin mutations 1 (SAC1) is crucial for the spatial regulation of Golgi PI(4)P. Ultrastructural analysis revealed that SAC1 is predominantly located at cisternal Golgi membranes but is absent from the TGN, thus confining PI(4)P to the TGN. RNAi-mediated knockdown of SAC1 caused changes in Golgi morphology and mislocalization of Golgi enzymes. Enzymes involved in glycan processing such as mannosidase-II (Man-II) and N-acetylglucosamine transferase-I (GnT-I) redistributed to aberrant intracellular structures and to the cell surface in SAC1 knockdown cells. SAC1 depletion also induced a unique pattern of Golgi-specific defects in N- and O-linked glycosylation. These results indicate that SAC1 organizes PI(4)P distribution between the Golgi complex and the TGN, which is instrumental for resident enzyme partitioning and Golgi morphology.

Chiang, M. F., Read-Brown, S., Tu, D. C., Choi, D., Sanders, D. S., Hwang, T. S., . . . Yackel, T. R. (2013). Evaluation of electronic health record implementation in ophthalmology at an academic medical center (an American ophthalmological society thesis). *Transactions of the American Ophthalmological Society*, *111*, 70-92.

PURPOSE: TO EVALUATE THREE MEASURES RELATED TO ELECTRONIC HEALTH RECORD (EHR)

IMPLEMENTATION: clinical volume, time requirements, and nature of clinical documentation.

Comparison is made to baseline paper documentation. METHODS: An academic ophthalmology department implemented an EHR in 2006. A study population was defined of faculty providers who worked the 5 months before and after implementation. Clinical volumes, as well as time length for each patient encounter, were collected from the EHR reporting system. To directly compare time requirements, two faculty providers who utilized both paper and EHR systems completed time-motion logs to record the number of patients, clinic time, and nonclinic time to complete documentation. Faculty providers and databases were queried to identify patient

records containing both paper and EHR notes, from which three cases were identified to illustrate representative documentation differences. RESULTS: Twenty-three faculty providers completed 120,490 clinical encounters during a 3-year study period. Compared to baseline clinical volume from 3 months pre-implementation, the post-implementation volume was 88% in quarter 1, 93% in year 1, 97% in year 2, and 97% in year 3. Among all encounters, 75% were completed within 1.7 days after beginning documentation. The mean total time per patient was 6.8 minutes longer with EHR than paper ( $P < .01$ ). EHR documentation involved greater reliance on textual interpretation of clinical findings, whereas paper notes used more graphical representations, and EHR notes were longer and included automatically generated text. CONCLUSION: This EHR implementation was associated with increased documentation time, little or no increase in clinical volume, and changes in the nature of ophthalmic documentation.

Chiang, W. -., Ko, P. C. -., Chang, A. M., Chen, W. -., Liu, S. S. -., Huang, Y. -., . . . Ma, M. H. -.  
(2013). Bystander-initiated CPR in an Asian metropolitan: Does the socioeconomic status matter?  
*Resuscitation*, doi:10.1016/j.resuscitation.2013.07.033

Objectives: To determine the association of neighborhood socioeconomic status (SES) with bystander-initiated cardiopulmonary resuscitation (CPR) and patient outcomes of out of hospital cardiac arrests (OHCAs) in an Asian metropolitan area. Methods: We performed a retrospective study in a prospectively collected cohort from the Utstein registry of adult non-traumatic OHCAs in Taipei, Taiwan. Average real estate value was assessed as the first proxy of SES. Twelve administrative districts in Taipei City were categorized into low versus high SES areas to test the association. The primary outcome was bystander-initiated CPR, and the secondary outcome was patient survival status. Factors associated with bystander-initiated CPR were adjusted for in multivariate analysis. The mean household income was assessed as the second proxy of SES to validate the association. Results: From January 1, 2008 to December 30, 2009, 3573 OHCAs received prehospital resuscitation in the community. Among these, 617 (17.3%) cases received bystander CPR. The proportion of bystander CPR in low-SES vs. high-SES areas was 14.5% vs. 19.6% ( $p < 0.01$ ). Odds ratio of receiving bystander-initiated CPR in low-SES areas was 0.72 (95% confidence interval: [0.60-0.88]) after adjusting for age, gender, witnessed status, public collapse, and OHCA unrecognized by the online dispatcher. Survival to discharge rate was

significantly lower in low-SES areas vs. high-SES areas (4.3% vs. 6.8%;  $p < 0.01$ ). All results above remained consistent in the analyses by mean household income. Conclusions: Patients who experienced an OHCA in low-SES areas were less likely to receive bystander-initiated CPR, and demonstrated worse survival outcomes. © 2013 Elsevier Ireland Ltd. All rights reserved.

Chieffo, C., Cook, D., Xiang, Q., & Frohman, L. A. (2013). Efficacy and safety of an octreotide implant in the treatment of patients with acromegaly. *Journal of Clinical Endocrinology and Metabolism*, 98(10), 4047-4054. doi:10.1210/jc.2013-2262

Context: Acromegaly is caused by excessive GH secretion and IGF-I overproduction. The goals of treatment are to reduce GH and IGF-I values to normal and relieve the associated symptoms.

Objective: The purpose of this article was to demonstrate that an octreotide implant (84 mg) is safe and efficacious in patients with acromegaly who were responsive to prior monthly octreotide long-acting release (LAR) injections. Design: This was a phase 3, open-label study. Before treatment, subjects received a stable monthly dose of octreotide LAR injections (10-40 mg) for >3 months. Randomization was in a 3: 1 ratio to either a 6-month octreotide implant or monthly octreotide LAR injections. Setting: This was a multicenter, international study conducted in private or institutional practices. Subjects: Enrollment included 163 subjects (aged >18 years) with acromegaly. Main Outcome Measure: The efficacy, safety, and tolerability of the octreotide implant during 24 weeks of treatment was evaluated. Results: After 24 weeks, the success rate of the implant for maintenance of IGF-I and GH levels was 86% (95% confidence interval, 80.3%) compared with a rate of 84% (95% confidence interval, 73.8%) for octreotide LAR. Serum octreotide concentrations after implant insertion increased within 8 days and peaked between days 14 and 28. The overall safety of the octreotide implant and octreotide LAR were similar. Diarrhea and headache were more frequent with the implant, whereas cholecystitis and hypertension were more frequent with octreotide LAR. Conclusions: In this pivotal phase 3 study, the octreotide implant maintained reduced blood levels of GH and IGF-I with continuous octreotide release over 6 months, which was well tolerated. Copyright © 2013 by The Endocrine Society.

Chiovaro, J. C., & Gaggari, A. (2013). Crystalline Bone Marrow in Systemic Oxalosis. *Journal of General Internal Medicine*, doi:10.1007/s11606-013-2618-7

Chun, R. F., Peercy, B. E., Orwoll, E. S., Nielson, C. M., Adams, J. S., & Hewison, M. (2013). Vitamin D and DBP: The free hormone hypothesis revisited. *Journal of Steroid Biochemistry and Molecular Biology*, doi:10.1016/j.jsbmb.2013.09.012

The last five years have witnessed a remarkable renaissance in vitamin D research and a complete re-evaluation of its benefits to human health. Two key factors have catalyzed these changes. First, it now seems likely that localized, tissue-specific, conversion of 25-hydroxyvitamin D (25OHD) to 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) drives many of the newly recognized effects of vitamin D on human health. The second key factor concerns the ongoing discussion as to what constitutes adequate or optimal serum vitamin D (25OHD) status, with the possibility that vitamin D-deficiency is common to communities across the globe. These two concepts appear to be directly linked when low serum concentrations of 25OHD compromise intracrine generation of 1,25(OH)<sub>2</sub>D within target tissues. But, is this an over-simplification? Pro-hormone 25OHD is a lipophilic molecule that is transported in the circulation bound primarily to vitamin D binding protein (DBP). While the association between 25OHD and DBP is pivotal for renal handling of 25OHD and endocrine synthesis of 1,25(OH)<sub>2</sub>D, what is the role of DBP for extra-renal synthesis of 1,25(OH)<sub>2</sub>D? We hypothesize that binding to DBP impairs delivery of 25OHD to the vitamin D-activating enzyme 1 $\alpha$ -hydroxylase in some target cells. Specifically, it is unbound, 'free' 25OHD that drives many of the non-classical actions of vitamin D. Levels of 'free' 25OHD are dependent on the concentration of DBP and alternative serum binding proteins such as albumin, but will also be influenced by variations in DBP binding affinity for specific vitamin D metabolites. The aim of this review will be to discuss the merits of 'free 25OHD' as an alternative marker of vitamin D status, particularly in the context of non-classical responses to vitamin D. This article is part of a Special Issue entitled '16th Vitamin D Workshop'. © 2013 Elsevier Ltd. All rights reserved.

Church, S. E., Jensen, S. M., Antony, P. A., Restifo, N. P., & Fox, B. A. (2013). Tumor-specific CD4 T cells maintain effector and memory tumor-specific CD8 T cells. *European Journal of Immunology*,

doi:10.1002/eji.201343718; 10.1002/eji.201343718

Immunotherapies that augment anti-tumor T cells have had recent success for treating patients with cancer. Here we examined whether tumor-specific CD4+ T cells enhance CD8+ T-cell adoptive immunotherapy in a lymphopenic environment. Our model employed physiological doses of TRP-1-CD4+ T cells and pmel-CD8+ T cells that when transferred individually were subtherapeutic; however, when transferred together provided significant ( $p \leq 0.001$ ) therapeutic efficacy. Therapeutic efficacy correlated with increased numbers of effector and memory CD8+ T cells with tumor-specific cytokine expression. When combined with CD4+ T cells, transfer of total (naive and effector) or effector CD8+ T cells were highly effective, suggesting CD4+ T cells can help mediate therapeutic effects by maintaining function of activated CD8+ T cells. In addition, CD4+ T cells had a pronounced effect in the early post-transfer period, as their elimination within the first 3-days significantly ( $p < 0.001$ ) reduced therapeutic efficacy. The CD8+ T cells recovered from mice treated with both CD8+ and CD4+ T cells had decreased expression of PD-1 and PD-1-blockade enhanced the therapeutic efficacy of pmel-CD8 alone, suggesting that CD4+ T cells help reduce CD8+ T-cell exhaustion. These data support combining immunotherapies that elicit both tumor-specific CD4+ and CD8+ T cells for treatment of patients with cancer. This article is protected by copyright. All rights reserved.

Coleman, C. A., Hudson, S., & Maine, L. L. (2013). Health literacy practices and educational competencies for health professionals: a consensus study. *Journal of Health Communication, 18 Suppl 1*, 82-102. doi:10.1080/10810730.2013.829538; 10.1080/10810730.2013.829538

Health care professionals often lack adequate knowledge about health literacy and the skills needed to address low health literacy among patients and their caregivers. Many promising practices for mitigating the effects of low health literacy are not used consistently. Improving health literacy training for health care professionals has received increasing emphasis in recent years. The development and evaluation of curricula for health professionals has been limited by the lack of agreed-upon educational competencies in this area. This study aimed to identify a set of health literacy educational competencies and target behaviors, or practices, relevant to the training of all health care professionals. The authors conducted a thorough literature review to identify a comprehensive list of potential health literacy competencies and practices, which they

categorized into 1 or more educational domains (i.e., knowledge, skills, attitudes) or a practice domain. The authors stated each item in operationalized language following Bloom's Taxonomy. The authors then used a modified Delphi method to identify consensus among a group of 23 health professions education experts representing 11 fields in the health professions. Participants rated their level of agreement as to whether a competency or practice was both appropriate and important for all health professions students. A predetermined threshold of 70% agreement was used to define consensus. After 4 rounds of ratings and modifications, consensus agreement was reached on 62 out of 64 potential educational competencies (24 knowledge items, 27 skill items, and 11 attitude items), and 32 out of 33 potential practices. This study is the first known attempt to develop consensus on a list of health literacy practices and to translate recommended health literacy practices into an agreed-upon set of measurable educational competencies for health professionals. Further work is needed to prioritize the competencies and practices in terms of relative importance.

Coleman, K., Bloomsmith, M. A., Crockett, C. M., Weed, J. L., & Schapiro, S. J. (2012). *Behavioral Management, Enrichment, and Psychological Well-being of Laboratory Nonhuman Primates* Elsevier Inc. doi:10.1016/B978-0-12-381365-7.00006-6

Conlin, M. J. (2012). *Diagnostic Ureteroscopy* Wiley-Blackwell. doi:10.1002/9781444345148.ch40  
Improvements in ureteroscopes now allow us to better evaluate and treat patients with possible upper urinary tract disorders. Flexible ureteroscopy is particularly useful in evaluating patients with upper urinary tract filling defects and patients with benign essential hematuria. The indications, technique, and results of diagnostic ureteroscopy are reviewed. © 2012 Blackwell Publishing Ltd.

Conlin, M. J. (2013). Editorial Comment on END-2013-0436-OR.R1. *Journal of Endourology / Endourological Society*, doi:10.1089/end.2013.0605

This is an editorial comment.

Cook, K. A., Marienau, M. S., Wildgust, B., Gerbasi, F., & Watkins, J. (2013). Assessment of Recent Graduates Preparedness for Entry into Practice. *AANA Journal*, 81(5), 341-346.

To date no studies have been conducted to assess the preparedness of CRNA graduates for entry into practice by asking graduates and their respective employers to assess specific competencies. The purpose of this study was to assess recent graduates' preparation and performance. It was hypothesized recent graduates are prepared for entry into nurse anesthesia practice. This study was conducted between August 2011 and February 2012. An online survey tool was used to rate graduates' preparedness to perform 17 professional competencies. Surveys were distributed to 2,349 CRNAs who graduated in 2009 and 2,663 employers who hired recent graduates. A power of 90% for employers and 85% for graduates was obtained ( $P = .05$ ). Analysis of a sample size of 148 matched graduate-employer pairs provided 88% power. Overall, 98% of the graduates and 97% of the employers indicated graduates were prepared for practice. Of the 1,407 graduates assessed by employers, 1,343 (96%) would be hired again. Competencies identified as opportunities to enhance include administration of peripheral nerve blocks, insertion of central lines, insertion of pulmonary artery (PA) catheters, and chronic pain management techniques. The majority of employers rated these competencies as not applicable in their practice setting. Results suggest recent graduates are prepared and perform the competencies for entry into practice. While graduates and employers identified opportunities to enhance preparation it may not be sufficient to simply improve education without changing CRNA practice expectations.

Cramer, A. K., Haile, A. G., Ognjenovic, S., Doshi, T. S., Reilly, W. M., Rubinstein, K. E., . . . Hung, A. Y. (2013). Real-time prostate motion assessment: Image-guidance and the temporal dependence of intra-fraction motion. *BMC Medical Physics*, *13*(1) doi:10.1186/1756-6649-13-4

Background: The rapid adoption of image-guidance in prostate intensity-modulated radiotherapy (IMRT) results in longer treatment times, which may result in larger intrafraction motion, thereby negating the advantage of image-guidance. This study aims to qualify and quantify the contribution of image-guidance to the temporal dependence of intrafraction motion during prostate IMRT. Methods: One-hundred and forty-three patients who underwent conventional IMRT ( $n=67$ ) or intensity-modulated arc therapy (IMAT/RapidArc,  $n=76$ ) for localized prostate cancer were evaluated. Intrafraction motion assessment was based on continuous RL (lateral), SI (longitudinal), and AP (vertical) positional detection of electromagnetic transponders at 10 Hz. Daily motion amplitudes were reported as session mean, median, and root-mean-square (RMS)



at a stage when oligodendrocytes were just beginning to myelinate axons. The neuroapoptosis response was most prominent in the cerebellum, caudate, putamen, amygdala, and several cerebrocortical regions. Oligodendrocyte apoptosis was diffusely distributed over many white matter regions. The total number of apoptotic profiles (neurons + oligodendrocytes) in the isoflurane-exposed brains was increased 4.1-fold, compared with the brains from drug-naive controls. The total number of oligodendrocytes deleted by isoflurane was higher than the number of neurons deleted. CONCLUSIONS:: Isoflurane anesthesia for 5 h causes death of neurons and oligodendrocytes in the G120 fetal NHP brain. In the fetal brain, as the authors previously found in the neonatal NHP brain, oligodendrocytes become vulnerable when they are just achieving myelination competence. The neurotoxic potential of isoflurane increases between the third trimester (G120) and the neonatal period in the NHP brain.

Crisp, S., Meyer, E., Gregory, A., Archer, H., Hayflick, S., Kurian, M. A., & de Silva, R. (2013). A rett-like disorder with brain iron accumulation. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*(11), e2. doi:10.1136/jnnp-2013-306573.38; 10.1136/jnnp-2013-306573.38

A 31-year old female presented with progressive loss of motor and social skills, on a background of previously static global developmental delay. Her history and examination were consistent with atypical Rett syndrome, but MECP2 sequencing failed to demonstrate a pathogenic mutation. Magnetic resonance imaging (MRI) of brain in adulthood revealed a pattern of iron accumulation in the basal ganglia and cerebral peduncles characteristic of the newly described entity of beta-propeller protein-associated neurodegeneration (BPAN).(1-3) Genetic analysis confirmed the presence of a novel mutation in the associated WDR45 gene on the X-chromosome. Video data demonstrating the patient's phenotype, detailed MRI findings and their discrimination from other forms of brain iron accumulation are presented. Classically, the clinical features of BPAN are global developmental delay in childhood and neurological degeneration in adulthood, with progressive dystonia, parkinsonism and dementia.(2) However, our patient presented predominantly with a Rett-like phenotype, features of which may be present in approximately 25% of BPAN cases.(2) The proportion of patients with atypical Rett syndrome, particularly those with negative conventional genetic tests, who actually have BPAN remains to be established. Like Rett syndromes, this disorder is more common in females consistent with sensitivity to X-

inactivation.(1) The phenotypic variability may be attributable to variation in the pattern of inactivation.

Cruccu, G., Gronseth, G., Alksne, J., Argoff, C., Brainin, M., Burchiel, K., . . . Zakrzewska, J. M. (2011). *Trigeminal Neuralgia Management* Wiley-Blackwell. doi:10.1002/9781444346268.ch3

Cuenca, N., Fernández-Sánchez, L., McGill, T. J., Lu, B., Wang, S., Lund, R., . . . Capela, A. (2013). Phagocytosis of photoreceptor outer segments by transplanted human neural stem cells as a neuroprotective mechanism in retinal degeneration. *Investigative Ophthalmology and Visual Science*, 54(10), 6745-6756. doi:10.1167/iovs.13-12860

**PURPOSE.** Transplantation of human central nervous system stem cells (HuCNS-SC) into the subretinal space of Royal College of Surgeons (RCS) rats preserves photoreceptors and visual function. To explore possible mechanism(s) of action underlying this neuroprotective effect, we performed a detailed morphologic and ultrastructure analysis of HuCNS-SC transplanted retinas.

**METHODS.** The HuCNS-SC were transplanted into the subretinal space of RCS rats. Histologic examination of the transplanted retinas was performed by light and electron microscopy. Areas of the retina adjacent to HuCNS-SC graft (treated regions) were analyzed and compared to control sections obtained from the same retina, but distant from the transplant site (untreated regions).

**RESULTS.** The HuCNS-SC were detected as a layer of STEM 121 immunopositive cells in the subretinal space. In treated regions, preserved photoreceptor nuclei, as well as inner and outer segments were identified readily. In contrast, classic signs of degeneration were observed in the untreated regions. Interestingly, detailed ultrastructure analysis revealed a striking preservation of the photoreceptor-bipolar-horizontal cell synaptic contacts in the outer plexiform layer (OPL) of treated areas, in stark contrast with untreated areas. Finally, the presence of phagosomes and vesicles exhibiting the lamellar structure of outer segments also was detected within the cytosol of HuCNS-SC, indicating that these cells have phagocytic capacity in vivo.

**CONCLUSIONS.** This study reveals the novel finding that preservation of specialized synaptic contacts between photoreceptors and second order neurons, as well as phagocytosis of photoreceptor outer segments, are potential mechanism(s) of HuCNS-SC transplantation, mediating functional rescue in retinal degeneration. © 2013 The Association for Research in Vision and Ophthalmology, Inc.

Curry, M., Whitney, N., Roundy, N., & Selden, N. R. (2013). A case of acute traumatic subdural hematoma in a child with previous bilateral encephaloduroarteriosynangiosis. *Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery*, doi:10.1007/s00381-013-2285-3

The authors report the case of a 5-year-old female with right-sided hemiparesis and aphasia secondary to moyamoya disease, who had previously undergone staged bilateral encephaloduroarteriosynangiosis procedures. A subsequent ground-level fall caused an acute traumatic subdural hematoma with mass effect and neurological decline. She underwent emergency hematoma evacuation and decompressive craniectomy, which required interruption of the superficial temporal artery that had been used for indirect bypass, followed later by autologous cranioplasty. There were no acute or long-term ischemic events related to the occurrence or treatment of the traumatic hematoma. Follow-up angiography revealed extensive spontaneous vascular collateralization in the field of the decompressive craniectomy and cranioplasty. The patient returned to her pre-injury neurological baseline.

Darney, B. G., Snowden, J. M., Cheng, Y. W., Jacob, L., Nicholson, J. M., Kaimal, A., . . . Caughey, A. B. (2013). Elective induction of labor at term compared with expectant management: maternal and neonatal outcomes. *Obstetrics and Gynecology*, 122(4), 761-769.

doi:10.1097/AOG.0b013e3182a6a4d0; 10.1097/AOG.0b013e3182a6a4d0

OBJECTIVE: To test the association of elective induction of labor at term compared with expectant management and maternal and neonatal outcomes. METHODS: This was a retrospective cohort study of all deliveries without prior cesarean delivery in California in 2006 using linked hospital discharge and vital statistics data. We compared elective induction at each term gestational age (37-40 weeks) as defined by The Joint Commission with expectant management in vertex, nonanomalous, singleton deliveries. We used multivariable logistic regression to test the association of elective induction and cesarean delivery, operative vaginal delivery, maternal third- or fourth-degree lacerations, perinatal death, neonatal intensive care unit admission, respiratory distress, shoulder dystocia, hyperbilirubinemia, and macrosomia (birth weight greater than 4,000 g) at each gestational week, stratified by parity. RESULTS: The cesarean delivery rate was 16%, perinatal mortality was 0.2%, and neonatal intensive care unit

admission was 6.2% (N=362,154). The odds of cesarean delivery were lower among women with elective induction compared with expectant management across all gestational ages and parity (37 weeks [odds ratio (OR) 0.44, 95% confidence interval (CI) 0.34-0.57], 38 weeks [OR 0.43, 95% CI 0.38-0.50], 39 weeks [OR 0.46, 95% CI 0.41-0.52], 40 weeks [OR 0.57, CI 0.50-0.65]). Elective induction was not associated with increased odds of severe lacerations, operative vaginal delivery, perinatal death, neonatal intensive care unit admission, respiratory distress, shoulder dystocia, or macrosomia at any term gestational age. Elective induction was associated with increased odds of hyperbilirubinemia at 37 and 38 weeks of gestation and shoulder dystocia at 39 weeks of gestation. CONCLUSION: Elective induction of labor is associated with decreased odds of cesarean delivery when compared with expectant management. LEVEL OF EVIDENCE: : II.

Davis, M. Y., Keene, C. D., Swanson, P. D., Sheehy, C., & Bird, T. D. (2013). Novel mutations in ataxia telangiectasia and AOA2 associated with prolonged survival. *Journal of the Neurological Sciences*, doi:10.1016/j.jns.2013.09.014

Ataxia telangiectasia (AT) and ataxia oculomotor apraxia type 2 (AOA2) are autosomal recessive ataxias caused by mutations in genes involved in maintaining DNA integrity. Lifespan in AT is greatly shortened (20s-30s) due to increased susceptibility to malignancies (leukemia/lymphoma). Lifespan in AOA2 is uncertain. We describe a woman with variant AT with two novel mutations in ATM (IVS14 + 2 T > G and 5825C > T, p.A1942V) who died at age 48 with pancreatic adenocarcinoma. Her mutations are associated with an unusually long life for AT and with a cancer rarely associated with that disease. We also describe two siblings with AOA2, heterozygous for two novel mutations in senataxin (3 bp deletion c.343-345 and 1398 T > G, p.I466M) who have survived into their 70s, allowing us to characterize the longitudinal course of AOA2. In contrast to AT, we show that persons with AOA2 can experience a prolonged lifespan with considerable motor disability.

Deiorio, N. M., Yarris, L. M., & Hauswald, M. (2013). Education Research: Priority Designs and Common Misperceptions. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine*, doi:10.1111/acem.12246; 10.1111/acem.12246

In this commentary, common misperceptions about education research, and specifically for

emergency medicine education research, are addressed. Recommendations for designing and publishing high-quality projects are also provided.

DeLoughery, T. (2013). Commentary. *Annals of Internal Medicine*, 159(8) doi:10.7326/0003-4819-159-8-201310150-02002

DeMatteo, R. P., Ballman, K. V., Antonescu, C. R., Corless, C., Kolesnikova, V., Von Mehren, M., . . .

Owzar, K. (2013). Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. *Annals of Surgery*, 258(3), 422-428. doi:10.1097/SLA.0b013e3182a15eb7

Objective: To conduct the first adjuvant trial of imatinib mesylate for treatment of gastrointestinal stromal tumor (GIST). Background: GIST is the most common sarcoma. Although surgical resection has been the mainstay of therapy for localized, primary GIST, postoperative tumor recurrence is common. The KIT protooncogene or, less frequently, platelet-derived growth factor receptor alpha is mutated in GIST; the gene products of both are inhibited by imatinib mesylate. Methods: This was a phase II, intergroup trial led by the American College of Surgeons Oncology Group, registered at ClinicalTrials.gov as NCT00025246. From September 2001 to September 2003, we accrued 106 patients who had undergone complete gross tumor removal but were deemed at high risk for recurrence. Patients were prescribed imatinib 400 mg per day for 1 year and followed with serial radiologic evaluation. The primary endpoint was overall survival (OS). Results: After a median follow-up of 7.7 years, the 1-, 3-, and 5-year OS rates were 99%, 97%, and 83%, which compared favorably with a historical 5-year OS rate of 35%. The 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 96%, 60%, and 40%. On univariable analysis, age and mitotic rate were associated with OS. On multivariable analysis, the RFS rate was lower with increasing tumor size, small bowel site, KIT exon 9 mutation, high mitotic rate, and older age. Conclusions: Adjuvant imatinib in patients with primary GIST who are at high risk of recurrence prolongs OS compared with that of historical controls. Optimal duration of adjuvant therapy remains undefined. © 2013 Lippincott Williams & Wilkins.

Denard, P. J., & Burkhart, S. S. (2013). Arthroscopic Recognition and Repair of the Torn Subscapularis Tendon. *Arthroscopy Techniques*, doi:10.1016/j.eats.2013.05.007

Although the subscapularis has historically received less attention than posterosuperior rotator cuff tears, repair of a torn subscapularis tendon is critically important to restoring anatomy and achieving the best functional outcome possible. Arthroscopic repair begins with proper recognition of the tear. A systematic approach can then be used to arthroscopically repair all types of subscapularis tendon tears, from partial tears to full-thickness tears, as well as those which are retracted and have adhesions medially. Subscapularis footprint restoration can be accomplished with a variety of repair techniques that must be matched to the extent of the tear and mobility of the tendon. © 2013 Arthroscopy Association of North America.

Denicoff, A. M., McCaskill-Stevens, W., Grubbs, S. S., Bruinooge, S. S., Comis, R. L., Devine, P., . . .

Meropol, N. J. (2013). The National Cancer Institute-American Society of Clinical Oncology Cancer Trial Accrual Symposium: Summary and Recommendations. *Journal of Oncology Practice / American Society of Clinical Oncology*, doi:10.1200/JOP.2013.001119

**INTRODUCTION:** Many challenges to clinical trial accrual exist, resulting in studies with inadequate enrollment and potentially delaying answers to important scientific and clinical questions. **METHODS:** The National Cancer Institute (NCI) and the American Society of Clinical Oncology (ASCO) cosponsored the Cancer Trial Accrual Symposium: Science and Solutions on April 29-30, 2010 to examine the state of accrual science related to patient/community, physician/provider, and site/organizational influences, and identify new interventions to facilitate clinical trial enrollment. The symposium featured breakout sessions, plenary sessions, and a poster session including 100 abstracts. Among the 358 attendees were clinical investigators, researchers of accrual strategies, research administrators, nurses, research coordinators, patient advocates, and educators. A bibliography of the accrual literature in these three major areas was provided to participants in advance of the meeting. After the symposium, the literature in these areas was revisited to determine if the symposium recommendations remained relevant within the context of the current literature. **RESULTS:** Few rigorously conducted studies have tested interventions to address challenges to clinical trials accrual. Attendees developed recommendations for improving accrual and identified priority areas for future accrual research at the patient/community, physician/provider, and site/organizational levels. Current literature continues to support the symposium recommendations. **CONCLUSIONS:** A combination of

approaches addressing both the multifactorial nature of accrual challenges and the characteristics of the target population may be needed to improve accrual to cancer clinical trials.

Recommendations for best practices and for future research developed from the symposium are provided.

Derdeyn, C. P., Fiorella, D., Lynn, M. J., Barnwell, S. L., Zaidat, O., Meyers, P. M., . . . Chimowitz, M. I. (2013). Impact of operator and site experience on outcomes after angioplasty and stenting in the SAMMPRIS trial. *Journal of NeuroInterventional Surgery*, 5(6), 528-533.

doi:10.1136/neurintsurg-2012-010504

**Background and purpose** To investigate the relationship between physician and site experience and the risk of 30 day hemorrhagic and ischemic strokes in the stenting arm of the Stenting and Aggressive Medical Management for the Prevention of Recurrent Ischemic Stroke (SAMMPRIS) trial. **Methods** Study records and an investigator survey were examined for physician and site related factors, including: number of Wingspan and aneurysm stents submitted for credentialing, number of study procedures performed in SAMMPRIS, years in practice after training, primary specialty, and site enrollment. Bivariate and multivariate analyses were performed to determine if these factors were associated with the 30 day rate of cerebrovascular events after angioplasty and stenting. **Results** 213 patients underwent angioplasty alone (n=5) or angioplasty and stenting (n=208) with study devices by 63 interventionists at 48 sites. For credentialing, the median number of Wingspan and similar aneurysm stent cases submitted by study interventionists were 10 and 6, respectively. Interventionists with higher numbers (>10) of Wingspan cases submitted for credentialing tended to have higher rates of 30 day events (19.0% vs 9.9%) than those with 12 patients). **Conclusions** Interventionists credentialed with less Wingspan experience were not responsible for the high rate of periprocedural stroke in SAMMPRIS. Hemorrhagic stroke may be related to low enrollment in the trial but not previous Wingspan experience.

Deshpande, A., Nelson, D., Corless, C. L., Deshpande, V., & O'Brien, M. J. (2013). Leiomyoma of the Gastrointestinal Tract With Interstitial Cells of Cajal: A Mimic of Gastrointestinal Stromal Tumor. *The American Journal of Surgical Pathology*, doi:10.1097/PAS.0b013e3182a0d134

Leiomyomas (LMs) of the gastrointestinal tract arise within the muscularis mucosae (superficial) and muscularis propria (deep). There are isolated reports of KIT-positive cells, presumed interstitial cells of Cajal (ICCs), within gastrointestinal LMs. We have encountered esophageal LMs with a high proportion of KIT-positive and DOG1-positive spindle-shaped cells, an appearance that mimicked gastrointestinal stromal tumor. Our aim was to explore the prevalence of ICCs in LMs of the gastrointestinal tract and the etiopathogenic significance of these cells in this benign neoplasm. We identified 34 esophageal LMs (28 deep, 6 superficial), 8 gastric LMs, and 5 small-bowel LMs (all lesions in muscularis propria). We performed immunohistochemical staining studies for desmin, DOG1, and KIT on these neoplasms. We also evaluated 12 superficial colonic LMs. ICCs were distinguished from mast cells on the basis of morphology (elongated and occasionally branching spindle-shaped cells) and the presence of DOG1 reactivity. Four cases were screened for mutations in PDGFRA exons 12, 14, and 18 and KIT exons 9, 11, 13, and 17. ICCs were identified in all deep esophageal LMs and constituted an average of 20% of the lesional cells; focally, these cells comprised >50% of cells. The density of these cells was significantly higher than the background muscularis propria, and hyperplasia of ICCs was not identified in the adjacent muscle. ICCs were identified in 6 of 8 gastric LMs and 1 of 5 small-bowel LMs and were entirely absent in all superficial esophageal and colonic/rectal LMs. There were no mutations in KIT or PDGFRA. ICCs are universally present in deep esophageal LMs, and thus these neoplasms could be mistaken for gastrointestinal stromal tumors, particularly on biopsy samples, an error associated with adverse clinical consequences. ICCs are also identified in gastric and intestinal LMs, albeit in a smaller proportion of cases. Colonization and hyperplasia by non-neoplastic ICCs likely account for this phenomenon.

Dodge, H. H., Ybarra, O., & Kaye, J. A. (2013). Tools for advancing research into social networks and cognitive function in older adults. *International Psychogeriatrics / IPA*, , 1-7.

doi:10.1017/S1041610213001750

Dooley, J., Chang, A. M., Salhi, R. A., & Hollander, J. E. (2013). Relationship between body mass index and prognosis of patients presenting with potential acute coronary syndromes. *Academic Emergency Medicine*, 20(9), 904-910. doi:10.1111/acem.12211

Objectives Studies examining the relationship between obesity and acute coronary syndrome (ACS) have been limited to patients with confirmed diagnoses. The authors sought to determine the relationship between body mass index (BMI) and 30-day cardiovascular events in emergency department (ED) patients with potential ACS. Methods This was a secondary analysis of a prospective cohort study of patients who presented to the ED with potential ACS. Patients were stratified according to their BMI: underweight (BMI < 18.5 kg/m<sup>2</sup>), normal weight (BMI 18.5–24.9 kg/m<sup>2</sup>), overweight (BMI 25–29.9 kg/m<sup>2</sup>), obese (BMI 30–34.9 kg/m<sup>2</sup>), and very obese (BMI ≥ 35 kg/m<sup>2</sup>). The primary outcome was acute myocardial infarction (AMI), death, or revascularization within 30 days of presentation. A logistic regression analysis was used to adjust for confounding variables and adjusted odds ratios (aOR) with 95% confidence intervals (CIs) are presented for cardiac events and readmission outcomes. Results Of the 3,946 patients included in this study, 73 (1.9%) were underweight, 911 (23%) were normal weight, 1,199 (30.4%) were overweight, 872 (22.1%) were obese, and 891 (22.6%) were very obese. Although increased levels of obesity were associated with a greater number of cardiac risk factors, there was no difference in 30-day cardiovascular events between those of normal weight and underweight (aOR = 1.1; 95% CI = 0.4 to 2.7), overweight (aOR = 1.0; 95% CI = 0.7 to 1.4), obese (aOR = 1.2; 95% CI = 0.8 to 1.7), or very obese (aOR = 0.8; 95% CI = 0.5 to 1.3). Those who were underweight were more likely to be readmitted within 30 days (aOR = 1.9; 95% CI = 1.0 to 3.7), and those who were very obese were less likely to be readmitted within 30 days (aOR = 0.7; 95% CI = 0.5 to 0.9). Conclusions Among patients who present to the ED with potential ACS, BMI is not associated with higher risk of cardiovascular outcomes at 30 days. © 2013 by the Society for Academic Emergency Medicine.

Doolittle, N. D., Dosa, E., Fu, R., Muldoon, L. L., Maron, L. M., Lubow, M. A., . . . Neuwelt, E. A. (2013). Preservation of cognitive function in primary CNS lymphoma survivors a median of 12 years after enhanced chemotherapy delivery. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *31*(31), 4026-4027. doi:10.1200/JCO.2013.52.7747; 10.1200/JCO.2013.52.7747

Doss, A., & Pereira, L. (2013). Strip of the month: October 2013. *Neoreviews*, *14*(10), e526-e535. doi:10.1542/neo.14-10-e526

Dougados, M., Soubrier, M., Antunez, A., Balint, P., Balsa, A., Buch, M., . . . Kay, J. (2013).

Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: Results of an international, cross-sectional study (COMORA). *Annals of the Rheumatic Diseases*, doi:10.1136/annrheumdis-2013-204223

Background: Patients with rheumatoid arthritis (RA) are at increased risk of developing comorbid conditions. Objectives: To evaluate the prevalence of comorbidities and compare their management in RA patients from different countries worldwide. Methods: Study design: international, cross-sectional. Patients: consecutive RA patients. Data collected: demographics, disease characteristics (activity, severity, treatment), comorbidities (cardiovascular, infections, cancer, gastrointestinal, pulmonary, osteoporosis and psychiatric disorders). Results: Of 4586 patients recruited in 17 participating countries, 3920 were analysed (age, 56±13 years; disease duration, 10±9 years (mean±SD); female gender, 82%; DAS28 (Disease Activity Score using 28 joints)-erythrocyte sedimentation rate, 3.7±1.6 (mean±SD); Health Assessment Questionnaire, 1.0±0.7 (mean±SD); past or current methotrexate use, 89%; past or current use of biological agents, 39%. The most frequently associated diseases (past or current) were: depression, 15%; asthma, 6.6%; cardiovascular events (myocardial infarction, stroke), 6%; solid malignancies (excluding basal cell carcinoma), 4.5%; chronic obstructive pulmonary disease, 3.5%. High intercountry variability was observed for both the prevalence of comorbidities and the proportion of subjects complying with recommendations for preventing and managing comorbidities. The systematic evaluation of comorbidities in this study detected abnormalities in vital signs, such as elevated blood pressure in 11.2%, and identified conditions that manifest as laboratory test abnormalities, such as hyperglycaemia in 3.3% and hyperlipidaemia in 8.3%. Conclusions: Among RA patients, there is a high prevalence of comorbidities and their risk factors. In this multinational sample, variability among countries was wide, not only in prevalence but also in compliance with recommendations for preventing and managing these comorbidities. Systematic measurement of vital signs and laboratory testing detects otherwise unrecognised comorbid conditions. © 2013 BMJ Publishing Group Ltd & European League Against Rheumatism.

Dreumont, S. E., & Cunningham, C. L. (2013). Effects of acute withdrawal on ethanol-induced conditioned place preference in DBA/2J mice. *Psychopharmacology*, doi:10.1007/s00213-013-

3291-6

**RATIONALE:** Reexposure to ethanol during acute withdrawal might facilitate the transition to alcoholism by enhancing the rewarding effect of ethanol. **OBJECTIVE:** The conditioned place preference (CPP) procedure was used to test whether ethanol reward is enhanced during acute withdrawal. **METHODS:** DBA/2J mice were exposed to an unbiased one-compartment CPP procedure. Ethanol (0.75, 1.0, or 1.5 g/kg IP) was paired with a distinctive floor cue (CS+), whereas saline was paired with a different floor cue (CS-). The withdrawal (W) group received CS+ trials during acute withdrawal produced by a large dose of ethanol (4 g/kg) given 8 h before each trial. The no-withdrawal (NW) group did not experience acute withdrawal during conditioning trials but was matched for acute withdrawal experience. Floor preference was tested in the absence of ethanol or acute withdrawal. **RESULTS:** All groups eventually showed a dose-dependent preference for the ethanol-paired cue, but development of CPP was generally more rapid and stable in the W groups than in the NW groups. Acute withdrawal suppressed the normal activating effect of ethanol during CS+ trials, but there were no group differences in test activity. **CONCLUSIONS:** Acute withdrawal enhanced ethanol's rewarding effect as indexed by CPP. Since this effect depended on ethanol exposure during acute withdrawal, the enhancement of ethanol reward was likely mediated by the alleviation of acute withdrawal, i.e., negative reinforcement. Enhancement of ethanol reward during acute withdrawal may be a key component in the shift from episodic to chronic ethanol consumption that characterizes alcoholism.

Dreyer, H. C., Strycker, L. A., Senesac, H. A., Hocker, A. D., Smolkowski, K., Shah, S. N., & Jewett, B. A. (2013). Essential amino acid supplementation in patients following total knee arthroplasty. *The Journal of Clinical Investigation*, 123(11), 4654-4666. doi:10.1172/JCI70160; 10.1172/JCI70160

Background. By the year 2030, 3.48 million older U.S. adults are projected to undergo total knee arthroplasty (TKA). Following this surgery, considerable muscle atrophy occurs, resulting in decreased strength and impaired functional mobility. Essential amino acids (EAAs) have been shown to attenuate muscle loss during periods of reduced activity and may be beneficial for TKA patients. Methods. We used a double-blind, placebo-controlled, randomized clinical trial with 28 older adults undergoing TKA. Patients were randomized to ingest either 20 g of EAAs (n = 16) or placebo (n = 12) twice daily between meals for 1 week before and 2 weeks after TKA. At

baseline, 2 weeks, and 6 weeks after TKA, an MRI was performed to determine mid-thigh muscle and adipose tissue volume. Muscle strength and functional mobility were also measured at these times. Results. TKA patients receiving placebo exhibited greater quadriceps muscle atrophy, with a  $-14.3 \pm 3.6\%$  change from baseline to 2 weeks after surgery compared with  $-3.4 \pm 3.1\%$  for the EAA group ( $F = 5.16, P = 0.036$ ) and a  $-18.4 \pm 2.3\%$  change from baseline to 6 weeks after surgery for placebo versus  $-6.2 \pm 2.2\%$  for the EAA group ( $F = 14.14, P = 0.001$ ). EAAs also attenuated atrophy in the nonoperated quadriceps and in the hamstring and adductor muscles of both extremities. The EAA group performed better at 2 and 6 weeks after surgery on functional mobility tests (all  $P < 0.05$ ). Change in quadriceps muscle atrophy was significantly associated with change in functional mobility ( $F = 5.78, P = 0.021$ ). Conclusion. EAA treatment attenuated muscle atrophy and accelerated the return of functional mobility in older adults following TKA. Trial registration. Clinicaltrials.gov NCT00760383. Funding. Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Office of the Director (OD), and the National Institutes of Health Office of Dietary Supplements (ODS), NIH grant K01HD057332, and the Medical Research Foundation, Oregon Health and Science University. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

Driessnack, M., & Gallo, A. M. (2013). Children 'draw-and-tell' their knowledge of genetics. *Pediatric Nursing, 39*(4), 173-180.

The purpose of this study was to explore children's early understanding of basic genetic/genomic concepts using an innovative, child-sensitive approach to data collection. Exploratory, qualitative study using art-based "Draw-and-Tell Conversation" interviews with children were used. Each conversational interview was guided by two drawing completion tasks and a semi-structured interview guide. Data were analyzed using qualitative content analysis. In this study, 27 children 7 to 10 years of age shared their understanding of basic genetic/genomic concepts in their drawings and conversations. Data were organized into four categories: 1) Inside the Body, 2) Under the Microscope, 3) It's Genetic, and 4) In Our World. Using a child-sensitive approach to data collection, children revealed a range of understanding about basic genetic concepts,

including DNA, disease causation, risk, and inheritance. Data suggest informal family conversations and media exposure inform children's early understanding, highlighting the need to be aware of the sources and content of information available to children. Nurses play a central role in assessing children's genetic/genomic knowledge. The Draw-and-Tell Conversation is a novel approach that can be used to support parents as they approach and discuss genetic concepts with their children.

Eastwood, E. C., & Phillips, T. J. (2013). Morphine intake and the effects of naltrexone and buprenorphine on the acquisition of methamphetamine intake. *Genes, Brain, and Behavior*, doi:10.1111/gbb.12100; 10.1111/gbb.12100

Some common genetic factors appear to influence risk for drug dependence across multiple drugs of abuse. In previous research, mice that were selectively bred for higher amounts of methamphetamine consumption, using a two-bottle choice methamphetamine drinking procedure, were found to be less sensitive to the locomotor stimulant effects of morphine and the more mu-opioid receptor selective agonist fentanyl, compared to mice that were bred for low methamphetamine consumption. This suggested that mu-opioid receptor mediated pathways may influence genetic risk for methamphetamine consumption. We hypothesized that these differences in opioid sensitivity would impact opioid intake in the methamphetamine drinking lines and that drugs with mu-opioid receptor activity would impact methamphetamine intake. Consumption of morphine was examined in 2, two-bottle choice studies, one that compared morphine to quinine consumption and another that used a saccharin fading procedure. Next, naltrexone (0, 0.5, 1, 2, 5, 10, 20 mg/kg), a mu-opioid receptor antagonist, and buprenorphine (0, 1, 2, or 4 mg/kg), a mu-opioid receptor partial agonist, were each examined for their effects on the acquisition of methamphetamine consumption. Low methamphetamine drinking mice consumed more morphine compared to high methamphetamine drinking mice. Naltrexone did not alter methamphetamine consumption in either selected line; however, buprenorphine reduced methamphetamine intake in the high methamphetamine drinking line. These data show that greater sensitivity to opioids is associated with greater opioid intake and indicate a need for investigation of drugs with mu-opioid receptor-specific agonist activity in genetically-determined differences in methamphetamine consumption.

Eil, R., Hansen, P. D., Cassera, M., Orloff, S. L., Sheppard, B. C., Diggs, B., & Billingsley, K. G. (2013).

Bile duct involvement portends poor prognosis in resected gallbladder carcinoma. *Gastrointestinal Cancer Research : GCR*, 6(4), 101-105.

BACKGROUND: Gallbladder cancer (GBC) carries an unfavorable prognosis with high mortality.

This retrospective study was conducted to identify prognostic factors after resection of GBC, to assist in selecting appropriate surgical and adjuvant therapy. METHODS: Sixty-two patients from two institutions were identified with GBC by pathology. In 25, the cancer was unresectable at presentation. The remaining 37 patients comprised the study population. Log-rank analysis was used to assess univariate association with disease-free survival (DFS) and disease-specific survival (DSS). Cox regression was used for multivariate analysis. RESULTS: Median DFS and DSS were 22.6 and 28.5 months respectively, with a median follow-up of 44.2 months. On univariate analysis, bile duct (BD) involvement was significantly associated with decreased DFS ( $P \leq .001$ ) and DSS ( $P = .004$ ). BD involvement was uniformly fatal. LN involvement was not significantly associated with DFS or DSS ( $P = .85$ ,  $P = .54$ ). CONCLUSIONS: All patients with BD involvement in our population died of the disease. The subset of patients with resectable GBC and BD involvement is a group that is at high risk for recurrence and should be treated as such. In our small population, preoperative and intraoperative methods evaluating BD involvement were unreliable.

Englitz, B., Akram, S., David, S. V., Chambers, C., Pressnitzer, D., Depireux, D., . . . Shamma, S. A. (2013). *Putting the tritone paradox into context: Insights from neural population decoding and human psychophysics* doi:10.1007/978-1-4614-1590-9-18

The context in which a stimulus occurs can influence its perception. We study contextual effects in audition using the tritone paradox, where a pair of complex (Shepard) tones separated by half an octave can be perceived as ascending or descending. While ambiguous in isolation, they are heard with a clear upward or downward change in pitch, when preceded by spectrally matched biasing sequences. We presented these biased Shepard pairs to awake ferrets and obtained neuronal responses from primary auditory cortex. Using dimensionality reduction from the neural population response, we decode the perceived pitch for each tone. The bias sequence is found to reliably shift the perceived pitch of the tones away from its central frequency. Using human

psychophysics, we provide evidence that this shift in pitch is present in active human perception as well. These results are incompatible with the standard absolute distance decoder for Shepard tones, which would have predicted the bias to attract the tones. We propose a relative decoder that takes the stimulus history into account and is consistent with the present and other data sets. © Springer Science+Business Media New York 2013.

Enjuanes, A., Albero, R., Clot, G., Navarro, A., Beà, S., Pinyol, M., . . . Jares, P. (2013). Genome-wide methylation analyses identify a subset of mantle cell lymphoma with a high number of methylated CpGs and aggressive clinicopathological features. *International Journal of Cancer*, 133(12), 2852-2863. doi:10.1002/ijc.28321

Mantle cell lymphoma (MCL) is a B-cell neoplasm with an aggressive clinical behavior characterized by the t(11;14)(q13;q32) and cyclin D1 overexpression. To clarify the potential contribution of altered DNA methylation in the development and/or progression of MCL, we performed genome-wide methylation profiling of a large cohort of primary MCL tumors (n = 132), MCL cell lines (n = 6) and normal lymphoid tissue samples (n = 31), using the Infinium HumanMethylation27 BeadChip. DNA methylation was compared to gene expression, chromosomal alterations and clinicopathological parameters. Primary MCL displayed a heterogeneous methylation pattern dominated by DNA hypomethylation when compared to normal lymphoid samples. A total of 454 hypermethylated and 875 hypomethylated genes were identified as differentially methylated in at least 10% of primary MCL. Annotation analysis of hypermethylated genes recognized WNT pathway inhibitors and several tumor suppressor genes as frequently methylated, and a substantial fraction of these genes (22%) showed a significant downregulation of their transcriptional levels. Furthermore, we identified a subset of tumors with extensive CpG methylation that had an increased proliferation signature, higher number of chromosomal alterations and poor prognosis. Our results suggest that a subset of MCL displays a dysregulation of DNA methylation characterized by the accumulation of CpG hypermethylation highly associated with increased proliferation that may influence the clinical behavior of the tumors. © 2013 UICC.

Erker, L., Azuma, H., Lee, A. Y., Guo, C., Orloff, S., Eaton, L., . . . Grompe, M. (2010). Therapeutic liver reconstitution with murine cells isolated long after death. *Gastroenterology*, 139(3), 1019-1029. doi:10.1053/j.gastro.2010.05.082; 10.1053/j.gastro.2010.05.082

BACKGROUND & AIMS: Due to the shortage of donor organs, many patients needing liver transplantation cannot receive one. For some liver diseases, hepatocyte transplantation could be a viable alternative, but donor cells currently are procured from the same sources as whole organs, and thus the supply is severely limited. METHODS: Here, we investigated the possibility of isolating viable hepatocytes for liver cell therapy from the plentiful source of morgue cadavers. To determine the utility of this approach, cells were isolated from the livers of non-heart-beating cadaveric mice long after death and transplanted into fumarylacetoacetate hydrolase-deficient mice, a model for the human metabolic liver disease hereditary tyrosinemia type I and a stringent in vivo model for hepatic cell transplantation. RESULTS: Surprisingly, complete and therapeutic liver repopulation could be achieved with hepatocytes derived up to 27 hours post mortem. CONCLUSIONS: Competitive repopulation experiments showed that cadaveric liver cells had a repopulation capacity similar to freshly isolated hepatocytes. Importantly, viable hepatocytes also could be isolated from cadaveric primate liver (monkey and human) efficiently. These data provide evidence that non-heart-beating donors could be a suitable source of hepatocytes for much longer time periods than previously thought possible.

Feller, D. (2011). *[D-Ala<sup>2</sup>]Deltorphin* Elsevier Inc. doi:10.1016/B978-008055232-3.63071-5  
[D-Ala<sup>2</sup>]Deltorphin I and II, heptapeptide relatives of deltorphin, are isolated from the skin of the Argentinian frog *Phyllomedusa bicolor* ... © 2007 Copyright © 2007 Elsevier Inc. All rights reserved.

Feller, D. (2011). *Beta funaltrexamine* Elsevier Inc. doi:10.1016/B978-008055232-3.61304-2  
Beta Funaltrexamine, a fumarate methyl ester derivative of naltrexone, is an irreversible mu-opioid receptor antagonist and a reversible kappa agonist .... © 2007 Elsevier Inc.

Feller, D. (2011). *CI 977* Elsevier Inc. doi:10.1016/B978-008055232-3.61459-X  
CI 977, an arylacetamide derivative, is a non-peptide, kappa-opioid receptor selective agonist with analgesic and diuretic activity. © 2007 Elsevier Inc. All rights reserved.

Feller, D. (2011). *Cyprodime* Elsevier Inc. doi:10.1016/B978-008055232-3.61533-8

Cyprodime, a mu-selective opioid receptor antagonist, is an alkoymorphinan derivative. It is active in a wide variety of in vivo and in vitro preparations, and behavioral tests. Cyprodime is more potent at mu-receptor sites compared to both kappa- and delta-receptor sites. © 2007 Copyright © 2007 Elsevier Inc. All rights reserved..

Feller, D. (2011). *Endomorphin 1* Elsevier Inc. doi:10.1016/B978-008055232-3.61680-0

Endomorphin-1, a mu-opioid agonist, is an endogenous peptide widely distributed throughout the nervous system in a variety of mammalian species including humans. It is efficacious in a wide spectrum of pain tests. In addition, endomorphin-1 acts as a vasodilator. Studies also suggest that it may be active in respiratory, inflammatory, and immunological processes. Horvath .... © 2007 Copyright © 2007 Elsevier Inc.

Feller, D. (2011). *Endomorphin 2* Elsevier Inc. doi:10.1016/B978-008055232-3.61681-2

Endomorphin-2, a mu-opioid agonist, is an endogenous peptide distributed throughout the nervous system with the highest concentration in the spinal cord. It has been found in a variety of mammalian species including humans. It is efficacious in a wide spectrum of pain tests. In addition, endomorphin-2 is active in gastrointestinal function, vasodilatation, and respiration. Horvath .... © 2007 Copyright © 2007 Elsevier Inc.

Feller, D. (2011). *Ethylketocyclazocine* Elsevier Inc. doi:10.1016/B978-008055232-3.61723-4

Ethylketocyclazocine, a benzomorphan derivative, is a kappa-opioid receptor agonist. It has analgesic activity in a variety of mammalian systems. © 2007 Copyright © 2007 Elsevier Inc. All rights reserved..

Feller, D. (2011). *Naloxone benzoylhydrazone* Elsevier Inc. doi:10.1016/B978-008055232-3.62240-8

Naloxone benzoylhydrazone, a derivative of naloxone, has complex pharmacological actions. It is a mixed mu-opioid antagonist, kappa-opioid agonist, and nociceptin (ORL1/orphaninFQ) antagonist. © 2007 Copyright © 2007 Elsevier Inc. All rights reserved.

Feller, D. (2011). *Norbinaltorphimine* Elsevier Inc. doi:10.1016/B978-008055232-3.62300-1

Norbinaltorphimine, a bivalent ligand, is a highly selective kappa opioid receptor antagonist. © 2007 Copyright © 2007 Elsevier Inc. All rights reserved.

Feller, D. (2011). *PL017* Elsevier Inc. doi:10.1016/B978-008055232-3.62436-5

PL017, an analog of the peptide morphiceptin, is a beta-casomorphin derivative, with potent analgesic activity .... © 2007 Copyright © 2007 Elsevier Inc. All rights reserved.

Feller, D. (2011). *Spiradoline* Elsevier Inc. doi:10.1016/B978-008055232-3.62656-X

Spiradoline (U62066), an arylacetamide, is a selective kappa-opioid agonist with analgesic activity. The (-)-enantiomer is the kappa-selective active form of the drug. © 2007 Copyright © 2007 Elsevier Inc. All rights reserved.

Feller, D. (2011). *U 69593* Elsevier Inc. doi:10.1016/B978-008055232-3.62830-2

U69593, a benzeneacetamide derivative, is a high affinity and selective kappa opioid receptor agonist with analgesic activity. © 2007 Elsevier Inc.

Ferracane, J., Fisher, J., Eisele, J. L., & Fox, C. H. (2013). Ensuring the Global Availability of High-quality Dental Restorative Materials. *Advances in Dental Research*, 25(1), 41-45.

doi:10.1177/0022034513502208; 10.1177/0022034513502208

The Minamata Convention, a global legally binding instrument (treaty) on mercury, has been the catalyst for the emerging agenda on global dental materials research. If the current and future challenges of oral health maintenance and healing on a global scale are to be met, a logical and effective research agenda for the discovery and introduction of new, environmentally sustainable, dental materials must be developed through a coordinated effort involving materials scientists, dental clinicians, representatives of industry, members of regional and national regulatory bodies, and advocacy from research organizations. For universal impact, this agenda should be created with awareness of several important ongoing initiatives, such as the WHO non-communicable diseases action plan, the UN sustainable development agenda, and the IADR Global Oral Health Inequalities Research Agenda (GOHIRA). A significant contributor to this cause is the FDI and its membership, who, through their Vision 2020 initiative, acknowledge their role and

responsibility in globally preventing and managing dental disease and providing leadership to the profession in terms of information dissemination and affecting change. Dental researchers also have an obligation to advocate for appropriate funding to match the identified research needs, thus enhancing the possibility that key decision-makers will provide the needed support to achieve the research agenda agreed upon by this diverse group of stakeholders.

Flaxel, C. J., Yeh, S., & Lauer, A. K. (2013). Combination systemic and intravitreal antiviral therapy in the management of acute retinal necrosis syndrome. *Transactions of the American Ophthalmological Society*, 111, 133-144.

Purpose: To compare the outcomes of combination systemic and intravitreal antiviral therapy vs systemic antiviral therapy alone for treating acute retinal necrosis syndrome (ARN). We hypothesize that combination therapy might result in superior visual acuity (VA) and retinal detachment (RD) outcomes vs traditional systemic antiviral therapy alone. Methods: A retrospective, interventional, comparative single-center study of patients with ARN. We reviewed demographic data, herpesvirus diagnoses, polymerase chain reaction (PCR) results, VA, RD, and the use of systemic and intravitreal antiviral therapy. Outcome measures included VA improvement by 2 or more lines, severe visual loss, VA  $\leq 20/200$ , and RD. Results: We studied 29 eyes of 24 patients, treated from 1987 through 2009. Mean age was 42.6 years and mean follow-up was 44.0 months. Twelve patients (14 eyes) were treated with combined systemic and intravitreal antiviral therapy and 12 patients (15 eyes) with systemic therapy alone. Kaplan-Meier survival analysis revealed that patients receiving combination intravitreal and systemic antiviral therapy were more likely to have VA improved by 2 lines or greater ( $P=.006$ ). Patients receiving combination therapy also showed a decreased incidence of progression to severe visual loss (0.13/patient-years [PY]) compared to patients receiving systemic therapy alone (0.54/PY,  $P=.02$ ) and had decreased incidence of RD (0.29/PY vs 0.74/PY,  $P=.03$ ). Conclusions: Combination oral and intravitreal antiviral therapy may improve visual and functional outcomes in patients with ARN. Clinicians should consider prompt administration of combination systemic and intravitreal antiviral therapy as first-line treatment for patients with clinical features of ARN.

Fleischman, A. G., Maxson, J. E., Luty, S. B., Agarwal, A., Royer, L. R., Abel, M. L., . . . Tyner, J. W.

(2013). The CSF3R T618I mutation causes a lethal neutrophilic neoplasia in mice that is responsive to therapeutic JAK inhibition. *Blood*, doi:10.1182/blood-2013-06-509976

We have recently identified targetable mutations in CSF3R (GCSFR) in 60% of chronic neutrophilic leukemia (CNL) and atypical (BCR-ABL-negative) chronic myeloid leukemia (aCML) patients. Here we demonstrate that the most prevalent, activating mutation, CSF3R T618I, is sufficient to drive a lethal myeloproliferative disorder in a murine bone marrow transplantation model. Mice transplanted with CSF3R T618I-expressing hematopoietic cells developed a myeloproliferative disorder characterized by overproduction of granulocytes and granulocytic infiltration of the spleen and liver, which was uniformly fatal. Treatment with the JAK1/2 inhibitor ruxolitinib lowered the white blood count and reduced spleen weight. This demonstrates that activating mutations in CSF3R are sufficient to drive a myeloproliferative disorder resembling aCML and CNL that is sensitive to pharmacologic JAK inhibition. This murine model is an excellent tool for the further study of neutrophilic myeloproliferative neoplasms and implicates the clinical use of JAK inhibitors for this disease.

Fleischman, R. J., Devine, M. K., Yagapen, M. A., Steichen, A. J., Hansen, M. L., Zigman, A. F., &

Spiro, D. M. (2013). Evaluation of a novel pediatric appendicitis pathway using high- and low-risk scoring systems. *Pediatric Emergency Care*, 29(10), 1060-1065.

doi:10.1097/PEC.0b013e3182a5c9b6; 10.1097/PEC.0b013e3182a5c9b6

**OBJECTIVES:** This study aimed to determine the test characteristics of a pathway for pediatric appendicitis and its effects on emergency department (ED) length of stay, imaging, and admissions. **METHODS:** Children age 3 to 18 years with suspicion for appendicitis at 1 tertiary care ED were prospectively enrolled, using validated low- and high-risk scoring systems incorporating history, physical examination, and white blood cell count. Low-risk patients were discharged or observed in the ED. High-risk patients were admitted. Those meeting neither low-risk nor high-risk criteria were evaluated by surgery, with imaging at their discretion. Chart review or telephone follow-up was conducted 2 weeks after the visit. A retrospective study before and after was also performed. Charts of a random sample of patients evaluated for appendicitis in the 8 months before and after the pathway implementation were reviewed. **RESULTS:**

Appendicitis was diagnosed in 65 of 178 patients. Of those with appendicitis, 63 were not low-risk (sensitivity, 96.9%; specificity, 40.7%). The high-risk criteria had a sensitivity of 75.3% and specificity of 75.2%. We reviewed 292 visits before and 290 after the pathway implementation. Emergency department length of stay was similar (253 minutes before vs 257 minutes after,  $P = 0.77$ ). Computed tomography was used in 12.7% of visits before and 6.9% of visits after ( $P = 0.02$ ). Use of ultrasound was not significantly different (47.3% vs 53.7%). Admission rates were not significantly different (45.5% vs 42.7%). CONCLUSIONS: The low-risk criteria had good sensitivity in ruling out appendicitis. The high-risk criteria could be used to guide referral or admission. Neither outperformed the a priori judgment of experienced providers.

Follett, K. A., Burchiel, K., Deer, T., Dupen, S., Prager, J., Turner, M. S., & Coffey, R. J. (2003).

Prevention of intrathecal drug delivery catheter-related complications. *Neuromodulation : Journal of the International Neuromodulation Society*, 6(1), 32-41. doi:10.1046/j.1525-1403.2003.03005.x; 10.1046/j.1525-1403.2003.03005.x

In an effort to improve the performance of implantable intrathecal drug delivery systems, a group of physicians experienced in the management of such devices reviewed surgical practices and principles that were associated with low catheter-related complication rates. Clinical study and postmarket data identified physicians whose patients experienced a relatively low rate of catheter-related complications. Six of those physicians (three anesthesiologists and three neurosurgeons) reviewed the number and types of intrathecal drug pumps and catheters they had implanted, with an emphasis on the specific details of successful catheter implantation techniques. The authors pooled their experiences to reach a consensus on implant techniques that are associated with a low rate of postoperative complications. The authors found that complications were minimized by the use of specific methods for catheter placement that included: a mid-to-upper lumbar dural entry level, a shallow-angle paramedian oblique insertion trajectory, and meticulous catheter anchoring and tunneling techniques. Systemic antibiotic prophylaxis, attention to pump pocket location, and surgical wound closure techniques also were important in reducing the incidence of postoperative device-related complications. Their experience indicates that specific implantation techniques using a variety of catheters and

accessories can be expected to reduce the incidence of complications after implantation of intrathecal drug administration systems.

Fonseca, V., McDuffie, R., Calles, J., Cohen, R. M., Feeney, P., Feinglos, M., . . . Riddle, M. C. (2013).

Determinants of weight gain in the action to control cardiovascular risk in diabetes trial. *Diabetes Care*, 36(8), 2162-2168. doi:10.2337/dc12-1391

OBJECTIVE-Identify determinants of weight gain in people with type 2 diabetes mellitus (T2DM) allocated to intensive versus standard glycemic control in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. RESEARCH DESIGN AND METHODS-We studied determinants of weight gain over 2 years in 8,929 participants (4,425 intensive arm and 4,504 standard arm) with T2DM in the ACCORD trial. We used general linear models to examine the association between each baseline characteristic and weight change at the 2-year visit. We fit a linear regression of change in weight and A1C and used general linear models to examine the association between each medication at baseline and weight change at the 2-year visit, stratified by glycemia allocation. RESULTS-There was significantly more weight gain in the intensive glycemia arm of the trial compared with the standard arm ( $3.0 \pm 6.7$  vs.  $0.36 \pm 6.3$  kg). On multivariate analysis, younger age, male sex, Asian race, no smoking history, high A1C, baseline BMI of 25-35, high waist circumference, baseline insulin use, and baseline metformin use were independently associated with weight gain over 2 years. Reduction of A1C from baseline was consistently associated with weight gain only when baseline A1C was elevated. Medication usage accounted for <15% of the variability of weight change, with initiation of thiazolidinedione (TZD) use the most prominent factor. Intensive participants who never took insulin or a TZD had an average weight loss of 2.9 kg during the first 2 years of the trial. In contrast, intensive participants who had never previously used insulin or TZD but began this combination after enrolling in the ACCORD trial had a weight gain of 4.6-5.3 kg at 2 years. CONCLUSIONS-Weight gain in ACCORD was greater with intensive than with standard treatment and generally associated with reduction of A1C from elevated baseline values. Initiation of TZD and/or insulin therapy was the most important medication-related factor associated with weight gain. © 2013 by the American Diabetes Association.

Fraunfelder, F. W. (2013). Liquid nitrogen cryotherapy of pterygia. *Ophthalmology*, 120(10), e70.  
doi:10.1016/j.ophtha.2013.07.009; 10.1016/j.ophtha.2013.07.009

Freeman, M. D., Eriksson, A., & Leith, W. (2013). Head and neck injury patterns in fatal falls: Epidemiologic and biomechanical considerations. *Journal of Forensic and Legal Medicine*,  
doi:10.1016/j.jflm.2013.08.005

Fatal falls often involve a head impact, which are in turn associated with a fracture of the skull or cervical spine. Prior authors have noted that the degree of inversion of the victim at the time of impact is an important predictor of the distribution of skull fractures, with skull base fractures more common than skull vault fractures in falls with a high degree of inversion. The majority of fatal fall publications have focused on skull fractures, and no research has described the association between fall circumstances and the distribution of fractures in the skull and neck. In the present study, we accessed data regarding head and neck fractures resulting from fatal falls from a Swedish autopsy database for the years 1992-2010, for the purposes of examining the relationships between skull and cervical spine fracture distribution and the circumstances of the fatal fall. Out of 102,310 medico-legal autopsies performed there were 1008 cases of falls associated with skull or cervical spine fractures. The circumstances of the falls were grouped in 3 statistically homogenous categories; falls occurring at ground level, falls from a height of <3 m or down stairs, and falls from  $\geq 3$  m. Only head and neck injuries and fractures that were associated with the fatal CNS injuries were included for study, and categorized as skull vault and skull base fractures, upper cervical injuries (C0-C1 dislocation, C1 and C2 fractures), and lower cervical fractures. Logistic regression modeling revealed increased odds of skull base and lower cervical fracture in the middle and upper fall severity groups, relative to ground level falls (lower cervical <3 m falls, OR = 2.55 [1.32, 4.92]; lower cervical  $\geq 3$  m falls, OR = 2.23 [0.98, 5.08]; skull base <3 m falls, OR = 1.82 [1.32, 2.50]; skull base  $\geq 3$  m falls, OR = 2.30 [1.55, 3.40]). C0-C1 dislocations were strongly related to fall height, with an OR of 8.3 for  $\geq 3$  m falls versus ground level. The findings of increased odds of skull base and lower cervical spine fracture in falls from a height are consistent with prior observations that the risk of such injuries is related to the degree of victim inversion at impact. The finding that C0-C1 dislocations are most common in falls from more than 3 m is unique, an indication that the injuries likely result from high energy shear

forces rather than pure tension, as previously thought. © 2013 Elsevier Ltd and Faculty of Forensic and Legal Medicine.

Fukazawa, Y. (2012). Protective immune responses against HIV/SIV by live attenuated vaccine in non-human primate models. *Virus*, 62(2), 167-174.

Live attenuated simian immunodeficiency virus (SIV) vaccines (LAVs) are currently the most effective vaccines in nonhuman primate models for AIDS, yet the basis of their robust protection remains poorly understood. Our recent immune correlate study revealed that degree of protection against pathogenic SIV challenge strongly correlated with the SIV-specific CD4+ and CD8+ T cell responses in the lymph node but neither with the responses of such T cells in the peripheral blood and mucosal tissues nor with humoral immune responses. Interestingly, the maintenance of protective T cell responses in the lymph node was associated with the amount of persistent LAV replication in the lymph node, which localized almost exclusively in follicular helper T cells. The protected monkeys manifested greater magnitude of functional effector CD8+ T cells in the lymph node, suggesting that the induction and maintenance of antiviral effector memory T cells derived by persistent antigen production have a vital role in establishment of protection. This article reviews the mechanisms of the protection in monkeys vaccinated with LAV and their implication for development of successful AIDS vaccine.

Furr, M. C., Cannady, S., Nance, R., & Wax, M. K. (2013). The use of nuclear bone scanning after fibula free tissue transfer. *The Laryngoscope*, doi:10.1002/lary.21744; 10.1002/lary.21744  
OBJECTIVES/HYPOTHESIS: To understand the role of nuclear bone scanning in the evaluation of threatened osteocutaneous free tissue transfers, identify patients who may benefit from nuclear bone scanning after head and neck reconstructive surgery, and be able to use nuclear bone scanning to help guide management of the threatened free flap. STUDY DESIGN: Retrospective case series design set in a tertiary referral center. METHODS: Records of patients undergoing bone scan in the context of threatened osteocutaneous free tissue transfer between July 1998 and December 2008 were reviewed. RESULTS: Over a 10-year period, 205 fibula free tissue transfers were performed, with an overall 94% success rate. Fifteen fibular free flaps in 14 patients were determined to be threatened in the late postoperative period, and nuclear bone

scanning was performed. Seven of 15 flaps had regions of certain flap nonviability, with five flaps clearly appearing viable on bone scanning. No graft read as potentially viable eventually failed. All grafts read as nonviable underwent exploration and debridement, with confirmation of nonviability in all cases. In eight cases, bone scanning allowed preoperative planning for soft tissue flap reconstruction. CONCLUSIONS: In those instances in which the skin paddle dies in the late postoperative period and determination of bone viability is required, a bone scan can demonstrate whether or not the bone is alive. This information can help determine the future operative and reconstructive options available for the patient. Level of Evidence: 4. Laryngoscope, 2013.

Gaba, A., Jacobson, A., & Sachs, M. S. (2005). Ribosome occupancy of the yeast CPA1 upstream open reading frame termination codon modulates nonsense-mediated mRNA decay. *Molecular Cell*, 20(3), 449-460. doi:10.1016/j.molcel.2005.09.019

*Saccharomyces cerevisiae* CPA1 mRNA contains an upstream open reading frame (uORF) encoding the arginine attenuator peptide (AAP). Negative translational regulation of CPA1 occurs when the nascent AAP responds to arginine (Arg) by stalling ribosomes at the uORF termination codon. CPA1 expression is also controlled by nonsense-mediated mRNA decay (NMD). Using wild-type and decay-defective strains expressing CPA1-LUC, we determined how this uORF contributes to NMD control. Arg addition to media rapidly destabilized the CPA1 transcript in wild-type but not *upf1delta* cells. The wild-type uORF exerted translational control and induced NMD of CPA1-LUC; the mutated D13N uORF, which eliminates stalling and regulation, did not. Thus, regulation by NMD was not governed simply by ribosomes encountering the uORF terminator but appeared dependent on the AAP's ribosome-stalling ability. Improving the D13N uORF initiation context also promoted NMD. Hence, NMD appears to be triggered by increased ribosomal occupancy of the uORF termination codon.

Gaier, E. D., Miller, M. B., Ralle, M., Aryal, D., Wetsel, W. C., Mains, R. E., & Eipper, B. A. (2013). Peptidylglycine  $\alpha$ -amidating monooxygenase heterozygosity alters brain copper handling with region specificity. *Journal of Neurochemistry*, doi:10.1111/jnc.12438

Copper (Cu), an essential trace element present throughout the mammalian nervous system, is

crucial for normal synaptic function. Neuronal handling of Cu is poorly understood. We studied the localization and expression of Atp7a, the major intracellular Cu transporter in the brain, and its relation to peptidylglycine  $\alpha$ -amidating monooxygenase (PAM), an essential cuproenzyme and regulator of Cu homeostasis in neuroendocrine cells. Based on biochemical fractionation and immunostaining of dissociated neurons, Atp7a was enriched in post-synaptic vesicular fractions. Cu followed a similar pattern, with  $\sim 20\%$  of total Cu in synaptosomes. A mouse model heterozygous for the Pam gene (PAM $+/$ -) was selectively Cu deficient in the amygdala. As in cortex and hippocampus, Atp7a and PAM expression overlap in the amygdala, with highest expression in interneurons. Messenger RNA levels of Atox-1 and Atp7a, which deliver Cu to the secretory pathway, were reduced in the amygdala but not in the hippocampus in PAM $+/$ - mice, GABAB receptor mRNA levels were similarly affected. Consistent with Cu deficiency, dopamine  $\beta$ -monooxygenase function was impaired as evidenced by elevated dopamine metabolites in the amygdala, but not in the hippocampus, of PAM $+/$ - mice. These alterations in Cu delivery to the secretory pathway in the PAM $+/$ - amygdala may contribute to the physiological and behavioral deficits observed. Atp7a, a Cu-transporting P-type ATPase, is localized to the trans-Golgi network and to vesicles distributed throughout the dendritic arbor. Tissue-specific alterations in Atp7a expression were found in mice heterozygous for peptidylglycine  $\alpha$ -amidating monooxygenase (PAM), an essential neuropeptide-synthesizing cuproenzyme. Atp7a and PAM are highly expressed in amygdalar interneurons. Reduced amygdalar expression of Atox-1 and Atp7a in PAM heterozygous mice may lead to reduced synaptic Cu levels, contributing to the behavioral and neurochemical alterations seen in these mice. Atp7a, a Cu-transporting P-type ATPase, is localized to the trans-Golgi network and to vesicles distributed throughout the dendritic arbor. Tissue-specific alterations in Atp7a expression were found in mice heterozygous for peptidylglycine  $\alpha$ -amidating monooxygenase (PAM), an essential neuropeptide-synthesizing cuproenzyme. Atp7a and PAM are highly expressed in amygdalar interneurons. Reduced amygdalar expression of Atox-1 and Atp7a in PAM heterozygous mice may lead to reduced synaptic Cu levels, contributing to the behavioral and neurochemical alterations seen in these mice. © 2013 International Society for Neurochemistry.

Ganzini, L. (2013). Psychiatric evaluations for individuals requesting assisted death in Washington and Oregon should not be mandatory. *General Hospital Psychiatry*, doi:10.1016/j.genhosppsy.2013.08.006; 10.1016/j.genhosppsy.2013.08.006

Gerber, D. E., Dahlberg, S. E., Sandler, A. B., Ahn, D. H., Schiller, J. H., Brahmer, J. R., & Johnson, D. H. (2013). Baseline tumour measurements predict survival in advanced non-small cell lung cancer. *British Journal of Cancer*, *109*(6), 1476-1481. doi:10.1038/bjc.2013.472

Background: The association between tumour measurements and survival has been studied extensively in early-stage and locally advanced non-small cell lung cancer (NSCLC). We analysed these factors in patients with advanced NSCLC. Methods: Data were derived from the E4599 trial of paclitaxel-carboplatin±bevacizumab. Associations between the Response Evaluation Criteria in Solid Tumors (RECIST) baseline sum longest diameter (BSLD), response rate, progression-free survival (PFS) and overall survival (OS) were evaluated using univariate and multivariable Cox regression models. Results: A total of 759 of the 850 patients (89%) in the E4599 trial had measurable diseases and were included in this analysis. The median BSLD was 7.5 cm. BSLD predicted OS (hazard ratio (HR) 1.41;  $P < 0.001$ ) and had a trend towards association with PFS (HR 1.14;  $P = 0.08$ ). The median OS was 12.6 months for patients with BSLD  $< 7.5$  cm compared with 9.5 months for BSLD  $\geq 7.5$  cm. This association persisted in a multivariable model controlling multiple prognostic factors, including the presence and sites of extrathoracic disease (HR 1.24;  $P = 0.01$ ). There was no association between BSLD and response rate. Conclusion: Tumour measurements are associated with survival in the E4599 trial. If validated in other populations, this parameter may provide important prognostic information to patients and clinicians. © 2013 Cancer Research UK.

Giladi, N., Horak, F. B., & Hausdorff, J. M. (2013). Classification of gait disturbances: Distinguishing between continuous and episodic changes. *Movement Disorders*, *28*(11), 1469-1473. doi:10.1002/mds.25672

The increased awareness of the importance of gait and postural control to quality of life and functional independence has led many research groups to study the pathophysiology, epidemiology, clinical, and therapeutic aspects of these motor functions. In recognition of the

increased awareness of the significance of this topic, the Movement Disorders journal is devoting this entire issue to gait and postural control. Leading research groups provide critical reviews of the current knowledge and propose future directions for this evolving field. The intensive work in this area throughout the world has created an urgent need for a unified language. Because gait and postural disturbances are so common, the clinical classification should be clear, straightforward, and simple to use. As an introduction to this special issue, we propose a new clinically based classification scheme that is organized according to the dominant observed disturbance, while taking into account the results of a basic neurological exam. The proposed classification differentiates between continuous and episodic gait disturbances because this subdivision has important ramifications from the functional, prognostic, and mechanistic perspectives. We anticipate that research into gait and postural control will continue to flourish over the next decade as the search for new ways of promoting mobility and independence aims to keep up with the exponentially growing population of aging older adults. Hopefully, this new classification scheme and the articles focusing on gait and postural control in this special issue of the Movement Disorders journal will help to facilitate future investigations in this exciting, rapidly growing area. © 2013 Movement Disorder Society.

Goswami, N. D., Pfeiffer, C. D., Horton, J. R., Chiswell, K., Tasneem, A., & Tsalik, E. L. (2013). The State of Infectious Diseases Clinical Trials: A Systematic Review of ClinicalTrials.gov. *Plos One*, 8(10) doi:10.1371/journal.pone.0077086

Background: There is a paucity of clinical trials informing specific questions faced by infectious diseases (ID) specialists. The ClinicalTrials.gov registry offers an opportunity to evaluate the ID clinical trials portfolio. Methods: We examined 40,970 interventional trials registered with ClinicalTrials.gov from 2007-2010, focusing on study conditions and interventions to identify ID-related trials. Relevance to ID was manually confirmed for each programmatically identified trial, yielding 3570 ID trials and 37,400 non-ID trials for analysis. Results: The number of ID trials was similar to the number of trials identified as belonging to cardiovascular medicine (n = 3437) or mental health (n = 3695) specialties. Slightly over half of ID trials were treatment-oriented trials (53%, vs. 77% for non-ID trials) followed by prevention (38%, vs. 8% in non-ID trials). ID trials tended to be larger than those of other specialties, with a median enrollment of 125 subjects

(interquartile range [IQR], 45-400) vs. 60 (IQR, 30-160) for non-ID trials. Most ID studies are randomized (73%) but nonblinded (56%). Industry was the funding source in 51% of ID trials vs. 10% that were primarily NIH-funded. HIV-AIDS trials constitute the largest subset of ID trials (n = 815 [23%]), followed by influenza vaccine (n = 375 [11%]), and hepatitis C (n = 339 [9%]) trials. Relative to U.S. and global mortality rates, HIV-AIDS and hepatitis C virus trials are over-represented, whereas lower respiratory tract infection trials are under-represented in this large sample of ID clinical trials. Conclusions: This work is the first to characterize ID clinical trials registered in ClinicalTrials.gov, providing a framework to discuss prioritization, methodology, and policy. © 2013 Goswami et al.

Grunwald, J. E., Daniel, E., Huang, J., Ying, G. -, Maguire, M. G., Toth, C. A., . . . Martin, D. F.

(2013). Risk of Geographic Atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials. *Ophthalmology*, doi:10.1016/j.ophtha.2013.08.015

Purpose: To describe risk factors for geographic atrophy (GA) in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT). Design: Cohort within a randomized clinical trial.

Participants: We analyzed 1024 CATT patients with no GA visible on color fundus photographs (CFPs) and/or fluorescein angiograms (FAs) at enrollment. Methods: Eyes were assigned to

ranibizumab (0.5 mg) or bevacizumab (1.25 mg) treatment and to a 2-year monthly or pro re nata (PRN) injection regimen, or monthly injections for 1 year and PRN for 1 year. Demographic, genetic, and baseline ocular characteristics and lesion features of CFP/FA and optical coherence tomography (OCT) were evaluated as risk factors for GA through 2 years of follow-up. Time-dependent Cox proportional hazard models were used to estimate adjusted hazard ratios (aHRs).

Main Outcome Measures: Development of GA. Results: By 2 years, GA developed in 187 of 1024 patients (18.3%). Baseline risk factors for GA development included baseline visual acuity (VA)  $\leq 20/200$  (aHR, 2.65; 95% confidence interval [CI], 1.43-4.93), retinal angiomatous proliferation (RAP; aHR, 1.69; 95% CI, 1.16-2.47), GA in the fellow eye (aHR, 2.07; 95% CI, 1.40-3.08), and intraretinal fluid at the foveal center (aHR, 2.10; 95% CI, 1.34-3.31). Baseline factors associated with lower risk for GA development included blocked fluorescence (aHR, 0.49; 95% CI, 0.29-0.82), OCT measurements of subretinal fluid thickness of  $>25 \mu$  (aHR, 0.52; 95% CI, 0.35-0.78), subretinal tissue complex thickness of  $>275$  compared with  $\leq 75 \mu$  (aHR, 0.31; 95% CI, 0.19-

0.50), and vitreomacular attachment (aHR, 0.55; 95% CI, 0.31-0.97). Ranibizumab compared with bevacizumab had a higher risk (aHR, 1.43; 95% CI, 1.06-1.93), and monthly dosing had a higher risk (aHR, 1.59; 95% CI, 1.17-2.16) than PRN dosing. There were no strong associations between development of GA and the presence of risk alleles for CFH, ARMS 2, HTRA1, C3, or TLR3. Conclusions: Approximately one fifth of CATT patients developed GA within 2 years of treatment. Independent baseline risk factors included poor VA, RAP, foveal intraretinal fluid, monthly dosing, and treatment with ranibizumab. Anti-vascular endothelial growth factor therapy may have a role in the development of GA. Financial Disclosure(s): The authors have no proprietary or commercial interest in any of the materials discussed in this article. © 2013 American Academy of Ophthalmology.

Gur, I., Diggs, B. S., Wagner, J. A., Vaccaro, G. M., Lopez, C. D., Sheppard, B. C., . . . Billingsley, K. G. (2013). Safety and Outcomes Following Resection of Colorectal Liver Metastases in the Era of Current Perioperative Chemotherapy. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, doi:10.1007/s11605-013-2295-1

BACKGROUND: Preoperative chemotherapy is increasingly utilized in the treatment of colorectal liver metastases (CRLM). Although this strategy may improve resectability, long-term advantages of preoperative chemotherapy for resectable CRLM are less clear. The objective of this study is to report safety and outcomes when perioperative chemotherapy is routinely added to surgery for CRLM. METHODS: A retrospective review of patients undergoing liver resections for CRLM during 2003-2011 in single academic oncology center. Demographic data, tumor characteristics, chemotherapy, surgical details, complications and survival were analyzed. RESULTS: The study included 157 patients that underwent 168 liver operations. One hundred eighteen patients (70 %) underwent preoperative chemotherapy (75 % oxaliplatin-based). Preoperative portal vein embolization was utilized in 16 (10.1 %) patients. Overall survival (OS) was 89, 57, and 27 % at 1, 3, and 5 years, respectively (median survival-42.8 months). Eleven (7 %) patients had repeat resections for liver recurrence. Thirty-day mortality was 1.26 %, morbidity-24 % (6 %-liver related). Complications were not significantly different in patients that had preoperative chemotherapy. On a multivariate analysis advanced age and >3 lesions predicted poor OS, while advanced age, lesions >5 cm, synchronous lesions, margin-positivity and resection less than

hepatectomy were associated with decreased DFS. CONCLUSIONS: Our results suggest that even with chemotherapy and resection only a subset of patients remain disease-free after 5 years. However, even in a high-risk patient with multiple lesions, preoperative chemotherapy can be administered safely without apparent increase in postoperative complications. Perioperative chemotherapy should be considered particularly in patients with multifocal or large lesions, synchronous disease and short disease-free interval.

Hakki, M., Goldman, D. C., Streblow, D. N., Hamlin, K. L., Krekylwich, C. N., Fleming, W. H., & Nelson, J. A. (2013). HCMV infection of humanized mice after transplantation of G-CSF mobilized peripheral blood stem cells from HCMV-seropositive donors. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*, doi:10.1016/j.bbmt.2013.10.019; 10.1016/j.bbmt.2013.10.019

Human cytomegalovirus (HCMV) infection remains a significant problem in the setting of peripheral blood stem cell transplant (PBSCT), including primary infection resulting from transmission from a seropositive donor to a seronegative recipient (D+/R-). The lack of an animal model suitable for studying HCMV transmission after PBSCT is a major barrier in understanding this process and, consequently, the development of novel interventions to prevent HCMV infection. Our previous work demonstrated that human CD34+ progenitor cell engrafted NOD-scid IL2Rgammacnull (NSG) mice support latent HCMV infection after direct inoculation, and reactivation after treatment with G-CSF. To more accurately recapitulate HCMV infection in the D+/R- PBSCT setting, granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSCs) from seropositive donors were used to engraft NSG mice. All recipient mice demonstrated evidence of HCMV infection in liver, spleen, and bone marrow. These observations validate the NSG mouse model as a means to study HCMV transmission during PBSCT.

Han, A. W., Sandy, M., Fishman, B., Trindade-Silva, A. E., Soares, C. A., Distel, D. L., . . . Haygood, M. G. (2013). Turnerbactin, a Novel Triscatecholate Siderophore from the Shipworm Endosymbiont *Teredinibacter turnerae* T7901. *PLoS One*, 8(10), e76151. doi:10.1371/journal.pone.0076151; 10.1371/journal.pone.0076151

Shipworms are marine bivalve mollusks (Family Teredinidae) that use wood for shelter and food.

They harbor a group of closely related, yet phylogenetically distinct, bacterial endosymbionts in bacteriocytes located in the gills. This endosymbiotic community is believed to support the host's nutrition in multiple ways, through the production of cellulolytic enzymes and the fixation of nitrogen. The genome of the shipworm endosymbiont *Teredinibacter turnerae* T7901 was recently sequenced and in addition to the potential for cellulolytic enzymes and diazotrophy, the genome also revealed a rich potential for secondary metabolites. With nine distinct biosynthetic gene clusters, nearly 7% of the genome is dedicated to secondary metabolites. Bioinformatic analyses predict that one of the gene clusters is responsible for the production of a catecholate siderophore. Here we describe this gene cluster in detail and present the siderophore product from this cluster. Genes similar to the entCEBA genes of enterobactin biosynthesis involved in the production and activation of dihydroxybenzoic acid (DHB) are present in this cluster, as well as a two-module non-ribosomal peptide synthetase (NRPS). A novel triscatecholate siderophore, turnerbactin, was isolated from the supernatant of iron-limited *T. turnerae* T7901 cultures. Turnerbactin is a trimer of N-(2,3-DHB)-L-Orn-L-Ser with the three monomeric units linked by Ser ester linkages. A monomer, dimer, dehydrated dimer, and dehydrated trimer of 2,3-DHB-L-Orn-L-Ser were also found in the supernatant. A link between the gene cluster and siderophore product was made by constructing a NRPS mutant, TtAH03. Siderophores could not be detected in cultures of TtAH03 by HPLC analysis and Fe-binding activity of culture supernatant was significantly reduced. Regulation of the pathway by iron is supported by identification of putative Fur box sequences and observation of increased Fe-binding activity under iron restriction. Evidence of a turnerbactin fragment was found in shipworm extracts, suggesting the production of turnerbactin in the symbiosis.

Hansen, M., Cedar, A., Yarris, L., Spiro, D., Ilgen, J. S., & Meckler, G. (2013). Development and implementation of a web-based instrument to assess management of pediatric respiratory emergencies among trainees. *Pediatric Emergency Care*, 29(9), 1037-1040.  
doi:10.1097/PEC.0b013e3182a36082

Hansen, S. G., Vieville, C., Whizin, N., Coyne-Johnson, L., Siess, D. C., Drummond, D. D., . . . Picker, L. J. (2009). Effector memory T cell responses are associated with protection of rhesus monkeys

from mucosal simian immunodeficiency virus challenge. *Nature Medicine*, 15(3), 293-299.

doi:10.1038/nm.1935; 10.1038/nm.1935

The rapid onset of massive, systemic viral replication during primary HIV or simian immunodeficiency virus (SIV) infection and the immune evasion capabilities of these viruses pose fundamental problems for vaccines that depend upon initial viral replication to stimulate effector T cell expansion and differentiation. We hypothesized that vaccines designed to maintain differentiated effector memory T cell (TEM cell) responses at viral entry sites might improve efficacy by impairing viral replication at its earliest stage, and we have therefore developed SIV protein-encoding vectors based on rhesus cytomegalovirus (RhCMV), the prototypical inducer of life-long TEM cell responses. RhCMV vectors expressing SIV Gag, Rev-Tat-Nef and Env persistently infected rhesus macaques, regardless of preexisting RhCMV immunity, and primed and maintained robust, SIV-specific CD4+ and CD8+ TEM cell responses (characterized by coordinate tumor necrosis factor, interferon-gamma and macrophage inflammatory protein-1beta expression, cytotoxic degranulation and accumulation at extralymphoid sites) in the absence of neutralizing antibodies. Compared to control rhesus macaques, these vaccinated rhesus macaques showed increased resistance to acquisition of progressive SIVmac239 infection upon repeated limiting-dose intrarectal challenge, including four macaques who controlled rectal mucosal infection without progressive systemic dissemination. These data suggest a new paradigm for AIDS vaccine development--vaccines capable of generating and maintaining HIV-specific TEM cells might decrease the incidence of HIV acquisition after sexual exposure.

Hartung, D. M., Zerzan, J., Yamashita, T., Tong, S., Morden, N. E., & Libby, A. M. (2013).

Characteristics and trends of low-dose quetiapine use in two western state Medicaid programs.

*Pharmacoepidemiology and Drug Safety*, doi:10.1002/pds.3538; 10.1002/pds.3538

PURPOSE: Medicaid programs are concerned about inappropriate, potentially hazardous, and costly off-label use of second-generation antipsychotics (SGAs). Several states are exploring policies aimed at managing low-dose quetiapine, commonly prescribed for off-label conditions. This study aimed to characterize longitudinal trends and patient characteristics associated with low-dose quetiapine in two state Medicaid programs. We further aimed to quantify changes in the use of quetiapine associated with a legal settlement that curtailed off-label promotion of this

product. METHODS: Using administrative data from two state Medicaid programs, Oregon and Colorado, we identified SGA initiators and determined patient level factors associated with receipt of low-dose SGAs. We evaluated changes in low-dose quetiapine initiation during and after a period in which quetiapine was being promoted illegally for off-label purposes. RESULTS: We identified 14 763 new SGA starts during the study period. Low-dose (versus therapeutic dose) SGA use was common in both states, representing 53% to 56% of initiators. Quetiapine was the most commonly used SGA in both states and both dose ranges. Diagnoses of schizophrenia, bipolar disorder, posttraumatic stress disorder, anxiety disorder, and use of newer sedative hypnotics were associated with lower likelihood of initiating low-dose quetiapine. Initiation of low-dose quetiapine as a proportion of all SGA initiation and of all quetiapine initiation significantly declined in Oregon following suspension of off-label promotional activities. CONCLUSIONS: Low-dose SGA and specifically low-dose quetiapine use remains common. Medicaid programs must set policies carefully to maximize the net safety of prescription use while optimizing disease management considering the potential for substitution effects. Copyright (c) 2013 John Wiley & Sons, Ltd.

Hayes, M., Muhota, J., Nguyen, L., Nedrow, A., Calabrese, C., & Shinto, L. (2013). A Framework for Credentialing Naturopathic Physicians in Academic Health Centers: Oregon Health and Science University. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, doi:10.1089/acm.2013.0299

Hayes, T. L., Riley, T., Mattek, N., Pavel, M., & Kaye, J. A. (2013). Sleep Habits in Mild Cognitive Impairment. *Alzheimer Disease and Associated Disorders*, doi:10.1097/WAD.000000000000010

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 amnesic MCI (aMCI) volunteers had

less disturbed sleep than both nonamnesic 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 ( $F_{2,1078}=41.6$ ,  $P<0.001$ ), and number of times up at night ( $F_{2,1078}=26.7$ ,  $P<0.001$ ). 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.

Heinonen, K., Eriksson, J. G., Kajantie, E., Pesonen, A. -, Barker, D. J., Osmond, C., & Raikonen, K.

(2013). Late-preterm birth and lifetime socioeconomic attainments: The Helsinki Birth Cohort Study. *Pediatrics*, *132*(4), 647-655. doi:10.1542/peds.2013-0951

Objective: We examined if those born late-preterm (at 34 to 36 weeks of gestation) differed from those born at term in their maximum attained lifetime socioeconomic position (SEP) across the adult years up to 56 to 66 years, and in intergenerational social mobility from childhood parental SEP to own attained SEP. Methods: Participants were 8993 Finnish men and women of the Helsinki Birth Cohort Study born between 1934 and 1944. Gestational age was extracted from hospital birth records and socioeconomic attainments from Finnish National Census. Results: Compared with those born at term, those born late-preterm were more likely to be manual workers, have a basic or upper secondary level of education, belong to the lowest third based on their incomes, and less likely to belong to the highest third based on their incomes. Late-preterm individuals were also less likely to be upwardly mobile and more likely to be downwardly mobile; they were less likely to have higher occupations and more likely to have lower occupations than their fathers. They were also less likely to be upwardly mobile if incomes were used as the outcome of own attained SEP, and men were more likely to be downwardly mobile if education was used as the outcome of own attained SEP. Conclusions: This study demonstrates that there are considerable long-term socioeconomic disadvantages associated with latepreterm birth, which are not explained by the parent-of-origin SEP. © 2013 by the American Academy of Pediatrics.

Hidayatullah, M., & Fromme, E. K. (2013). Die in a foreign land or forgo cancer care: Difficult choices faced by the expatriate workers in the United Arab Emirates. *Journal of Pain and Symptom Management*, 46(4), e8-e10. doi:10.1016/j.jpainsymman.2013.07.002

Horak, F. B., & Mancini, M. (2013). Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Movement Disorders : Official Journal of the Movement Disorder Society*, 28(11), 1544-1551. doi:10.1002/mds.25684; 10.1002/mds.25684

Balance and gait impairments characterize the progression of Parkinson's disease (PD), predict the risk of falling, and are important contributors to reduced quality of life. Advances in technology of small, body-worn, inertial sensors have made it possible to develop quick, objective measures of balance and gait impairments in the clinic for research trials and clinical practice. Objective balance and gait metrics may eventually provide useful biomarkers for PD. In fact, objective balance and gait measures are already being used as surrogate endpoints for demonstrating clinical efficacy of new treatments, in place of counting falls from diaries, using stop-watch measures of gait speed, or clinical balance rating scales. This review summarizes the types of objective measures available from body-worn sensors. The metrics are organized based on the neural control system for mobility affected by PD: postural stability in stance, postural responses, gait initiation, gait (temporal-spatial lower and upper body coordination and dynamic equilibrium), postural transitions, and freezing of gait. However, the explosion of metrics derived by wearable sensors during prescribed balance and gait tasks, which are abnormal in individuals with PD, do not yet qualify as behavioral biomarkers, because many balance and gait impairments observed in PD are not specific to the disease, nor have they been related to specific pathophysiologic biomarkers. In the future, the most useful balance and gait biomarkers for PD will be those that are sensitive and specific for early PD and are related to the underlying disease process. (c) 2013 International Parkinson and Movement Disorder Society.

Hsu, Y. -, & Wright, C. L. (2013). The association between participation in social activity and depressive symptoms in institutionalized elders in Taiwan. *Geriatric Nursing*, doi:10.1016/j.gerinurse.2013.09.004

Depression can be a significant predictor of rapid health decline in institutionalized elders. Non-

pharmacologic interventions for depression may include meaningful and enjoyable social activities. This cross-sectional, descriptive correlational study was to examine the associations between three components (frequency, meaningfulness and enjoyment) of nine types of social activities and depressive symptoms in a sample of Taiwanese elders living in long-term care facilities. Results indicated that meaningful and enjoyable activities were associated with fewer depressive symptoms among institutionalized elders. Clinically depressed elders (GDS score  $\geq 6$ ) were significantly less likely to report a sense of meaning in 6 of 9 social activities, or to report as enjoyable 7 of 9 social activities investigated. Findings suggest that elders' contemplate assignation of meaning of their subjective experiences with social activities, and it would behoove clinical nurses to pay attention to the essential purpose and perceived benefit of the designed social activities. © 2013 Mosby, Inc. All rights reserved.

Huang, D., Tang, M., Wang, L., Zhang, X., Armour, R. L., Gattety, D. M., . . . Koch, D. D. (2013).

Optical coherence tomography-based corneal power measurement and intraocular lens power calculation following laser vision correction (an american ophthalmological society thesis).

*Transactions of the American Ophthalmological Society*, 111, 34-45.

PURPOSE: To use optical coherence tomography (OCT) to measure corneal power and improve the selection of intraocular lens (IOL) power in cataract surgeries after laser vision correction.

METHODS: Patients with previous myopic laser vision corrections were enrolled in this prospective study from two eye centers. Corneal thickness and power were measured by Fourier-domain OCT. Axial length, anterior chamber depth, and automated keratometry were measured by a partial coherence interferometer. An OCT-based IOL formula was developed. The mean absolute error of the OCT-based formula in predicting postoperative refraction was compared to two regression-based IOL formulae for eyes with previous laser vision correction. RESULTS: Forty-six eyes of 46 patients all had uncomplicated cataract surgery with monofocal IOL implantation. The mean arithmetic prediction error of postoperative refraction was 0.05 +/- 0.65 diopter (D) for the OCT formula, 0.14 +/- 0.83 D for the Haigis-L formula, and 0.24 +/- 0.82 D for the no-history Shammas-PL formula. The mean absolute error was 0.50 D for OCT compared to a mean absolute error of 0.67 D for Haigis-L and 0.67 D for Shammas-PL. The adjusted mean absolute error (average prediction error removed) was 0.49 D for OCT, 0.65 D for Haigis-L

( $P=.031$ ), and 0.62 D for Shammas-PL ( $P=.044$ ). For OCT, 61% of the eyes were within 0.5 D of prediction error, whereas 46% were within 0.5 D for both Haigis-L and Shammas-PL ( $P=.034$ ).

CONCLUSIONS: The predictive accuracy of OCT-based IOL power calculation was better than Haigis-L and Shammas-PL formulas in eyes after laser vision correction.

Iams, J. D., Grobman, W. A., Lozitska, A., Spong, C. Y., Saade, G., Mercer, B. M., . . . Van Dorsten, P. J. (2013). Adherence to criteria for transvaginal ultrasound imaging and measurement of cervical length. *American Journal of Obstetrics and Gynecology*, 209(4), 365.e1-365.e5.

doi:10.1016/j.ajog.2013.07.032

Objective Adherence to published criteria for transvaginal imaging and measurement of cervical length is uncertain. We sought to assess adherence by evaluating images submitted to certify research sonographers for participation in a clinical trial. Study Design We reviewed qualifying test results of sonographers seeking certification to image and measure cervical length in a clinical trial. Participating sonographers were required to access training materials and submit 15 images, 3 each from 5 pregnant women not enrolled in the trial. One of 2 sonologists reviewed all qualifying images. We recorded the proportion of images that did not meet standard criteria (excess compression, landmarks not seen, improper image size, or full maternal bladder) and the proportion in which the cervical length was measured incorrectly. Failure for a given patient was defined as >1 unacceptable image, or >2 acceptable images with incorrect caliper placement or erroneous choice of the "shortest best" cervical length. Certification required satisfactory images and cervical length measurement from  $\geq 4$  patients. Results A total of 327 sonographers submitted 4905 images. A total of 271 sonographers (83%) were certified on the first, 41 (13%) on the second, and 2 (0.6%) on the third submission. Thirteen never achieved certification. Of 314 who passed, 196 submitted 15 acceptable images that were appropriately measured for all 5 women. There were 1277 deficient images: 493 were acceptable but incorrectly measured images from sonographers who passed certification because mismeasurement occurred no more than twice. Of 784 deficient images submitted by sonographers who failed the certification, 471 were rejected because of improper measurement (caliper placement and/or failure to identify the shortest best image), and 313 because of failure to obtain a satisfactory image (excessive compression, required landmarks not visible, incorrect image size, brief examination, and/or full

maternal bladder). Conclusion Although 83% of sonographers were certified on their first submission, >1 in 4 ultrasound images submitted did not meet published quality criteria. Increased attention to standardized education and credentials is warranted for persons who perform ultrasound examinations of the cervix in pregnancy. © 2013 Mosby, Inc. All rights reserved.

Iwamoto, M., Mu, Y., Lynfield, R., Bulens, S. N., Nadle, J., Aragon, D., . . . Lessa, F. C. (2013). Trends in invasive methicillin-resistant *Staphylococcus aureus* infections. *Pediatrics*, *132*(4), e817-e824. doi:10.1542/peds.2013-1112

Objective: To describe trends in the incidence of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in children during 2005-2010. Methods: We evaluated reports of invasive MRSA infections in pediatric patients identified from population-based surveillance during 2005-2010. Cases were defined as isolation of MRSA from a normally sterile site and classified on the basis of the setting of the positive culture and presence or absence of health care exposures. Estimated annual changes in incidence were determined by using regression models. National age- and race-specific incidences for 2010 were estimated by using US census data. Results: A total of 876 pediatric cases were reported; 340 (39%) were among infants. Overall, 35% of cases were hospital-onset, 23% were health care-associated community-onset, and 42% were community-associated (CA). The incidence of invasive CA-MRSA infection per 100 000 children increased from 1.1 in 2005 to 1.7 in 2010 (modeled yearly increase: 10.2%; 95% confidence interval: 2.7%-18.2%). No significant trends were observed for health care-associated community-onset and hospital-onset cases. Nationally, estimated invasive MRSA incidence in 2010 was higher among infants aged <90 days compared with older infants and children (43.9 vs 2.0 per 100 000) and among black children compared with other races (6.7 vs 1.6 per 100 000). Conclusions: Invasive MRSA infection in children disproportionately affects young infants and black children. In contrast to reports of declining incidence among adults, there were no significant reductions in health care-associated MRSA infections in children. Concurrently, the incidence of CA-MRSA infections has increased, underscoring the need for defining optimal strategies to prevent MRSA infections among children with and without health care exposures. © 2013 by the American Academy of Pediatrics.

Izumi, S., Vandermause, R., & Benavides-Vaello, S. (2013). Adapting cognitive interviewing for nursing research. *Research in Nursing & Health*, doi:10.1002/nur.21567; 10.1002/nur.21567

Cognitive interviewing (CI) has been used by instrument developers to examine how well an instrument generates the intended data when tested with prospective respondents. In using CI to test a new instrument to measure patients' perceptions of the quality of nursing care, the authors found challenges in applying a theory-based traditional CI approach derived from experimental psychology to more clinically oriented nursing research. The purposes of this article are to describe these challenges and the modifications of CI to capture the nursing care perspectives of hospitalized participants, and to present interpretive phenomenology as a theoretical orientation for clinically situated CI. (c) 2013 Wiley Periodicals, Inc. Res Nurs Health.

Jack, A., Mauro, M. J., & Ehst, B. D. (2013). Pityriasis rubra pilaris-like eruption associated with the multikinase inhibitor ponatinib. *Journal of the American Academy of Dermatology*, 69(5), e249-50. doi:10.1016/j.jaad.2013.04.061; 10.1016/j.jaad.2013.04.061

Jennes, L., Ulloa-Aguirre, A., Janovick, J. A., Adjan, V. V., & Conn, P. M. (2010). *The gonadotropin-releasing hormone and its receptor* Elsevier Inc. doi:10.1016/B978-008088783-8.00051-6

Gonadotropin-releasing hormone (GnRH) is the central neuropeptide in vertebrates that controls the synthesis and release of luteinizing hormone and follicle-stimulating hormone in the anterior pituitary. Its prevalence suggests that it is required for the reproductive success of many species. It is therefore important to understand the factors that control the synthesis and release of GnRH in the brain as well as the mechanisms by which GnRH controls the responses of its targets in the central nervous system and in the anterior pituitary. This chapter focuses on the development and anatomy of the GnRH neuronal system; some of the actions and mechanisms that regulate GnRH neurons; and the localization, regulation, and functional aspects of GnRH receptors in the brain. Finally, the mechanisms of action of GnRH in the anterior pituitary or pituitary-derived cell lines are discussed. © 2009 Elsevier Inc. All rights reserved.

Johnatty, S. E., Beesley, J., Gao, B., Chen, X., Lu, Y., Law, M. H., . . . Chenevix-Trench, G. (2013). ABCB1 (MDR1) polymorphisms and ovarian cancer progression and survival: A comprehensive analysis from the Ovarian Cancer Association Consortium and the Cancer Genome Atlas.

*Gynecologic Oncology*, 131(1), 8-14. doi:10.1016/j.ygyno.2013.07.107

Objective. ABCB1 encodes the multi-drug efflux pump P-glycoprotein (P-gp) and has been implicated in multi-drug resistance. We comprehensively evaluated this gene and flanking regions for an association with clinical outcome in epithelial ovarian cancer (EOC). Methods. The best candidates from fine-mapping analysis of 21 ABCB1 SNPs tagging C1236T (rs1128503), G2677T/A (rs2032582), and C3435T (rs1045642) were analysed in 4616 European invasive EOC patients from thirteen Ovarian Cancer Association Consortium (OCAC) studies and The Cancer Genome Atlas (TCGA). Additionally we analysed 1,562 imputed SNPs around ABCB1 in patients receiving cytoreductive surgery and either 'standard' first-line paclitaxel-carboplatin chemotherapy (n = 1158) or any first-line chemotherapy regimen (n = 2867). We also evaluated ABCB1 expression in primary tumours from 143 EOC patients. Result. Fine-mapping revealed that rs1128503, rs2032582, and rs1045642 were the best candidates in optimally debulked patients. However, we observed no significant association between any SNP and either progression-free survival or overall survival in an analysis of data from 14 studies. There was a marginal association between rs1128503 and overall survival in patients with nil residual disease (HR 0.88, 95% CI 0.77-1.01; p = 0.07). In contrast, ABCB1 expression in the primary tumour may confer worse prognosis in patients with sub-optimally debulked tumours. Conclusion. Our study represents the largest analysis of ABCB1 SNPs and EOC progression and survival to date, but has not identified additional signals, or validated reported associations with progression-free survival for rs1128503, rs2032582, and rs1045642. However, we cannot rule out the possibility of a subtle effect of rs1128503, or other SNPs linked to it, on overall survival. © 2013 The Authors. Published by Elsevier Inc. All rights reserved.

Kajino, K., Kitamura, T., Iwami, T., Daya, M., Ong, M. E. H., Nishiyama, C., . . . Shimazu, T. (2013).

Impact of the number of on-scene emergency life-saving technicians and outcomes from out-of-hospital cardiac arrest in Osaka City. *Resuscitation*, doi:10.1016/j.resuscitation.2013.09.002

Backgrounds: In Japan, ambulance staffing for cardiac arrest responses consists of a 3-person unit with at least one emergency life-saving technician (ELST). Recently, the number of ELSTs on ambulances has increased since it is believed that this improves the quality of on-scene care leading to better outcomes from out-of-hospital cardiac arrest (OHCA). The objective of this

study was to evaluate the association between the number of on-scene ELSTs and OHCA outcome. Methods: This was a prospective cohort study of all bystander-witnessed OHCA patients aged  $\geq 18$  years in Osaka City from January 2005 to December 2007 using an Utstein-style database. The primary outcome measure was one-month survival with favorable neurological outcome defined as a cerebral performance category  $\leq 2$ . Multivariable logistic regression models were used to assess the contribution of the number of on-scene ELSTs to the outcome after adjusting for confounders. Results: Of the 2408 bystander-witnessed OHCA patients, one ELST group was present in 639 (26.5%), two ELST were present in 1357 (56.4%), and three ELST group in 412 (17.1%). The three ELST group had a significantly higher rate of one-month survival with favorable neurological outcome compared with the one ELST group (8.0% versus 4.5%, adjusted OR 2.26, 95% CI 1.27-4.04), while the two ELST group did not (5.4% versus 4.5%, adjusted OR 1.34, 95% CI 0.82-2.19). Conclusions: Compared with the one on-scene ELST group, the three on-scene ELST group was associated with the improved one-month survival with favorable neurological outcome from OHCA in Osaka City. © 2013 Elsevier Ireland Ltd. All rights reserved.

Kantor, M., Wright, A., Burton, M., Fraser, G., Krall, M., Maviglia, S., . . . Middleton, B. (2011).

Comparison of computer-based clinical decision support systems and content for diabetes mellitus. *Applied Clinical Informatics*, 2(3), 284-303. doi:10.4338/ACI-2011-02-RA-0012

Background: Computer-based clinical decision support (CDS) systems have been shown to improve quality of care and workflow efficiency, and health care reform legislation relies on electronic health records and CDS systems to improve the cost and quality of health care in the United States; however, the heterogeneity of CDS content and infrastructure of CDS systems across sites is not well known. Objective: We aimed to determine the scope of CDS content in diabetes care at six sites, assess the capabilities of CDS in use at these sites, characterize the scope of CDS infrastructure at these sites, and determine how the sites use CDS beyond individual patient care in order to identify characteristics of CDS systems and content that have been successfully implemented in diabetes care. Methods: We compared CDS systems in six collaborating sites of the Clinical Decision Support Consortium. We gathered CDS content on care for patients with diabetes mellitus and surveyed institutions on characteristics of their site, the

infrastructure of CDS at these sites, and the capabilities of CDS at these sites. Results: The approach to CDS and the characteristics of CDS content varied among sites. Some commonalities included providing customizability by role or user, applying sophisticated exclusion criteria, and using CDS automatically at the time of decision-making. Many messages were actionable recommendations. Most sites had monitoring rules (e.g. assessing hemoglobin A1c), but few had rules to diagnose diabetes or suggest specific treatments. All sites had numerous prevention rules including reminders for providing eye examinations, influenza vaccines, lipid screenings, nephropathy screenings, and pneumococcal vaccines. Conclusion: Computer-based CDS systems vary widely across sites in content and scope, but both institution-created and purchased systems had many similar features and functionality, such as integration of alerts and reminders into the decision-making workflow of the provider and providing messages that are actionable recommendations. © Schattauer 2011.

Kaplan, J. S., Mohr, C., & Rossi, D. J. (2013). Opposite actions of alcohol on tonic GABA receptor currents mediated by nNOS and PKC activity. *Nature Neuroscience*, doi:10.1038/nn.3559; 10.1038/nn.3559

The molecular mechanisms that mediate genetic variability in response to alcohol are unclear. We found that alcohol had opposite actions (enhancement or suppression) on GABA<sub>A</sub> receptor (GABA<sub>A</sub>R) inhibition in granule cells from the cerebellum of behaviorally sensitive, low alcohol-consuming Sprague-Dawley rats and DBA/2 mice and behaviorally insensitive, high alcohol-consuming C57BL/6 mice, respectively. The effect of alcohol on granule cell GABA<sub>A</sub>R inhibition was determined by a balance between two opposing effects: enhanced presynaptic vesicular release of GABA via alcohol inhibition of nitric oxide synthase (NOS) and a direct suppression of the activity of postsynaptic GABA<sub>A</sub>Rs. The balance of these two processes was determined by differential expression of neuronal NOS (nNOS) and postsynaptic PKC activity, both of which varied across the rodent genotypes. These findings identify opposing molecular processes that differentially control the magnitude and polarity of GABA<sub>A</sub>R responses to alcohol across rodent genotypes.

Katznelson, L., Loriaux, D. L., Feldman, D., Braunstein, G. D., Scheingart, D. E., & Gross, C. (2013).

Global clinical response in Cushing's syndrome patients treated with mifepristone. *Clinical Endocrinology*, doi:10.1111/cen.12332

Objective: Mifepristone, a glucocorticoid receptor antagonist, improves clinical status in patients with Cushing's syndrome (CS). We examined the pattern, reliability and correlates of global clinical response (GCR) assessments during a 6-month clinical trial of mifepristone in CS. Design: Post hoc analysis of secondary end-point data from a 24-week multicentre, open-label trial of mifepristone (300-1200 mg daily) in CS. Intraclass correlation coefficient (ICC) was used to examine rater concordance, and drivers of clinical improvement were determined by multivariate regression analysis. Patients: Forty-six adult patients with refractory CS along with diabetes mellitus type 2 or impaired glucose tolerance, and/or a diagnosis of hypertension. Measurements: Global clinical assessment made by three independent reviewers using a three-point ordinal scale (+1 = improvement; 0 = no change; -1 = worsening) based on eight broad clinical categories including glucose control, lipids, blood pressure, body composition, clinical appearance, strength, psychiatric/cognitive symptoms and quality of life at Weeks 6, 10, 16, and 24. Results: Positive GCR increased progressively over time with 88% of patients having improved at Week 24 ( $P < 0.001$ ). The full concordance among reviewers occurred in 76.6% of evaluations resulting in an ICC of 0.652 ( $P < 0.001$ ). Changes in body weight ( $P < 0.0001$ ), diastolic blood pressure ( $P < 0.0001$ ), two-hour postoral glucose challenge glucose concentration ( $P = 0.0003$ ), and Cushingoid appearance ( $P = 0.022$ ) were strong correlates of GCR. Conclusions: Mifepristone treatment for CS results in progressive clinical improvement. Overall agreement among clinical reviewers was substantial and determinants of positive GCR included change in weight, blood pressure, glucose levels and appearance. © 2013 The Authors.

Kaufman, J. A. (2013). Still so far to go. *Journal of Vascular and Interventional Radiology : JVIR*, 24(11), 1669-1670. doi:10.1016/j.jvir.2013.08.019; 10.1016/j.jvir.2013.08.019

Knoll, J. G., Clay, C. M., Bouma, G. J., Henion, T. R., Schwarting, G. A., Millar, R. P., & Tobet, S. A. (2013). Developmental profile and sexually dimorphic expression of kiss1 and kiss1r in the fetal mouse brain. *Frontiers in Endocrinology*, 4, 140. doi:10.3389/fendo.2013.00140;

10.3389/fendo.2013.00140

The hypothalamic-pituitary-gonadal axis (HPG) is a complex neuroendocrine circuit involving multiple levels of regulation. Kisspeptin neurons play essential roles in controlling the HPG axis from the perspectives of puberty onset, oscillations of gonadotropin releasing hormone (GnRH) neuron activity, and the pre-ovulatory LH surge. The current studies focus on the expression of kisspeptin during murine fetal development using in situ hybridization (ISH), quantitative reverse transcription real-time PCR (QPCR), and immunocytochemistry. Expression of mRNA coding for kisspeptin (KISS1) and its receptor KISS1R was observed at embryonic (E) day 13 by ISH. At E13 and other later ages examined, Kiss1 signal in individual cells within the arcuate nucleus (ARC) appeared stronger in females than males. ISH examination of gonadal steroidogenic factor-1 (Sf1) knockout mice revealed that E17 XY knockouts (KO) resembled wild-type (WT) XX females. These findings raise the possibility that gonadal hormones modulate the expression of Kiss1 in the ARC prior to birth. The sex and genotype differences were tested quantitatively by QPCR experiments in dissected hypothalami from mice at E17 and adulthood. Females had significantly more Kiss1 than males at both ages, even though the number of cells detected by ISH was similar. In addition, QPCR revealed a significant difference in the amount of Kiss1 mRNA in Sf1 mice with WT XY mice expressing less than XY KO and XX mice of both genotypes. The detection of immunoreactive KISS1 in perikarya of the ARC at E17 indicates that early mRNA is translated to peptide. The functional significance of this early expression of Kiss1 awaits elucidation.

Kobau, R., Bann, C., Lewis, M., Zack, M. M., Boardman, A. M., Boyd, R., . . . Lucas, R. E. (2013).

Mental, social, and physical well-being in new hampshire, oregon, and washington, 2010 behavioral risk factor surveillance system: Implications for public health research and practice related to healthy people 2020 foundation health measures on well-being. *Population Health Metrics*, 11(1) doi:10.1186/1478-7954-11-19

Background: Well-being is now accepted as one of four cross-cutting measures in gauging progress for Healthy People 2020. This shift to population indicators of well-being redresses notions of health that have focused on absence of illness (negative health) as a primary or sufficient indicator of positive functioning. The purpose of this study was to estimate mental,

social, and physical well-being in three US states using new measures piloted on the 2010 Behavioral Risk Factor Surveillance Survey System (BRFSS). Baseline estimates were provided for states overall, and within states for demographic subgroups, those with chronic health conditions or disabilities, and those with behavioral risk factors. Methods: Ten validated questions designed to assess mental (e.g., satisfaction with life, satisfaction with life domains, happiness), physical (e.g., satisfaction with energy level), and social dimensions (e.g., frequency of social support) of well-being were selected with state input for inclusion on BRFSS. 18,622 individuals responded to the BRFSS surveys administered by New Hampshire (N = 3,139), Oregon (N = 2,289), and Washington (N = 13,194). Multivariate adjusted proportions of positive responses to well-being items were examined. Results: After adjustment for confounders, about 67% of adults in these states had high levels of well-being, including >80% reporting experiencing happiness. Most adults were satisfied with their work, neighborhood, and education, but significant differences were seen in subgroups. Well-being differed by demographic characteristics such as marital status, health behaviors, chronic conditions, and disability status, with those who reported a disability and smokers consistently experiencing the worst well-being. Conclusions: Well-being is accepted as one of four cross-cutting measures in gauging progress for Healthy People 2020. Well-being differs by important sociodemographic factors and health conditions (e.g., age, employment, smoking, disability status). These findings provide baseline estimates for the three states to use in gauging improvements in well-being and can serve as a model for other state-level or national surveillance systems. These findings also assist states in identifying vulnerable subgroups who may benefit from potential interventions such as those in the National Prevention Strategy that focus on enhancing well-being where such disparities exist. © 2013 Kobau et al.; licensee BioMed Central Ltd.

Kong, B., Qia, C., Erkan, M., Kleeff, J., & Michalski, C. W. (2013). Overview on how oncogenic Kras promotes pancreatic carcinogenesis by inducing low intracellular ROS levels. *Frontiers in Physiology*, 4 SEP doi:10.3389/fphys.2013.00246

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease without clearly known disease causes. Recent epidemiological and animal studies suggest that the supplementation of dietary antioxidants (e.g., vitamins C and E) decreases cancer risk, implying that increased reactive

oxygen species (ROS) may play a role in pancreatic carcinogenesis. However, oncogenic Kras mutations (e.g., KrasG12D), which are present in more than 90% of PDAC, have been proven to foster low intracellular ROS levels. Here, oncogenic Kras activates expression of a series of anti-oxidant genes via Nrf2 (nuclear factor, erythroid derived 2, like 2) and also mediates an unusual metabolic pathway of glutamine to generate NADPH. This can then be used as the reducing power for ROS detoxification, leading collectively to low ROS levels in pancreatic pre-neoplastic cells and in cancer cells. In adult stem cells and cancer stem cells, low ROS levels have been associated with the formation of a proliferation-permissive intracellular environment and with perseverance of selfrenewal capacities. Therefore, it is conceivable that low intracellular ROS levels may contribute significantly to oncogenic Krasmediated PDAC formation. © 2013 Kong, Qia, Erkan, Kleeffand Michalski.

Kroenke, C. D., Rohlfing, T., Park, B., Sullivan, E. V., Pfefferbaum, A., & Grant, K. A. (2013). Monkeys

that Voluntarily and Chronically Drink Alcohol Damage their Brains: A Longitudinal MRI Study.

*Neuropsychopharmacology : Official Publication of the American College of*

*Neuropsychopharmacology*, doi:10.1038/npp.2013.259; 10.1038/npp.2013.259

Neuroimaging has consistently documented reductions in brain tissue of alcoholics. Inability to control comorbidity, environmental insult, and nutritional deficiency, however, confound the ability to assess whether ethanol itself is neurotoxic. Here we report monkey oral ethanol self-administration combined with MR imaging to characterize brain changes over 15 months in 18 well-nourished rhesus macaques. Significant brain volume shrinkage occurred in the cerebral cortices of monkeys drinking  $\geq 3$  g/kg ethanol/day (12 alcoholic drinks) at 6 months, and this persisted throughout the period of continuous access to ethanol. Correlation analyses revealed a cerebral cortical volumetric loss of approximately 0.11% of the intracranial vault for each daily drink (0.25 g/kg), and selective vulnerability of cortical and non-cortical brain regions. These results demonstrate for the first time a direct relation between oral ethanol intake and measures of decreased brain gray matter volume in vivo in primates. Notably, greater volume shrinkage occurred in monkeys with younger drinking onset that ultimately became heavier drinkers than monkeys with older drinking onset. The pattern of volumetric changes observed in nonhuman primates following 15 months of drinking suggests that cerebral cortical gray matter changes are

the first macroscopic manifestation of chronic ethanol exposure in the brain. *Neuropsychopharmacology* accepted article preview online, 27 September 2013.  
doi:10.1038/npp.2013.259.

Kweon, H. -, Ferracane, J., Kang, K., Dhont, J., & Lee, I. -. (2013). Spatio-temporal analysis of shrinkage vectors during photo-polymerization of composite. *Dental Materials*,  
doi:10.1016/j.dental.2013.09.011

**Objectives:** The purpose of this study was to validate a new method to investigate the polymerization shrinkage vectors of composite during light curing and to evaluate the overall utility and significance of the technique. **Methods:** An optical instrument was developed to measure the location and direction of the polymerization shrinkage strain vectors of dental composite during light curing using a particle tracking method with computer vision. The measurement system consisted of a CCD color camera, a lens and a filter, and software for multi-particle tracking. A universal hybrid composite (Z250, 3M ESPE, St. Paul MN, USA) was molded into thin disk-shaped specimens (un-bonded and bonded) or filled into a cavity within a tooth slab (bonded). The composite surface was coated with fluorescent particles prior to light curing. The images of the fluorescent particles were stored at 2 frames/s for 10 min, and the movements of the particles on the composite surface were tracked with computer vision during curing. The polymerization shrinkage strain vectors as a function of time and location were analyzed. The volume shrinkage of the composite was also measured for comparison. **Results:** The linear and volume shrinkage of the composite at 10 min were 0.75 (0.12)% and 2.26 (0.18)%, respectively. The polymerization shrinkage vectors were directed toward the center of the specimen and were isotropic in all directions when the composite was allowed to shrinkage freely without bonding. In contrast, the shrinkage vectors were directed toward the bonding surface and were anisotropic when the composite was bonded to a fixed wall. The regional displacement vectors of composite in a tooth cavity were dependent on the location, depth and time. **Significance:** The new instrument was able to measure the regional linear shrinkage strain vectors over an entire surface of a composite specimen as a function of time and location. Therefore, this instrument can be used to characterize the shrinkage behaviors for a wide range of commercial and

experimental visible-light-cure materials in relation to the composition, boundary condition and cavity geometry. © 2013 Academy of Dental Materials.

LaBarbera, J. M., Ellenby, M. S., Bouressa, P., Burrell, J., Flori, H. R., & Marcin, J. P. (2013). The impact of telemedicine intensivist support and a pediatric hospitalist program on a community hospital. *Telemedicine and e-Health*, 19(10), 760-766. doi:10.1089/tmj.2012.0303

Background: Because of centralization of care, pediatric patients often require transfer for subspecialty care. We evaluated the impact of telemedicine critical care consultation and a pediatric hospitalist program on enabling patients to remain at a community hospital. Patients and Methods: This is a retrospective chart review of pediatric patients at a community hospital receiving critical care consultation from a tertiary children's hospital from January 2006 to October 2009. Patient cohorts differed by modality of intensivist consultation (telephone versus telemedicine) and modality of inpatient ward care at the community hospital (primary care physician versus hospitalist). Patients were compared for differences in transfer rate and rate of diversion from the pediatric intensive care unit to the tertiary ward. Results: One hundred fifty-three charts were analyzed: 41 from prior to hospitalist and telemedicine implementation (Cohort 1), 56 from post-implementation of telemedicine but pre-hospitalist program (Cohort 2), and 56 after implementation of both the telemedicine and hospitalist programs (Cohort 3). Baseline data did not differ among cohorts. Transfer rates after intensivist consultation were lower after implementation of telemedicine consultation (100%, 85.7%, and 87.5% in Cohorts 1-3, respectively;  $p=0.04$ ). The proportion of transferred patients who were diverted to the tertiary ward decreased over time (19.5%, 14.5%, and 6.1% in Cohorts 1-3, respectively;  $p=0.003$ ). Conclusions: Telemedicine consultation between pediatric intensivists and community hospital physicians combined with a pediatric hospitalist program at the community hospital has the potential to improve triage of pediatric patients and reduce the need to transfer patients. © Copyright 2013, Mary Ann Liebert, Inc. 2013.

Laharnar, N., Glass, N., Perrin, N., Hanson, G., & Kent Anger, W. (2013). A training intervention for supervisors to support a work-life policy implementation. *Safety and Health at Work*, 4(3), 166-176. doi:10.1016/j.shaw.2013.07.001; 10.1016/j.shaw.2013.07.001

**BACKGROUND:** Effective policy implementation is essential for a healthy workplace. The Ryan-Kossek 2008 model for work-life policy adoption suggests that supervisors as gatekeepers between employer and employee need to know how to support and communicate benefit regulations. This article describes a workplace intervention on a national employee benefit, Family and Medical Leave Act (FMLA), and evaluates the effectiveness of the intervention on supervisor knowledge, awareness, and experience with FMLA. **METHODS:** The intervention consisted of computer-based training (CBT) and a survey measuring awareness and experience with FMLA. The training was administered to 793 county government supervisors in the state of Oregon, USA. **RESULTS:** More than 35% of supervisors reported no previous training on FMLA and the training pre-test revealed a lack of knowledge regarding benefit coverage and employer responsibilities. The CBT achieved: (1) a significant learning effect and large effect size of  $d = 2.0$ , (2) a positive reaction to the training and its design, and (3) evidence of increased knowledge and awareness regarding FMLA. **CONCLUSION:** CBT is an effective strategy to increase supervisors' knowledge and awareness to support policy implementation. The lack of supervisor training and knowledge of an important but complex employee benefit exposes a serious impediment to effective policy implementation and may lead to negative outcomes for the organization and the employee, supporting the Ryan-Kossek model. The results further demonstrate that long-time employees need supplementary training on complex workplace policies such as FMLA.

Largent-Milnes, T. M., Brookshire, S. W., Skinner Jr., D. P., Hanlon, K. E., Giuvelis, D., Yamamoto, T., . . . Vanderah, T. W. (2013). Building a better analgesic: Multifunctional compounds that address injury-induced pathology to enhance analgesic efficacy while eliminating unwanted side effects. *Journal of Pharmacology and Experimental Therapeutics*, *347*(1), 7-19.  
doi:10.1124/jpet.113.205245

The most highly abused prescription drugs are opioids used for the treatment of pain. Physician-reported drug-seeking behavior has resulted in a significant health concern among doctors trying to adequately treat pain while limiting the misuse or diversion of pain medications. In addition to abuse liability, opioid use is associated with unwanted side effects that complicate pain management, including opioid-induced emesis and constipation. This has resulted in restricting

long-term doses of opioids and inadequate treatment of both acute and chronic debilitating pain, demonstrating a compelling need for novel analgesics. Recent reports indicate that adaptations in endogenous substance P/neurokinin-1 receptor (NK1) are induced by chronic pain and sustained opioid exposure, and these changes may contribute to processes responsible for opioid abuse liability, emesis, and analgesic tolerance. Here, we describe a multifunctional mu-/delta-opioid agonist/NK1 antagonist compound [Tyr-D-Ala-Gly-Phe-Met-Pro-Leu-Trp-NH-Bn(CF<sub>3</sub>)<sub>2</sub> (TY027)] that has a preclinical profile of excellent antinociceptive efficacy, low abuse liability, and no opioid-related emesis or constipation. In rodent models of acute and neuropathic pain, TY027 demonstrates analgesic efficacy following central or systemic administration with a plasma half-life of more than 4 hours and central nervous system penetration. These data demonstrate that an innovative opioid designed to contest the pathology created by chronic pain and sustained opioids results in antinociceptive efficacy in rodent models, with significantly fewer side effects than morphine. Such rationally designed, multitargeted compounds are a promising therapeutic approach in treating patients who suffer from acute and chronic pain. Copyright © 2013 by The American Society for Pharmacology and Experimental Therapeutics.

Larkin, K. L., Saboo, U. S., Comer, G. M., Forooghian, F., Mackensen, F., Merrill, P., . . . Smith, J. R. (2013). Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. *The British Journal of Ophthalmology*, doi:10.1136/bjophthalmol-2013-304043; 10.1136/bjophthalmol-2013-304043

AIM: Vitreoretinal lymphoma is a diffuse large B cell non-Hodgkin lymphoma. Targeting malignant cells with rituximab is being used increasingly as local chemotherapy, but information on this treatment is scant. We aimed to describe current therapeutic approaches, as well as responses to and complications of, intravitreal rituximab in patients with vitreoretinal lymphoma.

METHODS: Clinical data were collected in a standardised manner retrospectively on patients with vitreoretinal lymphoma treated with intravitreal rituximab. RESULTS: 48 eyes (34 patients) with vitreoretinal lymphoma were treated with a median of 3.5 intravitreal injections of rituximab (1 mg/0.1 mL) for new diagnosis (68.8%), progressive disease (29.9%) and maintenance therapy (2.1%). Intravitreal rituximab+/-methotrexate was the sole treatment in 19 eyes (39.6%). 31 eyes (64.6%) eyes achieved complete remission, after a median of 3 injections; 7 of these eyes developed recurrent disease. 11 eyes (22.9%) achieved partial remission. Although rituximab

may have contributed to complications reported in 12 eyes (25.0%), a 2-line loss of Snellen visual acuity occurred in only 2 of those eyes (4.2%). CONCLUSIONS: Approaches in rituximab-based intravitreal chemotherapy vary widely, but our findings suggest that this treatment may be safe and effective in inducing remission in a majority of eyes with vitreoretinal lymphoma.

Le, T. D., Carney, P. A., Lee-Lin, F., Mori, M., Chen, Z., Leung, H., . . . Lieberman, D. A. (2013).

Differences in Knowledge, Attitudes, Beliefs, and Perceived Risks Regarding Colorectal Cancer Screening Among Chinese, Korean, and Vietnamese Sub-Groups. *Journal of Community Health*, doi:10.1007/s10900-013-9776-8

Asian ethnic subgroups are often treated as a single demographic group in studies looking at cancer screening and health disparities. To evaluate knowledge and health beliefs associated with colorectal cancer (CRC) and CRC screening among Chinese, Korean, and Vietnamese subgroups, a survey assessed participants' demographic characteristics, healthcare utilization, knowledge, beliefs, attitudes associated with CRC and CRC screening. Exploratory factor analysis identified six factors accounting >60 % of the total variance in beliefs and attitudes. Cronbach's alpha coefficients assessed internal consistency. Differences among Asian subgroups were assessed using a Chi square, Fisher's exact, or Kruskal-Wallis test. Pearson's correlation coefficient assessed an association among factors. 654 participants enrolled: 238 Chinese, 217 Korean, and 199 Vietnamese. Statistically significant differences existed in demographic and health care provider characteristics, knowledge, and attitude/belief variables regarding CRC. These included knowledge of CRC screening modalities, reluctance to discuss cancer, belief that cancer is preventable by diet and lifestyle, and intention to undergo CRC screening. Chinese subjects were more likely to use Eastern medicine (52 % Chinese, 25 % Korean, 27 % Vietnamese;  $p < 0.001$ ); Korean subjects were less likely to see herbs as a form of cancer prevention (34 % Chinese, 20 % Korean, 35 % Vietnamese;  $p < 0.001$ ). Vietnamese subjects were less likely to consider CRC screening (95 % Chinese, 95 % Korean, 80 % Vietnamese;  $p < 0.0001$ ). Important differences exist in knowledge, attitudes, and health beliefs among Asian subgroups. Understanding these differences will enable clinicians to deliver tailored, effective health messages to improve CRC screening and other health behaviors.

Leclair, C. M., Goetsch, M. F., Li, H., & Morgan, T. K. (2013). Histopathologic characteristics of menopausal vestibulodynia. *Obstetrics and Gynecology*, 122(4), 787-793.

doi:10.1097/AOG.0b013e3182a5f25f; 10.1097/AOG.0b013e3182a5f25f

**OBJECTIVE:** To assess whether premenopausal and postmenopausal vestibulodynia have different histologic features. **METHODS:** We conducted a retrospective analysis of vestibulectomy specimens from 21 women with postmenopausal vestibulodynia and compared them with 88 premenopausal patients (42 primary, 46 secondary). Women with primary vestibulodynia experienced pain at first introital touch and women with secondary vestibulodynia experienced pain after an interval of painless intercourse. Clinical records established the type of vestibulodynia, duration of symptoms, and hormone status. Tissues were stained for inflammation, nerves, mast cells, estrogen receptor alpha, and progesterone receptor. Histologic findings in the postmenopausal patients were compared with primary and secondary premenopausal patients using proportional odds logistic regression and analysis of variance. **RESULTS:** Seventy-one percent (15/21) of postmenopausal women reported vestibular dyspareunia related to a drop in estrogen either with menopause (13/21) or previously, postpartum (2/21). Eighty-six percent (18/21) of postmenopausal patients were using local or systemic estrogen but pain persisted. Compared with premenopausal primary and secondary vestibular biopsies, postmenopausal tissues had more lymphocytes (unadjusted odds ratio [OR] 9.0, 95% confidence interval [CI] 2.8-33.3; adjusted OR for parity and duration of symptoms 9.1, 95% CI 2.6-31.9; unadjusted OR 6.2, 95% CI 1.9-20.0; adjusted OR 6.6, 95% CI 2.0-21.9, respectively) and mast cells (mean 36 compared with 28 and 36 compared with 26, respectively). There was significantly less neural hyperplasia and progesterone receptor expression in postmenopausal biopsies compared with primary cases but less progesterone receptor and similar neural hyperplasia compared with premenopausal secondary cases. Estrogen receptor alpha did not vary among groups. **CONCLUSION:** Premenopausal and postmenopausal vestibulodynia share histologic features of neurogenic inflammation but differ strikingly in degree. When estrogen supplement does not alleviate symptoms of postmenopausal dyspareunia, vestibulodynia should be considered. **LEVEL OF EVIDENCE:** : II.

Leeman, R. F., Beseler, C. L., Helms, C. M., Patock-Peckham, J. A., Wakeling, V. A., & Kahler, C. W.

(2013). A Brief, Critical Review of Research on Impaired Control Over Alcohol Use and Suggestions for Future Studies. *Alcoholism: Clinical and Experimental Research*, doi:10.1111/acer.12269

Impaired control, defined as "a breakdown of an intention to limit consumption" (Heather et al. *J Stud Alcohol* 1993; 54, 701), has historically been considered an important aspect of addiction. Despite recognition of its importance to addiction and potential value as an early indicator of problem drinking risk, we argue that impaired control over alcohol use has not received sufficient research attention. In an effort to spark further research, the present critical review offers brief discussion of the current state of knowledge regarding impaired control and avenues for future research. Three main research areas are addressed: (i) epidemiology; (ii) measurement issues; and (iii) potential mechanisms underlying relationships between impaired control and subsequent problem drinking. Measurement issues include complexities involved in self-report assessment of impaired control, development and validation of human and animal laboratory models, and impaired control's relationship to other constructs (i.e., impulsivity and other difficulties with self-control; symptoms of dependence such as craving). We discuss briefly 2 potential mechanisms that may help to explain why some drinkers experience impaired control while others do not: neurobiological dysfunction and family history/genetics. Suggestions for future research are focused on ways in which the impaired control construct may enhance prediction of who might be at particular risk of subsequent problem drinking and to facilitate intervention to reduce problem alcohol use. © 2013 by the Research Society on Alcoholism.

Lesselroth, B. J., Adams, K., Tallett, S., Wood, S. D., Keeling, A., Cheng, K., . . . Tran, H. (2013).

Design of admission medication reconciliation technology: A human factors approach to requirements and prototyping. *Health Environments Research and Design Journal*, 6(3), 30-48.

OBJECTIVE: Our objectives were to (1) develop an in-depth understanding of the workflow and information flow in medication reconciliation, and (2) design medication reconciliation support technology using a combination of rapid-cycle prototyping and human-centered design.

BACKGROUND: Although medication reconciliation is a national patient safety goal, limitations both of physical environment and in workflow can make it challenging to implement durable

systems. We used several human factors techniques to gather requirements and develop a new process to collect a medication history at hospital admission. METHODS: We completed an ethnography and time and motion analysis of pharmacists in order to illustrate the processes used to reconcile medications. We then used the requirements to design prototype multimedia software for collecting a bedside medication history. We observed how pharmacists incorporated the technology into their physical environment and documented usability issues. RESULTS: Admissions occurred in three phases: (1) list compilation, (2) order processing, and (3) team coordination. Current medication reconciliation processes at the hospital average 19 minutes to complete and do not include a bedside interview. Use of our technology during a bedside interview required an average of 29 minutes. The software represents a viable proof-of-concept to automate parts of history collection and enhance patient communication. However, we discovered several usability issues that require attention. CONCLUSIONS: We designed a patient-centered technology to enhance how clinicians collect a patient's medication history. By using multiple human factors methods, our research team identified system themes and design constraints that influence the quality of the medication reconciliation process and implementation effectiveness of new technology. © 2013 VENDOME GROUP LLC.

Lewy, A. J., Emens, J., Songer, J., & Rough, J. (2010). *The neurohormone melatonin as a marker, medicament, and mediator* Elsevier Inc. doi:10.1016/B978-008088783-8.00080-2

This chapter is an update of what was originally published several years ago (Vessely and Lewy, 2002). Melatonin is a hormone produced by the pineal gland during nighttime darkness under the control of the endogenous circadian pacemaker (ECP) in the suprachiasmatic nucleus of the hypothalamus. The ECP is entrained (synchronized) to the 24-h light/dark cycle. The endogenous melatonin profile can be used to assess the phase position (time) of the ECP, and both bright light exposure and exogenous melatonin can influence its phase. Totally blind people often have free-running circadian rhythms that are not entrained to the 24-h light/dark cycle. In these blind free-runners (BFRs), circadian phase drifts each day, causing recurrent insomnia; properly timed low-dose melatonin can entrain BFRs to the 24-h day. Sighted people can have circadian rhythm disturbances as well. Both light and melatonin can be used to delay or advance circadian rhythms that are out of phase due to jet travel, shift work, or advanced or delayed sleep phase

syndromes. Another group of people with circadian rhythm disorders are those suffering from seasonal affective disorder (SAD), or winter depression. Most people with SAD have circadian rhythms that delay in the winter, causing them to develop depressed moods and vegetative symptoms; light therapy timed to cause phase advances can lead to clear improvement. Preliminary work suggests that low-dose melatonin therapy may also be beneficial in treating SAD. The function of endogenous melatonin in humans may be to entrain the third-trimester fetus and suckling newborn to the mother's sleep/wake cycle. © 2009 Elsevier Inc. All rights reserved.

Lieberman, D. (2013). Screening for Colorectal Cancer in Individuals at Average Risk: Current Methods and Emerging Issues. *JAMA Internal Medicine*, doi:10.1001/jamainternmed.2013.11499; 10.1001/jamainternmed.2013.11499

Lin, D. S., Steiner, R. D., Merkens, L. S., Pappu, A. S., & Connor, W. E. (2010). The effects of sterol structure upon sterol esterification. *Atherosclerosis*, 208(1), 155-160. doi:10.1016/j.atherosclerosis.2009.07.031; 10.1016/j.atherosclerosis.2009.07.031

Cholesterol is esterified in mammals by two enzymes: LCAT (lecithin cholesterol acyltransferase) in plasma and ACAT(1) and ACAT(2) (acyl-CoA cholesterol acyltransferases) in the tissues. We hypothesized that the sterol structure may have significant effects on the outcome of esterification by these enzymes. To test this hypothesis, we analyzed sterol esters in plasma and tissues in patients having non-cholesterol sterols (sitosterolemia and Smith-Lemli-Opitz syndrome). The esterification of a given sterol was defined as the sterol ester percentage of total sterols. The esterification of cholesterol in plasma by LCAT was 67% and in tissues by ACAT was 64%. Esterification of nine sterols (cholesterol, cholestanol, campesterol, stigmasterol, sitosterol, campestanol, sitostanol, 7-dehydrocholesterol and 8-dehydrocholesterol) was examined. The relative esterification (cholesterol being 1.0) of these sterols by the plasma LCAT was 1.00, 0.95, 0.89, 0.40, 0.85, 0.82 and 0.80, 0.69 and 0.82, respectively. The esterification by the tissue ACAT was 1.00, 1.29, 0.75, 0.49, 0.45, 1.21 and 0.74, respectively. The predominant fatty acid of the sterol esters was linoleic acid for LCAT and oleic acid for ACAT. We compared the esterification of two sterols differing by only one functional group (a chemical group attached to

sterol nucleus) and were able to quantify the effects of individual functional groups on sterol esterification. The saturation of the A ring of cholesterol increased ester formation by ACAT by 29% and decreased the esterification by LCAT by 5.9%. Esterification by ACAT and LCAT was reduced, respectively, by 25 and 11% by the presence of an additional methyl group on the side chain of cholesterol at the C-24 position. This data supports our hypothesis that the structure of the sterol substrate has a significant effect on its esterification by ACAT or LCAT.

Lin, P., Suhler, E. B., & Rosenbaum, J. T. (2013). The Future of Uveitis Treatment. *Ophthalmology*, doi:10.1016/j.ophtha.2013.08.029; 10.1016/j.ophtha.2013.08.029

PURPOSE: Uveitis is a heterogeneous collection of diseases with polygenic and environmental influences. This heterogeneity presents challenges in trial design and selection of end points. Despite the multitude of causes, therapeutics targeting common inflammatory pathways are effective in treating diverse forms of uveitis. These treatments, including corticosteroids and immunomodulatory agents, although often effective, can have untoward side effects, limiting their utility. The search for drugs with equal or improved efficacy that are safe is therefore paramount. A mechanism-based approach is most likely to yield the future breakthroughs in the treatment of uveitis. We review the literature and provide examples of the nuances of immune regulation and dysregulation that can be targeted for therapeutic benefit. As our understanding of the causes of uveitis grows we will learn how to better apply antibodies designed to block interaction between inflammatory cytokines and their receptors. T-lymphocyte activation can be targeted by blocking co-stimulatory pathways or inhibiting major histocompatibility complex protein interactions. Furthermore, intracellular downstream molecules from cytokine or other pathways can be inhibited using small molecule inhibitors, which have the benefit of being orally bioavailable. An emerging field is the lipid-mediated inflammatory and regulatory pathways. Alternatively, anti-inflammatory cytokines can be provided by administering recombinant protein, and intracellular "brakes" of inflammatory pathways can be introduced potentially by gene therapy. Novel approaches of delivering a therapeutic substance include, but are not limited to, the use of small interfering RNA, viral and nonviral gene therapy, and microparticle or viscous gel sustained-release drug-delivery platforms. FINANCIAL DISCLOSURE(S): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Lindner, J. R., & Sinusas, A. (2013). Molecular imaging in cardiovascular disease: Which methods, which diseases? *Journal of Nuclear Cardiology : Official Publication of the American Society of Nuclear Cardiology*, doi:10.1007/s12350-013-9785-0

Techniques for in vivo assessment of disease-related molecular changes are being developed for all forms of non-invasive cardiovascular imaging. The ability to evaluate tissue molecular or cellular phenotype in patients has the potential to not only improve diagnostic capabilities but to enhance clinical care either by detecting disease at an earlier stage when it is more amenable to therapy, or by guiding most appropriate therapies. These new techniques also can be used in research programs in order to characterize pathophysiology and as a surrogate endpoint for therapeutic efficacy. The most common approach for molecular imaging involves the creation of novel-targeted contrast agents that are designed so that their kinetic properties are different in disease tissues. The main focus of this review is not to describe all the different molecular imaging approaches that have been developed, but rather to describe the status of the field and highlight some of the clinical and research applications that molecular imaging will likely provide meaningful benefit. Specific target areas include assessment of atherosclerotic disease, tissue ischemia, and ventricular and vascular remodeling.

Liu, Z., Lim, C. Y., Su, M. Y. -, Soh, S. L. Y., Shui, G., Wenk, M. R., . . . Xiao, X. (2013). Neonatal overnutrition in mice exacerbates high-fat diet-induced metabolic perturbations. *Journal of Endocrinology*, 219(2), 131-143. doi:10.1530/JOE-13-0111

Neonatal overnutrition results in accelerated development of high-fat diet (HFD)-induced metabolic defects in adulthood. To understand whether the increased susceptibility was associated with aggravated inflammation and dysregulated lipid metabolism, we studied metabolic changes and insulin signaling in a chronic postnatal overnutrition (CPO) mouse model. Male Swiss Webster pups were raised with either three pups per litter to induce CPO or ten pups per litter as control (CTR) and weaned to either low-fat diet (LFD) or HFD. All animals were killed on the postnatal day 150 (P150) except for a subset of mice killed on P15 for the measurement of stomach weight and milk composition. CPO mice exhibited accelerated body weight gain and increased body fat mass prior to weaning and the difference persisted into adulthood under conditions of both LFD and HFD. As adults, insulin signaling was more severely impaired in

epididymal white adipose tissue (WAT) from HFD-fed CPO (CPO-HFD) mice. In addition, HFD-induced upregulation of pro-inflammatory cytokines was exaggerated in CPO-HFD mice. Consistent with greater inflammation, CPO-HFD mice showed more severe macrophage infiltration than HFD-fed CTR (CTR-HFD) mice. Furthermore, when compared with CTR-HFD mice, CPO-HFD mice exhibited reduced levels of several lipogenic enzymes in WAT and excess intramyocellular lipid accumulation. These data indicate that neonatal overnutrition accelerates the development of insulin resistance and exacerbates HFD-induced metabolic defects, possibly by worsening HFD-induced inflammatory response and impaired lipid metabolism. © 2013 Society for Endocrinology.

Lo, J. O., Reddy, A. P., Wilmarth, P. A., Roberts, V. H., Kinhnarath, A., Snyder, J., . . . Pereira, L. M. (2013). Proteomic analysis of cervical vaginal fluid proteins among women in recurrent preterm labor. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, doi:10.3109/14767058.2013.852172

Abstract Objective: Proteomic analysis of 4 cervical vaginal fluid (CVF) proteins to identify biomarkers of recurrent preterm birth (rPTB) in at-risk women prior to onset of preterm labor.

Methods: Nested case control study from 2007-2011 of women with prior spontaneous preterm birth(s) (PTB) who underwent serial CVF sampling. Mass spectrometry analysis was used and ELISA analysis was performed to validate candidates. Results: 108 patients were enrolled and 10 cases and 20 gestational age matched controls were analyzed after exclusions. Of 748 CVF proteins identified, 72 had statistically significant ( $p < 0.05$ ) expression differences and 38 were highly differentially expressed ( $p < 0.01$ ). Four candidate proteins were abundant and involved in immune/inflammatory response, but ELISA analysis did not confirm altered expression patterns.

Conclusion: The lack of confirmation of potential biomarkers identified by mass spectrometry and ELISA demonstrates the challenges of validating PTB biomarkers and suggests that a panel of biomarkers would improve the predictive value of CVF testing.

Lobo, M. R., Green, S. C., Schabel, M. C., Gillespie, G. Y., Woltjer, R. L., & Pike, M. M. (2013). Quinacrine synergistically enhances the antivasculature and antitumor efficacy of cediranib in

intracranial mouse glioma. *Neuro-Oncology*, doi:10.1093/neuonc/not119

**Background** Despite malignant glioma vascularity, anti-angiogenic therapy is largely ineffective. We hypothesize that efficacy of the antiangiogenic agent cediranib is synergistically enhanced in intracranial glioma via combination with the late-stage autophagy inhibitor quinacrine. **Methods** Relative cerebral blood flow and volume (rCBF, rCBV), vascular permeability (K<sub>trans</sub>), and tumor volume were assessed in intracranial 4C8 mouse glioma using a dual-bolus perfusion MRI approach. Tumor necrosis and tumor mean vessel density (MVD) were assessed immunohistologically. Autophagic vacuole accumulation and apoptosis were assessed via Western blot in 4C8 glioma in vitro. **Results** Cediranib or quinacrine treatment alone did not alter tumor growth. Survival was only marginally improved by cediranib and unchanged by quinacrine. In contrast, combined cediranib/quinacrine reduced tumor growth by >2-fold (P < .05), compared with untreated controls (P < .05). Cediranib or quinacrine treatment alone did not significantly alter mean tumor rCBF or K<sub>trans</sub> compared with untreated controls, while combined cediranib/quinacrine substantially reduced both (P < .05), indicating potent tumor devascularization. MVD and necrosis were unchanged by cediranib or quinacrine treatment. In contrast, MVD was reduced by nearly 2-fold (P < .01), and necrosis increased by 3-fold (P < .05, one-tailed), in cediranib + quinacrine treated vs untreated groups. Autophagic vacuole accumulation was induced by cediranib and quinacrine in vitro. Combined cediranib/quinacrine treatment under hypoxic conditions induced further accumulation and apoptosis. **Conclusion** Combined cediranib/quinacrine treatment synergistically increased antivasular/antitumor efficacy in intracranial 4C8 mouse glioma, suggesting a promising and facile treatment strategy for malignant glioma. Modulations in the autophagic pathway may play a role in the increased efficacy.

Loftis, J. M., & Hauser, P. (2013). Pain and opioid use in chronic liver disease: Optimal treatment must address the mental health care needs of the patient. *Digestive Diseases and Sciences*, 58(10), 2753-2755. doi:10.1007/s10620-013-2809-4

Lomond, K. V., Henry, S. M., Jacobs, J. V., Hitt, J. R., Horak, F. B., Cohen, R. G., . . . Desarno, M. J. (2013). Protocol to assess the neurophysiology associated with multi-segmental postural

coordination. *Physiological Measurement*, 34(10), N97-N105. doi:10.1088/0967-3334/34/10/N97

Anticipatory postural adjustments (APAs) stabilize potential disturbances to posture caused by movement. Impaired APAs are common with disease and injury. Brain functions associated with generating APAs remain uncertain due to a lack of paired tasks that require similar limb motion from similar postural orientations, but differ in eliciting an APA while also being compatible with brain imaging techniques (e.g., functional magnetic resonance imaging; fMRI). This study developed fMRI-compatible tasks differentiated by the presence or absence of APAs during leg movement. Eighteen healthy subjects performed two leg movement tasks, supported leg raise (SLR) and unsupported leg raise (ULR), to elicit isolated limb motion (no APA) versus multi-segmental coordination patterns (including APA), respectively. Ground reaction forces under the feet and electromyographic activation amplitudes were assessed to determine the coordination strategy elicited for each task. Results demonstrated that the ULR task elicited a multi-segmental coordination that was either minimized or absent in the SLR task, indicating that it would serve as an adequate control task for fMRI protocols. A pilot study with a single subject performing each task in an MRI scanner demonstrated minimal head movement in both tasks and brain activation patterns consistent with an isolated limb movement for the SLR task versus multi-segmental postural coordination for the ULR task. © 2013 Institute of Physics and Engineering in Medicine.

López, C. S., Tsagli, S. M., Sloan, R., Eccles, J., & Barklis, E. (2013). Second site reversion of a mutation near the amino terminus of the HIV-1 capsid protein. *Virology*, 447(1-2), 95-103. doi:10.1016/j.virol.2013.08.023

During HIV-1 morphogenesis, the precursor Gag protein is processed to release capsid (CA) proteins that form the mature virus core. In this process, the CA proteins assemble a lattice in which N-terminal domain (NTD) helices 1-3 are critical for multimer formation. Mature core assembly requires refolding of the N-terminus of CA into a  $\beta$ -hairpin, but the precise contribution of the hairpin core morphogenesis is unclear. We found that mutations at isoleucine 15 (I15), between the  $\beta$ -hairpin and NTD helix 1 are incompatible with proper mature core assembly. However, a compensatory mutation of histidine 12 in the  $\beta$ -hairpin to a tyrosine was selected by long term passage of an I15 mutant virus in T cells. The tyrosine does not interact directly with

residue 15, but with NTD helix 3, supporting a model in which  $\beta$ -hairpin folding serves to align helix 3 for mature NTD multimerization. © 2013 Elsevier Inc.

Love, J. N., Deiorio, N. M., Ronan-Bentle, S., Howell, J. M., Doty, C. I., Lane, D. R., & Hegarty, C. (2013). Characterization of the council of emergency medicine residency directors' standardized letter of recommendation in 2011-2012. *Academic Emergency Medicine*, 20(9), 926-932. doi:10.1111/acem.12214

**Objectives** The Council of Emergency Medicine Residency Directors (CORD) introduced the standardized letter of recommendation (SLOR) in 1997, and it has become a critical tool for assessing candidates for emergency medicine (EM) training. It has not itself been evaluated since the initial studies associated with its introduction. This study characterizes current SLOR use to evaluate whether it serves its intended purpose of being standardized, concise, and discriminating. **Methods** This retrospective, multi-institutional study evaluated letters of recommendation from U.S. allopathic applicants to three EM training programs during the 2011-2012 Electronic Residency Application Service (ERAS) application cycle. Distributions of responses to each question on the SLOR were calculated, and the free-text responses were analyzed. Two pilots, performed on five applicants each, assisted in developing a strategy for limiting interrater reliability. **Results** Each of the three geographically diverse programs provided a complete list of U.S. allopathic applicants to their program. Upon randomization, each program received a list of coded applicants unique to their program randomly selected for data collection. The number of applicants was selected to reach a goal of approximately 200 SLORs per site ( $n = 602$ ). Among this group, comprising 278 of 1,498 applicants (18.6%) from U.S. allopathic schools, a total of 1,037 letters of recommendation were written, with 724 (69.8%) written by emergency physicians. SLORs represented 57.9% (602/1037) of all LORs (by any kind of author) and 83.1% (602/724) of letters written by emergency physicians. Three hundred ninety-two of 602 SLORs had a single author (65.1%). For the question on "global assessment," students were scored in the top 10% in 234 of 583 of applications (40.1%; question not answered by some), and 485 of 583 (83.2%) of the applicants were ranked above the level of their peers. Similarly, >95% of all applicants were ranked in the top third compared to peers, for all but one section under "qualifications for emergency medicine." For 405 of 602 of all SLORs (67.2%), one or more

questions were left unanswered, while 76 of all SLORs (12.6%) were "customized" or changed from the standard template. Finally, in 291 of 599 of SLORs (48.6%), the word count was greater than the recommended maximum of 200 words. Conclusions Grade inflation is marked throughout the SLOR, limiting its ability to be discriminating. Furthermore, template customization and skipped questions work against the intention to standardize the SLOR. Finally, it is not uncommon for comments to be longer than guideline recommendations. As an assessment tool, the SLOR could be more discerning, concise, and standardized to serve its intended purpose. © 2013 by the Society for Academic Emergency Medicine.

Lovering, A. T., Laurie, S. S., Elliott, J. E., Beasley, K. M., Yang, X., Gust, C. E., . . . Gladstone, I. M.

(2013). Normal pulmonary gas exchange efficiency and absence of exercise-induced arterial hypoxemia in adults with bronchopulmonary dysplasia. *Journal of Applied Physiology*, *115*(7), 1050-1056. doi:10.1152/jappphysiol.00592.2013

Cardiopulmonary function is reduced in adults born very preterm, but it is unknown if this results in reduced pulmonary gas exchange efficiency during exercise and, consequently, leads to reduced aerobic capacity in subjects with and without bronchopulmonary dysplasia (BPD). We hypothesized that an excessively large alveolar to arterial oxygen difference (AaDO<sub>2</sub>) and resulting exercise-induced arterial hypoxemia (EIAH) would contribute to reduced aerobic fitness in adults born very preterm with and without BPD. Measurements of pulmonary function, lung volumes and diffusion capacity for carbon monoxide (DL<sub>co</sub>) were made at rest. Measurements of maximal oxygen consumption, peak workload, temperature- and tonometry-corrected arterial blood gases, and direct measure of hemoglobin saturation with oxygen (SaO<sub>2</sub>) were made preexercise and during cycle ergometer exercise in ex-preterm subjects ≤32-wk gestational age, with BPD (n = 12), without BPD (PRE; n = 12), and full term controls (CONT; n = 12) breathing room air. Both BPD and PRE had reduced pulmonary function and reduced DL<sub>co</sub> compared with CONT. The AaDO<sub>2</sub> was not significantly different between groups, and there was no evidence of EIAH (SaO<sub>2</sub> < 95% and/or AaDO<sub>2</sub> ≥ 40 Torr) in any subject group preexercise or at any workload. Arterial O<sub>2</sub> content was not significantly different between the groups preexercise or during exercise. However, peak power output was decreased in BPD and PRE subjects compared with CONT. We conclude that EIAH in adult subjects born very preterm with and without BPD

does not likely contribute to the reduction in aerobic exercise capacity observed in these subjects.

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Lowas, S., Malempati, S., & Marks, D. (2009). Body mass index predicts insulin resistance in survivors of pediatric acute lymphoblastic leukemia. *Pediatric Blood & Cancer*, 53(1), 58-63.

doi:10.1002/pbc.21993; 10.1002/pbc.21993

BACKGROUND: Pediatric acute lymphoblastic leukemia (ALL) therapies have been associated with many late effects, including obesity, hyperglycemia, and insulin resistance. Few data are available linking these abnormalities to specific risk factors present during ALL treatment.

METHODS: Retrospective cohort study with prospective follow-up. Subjects had been diagnosed with ALL at ages 1-18 years and had been off chemotherapy for >9 months. Oral glucose tolerance testing (OGTT) was performed and these results compared to demographic, treatment, and anthropomorphic data from medical records. RESULTS: Twenty-seven subjects (11 female) were evaluated. Mean (+/-SD) diagnosis age 5.7 +/- 3.5 years, mean study age 11.3 +/- 3.7 years, mean time off therapy 2.8 +/- 1.5 years. Six subjects had transient hyperglycemia during ALL treatment. At study time, one subject had prediabetes; eight (29.6%) had insulin resistance. Insulin resistance was not predicted by glucose levels during treatment, cumulative steroid or asparaginase dose, or type of steroid received. Body mass index (BMI) for age correlated significantly with several measures of insulin resistance, including fasting insulin, HOMA index, Matsuda index and insulin AUC (P = 0.001-0.009). Waist/hip ratio and BMI at ALL diagnosis also correlated with insulin resistance, but these factors' effects could not be separated from BMI at study time. CONCLUSIONS: Variations in ALL therapy and presence of transient hyperglycemia do not appear to increase risk of glucose intolerance or insulin resistance in the first few years after completion of therapy. Elevated BMI strongly predicted insulin resistance in this study, as it does in the general population.

Luoh, S. W., Ramsey, B., Hanlon Newell, A., Troxell, M., Hu, Z., Chin, K., . . . Keenan, E. (2013). HER-2 gene amplification in human breast cancer without concurrent HER-2 over-expression.

*Springerplus*, 2, 386-1801-2-386. doi:10.1186/2193-1801-2-386; 10.1186/2193-1801-2-386

BACKGROUND: Testing for human epidermal growth factor receptor-2 (HER-2) in breast cancer is

performed by either immunohistochemistry (IHC) or in situ hybridization (ISH). The growth factor receptor-bound protein-7 (GRB7) gene is in close proximity to HER-2 on chromosome 17q11-12 and codes a signal transduction molecule shown to be an independent adverse marker in breast cancer. METHODS: HER-2 and GRB7 protein expression from 613 frozen breast tumors was determined by Western analysis. HER-2 protein results were confirmed with IHC. Commercial HER-2 FISH was performed on a subset of tumors with multi-probe FISH used to assess the extent of HER-2 gene amplification. mRNA expression was determined by Multi-plex RT-PCR. RESULTS: Seven tumors with GRB7 protein over-expression scored HER-2 FISH amplified but had no HER-2 protein over-expression. Four of the 7 tumors showed elevated GRB7 but not HER-2 mRNA over-expression. The breast cancer cell line HCC3153 did not over-express HER-2 protein but showed HER-2 FISH amplification of a limited segment around the HER-2 gene. Ten breast cancer tumors from the TCGA database had gene copy number increases around HER-2 without HER-2 mRNA or protein over-expression. CONCLUSIONS: A subset of human breast cancers that test positive with FISH for HER-2 gene amplification do not over-express HER-2 protein. One mechanism for this discordance is the incomplete amplification of the smallest HER-2 region of chromosome 17q11-12, which includes GRB7. HER-2 gene amplification without protein over-expression is clinically significant because patients with such tumors are unlikely to benefit from HER-2 targeted therapy.

Macarthur, C. J., Hausman, F., Kempton, J. B., Choi, D., & Trune, D. R. (2013). Otitis media impacts hundreds of mouse middle and inner ear genes. *PloS One*, 8(10), e75213.

doi:10.1371/journal.pone.0075213; 10.1371/journal.pone.0075213

OBJECTIVE: Otitis media is known to alter expression of cytokine and other genes in the mouse middle ear and inner ear. However, whole mouse genome studies of gene expression in otitis media have not previously been undertaken. Ninety-nine percent of mouse genes are shared in the human, so these studies are relevant to the human condition. METHODS: To assess inflammation-driven processes in the mouse ear, gene chip analyses were conducted on mice treated with trans-tympanic heat-killed *Hemophilus influenzae* using untreated mice as controls. Middle and inner ear tissues were separately harvested at 6 hours, RNA extracted, and samples for each treatment processed on the Affymetrix 430 2.0 Gene Chip for expression of its 34,000

genes. RESULTS: Statistical analysis of gene expression compared to control mice showed significant alteration of gene expression in 2,355 genes, 11% of the genes tested and 8% of the mouse genome. Significant middle and inner ear upregulation (fold change >1.5,  $p < 0.05$ ) was seen in 1,081 and 599 genes respectively. Significant middle and inner ear downregulation (fold change <0.67,  $p < 0.05$ ) was seen in 978 and 287 genes respectively. While otitis media is widely believed to be an exclusively middle ear process with little impact on the inner ear, the inner ear changes noted in this study were numerous and discrete from the middle ear responses. This suggests that the inner ear does indeed respond to otitis media and that its response is a distinctive process. Numerous new genes, previously not studied, are found to be affected by inflammation in the ear. CONCLUSION: Whole genome analysis via gene chip allows simultaneous examination of expression of hundreds of gene families influenced by inflammation in the middle ear. Discovery of new gene families affected by inflammation may lead to new approaches to the study and treatment of otitis media.

Magness, S. T., Puthoff, B. J., Crissey, M. A., Dunn, J., Henning, S. J., Houchen, C., . . . Wong, M. H. (2013). A multicenter study to standardize reporting and analyses of fluorescence-activated cell-sorted murine intestinal epithelial cells. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, 305(8), G542-G551. doi:10.1152/ajpgi.00481.2012

Fluorescence-activated cell sorting (FACS) is an essential tool for studies requiring isolation of distinct intestinal epithelial cell populations. Inconsistent or lack of reporting of the critical parameters associated with FACS methodologies has complicated interpretation, comparison, and reproduction of important findings. To address this problem a comprehensive multicenter study was designed to develop guidelines that limit experimental and data reporting variability and provide a foundation for accurate comparison of data between studies. Common methodologies and data reporting protocols for tissue dissociation, cell yield, cell viability, FACS, and postsort purity were established. Seven centers tested the standardized methods by FACS isolating a specific crypt-based epithelial population (EpCAM<sub>+</sub>/CD44<sub>-</sub>) from murine small intestine. Genetic biomarkers for stem/progenitor (Lgr5 and Atoh 1) and differentiated cell lineages (lysozyme, mucin2, chromogranin A, and sucrase isomaltase) were interrogated in target and control populations to assess intra- and intercenter variability. Wilcoxon's rank sum test on gene

expression levels showed limited intracenter variability between biological replicates. Principal component analysis demonstrated significant intercenter reproducibility among four centers. Analysis of data collected by standardized cell isolation methods and data reporting requirements readily identified methodological problems, indicating that standard reporting parameters facilitate post hoc error identification. These results indicate that the complexity of FACS isolation of target intestinal epithelial populations can be highly reproducible between biological replicates and different institutions by adherence to common cell isolation methods and FACS gating strategies. This study can be considered a foundation for continued method development and a starting point for investigators that are developing cell isolation expertise to study physiology and pathophysiology of the intestinal epithelium. © 2013 the American Physiological Society.

Marcinek, D. J., & Siegel, M. P. (2013). Targeting redox biology to reverse mitochondrial dysfunction. *Aging*, 5(8), 588-589.

Marhenke, S., Buitrago-Molina, L. E., Endig, J., Orlik, J., Schweitzer, N., Klett, S., . . . Vogel, A. (2013). p21 promotes sustained liver regeneration and hepatocarcinogenesis in chronic cholestatic liver injury. *Gut*, doi:10.1136/gutjnl-2013-304829

Background and aims: The cyclin-dependent kinase inhibitor p21 has been implicated as a tumour suppressor. Moreover, recent genetic studies suggest that p21 might be a potential therapeutic target to improve regeneration in chronic diseases. The aim of this study was to delineate the role of p21 in chronic liver injury and to specify its role in hepatocarcinogenesis in a mouse model of chronic cholestatic liver injury. Methods: The degree of liver injury, regeneration and tumour formation was assessed in Mdr2<sup>-/-</sup> mice and compared with Mdr2/p21<sup>-/-</sup> mice. Moreover, the role of p21 was evaluated in hepatoma cells in vitro and in human hepatocellular carcinoma (HCC). Results: Mdr2<sup>-/-</sup> mice developed HCCs as a consequence of chronic inflammatory liver injury. In contrast, tumour development was profoundly delayed in Mdr2/p21<sup>-/-</sup> mice. Delayed tumour development was accompanied by markedly impaired liver regeneration in Mdr2/p21<sup>-/-</sup> mice. Moreover, the regenerative capacity of the Mdr2/p21<sup>-/-</sup> livers in response to partial hepatectomy declined with age in these mice. Hepatocyte transplantation experiments revealed that impaired liver regeneration was due to intrinsic factors within the cells and changes

in the Mdr2/p21<sup>-/-</sup> microenvironment. In human HCCs, a subset of tumours expressed p21, which was associated with a significant shorter patient survival. Conclusions: We provide experimental evidence that p21 is required for sustained liver regeneration and tumour development in chronic liver injury indicating that p21 needs to be tightly regulated in order to balance liver regeneration and cancer risk. Moreover, we identify p21 as a negative prognostic marker in human HCC. © 2013 BMJ Publishing Group Ltd & British Society of Gastroenterology.

Matthaeus, J., Hayden, R., Kim, M., & Donald, C. (2013). Understanding facial nerve paralysis. *JAAPA : Official Journal of the American Academy of Physician Assistants*, 26(11), 33-36.

doi:10.1097/01.JAA.0000436288.50067.43; 10.1097/01.JAA.0000436288.50067.43

Facial nerve paralysis has many causes and can be acute or chronic. Understanding the signs and symptoms, performing a careful patient evaluation, and obtaining appropriate diagnostic testing can help guide clinicians and improve outcomes.

Matulef, K., Komarov, A. G., Costantino, C. A., & Valiyaveetil, F. I. (2013). Using protein backbone mutagenesis to dissect the link between ion occupancy and C-type inactivation in K<sup>+</sup> channels. *Proceedings of the National Academy of Sciences of the United States of America*, 110(44), 17886-17891. doi:10.1073/pnas.1314356110; 10.1073/pnas.1314356110

K<sup>(+)</sup> channels distinguish K<sup>(+)</sup> from Na<sup>(+)</sup> in the selectivity filter, which consists of four ion-binding sites (S1-S4, extracellular to intracellular) that are built mainly using the carbonyl oxygens from the protein backbone. In addition to ionic discrimination, the selectivity filter regulates the flow of ions across the membrane in a gating process referred to as C-type inactivation. A characteristic of C-type inactivation is a dependence on the permeant ion, but the mechanism by which permeant ions modulate C-type inactivation is not known. To investigate, we used amide-to-ester substitutions in the protein backbone of the selectivity filter to alter ion binding at specific sites and determined the effects on inactivation. The amide-to-ester substitutions in the protein backbone were introduced using protein semisynthesis or in vivo nonsense suppression approaches. We show that an ester substitution at the S1 site in the KcsA channel does not affect inactivation whereas ester substitutions at the S2 and S3 sites dramatically reduce inactivation. We determined the structure of the KcsA S2 ester mutant and

found that the ester substitution eliminates K(+) binding at the S2 site. We also show that an ester substitution at the S2 site in the KvAP channel has a similar effect of slowing inactivation. Our results link C-type inactivation to ion occupancy at the S2 site. Furthermore, they suggest that the differences in inactivation of K(+) channels in K(+) compared with Rb(+) are due to different ion occupancies at the S2 site.

McCully, S. P., & Schreiber, M. A. (2013). Traumatic brain injury and its effect on coagulopathy. *Seminars in Thrombosis and Hemostasis*, 39(8), 896-901. doi:10.1055/s-0033-1357484; 10.1055/s-0033-1357484

Polytraumatic injury results in tissue factor (TF) release from damaged cells. The acute coagulopathy of trauma (ACT) occurs early and results from significant tissue injury and tissue hypoperfusion. ACT is augmented by therapies resulting in acidemia, hypothermia, and hemodilution contributing to trauma-induced coagulopathy. Coagulopathy associated with traumatic brain injury (TBI) results from the interplay of numerous variables. Because of the high concentration of TF in brain tissue, TBI has been believed to be associated with a greater degree of coagulopathy compared with injury in other body systems. TBI has also recently been shown to cause platelet dysfunction. Platelet receptor inhibition prevents cellular initiation and amplification of the clotting cascade, limiting thrombin incorporation, and stabilization of clot to stop hemorrhage. Therefore, head injury in the presence of polytrauma does appear to augment ACT and warrants close monitoring and appropriate intervention.

McGregor, J. C., Quach, Y., Bearden, D. T., Smith, D. H., Sharp, S. E., & Guzman-Cottrill, J. A. (2013). Variation in Antibiotic Susceptibility of Uropathogens by Age Among Ambulatory Pediatric Patients. *Journal of Pediatric Nursing*, doi:10.1016/j.pedn.2013.09.001; 10.1016/j.pedn.2013.09.001

We compared uropathogen antibiotic susceptibility across age groups of ambulatory pediatric patients. For *Escherichia coli* (n=5,099) and other Gram-negative rods (n=626), significant differences (p<0.05) existed across age groups for ampicillin, cefazolin, and trimethoprim/sulfamethoxazole susceptibility. In *E. coli*, differences in trimethoprim/sulfamethoxazole susceptibility varied from 79% in children under 2 to 88% in ages

16-18 ( $p < 0.001$ ) while ampicillin susceptibility varied from 30% in children under 2 to 53% in ages 2-5 ( $p = 0.015$ ). Uropathogen susceptibility to common urinary anti-infectives may be lower in the youngest children. Further investigation into these differences is needed to facilitate appropriate and prudent treatment of urinary tract infections.

Mehalick, M. L., Ingram, S. L., Aicher, S. A., & Morgan, M. M. (2013). Chronic Inflammatory Pain Prevents Tolerance to the Antinociceptive Effect of Morphine Microinjected into the Ventrolateral Periaqueductal Gray of the Rat. *Journal of Pain*, doi:10.1016/j.jpain.2013.08.003

The ventrolateral periaqueductal gray (vlPAG) contributes to morphine antinociception and tolerance. Chronic inflammatory pain causes changes within the PAG that are expected to enhance morphine tolerance. This hypothesis was tested by assessing antinociception and tolerance following repeated microinjections of morphine into the vlPAG of rats with chronic inflammatory pain. Microinjection of morphine into the vlPAG reversed the allodynia caused by intraplantar administration of complete Freund's adjuvant and produced antinociception on the hot plate test. Although there was a gradual decrease in morphine antinociception with repeated testing, there was no evidence of tolerance when morphine- and saline-treated rats with hind paw inflammation were tested with cumulative doses of morphine. In contrast, repeated morphine injections into the vlPAG caused a rightward shift in the morphine dose-response curve in rats without hind paw inflammation, as would be expected with the development of tolerance. The lack of tolerance in complete Freund's adjuvant-treated rats was evident whether rats were exposed to repeated behavioral testing or not (experiment 2) and whether they were treated with 4 or 8 prior microinjections of morphine into the vlPAG (experiment 3). These data demonstrate that chronic inflammatory pain does not disrupt the antinociceptive effect of microinjecting morphine into the vlPAG, but it does disrupt the development of tolerance. Perspective: The present data show that induction of chronic inflammatory pain does not disrupt the antinociceptive effect of microinjecting morphine into the vlPAG, but it does attenuate the development of tolerance. This finding indicates that tolerance to opioids in rats with inflammatory pain is mediated by structures other than the vlPAG. © 2013 American Pain Society.

Miljkovic, I., Cauley, J. A., Wang, P. Y., Holton, K. F., Lee, C. G., Sheu, Y., . . . Marshall, L. M. (2013).

Abdominal myosteatorosis is independently associated with hyperinsulinemia and insulin resistance among older men without diabetes. *Obesity*, 21(10), 2118-2125. doi:10.1002/oby.20346

Objective Skeletal muscle adipose tissue (AT) infiltration (myosteatorosis) increases with aging and may contribute to the development of Type 2 diabetes mellitus (T2DM). It remains unclear if myosteatorosis is associated to glucose and insulin homeostasis independent of total and central adiposity. Design and Methods The association between intermuscular AT (IMAT) in the abdominal skeletal muscles (total, paraspinal, and psoas) and fasting serum glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) in 393 nondiabetic Caucasian men aged 65+ was evaluated. Abdominal IMAT, visceral AT (VAT), and subcutaneous AT (SAT) (cm<sup>3</sup>) were measured by quantitative computed tomography at the L4-L5 intervertebral space. Results In age, study site, height, and muscle volume adjusted regression analyses, total abdominal and psoas (but not paraspinal) IMAT were positively associated with glucose, insulin, and HOMA-IR (all P < 0.003). The associations between total abdominal and psoas IMAT and insulin and HOMA-IR remained significant after further adjusting for lifestyle factors, as well as dual-energy x-ray absorptiometry (DXA) measured total body fat, VAT, or SAT in separate models (all P < 0.009). Conclusions A previously unreported, independent association between abdominal myosteatorosis and hyperinsulinemia and insulin resistance among older Caucasian men was indicated. These associations may be specific for particular abdominal muscle depots, illustrating the potential importance of separately studying specific muscle groups. Copyright © 2013 The Obesity Society.

Milner, L. C., Shirley, R. L., Kozell, L. B., Walter, N. A., Kruse, L. C., Komiyama, N. H., . . . Buck, K. J.

(2013). Novel MPDZ/MUPP1 transgenic and knockdown models confirm Mpdz's role in ethanol withdrawal and support its role in voluntary ethanol consumption. *Addiction Biology*, doi:10.1111/adb.12087; 10.1111/adb.12087

Association studies implicate multiple PDZ domain protein (MPDZ/MUPP1) sequence and/or expression in risk for alcoholism in humans and ethanol withdrawal (EW) in mice, but confirmation has been hindered by the dearth of targeted genetic models. We report the creation of transgenic (MPDZ-TG) and knockout heterozygote (Mpdz<sup>+/-</sup>) mice, with increased (2.9-fold)

and decreased (53%) target expression, respectively. Both models differ in EW compared with wild-type littermates ( $P \leq 0.03$ ), providing compelling evidence for an inverse relationship between Mpdz expression and EW severity. Additionally, ethanol consumption is reduced up to 18% ( $P = 0.006$ ) in Mpdz $^{+/-}$ , providing the first evidence implicating Mpdz in ethanol self-administration.

Mokhtarani, M., Diaz, G. A., Rhead, W., Berry, S. A., Lichter-Konecki, U., Feigenbaum, A., . . .

Scharschmidt, B. F. (2013). Elevated phenylacetic acid levels do not correlate with adverse events in patients with urea cycle disorders or hepatic encephalopathy and can be predicted based on the plasma PAA to PAGN ratio. *Molecular Genetics and Metabolism*, doi:10.1016/j.ymgme.2013.09.017

Background: Phenylacetic acid (PAA) is the active moiety in sodium phenylbutyrate (NaPBA) and glycerol phenylbutyrate (GPB, HPN-100). Both are approved for treatment of urea cycle disorders (UCDs) - rare genetic disorders characterized by hyperammonemia. PAA is conjugated with glutamine in the liver to form phenylacetylglutamine (PAGN), which is excreted in urine. PAA plasma levels  $\geq 500 \mu\text{g/dL}$  have been reported to be associated with reversible neurological adverse events (AEs) in cancer patients receiving PAA intravenously. Therefore, we have investigated the relationship between PAA levels and neurological AEs in patients treated with these PAA pro-drugs as well as approaches to identifying patients most likely to experience high PAA levels. Methods: The relationship between nervous system AEs, PAA levels and the ratio of plasma PAA to PAGN were examined in 4683 blood samples taken serially from: [1] healthy adults [2], UCD patients of  $\geq 2$  months of age, and [3] patients with cirrhosis and hepatic encephalopathy (HE). The plasma ratio of PAA to PAGN was analyzed with respect to its utility in identifying patients at risk of high PAA values. Results: Only 0.2% (11) of 4683 samples exceeded  $500 \mu\text{g/ml}$ . There was no relationship between neurological AEs and PAA levels in UCD or HE patients, but transient AEs including headache and nausea that correlated with PAA levels were observed in healthy adults. Irrespective of population, a curvilinear relationship was observed between PAA levels and the plasma PAA:PAGN ratio, and a ratio  $> 2.5$  (both in  $\mu\text{g/mL}$ ) in a random blood draw identified patients at risk for PAA levels  $> 500 \mu\text{g/ml}$ . Conclusions: The presence of a relationship between PAA levels and reversible AEs in healthy adults but not in UCD

or HE patients may reflect intrinsic differences among the populations and/or metabolic adaptation with continued dosing. The plasma PAA:PAGN ratio is a functional measure of the rate of PAA metabolism and represents a useful dosing biomarker. © 2013.

Morgan, C. P., & Barr-Gillespie, P. G. (2013). Mechanotransduction: the elusive hair cell transduction channel revealed? *Current Biology : CB*, 23(19), R887-90. doi:10.1016/j.cub.2013.08.031; 10.1016/j.cub.2013.08.031

A family of transmembrane proteins has been shown to modulate both the calcium permeability and single-channel conductance of the vertebrate hair-cell mechanosensor, implicating them directly in inner ear mechanosensation.

Morton, J. M., & Wolfe, B. (2013). Letters to the editor: Response to JAMA article which did not accept these letters delineating numerous problems with the published study. *Surgery for Obesity and Related Diseases*, 9(5), 831-832. doi:10.1016/j.soard.2013.06.001

Murasawa, Y., Watanabe, K., Yoneda, M., Zako, M., Kimata, K., Sakai, L. Y., & Isogai, Z. (2013). Homotypic versican G1 domain interactions enhance hyaluronan incorporation into fibrillin microfibrils. *Journal of Biological Chemistry*, 288(40), 29170-29181. doi:10.1074/jbc.M113.456947

Background:Versican interacts with hyaluronan (HA) via its G1 domain and with fibrillin microfibrils via its G3 domain. However, the roles of versican G1 domain-containing fragments (VG1Fs) in the HA-versican-microfibril macrocomplex are not clear. Results:VG1Fs interact homotypically and are recaptured by versican-containing fibrillin microfibrils.

Conclusion:Homotypical interactions of VG1Fs enhance HA recruitment to microfibrils.

Significance:VG1Fs stabilize HA-versican-microfibril macrocomplexes. © 2013 by The American Society for Biochemistry and Molecular Biology, Inc.

Murray, D. S., Chinnam, N., Tonthat, N. K., Whitfill, T., Wray, L. V., Fisher, S. H., & Schumacher, M. A. (2013). Structures of the *B. subtilis* glutamine synthetase dodecamer reveal large intersubunit catalytic conformational changes linked to a unique feedback inhibition mechanism. *The Journal of Biological Chemistry*, doi:10.1074/jbc.M113.519496

Glutamine synthetase (GS), which catalyzes the production of glutamine (Q), plays essential roles in nitrogen metabolism. There are two main bacterial GS isoenzymes, GSI-alpha and GSI-beta. GSI-alpha enzymes, which have not been structurally characterized, are uniquely feedback inhibited by Q. To gain insight into GSI-alpha function, we performed biochemical and cellular studies and obtained structures for all GSI-alpha catalytic and regulatory states. GSI-alpha forms a massive 600 kDa dodecameric machine. Unlike other characterized GS, the *B. subtilis* enzyme undergoes dramatic intersubunit conformational alterations during formation of the transition state. Remarkably, these changes are required for active site construction. Feedback inhibition arises from a hydrogen-bond network between Q, the catalytic glutamate and GSI-alpha specific residue, Arg62, from an adjacent subunit. Notably, Arg62 must be ejected for proper active site reorganization. Consistent with these findings, a R62A mutation abrogates Q-feedback inhibition but does not affect catalysis. Thus, these data reveal a heretofore unseen restructuring of an enzyme active site that is coupled with an isoenzyme-specific regulatory mechanism. This GSI-alpha-specific regulatory network could be exploited for inhibitor design against Gram-positive pathogens.

Nahir, B., & Jahr, C. E. (2013). Activation of Extrasynaptic NMDARs at Individual Parallel Fiber-Molecular Layer Interneuron Synapses in Cerebellum. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 33(41), 16323-16333. doi:10.1523/JNEUROSCI.1971-13.2013; 10.1523/JNEUROSCI.1971-13.2013

NMDA receptors (NMDARs) expressed by cerebellar molecular layer interneurons (MLIs) are not activated by single exocytotic events but can respond to glutamate spillover following coactivation of adjacent parallel fibers (PFs), indicating that NMDARs are perisynaptic. Several types of synaptic plasticity rely on these receptors but whether they are activated at isolated synapses is not known. Using a combination of electrophysiological and optical recording techniques in acute slices of rat cerebellum, along with modeling, we find that repetitive activation of single PF-MLI synapses can activate NMDARs in MLIs. High-frequency stimulation, multivesicular release (MVR), or asynchronous release can each activate NMDARs. Frequency facilitation was found at all PF-MLI synapses but, while some showed robust MVR with increased

release probability, most were limited to univesicular release. Together, these results reveal a functional diversity of PF synapses, which use different mechanisms to activate NMDARs.

Newgard, C. D., Kuppermann, N., Holmes, J. F., Haukoos, J. S., Wetzel, B., Hsia, R. Y., . . . WESTRN Investigators. (2013). Gunshot injuries in children served by emergency services. *Pediatrics*, *132*(5), 862-870. doi:10.1542/peds.2013-1350; 10.1542/peds.2013-1350

OBJECTIVE: To describe the incidence, injury severity, resource use, mortality, and costs for children with gunshot injuries, compared with other injury mechanisms. METHODS: This was a population-based, retrospective cohort study (January 1, 2006-December 31, 2008) including all injured children age  $\geq 16$ , major surgery, blood transfusion, mortality, and average per-patient acute care costs. RESULTS: A total of 49 983 injured children had a 9-1-1 emergency medical services response, including 505 (1.0%) with gunshot injuries (83.2% age 15-19 years, 84.5% male). The population-adjusted annual incidence of gunshot injuries was 7.5 cases/100 000 children, which varied 16-fold between regions. Compared with children who had other mechanisms of injury, those injured by gunshot had the highest proportion of serious injuries (23%, 95% confidence interval [CI] 17.6-28.4), major surgery (32%, 95% CI 26.1-38.5), in-hospital mortality (8.0%, 95% CI 4.7-11.4), and costs (\$28 510 per patient, 95% CI 22 193-34 827). CONCLUSIONS: Despite being less common than other injury mechanisms, gunshot injuries cause a disproportionate burden of adverse outcomes in children, particularly among older adolescent males. Public health, injury prevention, and health policy solutions are needed to reduce gunshot injuries in children.

Newgard, C. D., Rudser, K., Hedges, J. R., Kerby, J. D., Stiell, I. G., Davis, D. P., . . . ROC Investigators. (2010). A critical assessment of the out-of-hospital trauma triage guidelines for physiologic abnormality. *The Journal of Trauma*, *68*(2), 452-462.

doi:10.1097/TA.0b013e3181ae20c9; 10.1097/TA.0b013e3181ae20c9

BACKGROUND: It remains unclear whether the American College of Surgeons Committee on Trauma (ACSCOT) "step 1" field physiologic criteria could be further restricted without substantially sacrificing sensitivity. We assessed whether more restrictive physiologic criteria would improve the specificity of this triage step without missing high-risk patients. METHODS:

We analyzed an out-of-hospital, consecutive patient, prospective cohort of injured adults  $\geq 15$  years collected from December 1, 2005, to February 28, 2007, by 237 emergency medical service agencies transporting to 207 acute care hospitals in 11 sites across the United States and Canada. Patients were included based on ACSCOT field decision scheme physiologic criteria systolic blood pressure  $\geq 90$  mmHg, respiratory rate  $\geq 10$  breaths/min, Glasgow Coma Scale score  $\geq 9$  2 days. RESULTS: Of 7,127 injured persons, 6,259 had complete outcome information and were included in the analysis. There were 3,631 (58.0%) persons with death or LOS  $> 2$  days. Using only physiologic measures, the derived rule included advanced airway intervention, shock index  $> 1.4$ , Glasgow Coma Scale  $< 11$ , and pulse oximetry  $< 93\%$ . Rule validation demonstrated sensitivity 72% (95% confidence interval: 70%-74%) and specificity 69% (95% confidence interval: 67%-72%). Inclusion of demographic and mechanism variables did not significantly improve performance measures. CONCLUSIONS: We were unable to omit or further restrict any ACSCOT step 1 physiologic measures in a decision rule practical for field use without missing high-risk trauma patients.

Newgard, C. D., Staudenmayer, K., Hsia, R. Y., Mann, N. C., Bulger, E. M., Holmes, J. F., . . .

McConnell, K. J. (2013). The cost of overtriage: More than one-third of low-risk injured patients were taken to major trauma centers. *Health Affairs*, 32(9), 1591-1599.

doi:10.1377/hlthaff.2012.1142

Regionalized trauma care has been widely implemented in the United States, with field triage by emergency medical services (EMS) playing an important role in identifying seriously injured patients for transport to major trauma centers. In this study we estimated hospital-level differences in the adjusted cost of acute care for injured patients transported by 94 EMS agencies to 122 hospitals in 7 regions, overall and by injury severity. Among 301,214 patients, the average adjusted per episode cost of care was \$5,590 higher in a level 1 trauma center than in a nontrauma hospital. We found hospital-level differences in cost among patients with minor, moderate, and serious injuries. Of the 248,342 low-risk patients—those who did not meet field triage guidelines for transport to trauma centers—85,155 (34.3 percent) were still transported to major trauma centers, accounting for up to 40 percent of acute injury costs. Adhering to field triage guidelines that minimize the overtriage of low-risk injured patients to major trauma

centers could save up to \$136.7 million annually in the seven regions we studied. © 2013 Project HOPE-The People-to-People Health Foundation, Inc.

Nicolini, F. E., Ibrahim, A. R., Soverini, S., Martinelli, G., Müller, M. C., Hochhaus, A., . . . Etienne, G. (2013). The BCR-ABL T315I mutation compromises survival in chronic phase chronic myelogenous leukemia patients resistant to tyrosine kinase inhibitors, in a matched pair analysis.

*Haematologica*, 98(10), 1510-1516. doi:10.3324/haematol.2012.080234

The BCR-ABL T315I mutation confers resistance to currently licensed tyrosine kinase inhibitors in chronic myelogenous leukemia. However, the impact of this mutation on survival in early stages of disease, in chronic phase, has never been detailed. Using matched pair analysis, a cohort of 64 patients with chronic phase chronic myelogenous leukemia harboring a T315I mutation and resistant to imatinib mesylate was compared to a similar cohort of 53 chronic phase patients resistant to imatinib, but with no detectable T315I mutation, in the pre-ponatinib era. These patients were matched according to age at diagnosis, interval between disease diagnosis and start of imatinib treatment, and duration of imatinib therapy. Kaplan-Meier survival analyses demonstrated the significant negative impact of the presence of the T315I mutation on overall survival (since imatinib-resistance: 48.4 months for T315I+ patients versus not reached for T315I- ones;  $P=0.006$ ) and failure-free survival (since imatinib-resistance: 34.7 months for T315I+ patients versus not reached for T315I- patients;  $P=0.003$ ). In addition, Cox proportional hazard models adjusted on overall survival demonstrated the negative influence of the T315I mutation ( $P=0.02$ ,  $HR=2.54$ ). These results confirm early assumptions concerning the poor prognosis of chronic phase chronic myelogenous leukemia patients with the T315I mutation who are not eligible for allogeneic transplantation, and demonstrate the need for more therapeutic options. © 2013 Ferrata Storti Foundation.

Norris, S. L., Holmer, H. K., Ogden, L. A., Burda, B. U., & Fu, R. (2013). Conflicts of Interest among Authors of Clinical Practice Guidelines for Glycemic Control in Type 2 Diabetes Mellitus. *PLoS One*, 8(10), e75284. doi:10.1371/journal.pone.0075284; 10.1371/journal.pone.0075284

BACKGROUND: Conflict of interest (COI) is an important potential source of bias in the development of clinical practice guidelines (CPGs). OBJECTIVES: To examine rates of disclosure

of COI, including financial interests in companies that manufacture drugs that are recommended in CPGs on glycemic control in type 2 diabetes mellitus, and to explore the relationship between recommendations for specific drugs in a guideline and author COI. METHODS: We identified a cohort of relevant guidelines from the National Guideline Clearinghouse (NGC) and abstracted COI disclosures from all guideline authors for this observational, cross-sectional study. We determined which hypoglycemic drugs were recommended in each guideline, and explored the relationship between specific disclosures and whether a drug was recommended. RESULTS: Among 13 included guidelines, the percentage of authors with one or more financial disclosures varied from 0 to 94% (mean 44.2%), and was particularly high for two US-based guidelines (91% and 94%). Three guidelines disclosed no author financial COI. The percentage of authors with disclosures of financial interests in manufacturers of recommended drugs was also high (mean 30%). On average, 56% of manufacturers of patented drugs recommended in each guideline had one or more authors with a financial interest in their company. We did not find a significant relationship between financial interests and whether a drug was recommended in our sample; US-based guidelines were more likely to make recommendations for a specific drug compared to non-US based guidelines. DISCUSSION: Authors of this cohort of guidelines have financial interests directly related to the drugs that they are recommending. Although we did not find an association between author COI and drugs recommended in these guidelines and we cannot draw conclusions about the validity of the recommendations, the credibility of many of these guidelines is in doubt.

Nousen, E. K., Franco, J. G., & Sullivan, E. L. (2013). Unraveling the Mechanisms Responsible for the Comorbidity between Metabolic Syndrome and Mental Health Disorders. *Neuroendocrinology*, doi:10.1159/000355632

The increased prevalence and high comorbidity of metabolic syndrome and mental health disorders have prompted investigation into the potential contributing mechanisms. There is a bidirectional association between metabolic syndrome and mental health disorders including schizophrenia, bipolar disorder, depression, anxiety, attention deficit/hyperactivity disorder, and autism spectrum disorders. Medication side effects and social repercussions are contributing environmental factors, but there are a number of shared underlying neurological and

physiological mechanisms that explain the high comorbidity between these two disorders. Inflammation is a state shared by both disorders, and it contributes to disruptions of neuroregulatory systems, including the serotonergic, dopaminergic, and neuropeptide Y systems, as well as dysregulation of the hypothalamic-pituitary-adrenal axis. Metabolic syndrome in pregnant women also exposes the developing fetal brain to inflammatory factors that predispose the offspring to metabolic syndrome and mental health disorders. Due to the shared nature of these conditions, treatment should address aspects of both mental health and metabolic disorders. Additionally, interventions need to be developed that can interrupt the transfer of increased risk of the disorders to the next generation. (c) 2013 S. Karger AG, Basel.

Nutt, J. G. (2013). Higher-level gait disorders: An open frontier. *Movement Disorders : Official Journal of the Movement Disorder Society*, 28(11), 1560-1565. doi:10.1002/mds.25673; 10.1002/mds.25673

The term higher-level gait disorders (HLGD) defines a category of balance and gait disorders that are not explained by deficits in strength, tone, sensation, or coordination. HLGD are characterized by various combinations of disequilibrium and impaired locomotion. A plethora of new imaging techniques are beginning to determine the neural circuits that are the basis of these disorders. Although a variety of neurodegenerative and other pathologies can produce HLGD, the most common cause appears to be microvascular disease that causes white-matter lesions and thereby disrupts balance/locomotor circuits. (c) 2013 International Parkinson and Movement Disorder Society.

Oakley, J. C., Espinosa, F., Bothe, H., McKean, J., Allen, P., Burchiel, K., . . . Holsheimer, J. (2006). Transverse tripolar spinal cord stimulation: results of an international multicenter study. *Neuromodulation : Journal of the International Neuromodulation Society*, 9(3), 192-203. doi:10.1111/j.1525-1403.2006.00060.x; 10.1111/j.1525-1403.2006.00060.x

Experienced neurosurgeons at eight spinal cord stimulation centers in the United States, Canada, and Europe participated in a study from 1997 to 2000 investigating the safety, performance, and efficacy of a Transverse Tripolar Stimulation (TTS) system invented at the University of Twente, the Netherlands. This device was proposed to improve the ability of spinal cord stimulation to

adequately overlap paresthesia to perceived areas of pain. Fifty-six patients with chronic, intractable neuropathic pain of the trunk and/or limbs more than three months' duration (average 105 months) were enrolled with follow-up periods at 4, 12, 26, and 52 weeks. All patients had a new paddle-type lead implanted with four electrodes, three of them aligned in a row perpendicular to the cord. Fifteen of these patients did not undergo permanent implantation. Of the 41 patients internalized, 20 patients chose conventional programming using an implanted pulse generator to drive four electrodes, while 21 patients chose a tripole stimulation system, which used radiofrequency power and signal transmission and an implanted dual-channel receiver to drive three electrodes using simultaneous pulses of independently variable amplitude. On average, the visual analog scale scores dropped more for patients with TTS systems (32%) than for conventional polarity systems (16%). Conventional polarity systems were using higher frequencies on average, while usage range was similar. Most impressive was the well-controlled "steering" of the paresthesias according to the dermatomal topography of the dorsal columns when using the TTS-balanced pulse driver. The most common complication was lead migration. While the transverse stimulation system produced acceptable outcomes for overall pain relief, an analysis of individual pain patterns suggests that it behaves like spinal cord stimulation in general with the best control of extremity neuropathic pain. This transverse tripole lead and driving system introduced the concept of electrical field steering by selective recruitment of axonal nerve fiber tracts in the dorsal columns.

O'Hare, T., Shakespeare, W. C., Zhu, X., Eide, C. A., Rivera, V. M., Wang, F., . . . Clackson, T. (2009).

AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. *Cancer Cell*, 16(5), 401-412.

doi:10.1016/j.ccr.2009.09.028; 10.1016/j.ccr.2009.09.028

Inhibition of BCR-ABL by imatinib induces durable responses in many patients with chronic myeloid leukemia (CML), but resistance attributable to kinase domain mutations can lead to relapse and a switch to second-line therapy with nilotinib or dasatinib. Despite three approved therapeutic options, the cross-resistant BCR-ABL(T315I) mutation and compound mutants selected on sequential inhibitor therapy remain major clinical challenges. We report design and preclinical evaluation of AP24534, a potent, orally available multitargeted kinase inhibitor active

against T315I and other BCR-ABL mutants. AP24534 inhibited all tested BCR-ABL mutants in cellular and biochemical assays, suppressed BCR-ABL(T315I)-driven tumor growth in mice, and completely abrogated resistance in cell-based mutagenesis screens. Our work supports clinical evaluation of AP24534 as a pan-BCR-ABL inhibitor for treatment of CML.

Onoday, H. (2013). Quality measures in dermatology. *Journal of the Dermatology Nurses' Association*, 5(3), 167-169. doi:10.1097/JDN.0b013e31829329d8

Orgeig, S., Bernhard, W., Biswas, S. C., Daniels, C. B., Hall, S. B., Hetz, S. K., . . . Yan, W. (2007).

The anatomy, physics, and physiology of gas exchange surfaces: is there a universal function for pulmonary surfactant in animal respiratory structures? *Integrative and Comparative Biology*, 47(4), 610-627. doi:10.1093/icb/icm079

(Orgeig and Daniels) This surfactant symposium reflects the integrative and multidisciplinary aims of the 1st ICRB, by encompassing in vitro and in vivo research, studies of vertebrates and invertebrates, and research across multiple disciplines. We explore the physical and structural challenges that face gas exchange surfaces in vertebrates and insects, by focusing on the role of the surfactant system. Pulmonary surfactant is a complex mixture of lipids and proteins that lines the air-liquid interface of the lungs of all air-breathing vertebrates, where it functions to vary surface tension with changing lung volume. We begin with a discussion of the extraordinary conservation of the blood-gas barrier among vertebrate respiratory organs, which has evolved to be extremely thin, thereby maximizing gas exchange, but simultaneously strong enough to withstand significant distension forces. The principal components of pulmonary surfactant are highly conserved, with a mixed phospholipid and neutral lipid interfacial film that is established, maintained and dynamically regulated by surfactant proteins (SP). A wide variation in the concentrations of individual components exists, however, and highlights lipidomic as well as proteomic adaptations to different physiological needs. As SP-B deficiency in mammals is lethal, oxidative stress to SP-B is detrimental to the biophysical function of pulmonary surfactant and SP-B is evolutionarily conserved across the vertebrates. It is likely that SP-B was essential for the evolutionary origin of pulmonary surfactant. We discuss three specific issues of the surfactant system to illustrate the diversity of function in animal respiratory structures. (1) Temperature: In

vitro analyses of the behavior of different model surfactant films under dynamic conditions of surface tension and temperature suggest that, contrary to previous beliefs, the alveolar film may not have to be substantially enriched in the disaturated phospholipid, dipalmitoylphosphatidylcholine (DPPC), but that similar properties of rate of film formation can be achieved with more fluid films. Using an in vivo model of temperature change, a mammal that enters torpor, we show that film structure and function varies between surfactants isolated from torpid and active animals. (2) Spheres versus tubes: Surfactant is essential for lung stabilization in vertebrates, but its function is not restricted to the spherical alveolus. Instead, surfactant is also important in narrow tubular respiratory structures such as the terminal airways of mammals and the air capillaries of birds. (3). Insect tracheoles: We investigate the structure and function of the insect tracheal system and ask whether pulmonary surfactant also has a role in stabilizing these minute tubules. Our theoretical analysis suggests that a surfactant system may be required, in order to cope with surface tension during processes, such as molting, when the tracheae collapse and fill with water. Hence, despite observations by Wigglesworth in the 1930s of fluid-filled tracheoles, the challenge persists into the 21st century to determine whether this fluid is associated with a pulmonary-type surfactant system. Finally, we summarize the current status of the field and provide ideas for future research.

Packer, M., Fry, L., Lavery, K. T., Lehmann, R., McDonald, J., Nichamin, L., . . . Khodai, O. (2013).

Safety and effectiveness of a glistening-free single-piece hydrophobic acrylic intraocular lens (enVista). *Clinical Ophthalmology (Auckland, N.Z.)*, 7, 1905-1912. doi:10.2147/OPHTH.S50499; 10.2147/OPHTH.S50499

PURPOSE: To evaluate the safety and effectiveness of a single-piece hydrophobic acrylic intraocular lens (IOL; enVista model MX60; Bausch & Lomb, Rochester, NY, USA) when used to correct aphakia following cataract extraction in adults. METHODS: This was a prospective case series (NCT01230060) conducted in private practices in the US. Eligible subjects were adult patients with age-related cataract amenable to treatment with standard phacoemulsification/extracapsular cataract extraction. With follow-up of 6 months, primary safety and effectiveness end points included the rates of US Food and Drug Administration (FDA)-defined cumulative and persistent adverse events and the percentage of subjects who achieved

best-corrected visual acuity (BCVA) of 20/40 or better at final visit. To evaluate rotational stability, subjects were randomized (1:1:1:1) to have the lens implanted in one of four axis positions in 45 degrees increments. RESULTS: A total of 122 subjects were enrolled. The rate of cumulative and persistent adverse events did not significantly exceed historical controls, as per FDA draft guidance. At the final postoperative visit, all subjects (100%) achieved a BCVA of 20/40 compared with the FDA historical control of 96.7%. Rotation of the IOL between the two final follow-up visits was  $\leq 5$  degrees for 100% of eyes, and refractive stability was demonstrated. A low evaluation of posterior capsule opacification score was demonstrated, and no glistenings of any grade were reported for any subject at any visit. CONCLUSION: This study demonstrated the safety and effectiveness of the MX60 IOL. Favorable clinical outcomes included preserved BCVA, excellent rotational and refractive stability, no glistenings, and a low evaluation of posterior capsule opacification score.

Paul, F., & Bourdette, D. (2013). Tumefactive multiple sclerosis and fingolimod: Immunotherapies and unintended consequences. *Neurology*, doi:10.1212/01.wnl.0000435305.95271.84

Our knowledge of the substantial complexities of the immune system and understanding of the immunopathogenesis of autoimmune diseases are increasing at such a rapid pace that it is impossible for the non-immunologist to stay abreast of the field. However, there are 2 general principles that are important for clinicians to keep in mind. One is that the immune system regulates itself. The effector arm of the adaptive immune system consists of subsets of lymphocytes that recognize and respond to non-self antigens expressed by infectious agents and malignant cells. Other subsets of lymphocytes regulate the effector arm of the immune system, thereby fine-tuning and limiting responses. A second principle is that autoimmune diseases, such as multiple sclerosis (MS), result from a failure of regulation of lymphocytes capable of reacting to self-antigens. Thus autoimmunity is conceived of as a loss of active tolerance to self-antigens related to activation of effector autoreactive lymphocytes and reduction in activity of regulatory lymphocytes. Much is known about the cellular subsets and molecules involved in autoimmune diseases, allowing rational development of immunotherapies. No better example of this exists than in the expanding armamentarium of immunotherapies for the treatment of MS.

Petersen, J., Austin, D., Sack, R., & Hayes, T. L. (2013). Actigraphy-based scratch detection using logistic regression. *IEEE Journal of Biomedical and Health Informatics*, 17(2), 277-283.

doi:10.1109/TITB.2012.2204761

Incessant scratching as a result of diseases such as atopic dermatitis causes skin break down, poor sleep quality, and reduced quality of life for affected individuals. In order to develop more effective therapies, there is a need for objective measures to detect scratching. Wrist actigraphy, which detects wrist movements over time using microaccelerometers, has shown great promise in detecting scratch because it is lightweight, usable in the home environment, can record longitudinally, and does not require any wires. However, current actigraphy-based scratch-detection methods are limited in their ability to discriminate scratch from other nighttime activities. Our previous work demonstrated the separability of scratch from both walking and restless sleep using a clustering technique which employed four features derived from the actigraphic data: number of accelerations above 0.01 g's, epoch variance, peak frequency, and autocorrelation value at one lag. In this paper, we extended these results by employing these same features as independent variables in a logistic regression model. This allows us to directly estimate the conditional probability of scratching for each epoch. Our approach outperforms competing actigraphy-based approaches and has both high sensitivity (0.96) and specificity (0.92) for identifying scratch as validated on experimental data collected from 12 healthy subjects. The model must still be fully validated on clinical data, but shows promise for applications to clinical trials and longitudinal studies of scratch.

Peterson, A. L., Murchison, C., Zabetian, C., Leverenz, J., Watson, G. S., Montine, T., . . . Quinn, J. F. (2013). Memory, Mood, and Vitamin D in Persons with Parkinson's Disease. *Journal of Parkinson's Disease*, doi:10.3233/JPD-130206

Background: Research in recent years has suggested a role of vitamin D in the central nervous system. The final converting enzyme and the vitamin D receptor are found throughout the human brain. From animal studies vitamin D appears important in neurodevelopment, up-regulation of neurotrophic factors, stabilization of mitochondrial function, and antioxidation. Objective: To examine the relationship between serum vitamin D and neuropsychiatric function in persons with Parkinson's disease (PD). Methods: This is an add-on study to a longitudinal study following

neuropsychiatric function in persons with PD. Baseline neuropsychiatric performance and serum 25-hydroxyvitamin D were examined for 286 participants with PD. Measures of global cognitive function (MMSE, MOCA, Mattis Dementia Scale), verbal memory (Hopkins Verbal Learning Test), fluency (animals, vegetables, and FAS words), visuospatial function (Benton Line Orientation), executive function (Trails Making Test and Digit-Symbol Substitution), PD severity (Hoehn & Yahr and Unified Parkinson's Disease Rating Scale) and depression (Geriatric Depression Scale (GDS)) were administered. Multivariate linear regression assessed the association between vitamin D concentration and neuropsychiatric function, in the entire cohort as well as the non-demented and demented subsets. Results: Using a multivariate model, higher vitamin D concentrations were associated with better performance on numerous neuropsychiatric tests in the non-demented subset of the cohort. Significant associations were specifically found between vitamin D concentration and verbal fluency and verbal memory ( $t = 4.31, p < 0.001$  and  $t = 3.04, p = 0.0083$ ). Vitamin D concentrations also correlated with depression scores ( $t = -3.08, p = 0.0083$ ) in the non-demented subset. Conclusions: Higher plasma vitamin D is associated with better cognition and better mood in this sample of PD patients without dementia. Determination of causation will require a vitamin D intervention study.

Petzinger, G. M., Fisher, B. E., Meshul, C. K., Walsh, J. P., Akopian, G., & Jakowec, M. W. (2011). *Effects of Exercise on Basal Ganglia Function in Parkinson's Disease and its Animal Models* Blackwell Publishing Ltd. doi:10.1002/9781444397970.ch37

Phillips, K. G., Kuhn, P., & McCarty, O. J. (2013). Theme: Physical Biology in Cancer. 2. The physical biology of circulating tumor cells. *American Journal of Physiology. Cell Physiology*, doi:10.1152/ajpcell.00294.2013

The identification, isolation, and characterization of circulating tumor cells (CTCs) promises to enhance our understanding of the evolution of cancer in humans. CTCs provide a window into the hematogenous, or "fluid phase" of cancer, underlying the metastatic transition in which a locally contained tumor spreads to other locations in the body through the bloodstream. With the development of sensitive and specific CTC identification and isolation methodologies, the role of CTCs in clinical diagnostics, disease surveillance, and the physical basis of metastasis continues

to be established. This review focuses on the quantification of the basic biophysical properties of CTCs and the use of these metrics to understand the hematogenous dissemination of these enigmatic cells.

Poole, K. A., Weber, N., & Aziz, M. (2013). Case report: quetiapine and refractory hypotension during general anesthesia in the operating room. *Anesthesia and Analgesia*, *117*(3), 641-643.

doi:10.1213/ANE.0b013e3182999689; 10.1213/ANE.0b013e3182999689

Quetiapine is an atypical antipsychotic with known alpha-adrenergic antagonism. We present a case of refractory hypotension that occurred after induction of general anesthesia in a patient being treated with quetiapine. This patient was not currently taking antihypertensives and had no known cardiovascular abnormalities. We observed that the hypotension was most responsive to vasopressin. We recommend further investigation regarding the interaction of quetiapine and general anesthesia.

Pugh, J. R., & Jahr, C. E. (2013). Activation of Axonal Receptors by GABA Spillover Increases Somatic Firing. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *33*(43), 16924-16929. doi:10.1523/JNEUROSCI.2796-13.2013; 10.1523/JNEUROSCI.2796-13.2013

Axons can be depolarized by ionotropic receptors and transmit subthreshold depolarizations to the soma by passive electrical spread. This raises the possibility that axons and axonal receptors can participate in integration and firing in neurons. Previously, we have shown that exogenous GABA depolarizes cerebellar granule cell axons through local activation of GABAA receptors (GABAARs) and the soma through electrotonic spread of the axonal potential resulting in increased firing. We show here that excitability of granule cells is also increased by release of endogenous GABA from molecular layer interneurons (MLIs) and spillover activation of parallel fiber GABAARs in mice and rats. Changes in granule cell excitability were assessed by excitability testing after activation of MLIs with channelrhodopsin or electrical stimulation in the molecular layer. In granule cells lacking an axon, excitability was not changed, suggesting that axonal receptors are required. To determine the distance over which subthreshold potentials may spread, we estimated the effective axonal electrical length constant (520  $\mu\text{m}$ ) by excitability testing and focal uncaging of RuBi-GABA on the axon at varying distances from the soma. These

data suggest that GABAAR-mediated axonal potentials can participate in integration and firing of cerebellar granule cells.

Puthussery, T., Venkataramani, S., Gayet-Primo, J., Smith, R. G., & Taylor, W. R. (2013). NaV1.1 Channels in Axon Initial Segments of Bipolar Cells Augment Input to Magnocellular Visual Pathways in the Primate Retina. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 33(41), 16045-16059. doi:10.1523/JNEUROSCI.1249-13.2013; 10.1523/JNEUROSCI.1249-13.2013

In the primate visual system, the ganglion cells of the magnocellular pathway underlie motion and flicker detection and are relatively transient, while the more sustained ganglion cells of the parvocellular pathway have comparatively lower temporal resolution, but encode higher spatial frequencies. Although it is presumed that functional differences in bipolar cells contribute to the tuning of the two pathways, the properties of the relevant bipolar cells have not yet been examined in detail. Here, by making patch-clamp recordings in acute slices of macaque retina, we show that the bipolar cells within the magnocellular pathway, but not the parvocellular pathway, exhibit voltage-gated sodium (NaV), T-type calcium (CaV), and hyperpolarization-activated, cyclic nucleotide-gated (HCN) currents, and can generate action potentials. Using immunohistochemistry in macaque and human retinæ, we show that NaV1.1 is concentrated in an axon initial segment (AIS)-like region of magnocellular pathway bipolar cells, a specialization not seen in transient bipolar cells of other vertebrates. In contrast, CaV3.1 channels were localized to the somatodendritic compartment and proximal axon, but were excluded from the AIS, while HCN1 channels were concentrated in the axon terminal boutons. Simulations using a compartmental model reproduced physiological results and indicate that magnocellular pathway bipolar cells initiate spikes in the AIS. Finally, we demonstrate that NaV channels in bipolar cells augment excitatory input to parasol ganglion cells of the magnocellular pathway. Overall, the results demonstrate that selective expression of voltage-gated channels contributes to the establishment of parallel processing in the major visual pathways of the primate retina.

Quinn, M., Mathan, S., & Pavel, M. (2013). *Removal of ocular artifacts from EEG using learned templates* (Las Vegas, NV ed.) doi:10.1007/978-3-642-39454-6\_39

Electroencephalogram (EEG) data can provide information on cognitive states and processes with high temporal resolution, but to take full advantage of this temporal resolution, common transients such as blinks and eye movements must be accounted for without censoring data. This can require additional hardware, large amounts of data, or manual inspection. In this paper we introduce a greedy, template-based method for modeling and removing transient activity. The method iteratively models an input and updates a template; a process which quickly converges to a unique and efficient approximation of the input. When combined with standard source separation techniques such as Independent Component Analysis (ICA) or Principal Component Analysis (PCA), the method shows promise for the automatic and data driven removal of ocular artifacts from EEG data. In this paper we outline our method, provide evidence for its effectiveness using synthetic EEG data, and demonstrate its effect on real EEG data recorded as part of a minimally constrained cognitive task. © 2013 Springer-Verlag Berlin Heidelberg.

Raber, J., Allen, A. R., Rosi, S., Sharma, S., Dayger, C., Davis, M. J., & Fike, J. R. (2013). Effects of (56)Fe radiation on hippocampal function in mice deficient in chemokine receptor 2 (CCR2).

*Behavioural Brain Research*, 246, 69-75. doi:10.1016/j.bbr.2013.03.003;  
10.1016/j.bbr.2013.03.003

(56)Fe irradiation affects hippocampus-dependent cognition. The underlying mechanisms may involve alterations in neurogenesis, expression of the plasticity-related immediate early gene Arc, and inflammation. Chemokine receptor-2 (CCR2), which mediates the recruitment of infiltrating and resident microglia to sites of CNS inflammation, is upregulated by (56)Fe irradiation. CCR2 KO and wild-type mice were used to compare effects of (56)Fe radiation (600MeV, 0.25Gy) on hippocampal function using contextual fear conditioning involving tone shock pairing during training (+/+) and exposure to the same environment without tone shock pairings (-/-). In the -/- condition, irradiation enhanced habituation in WT mice, but not CCR2 KO mice, suggesting that a lack of CCR2 was associated with reduced cognitive performance. In the +/+ condition, irradiation reduced freezing but there was no genotype differences. There were no significant correlations between the number of Arc-positive cells in the dentate gyrus and freezing in either genotype. While measures of neurogenesis and gliogenesis appeared to be modulated by CCR2, there were no effects of genotype on the total numbers of newly born activated microglia before

or after irradiation, indicating that other mechanisms are involved in the genotype-dependent radiation response.

Randall, C., Bridges, D., Guerri, R., Nogues, X., Puig, L., Torres, E., . . . Hansma, P. K. (2013).

Applications of a new handheld reference point indentation instrument measuring bone material strength. *Journal of Medical Devices, Transactions of the ASME*, 7(4) doi:10.1115/1.4024829

A novel, hand-held Reference Point Indentation (RPI) instrument, measures how well the bone of living patients and large animals resists indentation. The results presented here are reported in terms of Bone Material Strength, which is a normalized measure of how well the bone resists indentation, and is inversely related to the indentation distance into the bone. We present examples of the instrument's use in: (1) laboratory experiments on bone, including experiments through a layer of soft tissue, (2) three human clinical trials, two ongoing in Barcelona and at the Mayo Clinic, and one completed in Portland, OR, and (3) two ongoing horse clinical trials, one at Purdue University and another at Alamo Pintado Stables in California. The instrument is capable of measuring consistent values when testing through soft tissue such as skin and periosteum, and does so handheld, an improvement over previous Reference Point Indentation instruments. Measurements conducted on horses showed reproducible results when testing the horse through tissue or on bare bone. In the human clinical trials, reasonable and consistent values were obtained, suggesting the Osteoprobe VR is capable of measuring Bone Material Strength in vivo, but larger studies are needed to determine the efficacy of the instrument's use in medical diagnosis.

Rao, X., Evans, J., Chae, H., Pilrose, J., Kim, S., Yan, P., . . . Nephew, K. P. (2013). CpG island shore methylation regulates caveolin-1 expression in breast cancer. *Oncogene*, 32(38), 4519-4528. doi:10.1038/onc.2012.474

Caveolin-1 (Cav1) is an integral membrane, scaffolding protein found in plasma membrane invaginations (caveolae). Cav1 regulates multiple cancer-associated processes. In breast cancer, a tumor suppressive role for Cav1 has been suggested; however, Cav1 is frequently overexpressed in aggressive breast cancer subtypes, suggesting an oncogenic function in advanced-stage disease. To further delineate Cav1 function in breast cancer progression, we

evaluated its expression levels among a panel of cell lines representing a spectrum of breast cancer phenotypes. In basal-like (the most aggressive BC subtype) breast cancer cells, Cav1 was consistently upregulated, and positively correlated with increased cell proliferation, anchorage-independent growth, and migration and invasion. To identify mechanisms of Cav1 gene regulation, we compared DNA methylation levels within promoter 'CpG islands' (CGIs) with 'CGI shores', recently described regions that flank CGIs with less CG-density. Integration of genome-wide DNA methylation profiles ('methylomes') with Cav1 expression in 30 breast cancer cell lines showed that differential methylation of CGI shores, but not CGIs, significantly regulated Cav1 expression. In breast cancer cell lines having low Cav1 expression (despite promoter CGI hypomethylation), we found that treatment with a DNA methyltransferase inhibitor induced Cav1 expression via CGI shore demethylation. In addition, further methylome assessments revealed that breast cancer aggressiveness associated with Cav1 CGI shore methylation levels, with shore hypermethylation in minimally aggressive, luminal breast cancer cells and shore hypomethylation in highly aggressive, basal-like cells. Cav1 CGI shore methylation was also observed in human breast tumors, and overall survival rates of breast cancer patients lacking estrogen receptor  $\alpha$  (ER $\alpha$ ) negatively correlated with Cav1 expression. Based on this first study of Cav1 (a potential oncogene) CGI shore methylation, we suggest this phenomenon may represent a new prognostic marker for ER $\alpha$ -negative, basal-like breast cancer. © 2013 Macmillan Publishers Limited.

Reiss, L. A., Turner, C. W., Karsten, S. A., & Gantz, B. J. (2013). Plasticity in Human Pitch Perception Induced by Tonotopically Mismatched Electro-Acoustic Stimulation. *Neuroscience*, doi:10.1016/j.neuroscience.2013.10.024; 10.1016/j.neuroscience.2013.10.024

Under normal conditions, the acoustic pitch percept of a pure tone is determined mainly by the tonotopic place of the stimulation along the cochlea. Unlike acoustic stimulation, electric stimulation of a cochlear implant (CI) allows for the direct manipulation of the place of stimulation in human subjects. CI sound processors analyze the range of frequencies needed for speech perception and allocate portions of this range to the small number of electrodes distributed in the cochlea. Because the allocation is assigned independently of the original resonant frequency of the basilar membrane associated with the location of each electrode, CI users who have access to residual hearing in either or both ears often have tonotopic mismatches

between the acoustic and electric stimulation. Here we demonstrate plasticity of place pitch representations of up to 3 octaves in Hybrid CI users after experience with combined electro-acoustic stimulation. The pitch percept evoked by single CI electrodes, measured relative to acoustic tones presented to the non-implanted ear, changed over time in directions that reduced the electro-acoustic pitch mismatch introduced by the CI programming. This trend was particularly apparent when the allocations of stimulus frequencies to electrodes were changed over time, with pitch changes even reversing direction in some subjects. These findings show that pitch plasticity can occur more rapidly and on a greater scale in the mature auditory system than previously thought possible. Overall, the results suggest that the adult auditory system can impose perceptual order on disordered arrays of inputs.

Renner, R. -, & Jensen, J. T. (2011). *Progestin-Only Oral Contraceptive Pills* Wiley-Blackwell.  
doi:10.1002/9781444342642.ch4

Rich, P., Bourcier, M., Sofen, H., Fakharzadeh, S., Wasfi, Y., Wang, Y., . . . The PHOENIX 1 Investigators. (2013). Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. *The British Journal of Dermatology*, doi:10.1111/bjd.12632; 10.1111/bjd.12632

BACKGROUND: Most patients with psoriasis have nail changes, and treating nail psoriasis is challenging. OBJECTIVES: To assess improvement in fingernail psoriasis with ustekinumab treatment in PHOENIX 1. METHODS: Patients received ustekinumab 45 mg or 90 mg or placebo at weeks 0 and 4. Ustekinumab-randomized patients continued maintenance dosing every 12 weeks, while placebo patients crossed over to receive ustekinumab 45 mg or 90 mg at weeks 12/16 followed by every 12 week dosing. At week 40, Initial Responders (those with  $\geq 75\%$  improvement from baseline in Psoriasis Area and Severity Index score [PASI 75]) were re-randomized to either continue maintenance dosing or withdraw from treatment. Nail involvement was evaluated using the Nail Psoriasis Severity Index (NAPSI) on a target fingernail, Nail Physician's Global Assessment (Nail PGA), and mean number of nails involved. RESULTS: Of 766 randomized patients, 545 (71.1%) had nail psoriasis. At week 24, the percent improvement from baseline NAPSI score was 46.5% [ustekinumab 45 mg] and 48.7% [ustekinumab 90 mg].

Percent improvements in NAPSI ranged from 29.7% ( /=PASI 90). Mean NAPSI scores improved from 4.5 at baseline to 2.4 at week 24 (45 mg) and from 4.4 to 2.2 (90 mg). Nail PGA scores and mean number of psoriatic nails improved by week 24. Further improvement was observed for all endpoints among Initial Responders continuing maintenance treatment through week 52. CONCLUSIONS: Ustekinumab significantly improves nail psoriasis, and improvements continue over time through up to one year of treatment in those receiving maintenance treatment. This article is protected by copyright. All rights reserved.

Rich, P., Elewski, B., Scher, R. K., & Pariser, D. (2013). Diagnosis, clinical implications, and complications of onychomycosis. *Seminars in Cutaneous Medicine and Surgery*, 32(2 Suppl 1), S5-8.

The diagnosis of onychomycosis is suggested by the clinical presentation as well as the family history and patient age. The definitive diagnosis of onychomycosis is based on (1) establishing the presence or absence of fungal elements using laboratory methods and/or (2) identifying the fungus using fungal culture or, in the future, by polymerase chain reaction as new developments emerge in this technology, making more widespread application of this technique possible.

Riddle, M. C., Rosenstock, J., Vlajnic, A., & Gao, L. (2013). Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. *Diabetes, Obesity & Metabolism*, doi:10.1111/dom.12225; 10.1111/dom.12225

BACKGROUND: Many patients with type 2 diabetes mellitus (T2DM) initiate insulin therapy when other treatments fail; how best to do this is poorly defined. METHODS: People with T2DM (n = 588; glycated hemoglobin A1C [A1C] > 7.0%, mean baseline 9.4%) were randomized to twice-daily premixed protamine-aspart/aspart insulin (PM-2), once-daily insulin glargine plus zero to one prandial insulin glulisine injection (G + 1), or insulin glargine plus zero to three prandial injections (G + 3). Insulin was titrated for 60 weeks. Efficacy and safety outcomes were assessed. RESULTS: Discontinuation rates were 53/194 (27%), 44/194 (23%), and 38/194 (20%), for PM-2, G + 1, and G + 3. Glycemic control improved in all groups (A1C 7.2 +/- 1.37, 7.1 +/- 1.68, and 7.0 +/- 1.21% at 60 weeks; 7.5 +/- 1.29, 7.2 +/- 1.62, and 7.2 +/- 1.63% at

endpoint). G + 1 was statistically non-inferior to PM-2 in reducing A1C. G + 3 was slightly superior to PM-2 in attaining < 7.0% at 60 weeks, but only when the analysis included Good Clinical Practice non-adherent sites. Hypoglycemia with plasma glucose < 2.8 mmol/L was more frequent with PM-2 versus G + 1 and G + 3; (adjusted incidence: 46 [p = 0.0087]; vs 33 [p = 0.0045] and 31.5%; events-patient-year: 1.9 vs 0.8 and 0.9, p <= 0.0001). Insulin dosage and weight-gain were similar. CONCLUSION: Basal insulin plus a single prandial injection is as effective in improving glycemic control as premixed insulin. Full basal-prandial therapy is only slightly more effective than premixed insulin. Stepwise basal-prandial regimens improve glycemic control with less hypoglycemia than twice-daily premixed insulin.

Riley, K. J., Srikanth, P., Choi, D., & McCarty, D. (2012). Treatment length and outcomes among adolescents: a secondary data analysis. *Substance Abuse Treatment, Prevention, and Policy*, 7, 35-597X-7-35. doi:10.1186/1747-597X-7-35; 10.1186/1747-597X-7-35

BACKGROUND: Adaptations to evidence-based substance abuse treatment programs may impact their effectiveness. A qualitative study of MET/CBT-5 implementation in community agencies treating adolescents found that the majority of the agencies made adaptations and that the most frequent adaptation was to provide more than five treatment sessions. METHODS: Baseline and outcome data from SAMHSA's Effective Adolescent Treatment demonstration were analyzed to assess associations between length of treatment, client characteristics, and outcomes at three months. RESULTS: Adolescents who received more or less than the protocol length of 5 sessions were less likely to be discharged to the community than those who received the 5 session protocol. Those who received more than five sessions were more likely to have higher severity scores at intake but almost 50% of those with more than five sessions had low intake severity scores. Clients who received less than five sessions tended to have lower severity scores than clients who received more than five sessions. CONCLUSIONS: Length of treatment tended to vary by site rather than severity of substance problems or frequency of use. There was no significant improvement of substance abuse problems or decrease in frequency of use with longer treatment. Implementation of the MET/CBT-5 component of the Cannabis Youth Treatment trial in the EAT project illustrates the difficulty of adherence to an evidence based protocol in the field.

Rnnekleiv, O. K., & Kelly, M. J. (2010). *Membrane-initiated effects of estrogen in the central nervous system* Elsevier Inc. doi:10.1016/B978-008088783-8.00032-2

It is well known that many of the actions of estrogen in the central nervous system are mediated via intracellular receptor/transcription factors that interact with steroid response elements on target genes. However, there now exists compelling evidence for membrane steroid receptors for estrogen in hypothalamic and other brain neurons. But, it is not well understood how estrogen signals via membrane receptors, and how these signals impact not only membrane excitability but also gene transcription in neurons. Indeed, it has been known for sometime that estrogen can rapidly alter neuronal activity within seconds, indicating that some cellular effects can occur via membrane delimited events. In addition, estrogen can affect second messenger systems, including calcium mobilization and a plethora of kinases to alter cell signaling. Therefore, this chapter considers our current knowledge of rapid membrane-initiated and intracellular signaling by estrogen in the brain, the nature of receptors involved, and how they contribute to homeostatic functions. © 2009 Elsevier Inc. All rights reserved.

Rodriguez, M. I., & Caughey, A. B. (2013). Cost-effectiveness analyses and their role in improving healthcare strategies. *Current Opinion in Obstetrics & Gynecology*, doi:10.1097/GCO.000000000000020

PURPOSE OF REVIEW: In this era of healthcare reform, attention is focused on increasing the quality of care and access to services, while simultaneously reducing the cost. Economic evaluations can play an important role in translating research to evidence-based practice and policy. RECENT FINDINGS: Cost-effectiveness analysis (CEA) and its utility for clinical and policy decision making among U.S. obstetricians and gynecologists is reviewed. Three case examples demonstrating the value of this methodology in decision making are considered. A discussion of the methodologic principles of CEA, the advantages, and the limitations of the methodology are presented. SUMMARY: CEA can play an important role in evidence-based decision making, with value for clinicians and policy makers alike. These studies are of particular interest in the field of obstetrics and gynecology, in which uncertainty from epidemiologic or clinical trials exists, or multiple perspectives need to be considered (maternal, neonatal, and societal). As with all research, it is essential that economic evaluations are conducted according to established

methodologic standards. Interpretation and application of results should occur with a clear understanding of both the value and the limitations of economic evaluations.

Rosenstein, M. G., Kuppermann, M., Gregorich, S. E., Cottrell, E. K., Caughey, A. B., & Cheng, Y. W. (2013). Association between vaginal birth after cesarean delivery and primary cesarean delivery rates. *Obstetrics and Gynecology*, *122*(5), 1010-1017. doi:10.1097/AOG.0b013e3182a91e0f; 10.1097/AOG.0b013e3182a91e0f

**OBJECTIVE:** To estimate the association between vaginal birth after cesarean delivery (VBAC) rates and primary cesarean delivery rates in California hospitals. **METHODS:** Hospital VBAC rates were calculated using birth certificate and discharge data from 2009, and hospitals were categorized by quartile of VBAC rate. Multivariable logistic regression analysis was performed to estimate the odds of cesarean delivery among low-risk nulliparous women with singleton pregnancies at term in vertex presentation (nulliparous term singleton vertex) by hospital VBAC quartile while controlling for many patient-level and hospital-level confounders. **RESULTS:** There were 468,789 term singleton births in California in 2009 at 255 hospitals, 125,471 of which were low-risk nulliparous term singleton vertex. Vaginal birth after cesarean delivery rates varied between hospitals, with a range of 0-44.6%. Rates of cesarean delivery among low-risk nulliparous term singleton vertex women declined significantly with increasing VBAC rate. When adjusted for maternal and hospital characteristics, low-risk nulliparous term singleton vertex women who gave birth in hospitals in the highest VBAC quartile had an odds ratio of 0.55 (95% confidence interval 0.46-0.66) of cesarean delivery compared with women at hospitals with the lowest VBAC rates. Each percentage point increase in a hospital's VBAC rate was associated with a 0.65% decrease in the low-risk nulliparous term singleton vertex cesarean delivery rate.

**CONCLUSION:** Hospitals with higher rates of VBAC have lower rates of primary cesarean delivery among low-risk nulliparous women with singleton pregnancies at term in vertex presentation.

**LEVEL OF EVIDENCE:** : II.

Rosso, A. L., Studenski, S. A., Chen, W. G., Aizenstein, H. J., Alexander, N. B., Bennett, D. A., . . . Rosano, C. (2013). Aging, the central nervous system, and mobility. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *68*(11), 1379-1386.

doi:10.1093/gerona/glt089

**Background.** Mobility limitations are common and hazardous in community-dwelling older adults but are largely understudied, particularly regarding the role of the central nervous system (CNS). This has limited development of clearly defined pathophysiology, clinical terminology, and effective treatments. Understanding how changes in the CNS contribute to mobility limitations has the potential to inform future intervention studies. **Methods.** A conference series was launched at the 2012 conference of the Gerontological Society of America in collaboration with the National Institute on Aging and the University of Pittsburgh. The overarching goal of the conference series is to facilitate the translation of research results into interventions that improve mobility for older adults. **Results.** Evidence from basic, clinical, and epidemiological studies supports the CNS as an important contributor to mobility limitations in older adults without overt neurologic disease. Three main goals for future work that emerged were as follows: (a) develop models of mobility limitations in older adults that differentiate aging from disease-related processes and that fully integrate CNS with musculoskeletal contributors; (b) quantify the contribution of the CNS to mobility loss in older adults in the absence of overt neurologic diseases; (c) promote cross-disciplinary collaboration to generate new ideas and address current methodological issues and barriers, including real-world mobility measures and life-course approaches. **Conclusions.** In addition to greater cross-disciplinary research, there is a need for new approaches to training clinicians and investigators, which integrate concepts and methodologies from individual disciplines, focus on emerging methodologies, and prepare investigators to assess complex, multisystem associations. © 2013 The Author.

Ruffell, B., Affara, N. I., Cottone, L., Junankar, S., Johansson, M., DeNardo, D. G., . . . Coussens, L. M. (2013). Cathepsin C is a tissue-specific regulator of squamous carcinogenesis. *Genes and Development*, 27(19), 2086-2098. doi:10.1101/gad.224899.113

Serine and cysteine cathepsin (Cts) proteases are an important class of intracellular and pericellular enzymes mediating multiple aspects of tumor development. Emblematic of these is CtsB, reported to play functionally significant roles during pancreatic islet and mammary carcinogenesis. CtsC, on the other hand, while up-regulated during pancreatic islet carcinogenesis, lacks functional significance in mediating neoplastic progression in that organ.

Given that protein expression and enzymatic activity of both CtsB and CtsC are increased in numerous tumors, we sought to understand how tissue specificity might factor into their functional significance. Thus, whereas others have reported that CtsB regulates metastasis of mammary carcinomas, we found that development of squamous carcinomas occurs independently of CtsB. In contrast to these findings, our studies found no significant role for CtsC during mammary carcinogenesis but revealed squamous carcinogenesis to be functionally dependent on CtsC. In this context, dermal/stromal fibroblasts and bone marrow-derived cells expressed increased levels of enzymatically active CtsC that regulated the complexity of infiltrating immune cells in neoplastic skin, development of angiogenic vasculature, and overt squamous cell carcinoma growth. These studies highlight the important contribution of tissue/microenvironment context to solid tumor development and indicate that tissue specificity defines functional significance for these two members of the cysteine protease family. © 2013 Ruffell et al.

Sachs, M. S., Wang, Z., Gaba, A., Fang, P., Belk, J., Ganesan, R., . . . Jacobson, A. (2002). Toeprint analysis of the positioning of translation apparatus components at initiation and termination codons of fungal mRNAs. *Methods (San Diego, Calif.)*, 26(2), 105-114. doi:10.1016/S1046-2023(02)00013-0

The ability to map the position of ribosomes and their associated factors on mRNAs is critical for an understanding of translation mechanisms. Earlier approaches to monitoring these important cellular events characterized nucleotide sequences rendered nuclease-resistant by ribosome binding. While these approaches furthered our understanding of translation initiation and ribosome pausing, the pertinent techniques were technically challenging and not widely applied. Here we describe an alternative assay for determining the mRNA sites at which ribosomes or other factors are bound. This approach uses primer extension inhibition, or "toeprinting," to map the 3' boundaries of mRNA-associated complexes. This methodology, previously used to characterize initiation mechanisms in prokaryotic and eukaryotic systems, is used here to gain an understanding of two interesting translational regulatory phenomena in the fungi *Neurospora crassa* and *Saccharomyces cerevisiae*: (a) regulation of translation in response to arginine

concentration by an evolutionarily conserved upstream open reading frame, and (b) atypical termination events that occur as a consequence of the presence of premature stop codons.

Sakamoto, M., Woods, S. P., Kolessar, M., Kriz, D., Anderson, J. R., Olavarria, H., . . . Huckans, M. (2013). Protective effects of higher cognitive reserve for neuropsychological and daily functioning among individuals infected with hepatitis C. *Journal of Neurovirology*, *19*(5), 442-451.  
doi:10.1007/s13365-013-0196-4

Higher levels of cognitive reserve (CR) can be protective against the neuropsychological manifestation of neural injury across a variety of clinical disorders. However, the role of CR in the expression of neurocognitive deficits among persons infected with the hepatitis C virus (HCV) is not well understood. Thirty-nine HCV-infected participants were classified as having either high (n = 19) or low (n = 20) CR based on educational attainment, oral word reading, and IQ scores. A sample of 40 demographically comparable healthy adults (HA) was also included. All participants completed the Neuropsychological Assessment Battery, Delis-Kaplan Executive Function System, and Behavioral Rating Inventory of Executive Function, Adult Version (BRIEF-A). Linear regression analyses, controlling for gender, depression, and lifetime substance use disorders, found significant effects of HCV/CR group on verbal fluency, executive functions, and daily functioning T scores, but not in learning or the BRIEF-A. Pairwise comparisons revealed that the HCV group with low CR performed significantly below the HCV high CR and HA cohorts, who did not differ from one another. Findings indicate that higher levels of CR may be a protective factor in the neurocognitive and real-world manifestation of neural injury commonly associated with HCV infection. © 2013 Journal of NeuroVirology, Inc.

Santo, V. J., Dargon, P. T., Azarbal, A. F., Liem, T. K., Mitchell, E. L., Moneta, G. L., & Landry, G. J. (2013). Open versus endoscopic great saphenous vein harvest for lower extremity revascularization of critical limb ischemia. *Journal of Vascular Surgery*,  
doi:10.1016/j.jvs.2013.08.007; 10.1016/j.jvs.2013.08.007

OBJECTIVE: This study determined wound complication rates, intervention rates, failure mechanisms, patency, limb salvage, and overall survival after lower extremity revascularization using open vein harvest (OVH) vs endoscopic vein harvest (EVH) for critical limb ischemia.

**METHODS:** A single-institution review was conducted of consecutive patients who underwent infrainguinal bypass with a single-segment reversed great saphenous vein between 2005 and 2012. **RESULTS:** A total of 251 patients with critical limb ischemia underwent revascularization, comprising 153 with OVH and 98 with EVH. The OVH group had a lower mean body mass index (26.7 vs 29.9 kg/m<sup>2</sup>; P = .001). There were no other differences in demographics, comorbidities, medications, smoking, or in the proximal or distal anastomotic site. Median operative times were 249 minutes (OVH) vs 316 minutes (EVH; P < .001). Median postoperative hospital length of stay was 7 days (OVH) vs 5 days (EVH; P < .001). Median follow-up was 295 days (OVH) vs 313 days (EVH; P = .416). During follow-up, 21 OVH grafts (14%) and 27 EVH grafts (28%) underwent an intervention (P = .048). There were a similar number of surgical interventions: 50% (OVH) vs 61% (EVH; P = .449). Failed grafts had a mean of 1.2 stenoses per graft, regardless of harvest method. Median stenosis length was 2.1 cm (OVH) vs 2.5 cm (EVH; P = .402). At 1 and 3 years, the primary patency was 71% and 52% (OVH) vs 58% and 41% (EVH; P = .010), and secondary patency was 88% and 71% (OVH) vs 88% and 64% (EVH; P = .266). A secondary patency Cox proportional hazard model showed EVH had a hazard ratio of 2.93 (95% confidence interval, 1.03-8.33; P = .044). Overall and harvest-related wound complications were 44% and 29% (OVH) vs 37% and 12% (EVH; P = .226 and P = .002). At 5 years, amputation-free survival was 48% (OVH) vs 54% (EVH; P = .305), and limb salvage was 89% (OVH) and 91% (EVH; P = .615). **CONCLUSIONS:** OVH and EVH have similar failure mechanisms, limb salvage, amputation-free survival, and overall survival. EVH is associated with impaired patency, increased need for intervention, longer operative times, shorter hospital stays, and decreased vein harvest site wound complications. OVH of the great saphenous vein may provide optimal patency but was not necessarily associated with better patient-centered outcomes. Similar limb salvage rates and amputation-free survival may justify the use of EVH, despite inferior patency, to capture shorter hospital stays and decreased wound complications.

Saultz, J. (2013). Responsible and capable family physicians. *Family Medicine*, 45(9), 665-666.

Scheer, J. K., Tang, J. A., Smith, J. S., Klineberg, E., Hart, R. A., Mundis Jr., G. M., . . . Ames, C. P. (2013). Reoperation rates and impact on outcome in a large, prospective, multicenter, adult

spinal deformity database. *Journal of Neurosurgery: Spine*, 19(4), 464-470.

doi:10.3171/2013.7.SPINE12901

**Object.** Complications and reoperation for surgery to correct adult spinal deformity are not infrequent, and many studies have analyzed the rates and factors that influence the likelihood of reoperation. However, there is a need for more comprehensive analyses of reoperation in adult spinal deformity surgery from a global standpoint, particularly focusing on the 1st year following operation and considering radiographic parameters and the effects of reoperation on health-related quality of life (HRQOL). This study attempts to determine the prevalence of reoperation following surgery for adult spinal deformity, assess the indications for these reoperations, evaluate for a relation between specific radiographic parameters and the need for reoperation, and determine the potential impact of reoperation on HRQOL measures. **Methods.** A retrospective review was conducted of a prospective, multicenter, adult spinal deformity database collected through the International Spine Study Group. Data collected included age, body mass index, sex, date of surgery, information regarding complications, reoperation dates, length of stay, and operation time. The radiographic parameters assessed were total number of levels instrumented, total number of interbody fusions, C-7 sagittal vertical axis, uppermost instrumented vertebra (UIV) location, and presence of 3-column osteotomies. The HRQOL assessment included Oswestry Disability Index (ODI), 36-Item Short Form Health Survey physical component and mental component summary, and SRS-22 scores. Smoking history, Charlson Comorbidity Index scores, and American Society of Anesthesiologists Physical Status classification grades were also collected and assessed for correlation with risk of early reoperation. Various statistical tests were performed for evaluation of specific factors listed above, and the level of significance was set at  $p < 0.05$ . **Results.** Fifty-nine (17%) of a total of 352 patients required reoperation. Forty-four (12.5%) of the reoperations occurred within 1 year after the initial surgery, including 17 reoperations (5%) within 30 days. Two hundred sixty-eight patients had a minimum of 1 year of follow-up. Fifty-three (20%) of these patients had a 3-column osteotomy, and 10 (19%) of these 53 required reoperation within 1 year of the initial procedure. However, 3-column osteotomy was not predictive of reoperation within 1 year,  $p = 0.5476$ ). There were no significant differences between groups with regard to the distribution of UIV, and UIV did not have a significant effect on reoperation rates. Patients needing reoperation within 1 year had worse ODI and SRS-22

scores measured at 1-year follow-up than patients not requiring operation. Conclusions. Analysis of data from a large multicenter adult spinal deformity database shows an overall 17% reoperation rate, with a 19% reoperation rate for patients treated with 3-column osteotomy and a 16% reoperation rate for patients not treated with 3-column osteotomy. The most common indications for reoperation included instrumentation complications and radiographic failure. Reoperation significantly affected HRQOL outcomes at 1-year follow-up. The need for reoperation may be minimized by carefully considering spinal alignment, termination of fixation, and type of surgical procedure (presence of osteotomy). Precautions should be taken to avoid malposition or instrumentation (rod) failure.

Shaw, A. K., Paul, A. S., & Williams, R. (2013). Eigenlate-based HRR-ATR with multi-look and time-recursion. *IEEE Transactions on Aerospace and Electronic Systems*, 49(4), 2369-2385.  
doi:10.1109/TAES.2013.6621822

Automatic target recognition (ATR) using high range resolution (HRR) radar signatures is developed using classical Bayesian multiple hypothesis theory. An eigenlate-based matched filtering (ETMF) algorithm is presented where the templates are formed using the dominant range-space eigenvector of detected HRR training profiles and classification is performed using normalized matched filtering (MF). The proposed approach is extended to multi-look and sequential ATR where new observation profiles are recursively combined probabilistically with previous steps to update ATR results, which is useful for simultaneous recognition and tracking of moving targets. An HRR-specific profile normalization scheme is presented to satisfy matched filter requirements. Classification performance of the proposed method has been compared with a linear least-squares method and hidden Markov model (HMM) approach using MSTAR data collection. © 2013 IEEE.

Shi, L., Goenezen, S., Haller, S., Hinds, M. T., Thornburg, K. L., & Rugonyi, S. (2013). Alterations in pulse wave propagation reflect the degree of outflow tract banding in HH18 chicken embryos. *American Journal of Physiology. Heart and Circulatory Physiology*, 305(3), H386-96.  
doi:10.1152/ajpheart.00100.2013; 10.1152/ajpheart.00100.2013

Hemodynamic conditions play a critical role in embryonic cardiovascular development, and

altered blood flow leads to congenital heart defects. Chicken embryos are frequently used as models of cardiac development, with abnormal blood flow achieved through surgical interventions such as outflow tract (OFT) banding, in which a suture is tightened around the heart OFT to restrict blood flow. Banding in embryos increases blood pressure and alters blood flow dynamics, leading to cardiac malformations similar to those seen in human congenital heart disease. In studying these hemodynamic changes, synchronization of data to the cardiac cycle is challenging, and alterations in the timing of cardiovascular events after interventions are frequently lost. To overcome this difficulty, we used ECG signals from chicken embryos (Hamburger-Hamilton stage 18, approximately 3 days of incubation) to synchronize blood pressure measurements and optical coherence tomography images. Our results revealed that, after 2 h of banding, blood pressure and pulse wave propagation strongly depend on band tightness. In particular, while pulse transit time in the heart OFT of control embryos is approximately 10% of the cardiac cycle, after banding (35% to 50% band tightness) it becomes negligible, indicating a faster OFT pulse wave velocity. Pulse wave propagation in the circulation is likewise affected; however, pulse transit time between the ventricle and dorsal aorta (at the level of the heart) is unchanged, suggesting an overall preservation of cardiovascular function. Changes in cardiac pressure wave propagation are likely contributing to the extent of cardiac malformations observed in banded hearts.

Shinto, L., Quinn, J., Montine, T., Dodge, H. H., Woodward, W., Baldauf-Wagner, S., . . . Kaye, J. (2014). A randomized placebo-controlled pilot trial of omega-3 Fatty acids and alpha lipoic Acid in Alzheimer's disease. *Journal of Alzheimer's Disease : JAD*, *38*(1), 111-120. doi:10.3233/JAD-130722; 10.3233/JAD-130722

Oxidative stress, inflammation, and increased cholesterol levels are all mechanisms that have been associated with Alzheimer's disease (AD) pathology. Several epidemiologic studies have reported a decreased risk of AD with fish consumption. This pilot study was designed to evaluate the effects of supplementation with omega-3 fatty acids alone (omega-3) or omega-3 plus alpha lipoic acid (omega-3 + LA) compared to placebo on oxidative stress biomarkers in AD. The primary outcome measure was peripheral F2-isoprostane levels (oxidative stress measure). Secondary outcome measures included performance on: Mini-Mental State Examination (MMSE), Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL), and Alzheimer

Disease Assessment Scale-cognitive subscale (ADAS-cog). Thirty-nine AD subjects were randomized to one of three groups: 1) placebo, 2) omega-3, or 3) omega-3 + LA for a treatment duration of 12 months. Eighty seven percent (34/39) of the subjects completed the 12-month intervention. There was no difference between groups at 12 months in peripheral F2-isoprostane levels ( $p = 0.83$ ). The omega-3 + LA and omega-3 were not significantly different than the placebo group in ADAS-cog ( $p = 0.98$ ,  $p = 0.86$ ) and in ADL ( $p = 0.15$ ,  $p = 0.82$ ). Compared to placebo, the omega-3 + LA showed less decline in MMSE ( $p < 0.01$ ) and IADL ( $p = 0.01$ ) and the omega-3 group showed less decline in IADL ( $p < 0.01$ ). The combination of omega-3 + LA slowed cognitive and functional decline in AD over 12 months. Because the results were generated from a small sample size, further evaluation of the combination of omega-3 fatty acids plus alpha-lipoic acid as a potential treatment in AD is warranted.

Siegl, C., Hamminger, P., Jank, H., Ahting, U., Bader, B., Danek, A., . . . Salzer, U. (2013). Alterations of Red Cell Membrane Properties in Neuroacanthocytosis. *Plos One*, 8(10)  
doi:10.1371/journal.pone.0076715

Neuroacanthocytosis (NA) refers to a group of heterogenous, rare genetic disorders, namely chorea acanthocytosis (ChAc), McLeod syndrome (MLS), Huntington's disease-like 2 (HDL2) and pantothenate kinase associated neurodegeneration (PKAN), that mainly affect the basal ganglia and are associated with similar neurological symptoms. PKAN is also assigned to a group of rare neurodegenerative diseases, known as NBIA (neurodegeneration with brain iron accumulation), associated with iron accumulation in the basal ganglia and progressive movement disorder. Acanthocytosis, the occurrence of misshaped erythrocytes with thorny protrusions, is frequently observed in ChAc and MLS patients but less prevalent in PKAN (about 10%) and HDL2 patients. The pathological factors that lead to the formation of the acanthocytic red blood cell shape are currently unknown. The aim of this study was to determine whether NA/NBIA acanthocytes differ in their functionality from normal erythrocytes. Several flow-cytometry-based assays were applied to test the physiological responses of the plasma membrane, namely drug-induced endocytosis, phosphatidylserine exposure and calcium uptake upon treatment with lysophosphatidic acid. ChAc red cell samples clearly showed a reduced response in drug-induced endovesiculation, lysophosphatidic acid-induced phosphatidylserine exposure, and calcium

uptake. Impaired responses were also observed in acanthocyte-positive NBIA (PKAN) red cells but not in patient cells without shape abnormalities. These data suggest an "acanthocytic state" of the red cell where alterations in functional and interdependent membrane properties arise together with an acanthocytic cell shape. Further elucidation of the aberrant molecular mechanisms that cause this acanthocytic state may possibly help to evaluate the pathological pathways leading to neurodegeneration. © 2013 Siegl et al.

Silverberg, J. I., & Hanifin, J. M. (2013). Adult eczema prevalence and associations with asthma and other health and demographic factors: A US population-based study. *Journal of Allergy and Clinical Immunology*, doi:10.1016/j.jaci.2013.08.031

Background: Little is known about the epidemiology of eczema in adults. The goal of this study was to determine the prevalence of and associations with adult eczema in the United States.

Methods: We used the 2010 National Health Interview Survey from a nationally representative sample of 27,157 adults age 18 to 85 years. Results: Overall, the 1-year prevalence of eczema was 10.2% (95% CI, 9.7% to 10.6%). The 1-year prevalence of eczema with asthma and/or hay fever was 3.2% (95% CI, 2.8% to 3.3%). Adult eczema was associated with higher prevalence of asthma ( $P < .001$ , Rao-Scott  $\chi^2$  test), more asthma attacks in the past year ( $P < .001$ ), and more persistent asthma ( $P = .02$ ). In multivariate models eczema prevalence was significantly higher in older participants; female subjects; those with Hispanic ethnicity, US birthplace, and higher level of household education; and those currently working (all  $P \leq .02$ , logistic regression).

Conclusions: This study provides US population-based estimates of eczema prevalence and asthma associations in adults. The results suggest multiple demographic and socioeconomic influences on the US prevalence of adult eczema. © 2013 American Academy of Allergy, Asthma & Immunology.

Smith, L., & Harding, C. O. (2011). *Inborn Errors of Metabolism* Elsevier Inc. doi:10.1016/B978-0-323-07307-3.10076-X

Smith, M. D., Patterson, E., Wahed, A. S., Belle, S. H., Courcoulas, A. P., Flum, D., . . . Wolfe, B. (2013). Can technical factors explain the volume-outcome relationship in gastric bypass surgery? *Surgery for Obesity and Related Diseases*, 9(5), 623-629. doi:10.1016/j.soard.2012.09.013

Background: The existence of a relationship between surgeon volume and patient outcome has been reported for different complex surgical operations. This relationship has also been confirmed for patients undergoing Roux-en-Y gastric bypass (RYGB) in the Longitudinal Assessment of Bariatric Surgery (LABS) study. Despite multiple studies demonstrating volume-outcome relationships, fewer studies investigate the causes of this relationship. Objective: The purpose of the present study is to understand possible explanations for the volume-outcome relationship in LABS. Methods: LABS includes a 10-center, prospective study examining 30-day outcomes after bariatric surgery. The relationship between surgeon annual RYGB volume and incidence of a composite endpoint (CE) has been published previously. Technical aspects of RYGB surgery were compared between high and low volume surgeons. The previously published model was adjusted for select technical factors. Results: High-volume surgeons (>100 RYGBs/yr) were more likely to perform a linear stapled gastrojejunostomy, use fibrin sealant, and place a drain at the gastrojejunostomy compared with low-volume surgeons (<25 RYGBs/yr), and less likely to perform an intraoperative leak test. After adjusting for the newly identified technical factors, the relative risk of CE was .93 per 10 RYGB/yr increase in volume, compared with .90 for clinical risk adjustment alone. Conclusion: High-volume surgeons exhibited certain differences in technique compared with low-volume surgeons. After adjusting for these differences, the strength of the volume-outcome relationship previously found was reduced only slightly, suggesting that other factors are also involved. © 2013 American Society for Bariatric Surgery.

Smith, P. J. S., Davies, I., Galbraith, C. G., & Stemmer, A. (2013). Special issue on high-resolution optical imaging. *Journal of Optics (United Kingdom)*, 15(9) doi:10.1088/2040-8978/15/9/090201

Smyth, J. K., Deveney, K. E., & Sade, R. M. (2013). Who should adopt robotic surgery, and when? *Annals of Thoracic Surgery*, 96(4), 1132-1137. doi:10.1016/j.athoracsur.2013.06.084

Snowden, J. M., Darney, B. G., Cheng, Y. W., McConnell, K. J., & Caughey, A. B. (2013). Systems factors in obstetric care: the role of daily obstetric volume. *Obstetrics and Gynecology*, 122(4), 851-857. doi:10.1097/AOG.0b013e3182a2dd93; 10.1097/AOG.0b013e3182a2dd93

OBJECTIVE: To evaluate whether relatively high-volume days are associated with measures of obstetric care in California hospitals. METHODS: This is a population-based retrospective cohort

study of linked data from birth certificates and antepartum and postpartum hospital discharge records for California births in 2006. Birth asphyxia and nulliparous, term, singleton, vertex cesarean delivery rates were analyzed as markers of quality of obstetric care. Rates were compared between hospital-specific relatively high-volume days (days when the number of births exceeded the 75th percentile of daily volume for that hospital) and low-volume or average-volume days. Analyses were stratified by weekend and weekday and overall hospital obstetric volume. Multivariable logistic regression was used to control for confounders. RESULTS: On weekends, relatively high-volume days were significantly associated with an elevated risk of asphyxia (27 out of 10,000 compared with 17 out of 10,000;  $P=.013$ ), whereas no association was present on weekdays (13 out of 10,000 on high-volume days and 15 out of 10,000 on low-volume or average-volume days;  $P=.182$ ). The cesarean delivery rate among the nulliparous, term, singleton, vertex population was significantly lower on high-volume weekend days (22.0% compared with 23.6% on low-volume or average-volume weekend days;  $P=.009$ ), whereas no association was present on weekdays (27.1% on high-volume days and 27.6% on low-volume or average-volume days;  $P=.092$ ). CONCLUSION: Delivery on relatively high-volume weekend days is a risk factor for birth asphyxia in California. High-volume weekend days also are associated with a lower rate of cesarean delivery in nulliparous women with singleton, vertex presentation pregnancies at term. LEVEL OF EVIDENCE: : II.

Soler, Z. M., Rudmik, L., Hwang, P. H., Mace, J. C., Schlosser, R. J., & Smith, T. L. (2013). Patient-centered decision making in the treatment of chronic rhinosinusitis. *Laryngoscope*, *123*(10), 2341-2346. doi:10.1002/lary.24027

Objectives/Hypothesis To explore possible factors that might impact a patient's choice to pursue endoscopic sinus surgery (ESS) or continue with medical management for treatment of refractory chronic rhinosinusitis (CRS). Study Design Cross-sectional evaluation of a multicenter prospective cohort. Methods Two hundred forty-two subjects with CRS were prospectively enrolled within four academic tertiary care centers across North America with ongoing symptoms despite prior medical treatment. Subjects either self-selected continued medical management ( $n = 62$ ) or ESS ( $n = 180$ ) for treatment of sinonasal symptoms. Differences in demographics, comorbid conditions, and clinical measures of disease severity between subject groups were compared.

Validated metrics of social support, personality, risk aversion, and physician-patient relationships were compared using bivariate analyses, predicted probabilities, and receiver operating characteristic curves at the 0.05 alpha level. Results No significant differences were found between treatment groups for any demographic characteristic, clinical cofactor, or measure of social support, personality, or the physician-patient relationship. Subjects electing to pursue sinus surgery did report significantly worse average quality-of-life (QOL) scores on the 22-item Sinonasal Outcome Test (SNOT-22;  $P < .001$ ) compared to those electing continued medical therapy ( $54.6 \pm 18.9$  vs.  $39.4 \pm 17.7$ ), regardless of surgical history or polyp status. SNOT-22 score significantly predicted treatment selection (odds ratio, 1.046; 95% confidence interval, 1.028-1.065;  $P < .001$ ) and was found to accurately discriminate between subjects choosing endoscopic sinus surgery and those electing medical management 72% of the time. Conclusions Worse patient-reported disease severity, as measured by the SNOT-22, was significantly associated with the treatment choice for CRS. Strong consideration should be given for incorporating CRS-specific QOL measures into routine clinical practice. Level of Evidence 2b. Laryngoscope, 123:2341-2346, 2013 Copyright © 2013 The American Laryngological, Rhinological and Otological Society, Inc.

Spindel, E. R. (2013). *Bombesin Peptides* Elsevier Inc. doi:10.1016/B978-0-12-385095-9.00046-4

Stacey, B. R., & Moller, J. L. (2013). Marijuana for pain relief: don't jump to conclusions. *The Journal of Pain : Official Journal of the American Pain Society*, 14(10), 1250-1251. doi:10.1016/j.jpain.2013.07.002; 10.1016/j.jpain.2013.07.002

Staudenmayer, K. L., Hsia, R. Y., Mann, N. C., Spain, D. A., & Newgard, C. D. (2013). Triage of elderly trauma patients: A population-based perspective. *Journal of the American College of Surgeons*, 217(4), 569-576. doi:10.1016/j.jamcollsurg.2013.06.017

Background Elderly patients are frequently undertriaged. However, the associations between triage patterns and outcomes from a population perspective are unknown. We hypothesized that triage patterns would be associated with differences in outcomes. Study Design This is a population-based, retrospective, cohort study of all injured adults aged 55 years or older, from 3 counties in California and 4 in Utah (2006 to 2007). Prehospital data were linked to trauma

registry data, state-level discharge data, emergency department records, and death files. The primary outcome was 60-day mortality. Patients treated at trauma centers were compared with those treated at nontrauma centers. Undertriage was defined as an Injury Severity Score (ISS) >15, with transport to a nontrauma center. Results There were 6,015 patients in the analysis. Patients who were taken to nontrauma centers were, on average, older (79.4 vs 70.8 years, p 15 (2.2% vs 6.7%, p 15 and the undertriage rate was 32.8% (n = 80). Overall 60-day mortality for patients with an ISS >15 was 17%, with no difference between trauma and nontrauma centers in unadjusted or adjusted analyses. However, the median per-patient costs were \$21,000 higher for severely injured patients taken to trauma centers. Conclusions This is the first population-based analysis of triage patterns and outcomes in the elderly. We have shown high rates of undertriage that are not associated with higher mortality, but are associated with higher costs. Future work should focus on determining how to improve outcomes for this population. © 2013 by the American College of Surgeons Published by Elsevier Inc.

Stein, D. G., & Hurn, P. D. (2010). *Effects of sex steroids on damaged neural systems* Elsevier Inc.

doi:10.1016/B978-008088783-8.00069-3

Progestins and estrogens, although still widely considered sex hormones, are important steroidal agents affecting many central nervous system (CNS) functions. This chapter assesses recent evidence that progesterone and estrogens can promote repair after traumatic brain injury, spinal cord injury, stroke, and possibly other neural disorders, although many of their specific actions on CNS repair remain to be discovered. The first part of the chapter reviews the role of progesterone in the treatment of CNS injury and highlights some of the mechanisms by which this hormone acts to enhance neuronal sparing and recovery of function. The second part reviews the literature on estrogen's and testosterone's effects on CNS repair mechanisms to provide the reader with a better perspective from which to evaluate the neuroprotective effects of these important hormones. © 2009 Elsevier Inc. All rights reserved.

Stephens, S. M., Pau, F. K. Y., Yalcinkaya, T. M., May, M. C., Berga, S. L., Post, M. D., . . . Polotsky, A. J. (2013). Assessing the pulsatility of luteinizing hormone in female vervet monkeys (*Chlorocebus aethiops sabaeus*). *Comparative Medicine*, 63(5), 432-438.

Specific alterations in the pulsatility of luteinizing hormone (LH) are linked to obesity-related subfertility in ovulatory women. Vervet monkeys (*Chlorocebus aethiops sabaeus*) are an Old World nonhuman primate that develops obesity and has a menstrual cycle similar to humans. We evaluated follicular-phase LH pulses in 12 adult normal-weight female vervets. Serum was collected every 10 min for 4 h by using a tether device in conscious, freely moving monkeys on menstrual cycle days 2 through 5. Serum estradiol was collected daily during the follicular phase to identify the luteal-follicular transition. For comparison, we used data from 12 ovulatory normal-weight women who had undergone frequent blood sampling of early-follicular LH. LH pulse frequency was similar, with  $2.8 \pm 0.7$  LH pulses during 4 h in vervets compared with  $2.3 \pm 0.7$  LH pulses during 4 h in women. The LH pulse mass (percentage change in the pulse peak over the preceding nadir) was  $123.2\% \pm 27.4\%$  in vervets and  $60.9\% \pm 14.9\%$  in humans. The first day of low serum estradiol after the follicular-phase peak was denoted as the day of the luteal-follicular transition. Luteectomy was performed on luteal days 7 through 9, and corpora lutea were confirmed by histology. We demonstrate that follicular LH patterns in vervets are similar to those in humans and that the luteal phase is easily identified by monitoring daily serum estradiol. These findings demonstrate that vervet monkeys are a suitable animal model for evaluating LH pulse dynamics longitudinally in studies of diet-induced obesity. Copyright 2013 by the American Association for Laboratory Animal Science.

Stuart Gerstein, N., Hawks Gerstein, W., Christopher Carey, M., Chee Kong Lam, N., Ram, H., Ryan Spassil, N., & Mark Schulman, P. (2013). The Thrombotic and Arrhythmogenic Risks of Perioperative NSAIDs. *Journal of Cardiothoracic and Vascular Anesthesia*, doi:10.1053/j.jvca.2013.05.018

Sullivan, D. R., Ganzini, L., Duckart, J. P., Lopez-Chavez, A., Deffebach, M. E., Thielke, S. M., & Slatore, C. G. (2013). Treatment Receipt and Outcomes among Lung Cancer Patients with Depression. *Clinical Oncology (Royal College of Radiologists (Great Britain))*, doi:10.1016/j.clon.2013.09.001; 10.1016/j.clon.2013.09.001

AIMS: Among lung cancer patients, depression has been associated with increased mortality, although the mechanisms are unknown. We evaluated the association of depression with

mortality and receipt of cancer therapies among depressed veterans with lung cancer.

**MATERIALS AND METHODS:** A retrospective, cohort study of lung cancer patients in the Veterans Affairs-Northwest Health Network from 1995 to 2010. Depression was defined by ICD-9 coding within 24 months before lung cancer diagnosis. Multivariable Cox proportional analysis and logistic regression were used. **RESULTS:** In total, 3869 lung cancer patients were evaluated; 14% had a diagnosis of depression. A diagnosis of depression was associated with increased mortality among all stage lung cancer patients (hazard ratio = 1.14, 95% confidence interval: 1.03-1.27, P = 0.01). Among early-stage (I and II) non-small cell lung cancer (NSCLC) patients, the hazard ratio was 1.37 (95% confidence interval: 1.12-1.68, P = 0.003). There was no association of depression diagnosis with surgery (odds ratio = 0.83, 95% confidence interval: 0.56-1.22, P = 0.34) among early-stage NSCLC patients. A depression diagnosis was not associated with mortality (hazard ratio = 1.02, 95% confidence interval: 0.89-1.16, P = 0.78) or chemotherapy (odds ratio = 1.07, 95% confidence interval: 0.83-1.39, P = 0.59) or radiation (odds ratio = 1.04, 95% confidence interval: 0.81-1.34, P = 0.75) receipt among advanced-stage (III and IV) NSCLC patients. Increased utilisation of health services for depression was associated with increased mortality among depressed patients. **CONCLUSIONS:** Depression is associated with increased mortality in lung cancer patients and this association is higher among those with increased measures of depression care utilisation. Differences in lung cancer treatment receipt are probably not responsible for the observed mortality differences between depressed and non-depressed patients. Clinicians should recognise the significant effect of depression on lung cancer survival.

Sung, J., Barry, J. M., Jenkins, R., Rozansky, D., Iragorri, S., Conlin, M., & Al-Uzri, A. (2013).

Alemtuzumab induction with tacrolimus monotherapy in 25 pediatric renal transplant recipients. *Pediatric Transplantation*, 17(8), 718-725. doi:10.1111/petr.12159; 10.1111/petr.12159

ALA induction in transplantation has been shown to reduce the need for maintenance immunosuppression. We report the outcome of 25 pediatric renal transplants between 2007 and 2010 using ALA induction followed by tacrolimus maintenance monotherapy. Patient ages were 1-19 yr (mean 14 +/- 4.1 yr). Time of follow-up was 7-51 months (mean 26 +/- 13 months). Tacrolimus monotherapy was maintained in 48% of patients, and glucocorticoids were avoided in

80% of recipients. Mean plasma creatinine and GFR at one yr post-transplant were 0.88 +/- 0.3 mg/dL and 104.4 +/- 25 mL/min/1.73m<sup>2</sup> , respectively. One, two, and three-yr actuarial patient and graft survival rates were 100%. The incidence of early AR (<12 months after transplantation) was 12%, while the incidence of late AR (after 12 months) was 16%. Forty-four percent of the recipients recovered normal, baseline renal function after an episode of AR, and 44% had persistent renal dysfunction (plasma creatinine 1.0-1.8 mg/dL). One graft was lost four yr after transplantation due to medication non-compliance. Four (16%) patients developed BK or CMV infection. In our experience, ALA induction with tacrolimus monotherapy resulted in excellent short- and mid-term patient and graft survival in low-immunologic risk pediatric renal transplant recipients.

Symoens, S., Malfait, F., D'Hondt, S., Callewaert, B., Dheedene, A., Steyaert, W., . . . Coucke, P. J. (2013). Deficiency for the ER-stress transducer OASIS causes severe recessive osteogenesis imperfecta in humans. *Orphanet Journal of Rare Diseases*, 8(1) doi:10.1186/1750-1172-8-154  
Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous brittle bone disorder. Whereas dominant OI is mostly due to heterozygous mutations in either COL1A1 or COL1A2, encoding type I procollagen, recessive OI is caused by biallelic mutations in genes encoding proteins involved in type I procollagen processing or chaperoning. Hitherto, some OI cases remain molecularly unexplained. We detected a homozygous genomic deletion of CREB3L1 in a family with severe OI. CREB3L1 encodes OASIS, an endoplasmic reticulum-stress transducer that regulates type I procollagen expression during murine bone formation. This is the first report linking CREB3L1 to human recessive OI, thereby expanding the OI gene spectrum. © 2013 Symoens et al.; licensee BioMed Central Ltd.

Takahashi, C. E., Brambrink, A. M., Aziz, M. F., Macri, E., Raines, J., Multani-Kohol, A., . . . Fields, J. D. (2013). Association of Intraoperative Blood Pressure and End Tidal Carbon Dioxide with Outcome After Acute Stroke Intervention. *Neurocritical Care*, doi:10.1007/s12028-013-9921-3  
BACKGROUND: General anesthesia (GA) for acute stroke interventions may be associated with inferior functional outcomes. Our goal was to identify physiologic parameters that mediate this association. METHODS: Consecutive patients treated at our institution between August 2007 and

December 2010 were identified from a prospective database. Clinical data were then extracted by retrospective chart review. Variables significantly associated with outcome in univariate analysis were also examined in multivariate analysis, controlling for well-established prespecified predictors of functional outcome. RESULTS: Of the 106 patients identified, 20 were excluded (17 due to the absence of 90-day mRS and 3 due to insufficient anesthetic records). Blood pressure (BP) decreased significantly after induction of GA, but there was no association between BP and outcome. End tidal carbon dioxide values (ETCO<sub>2</sub>) at 60 and 90 min, however, were significantly associated with outcomes in both univariate and multivariate analyses. Mean ETCO<sub>2</sub> in patients with favorable outcomes (modified Rankin Scale (mRS) 0-3) was higher than in those with unfavorable outcomes (mRS 4-6): 35.2 mmHg versus 32.2 (p = 0.03) at 60 min and 34.9 versus 31.9 (p = 0.04) at 90 min. The adjusted odds ratios for poor outcomes for each 1 mmHg decrease in ETCO<sub>2</sub> were the same: 0.76 (95 % CI 0.65-0.92; p = 0.004) at 60 min and 0.76 (95 % CI 0.61-0.93; p = 0.01) at 90 min. CONCLUSIONS: While BP decreased significantly in patients undergoing GA for acute stroke intervention, it did not correlate with patient outcome. Decreases in ETCO<sub>2</sub> at 30 and 60 min, however, were associated with 90-day mRS.

Takahashi, M., Dillon, T. J., Liu, C., Kariya, Y., Wang, Z., & Stork, P. J. S. (2013). Protein kinase a-dependent phosphorylation of Rap1 regulates its membrane localization and cell migration. *Journal of Biological Chemistry*, 288(39), 27712-27723. doi:10.1074/jbc.M113.466904

Background: The small G protein Rap1 is phosphorylated within its carboxyl terminus by the cAMP-dependent protein kinase PKA. Results: This phosphorylation removes Rap1 from the plasma membrane to limit Rap1 signaling. Conclusion: Rap1 phosphorylation switches Rap1 off the membrane and terminates its activation. Significance: Carboxyl-terminal phosphorylation may be common among small G proteins to regulate GTP/GDP cycling and downstream signaling.

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Terasawa, E., & Ojeda, S. R. (2010). *Neuroendocrine regulation of puberty* Elsevier Inc.

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Puberty is the phase in life when individuals become capable of reproducing. During puberty, major hormonal, physical, and behavioral changes take place. Changes occurring through

puberty are accompanied by psychological modifications that significantly affect the role of individual members in society. Because the factor(s) that trigger puberty remains as a great mystery of our time, in this chapter the authors have approached this question systematically by analyzing the maturation of each component of the reproductive endocrine system and, in great detail, the developmental changes that occur in neurons and glia of the hypothalamus during reproductive maturation. Highlights of the chapter include discussion of: (1) the possible genes responsible for the onset of puberty, (2) a potential role of kisspeptin and its receptor GPR54 in the hypothalamic control of puberty, and (3) the maturation of neocortical and limbic circuits that determine the establishment of adolescent behaviors. © 2009 Elsevier Inc. All rights reserved.

Terris, D. J., Snyder, S., Carneiro-Pla, D., Inabnet, W. B., Kandil, E., Orloff, L., . . . Yeh, M. W. (2013). American thyroid association statement on outpatient thyroidectomy. *Thyroid*, *23*(10), 1193-1202. doi:10.1089/thy.2013.0049

Background: The primary goals of this interdisciplinary consensus statement are to define the eligibility criteria for outpatient thyroidectomy and to explore preoperative, intraoperative, and postoperative factors that should be considered in order to optimize the safe and efficient performance of ambulatory surgery. Summary: A series of criteria was developed that may represent relative contraindications to outpatient thyroidectomy, and these fell into the following broad categories: clinical, social, and procedural issues. Intraoperative factors that bear consideration are enumerated, and include choice of anesthesia, use of nerve monitoring, hemostasis, management of the parathyroid glands, wound closure, and extubation. Importantly, postoperative factors are described at length, including suggested discharge criteria and recognition of complications, especially bleeding, airway distress, and hypocalcemia. Conclusions: Outpatient thyroidectomy may be undertaken safely in a carefully selected patient population provided that certain precautionary measures are taken to maximize communication and minimize the likelihood of complications. © Copyright 2013, Mary Ann Liebert, Inc.

Thompson, A., Wilson, M., James, T., Symbal, J., & Izumi, S. (2013). Feasibility study to implement nurse-delivered massage for pain management. *Journal of Hospice and Palliative Nursing*, *15*(7), 403-409. doi:10.1097/NJH.0b013e31829e0ed2

Pain is a significant problem in acute health care settings and has consistently been found to be poorly managed. Furthermore, hospitalized patients are becoming more complex, and health care dollars, more scarce. Nurses at the bedside have a unique opportunity to affect these issues. Although pharmacological tools are used extensively to address pain in acute care settings, there is a gap in understanding how nondrug approaches can be included to manage pain and its accompanying distress. This article details the findings of a feasibility study initiated in a 250-bed, community-owned hospital in the northwestern United States. The purpose was to determine whether massage could be delivered by registered nurses in an acute care setting. Nurses were invited to participate in a class to learn massage techniques and were asked to incorporate their skills during normal work hours and within their usual work assignment. Data were collected on patients' reported pain and distress levels before and after 22 massage encounters. Nurses were asked to give feedback on the encounters and report on barriers and observed benefits. Patients reported favorable responses to the massages with reduced levels of pain and distress. In addition, the nurses providing the massages described personal benefit from performing the massage.

Thompson, M., & Van den Bruel, A. (2011). *Diagnostic Tests Toolkit* Wiley-Blackwell.

doi:10.1002/9781119951827

This new volume in the Toolkit series is designed for clinicians and junior researchers who need to interpret the evidence for the effectiveness of the many diagnostic tests now available. Exceptionally user-friendly, this pocket-sized textbook realizes readers are not experts in diagnostic test interpretation. The authors cover a variety of issues, from how to design diagnostic test studies to understanding the results of diagnostic tests and interpreting the findings for clinical practice and health care policy. © 2012 John Wiley & Sons Ltd.

Timmerman, L., Holton, T., Yuneva, M., Louie, R., Padró, M., Daemen, A., . . . Gray, J. (2013).

Glutamine Sensitivity Analysis Identifies the xCT Antiporter as a Common Triple-Negative Breast Tumor Therapeutic Target. *Cancer Cell*, 24(4), 450-465. doi:10.1016/j.ccr.2013.08.020

A handful of tumor-derived cell lines form the mainstay of cancer therapeutic development, yielding drugs with an impact typically measured as months to disease progression. To develop

more effective breast cancer therapeutics and more readily understand their clinical impact, we constructed a functional metabolic portrait of 46 independently derived breast cell lines. Our analysis of glutamine uptake and dependence identified a subset of triple-negative samples that are glutamine auxotrophs. Ambient glutamine indirectly supports environmental cystine acquisition via the xCT antiporter, which is expressed on one-third of triple-negative tumors *in vivo*. xCT inhibition with the clinically approved anti-inflammatory sulfasalazine decreases tumor growth, revealing a therapeutic target in breast tumors of poorest prognosis and a lead compound for rapid, effective drug development. © 2013 Elsevier Inc.

Tokayer, J., Jia, Y., Dhalla, A. -, & Huang, D. (2013). Blood flow velocity quantification using splitspectrum amplitude-decorrelation angiography with optical coherence tomography. *Biomedical Optics Express*, 4(10), 1909-1924. doi:10.1364/BOE.4.001909

The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was recently developed as a method for imaging blood flow in the human retina without the use of phase information. In order to enable absolute blood velocity quantification, *in vitro* phantom experiments are performed to correlate the SSADA signal at multiple time scales with various preset velocities. A linear model relating SSADA measurements to absolute flow velocities is derived using the phantom data. The operating range for the linear model is discussed along with its implication for velocity quantification with SSADA in a clinical setting. © 2013 Optical Society of America.

Tormoen, G. W., Recht, O., Gruber, A., Levine, R. L., & McCarty, O. J. (2013). Phosphatidylserine index as a marker of the procoagulant phenotype of acute myelogenous leukemia cells. *Physical Biology*, 10(5), 056010-3975/10/5/056010. Epub 2013 Oct 8. doi:10.1088/1478-3975/10/5/056010; 10.1088/1478-3975/10/5/056010

Patients with acute myelogenous leukemia (AML) are at risk for thrombotic complications. Risk to develop thrombosis is closely tied to leukemia subtype, and studies have shown an association between leukocytosis and thrombosis in AML M3. We evaluated the relative roles of cell count and the surface expression of tissue factor (TF) and phosphatidylserine (PS) in the procoagulant phenotype of AML cell lines. The TF-positive AML M3 cell lines, NB4 and HL60, and AML M2 cell

line, AML14, exhibited both extrinsic tenase and prothrombinase activity in a purified system and promoted experimental thrombus formation. In contrast, the TF-negative AML cell line, HEL, exhibited only prothrombinase activity and did not affect the rate of occlusive thrombus formation. In plasma, NB4, HL60 and AML14 shortened clotting times in a cell-count, PS- and TF-dependent manner. Exposure of cultured NB4, HL60, and AML14 cells to the chemotherapeutic agent daunorubicin increased their extrinsic tenase activity and PS expression. Clot initiation time inversely correlated with logarithm of PS index, defined as the product of multiplying leukocyte count with cell surface PS exposure. We propose that leukemia cell PS index may serve as a biomarker for procoagulant activity.

Tsukamoto, H., & Farrens, D. L. (2013). A constitutively activating mutation alters the dynamics and energetics of a key conformational change in a ligand-free G protein-coupled receptor. *Journal of Biological Chemistry*, 288(39), 28207-28216. doi:10.1074/jbc.M113.472464

Background: Constitutively active mutations (CAMs) affect the dynamics of G protein-coupled receptors (GPCRs), through undefined mechanisms. Results: Site-directed fluorescence labeling (SDFL) studies find a CAM (M257Y) alters the dynamics of the GPCR ligand-free opsin.

Conclusion: The M257Y CAM alters the dynamics of the conversion between active and inactive opsin conformations. Significance: SDFL can be used to gain insights into how CAMs affect the dynamics of G protein-coupled receptors. © 2013 by The American Society for Biochemistry and Molecular Biology, Inc.

Urbanski, H. F., Sorwell, K., Garyfallou, V., Garten, J., Weiss, A., Renner, L., . . . Kohama, S. G. (2013). Androgen Supplementation During Aging: Development of a Physiologically Appropriate Protocol. *Rejuvenation Research*, doi:10.1089/rej.2013.1518

Men show an age-related decline in the circulating levels of testosterone (T) and dehydroepiandrosterone sulphate (DHEAS). Consequently, there is interest in developing androgen supplementation paradigms for old men that replicate the hormone profiles of young adults. In the present study we used old (21-26 years) male rhesus monkeys as a model to examine the efficacy of an androgen supplementation paradigm that comprised oral T administration (12 mg/kg body weight, dissolved in sesame oil/chocolate) in the evening, and

two oral DHEA administrations, 3 hours apart, (0.04 mg/kg body weight, dissolved in sesame oil/chocolate) in the morning. After 5 days of repeated hormone supplementation, serial blood samples were remotely collected from each animal hourly across the 24-hour day, and assayed for cortisol, DHEAS, T, 5-alpha dihydrotestosterone (DHT), estrone (E1), and 17-beta estradiol (E2). Following androgen supplementation, T levels were significantly elevated and this was associated with a more sustained nocturnal elevation of T's primary bioactive metabolites, DHT and E1 and E2. Plasma DHEAS levels were also significantly elevated after androgen supplementation; DHEAS levels rose in the early morning and gradually declined during the course of the day, closely mimicking the profiles observed in young adults; in contrast, cortisol levels were unaltered by the supplementation. Together the data demonstrate a non-invasive androgen supplementation paradigm that restores youthful circulating androgen levels in old male primates. Because this paradigm preserves the natural circulating circadian hormone patterns, we predict that it will produce fewer adverse side effects, such as perturbed sleep or cognitive impairment.

Vajtai, Z., Korngold, E., Hooper, J. E., Sheppard, B. C., Foster, B. R., & Coakley, F. V. (2013).

Suprarenal retroperitoneal liposarcoma with intracaval tumor thrombus: an imaging mimic of adrenocortical carcinoma. *Clinical Imaging*, doi:10.1016/j.clinimag.2013.08.016; 10.1016/j.clinimag.2013.08.016

We report a 57-year-old previously healthy man who presented with dull right upper quadrant pain, weight loss, fatigue, and night sweats. Computed tomography demonstrated a large, heterogeneously enhancing, soft tissue mass with no macroscopic fat above the right kidney with tumor thrombus extending into the inferior vena cava and right atrium. Positron Emission Tomography scanning demonstrated intense Fluorodeoxyglucose avidity in the primary tumor and tumor thrombus. The presumptive radiological diagnosis was adrenocortical carcinoma, but surgical pathology revealed a dedifferentiated liposarcoma. We conclude that suprarenal retroperitoneal liposarcoma should be included in the differential diagnosis for an apparent adrenal mass with venous invasion.

van der Kolk, N. M., & King, L. A. (2013). Effects of exercise on mobility in people with Parkinson's disease. *Movement Disorders*, 28(11), 1587-1596. doi:10.1002/mds.25658

Parkinson's disease is a prevalent neurodegenerative disorder for which only symptomatic treatment exists. Gait and balance disturbance is common in Parkinson's disease and is a major contributor to increased disability and decreased health-related quality of life and survival. Balance and gait deficits in Parkinson's disease are notoriously difficult to treat and are not significantly helped by pharmacological or surgical treatment. The last two decades have seen a dramatic increase in the research and clinical interest in using exercise as a treatment for mobility problems in people with Parkinson's disease. With exciting advances in basic science research suggesting neurochemical and neuroplastic changes after exercise, an increasing number of high-quality studies are documenting particular aspects of mobility improving after exercise. Exercise has the potential to help both motor (gait, balance, strength) and nonmotor (depression, apathy, fatigue, constipation) aspects of Parkinson's disease as well as secondary complications of immobility (cardiovascular, osteoporosis). This perspective article focuses primarily on recent evidence on the effects of exercise in improving mobility while highlighting the importance of targeted exercise intervention for maximizing the benefits of exercise. Suggestions for exercise guidelines, adherence issues, and directions for future research are provided. © 2013 Movement Disorder Society.

Ventres, W. (2013). Drugs for life: how pharmaceutical companies define our health. *Family Medicine*, 45(9), 663-664.

Wallace, N. T., & McConnell, K. J. (2013). Impact of comprehensive insurance parity on follow-up care after psychiatric inpatient treatment in Oregon. *Psychiatric Services*, 64(10), 961-966. doi:10.1176/appi.ps.201200465

Objective: This study assessed the impact of Oregon's 2007 parity law, which required behavioral health insurance parity, on rates of followup care provided within 30 days of psychiatric inpatient care. Methods: Data sources were claims (2005-2008) for 737 individuals with inpatient stays for a mental disorder who were continuously enrolled in insurance plans affected by the parity law (intervention group) or in commercial, self-insured plans that were not affected by the law

(control group). A difference-in-difference analysis was used to compare rates of follow-up care before and after the parity law between discharges of individuals in the intervention group and the control group and between discharges of individuals in the intervention group who had or had not met parity quantitative coverage limits during a coverage year. Estimates of the marginal effects of the parity law were adjusted for gender, discharge diagnosis, relationship to policy holder, and calendar quarter of discharge. Results: The study included 353 discharges in the intervention group and 535 discharges in the control group. After the parity law, follow-up rates increased by 11% ( $p=.042$ ) overall and by 20% for discharges of individuals who had met coverage limits ( $p=.028$ ). Conclusions: The Oregon parity law was associated with a large increase in the rate of follow-up care, predominantly for discharges of individuals who had met parity quantitative coverage limits. Given similarities between the law and the 2008 Mental Health Parity and Addiction Equity Act, the results may portend a national effect of more comprehensive parity laws.

Wang, H., Goehring, A., Wang, K. H., Penmatsa, A., Ressler, R., & Gouaux, E. (2013). Structural basis for action by diverse antidepressants on biogenic amine transporters. *Nature*, doi:10.1038/nature12648; 10.1038/nature12648

The biogenic amine transporters (BATs) regulate endogenous neurotransmitter concentrations and are targets for a broad range of therapeutic agents including selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs). Because eukaryotic BATs are recalcitrant to crystallographic analysis, our understanding of the mechanism of these inhibitors and antidepressants is limited. LeuT is a bacterial homologue of BATs and has proven to be a valuable paradigm for understanding relationships between their structure and function. However, because only approximately 25% of the amino acid sequence of LeuT is in common with that of BATs, and as LeuT is a promiscuous amino acid transporter, it does not recapitulate the pharmacological properties of BATs. Indeed, SSRIs and TCAs bind in the extracellular vestibule of LeuT and act as non-competitive inhibitors of transport. By contrast, multiple studies demonstrate that both TCAs and SSRIs are competitive inhibitors for eukaryotic BATs and bind to the primary binding pocket. Here we engineered LeuT to harbour human BAT-like pharmacology by mutating key residues around the primary binding

pocket. The final LeuBAT mutant binds the SSRI sertraline with a binding constant of 18 nM and displays high-affinity binding to a range of SSRIs, SNRIs and a TCA. We determined 12 crystal structures of LeuBAT in complex with four classes of antidepressants. The chemically diverse inhibitors have a remarkably similar mode of binding in which they straddle transmembrane helix (TM) 3, wedge between TM3/TM8 and TM1/TM6, and lock the transporter in a sodium- and chloride-bound outward-facing open conformation. Together, these studies define common and simple principles for the action of SSRIs, SNRIs and TCAs on BATs.

Watnick, S. (2013). Financial and Medico-Legal Implications of Late-Start Dialysis: Understanding the Present Policies through a Window of Past Performance. *Seminars in Dialysis*, doi:10.1111/sdi.12135; 10.1111/sdi.12135

In the United States, multiple stakeholders have impacted the timing of dialysis initiation for patients with end-stage renal disease. The optimal policy to start dialysis for this vulnerable population remains unknown. Historically, patients initiated dialysis weeks after the appearance of uremic symptoms. This changed not only due to an evolution in medical providers' practice but also due to changes in the care delivery system, the political imperatives, and the economic driving forces surrounding the care of these patients. One large randomized control trial looked at patient outcomes with strategies of early versus late start. The trial included an economic analysis. Depending on the specific comparison, cost was either lower in the late-start group or was equivalent between groups. This result would tend to favor a late-start strategy, where patients had an additional 6 months of dialysis-free time. However, the generalizability of this analysis has been questioned. Future care models that would include patients before and after dialysis initiation would be ideal to study cost and quality at the time of this transition of care. The recently implemented CMS Quality Incentive Program is one mechanism that could use such findings to implement a high-value strategy for patients starting chronic dialysis therapies.

Weddle, M. (2013). Rock paper scissors. *Patient Education and Counseling*, doi:10.1016/j.pec.2013.09.011; 10.1016/j.pec.2013.09.011

Wehrwein, E. A., Novotny, M., Swain, G. M., Parker, L. M., Esfahanian, M., Spitsbergen, J. M., . . .

Kreulen, D. L. (2013). Regional changes in cardiac and stellate ganglion norepinephrine

transporter in DOCA-salt hypertension. *Autonomic Neuroscience: Basic and Clinical*,

doi:10.1016/j.autneu.2013.08.070

Uptake of norepinephrine via the neuronal norepinephrine transporter is reduced in the heart during deoxycorticosterone (DOCA)-salt hypertension. We hypothesized that this was due to reduced norepinephrine transporter mRNA and/or protein expression in the stellate ganglia and heart. After 4 weeks of DOCA-salt treatment there was no change in norepinephrine transporter mRNA in either the right or the left stellate ganglia from hypertensive rats ( $n = 5-7$ ,  $p > 0.05$ ). Norepinephrine transporter immunoreactivity in the left stellate ganglion was significantly increased ( $n = 4$ ,  $p 0.05$ ). Whole heart norepinephrine content was significantly reduced in DOCA rats consistent with reduced uptake function; however, when norepinephrine was assessed by chamber, a significant decrease was noted only in the right atrium and right ventricle ( $n = 6$ ,  $p 0.05$ ). Therefore, 1) contrary to our hypothesis reduced reuptake in the hypertensive heart is not exclusively due to an overall reduction in norepinephrine transporter mRNA or protein in the stellate ganglion or heart, and 2) norepinephrine transporter regulation occurs regionally in the heart and stellate ganglion in the hypertensive rat heart. © 2013 Elsevier B.V. All rights reserved.

Weinstein, J. N., Collisson, E. A., Mills, G. B., Shaw, K. R. M., Ozenberger, B. A., Ellrott, K., . . . Kling, T. (2013). The cancer genome atlas pan-cancer analysis project. *Nature Genetics*, *45*(10), 1113-1120. doi:10.1038/ng.2764

The Cancer Genome Atlas (TCGA) Research Network has profiled and analyzed large numbers of human tumors to discover molecular aberrations at the DNA, RNA, protein and epigenetic levels. The resulting rich data provide a major opportunity to develop an integrated picture of commonalities, differences and emergent themes across tumor lineages. The Pan-Cancer initiative compares the first 12 tumor types profiled by TCGA. Analysis of the molecular aberrations and their functional roles across tumor types will teach us how to extend therapies effective in one cancer type to others with a similar genomic profile. © 2013 Nature America, Inc. All rights reserved.

White, J., & Fromme, E. K. (2013). "In the Beginning... ": Tools for Talking About Resuscitation and Goals of Care Early in the Admission. *American Journal of Hospice and Palliative Medicine*, 30(7), 676-682. doi:10.1177/1049909112468609

Quality standards no longer allow physicians to delay discussing goals of care and resuscitation. We propose 2 novel strategies for discussing goals and resuscitation on admission. The first, SPAM (determine Surrogate decision maker, determine resuscitation Preferences, Assume full care, and advise them to expect More discussion especially with clinical changes), helps clinicians discover patient preferences and decision maker during routine admissions. The second, UFO-UFO (Understand what they know, Fill in knowledge gaps, ask about desired Outcomes, Understand their reasoning, discuss the spectrum Feasible Outcomes), helps patients with poor or uncertain prognosis or family-team conflict. Using a challenging case example, this article illustrates how SPAM and UFO-UFO can help clinicians have patient-centered resuscitation and goals of care discussions at the beginning of care. © The Author(s) 2012.

White, R. A., Neiman, J. M., Reddi, A., Han, G., Birlea, S., Mitra, D., . . . Wang, X. -. (2013). Epithelial stem cell mutations that promote Squamous cell carcinoma metastasis. *Journal of Clinical Investigation*, 123(10), 4390-4404. doi:10.1172/JCI65856

Squamous cell carcinomas (SCCs) originate in stratified epithelia, with a small subset becoming metastatic. Epithelial stem cells are targets for driver mutations that give rise to SCCs, but it is unknown whether they contribute to oncogenic multipotency and metastasis. We developed a mouse model of SCC by targeting two frequent genetic mutations in human SCCs, oncogene Kras G12D activation and Smad4 deletion, to mouse keratin 15-expressing (K15+) stem cells. We show that transgenic mice developed multilineage tumors, including metastatic SCCs. Among cancer stem cell-enriched (CSC-enriched) populations, those with increased side population (SP) cells correlated with epithelial-mesenchymal transition (EMT) and lung metastasis. We show that microRNA-9 (miR-9) contributed to SP expansion and metastasis, and miR-9 inhibition reduced the number of SP cells and metastasis. Increased miR-9 was detected in metastatic human primary SCCs and SCC metastases, and miR-9-transduced human SCC cells exhibited increased invasion. We identified  $\alpha$ -catenin as a predominant miR-9 target. Increased miR-9 in human SCC metastases correlated with  $\alpha$ -catenin loss but not E-cadherin loss. Our results demonstrate that

stem cells with KrasG12D activation and Smad4 depletion can produce tumors that are multipotent and susceptible to EMT and metastasis. Additionally, tumor initiation and metastatic properties of CSCs can be uncoupled, with miR-9 regulating the expansion of metastatic CSCs.

Wilcox, A. B., Shen, S., Dorr, D. A., Hripcsak, G., Heermann, L., & Narus, S. P. (2012). Improving access to longitudinal patient health information within an emergency department. *Applied Clinical Informatics*, 3(3), 290-300. doi:10.4338/ACI-2011-03-RA-0019

We designed and implemented an electronic patient tracking system with improved user authentication and patient selection. We then measured access to clinical information from previous clinical encounters before and after implementation of the system. Clinicians accessed longitudinal information for 16% of patient encounters before, and 40% of patient encounters after the intervention, indicating such a system can improve clinician access to information. We also attempted to evaluate the impact of providing this access on inpatient admissions from the emergency department, by comparing the odds of inpatient admission from an emergency department before and after the improved access was made available. Patients were 24% less likely to be admitted after the implementation of improved access. However, there were many potential confounders, based on the inherent pre-post design of the evaluation. Our experience has strong implications for current health information exchange initiatives. © Schattauer 2012.

Wong, V. W., Martindale, R. G., Longaker, M. T., & Gurtner, G. C. (2013). From germ theory to germ therapy: skin microbiota, chronic wounds, and probiotics. *Plastic and Reconstructive Surgery*, 132(5), 854e-61e. doi:10.1097/PRS.0b013e3182a3c11e; 10.1097/PRS.0b013e3182a3c11e

BACKGROUND: Microorganisms living throughout the body comprise the human "microbiota" and play an important role in health and disease. Recent research suggests that alterations in the skin microbiota may underlie chronic wound pathology. Probiotics are bacteria or yeast that confer a health benefit on the host and may have a role in preventing and treating nonhealing wounds by modulating host-microbe interactions. METHODS: The English literature on skin microbiota, chronic wounds, biofilms, and probiotics is reviewed. RESULTS: Recent evidence indicates that disruption of microbial communities and bacteria-host interactions may contribute to impaired wound healing. Preclinical and human studies highlight the potential of probiotics to prevent or

treat various infectious, immune-mediated, and inflammatory diseases. CONCLUSIONS:

Advances in molecular sequencing and microbiology have shed light on the importance of the human microbiota in development, health, and disease. Probiotics represent a novel approach to altering the microbial environment with beneficial bacteria. Ongoing challenges include the need for better understanding of therapeutic mechanisms, improved regulation of manufacturing practices, and validation in controlled human trials. Current evidence suggests that probiotic-based therapies have considerable potential to exploit host-microbe relationships and improve clinical outcomes.

Wu, W. W., Bryant, D. N., Dorsa, D. M., Adelman, J. P., & Maylie, J. (2013). Ovarian Hormone Loss Impairs Excitatory Synaptic Transmission at Hippocampal CA3-CA1 Synapses. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 33(41), 16158-16169. doi:10.1523/JNEUROSCI.2001-13.2013; 10.1523/JNEUROSCI.2001-13.2013

Premature and long-term ovarian hormone loss following ovariectomy (OVX) is associated with cognitive impairment. This condition is prevented by estradiol (E2) therapy when initiated shortly following OVX but not after substantial delay. To determine whether these clinical findings are correlated with changes in synaptic functions, we used adult OVX rats to evaluate the consequences of short-term (7-10 d, OVXControl) and long-term (approximately 5 months, OVXLT) ovarian hormone loss, as well as subsequent in vivo E2 treatment, on excitatory synaptic transmission at the hippocampal CA3-CA1 synapses important for learning and memory. The results show that ovarian hormone loss was associated with a marked decrease in synaptic strength. E2 treatment increased synaptic strength in OVXControl but not OVXLT rats, demonstrating a change in the efficacy for E2 5 months following OVX. E2 also had a more rapid effect: within minutes of bath application, E2 acutely increased synaptic strength in all groups except OVXLT rats that did not receive in vivo E2 treatment. E2's acute effect was mediated postsynaptically, and required Ca(2+) influx through the voltage-gated Ca(2+) channels. Despite E2's acute effect, synaptic strength of OVXLT rats remained significantly lower than that of OVXControl rats. Thus, changes in CA3-CA1 synaptic transmission associated with ovarian hormone loss cannot be fully reversed with delayed E2 treatment. Given that synaptic strength at CA3-CA1 synapses is related to the ability to learn hippocampus-dependent tasks, these findings

provide additional insights for understanding cognitive impairment-associated long-term ovarian hormone loss and ineffectiveness for delayed E2 treatment to maintain cognitive functions.

Xu, J., Xu, M., Bernuci, M. P., Fisher, T. E., Shea, L. D., Woodruff, T. K., . . . Stouffer, R. L. (2013).

Primate follicular development and oocyte maturation in vitro. *Advances in Experimental Medicine and Biology*, 761, 43-67. doi:10.1007/978-1-4614-8214-7\_5; 10.1007/978-1-4614-8214-7\_5

The factors and processes involved in primate follicular development are complex and not fully understood. An encapsulated three-dimensional (3D) follicle culture system could be a valuable in vitro model to study the dynamics and regulation of folliculogenesis in intact individual follicles in primates. Besides the research relevance, in vitro follicle maturation (IFM) is emerging as a promising approach to offer options for fertility preservation in female patients with cancer. This review summarizes the current published data on in vitro follicular development from the preantral to small antral stage in nonhuman primates, including follicle survival and growth, endocrine (ovarian steroid hormone) and paracrine/autocrine (local factor) function, as well as oocyte maturation and fertilization. Future directions include major challenges and strategies to further improve follicular growth and differentiation with oocytes competent for in vitro fertilization and subsequent embryonic development, as well as opportunities to investigate primate folliculogenesis by utilizing this 3D culture system. The information may be valuable in identifying optimal conditions for human follicle culture, with the ultimate goal of translating the experimental results and products to patients, thereby facilitating diagnostic and therapeutic approaches for female fertility.

Yehia, B. R., French, B., Fleishman, J. A., Metlay, J. P., Berry, S. A., Korthuis, P. T., . . . for the HIV Research Network. (2013). Retention in Care is More Strongly Associated with Viral Suppression in HIV-Infected Patients with Lower versus Higher CD4 Counts. *Journal of Acquired Immune Deficiency Syndromes (1999)*, doi:10.1097/QAI.0000000000000023

BACKGROUND.: Retention in care is important for all HIV-infected patients, but may be more important for people with advanced HIV disease. We evaluated whether the association between retention in care and viral suppression differed by HIV disease severity. METHODS.: A repeated cross-sectional analysis (2006-2011) involving 35,433 adults at 18 U.S. HIV clinics. Multivariable

logistic regression models examined associations between retention measures (HRSA retention measure, 6-month gap, and 3-month visit constancy) and viral suppression (HIV-1 RNA 500 cells/mm. RESULTS.: Overall, patients met the HRSA measure in 84% of person-years, did not have a 6-month gap in 76%, and had visits in all 4 quarters in 37%; patients achieved viral suppression in 72% of person-years. The association between retention in care and viral suppression differed by disease severity, and was strongest for patients with lower CD4 counts: 500 cells/mm [1.22, 1.14-1.30] using the HRSA retention measure as a representative example. CONCLUSIONS.: This is one of the first studies to report the impact of HIV disease severity on retention in care and viral suppression, demonstrating that retention in care is more strongly associated with viral suppression in patients with lower CD4 counts. These results have important implications for improving the health of patients with advanced HIV disease and for test and treat approaches to HIV prevention.

Zhang, L. -, Bhattacharya, S., Leid, M., Ganguli-Indra, G., & Indra, A. K. (2012). Ctip2 is a dynamic regulator of epidermal proliferation: And differentiation by integrating EGFR and Notch signaling. *Journal of Cell Science*, 125(23), 5733-5744. doi:10.1242/jcs.108969

Epidermal morphogenesis results from a delicate balance between keratinocyte proliferation and differentiation, and this balance is perturbed upon deletion of transcription factor Ctip2. Here we demonstrate that Ctip2, in a cell autonomous manner, controls keratinocyte proliferation and cytoskeletal organization, and regulates the onset and maintenance of differentiation in keratinocytes in culture. Ctip2 integrates keratinocyte proliferation and the switch to differentiation by directly and positively regulating EGFR transcription in proliferating cells and Notch1 transcription in differentiating cells. In proliferative cells, the EGFR promoter is occupied by Ctip2, whereas Ctip2 is only recruited to the Notch1 promoter under differentiating conditions. Activation of EGFR signaling downregulates Ctip2 at the transcript level, whereas high calcium signaling triggers SUMOylation, ubiquitination and proteasomal degradation of Ctip2 at the protein level. Together, our findings demonstrate a novel mechanism(s) of Ctip2-mediated, coordinated control of epidermal proliferation and terminal differentiation, and identify a pathway of negative feedback regulation of Ctip2 during epidermal development. © 2012. Published by The Company of Biologists Ltd.

Zhang, Q. S., Marquez-Loza, L., Sheehan, A. M., Watanabe-Smith, K., Eaton, L., Benedetti, E., . . .

Grompe, M. (2013). Evaluation of resveratrol and N-acetylcysteine for cancer chemoprevention in a Fanconi anemia murine model. *Pediatric Blood & Cancer*, doi:10.1002/pbc.24780;

10.1002/pbc.24780

Fanconi anemia (FA) patients suffer from progressive bone marrow failure and often develop cancers. Previous studies showed that antioxidants tempol and resveratrol (RV) delayed tumor onset and reduced hematologic defects in FA murine models, respectively. Here we tested whether antioxidants N-acetylcysteine (NAC) or RV could delay cancer in tumor prone *Fancd2<sup>-/-</sup>/Trp53<sup>+/-</sup>* mice. Unlike tempol, neither compound had any significant chemopreventive effect in this model. We conclude that not all anti-oxidants are chemopreventive in FA. In addition, when given to *Fancd2<sup>-/-</sup>* mice, NAC helped maintain *Fancd2<sup>-/-</sup>* KSL cells in quiescence while tempol did not. The mechanisms behind the different actions of these antioxidants await further investigation. *Pediatr Blood Cancer* (c) 2013 Wiley Periodicals, Inc.

Zhang, Z., Sahn, D. J., & Song, X. (2013). *Cardiac motion estimation by optimizing transmural homogeneity of the myofiber strain and its validation with multimodal sequences* (Nagoya ed.) doi:10.1007/978-3-642-40811-3\_62

Quantitative motion analysis from cardiac imaging is important to study the function of heart. Most of existing image-based motion estimation methods model the myocardium as an isotropically elastic continuum. We propose a novel anisotropic regularization method which enforces the transmural homogeneity of the strain along myofiber. The myofiber orientation in the end-diastolic frame is obtained by registering it with a diffusion tensor atlas. Our method is formulated in a diffeomorphic registration framework, and tested on multimodal cardiac image sequences of two subjects using 3D echocardiography and cine and tagged MRI. Results show that the estimated transformations in our method are more smooth and more accurate than those in isotropic regularization. © 2013 Springer-Verlag.

Zhao, D., McCully, B. H., & Brooks, V. L. (2012). Rosiglitazone improves insulin sensitivity and baroreflex gain in rats with diet-induced obesity. *The Journal of Pharmacology and Experimental Therapeutics*, 343(1), 206-213. doi:10.1124/jpet.112.194738; 10.1124/jpet.112.194738

Obesity decreases baroreflex gain (BRG); however, the mechanisms are unknown. We tested the hypothesis that impaired BRG is related to the concurrent insulin resistance, and, therefore, BRG would be improved after treatment with the insulin-sensitizing drug rosiglitazone. Male rats fed a high-fat diet diverged into obesity-prone (OP) and obesity-resistant (OR) groups after 2 weeks. Then, OP and OR rats, as well as control (CON) rats fed a standard diet, were treated daily for 2 to 3 weeks with rosiglitazone (3 or 6 mg/kg) or its vehicle by gavage. Compared with OR and CON rats, conscious OP rats exhibited reductions in BRG (OP, 2.9 +/- 0.1 bpm/mm Hg; OR, 4.0 +/- 0.2 bpm/mm Hg; CON, 3.9 +/- 0.2 bpm/mm Hg;  $P < 0.05$ ) and insulin sensitivity (hyperinsulinemic euglycemic clamp; OP, 6.8 +/- 0.9 mg/kg . min; OR, 22.2 +/- 1.2 mg/kg . min; CON, 17.7 +/- 0.8 mg/kg . min;  $P < 0.05$ ), which were well correlated ( $r(2) = 0.49$ ;  $P < 0.01$ ). In OP rats, rosiglitazone dose-dependently improved ( $P < 0.05$ ) insulin sensitivity (12.8 +/- 0.6 mg/kg . min at 3 mg/kg; 16.0 +/- 1.5 mg/kg . min at 6 mg/kg) and BRG (3.8 +/- 0.4 bpm/mm Hg at 3 mg/kg; 5.3 +/- 0.7 bpm/mm Hg at 6 mg/kg). However, 6 mg/kg rosiglitazone also increased BRG in OR rats without increasing insulin sensitivity, disrupted the correlation between BRG and insulin sensitivity ( $r(2) = 0.08$ ), and, in OP and OR rats, elevated BRG relative to insulin sensitivity (analysis of covariance;  $P < 0.05$ ). Moreover, in OP rats, stimulation of the aortic depressor nerve, to activate central baroreflex pathways, elicited markedly reduced decreases in heart rate and arterial pressure, but these responses were not improved by rosiglitazone. In conclusion, diet-induced obesity impairs BRG via a central mechanism that is related to the concurrent insulin resistance. Rosiglitazone normalizes BRG, but not by improving brain baroreflex processing or insulin sensitivity.