References

Affronti, M. L. (2014). Palonosetron in the management of chemotherapy- induced nausea and vomiting in patients receiving multiple-day chemotherapy. *Cancer Management and Research, 6*, 329-337.

Prevention of chemotherapy-induced nausea and vomiting (CINV) is a key component of treatment for patients with cancer. Guidelines are available to assist prescribers in the management of CINV associated with single-day chemotherapy regimens. However, currently there are no clear guidelines for management of CINV in patients receiving multiple-day chemotherapy regimens. Serotonin (5-HT3) receptor antagonists are a mainstay in preventing CINV, and palonosetron, given its longer half-life and duration of action relative to other 5-HT3 receptor antagonists, may be a useful option for managing CINV in multiple-day chemotherapy. Here we provide an overview of CINV and CINV treatment options, with a focus on palonosetron. We describe existing challenges in managing CINV, and discuss two patients receiving multiple-day chemotherapy, in whom CINV was managed successfully with palonosetron.

Agarwal, A., Mackenzie, R. J., Besson, A., Jeng, S., Carey, A., LaTocha, D. H., et al. (2014). BCR-ABL1 promotes leukemia by converting p27 into a cytoplasmic oncoprotein. *Blood,*

Recent studies have revealed that p27, a nuclear cyclin dependent kinase (Cdk) inhibitor and tumor-suppressor, can acquire oncogenic activities upon mislocalization to the cytoplasm. To understand how these antagonistic activities influence oncogenesis we dissected the nuclear and cytoplasmic functions of p27 in chronic myeloid leukemia (CML), a well-characterized malignancy caused by the BCR-ABL1 tyrosine kinase. p27 is predominantly cytoplasmic in CML and nuclear in normal cells. BCR-ABL1 regulates nuclear and cytoplasmic p27 abundance by kinase-dependent and -independent mechanisms, respectively. p27 knockdown in CML cell lines with predominantly cytoplasmic p27 induces apoptosis, consistent with a leukemogenic role of cytoplasmic p27. Accordingly, a p27 mutant (p27CK-) devoid of Cdk inhibitory nuclear functions enhances leukemogenesis in a murine CML model compared to complete absence of p27. In contrast, p27 mutations that enhance its stability (p27T187A) or nuclear retention (p27S10A) attenuate leukemogenesis over wild-type p27, validating the tumor-suppressor function of nuclear p27 in CML. We conclude that BCR-ABL1 kinase-dependent and kinase-independent mechanisms convert

p27 from a nuclear tumor suppressor to cytoplasmic oncogene. These findings suggest cytoplasmic mislocalization of p27 despite BCR-ABL1 inhibition by tyrosine kinase inhibitors may contribute to drug resistance and effective therapeutic strategies to stabilize nuclear p27 must also prevent cytoplasmic mislocalization.

Alarcon, G., Cservenka, A., Fair, D. A., & Nagel, B. J. (2014). Sex differences in the neural substrates of spatial working memory during adolescence are not mediated by endogenous testosterone. *Brain Research,*

Adolescence is a developmental period characterized by notable changes in behavior, physical attributes, and an increase in endogenous sex steroid hormones, which may impact cognitive functioning. Moreover, sex differences in brain structure are present, leading to differences in neural function and cognition. Here, we examine sex differences in performance and blood oxygen level-dependent (BOLD) activation in a sample of adolescents during a spatial working memory (SWM) task. We also examine whether endogenous testosterone levels mediate differential brain activity between the sexes. Adolescents between ages 10 and 16 completed a SWM functional magnetic resonance imaging (fMRI) task, and serum hormone levels were assessed within seven days of scanning. While there were no sex differences in task performance (accuracy and reaction time), differences in BOLD response between girls and boys emerged, with girls deactivating brain regions in the default mode network and boys showing increased response in SWM-related brain regions of the frontal cortex. These results suggest that adolescent boys and girls adopted distinct neural strategies, while maintaining spatial cognitive strategies that facilitated comparable cognitive performance of a SWM task. A nonparametric bootstrapping procedure revealed that testosterone did not mediate sex-specific brain activity, suggesting that sex differences in BOLD activation during SWM may be better explained by other factors, such as early organizational effects of sex steroids or environmental influences. Elucidating sex differences in neural function and the influence of gonadal hormones can serve as a basis of comparison for understanding sexually dimorphic neurodevelopment and inform sex-specific psychopathology that emerges in adolescence.

Allott, E. H., Howard, L. E., Cooperberg, M. R., Kane, C. J., Aronson, W. J., Terris, M. K., et al. (2014). Serum lipid profile and risk of prostate cancer recurrence: Results from the SEARCH database. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 23*(11), 2349-2356.

BACKGROUND: Evidence for an association between total cholesterol, low- and high-density lipoproteins (LDL and HDL, respectively), triglycerides, and prostate cancer is conflicting. Given that prostate cancer and dyslipidemia affect large proportions of Western society, understanding these associations has public health importance. METHODS: We conducted a retrospective cohort analysis of 843 radical prostatectomy (RP) patients who never used statins before surgery within the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Multivariable Cox proportional hazards analysis was used to investigate the association between cholesterol, LDL, HDL, and triglycerides and biochemical recurrence risk. In secondary analysis, we explored these associations in patients with dyslipidemia, defined using National Cholesterol Education Program guidelines. RESULTS: Elevated serum triglycerides were associated with increased risk of prostate cancer recurrence [HRper 10 mg/dl, 1.03; 95% confidence interval (CI), 1.01-1.05] but associations between total cholesterol, LDL and HDL, and recurrence risk were null. However, among men with dyslipidemia, each 10 mg/dl increase in cholesterol and HDL was associated with 9% increased recurrence risk (HR, 1.09; 95% CI, 1.01-1.17) and 39% reduced recurrence risk (HR, 0.61; 95% CI, 0.41-0.91), respectively. CONCLUSIONS: Elevated serum triglycerides were associated with increased risk of prostate cancer recurrence. Cholesterol, LDL, or HDL were not associated with recurrence risk among all men. However, among men with dyslipidemia, elevated cholesterol and HDL levels were associated with increased and decreased risk of recurrence, respectively. IMPACT: These findings, coupled with evidence that statin use is associated with reduced recurrence risk, suggest that lipid levels should be explored as a modifiable risk factor for prostate cancer recurrence. Cancer Epidemiol Biomarkers Prev; 23(11); 2349-56. (c)2014 AACR.

Asher, A. L., Speroff, T., Dittus, R. S., Parker, S. L., Davies, J. M., Selden, N., et al. (2014). The national neurosurgery quality and outcomes database (N2QOD): A collaborative north american

outcomes registry to advance value-based spine care. *Spine, 39*(22 Suppl 1), S106-16. STUDY DESIGN: National Prospective Observational Registry OBJECTIVE.: Describe our preliminary experience with the National Neurosurgery Quality and Outcomes Database (NQOD), a national collaborative registry of quality and outcomes reporting after low back surgery. SUMMARY OF BACKGROUND DATA: All major health care stakeholders are now requiring objective data regarding the value of medical services. Surgical therapies for spinal disorders have faced particular scrutiny in recent value-based discussions, in large part due to the dramatic growth in the cost and application of these procedures. Reliable data are fundamental to understanding the value of delivered health care. Clinical registries are increasingly used to provide such data. METHODS: The NQOD is a prospective observational registry designed to establish risk-adjusted expected morbidity and 1-year outcomes for the most common lumbar surgical procedures performed by spine surgeons; provide practice groups and hospitals immediate infrastructure for analyzing their 30-day morbidity and mortality and 3- and 12-month quality data in real-time; generate surgeon-, practice-, and specialty-specific quality and efficacy data; and generate nationwide quality and effectiveness data on specific surgical treatments. RESULTS: In its first 2 years of operation, the NQOD has proven to be a robust data collection platform that has helped demonstrate the objective quality of surgical interventions for medically refractory disorders of the lumbar spine. Lumbar spine surgery was found to be safe and effective at the group mean level in routine practice. Subgroups of patients did not report improvement using validated outcome measures. Substantial variation in treatment response was observed among individual patients. CONCLUSION: The NQOD is now positioned to determine the combined contribution of patient variables to specific clinical and patient-reported outcomes. These analyses will ultimately facilitate shared decision making and encourage efficient allocation of health care resources, thus significantly advancing the value paradigm in spine care. LEVEL OF EVIDENCE: 3.

Assassi, S., Weisman, M. H., Lee, M., Savage, L., Diekman, L., Graham, T. A., et al. (2014). New population-based reference values for spinal mobility measures based on the 2009-2010 national health and nutrition examination survey. *Arthritis and Rheumatology, 66*(9), 2628-2637. Objective. To report population-based percentile reference values for selected spinal mobility

measures in a nationally representative sample of 5,001 US adults ages 20-69 years who were examined in the 2009-2010 US National Health and Nutrition Examination Survey (NHANES). Methods. Occiput-to-wall distance (OWD), thoracic expansion (TE), and anterior lumbar flexion (ALF; by modified Schober test) were measured by trained examiners in a standardized manner. TE was measured at the xiphisternal level, while the lower reference point for ALF was a line marked at the level of the superior margin of the lateral iliac crests. We report reference values based on the 95th percentile for the OWD and the 5th percentile for TE and ALF, as well as other summary statistics for these measures, in the study population. Results. An OWD of >0 was present in 3.8% of the participants, while 8.8% of them had out-of-range values for TE based on the commonly used threshold of 2.5 cm. The 95th percentile of the OWD measurement was 0, while the 5th percentile for TE and ALF were 1.9 cm and 2 cm, respectively. The spinal measures were significantly associated with sex, age, ethnicity, height, and body mass index (BMI). Exclusion of individuals with severe obesity (BMI >35 kg/m2) changed the proposed reference values for TE and ALF to 2.2 cm and 1.9 cm, respectively. Conclusion. We verified a reference value of 0 for the OWD in the general population. Using the reported population-based percentile values, new reference values for TE and ALF can be derived. © 2014, American College of Rheumatology.

Baker, J. F., & Assaf, B. T. (2014). Preclinical study design for evaluation of stem cell-derived cellular therapy products: A pathologist's perspective. *Toxicologic Pathology,*

Despite-or perhaps because of-the rapid expansion of interest in stem cell-derived cellular therapy products, relatively few guidelines have been published to assist in the design of scientifically sound preclinical studies. The field is complex and wide ranging, and of necessity regulators tend to treat each project on a case by case basis. One of the core tenets remains the need to retain all tissues from the study, thereby allowing for further analysis of tissues should unexpected effects be seen in clinical studies; attempts to comply with this may result in an unmanageable financial burden. Judicious input from the pathologist at the earliest stages of study design may not only improve the scientific integrity of the study but also help to mitigate some of the cost. Careful animal selection, the development of robust cell markers, and justifiable triage of tissues based on phased tissue examination can all be discussed with the

regulatory authorities at pre-pre-investigational new drug (IND) and pre-IND meetings to achieve optimal study design.

Barouch, D. H., & Picker, L. J. (2014). Novel vaccine vectors for HIV-1. *Nature Reviews.Microbiology,* The ultimate solution to the global HIV-1 epidemic will probably require the development of a safe and effective vaccine. Multiple vaccine platforms have been evaluated in preclinical and clinical trials, but given the disappointing results of clinical efficacy studies so far, novel vaccine approaches are needed. In this Opinion article, we discuss the scientific basis and clinical potential of novel adenovirus and cytomegalovirus vaccine vectors for HIV-1 as two contrasting but potentially complementary vector approaches. Both of these vector platforms have demonstrated partial protection against stringent simian immunodeficiency virus challenges in rhesus monkeys using different immunological mechanisms.

Bartley, A. N., Christ, J., Fitzgibbons, P. L., Hamilton, S. R., Kakar, S., Shah, M. A., et al. (2014). Template for reporting results of HER2 (ERBB2) biomarker testing of specimens from patients with adenocarcinoma of the stomach or esophagogastric junction. *Archives of Pathology & Laboratory Medicine,*

Beachler, D. C., Abraham, A. G., Silverberg, M. J., Jing, Y., Fakhry, C., Gill, M. J., et al. (2014). Incidence and risk factors of HPV-related and HPV-unrelated head and neck squamous cell carcinoma in HIV-infected individuals. *Oral Oncology,*
OBJECTIVES: To examine the risk and trends of HPV-related and HPV-unrelated Head and Neck Squamous Cell Carcinoma (HNSCC) in HIV-infected individuals and assess whether immunosuppression (measured through CD4 cell count) and other risk factors impact HNSCC risk. MATERIALS AND METHODS: Incident HNSCCs at HPV-related and HPV-unrelated anatomic sites were detected in HIV-infected participants from pooled data from 17 prospective studies in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) between 1996 and 2009. HNSCC cases were validated using chart review or cancer registry matching. Risk factors for incident HPV-related and HPV-unrelated HNSCC were explored using mixed effects Poisson regression in a full prospective analysis, and the effect of CD4 prior to cancer diagnosis was examined in a nested case control analysis. RESULTS: 66 HPV-related and 182 HPV-

unrelated incident HNSCCs were detected among 82,375 HIV-infected participants. Standardized incidence ratios (SIRs) for both HPV-related (SIR=3.2, 95%CI=2.5-3.4) and HPV-unrelated (SIR=3.0, 95%CI=2.5-4.1) HNSCC were significantly elevated in HIV-infected individuals compared with the US general population. Between 1996 and 2009, the age-standardized HPV-related HNSCC incidence increased non-significantly from 6.8 to 11.4per 100,000 person-years (p-trend=0.31) while the age-standardized incidence of HPV-unrelated HNSCC decreased non-significantly from 41.9 to 29.3 per 100,000 person-years (p-trend=0.16). Lower CD4 cell count prior to cancer diagnosis was significantly associated with increased HPV-related and HPV-unrelated HNSCC risk. CONCLUSION: The standardized incidence of HPV-related and HPV-unrelated HNSCC are both elevated in HIV-infected individuals. Immunosuppression may have a role in the development of both HPV-related and HPV-unrelated HNSCC.

Bechtold, M. L., Nguyen, D. L., Palmer, L. B., Kiraly, L. N., Martindale, R. G., & McClave, S. A. (2014). Nasal bridles for securing nasoenteric tubes: A meta-analysis. *Nutrition in Clinical Practice, 29*(5), 667-671.

Background: Nasoenteric feeding tubes may easily become dislodged due to patient mental status, transfers, or positional changes. Nasal bridles were introduced to provide a better, more reliable system to secure these tubes. This meta-analysis was performed to evaluate the effectiveness of nasal bridles compared with the traditional method of adhesive tape alone in securing enteral feeding tubes. Materials and Methods: Multiple databases were searched (October 2013). All studies that evaluated the use of nasal bridles in adult patients were included in the analysis. Meta-analysis for the outcomes from use of a nasal bridle vs the more traditional method of adhesive tape alone for securing nasoenteric tubes was analyzed by calculating pooled estimates of dislodgement, skin complications, and sinusitis. Statistical analysis was performed using RevMan 5.1. Results: Six studies (n = 594) met the inclusion criteria. Use of a nasal bridle for securing enteral tubes resulted in a statistically significant reduction in tube dislodgement compared with traditional adhesive tape alone (odds ratio [OR], 0.16; 95% confidence interval [CI], 0.10-0.27; P <.01). The use of nasal bridles was associated with a higher rate of skin complications compared with traditional adhesive tape (OR, 4.27; 95% CI, 1.79-10.23; P <.01). Incidence of sinusitis was no different between the 2 groups (OR, 0.26; 95% CI, 0.03-2.28; P

=.22). Conclusion: Nasal bridles appear to be more effective at securing nasoenteric tubes and preventing dislodgement than traditional use of tape alone.

Benninger, B., & Maier, T. (2014). Using ATP-driven bioluminescence assay to monitor microbial safety in a contemporary human cadaver laboratory. *Clinical Anatomy (New York, N.Y.),* Introduction: The objective of this study was to utilize a cost-effective method for assessing the levels of bacterial, yeast, and mold activity during a human dissection laboratory course. Nowadays, compliance with safety regulations is policed by institutions at higher standards than ever before. Fear of acquiring an unknown infection is one of the top concerns of professional healthcare students, and it provokes anti-laboratory anxiety. Human cadavers are not routinely tested for bacteria and viruses prior to embalming. Human anatomy dissecting rooms that house embalmed cadavers are normally cleaned after the dissected cadavers have been removed. There is no evidence that investigators have ever assessed bacterial and fungal activities using adenosine triphosphate (ATP)-driven bioluminescence assays. Methods: A literature search was conducted on texts, journals, and websites regarding bacterial, yeast, and mold activities in an active cadaver laboratory. Midway into a clinical anatomy course, ATP bioluminescence assays were used to swab various sites within the dissection room, including entrance and exiting door handles, water taps, cadaver tables, counter tops, imaging material, X-ray box switches, and the cadaver surfaces. Results: The results demonstrated very low activities on cadaver tables, washing up areas, and exiting door handles. There was low activity on counter tops and X-ray boxes. There was medium activity on the entrance door handles. Conclusion: These findings suggest an inexpensive and accurate method for monitoring safety compliance and microbial activity. Students can feel confident and safe in the environment in which they work. Clin. Anat., 2014. (c) 2014 Wiley Periodicals, Inc.

Betsch, M., Blizzard, S. R., Shinseki, M., & Yoo, J. (2014). Prevalence of degenerative changes of the atlanto-axial joints. *The Spine Journal : Official Journal of the North American Spine Society,* BACKGROUND CONTEXT: Degeneration of the atlanto-dens and atlanto-axial joints is associated with cervical spine pain and may also be associated with an increased risk of dens fracture. However, there is paucity of literature describing the prevalence of specific degenerative changes

in the atlanto-dens and atlanto-axial facet joints. PURPOSE: To document age-related degenerative changes of the cervical spine in a large cohort of patients Study Design/Setting: This is a retrospective cohort study. PATIENT SAMPLE: Adult trauma patients admitted to our level 1 trauma center. OUTCOME MEASURES: Osteoarthritis of the atlanto-dens and atlanto-axial facet joints of the cervical spine as well as the presence of intraosseous cyst and calcific synovitis, as determined by CT scans. METHODS: We conducted a retrospective study of 1,543 adult trauma patients who received a cervical spine computed tomography scan. The anterior atlanto-dens joint interval was measured. The presence or absence of intraosseous cysts and calcific synovitis was recorded. Degeneration of the atlanto-dens and atlanto-axial facet joints at age intervals was quantified. RESULTS: The atlanto-dens interval narrowed linearly with age ($R2 = 0.992$; $p<0.001$). The prevalence of intraosseous cysts increased exponentially with age from 4.2% to 37.4%, and calcific synovitis increased from 0% to 11.1%. Intraosseous cyst formation generally began in the 2nd to 3rd decade of life and synovitis in the 5th and 6th decade of life. Facet joints also demonstrated age related changes; however, the rate of degenerative changes was lower than in the atlanto-dens joint. CONCLUSIONS: To our knowledge, this is the first study that documents specific changes of both atlanto-dens and atlanto-axial facet joints as a function of age in a large cohort of 1,543 patients. These changes increased exponentially with age, and may contribute to pain and limitation in motion. In light of our findings and recent studies demonstrating the association between degeneration and dens fracture in elderly, cervical spine radiographs of elderly patients should be carefully assessed for these changes.

Bharadwaj, A. S., Schewitz-Bowers, L. P., Wei, L., Lee, R. W. J., & Smith, J. R. (2014). Intercellular adhesion molecule 1 mediates migration of th1 and th17 cells across human retinal vascular endothelium. *Investigative Ophthalmology and Visual Science, 54*(10), 6917-6925. PURPOSE. Autoimmune inflammation of the retina causes vision loss in the majority of affected individuals. Th1 or Th17 cells initiate the disease on trafficking from the circulation into the eye across the retinal vascular endothelium. We investigated the ability of human Th1- and Th17-polarized cells to cross a simulated human retinal endothelium, and examined the role of IgG superfamily members in this process. METHODS. Th1- and Th17-polarized cell populations were generated from human peripheral blood CD4+ T cells, using two Th1- and Th17-polarizing

protocols. Transendothelial migration assays were performed over 18 hours in Boyden chambers, after seeding the transwell membrane with human retinal endothelial cells. In some assays intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), or activated leukocyte cell adhesion molecule (ALCAM) blocking antibody, or isotype- and concentrationmatched control antibody, was added to the upper chambers. RESULTS. Th1- and Th17-polarized cells migrated equally efficiently across the human retinal endothelial monolayer. The percentage of IL-17+ IFN-γ− Th17-polarized cells was reduced following migration. Blocking ICAM-1, but not VCAM-1 or ALCAM, significantly reduced migration of Th1- and Th17-polarized cells for a majority of human donors. CONCLUSIONS. Taken in the context of other literature on transendothelial migration, our results illustrate the importance of investigating the specific tissue and vascular endothelium when considering helper T cell migration in autoimmune inflammation. Our findings further indicate that while generalizations about involvement of specific adhesion molecules in uveitis and other autoimmune disease may be possible, these may not apply to individual patients universally. The observations are relevant to the use of adhesion blockade for therapeutic purposes.

Bleyer, A., Thomas, C. R.,Jr, Baines, C., & Miller, A. B. (2014). Flawed assumptions used to defend screening mammography. *Cancer,*

Butler, M. W., Ozgediz, D., Poenaru, D., Ameh, E., Andrawes, S., Azzie, G., et al. (2014). The global paediatric surgery network: A model of subspecialty collaboration within global surgery. *World Journal of Surgery,*

Campbell, L. J., Li, Q., & Li, Y. (2014). Healthcare worker influenza vaccination in oregon nursing homes: Correlates of facility characteristics. *Journal of the American Medical Directors Association, 15*(10), 768-772.

OBJECTIVES: Nursing home (NH) employee influenza vaccination is associated with reductions in morbidity and mortality among residents. Little is known regarding associations between NH characteristics and employee influenza vaccination rates (EVRs). This study identifies NH characteristics that may be associated with EVRs. DESIGN: Data on employee vaccination rates and programs were gathered from the Office for Oregon Health Policy and Research reports for 3

influenza seasons from 2009 to 2012 and merged with Online Survey, Certification, and Reporting files, from which facility characteristics were obtained. Market controls were obtained from the 2010 Area Health Resource File. Multivariate linear and logistic regression were used to model relationships between facility characteristics and EVR per facility per year, whether formal education for employees was conducted, and whether 2010, 2015, and 2020 Healthy People targets were met. SETTING: Oregon nursing homes from 2009 to 2012. PARTICIPANTS: NHs reporting sufficient data to calculate an EVR were included. Based on information obtained from 2009-2010, 2010-2011, and 2011-2012 surveys, EVRs were calculated for 113/140, 129/141, and 137/140 (81%, 91%, and 98% of) NHs, respectively. MEASUREMENTS: Dependent variables were EVR per facility per year, whether formal education for employees was conducted, and whether 2010, 2015, and 2020 Healthy People targets were met. Independent variables included facility characteristics and market controls. RESULTS: On average, chain-affiliated NHs had 9% higher EVRs (P = .01) and 73% higher odds of achieving 60% EVR (2010 target, P = .05) than free-standing NHs. For-profit NHs had, on average, 8% lower EVRs (P = .04) than not-for-profit NHs. Surprisingly, a 10% increase in proportion of Medicaid residents was associated with a 2% increase in EVR (P = .01) and higher odds of achieving 60% (odds ratio = 1.20, P = .004) and 70% (2015 target, odds ratio = 1.14, P = .05) EVR. CONCLUSION: Given that NHs generally have low employee influenza vaccination rates, it may be necessary to target low-performing facilities to achieve substantial improvements. However, significant correlates of this study cannot be easily addressed by NH management or policymakers. Without policy change encouraging key components of vaccination programs, public reporting may be insufficient to improve EVRs.

Carbonaro Sarracino, D., Tarantal, A. F., Lee, C. C., Martinez, M., Jin, X., Wang, X., et al. (2014). Effects of vector backbone and pseudotype on lentiviral vector-mediated gene transfer: Studies in infant ADA-deficient mice and rhesus monkeys. *Molecular Therapy : The Journal of the American Society of Gene Therapy, 22*(10), 1803-1816.

Systemic delivery of a lentiviral vector carrying a therapeutic gene represents a new treatment for monogenic disease. Previously, we have shown that transfer of the adenosine deaminase (ADA) cDNA in vivo rescues the lethal phenotype and reconstitutes immune function in ADA-

deficient mice. In order to translate this approach to ADA-deficient severe combined immune deficiency patients, neonatal ADA-deficient mice and newborn rhesus monkeys were treated with species-matched and mismatched vectors and pseudotypes. We compared gene delivery by the HIV-1-based vector to murine gamma-retroviral vectors pseudotyped with vesicular stomatitis virus-glycoprotein or murine retroviral envelopes in ADA-deficient mice. The vesicular stomatitis virus-glycoprotein pseudotyped lentiviral vectors had the highest titer and resulted in the highest vector copy number in multiple tissues, particularly liver and lung. In monkeys, HIV-1 or simian immunodeficiency virus vectors resulted in similar biodistribution in most tissues including bone marrow, spleen, liver, and lung. Simian immunodeficiency virus pseudotyped with the gibbon ape leukemia virus envelope produced 10- to 30-fold lower titers than the vesicular stomatitis virus-glycoprotein pseudotype, but had a similar tissue biodistribution and similar copy number in blood cells. The relative copy numbers achieved in mice and monkeys were similar when adjusted to the administered dose per kg. These results suggest that this approach can be scaled-up to clinical levels for treatment of ADA-deficient severe combined immune deficiency subjects with suboptimal hematopoietic stem cell transplantation options.

Carbone, L., Harris, R. A., Gnerre, S., Veeramah, K. R., Lorente-Galdos, B., Huddleston, J., et al. (2014). Gibbon genome and the fast karyotype evolution of small apes. *Nature, 513*(7517), 195-201.

Gibbons are small arboreal apes that display an accelerated rate of evolutionary chromosomal rearrangement and occupy a key node in the primate phylogeny between Old World monkeys and great apes. Here we present the assembly and analysis of a northern white-cheeked gibbon (Nomascus leucogenys) genome. We describe the propensity for a gibbon-specific retrotransposon (LAVA) to insert into chromosome segregation genes and alter transcription by providing a premature termination site, suggesting a possible molecular mechanism for the genome plasticity of the gibbon lineage. We further show that the gibbon genera (Nomascus, Hylobates, Hoolock and Symphalangus) experienced a near-instantaneous radiation ~5 million years ago, coincident with major geographical changes in southeast Asia that caused cycles of habitat compression and expansion. Finally, we identify signatures of positive selection in genes

important for forelimb development (TBX5) and connective tissues (COL1A1) that may have been involved in the adaptation of gibbons to their arboreal habitat.

Carleton, J. B., Lovell, P. V., McHugh, A., Marzulla, T., Horback, K. L., & Mello, C. V. (2014). An optimized protocol for high-throughput in situ hybridization of zebra finch brain. *Cold Spring Harbor Protocols,*

In situ hybridization (ISH) is a sensitive technique for documenting the tissue distribution of mRNAs. Advanced nonradioactive ISH methods that are based on the use of digoxigenin (DIG)-labeled probes and chromogenic detection have better spatial resolution than emulsion autoradiography techniques and, when paired with high-resolution digital imaging, allow for large-scale profiling of gene expression at cellular resolution within a histological context. However, technical challenges restrict the number of genes that can be investigated in a small laboratory setting. This protocol describes an optimized, low-cost, small-footprint, high-throughput ISH procedure to detect gene expression patterns in 10-microm brain sections from zebra finches. It uses DIG-labeled riboprobes synthesized from cDNA templates available through the Songbird Neurogenomics Consortium. The method is compatible with high-resolution digital imaging; it produces images with low background and a resolution approaching that of immunohistochemical methods. Approximately 180 slides can be processed each week using this protocol, but it can be scaled to accommodate a broad range of tissues from which cryosections can be obtained.

Carneiro-Pla, D., Miller, B. S., Wilhelm, S. M., Milas, M., Gauger, P. G., Cohen, M. S., et al. (2014). Feasibility of surgeon-performed transcutaneous vocal cord ultrasonography in identifying vocal cord mobility: A multi-institutional experience. *Surgery,*

BACKGROUND: Transcutaneous vocal cord ultrasonography (TVCUS) is a noninvasive study used to identify true vocal cord (TVC) mobility. Its sensitivity in predicting TVC paralysis when compared with indirect flexible laryngoscopy (IFL) ranges from 62 to 93%. This study aimed to evaluate the feasibility of surgeon-performed TVCUS in assessing TVC mobility in the outpatient setting. METHODS: At 5 institutions, 510 consecutive patients underwent 887 TVCUS performed by 8 surgeons during initial surgical evaluation. IFL was obtained in selected patients. TVCUS was

repeated during the first postoperative visit, and IFL was obtained only when judged necessary. Clinical parameters were collected and later correlated with TVC visualization. RESULTS: TVC visualization was possible in 688 of 887 TVCUS (77%); visibility ranged from 41 to 86% among performing surgeons. IFL was done in 81 patients (16%) and TVCUS predicted TVC paralysis in all cases when TVC were seen. TVC visualization was possible more often in females than males (83% vs 17%; P < .0005) and in patients without thyroid cartilage calcification than those with calcification (83% vs 42%; P < .0005). CONCLUSION: Experienced surgeon-ultrasonographers can use TVCUS to visualize TVC in most female patients and less so in males. TVCUS is highly sensitive, but operator dependent. This study demonstrates the feasibility of TVCUS and directs further attention to defining its optimal role in assessment of TVC mobility.

Carter, J. L., Ali, I. I., Isaacson, R. S., Safdieh, J. E., Finney, G. R., Sowell, M. K., et al. (2014). Status of neurology medical school education: Results of 2005 and 2012 clerkship director survey. *Neurology, 83*(19), 1761-1766.

OBJECTIVE: To survey all US medical school clerkship directors (CDs) in neurology and to compare results from a similar survey in 2005. METHODS: A survey was developed by a work group of the American Academy of Neurology Undergraduate Education Subcommittee, and sent to all neurology CDs listed in the American Academy of Neurology database. Comparisons were made to a similar 2005 survey. RESULTS: Survey response rate was 73%. Neurology was required in 93% of responding schools. Duration of clerkships was 4 weeks in 74% and 3 weeks in 11%. Clerkships were taken in the third year in 56%, third or fourth year in 19%, and fourth year in 12%. Clerkship duration in 2012 was slightly shorter than in 2005 (fewer clerkships of >/=4 weeks, p = 0.125), but more clerkships have moved into the third year (fewer neurology clerkships during the fourth year, p = 0.051). Simulation training in lumbar punctures was available at 44% of schools, but only 2% of students attempted lumbar punctures on patients. CDs averaged 20% protected time, but reported that they needed at least 32%. Secretarial full-time equivalent was 0.50 or less in 71% of clerkships. Eighty-five percent of CDs were "very satisfied" or "somewhat satisfied," but more than half experienced "burnout" and 35% had considered relinquishing their role. CONCLUSION: Trends in neurology undergraduate education since 2005 include shorter clerkships, migration into the third year, and increasing use of

technology. CDs are generally satisfied, but report stressors, including inadequate protected time and departmental support.

Castonguay, A. C., Zaidat, O. O., Novakovic, R., Nguyen, T. N., Taqi, M. A., Gupta, R., et al. (2014). Influence of age on clinical and revascularization outcomes in the north american solitaire: Stent-retriever acute stroke registry. *Stroke; a Journal of Cerebral Circulation,*

BACKGROUND AND PURPOSE: The Solitaire With the Intention for Thrombectomy (SWIFT) and thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO 2) trial results demonstrated improved recanalization rates with mechanical thrombectomy; however, outcomes in the elderly population remain poorly understood. Here, we report the effect of age on clinical and angiographic outcome within the North American Solitaire-FR Stent-Retriever Acute Stroke (NASA) Registry. METHODS: The NASA Registry recruited sites to submit data on consecutive patients treated with Solitaire-FR. Influence of age on clinical and angiographic outcomes was assessed by dichotomizing the cohort into 80 years of age. RESULTS: Three hundred fifty-four patients underwent treatment in 24 centers; 276 patients were 80 years of age. Mean age in the 80 cohorts was 62.2+/-13.2 and 85.2+/-3.8 years, respectively. Of patients >80 years, 27.3% had a 90-day modified Rankin Score 80 cohorts was 62.2+/-13.2 and 85.2+/-3.8 years, respectively. Of patients >80 years, 27.3% had a 90-day modified Rankin Score 80 and 80 years as an independent predictor of poor clinical outcome and mortality. Within the >80 cohort, National Institutes of Health Stroke Scale (NIHSS), revascularization rate, rescue therapy use, and symptomatic intracranial hemorrhage were independent predictors of mortality. CONCLUSION: Greater than 80 years of age is predictive of poor clinical outcome and increased mortality compared with younger patients in the NASA registry. However, intravenous tissue-type plasminogen activator use, lower NIHSS, and shorter revascularization time are associated with better outcomes. Further studies are needed to understand the endovascular therapy role in this cohort compared with medical therapy.

Cedfeldt, A. S., Bower, E., Flores, C., Brunett, P., Choi, D., & Girard, D. E. (2014). Promoting resident wellness: Evaluation of a time-off policy to increase residents' utilization of health care services. *Academic Medicine : Journal of the Association of American Medical Colleges,*

PURPOSE: To evaluate awareness and utilization of a new institutional policy to grant residents time off to access personal and family health care. METHOD: In 2012, two years after policy implementation, an electronic survey was sent to all 546 residents and fellows at a tertiary care academic medical center in the United States. Residents were asked questions regarding awareness of the time-off policy, use of the policy, health care status, reasons for policy use, and barriers to use. RESULTS: A total of 490 (90%) residents responded. Eighty-nine percent of those surveyed were aware of the policy. Of those who were aware, 49.7% used the policy to access health care. Top reasons for policy use were for personal routine or preventive health care, dental care, and urgent health care needs. The most commonly reported barrier to policy use was concern about the impact the resident's absence would have on colleagues. CONCLUSIONS: Implementation of policies to prospectively schedule residents' time off during business hours to address health care needs is an important means to promote resident wellness. Such policies remove one commonly cited barrier to residents' access to health care. However, residents still reported concerns about impact on peers and patients as the main reason they were reluctant to take the time off to address their health care needs. More work is needed on both wellness policy implementation practices and on refining the systems that will allow seamless and guiltless transitions of care.

Cejudo-Martin, P., Yuen, A., Vlahovich, N., Lock, P., Courtneidge, S. A., & Díaz, B. (2014). Genetic disruption of the Sh3pxd2a gene reveals an essential role in mouse development and the existence of a novel isoform of Tks5. *Plos One, 9*(9)

Tks5 is a scaffold protein and Src substrate involved in cell migration and matrix degradation through its essential role in invadosome formation and function. We have previously described that Tks5 is fundamental for zebrafish neural crest cell migration in vivo. In the present study, we sought to investigate the function of Tks5 in mammalian development by analyzing mice mutant for sh3pxd2a, the gene encoding Tks5. Homozygous disruption of the sh3pxd2a gene by genetrapping in mouse resulted in neonatal death and the presence of a complete cleft of the secondary palate. Interestingly, embryonic fibroblasts from homozygous gene-trap sh3pxd2a mice lacked only the highest molecular weight band of the characteristic Tks5 triplet observed in protein extracts, leaving the lower molecular weight bands unaffected. This finding, together with

the existence of two human Expressed Sequence Tags lacking the first 5 exons of SH3PXD2A, made us hypothesize about the presence of a second alternative transcription start site located in intron V. We performed 5′RACE on mouse fibroblasts and isolated a new transcript of the sh3pxd2a gene encoding a novel Tks5 isoform, that we named Tks5β. This novel isoform diverges from the long form of Tks5 in that it lacks the PX-domain, which confers affinity for phosphatidylinositol-3,4-bisphosphate. Instead, Tks5β has a short unique amino terminal sequence encoded by the newly discovered exon 6β; this exon includes a start codon located 29 bp from the 5′-end of exon 6. Tks5β mRNA is expressed in MEFs and all mouse adult tissues analyzed. Tks5β is a substrate for the Src tyrosine kinase and its expression is regulated through the proteasome degradation pathway. Together, these findings indicate the essentiality of the larger Tks5 isoform for correct mammalian development and the transcriptional complexity of the sh3pxd2a gene.

Chacon, K. N., Mealman, T. D., McEvoy, M. M., & Blackburn, N. J. (2014). Tracking metal ions through a Cu/Ag efflux pump assigns the functional roles of the periplasmic proteins. *Proceedings of the National Academy of Sciences of the United States of America, 111*(43), 15373-15378.
Copper is an essential nutrient for all aerobic organisms but is toxic in excess. At the host-pathogen interface, macrophages respond to bacterial infection by copper-dependent killing mechanisms, whereas the invading bacteria are thought to counter with an up-regulation of copper transporters and efflux pumps. The tripartite efflux pump CusCBA and its metallochaperone CusF are vital to the detoxification of copper and silver ions in the periplasm of Escherichia coli. However, the mechanism of efflux by this complex, which requires the activation of the inner membrane pump CusA, is poorly understood. Here, we use selenomethionine (SeM) active site labels in a series of biological X-ray absorption studies at the selenium, copper, and silver edges to establish a "switch" role for the membrane fusion protein CusB. We determine that metal-bound CusB is required for activation of cuprous ion transfer from CusF directly to a site in the CusA antiporter, showing for the first time (to our knowledge) the in vitro activation of the Cus efflux pump. This metal-binding site of CusA is unlike that observed in the crystal structures of the CusA protein and is composed of one oxygen and two sulfur ligands. Our results

suggest that metal transfer occurs between CusF and apo-CusB, and that, when metal-loaded, CusB plays a role in the regulation of metal ion transfer from CusF to CusA in the periplasm.

Chang, J. C., Hazelett, D. J., Stewart, J. A., & Morton, D. B. (2014). Motor neuron expression of the voltage-gated calcium channel cacophony restores locomotion defects in a drosophila, TDP-43 loss of function model of ALS. *Brain Research, 1584*, 39-51.

Dysfunction of the RNA-binding protein, TDP-43, is strongly implicated as a causative event in many neurodegenerative diseases including amyotrophic lateral sclerosis (ALS). TDP-43 is normally found in the nucleus and pathological hallmarks of ALS include the presence of cytoplasmic protein aggregates containing TDP-43 and an associated loss of TDP-43 from the nucleus. Loss of nuclear TDP-43 likely contributes to neurodegeneration. Using Drosophila melanogaster to model TDP-43 loss of function, we show that reduced levels of the voltage-gated calcium channel, cacophony, mediate some of the physiological effects of TDP-43 loss. Null mutations in the Drosophila orthologue of TDP-43, named TBPH, resulted in defective larval locomotion and reduced levels of cacophony protein in whole animals and at the neuromuscular junction. Restoring the levels of cacophony in all neurons or selectively in motor neurons rescued these locomotion defects. Using TBPH immunoprecipitation, we showed that TBPH associates with cacophony transcript, indicating that it is likely to be a direct target for TBPH. Loss of TBPH leads to reduced levels of cacophony transcript, possibly due to increased degradation. In addition, TBPH also appears to regulate the inclusion of some alternatively spliced exons of cacophony. If similar effects of cacophony or related calcium channels are found in human ALS patients, these could be targets for the development of pharmacological therapies for ALS. This article is part of a Special Issue entitled RNA Metabolism 2013.

Chen, M., Pendrill, R., Widmalm, G., Brady, J. W., & Wohlert, J. (2014). Molecular dynamics simulations of the ionic liquid 1-n-butyl-3-methylimidazolium chloride and its binary mixtures with ethanol. *Journal of Chemical Theory and Computation, 10*(10), 4465-4479.

Room temperature ionic liquids (ILs) of the imidazolium family have attracted much attention during the past decade for their capability to dissolve biomass. Besides experimental work, numerous compuational studies have been concerned with the physical properties of both neat

ILs and their interactions with different solutes, in particular, carbohydrates. Many classical force fields designed specifically for ILs have been found to yield viscosities that are too high for the liquid state, which has been attributed to the fact that the effective charge densities are too high due to the lack of electronic polarizability. One solution to this problem has been uniform scaling of the partial charges by a scale factor in the range 0.6-0.9, depending on model. This procedure has been shown to improve the viscosity of the models, and also to positively affect other properties, such as diffusion constants and ionic conductivity. However, less attention has been paid to how this affects the overall thermodynamics of the system, and the problems it might create when the IL models are combined with other force fields (e.g., for solutes). In the present work, we employ three widely used IL force fields to simulate 1-n-butyl-3-methyl-imidazolium chloride in both the crystal and the liquid state, as well as its binary mixture with ethanol. Two approaches are used: one in which the ionic charge is retained at its full integer value and one in which the partial charges are uniformly reduced to 85%. We investigate and calculate crystal and liquid structures, molar heat capacities, heats of fusion, self-diffusion constants, ionic conductivity, and viscosity for the neat IL, and ethanol activity as a function of ethanol concentration for the binary mixture. We show that properties of the crystal are less affected by charge scaling compared to the liquid. In the liquid state, transport properties of the neat IL are generally improved by scaling, whereas values for the heat of fusion are unaffected, and results for the heat capacity are ambiguous. Neither full nor reduced charges could reproduce experimental ethanol activities for the whole range of compositions.

Cheng, Y. W., Snowden, J. M., Handler, S. J., Tager, I. B., Hubbard, A. E., & Caughey, A. B. (2014). Litigation in obstetrics: Does defensive medicine contribute to increases in cesarean delivery? *Journal of Maternal-Fetal and Neonatal Medicine, 27*(16), 1668-1675.

Objective: Obstetrics is one of the most sued subspecialties in the US. This study aimed to examine clinicians' medical-legal experience and its association with recommending cesarean delivery. Design: Cross-sectional convenience survey. Population or sample: This is a survey study of clinicians in the US. Methods: Survey included eight common obstetric clinical vignettes and 27 questions regarding clinicians' practice environment. Chi-square test, multivariable logistic regression models were used for statistical comparisons. Main outcome measures: Likelihood of

recommending cesarean delivery. Results: There were 1486 clinicians who completed the survey. Clinicians were categorized based on answers to clinical vignettes. Having had lawsuits and daily worry of suits were associated with higher likelihood of recommending cesarean, compared to those without lawsuits (17.2 versus 11.3%, respectively; p=0.008) as was frequent worry of lawsuits (every day, 20.3% more likely; every week/month, 12.3%; few times a year/never, 11.4%, p<0.001). Conclusion: Obstetric malpractice lawsuit and frequent worry about lawsuit are associated with higher propensity of recommending cesarean delivery in common obstetric settings.

Cherala, G., & Edelman, A. (2014). How can we improve oral contraceptive success in obese women? *Expert Review of Clinical Pharmacology,* , 1-3.

A rapid increase in obesity rates worldwide further underscores the importance of better understanding the pharmacokinetic alterations in this sub-population and the subsequent effects on pharmacotherapeutics. Pharmacokinetics of contraceptive steroids is altered in obese oral contraceptive users, which may in turn impact efficacy. Our study has identified several dosing strategies that offset these pharmacokinetic changes and may improve effectiveness for obese oral contraception users.

Childers, R. (2014). Narcotized. *CMAJ : Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne,*

Chu, M., Sampath, H., Cahana, D. Y., Kahl, C. A., Somwar, R., Cornea, A., et al. (2014). Spatiotemporal dynamics of triglyceride storage in unilocular adipocytes. *Molecular Biology of the Cell,*

The spatiotemporal dynamics of triglyceride (TG) storage in unilocular adipocytes is not well understood. Here we applied ex vivo technology to study trafficking and metabolism of fluorescent fatty acid in adipose tissue explants. Live imaging revealed multiple cytoplasmic nodules surrounding the large central lipid droplet (cLD) of unilocular adipocytes. Each cytoplasmic nodule harbors a series of closely associated cellular organelles, including microlipid droplets (mLDs), mitochondria, and the endoplasmic reticulum. Exogenously added free fatty acids are rapidly adsorbed by mLDs and concurrently get esterified to TG. This process is greatly

accelerated by insulin. mLDs transfer their content to the cLD, serving as intermediates that mediate packaging of newly synthesized TG in the large interior of a unilocular adipocyte. This study reveals novel cell biological features that may contribute to the mechanism of adipocyte hypertrophy.

Clayton, C. C., Donthamsetti, P., Lambert, N. A., Javitch, J. A., & Neve, K. A. (2014). Mutation of three residues in the third intracellular loop of the dopamine D2 receptor creates an internalization-defective receptor. *The Journal of Biological Chemistry,*
Arrestins mediate desensitization and internalization of G protein-coupled receptors, and also direct receptor signaling towards heterotrimeric G protein-independent signaling pathways. We previously identified a four-residue segment (residues 212-215) of the dopamine D2 receptor that is necessary for arrestin binding in an in vitro heterologous expression system but that also impairs receptor expression. We now describe the characterization of additional mutations at that arrestin binding site in the third intracellular loop (IL3). Mutating two (residues 214-215) or three (residues 213-215) of the four residues to alanine partially decreased agonist-induced recruitment of arrestin3 without altering activation of a G protein. Arrestin-dependent receptor internalization, which requires arrestin binding to beta2-adaptin (the beta2 subunit of the clathrin-associated adaptor protein AP2) and clathrin, was disproportionately affected by the three-residue mutation, with no agonist-induced internalization observed even in the presence of overexpressed arrestin or G protein-coupled receptor kinase 2 (GRK2). The disjunction between arrestin recruitment and internalization could not be explained by alterations in the time course of the receptor-arrestin interaction, the recruitment of GRK2, or the receptor-induced interaction between arrestin and beta2-adaptin, suggesting that the mutation impairs a property of the internalization complex that has not yet been identified.

Connelly, K. J., Larson, E. A., Marks, D. L., & Klein, R. F. (2014). Neonatal estrogen exposure results in biphasic age-dependent effects on the skeletal development of male mice. *Endocrinology,* , en20141324.
Peak bone mass, one of the most important predictors for fracture risk later in life, is attained during puberty and adolescence and influenced by neonatal and pubertal sex-specific gonadal

hormones and growth hormone-IGF-1 secretion patterns. This study examined the effects of brief neonatal estrogen exposure on growth and skeletal development in C57BL/6J mice. A single injection of 100 mu g estradiol or vehicle was administered on the first day of life. Growth parameters were monitored and skeletal phenotyping performed at 16 weeks in female mice and at 4 and 16 weeks in the male mice. Neonatal estrogen exposure negatively impacted adult femoral length in both sexes but adult body weight, areal bone density and bone strength in female mice was unaffected. In contrast, somatic growth was attenuated in estrogen-exposed male mice throughout the study period. At the pre-pubertal time point, the estrogen-exposed males exhibited higher bone mineral density, cortical volume and cortical thickness compared to controls. However, by the time of peak bone mass acquisition, the early skeletal findings had reversed; estrogen-exposed mice had lower bone density with reduced cross-sectional area, cortical volume and cortical thickness, resulting in cortical bones that were less resistant to fracture. Neonatal estrogen exposure also resulted in reduced testicular volume and lower circulating IGF-1. Male mice exposed to estrogen on the first day of life experience age-dependent changes in skeletal development. Pre-pubertal animals experience greater endocortical bone acquisition as a result of estrogen exposure; however, by adulthood, continued developmental changes result in overall reduced skeletal integrity.

Cook, M. R., Louis, S. G., McCully, S. P., Stucke, R. S., Fabricant, S. P., & Schreiber, M. A. (2014). Positive blood alcohol is associated with reduced DVT in trauma. *Injury,*

INTRODUCTION: Trauma patients exhibit a complex coagulopathy which is not fully understood and deep venous thrombosis (DVT) rates remain high. The effects of alcohol (EtOH) consumption on coagulopathy in trauma patients have not been studied. We hypothesized that acute EtOH intoxication would produce a relative hypocoagulable state as measured by thrombelastography (TEG) and would be associated with reduced DVT rates. METHODS: Data were prospectively collected on 213 trauma patients at a level 1 trauma centre and analyzed in a retrospective secondary analysis. Thrombelastography (TEG), standard laboratory tests and ETOH levels were performed. If the level was positive, patients were grouped as EtOH+ and all patients were screened for DVT using a standard protocol. Statistical significance was $p<0.05$. RESULTS: The EtOH+ group was predominantly male (76%), was younger ($p<0.05$), had a lower BMI ($p<0.05$),

demonstrated a lower AIS extremity score (p<0.01) and was less likely to have a blunt injury (p<0.01) than the EtOH- group. Gender, ISS and other AIS scores were not significantly different. TEG values in the alcohol group demonstrated a relative hypocoagulable state that was associated with a reduced DVT incidence, 1.4% versus 16.2%, (p<0.01). This difference was not detected with conventional assays. A multivariate logistic regression was performed, controlling for common risk factors for DVT and a positive EtOH level on admission was independently associated with reduced DVT incidence. CONCLUSIONS: Alcohol consumption is associated with a relative hypocoagulable state on TEG that is associated with a decreased DVT incidence. This difference is not detected by conventional assays.

Cooke, C. R., Feemster, L. C., Wiener, R. S., O'Neil, M. E., & Slatore, C. G. (2014). Aggressiveness of intensive care use among patients with lung cancer in the surveillance, epidemiology, and end results-medicare registry. *Chest, 146*(4), 916-923.

BACKGROUND: Approximately 65% of elderly patients with lung cancer who are admitted to the ICU will die within 6 months. Efforts to improve end-of-life care for this population must first understand the patient factors that underlie admission to the ICU. METHODS: We performed a retrospective cohort study examining all fee-for-service inpatient claims in the Surveillance, Epidemiology, and End Results (SEER)-Medicare registry for elderly patients (aged . 65 years) who had received a diagnosis of lung cancer between 1992 and 2005 and who were hospitalized for reasons other than resection of their lung cancer. We calculated yearly rates of ICU admission per 1,000 hospitalizations via room and board codes or International Classification of Diseases, Ninth Revision, Clinical Modification and diagnosis-related group codes for mechanical ventilation, stratified the rates by receipt of mechanical ventilation and ICU type (medical/surgical/cardiac vs intermediate), and compared these rates over time. RESULTS: A total of 175,756 patients with lung cancer in SEER were hospitalized for a reason other than surgical resection of their tumor during the study period, 49,373 (28%) of whom had at least one ICU stay. The rate of ICU admissions per 1,000 hospitalizations increased over the study period from 140.7 in 1992 to 201.7 in 2005 (P < .001). The majority of the increase in ICU admissions (per 1,000 hospitalizations) between 1992 and 2005 occurred among patients who were not mechanically ventilated (118.2 to 173.3, P < .001) and among those who were in intermediate ICUs (20.0 to

61.9, P < .001), but increased only moderately in medical/surgical/cardiac units (120.7 to 139.9, P < .001). CONCLUSIONS: ICU admission for patients with lung cancer increased over time, mostly among patients without mechanical ventilation who were largely cared for in intermediate ICUs.

Crabbe, J. C. (2014). *Use of animal models of alcohol-related behavior* Elsevier.

Alcoholism (alcohol dependence and alcohol use disorder, AUD) is quintessentially behavioral in nature. AUD is behaviorally and genetically complex. This review discusses behavioral assessment of alcohol sensitivity, tolerance, dependence, withdrawal, and reinforcement. The focus is on using laboratory animal models to explore genetic contributions to individual differences in alcohol responses. Rodent genetic animal models based on selective breeding for high vs low alcohol response, and those based on the use of inbred strains, are reviewed. Genetic strategies have revealed the complexity of alcohol responses where genetic influences on multiple alcohol-related behaviors are mostly discrete. They have also identified areas where genetic influences are consistent across behavioral assays and have been used to model genetic differences among humans at different risk for AUD.

Dao, K. H. T., Solti, M. B., Maxson, J. E., Winton, E. F., Press, R. D., Druker, B. J., et al. (2015). *Significant clinical response to JAK1/2 inhibition in a patient with CSF3R-T618I-positive atypical chronic myeloid leukemia* Elsevier Ltd.

Mutations in CSF3R (colony-stimulating factor 3 receptor) are frequent oncogenic drivers in chronic neutrophilic leukemia (CNL) and atypical chronic myeloid leukemia (aCML). Here we describe a 75 year old man who was diagnosed with CSF3R-T618I-positive atypical CML. He presented with leukocytosis, anemia, and thrombocytopenia and developed massive splenomegaly and severe constitutional symptoms. Hydroxyurea was given over a 6 month period but failed to provide any measureable clinical benefit. Eventually, he was treated with ruxolitinib, an FDA-approved JAK1/2 inhibitor, which resulted in dramatic improvement of his blood counts. He also had significant reduction of spleen volume and constitutional symptoms. This case highlights the need for a clinical trial to interrogate JAK1/2 as a potential molecular target in CNL and aCML in patients with or without CSF3R mutation. A clinical trial evaluating the

safety and efficacy of ruxolitinib for this patient population is registered at ClinicalTrials.gov (NCT02092324).

Davulcu, O., Niu, X., Bruschweiler-Li, L., Bruschweiler, R., Skalicky, J. J., & Chapman, M. S. (2014). Backbone resonance assignments of the 42 kDa enzyme arginine kinase in the transition state analogue form. *Biomolecular NMR Assignments, 8*(2), 335-338.

Nearly complete backbone resonance assignments for the 357 residue, 42 kDa enzyme arginine kinase in a transition state analogue (TSA) complex are presented. The TSA is a quaternary complex of arginine kinase, MgADP, arginine, and nitrate. About 93% (320 of 344) of the non-proline backbone amides were assigned using an enzyme enriched with (2)H, (13)C, and (15)N in combination with three enzyme samples prepared with a single (15)N-labeled amino acid (K, L, and R). The amide assignments will provide the foundation for investigating the dynamics of arginine kinase when in a TSA complex.

DeLoughery, T. G. (2014). Microcytic anemia. *The New England Journal of Medicine, 371*(14), 1324-1331.

Deodhar, A., Reveille, J. D., van den Bosch, F., Braun, J., Burgos-Vargas, R., Caplan, L., et al. (2014). The concept of axial spondyloarthritis: Joint statement of the spondyloarthritis research and treatment network and the assessment of SpondyloArthritis international society in response to the US food and drug administration's comments and concerns. *Arthritis & Rheumatology (Hoboken, N.J.), 66*(10), 2649-2656.

Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., et al. (2014). Focus article: Report of the NIH task force on research standards for chronic low back pain. *European Spine Journal : Official Publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society, 23*(10), 2028-2045.

Despite rapidly increasing intervention, functional disability due to chronic low back pain (cLBP) has increased in recent decades. We often cannot identify mechanisms to explain the major negative impact cLBP has on patients' lives. Such cLBP is often termed non-specific and may be

due to multiple biologic and behavioral etiologies. Researchers use varied inclusion criteria, definitions, baseline assessments, and outcome measures, which impede comparisons and consensus. Therefore, NIH Pain Consortium charged a Research Task Force (RTF) to draft standards for research on cLBP. The resulting multidisciplinary panel recommended using 2 questions to define cLBP; classifying cLBP by its impact (defined by pain intensity, pain interference, and physical function); use of a minimum dataset to describe research participants (drawing heavily on the PROMIS methodology); reporting "responder analyses" in addition to mean outcome scores; and suggestions for future research and dissemination. The Pain Consortium has approved the recommendations, which investigators should incorporate into NIH grant proposals. The RTF believes that these recommendations will advance the field, help to resolve controversies, and facilitate future research addressing the genomic, neurologic, and other mechanistic substrates of chronic low back pain. We expect that the RTF recommendations will become a dynamic document and undergo continual improvement. PERSPECTIVE: A task force was convened by the NIH Pain Consortium with the goal of developing research standards for chronic low back pain. The results included recommendations for definitions, a minimum dataset, reporting outcomes, and future research. Greater consistency in reporting should facilitate comparisons among studies and the development of phenotypes.

Dickerson, M. F., Astorga, N. G., Astorga, N. R., & Lewis, A. D. (2014). Chagas disease in 2 geriatric rhesus macaques (macaca mulatta) housed in the pacific northwest. *Comparative Medicine, 64*(4), 323-328.

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite Trypanosoma cruzi. It is endemic in Latin America but also is found in the southern United States, particularly Texas and along the Gulf Coast. Typical clinical manifestations of Chagas disease are not well-characterized in rhesus macaques, but conduction abnormalities, myocarditis, and encephalitis and megaesophagus have been described. Here we report 2 cases of Chagas disease in rhesus macaques housed in the northwestern United States. The first case involved a geriatric male macaque with cardiomegaly, diagnosed as dilated cardiomyopathy on ultrasonographic examination. Postmortem findings included myocarditis as well as ganglioneuritis in the esophagus, stomach, and colon. The second case affected a geriatric female macaque

experimentally infected with SIV. She was euthanized for a protocol-related time point. Microscopic examination revealed chronic myocarditis with amastigotes present in the cardiomyocytes, ganglioneuritis, and opportunistic infections attributed to her immunocompromised status. Banked serum samples from both macaques had positive titers for T. cruzi. T. cruzi DNA was amplified by conventional PCR from multiple tissues from both animals. Review of their histories revealed that both animals had been obtained from facilities in South Texas more than 12 y earlier. Given the long period of clinical latency, Chagas disease may be more prevalent in rhesus macaques than typically has been reported. T. cruzi infection should be considered for animals with unexplained cardiac or gastrointestinal pathology and that originated from areas known to have a high risk for disease transmission.

Dieperink, E., Fuller, B., Isenhart, C., Mcmaken, K., Lenox, R., Pocha, C., et al. Efficacy of motivational enhancement therapy on alcohol use disorders in patients with chronic hepatitis C: A randomized controlled trial. *Addiction, 109*(11), 1869-1877.

Aims: To determine the efficacy of motivational enhancement therapy (MET) on alcohol use in patients with the hepatitis C virus (HCV) and an alcohol use disorder (AUD). Design: Randomized, single-blind, controlled trial comparing MET to a control education condition with 6-month follow-up. Setting: Patients were recruited from hepatitis clinics at the Minneapolis, Minnesota and Portland, Oregon Veterans Affairs Health Care Systems, USA. Participants and Intervention: Patients with HCV, an AUD and continued alcohol use (n=139) were randomized to receive either MET (n=70) or a control education condition (n=69) over 3 months. Measurements: Data were self-reported percentage of days abstinent from alcohol and number of standard alcohol drinks per week 6 months after randomization. Findings: At baseline, subjects in MET had 34.98% days abstinent, which increased to 73.15% at 6 months compared to 34.63 and 59.49% for the control condition. Multi-level models examined changes in alcohol consumption between MET and control groups. Results showed a significant increase in percentage of days abstinent overall ($F(1120.4)=28.04$, $P<0.001$) and a significant group×time effect ($F(1119.9)=5.23$, $P=0.024$) with the MET group showing a greater increase in percentage of days abstinent at 6 months compared with the education control condition. There were no significant differences between groups for drinks per week. The effect size of the MET intervention was moderate (0.45) for

percentage of days abstinent. Conclusion: Motivational enhancement therapy (MET) appears to increase the percentage of days abstinent in patients with chronic hepatitis C, alcohol use disorders and ongoing alcohol use.

Doolittle, N. D., Muldoon, L. L., Culp, A. Y., & Neuwelt, E. A. (2014). *Delivery of chemotherapeutics across the blood-brain barrier: Challenges and advances* Academic Press Inc.

The blood-brain barrier (BBB) limits drug delivery to brain tumors. We utilize intraarterial infusion of hyperosmotic mannitol to reversibly open the BBB by shrinking endothelial cells and opening tight junctions between the cells. This approach transiently increases the delivery of chemotherapy, antibodies, and nanoparticles to brain. Our preclinical studies have optimized the BBB disruption (BBBD) technique and clinical studies have shown its safety and efficacy. The delivery of methotrexate-based chemotherapy in conjunction with BBBD provides excellent outcomes in primary central nervous system lymphoma (PCNSL) including stable or improved cognitive function in survivors a median of 12 years (range 2-26 years) after diagnosis. The addition of rituximab to chemotherapy with BBBD for PCNSL can be safely accomplished with excellent overall survival. Our translational studies of thiol agents to protect against platinum-induced toxicities led to the development of a two-compartment model in brain tumor patients. We showed that delayed high-dose sodium thiosulfate protects against carboplatin-induced hearing loss, providing the framework for large cooperative group trials of hearing chemoprotection. Neuroimaging studies have identified that ferumoxytol, an iron oxide nanoparticle blood pool agent, appears to be a superior contrast agent to accurately assess therapy-induced changes in brain tumor vasculature, in brain tumor response to therapy, and in differentiating central nervous system lesions with inflammatory components. This chapter reviews the breakthroughs, challenges, and future directions for BBBD.

Dotson, A. L., Zhu, W., Libal, N., Alkayed, N. J., & Offner, H. (2014). Different immunological mechanisms govern protection from experimental stroke in young and older mice with recombinant TCR ligand therapy. *Frontiers in Cellular Neuroscience, 8*(SEP), 1-13.

Stroke is a leading cause of death and disability in the United States. The lack of clinical success in stroke therapies can be attributed, in part, to inadequate basic research on aging rodents. The

current study demonstrates that recombinant TCR ligand therapy uses different immunological mechanisms to protect young and older mice from experimental stroke. In young mice, RTL1000 therapy inhibited splenocyte efflux while reducing frequency of T cells and macrophages in the spleen. Older mice treated with RTL1000 exhibited a significant reduction in inflammatory cells in the brain and inhibition of splenic atrophy. Our data suggest age specific differences in immune response to stroke that allow unique targeting of stroke immunotherapies.

Dulic, M., Perona, J. J., & Gruic-Sovulj, I. (2014). Determinants for tRNA-dependent pretransfer editing in the synthetic site of isoleucyl-tRNA synthetase. *Biochemistry, 53*(39), 6189-6198. The accurate expression of genetic information relies on the fidelity of amino acid-tRNA coupling by aminoacyl-tRNA synthetases (aaRS). When the specificity against structurally similar noncognate amino acids in the synthetic reaction does not support a threshold fidelity level for translation, the aaRS employ intrinsic hydrolytic editing to correct errors in aminoacylation. Escherichia coli isoleucyl-tRNA synthetase (EcIleRS) is a class I aaRS that is notable for its use of tRNA-dependent pretransfer editing to hydrolyze noncognate valyl-adenylate prior to aminoacyl-tRNA formation. On the basis of the finding that IleRS possessing an inactivated post-transfer editing domain is still capable of robust tRNA-dependent editing, we have recently proposed that the pretransfer editing activity resides within the synthetic site. Here we apply an improved methodology that allows quantitation of the AMP fraction that arises particularly from tRNA-dependent aa-AMP hydrolysis. By this approach, we demonstrate that tRNA-dependent pretransfer editing accounts for nearly one-third of the total proofreading by EcIleRS and that a highly conserved tyrosine within the synthetic site modulates both editing and aminoacylation. Therefore, synthesis of aminoacyl-tRNA and hydrolysis of aminoacyl-adenylates employ overlapping amino acid determinants. We suggest that this overlap hindered the evolution of synthetic site-based pretransfer editing as the predominant proofreading pathway, because that activity is difficult to accommodate in the context of efficient aminoacyl-tRNA synthesis. Instead, the acquisition of a spatially separate domain dedicated to post-transfer editing alone allowed for the development of a powerful deacylation machinery that effectively competes with dissociation of misacylated tRNAs.

Duncan, C. N., Majhail, N. S., Brazauskas, R., Wang, Z., Cahn, J. Y., Frangoul, H. A., et al. (2014). Long-term survival and late effects among 1-year survivors of second allogeneic hematopoietic cell transplantation for relapsed acute leukemia and myelodysplastic syndromes. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation,*

We analyzed the outcomes of patients who survived disease-free for 1-year or more following second allogeneic hematopoietic cell transplantation (HCT) for relapsed acute leukemia or myelodysplastic syndromes between 1980 and 2009. A total of 1285 patients received a second allogeneic transplant following disease relapse; among these 325 survived relapse-free at 1-year after the second HCT. The median time from first to second HCT was 17 and 24 months for children and adults, respectively. A myeloablative preparative regimen was used in the second transplant in 62% of children and 45% of adult patients. The overall 10-year conditional survival rates after second transplantation in this cohort of patients who had survived disease-free for at least one year were 55% in children and 39% in adults. Relapse was the leading cause of mortality (77% and 54% of deaths in children and adults, respectively). In multivariate analyses, only disease status prior to second HCT was significantly associated with higher risk for overall mortality (HR 1.71 for patients with disease not in complete remission prior to second HCT, $P<0.01$). Chronic graft-versus-host disease (GVHD) developed in 43% and 75% of children and adults following second transplant. Chronic GVHD was the leading cause of non-relapse mortality followed by organ failure and infection. The cumulative incidence of developing at least one of the studied late effects at 10-years after second HCT was 63% in children and 55% in adults. The most frequent late effects in children were growth disturbance (10-year cumulative incidence 22%) and cataracts (20%), and in adults were cataracts (20%) and avascular necrosis (13%). Among patients with acute leukemia and myelodysplastic syndromes who receive a second allogeneic HCT for relapse and survive disease-free for at least 1-year, many can be expected to survive long term. However, they continue to be at risk for relapse and non-relapse morbidity and mortality. Novel approaches are needed to minimize relapse risk and long-term transplant morbidity in this population.

Evbuomwan, O. M., Lee, J., Woods, M., & Sherry, A. D. (2014). The presence of fast-exchanging proton species in aqueous solutions of paraCEST agents can impact rate constants measured for slower exchanging species when fitting CEST spectra to the bloch equations. *Inorganic Chemistry, 53*(19), 10012-10014.

LnDOTA-tetraamide complexes typically exist in solution as a mixture of square-antiprismatic (SAP) and twisted square-antiprismatic (TSAP) coordination isomers. In most cases, the SAP isomer, which is preferred for CEST imaging, predominates, and the presence of the minor TSAP isomer is assumed to have little influence on quantitative measures of the water-exchange rate constant for the SAP isomer. Here, we sought to confirm the validity of this assumption by mixing two chelates with different SAP and TSAP isomer populations while measuring the water-exchange rate constant of the SAP isomer. The results show that an increase in the population of the TSAP isomer in solution results in as much as a 30% overestimation of the water-exchange rate constant for the SAP isomer when CEST spectra are fit to the Bloch equations. This effect was shown to be significant only when the TSAP isomer population exceeded 50%.

Felius, J., Busettini, C., Lynn, M. J., Hartmann, E. E., Lambert, S. R., DuBois, L., et al. (2014). Nystagmus and related fixation instabilities following extraction of unilateral infantile cataract in the infant aphakia treatment study (IATS). *Investigative Ophthalmology and Visual Science, 55*(8), 5332-5337.

Purpose. To study eye movements in a large group of children after the removal of unilateral infantile cataract, and to compare fixation instabilities between treatment groups with or without IOL implantation. Methods. The Infant Aphakia Treatment Study (IATS) is a randomized, multicenter clinical trial comparing IOL to contact lens (CL) treatment with a unilateral infantile cataract in participants who underwent cataract surgery at 1 to 6 months of age. At age 4.5 years, eye movements were recorded in 103 participants, using a high-speed video camera while the child performed a fixation task. The recordings were inspected by masked readers for the presence of fixation instabilities (nystagmus and saccadic oscillations). Results. Overall, fixation instabilities were observed in 50 (60%) of 83 children who had evaluable recordings, with no differences between treatment groups (27 [64%] of 42 in the IOL group, 23 [56%] of 41 in the CL group; P = 0.51). Nystagmus was seen in 38% and saccadic oscillations in 31%, with no

differences between treatment groups (P > 0.33). Children without a fixation instability had better visual acuity (P = 0.04). Conclusions. Nystagmus and saccadic oscillations are well-known consequences of infantile cataracts, presumably the result of visual deprivation during the critical period of visual development. After early cataract extraction, successful optical correction may reduce further form deprivation and minimize the incidence of these fixation instabilities. In this study, no differences in the presence of fixation instabilities were found between the two treatment strategies (CL or IOL) for optical correction after cataract removal. (ClinicalTrials.gov number, NCT00212134.)

Flaherty, L. E., Othus, M., Atkins, M. B., Tuthill, R. J., Thompson, J. A., Vetto, J. T., et al. (2014). Southwest oncology group S0008: A phase III trial of high-dose interferon alfa-2b versus cisplatin, vinblastine, and dacarbazine DTIC, plus interleukin-2 and interferon in patients with high-risk melanoma-an intergroup study of cancer and leukemia group B, children's oncology group, eastern cooperative oncology group, and southwest oncology group. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,*

PURPOSE: High-dose interferon (IFN) for 1 year (HDI) is the US Food and Drug Administration-approved adjuvant therapy for patients with high-risk melanoma. Efforts to modify IFN dose and schedule have not improved efficacy. We sought to determine whether a shorter course of biochemotherapy would be more effective. PATIENTS AND METHODS: S0008 (S0008: Chemotherapy Plus Biological Therapy in Treating Patients With Melanoma) was an Intergroup phase III trial that enrolled high-risk patients (stage IIIA-N2a through IIIC-N3), randomly assigning them to receive either HDI or biochemotherapy consisting of dacarbazine DTIC, cisplatin, vinblastine, interleukin-2, IFN alfa-2b (IFN-alpha-2b) and granulocyte colony-stimulating factor given every 21 days for three cycles. Coprimary end points were relapse-free survival (RFS) and overall survival (OS). RESULTS: In all, 432 patients were enrolled. Grade 3 and 4 adverse events occurred in 57% and 7% of HDI patients and 36% and 40% of biochemotherapy patients, respectively. At a median follow-up of 7.2 years, biochemotherapy improved RFS (hazard ratio [HR], 0.75; 95% CI, 0.58 to 0.97;P = .015), with a median RFS of 4.0 years (95% CI, 1.9 years to not reached [NR]) versus 1.9 years for HDI (95% CI, 1.2 to 2.8 years) and a 5-year RFS of 48% versus 39%. Median OS was not different (HR, 0.98; 95% CI,

0.74 to 1.31;P = .55), with a median OS of 9.9 years (95% CI, 4.62 years to NR) for biochemotherapy versus 6.7 years (95% CI, 4.5 years to NR) for HDI and a 5-year OS of 56% for both arms. CONCLUSION: Biochemotherapy is a shorter, alternative adjuvant treatment for patients with high-risk melanoma that provides statistically significant improvement in RFS but no difference in OS and more toxicity compared with HDI.

Fling, B. W., Dutta, G. G., Schlueter, H., Cameron, M. H., & Horak, F. B. (2014). Associations between proprioceptive neural pathway structural connectivity and balance in people with multiple sclerosis. *Frontiers in Human Neuroscience, 8*, 814.

Mobility and balance impairments are a hallmark of multiple sclerosis (MS), affecting nearly half of patients at presentation and resulting in decreased activity and participation, falls, injuries, and reduced quality of life. A growing body of work suggests that balance impairments in people with mild MS are primarily the result of deficits in proprioception, the ability to determine body position in space in the absence of vision. A better understanding of the pathophysiology of balance disturbances in MS is needed to develop evidence-based rehabilitation approaches. The purpose of the current study was to (1) map the cortical proprioceptive pathway in vivo using diffusion-weighted imaging and (2) assess associations between proprioceptive pathway white matter microstructural integrity and performance on clinical and behavioral balance tasks. We hypothesized that people with MS (PwMS) would have reduced integrity of cerebral proprioceptive pathways, and that reduced white matter microstructure within these tracts would be strongly related to proprioceptive-based balance deficits. We found poorer balance control on proprioceptive-based tasks and reduced white matter microstructural integrity of the cortical proprioceptive tracts in PwMS compared with age-matched healthy controls (HC). Microstructural integrity of this pathway in the right hemisphere was also strongly associated with proprioceptive-based balance control in PwMS and controls. Conversely, while white matter integrity of the right hemisphere's proprioceptive pathway was significantly correlated with overall balance performance in HC, there was no such relationship in PwMS. These results augment existing literature suggesting that balance control in PwMS may become more dependent upon (1) cerebellar-regulated proprioceptive control, (2) the vestibular system, and/or (3) the visual system.

Frisoni, G. B., Jack, C. R., Bocchetta, M., Bauer, C., Frederiksen, K. S., Liu, Y., et al. (2014). The EADC-ADNI harmonized protocol for manual hippocampal segmentation on magnetic resonance: Evidence of validity. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association,* BACKGROUND: An international Delphi panel has defined a harmonized protocol (HarP) for the manual segmentation of the hippocampus on MR. The aim of this study is to study the concurrent validity of the HarP toward local protocols, and its major sources of variance. METHODS: Fourteen tracers segmented 10 Alzheimer's Disease Neuroimaging Initiative (ADNI) cases scanned at 1.5 T and 3T following local protocols, qualified for segmentation based on the HarP through a standard web-platform and resegmented following the HarP. The five most accurate tracers followed the HarP to segment 15 ADNI cases acquired at three time points on both 1.5 T and 3T. RESULTS: The agreement among tracers was relatively low with the local protocols (absolute left/right ICC 0.44/0.43) and much higher with the HarP (absolute left/right ICC 0.88/0.89). On the larger set of 15 cases, the HarP agreement within (left/right ICC range: 0.94/0.95 to 0.99/0.99) and among tracers (left/right ICC range: 0.89/0.90) was very high. The volume variance due to different tracers was 0.9% of the total, comparing favorably to variance due to scanner manufacturer (1.2), atrophy rates (3.5), hemispheric asymmetry (3.7), field strength (4.4), and significantly smaller than the variance due to atrophy (33.5%, P < .001), and physiological variability (49.2%, P < .001). CONCLUSIONS: The HarP has high measurement stability compared with local segmentation protocols, and good reproducibility within and among human tracers. Hippocampi segmented with the HarP can be used as a reference for the qualification of human tracers and automated segmentation algorithms.

Fu, X., Creighton, C. J., Biswal, N. C., Kumar, V., Shea, M., Herrera, S., et al. (2014). Overcoming endocrine resistance due to reduced PTEN levels in estrogen receptor-positive breast cancer by co-targeting mammalian target of rapamycin, protein kinase B, or mitogen-activated protein kinase kinase. *Breast Cancer Research, 16*(5)
Introduction: Activation of the phosphatidylinositol 3-kinase (PI3K) pathway in estrogen receptor α (ER)-positive breast cancer is associated with reduced ER expression and activity, luminal B subtype, and poor outcome. Phosphatase and tensin homolog (PTEN), a negative regulator of this pathway, is typically lost in ER-negative breast cancer. We set out to clarify the role of reduced

PTEN levels in endocrine resistance, and to explore the combination of newly developed PI3K downstream kinase inhibitors to overcome this resistance.Methods: Altered cellular signaling, gene expression, and endocrine sensitivity were determined in inducible PTEN-knockdown ER-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer cell and/or xenograft models. Single or two-agent combinations of kinase inhibitors were examined to improve endocrine therapy.Results: Moderate PTEN reduction was sufficient to enhance PI3K signaling, generate a gene signature associated with the luminal B subtype of breast cancer, and cause endocrine resistance in vitro and in vivo. The mammalian target of rapamycin (mTOR), protein kinase B (AKT), or mitogen-activated protein kinase kinase (MEK) inhibitors, alone or in combination, improved endocrine therapy, but the efficacy varied by PTEN levels, type of endocrine therapy, and the specific inhibitor(s). A single-agent AKT inhibitor combined with fulvestrant conferred superior efficacy in overcoming resistance, inducing apoptosis and tumor regression.Conclusions: Moderate reduction in PTEN, without complete loss, can activate the PI3K pathway to cause endocrine resistance in ER-positive breast cancer, which can be overcome by combining endocrine therapy with inhibitors of the PI3K pathway. Our data suggests that the ER degrader fulvestrant, to block both ligand-dependent and -independent ER signaling, combined with an AKT inhibitor is an effective strategy to test in patients.

Fujita, T., Burwitz, B. J., Chew, G. M., Reed, J. S., Pathak, R., Seger, E., et al. (2014). Expansion of dysfunctional tim-3-expressing effector memory CD8+ T cells during simian immunodeficiency virus infection in rhesus macaques. *Journal of Immunology (Baltimore, Md.: 1950),*
The T cell Ig- and mucin domain-containing molecule-3 (Tim-3) negative immune checkpoint receptor demarcates functionally exhausted CD8+ T cells arising from chronic stimulation in viral infections like HIV. Tim-3 blockade leads to improved antiviral CD8+ T cell responses in vitro and, therefore, represents a novel intervention strategy to restore T cell function in vivo and protect from disease progression. However, the Tim-3 pathway in the physiologically relevant rhesus macaque SIV model of AIDS remains uncharacterized. We report that Tim-3+CD8+ T cell frequencies are significantly increased in lymph nodes, but not in peripheral blood, in SIV-infected animals. Tim-3+PD-1+CD8+ T cells are similarly increased during SIV infection and positively correlate with SIV plasma viremia. Tim-3 expression was found primarily on effector

memory CD8+ T cells in all tissues examined. Tim-3+CD8+ T cells have lower Ki-67 content and minimal cytokine responses to SIV compared with Tim-3-CD8+ T cells. During acute-phase SIV replication, Tim-3 expression peaked on SIV-specific CD8+ T cells by 2 wk postinfection and then rapidly diminished, irrespective of mutational escape of cognate Ag, suggesting non-TCR-driven mechanisms for Tim-3 expression. Thus, rhesus Tim-3 in SIV infection partially mimics human Tim-3 in HIV infection and may serve as a novel model for targeted studies focused on rejuvenating HIV-specific CD8+ T cell responses.

Furuno, J. P., Comer, A. C., Johnson, J. K., Rosenberg, J. H., Moore, S. L., MacKenzie, T. D., et al. (2014). Using antibiograms to improve antibiotic prescribing in skilled nursing facilities. *Infection Control and Hospital Epidemiology : The Official Journal of the Society of Hospital Epidemiologists of America, 35 Suppl 3*, S56-61.

BACKGROUND: Antibiograms have effectively improved antibiotic prescribing in acute-care settings; however, their effectiveness in skilled nursing facilities (SNFs) is currently unknown. OBJECTIVE: To develop SNF-specific antibiograms and identify opportunities to improve antibiotic prescribing. DESIGN AND SETTING: Cross-sectional and pretest-posttest study among residents of 3 Maryland SNFs. METHODS: Antibiograms were created using clinical culture data from a 6-month period in each SNF. We also used admission clinical culture data from the acute care facility primarily associated with each SNF for transferred residents. We manually collected all data from medical charts, and antibiograms were created using WHONET software. We then used a pretest-posttest study to evaluate the effectiveness of an antibiogram on changing antibiotic prescribing practices in a single SNF. Appropriate empirical antibiotic therapy was defined as an empirical antibiotic choice that sufficiently covered the infecting organism, considering antibiotic susceptibilities. RESULTS: We reviewed 839 patient charts from SNF and acute care facilities. During the initial assessment period, 85% of initial antibiotic use in the SNFs was empirical, and thus only 15% of initial antibiotics were based on culture results. Fluoroquinolones were the most frequently used empirical antibiotics, accounting for 54.5% of initial prescribing instances. Among patients with available culture data, only 35% of empirical antibiotic prescribing was determined to be appropriate. In the single SNF in which we evaluated antibiogram effectiveness, prevalence of appropriate antibiotic prescribing increased from 32% to 45% after antibiogram

implementation; however, this was not statistically significant ([Formula: see text]). CONCLUSIONS: Implementation of antibiograms may be effective in improving empirical antibiotic prescribing in SNFs.

Garcia-Negredo, G., Soto, D., Llorente, J., Morato, X., Galenkamp, K. M., Gomez-Soler, M., et al. (2014). Coassembly and coupling of SK2 channels and mGlu5 receptors. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34*(44), 14793-14802. Group I metabotropic glutamate (mGlu) receptors regulate hippocampal CA1 pyramidal neuron excitability via Ca(2+) wave-dependent activation of small-conductance Ca(2+)-activated K(+) (SK) channels. Here, we show that mGlu5 receptors and SK2 channels coassemble in heterologous coexpression systems and in rat brain. Further, in cotransfected cells or rat primary hippocampal neurons, mGlu5 receptor stimulation activated apamin-sensitive SK2-mediated K(+) currents. In addition, coexpression of mGlu5 receptors and SK2 channels promoted plasma membrane targeting of both proteins and correlated with increased mGlu5 receptor function that was unexpectedly blocked by apamin. These results demonstrate a reciprocal functional interaction between mGlu5 receptors and SK2 channels that reflects their molecular coassembly.

Geltzeiler, M., Monroe, M., Givi, B., Vetto, J., Andersen, P., & Gross, N. (2014). Regional control of head and neck melanoma with selective neck dissection. *JAMA Otolaryngology-- Head & Neck Surgery,*

Importance: Historically, patients with cervical metastases from melanoma of the head and neck were treated with a radical neck dissection. This study evaluates the efficacy of limiting the extent of lymphadenectomy in this high-risk population. Objectives: To determine whether limiting the extent of lymphadenectomy for patients with biopsy-proven melanoma has a negative effect on regional control. Our hypothesis was that performing a more limited lymphadenectomy does not have a negative impact on regional control. Design, Setting, and Participants: A retrospective, single-cohort study was performed using a prospectively collected database of patients with head and neck melanoma with histopathologically positive lymph nodes after modified radical (MRND) or selective neck dissection (SNDs) performed at a high-volume, academic, tertiary care center. Interventions: Lymphadenectomy was performed as clinically

indicated. Main Outcomes and Measures: Primary end points were regional recurrence and regional recurrence free survival. Univariable and multivariable analyses were conducted using multiple patient characteristics. Results: Forty-one patients underwent SND or MRND from 2001 through 2010. The median number of positive nodes was 1 (range, 1-16). Twenty-six patients (63%) received adjuvant radiation and 23 patients (56%) received adjuvant immunotherapy or chemotherapy. The median follow-up time was 17 months (range, 1-116 months). Regional control was achieved in 29 patients (71%). Median regional recurrence-free survival was 21 months (range, 1-116 months). Age (hazard ratio [HR], 1.13; 95% CI, 1.01-1.26), total number of nodes examined (HR, 1.05; 95% CI, 1.01-1.10), and number of sentinel lymph nodes examined (HR, 1.45; 95% CI, 1.01-2.09) were all significantly associated with increased recurrence-free survival. Tumor depth, extracapsular spread, number of nodes positive, prior SLNB, extent of lymphadenectomy, and adjuvant therapy were not significant. Conclusions and Relevance: Limiting the extent of lymphadenectomy with frequent use of adjuvant radiation therapy is effective in achieving regional control of head and neck melanoma with cervical metastases.

Goehring, A., Lee, C. H., Wang, K. H., Michel, J. C., Claxton, D. P., Baconguis, I., et al. (2014). Screening and large-scale expression of membrane proteins in mammalian cells for structural studies. *Nature Protocols, 9*(11), 2574-2585.

Structural, biochemical and biophysical studies of eukaryotic membrane proteins are often hampered by difficulties in overexpression of the candidate molecule. Baculovirus transduction of mammalian cells (BacMam), although a powerful method to heterologously express membrane proteins, can be cumbersome for screening and expression of multiple constructs. We therefore developed plasmid Eric Gouaux (pEG) BacMam, a vector optimized for use in screening assays, as well as for efficient production of baculovirus and robust expression of the target protein. In this protocol, we show how to use small-scale transient transfection and fluorescence-detection size-exclusion chromatography (FSEC) experiments using a GFP-His8-tagged candidate protein to screen for monodispersity and expression level. Once promising candidates are identified, we describe how to generate baculovirus, transduce HEK293S GnTI(-) (N-acetylglucosaminyltransferase I-negative) cells in suspension culture and overexpress the

candidate protein. We have used these methods to prepare pure samples of chicken acid-sensing ion channel 1a (cASIC1) and Caenorhabditis elegans glutamate-gated chloride channel (GluCl) for X-ray crystallography, demonstrating how to rapidly and efficiently screen hundreds of constructs and accomplish large-scale expression in 4-6 weeks.

Goetz, J. J., Martin, G. M., Chowdhury, R., & Trimarchi, J. M. (2014). Onecut1 and Onecut2 play critical roles in the development of the mouse retina. *Plos One, 9*(10)

The entire repertoire of intrinsic factors that control the cell fate determination process of specific retinal neurons has yet to be fully identified. Single cell transcriptome profiling experiments of retinal progenitor cells revealed considerable gene expression heterogeneity between individual cells, especially among different classes of transcription factors. In this study, we show that two of those factors, Onecut1 and Onecut2, are expressed during mouse retinal development. Using mice that are deficient for each of these transcription factors, we further demonstrate a significant loss (~70-80%) of horizontal cells in the absence of either of these proteins, while the other retinal cells appear at normal numbers. Microarray profiling experiments performed on knockout retinas revealed defects in horizontal cell genes as early as E14.5. Additional profiling assays showed an upregulation of several stress response genes in the adult Onecut2 knockout, suggesting that the integrity of the retina is compromised in the absence of normal numbers of horizontal cells. Interestingly, melanopsin, the gene coding for the photopigment found in photosensitive ganglion cells, was observed to be upregulated in Onecut1 deficient retinas, pointing to a possible regulatory role for Onecut1. Taken together, our data show that similar to Onecut1, Onecut2 is also necessary for the formation of normal numbers of horizontal cells in the developing retina.

Gönen, M., & Margolin, A. A. (2014). Kernelized Bayesian transfer learning. *28th AAAI Conference on Artificial Intelligence, AAAI 2014, 26th Innovative Applications of Artificial Intelligence Conference, IAAI 2014 and the 5th Symposium on Educational Advances in Artificial Intelligence, EAAI 2014, , 3.* pp. 1831-1839.

Transfer learning considers related but distinct tasks defined on heterogenous domains and tries to transfer knowledge between these tasks to improve generalization performance. It is

particularly useful when we do not have sufficient amount of labeled training data in some tasks, which may be very costly, laborious, or even infeasible to obtain. Instead, learning the tasks jointly enables us to effectively increase the amount of labeled training data. In this paper, we formulate a kernelized Bayesian transfer learning framework that is a principled combination of kernel-based dimensionality reduction models with task-specific projection matrices to find a shared subspace and a coupled classification model for all of the tasks in this subspace. Our two main contributions are: (i) two novel probabilistic models for binary and multiclass classification, and (ii) very efficient variational approximation procedures for these models. We illustrate the generalization performance of our algorithms on two different applications. In computer vision experiments, our method outperforms the state-of-the-art algorithms on nine out of 12 benchmark supervised domain adaptation experiments defined on two object recognition data sets. In cancer biology experiments, we use our algorithm to predict mutation status of important cancer genes from gene expression profiles using two distinct cancer populations, namely, patient-derived primary tumor data and in-vitro-derived cancer cell line data. We show that we can increase our generalization performance on primary tumors using cell lines as an auxiliary data source.

Goode, T. D., Carter-Pokras, O. D., Horner-Johnson, W., & Yee, S. (2014). Parallel tracks: Reflections on the need for collaborative health disparities research on race/ethnicity and disability. *Medical Care, 52*(10 Suppl 3), S3-8.

Public policy driving health disparities research has overwhelmingly focused on racial and ethnic populations other than non-Hispanic whites; these groups have historically been and continue to be disproportionately impacted by health disparities. Only recently has public policy focused on the inclusion of people with disabilities as a distinct health disparities population. These 2 areas of research have traveled parallel paths with little recognition of the health disparities that affect people at the intersection of race, ethnicity, and disability. This commentary reflects on the history, foci, and current status of these 2 separate tracks of health disparities research. We conclude the commentary with suggestions for merging the 2 tracks to develop research that addresses both disability as well as race and ethnicity.

Goodrich, E., Wahbeh, H., Mooney, A., Miller, M., & Oken, B. S. (2014). Teaching mindfulness meditation to adults with severe speech and physical impairments: An exploratory study. *Neuropsychological Rehabilitation,* , 1-25.

People with severe speech and physical impairments may benefit from mindfulness meditation training because it has the potential to enhance their ability to cope with anxiety, depression and pain and improve their attentional capacity to use brain-computer interface systems. Seven adults with severe speech and physical impairments (SSPI) - defined as speech that is understood less than 25% of the time and/or severely reduced hand function for writing/typing - participated in this exploratory, uncontrolled intervention study. The objectives were to describe the development and implementation of a six-week mindfulness meditation intervention and to identify feasible outcome measures in this population. The weekly intervention was delivered by an instructor in the participant's home, and participants were encouraged to practise daily using audio recordings. The objective adherence to home practice was 10.2 minutes per day. Exploratory outcome measures were an n-back working memory task, the Attention Process Training-II Attention Questionnaire, the Pittsburgh Sleep Quality Index, the Perceived Stress Scale, the Positive and Negative Affect Schedule, and a qualitative feedback survey. There were no statistically significant pre-post results in this small sample, yet administration of the measures proved feasible, and qualitative reports were overall positive. Obstacles to teaching mindfulness meditation to persons with SSPI are reported, and solutions are proposed.

Hadd, A., & Perona, J. J. (2014). Recoding aminoacyl-tRNA synthetases for synthetic biology by rational protein-RNA engineering. *ACS Chemical Biology,*

We have taken a rational approach to redesigning the amino acid binding and aminoacyl-tRNA pairing specificities of bacterial glutaminyl-tRNA synthetase. The four-stage engineering incorporates generalizable design principles and improves the pairing efficiency of noncognate glutamate with tRNAGln by over 105-fold compared to the wild-type enzyme. Better optimized designs of the protein-RNA complex include substantial reengineering of the globular core region of the tRNA, demonstrating a role for specific tRNA nucleotides in specifying the identity of the genetically encoded amino acid. Principles emerging from this engineering effort open new prospects for combining rational and genetic selection approaches to design novel aminoacyl-

tRNA synthetases that ligate noncanonical amino acids onto tRNAs. This will facilitate reconstruction of the cellular translation apparatus for applications in synthetic biology.

Han, J. K., Forwith, K. D., Smith, T. L., Kern, R. C., Brown, W. J., Miller, S. K., et al. (2014). RESOLVE: A randomized, controlled, blinded study of bioabsorbable steroid-eluting sinus implants for in-office treatment of recurrent sinonasal polyposis. *International Forum of Allergy and Rhinology,*

Background: Patients with recurrent sinonasal polyposis after endoscopic sinus surgery (ESS) have limited treatment options. This study evaluated the safety and efficacy of a bioabsorbable steroid-eluting implant with 1350 μg of mometasone furoate for its ability to dilate obstructed ethmoid sinuses, reduce polyposis, and reestablish sinus patency. Methods: This was a randomized, controlled, blinded study including 100 patients chronic rhinosinusitis with nasal polyposis (CRSwNP) refractory to medical therapy and considered candidates for revision ESS. Follow-up included endoscopic grading by investigators and patient-reported outcomes. Results: Treated patients (n = 53; age as mean ± standard deviation [SD] 47.8 ± 12.6 years; 55% male) underwent in-office bilateral placement. Control patients (n = 47; age 51.6 ± 13.1 years; 66% male) underwent a sham procedure. At 3 months, treated patients experienced a significant reduction in bilateral polyp grade (p = 0.0269) and ethmoid sinus obstruction (p = 0.0001) compared to controls. Treated patients also experienced a 2-fold improvement in the mean nasal obstruction/congestion score (-1.33 ± 1.47 vs -0.67 ± 1.45; p = 0.1365). This improvement reached statistical significance (p = 0.025) in patients with greater polyp burden (grade ≥2 bilaterally; n = 74). At 3 months, 53% of treated patients compared to only 23% of controls were no longer indicated for repeat ESS. There was no serious adverse event or clinically significant increases in intraocular pressure or cataract formation. Conclusion: The symptomatic improvement and statistically significant reduction in polyp grade and ethmoid sinus obstruction supported the efficacy of the steroid-eluting implant for in-office treatment of CRS patient with recurrent polyposis after ESS. The study results demonstrated that the steroid-eluting implant represents a safe and effective alternative to current management for this patient population.

Heintzman, J., Gold, R., Bailey, S. R., & DeVoe, J. E. (2014). The oregon experiment re-examined: The need to bolster primary care. *BMJ (Clinical Research Ed.), 349*, g5976.

Hernandez, A. E., Marcus, M. D., Hirst, K., Faith, M. S., Goldberg, L., & Treviño, R. P. (2014). Impact of implementation and conduct of the HEALTHY primary prevention trial on student performance. *American Journal of Health Promotion, 29*(1), 55-58.

Purpose. To determine whether a school-wide intervention program to reduce risk factors for type 2 diabetes (T2D) affected student achievement, rates of disciplinary actions, and attendance rates. Copyright Design. The HEALTHY primary prevention trial was designed to evaluate a comprehensive schoolbased intervention to reduce factors for T2D, especially overweight and obesity. Students were followed up from beginning of sixth grade (Fall 2006) through end of eighth grade (Spring 2009). Setting. Forty-two middle schools at seven U.S. sites. Subjects. Schools were randomized in equal numbers at each site to intervention (21 schools, 2307 students) or control (21 schools, 2296 students). Intervention. An integrated school-wide program that focused on (1) foods and beverages, (2) physical education, (3) classroom-based behavior change and education, and (4) social marketing communication and promotional campaigns. Measures. Aggregate (grade- and school-wide) test performance (passing rate), attendance, and referrals for disciplinary actions. Analysis. Descriptive statistics and tests of intervention versus control using mixed linear models methods to adjust for the clustering of students within schools. Results. There were no differences between intervention and control schools in test performance for mathematics ($p = .7835$) or reading ($p = .6387$), attendance ($p = .5819$), or referrals for disciplinary action ($p = .8671$). Conclusion. The comprehensive HEALTHY intervention and associated research procedures did not negatively impact student achievement test scores, attendance, or referrals for disciplinary action.

Herzig, D. O., & Tsikitis, V. L. (2014). Molecular markers for colon diagnosis, prognosis and targeted therapy. *Journal of Surgical Oncology,*

Colorectal adenocarcinoma (CRC), the second leading cancer-related death in the United States, remains a global public health issue. Sporadic CRC is considered the result of sequential mucosal changes from normal colonic mucosa to adenocarcinoma. Efforts in understanding the molecular

pathways leading to CRC tumorigenesis may lead to identifying novel, individually tailored therapeutic targets for patients. In this review, we focus on well-published prognostic and predictive markers in CRC and examine their role in clinical practice. J. Surg. Oncol. (c) 2014 Wiley Periodicals, Inc.

Hnenny, L., Sabry, H. A., Raskin, J. S., Liu, J. J., Roundy, N. E., & Dogan, A. (2014). Migrating lumbar intrathecal catheter fragment associated with intracranial subarachnoid hemorrhage. *Journal of Neurosurgery.Spine,* , 1-5.

Intrathecal catheter placement into the lumbar cistern has varied indications, including drug delivery and CSF diversion. These Silastic catheters are elastic and durable; however, catheter-associated malfunctions are well reported in the literature. Fractured catheters are managed with some variability, but entirely intradural retained fragments are often managed conservatively with observation. The authors describe a case of a 70-year-old man with an implanted intrathecal morphine pump for failed back surgery syndrome who presented to an outside hospital with a history of headache, neck pain, nausea, and photophobia of 3 days' duration. He also described mild weakness and intermittent numbness of both legs. Unenhanced head CT demonstrated subarachnoid hemorrhage (SAH). A right C-5 hemilaminectomy was performed. This case is unique in that there was no indication that the lumbar intrathecal catheter had fractured prior to the patient's presentation with SAH. This case demonstrates that intrathecal catheter fragments are mobile and can precipitate intracranial morbidity. Extrication of known fragments is safe and should be attempted to prevent further neurosurgical morbidity.

Hoffman, B. D. (2014). Using self-determination theory to improve residency training: Learning to make omelets without breaking eggs. *Academic Medicine : Journal of the Association of American Medical Colleges,*

An inherent tension exists in clinical training between supervising learners to ensure quality and patient safety, and allowing learners to practice independently to gain experience. In this issue of Academic Medicine, Biondi and colleagues discuss this tension, highlighting the disconnect between faculty and resident perceptions of autonomous practice for housestaff. They report that each group perceives itself as more competent in its role than does the other group. Their work

leads us to consider how medical educators might safely and effectively transform the learning process.Self-determination theory (SDT) holds that there is a human tendency to develop toward self-directed and autonomous regulation of behavior. This development of intrinsic motivation is governed by the complex relationships among autonomy, competence, and relatedness as well as educational content and the learning milieu. Applying an SDT framework to their findings, Biondi and colleagues report that faculty desire from residents the evidence of internal motivation and demonstration of competence and self-confidence that will allow faculty to entrust learners with autonomy. They conclude, however, that these are qualities that faculty find lacking in many residents.To optimize the balance between autonomy and supervision, this Commentary's author proposes the use of "scaffolding," a construct from developmental psychology. In the scaffolding model, the role of teachers is to support the learner's development and to provide support structures to help the learner get to the next stage of entrustment and competence. Achieving a balance is essential to providing the best patient care now and in the future.

Horner-Johnson, W., & Dobbertin, K. (2014). Usual source of care and unmet health care needs: Interaction of disability with race and ethnicity. *Medical Care, 52*(10 Suppl 3), S40-50. BACKGROUND: Having a usual source of care (USC) and having unmet health care needs have been found to vary in relation to sociodemographic differences in the US population, including race, ethnicity, and disability status. People in underserved racial and ethnic groups who also have a disability may experience a complex mix of health care advantages and disparities. However, little is known about this intersection. OBJECTIVE: To determine how disability status, combined with membership in an underserved racial or ethnic group, is associated with having a USC and unmet health care needs. METHODS: We conducted multivariate regression analyses of 2002-2010 data from the Medical Expenditure Panel Survey, focused on working age adults (18-64 y). RESULTS: Although most racial and ethnic groups were less likely to have a USC than non-Hispanic whites, people with disabilities were more likely to have a USC; Hispanics with basic activity limitations were the only disability group with elevated odds of lacking a USC. Conversely, disability was strongly associated with unmet health care needs, but we did not find inflated impacts of both having a disability and belonging to an underserved racial or ethnic group. CONCLUSIONS: We found limited evidence of interaction or additive effects of disability

and race/ethnicity but did confirm separate disparities for each. Ongoing research is needed to track both disability-related and racial/ethnic disparities, to determine whether increased insurance coverage, provider training, care coordination, and other efforts under the Affordable Care Act lead to reductions in disparities.

Horner-Johnson, W., Fujiura, G. T., & Goode, T. D. (2014). Promoting a new research agenda: Health disparities research at the intersection of disability, race, and ethnicity. *Medical Care, 52*(10 Suppl 3), S1-2.

BACKGROUND: Differences in access to and receipt of health care have been extensively documented across racial and ethnic groups. Similarly, a growing body of research has documented disparities between people with and without disabilities in obtaining needed health care. However, our understanding of the intersection of disability with race and ethnicity in health care is very limited. OBJECTIVES: The purpose of this supplement is to begin to bridge the gap between research on racial and ethnic health disparities and research on disability-related health disparities. RESULTS: The papers in this supplement examine evidence of racial and ethnic disparities within various populations of people with disabilities, and explore unique issues at the intersection of disability, race, and ethnicity. CONCLUSIONS: The studies in this issue provide a starting point, and are intended to serve as an impetus for building a more robust literature on health care issues impacting the expanding segment of United States population that both experience disability and belong to racial and ethnic groups other than non-Hispanic white.

Hu, W., Whitten, B., Sedgley, C., & Svec, T. Effect of three NiTi files on transportation of the apical foramen. *International Endodontic Journal, 47*(11), 1064-1071.

Aim: To compare landed and nonlanded rotary file overinstrumentation on transportation of the apical foramen in the curved canals of extracted teeth. Methodology: Severely curved molar root canals (n = 45) were distributed into three equal groups (n = 15) according to angle (mean 54°) and radius of curvature (mean 5 mm). Canals were overinstrumented 0.5 mm beyond the foramen to a size 35 master apical file using landed (ProFile ISO), nonlanded (ProFile Vortex) or nonlanded, reduced shape memory (Vortex Blue) files. Post-instrumentation images of the apical foramen were compared with pre-instrumentation control images for differences in area,

circularity and ratio of Feret's diameters. Groups were compared using anova or Kruskal-Wallis tests with significance of P < 0.05. Results: There were no differences between pre-treatment groups in the parameters tested. All groups demonstrated alterations in the geometry of the apical foramen. There were no significant differences between ProFile ISO, ProFile Vortex or Vortex Blue in area, circularity and ratio of Feret's diameters. Conclusions: Landed, nonlanded and nonlanded reduced shape memory files all produced transportation of the apical foramen when overinstrumented by 0.5 mm in severely curved canals. There was no difference between these file systems with regard to the degree of this effect.

Huang, J. H., Saharan, S., McCammond, A., & Balaji, S. (2014). Belhassen tachycardia in a 19-month-old child. *The Journal of Pediatrics,*

Hunter, J. G. (2014). Antireflux surgery for dysplastic barrett's esophagus. *World Journal of Surgery,*

Iossifov, I., O'Roak, B. J., Sanders, S. J., Ronemus, M., Krumm, N., Levy, D., et al. (2014). The contribution of de novo coding mutations to autism spectrum disorder. *Nature,*
Whole exome sequencing has proven to be a powerful tool for understanding the genetic architecture of human disease. Here we apply it to more than 2,500 simplex families, each having a child with an autistic spectrum disorder. By comparing affected to unaffected siblings, we show that 13% of de novo missense mutations and 43% of de novo likely gene-disrupting (LGD) mutations contribute to 12% and 9% of diagnoses, respectively. Including copy number variants, coding de novo mutations contribute to about 30% of all simplex and 45% of female diagnoses. Almost all LGD mutations occur opposite wild-type alleles. LGD targets in affected females significantly overlap the targets in males of lower intelligence quotient (IQ), but neither overlaps significantly with targets in males of higher IQ. We estimate that LGD mutation in about 400 genes can contribute to the joint class of affected females and males of lower IQ, with an overlapping and similar number of genes vulnerable to contributory missense mutation. LGD targets in the joint class overlap with published targets for intellectual disability and schizophrenia, and are enriched for chromatin modifiers, FMRP-associated genes and embryonically expressed genes. Most of the significance for the latter comes from affected females.

Jacobs, P. G., El Youssef, J., Castle, J., Bakhtiani, P., Branigan, D., Breen, M., et al. (2014). Automated control of an adaptive bihormonal, dual-sensor artificial pancreas and evaluation during inpatient studies. *IEEE Transactions on Biomedical Engineering, 61*(10), 2569-2581.

Automated control of blood glucose in patients with type-1 diabetes has not yet been fully implemented. The aim of this study was to design and clinically evaluate a system that integrates a control algorithm with off-the-shelf subcutaneous sensors and pumps to automate the delivery of the hormones glucagon and insulin in response to continuous glucose sensor measurements. The automated component of the system runs an adaptive proportional derivative control algorithm which determines hormone delivery rates based on the sensed glucose measurements and the meal announcements by the patient. We provide details about the system design and the control algorithm, which incorporates both a fading memory proportional derivative controller (FMPD) and an adaptive system for estimating changing sensitivity to insulin based on a glucoregulatory model of insulin action. For an inpatient study carried out in eight subjects using Dexcom SEVEN PLUS sensors, prestudy HbA1c averaged 7.6, which translates to an estimated average glucose of 171 mg/dL. In contrast, during use of the automated system, after initial stabilization, glucose averaged 145 mg/dL and subjects were kept within the euglycemic range (between 70 and 180 mg/dL) for 73.1% of the time, indicating improved glycemic control. A further study on five additional subjects in which we used a newer and more reliable glucose sensor (Dexcom G4 PLATINUM) and made improvements to the insulin and glucagon pump communication system resulted in elimination of hypoglycemic events. For this G4 study, the system was able to maintain subjects' glucose levels within the near-euglycemic range for 71.6% of the study duration and the mean venous glucose level was 151 mg/dL.

Jacques, S. L. (2014). *Coupling 3D monte carlo light transport in optically heterogeneous tissues to photoacoustic signal generation* Elsevier GmbH.

The generation of photoacoustic signals for imaging objects embedded within tissues is dependent on how well light can penetrate to and deposit energy within an optically absorbing object, such as a blood vessel. This report couples a 3D Monte Carlo simulation of light transport to stress wave generation to predict the acoustic signals received by a detector at the tissue surface. The Monte Carlo simulation allows modeling of optically heterogeneous tissues, and a

simple MATLAB™ acoustic algorithm predicts signals reaching a surface detector. An example simulation considers a skin with a pigmented epidermis, a dermis with a background blood perfusion, and a 500-μm-dia. blood vessel centered at a 1-mm depth in the skin. The simulation yields acoustic signals received by a surface detector, which are generated by a pulsed 532-nm laser exposure before and after inserting the blood vessel. A MATLAB™ version of the acoustic algorithm and a link to the 3D Monte Carlo website are provided.

Jiang, M., Wang, Q., Karasawa, T., Koo, J. W., Li, H., & Steyger, P. S. (2014). Sodium-glucose transporter-2 (SGLT2; SLC5A2) enhances cellular uptake of aminoglycosides. *PloS One, 9*(9), e108941.

Aminoglycoside antibiotics, like gentamicin, continue to be clinically essential worldwide to treat life-threatening bacterial infections. Yet, the ototoxic and nephrotoxic side-effects of these drugs remain serious complications. A major site of gentamicin uptake and toxicity resides within kidney proximal tubules that also heavily express electrogenic sodium-glucose transporter-2 (SGLT2; SLC5A2) in vivo. We hypothesized that SGLT2 traffics gentamicin, and promotes cellular toxicity. We confirmed in vitro expression of SGLT2 in proximal tubule-derived KPT2 cells, and absence in distal tubule-derived KDT3 cells. D-glucose competitively decreased the uptake of 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose (2-NBDG), a fluorescent analog of glucose, and fluorescently-tagged gentamicin (GTTR) by KPT2 cells. Phlorizin, an SGLT2 antagonist, strongly inhibited uptake of 2-NBDG and GTTR by KPT2 cells in a dose- and time-dependent manner. GTTR uptake was elevated in KDT3 cells transfected with SGLT2 (compared to controls); and this enhanced uptake was attenuated by phlorizin. Knock-down of SGLT2 expression by siRNA reduced gentamicin-induced cytotoxicity. In vivo, SGLT2 was robustly expressed in kidney proximal tubule cells of heterozygous, but not null, mice. Phlorizin decreased GTTR uptake by kidney proximal tubule cells in Sglt2+/- mice, but not in Sglt2-/- mice. However, serum GTTR levels were elevated in Sglt2-/- mice compared to Sglt2+/- mice, and in phlorizin-treated Sglt2+/- mice compared to vehicle-treated Sglt2+/- mice. Loss of SGLT2 function by antagonism or by gene deletion did not affect gentamicin cochlear loading or auditory function. Phlorizin did not protect wild-type mice from kanamycin-induced ototoxicity. We conclude that SGLT2 can traffic gentamicin and contribute to gentamicin-induced cytotoxicity.

John McConnell, K., Marie Chang, A., Cohen, D. J., Wallace, N., Chernew, M. E., Kautz, G., et al. (2014). Oregon's medicaid transformation: An innovative approach to holding a health system accountable for spending growth. *Healthcare, 2*(3), 163-167.

In 2012, Oregon initiated a significant transformation of its Medicaid program, catalyzed in part through an innovative arrangement with the Centers for Medicare and Medicaid Services (CMS), which provided an upfront investment of $1.9 billion to the state. In exchange, Oregon agreed to reduce the rate of Medicaid spending by 2 percentage points without degrading quality. A failure to meet these targets triggers penalties on the order of hundreds of millions of dollars from CMS. We describe the novel arrangement with CMS and how the CCO structure compares to Accountable Care Organizations (ACOs) and managed care organizations (MCOs).

Johnson, D. A., Barkun, A. N., Cohen, L. B., Dominitz, J. A., Kaltenbach, T., Martel, M., et al. (2014). Optimizing adequacy of bowel cleansing for colonoscopy: Recommendations from the U.S. multi-society task force on colorectal cancer. *Gastrointestinal Endoscopy, 80*(4), 543-562.

Johnson, D. A., Barkun, A. N., Cohen, L. B., Dominitz, J. A., Kaltenbach, T., Martel, M., et al. (2014). Optimizing adequacy of bowel cleansing for colonoscopy: Recommendations from the US multi-society task force on colorectal cancer. *The American Journal of Gastroenterology, 109*(10), 1528-1545.

Jones Brunette, A. M., & Farrens, D. L. (2014). Distance mapping in proteins using fluorescence spectroscopy: Tyrosine, like tryptophan, quenches bimane fluorescence in a distance-dependent manner. *Biochemistry, 53*(40), 6290-6301.

Tryptophan-induced quenching of fluorophores (TrIQ) uses intramolecular fluorescence quenching to assess distances in proteins too small (<15 A) to be easily probed by traditional Forster resonance energy transfer methods. A powerful aspect of TrIQ is its ability to obtain an ultrafast snapshot of a protein conformation, by identifying "static quenching" (contact between the Trp and probe at the moment of light excitation). Here we report new advances in this site-directed fluorescence labeling (SDFL) approach, gleaned from recent studies of T4 lysozyme (T4L). First, we show that like TrIQ, tyrosine-induced quenching (TyrIQ) occurs for the fluorophore bimane in a distance-dependent fashion, although with some key differences. The Tyr "sphere of

quenching" for bimane (</=10 A) is smaller than for Trp (</=15 A, Calpha-Calpha distance), and the size difference between the quenching residue (Tyr) and control (Phe) differs by only a hydroxyl group. Second, we show how TrIQ and TyrIQ can be used together to assess the magnitude and energetics of a protein movement. In these studies, we placed a bimane (probe) and Trp or Tyr (quencher) on opposite ends of a "hinge" in T4L and conducted TrIQ and TyrIQ measurements. Our results are consistent with an approximately 5 A change in Calpha-Calpha distances between these sites upon substrate binding, in agreement with the crystal structures. Subsequent Arrhenius analysis suggests the activation energy barrier (Ea) to this movement is relatively low (approximately 1.5-2.5 kcal/mol). Together, these results demonstrate that TyrIQ, used together with TrIQ, significantly expands the power of quenching-based distance mapping SDFL studies.

Jones, D. (2014). Young woman with abdominal pain. *Annals of Emergency Medicine, 64*(4), 423-425.

Kahn, P., Herfort, L., Peterson, T. D., & Zuber, P. Discovery of a katablepharis sp. in the columbia river estuary that is abundant during the spring and bears a unique large ribosomal subunit sequence element. *Microbiologyopen, 3*(5), 764-776.

Heterotrophic protists play significant roles in pelagic food webs as bacterivorous and herbivorous consumers. However, heterotrophic protists-unlike autotrophic ones-are often difficult to track since they tend to lack features such as photosynthetic pigments that allow for remote sensing or for bulk characterization. Difficulty in the identification of heterotrophic protists has often resulted in lumping them into broad groups, but there is a strong need to develop methods that increase the spatial and temporal resolution of observations applied to particular organisms in order to discover the drivers of population structure and ecological function. In surveys of small subunit rRNA, gene (SSU) sequences of microbial eukaryotes from the Columbia River to the Pacific Ocean, the heterotrophic flagellate Katablepharis sp. were found to dominate protist assemblages (including autotrophic and heterotrophic fractions) in the spring, prior to the freshet. We discovered a 332 base pair unique sequence element (USE) insertion in the large subunit rRNA gene (28S) that is not present in other katablepharids or in any other eukaryote. Using this USE, we were able to detect Katablepharis within mixed assemblages in river, estuarine, and oceanic

samples and determine spatial and temporal patterns in absolute abundance through quantitative PCR and fluorescence in situ hybridization. Given their high abundance and repeatable temporal patterns of occurrence, we hypothesize that the Columbia River Estuary Katablepharis (Katablepharis CRE) plays an important role in estuarine biogeochemical and ecosystem function.

Kallmes, D. F., Hanel, R., Lopes, D., Boccardi, E., Bonafe, A., Cekirge, S., et al. (2014). International retrospective study of the pipeline embolization device: A multicenter aneurysm treatment study. *AJNR.American Journal of Neuroradiology,*

BACKGROUND AND PURPOSE: Flow diverters are increasingly used in the endovascular treatment of intracranial aneurysms. Our aim was to determine neurologic complication rates following Pipeline Embolization Device placement for intracranial aneurysm treatment in a real-world setting. MATERIALS AND METHODS: We retrospectively evaluated all patients with intracranial aneurysms treated with the Pipeline Embolization Device between July 2008 and February 2013 in 17 centers worldwide. We defined 4 subgroups: internal carotid artery aneurysms of >/=10 mm, ICA aneurysms of <10 mm, other anterior circulation aneurysms, and posterior circulation aneurysms. Neurologic complications included spontaneous rupture, intracranial hemorrhage, ischemic stroke, permanent cranial neuropathy, and mortality. Comparisons were made with t tests or ANOVAs for continuous variables and the Pearson chi2 or Fisher exact test for categoric variables. RESULTS: In total, 793 patients with 906 aneurysms were included. The neurologic morbidity and mortality rate was 8.4% (67/793), highest in the posterior circulation group (16.4%, 9/55) and lowest in the ICA <10-mm group (4.8%, 14/294) (P = .01). The spontaneous rupture rate was 0.6% (5/793). The intracranial hemorrhage rate was 2.4% (19/793). Ischemic stroke rates were 4.7% (37/793), highest in patients with posterior circulation aneurysms (7.3%, 4/55) and lowest in the ICA <10-mm group (2.7%, 8/294) (P = .16). Neurologic mortality was 3.8% (30/793), highest in the posterior circulation group (10.9%, 6/55) and lowest in the anterior circulation ICA <10-mm group (1.4%, 4/294) (P < .01). CONCLUSIONS: Aneurysm treatment with the Pipeline Embolization Device is associated with the lowest complication rates when used to treat small ICA aneurysms. Procedure-related morbidity and mortality are higher in the treatment of posterior circulation and giant aneurysms.

Kang, S. S., Kurti, A., Fair, D. A., & Fryer, J. D. (2014). Dietary intervention rescues maternal obesity induced behavior deficits and neuroinflammation in offspring. *Journal of Neuroinflammation, 11*(1)

Obesity induces a low-grade inflammatory state and has been associated with behavioral and cognitive alterations. Importantly, maternal environmental insults can adversely impact subsequent offspring behavior and have been linked with neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (AHDH). It is unknown if maternal obesity significantly alters offspring sociability, a key ASD feature, and if altering maternal diet will provide an efficacious intervention paradigm for behavioral deficits. Here we investigated the impact of maternal high fat diet (HFD) and maternal dietary intervention during lactation on offspring behavior and brain inflammation in mice. We found that maternal HFD increased anxiety and decreased sociability in female offspring. Additionally, female offspring from HFD-fed dams also exhibited increased brain IL-1β and TNFα and microglial activation. Importantly, maternal dietary intervention during lactation was sufficient to alleviate social deficits and brain inflammation. Maternal obesity during gestation alone was sufficient to increase hyperactivity in male offspring, a phenotype that was not ameliorated by dietary intervention. These data suggest that maternal HFD acts as a prenatal/perinatal insult that significantly impacts offspring behavior and inflammation and that dietary intervention during lactation may be an easily translatable, efficacious intervention to offset some of these manifestations.

Kansagara, D., Papak, J., Pasha, A. S., O'Neil, M., Freeman, M., Relevo, R., et al. (2014). Screening for hepatocellular carcinoma in chronic liver disease: A systematic review. *Annals of Internal Medicine, 161*(4), 261-269.

Guidelines recommend routine screening for hepatocellular carcinoma (HCC) in high-risk patients, but the strength of evidence supporting these recommendations is unclear. Purpose: To review the benefits and harms of HCC screening in patients with chronic liver disease. Data Sources: MEDLINE, PsycINFO, and ClinicalTrials.gov from inception to April 2014; Cochrane databases to June 2013; reference lists; and technical advisors. Study Selection: English-language trials and observational studies comparing screening versus no screening, studies of harms, and trials

comparing different screening intervals. Data Extraction: Mortality and adverse events were the outcomes of interest. Individual-study quality and the overall strength of evidence were dual-reviewed using published criteria. Data Synthesis: Of 13 801 citations, 22 studies met inclusion criteria. The overall strength of evidence on the effects of screening was very low. One large trial of patients with hepatitis B found decreased HCC mortality with periodic ultrasonographic screening (rate ratio, 0.63 [95% CI, 0.41 to 0.98]), but the study was limited by methodological flaws. Another trial in patients with hepatitis B found no survival benefit with periodic α-fetoprotein screening. In 18 observational studies, screened patients had earlier-stage HCC than clinically diagnosed patients, but lead- and length-time biases confounded the effects on mortality. Two trials found no survival differences between shorter (3- to 4-month) and longer (6- to 12-month) screening intervals. Harms of screening were not well-studied. Limitations: Only English-language studies were included. The evidence base is limited by methodological issues and a paucity of trials. Conclusion: There is very-low-strength evidence about the effects of HCC screening on mortality in patients with chronic liver disease. Screening tests can identify early-stage HCC, but whether systematic screening leads to a survival advantage over clinical diagnosis is uncertain.

Kardos, G. R., Dai, M. -., & Robertson, G. P. Growth inhibitory effects of large subunit ribosomal proteins in melanoma. *Pigment Cell and Melanoma Research, 27*(5), 801-812.

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

cycle arrest and decreased protein translation. Thus, targeting certain category 2 RPL proteins can inhibit melanoma tumor development mediated through the MDM2-p53 pathway.

Keene, D. R., Tufa, S. F., Wong, M. H., Smith, N. R., Sakai, L. Y., & Horton, W. A. (2014). *Correlation of the same fields imaged in the TEM, confocal, LM, and microCT by image registration: From specimen preparation to displaying a final composite image* Academic Press Inc.

Correlated imaging is the process of imaging a specimen with two complementary modalities and then registering and overlaying the fields obtained in each modality to create a composite view. One of the images is made somewhat transparent, allowing detail in the underlying image to be visible and assisting in the registration of the two images. As an example, an image localizing a specific tissue component by fluorescence may be overlaid atop a TEM image of the same field. The resulting composite image would demonstrate specific ultrastructural features in the high-resolution TEM field, which are colorized in the overlay. Other examples include composites from MicroCT or soft X-ray images overlaid atop light microscopy or TEM images. Automated image registration may be facilitated by a variety of sophisticated computer programs utilized by high-throughput laboratories. This chapter is meant for the more occasional user wishing to align images manually. ImageJ is a public domain, image processing program developed at the National Institutes of Health and is available to anyone as a free download. ImageJ performs marvelously well for the purpose of image registration; therefore, step-by-step instructions are included here. Specimen handling, including fixation and choice of embedding media, is not straightforward for correlative imaging. A step-by-step description of the protocols which work in our laboratory is included for simultaneous localization in LM, EM and micro-CT, as well as maintaining GFP emission in tissue embedded for TEM.

Kerns, S. L., Guevara-Aguirre, J., Andrew, S., Geng, J., Guevara, C., Guevara-Aguirre, M., et al. (2014). A novel variant in CDKN1C is associated with intrauterine growth restriction, short stature, and early-adulthood-onset diabetes. *The Journal of Clinical Endocrinology and Metabolism, 99*(10), E2117-22.

CONTEXT: CDKN1C, a cyclin-dependent kinase inhibitor and negative regulator of cellular proliferation, is paternally imprinted and has been shown to regulate beta-cell proliferation.

CDKN1C mutations are associated with growth disorders, including Beckwith-Wiedemann syndrome and IMAGe syndrome. OBJECTIVE: To investigate the genetic basis for a familial disorder characterized by intrauterine growth restriction, short stature, and early-adulthood-onset diabetes. DESIGN, SETTING, AND PARTICIPANTS: Genomic DNA samples (15 affected and 26 unaffected from a six-generation pedigree) were analyzed by genome-wide single nucleotide polymorphism arrays, whole exome and Sanger sequencing, and multiplex ligation-dependent probe amplification. MAIN OUTCOME MEASURE(S): Subjects were assessed for height, weight, adrenal gland size, ACTH, diabetes status, and testis volume. Linkage and sequence analyses were performed, and the identified genetic variant was functionally evaluated in reconstitution studies. RESULTS: The pedigree followed a paternally imprinted pattern of inheritance, and genetic linkage analysis identified a single significant 2.6-megabase locus on chromosome 11p15, within the imprinting center region 2. Multiplex ligation-dependent probe amplification did not detect copy number variants or methylation abnormalities. Whole exome sequencing revealed a single novel variant in the proliferating cell nuclear antigen-binding region of CDKN1C (c.842G>T, p.R281I) that co-segregated with affected status and, unlike variants found in IMAGe, did not entirely abrogate proliferating cell nuclear antigen binding. Clinical assessments revealed that affected individuals had low testicular volume but normal adrenal function. CONCLUSIONS: We report a novel CDKN1C mutation associated with features of IMAGe syndrome, but without adrenal insufficiency or metaphyseal dysplasia, and characterized by early-adulthood-onset diabetes. Our data expand the range of phenotypes observed with CDKN1C defects and suggest that CDKN1C mutations may represent a novel monogenic form of diabetes.

Kim, D. H., Rhee, J. C., Yeo, S., Shen, R., Lee, S. K., Lee, J. W., et al. (2014). Crucial roles of MLL3 and MLL4 as epigenetic switches of the hepatic circadian clock controlling bile acid homeostasis. *Hepatology (Baltimore, Md.),*

The histone H3-lysine-4 methyltransferase mixed-lineage leukemia-3 (MLL3) and its closest homolog MLL4 (aka KMT2D) belong to two homologous transcriptional coactivator complexes, named MLL3- and MLL4-complexes, respectively. We previously reported that MLL3 plays crucial roles in multiple metabolic processes. However, the physiological roles of MLL4 in metabolism and the relationship between MLL3 and MLL4 in metabolic gene regulation remained unclear. To

address these issues, we analyzed the phenotypes of newly generated MLL4 mutant mice, along with MLL3 mutant and MLL3;MLL4 compound mutant mice. We also performed comparative genome-wide transcriptome analyses in the livers of MLL3, MLL4 and MLL3;MLL4 mutant mice. These analyses revealed that MLL3- and MLL4-complexes are key epigenetic regulators of common metabolic processes and the hepatic circadian clock. Subsequent mechanistic analyses uncovered that MLL3/4-complexes function as pivotal coactivators of the circadian transcription factors retinoid-related orphan receptor-alpha and -gamma in the hepatic circadian clock. Consistent with disturbed hepatic clock gene expression in MLL4 mutant mice, we found that the rhythmic fluctuation of hepatic and serum bile acid levels over the circadian cycle is abolished in MLL4 mutant mice. Our analyses also demonstrate that MLL4 primarily impinges on hepatic bile acid production among several regulatory pathways to control bile acid homeostasis. Together, our results provide strong in vivo support for important roles of both MLL3 and MLL4 in similar metabolic pathways. Conclusion: Both MLL3- and MLL4-complexes act as major epigenetic regulators of diverse metabolic processes (including circadian control of bile acid homeostasis), and as critical transcriptional coactivators of the circadian transcription factors retinoid-related orphan receptors. (Hepatology 2014).

Kohler, S., Schoeneberg, U., Czeschik, J. C., Doelken, S. C., Hehir-Kwa, J. Y., Ibn-Salem, J., et al. (2014). Clinical interpretation of CNVs with cross-species phenotype data. *Journal of Medical Genetics, 51*(11), 766-772.

BACKGROUND: Clinical evaluation of CNVs identified via techniques such as array comparative genome hybridisation (aCGH) involves the inspection of lists of known and unknown duplications and deletions with the goal of distinguishing pathogenic from benign CNVs. A key step in this process is the comparison of the individual's phenotypic abnormalities with those associated with Mendelian disorders of the genes affected by the CNV. However, because often there is not much known about these human genes, an additional source of data that could be used is model organism phenotype data. Currently, almost 6000 genes in mouse and zebrafish are, when knocked out, associated with a phenotype in the model organism, but no disease is known to be caused by mutations in the human ortholog. Yet, searching model organism databases and comparing model organism phenotypes with patient phenotypes for identifying novel disease

genes and medical evaluation of CNVs is hindered by the difficulty in integrating phenotype information across species and the lack of appropriate software tools. METHODS: Here, we present an integrated ranking scheme based on phenotypic matching, degree of overlap with known benign or pathogenic CNVs and the haploinsufficiency score for the prioritisation of CNVs responsible for a patient's clinical findings. RESULTS: We show that this scheme leads to significant improvements compared with rankings that do not exploit phenotypic information. We provide a software tool called PhenogramViz, which supports phenotype-driven interpretation of aCGH findings based on multiple data sources, including the integrated cross-species phenotype ontology Uberpheno, in order to visualise gene-to-phenotype relations. CONCLUSIONS: Integrating and visualising cross-species phenotype information on the affected genes may help in routine diagnostics of CNVs.

Koilkonda, R. D., Yu, H., Talla, V., Porciatti, V., Feurer, W. J., Hauswirth, W. W., et al. (2014). LHON gene therapy vector prevents visual loss and optic neuropathy induced by G11778A mutant mitochondrial DNA: Biodistribution and toxicology profile. *Investigative Ophthalmology & Visual Science,*

Purpose: To demonstrate safety and efficacy of allotopic human ND4 for treatment of Leber's hereditary optic neuropathy (LHON) mouse model harboring G11778A mitochondrial mutation. Methods: We induced LHON in mice by intravitreal injection of mutant (G11778A) human ND4 DNA responsible for most cases of LHON that was directed to mitochondria using an AAV2 vector to which we appended a mitochondrial targeting sequence to the VP2 capsid. We then attempted rescue of visual loss using our test article (ScAAV2-P1ND4v2) containing a synthetic nuclear encoded G11778G ND4 gene that was allotopically expressed. Control mice were either un-injected or received AAV2-GFP or AAV2-mCherry. We performed RT-PCR and confocal microscopy at 2 weeks post injection. Pattern electroretinograms (PERGs), SD-OCT, histology and TEM were performed. For toxicology and biodistribution studies the test article was administered intravitreally to rats and rhesus macaques at different doses. Results: Mutant and wild-type ND4 were efficiently expressed in the mitochondria of retinal ganglion cells. Visual function assessed by PERGs and retinal structure by SD-OCT showed a significant rescue by the test article. Histology and ultrastructural analysis confirmed loss of RGCs and demise of axons was prevented

by ScAAV2-P1ND4v2. Rat and nonhuman primate biodistribution studies showed vector spread outside the injected eye into spleen and lymph nodes was minimal. Histopathology of tissues and organs including the eyes was comparable to uninfected and saline injected eyes. Conclusions: Allotopically expressed wild-type ND4 prevents the phenotype induced by G11778A mitochondrial DNA with a toxicology profile acceptable for testing in a phase I clinical trial.

Lahti, E. (2014). "Heart". *Journal of General Internal Medicine,*

Lam, R. K., England, A. H., Sheardy, A. T., Shih, O., Smith, J. W., Rizzuto, A. M., et al. (2014). The hydration structure of aqueous carbonic acid from X-ray absorption spectroscopy. *Chemical Physics Letters, 614*, 282-286.

Despite much effort, aqueous carbonic acid (H2CO3) remains poorly characterized because it is very short-lived. We describe the detection and characterization of aqueous H2CO3 by X-ray absorption spectroscopy, wherein protonation of a bicarbonate solution continuously generates the acid under ambient conditions. Accompanying first principles calculations of the carbon K-edge transitions facilitate spectral assignment and interpretation in terms of the H2CO3 π* orbital, which exhibits a small (0.2 eV), systematic blueshift relative to that of bicarbonate. These results establish the detailed hydration properties of this short-lived molecule and will thereby facilitate future studies of carbonate chemistry in biological and geological system.

Leach, J. M., Mancini, M., Peterka, R. J., Hayes, T. L., & Horak, F. B. (2014). Validating and calibrating the nintendo wii balance board to derive reliable center of pressure measures. *Sensors (Basel, Switzerland), 14*(10), 18244-18267.

The Nintendo Wii balance board (WBB) has generated significant interest in its application as a postural control measurement device in both the clinical and (basic, clinical, and rehabilitation) research domains. Although the WBB has been proposed as an alternative to the "gold standard" laboratory-grade force plate, additional research is necessary before the WBB can be considered a valid and reliable center of pressure (CoP) measurement device. In this study, we used the WBB and a laboratory-grade AMTI force plate (AFP) to simultaneously measure the CoP displacement of a controlled dynamic load, which has not been done before. A one-dimensional inverted pendulum was displaced at several different displacement angles and load heights to

simulate a variety of postural sway amplitudes and frequencies (<1 Hz). Twelve WBBs were tested to address the issue of inter-device variability. There was a significant effect of sway amplitude, frequency, and direction on the WBB's CoP measurement error, with an increase in error as both sway amplitude and frequency increased and a significantly greater error in the mediolateral (ML) (compared to the anteroposterior (AP)) sway direction. There was no difference in error across the 12 WBB's, supporting low inter-device variability. A linear calibration procedure was then implemented to correct the WBB's CoP signals and reduce measurement error. There was a significant effect of calibration on the WBB's CoP signal accuracy, with a significant reduction in CoP measurement error (quantified by root-mean-squared error) from 2-6 mm (before calibration) to 0.5-2 mm (after calibration). WBB-based CoP signal calibration also significantly reduced the percent error in derived (time-domain) CoP sway measures, from -10.5% (before calibration) to -0.05% (after calibration) (percent errors averaged across all sway measures and in both sway directions). In this study, we characterized the WBB's CoP measurement error under controlled, dynamic conditions and implemented a linear calibration procedure for WBB CoP signals that is recommended to reduce CoP measurement error and provide more reliable estimates of time-domain CoP measures. Despite our promising results, additional work is necessary to understand how our findings translate to the clinical and rehabilitation research domains. Once the WBB's CoP measurement error is fully characterized in human postural sway (which differs from our simulated postural sway in both amplitude and frequency content), it may be used to measure CoP displacement in situations where lower accuracy and precision is acceptable.

Lee, A., McCartney, S., Burbidge, C., Raslan, A. M., & Burchiel, K. (2014). Response. *Journal of Neurosurgery, 121*(4), 1004.

Lee, C. S., Hiatt, S. O., Denfeld, Q. E., Chien, C. V., Mudd, J. O., & Gelow, J. M. (2014). Gender-specific physical symptom biology in heart failure. *The Journal of Cardiovascular Nursing,* BACKGROUND:: There are several gender differences that may help explain the link between biology and symptoms in heart failure (HF). OBJECTIVE:: The aim of this study was to examine gender-specific relationships between objective measures of HF severity and physical symptoms.

METHODS:: Detailed clinical data, including left ventricular ejection fraction and left ventricular internal end-diastolic diameter, and HF-specific physical symptoms were collected as part of a prospective cohort study. Gender interaction terms were tested in linear regression models of physical symptoms. RESULTS:: The sample (101 women and 101 men) averaged 57 years of age and most participants (60%) had class III/IV HF. Larger left ventricle size was associated with better physical symptoms for women and worse physical symptoms for men. CONCLUSION:: Decreased ventricular compliance may result in worse physical HF symptoms for women and dilation of the ventricle may be a greater progenitor of symptoms for men with HF.

Lee, E. J., Allensworth, J. J., Clowers, J. S., & Rosenzweig, H. L. (2014). Aberrant interleukin-1 signalling does not increase susceptibility of mice to NOD2-dependent uveitis. *Clinical & Experimental Ophthalmology,*

BACKGROUND: NOD2 is the genetic cause of Blau syndrome, an autoinflammatory disease that manifests as coincident uveitis and arthritis. Since dysregulation of IL-1 signalling is considered a pathogenic mechanism in a number of related autoinflammatory conditions, we examined the extent to which unimpeded interleukin (IL)-1 signalling influences NOD2-dependent inflammation of the eye versus the joint. METHODS: Mice deficient for IL-1R antagonist (IL-1Ra) were administered the NOD2 agonist muramyl dipeptide (MDP) by systemic (intraperitoneal) or local (intraocular and/or intra-articular) injections. NOD2-deficient mice received an intraocular injection of recombinant IL-1beta. Uveitis was evaluated by intravital videomicroscopy and histopathology, and arthritis was assessed by near-infrared imaging and histopathology. Ocular levels of IL-1alpha, IL-1beta and IL-1Ra were quantified by enzyme-linked immunosorbent assay. RESULTS: IL-1Ra deficiency did not render mice more responsive to systemic exposure of MDP. Despite the increased production of IL-1R agonists IL-1alpha and IL-1beta in response to intraocular injection of MDP, deficiency in IL-1Ra did not predispose mice to MDP-triggered uveitis, albeit intravascular cell rolling and adherence were exacerbated. NOD2 expression was dispensable for the potential of IL-1 to elicit uveitis. However, we find that IL-1Ra does play an important protective role in arthritis induced locally by MDP injection in the joint. CONCLUSIONS: Our findings highlight the complexity of NOD2 activation and IL-1 signalling effects that can be compounded by local environmental factors of the target organ. These observations may impact

how we understand the molecular mechanisms by which NOD2 influences inflammation of the eye versus joint, and consequently, treatment options for uveitis versus arthritis.

Lee, S., Lee, K., Yoon, S., Lee, J. W., & Lee, D. (2014). Anomalies in network bridges involved in bile acid metabolism predict outcomes of colorectal cancer patients. *PloS One, 9*(9), e107925. Biomarkers prognostic for colorectal cancer (CRC) would be highly desirable in clinical practice. Proteins that regulate bile acid (BA) homeostasis, by linking metabolic sensors and metabolic enzymes, also called bridge proteins, may be reliable prognostic biomarkers for CRC. Based on a devised metric, "bridgeness," we identified bridge proteins involved in the regulation of BA homeostasis and identified their prognostic potentials. The expression patterns of these bridge proteins could distinguish between normal and diseased tissues, suggesting that these proteins are associated with CRC pathogenesis. Using a supervised classification system, we found that these bridge proteins were reproducibly prognostic, with high prognostic ability compared to other known markers.

Lewis, K. O., Frank, G. R., Nagel, R., Turner, T. L., Ferrell, C. L., Sangvai, S. G., et al. (2014). Pediatric trainees' engagement in the online nutrition curriculum: Preliminary results. *BMC Medical Education, 14*(1)

Conclusions: This initial assessment of the PNS modules shows that technology-mediated delivery of a nutrition curriculum in residency programs has great potential for providing rich learning environments for trainees while maintaining a high level of participant satisfaction. © 2014Lewis et al.; licensee BioMed Central Ltd. Background: The Pediatric Nutrition Series (PNS) consists of ten online, interactive modules and supplementary educational materials that have utilized web-based multimedia technologies to offer nutrition education for pediatric trainees and practicing physicians. The purpose of the study was to evaluate pediatric trainees' engagement, knowledge acquisition, and satisfaction with nutrition modules delivered online in interactive and non-interactive formats. Results: Three hundred and twenty-two (322) pediatric trainees completed one or more of six modules for a total of four hundred and forty-two (442) accessions. All trainees who completed at least one module were included in the study. Two-way analyses of variance (ANOVA) with repeated measures (pre/posttest by interactive/non-interactive format)

indicated significant knowledge gains from pretest to posttest ($p < 0.002$ for all six modules). Comparisons between interactive and non-interactive formats for Module 1 (N = 85 interactive, N = 95 non-interactive) and Module 5 (N = 5 interactive, N = 16 non-interactive) indicated a parallel improvement from the pretest to posttest, with the interactive format significantly higher than the non-interactive modules ($p <.05$). Both qualitative and quantitative data from module evaluations demonstrated that satisfaction with modules was high. However, there were lower ratings for whether learning objectives were met with Module 6 ($p < 0.03$) and lecturer rating ($p < 0.004$) compared to Module 1. Qualitative data also showed that completion of the interactive modules resulted in higher resident satisfaction. Methods. From December 2010 through August 2011, pediatric trainees from seventy-three (73) different U.S. programs completed online nutrition modules designed to develop residents' knowledge of counseling around and management of nutritional issues in children. Data were analyzed using SPSS version 19. Both descriptive and inferential statistics were used in comparing interactive versus non-interactive modules. Pretest/posttest and module evaluations measured knowledge acquisition and satisfaction.

Li, B. X., Xie, F., Fan, Q., Barnhart, K. M., Moore, C. E., Rheingold, A. L., et al. (2014). Novel type of prodrug activation through a long-range O,N-acyl transfer: A case of water-soluble CREB inhibitor. *ACS Medicinal Chemistry Letters, 5*(10), 1104-1109.

CREB (cAMP response element binding protein) has been shown to play an important role in tumor initiation, progression, and metastasis. We discovered that naphthol AS-E, a cell-permeable CREB inhibitor, presented antiproliferative activity in a broad panel of cancer cell lines in vitro. However, it has limited aqueous solubility. In this report, we described a water-soluble inhibitor (compound 6) of CREB-mediated gene transcription with in vivo anticancer activity. Unexpectedly, compound 6 was found to be a prodrug of compound 12 necessitating an unprecedented long-range O,N-acyl transfer. The rate of this transfer was pH- and temperature-dependent. To the best of our knowledge, this is the first time to show that a long-range O,N-acyl transfer could be exploited as a prodrug activation strategy to improve aqueous solubility. This type of prodrug may be applicable to other structures with spatially arranged hydroxyl amide to improve their aqueous solubility.

Li, M. H., Suchland, K. L., & Ingram, S. L. (2014). GABAergic transmission and enhanced modulation by opioids and endocannabinoids in adult rat rostral ventromedial medulla (RVM). *The Journal of Physiology,*

Neurons in the rostral ventromedial medulla (RVM) play critical and complex roles in pain modulation. Recent studies have shown that electrical stimulation of the RVM produces pain facilitation in young animals (postnatal (PN) day < 21) but predominantly inhibits pain behaviors in adults. The cellular mechanisms underlying these changes in RVM modulation of pain behaviors are not known. This is in part because whole-cell patch-clamp studies in RVM to date have been in young (PN day < 18) animals because the organization and abundance of myelinated fibers in this region make the RVM a challenging area for whole-cell patch-clamp recording in adults. Several neurotransmitter systems, including GABAergic neurotransmission undergo developmental changes that mature by PN day 21. Thus, we focused on optimizing whole-cell patch-clamp recordings for RVM neurons in animals older than PN day 30 and compared the results to animals PN day 10 - 21. Our results demonstrate that the probability of GABA release is lower and that opioid and endocannabinoid effects are more evident in adult rats (mature) compared to early postnatal (immature) rats. Differences in these properties of RVM neurons may contribute to the developmental changes in descending control of pain from the RVM to the spinal cord. This article is protected by copyright. All rights reserved.

Liebling, M. R. (2014). Questions and unresolved issues regarding headache in systemic lupus erythematosus: Comment on the article by hanly et al. *Arthritis & Rheumatology (Hoboken, N.J.), 66*(10), 2912.

Lo, J. O., Shaffer, B. L., Feist, C. D., & Caughey, A. B. (2014). Chromosomal microarray analysis and prenatal diagnosis. *Obstetrical & Gynecological Survey, 69*(10), 613-621.

Chromosomal microarray analysis (CMA) assesses chromosomal copy number alterations and affords higher resolution when compared with standard karyotype. This review provides the obstetric provider with an update on the technology, use, and controversies concerning CMA utilization in prenatal diagnosis. Chromosomal microarray analysis offers increased resolution for copy number abnormalities compared with traditional karyotype. There is high-quality evidence

for the added detection of clinically significant copy number alterations with CMA in prenatal diagnosis when the traditional karyotype is normal. Other potential advantages of CMA include a quicker turnaround time and utilization in clinical situations with a high probability of nondividing cells (ie, intrauterine fetal demise, spontaneous miscarriage, and third-trimester amniocentesis). Chromosomal microarray analysis may be beneficial when prenatally detected structural anomalies are associated with specific microdeletions and microduplications or to assess for copy number variants when a de novo balanced rearrangement or marker chromosome is diagnosed. Use of CMA includes the detection of copy number variants of uncertain significance. In light of these issues, large prospective cohort studies are needed to illustrate the diagnostic utility of CMA for detection of prenatal chromosomal abnormalities in low-risk populations before routine clinical use of CMA is recommended in all circumstances of prenatal diagnosis.

Lyons, K. S., Bennett, J. A., Nail, L. M., Fromme, E. K., Dieckmann, N., & Sayer, A. G. (2014). The role of patient pain and physical function on depressive symptoms in couples with lung cancer: A longitudinal dyadic analysis. *Journal of Family Psychology : JFP : Journal of the Division of Family Psychology of the American Psychological Association (Division 43), 28*(5), 692-700.

Drawing on the Developmental-Contextual Model (Berg & Upchurch, 2007), we examined the association between changes in patient physical health (pain severity and physical function) and changes in depressive symptoms in couples with lung cancer over a 12-month period. Patients and their spouses or partners (n = 77) were recruited using rapid case ascertainment and completed five waves of data collection (baseline, 3, 6, 9, and 12 months). Multilevel modeling was used to examine aggregate and time-varying effects of patient physical health on depressive symptoms. Results indicated that for patients and spouses, patient-rated mean pain severity was significantly positively associated with patient and spouse depressive symptoms and patient-rated mean physical function was significantly negatively associated with patient and spouse depressive symptoms. More importantly, increases in patient pain severity and declines in patient physical function were significantly associated with increases in patient depressive symptoms. However, only declines in patient physical function were significantly associated with increases in spouse depressive symptoms. These time-varying effects remained even when controlling for patient gender, patient age, patient stage of disease, spouse physical health, and relationship

quality. Findings suggest the importance of examining the changing illness context on the couple as a unit and the complexity of interpersonal processes in the presence of a life-threatening illness. (PsycINFO Database Record (c) 2014 APA, all rights reserved).

MacManiman, J. D., Meuser, A., Botto, S., Smith, P. P., Liu, F., Jarvis, M. A., et al. (2014). Human cytomegalovirus-encoded pUL7 is a novel CEACAM1-like molecule responsible for promotion of angiogenesis. *Mbio, 5*(6), 10.1128/mBio.02035-14.

Persistent human cytomegalovirus (HCMV) infection has been linked to several diseases, including atherosclerosis, transplant vascular sclerosis (TVS), restenosis, and glioblastoma. We have previously shown that factors secreted from HCMV-infected cells induce angiogenesis and that this process is due, at least in part, to increased secretion of interleukin-6 (IL-6). In order to identify the HCMV gene(s) responsible for angiogenesis promotion, we constructed a large panel of replication-competent HCMV recombinants. One HCMV recombinant deleted for UL1 to UL10 was unable to induce secretion of factors necessary for angiogenesis. Fine mapping using additional HCMV recombinants identified UL7 as a viral gene required for production of angiogenic factors from HCMV-infected cells. Transient expression of pUL7 induced phosphorylation of STAT3 and ERK1/2 MAP kinases and production of proangiogenic factors, including IL-6. Addition of recombinant pUL7 to cells was sufficient for angiogenesis and was again associated with increased IL-6 expression. Analysis of the UL7 structure revealed a conserved domain similar to the immunoglobulin superfamily domain and related to the N-terminal V-like domain of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1). Our report therefore identifies UL7 as a novel HCMV-encoded molecule that is both structurally and functionally related to cellular CEACAM1, a proangiogenic factor highly expressed during vasculogenesis.

IMPORTANCE: A hallmark of cytomegalovirus (CMV) infection is its ability to modulate the host cellular machinery, resulting in the secretion of factors associated with long-term diseases such as vascular disorders and cancer. We previously demonstrated that HCMV infection alters the types and quantities of bioactive proteins released from cells (designated the HCMV secretome) that are involved in the promotion of angiogenesis and wound healing. A key proangiogenic and antiapoptotic factor identified from a proteomic-based approach was IL-6. In the present report, we show for the first time that HCMV UL7 encodes a soluble molecule that is a structural and

functional homologue of the CEACAM1 proangiogenic cellular factor. This report thereby identifies a critical component of the HCMV secretome that may be responsible, at least in part, for the vascular dysregulation associated with persistent HCMV infection.

Magner, A., & Phillipi, C. A. (2014). Using a wellness program to promote a culture of breastfeeding in the workplace: Oregon health & science university's experience. *Journal of Human Lactation : Official Journal of International Lactation Consultant Association,*

In the United States, many women stop breastfeeding within the first month that they return to work. Working mothers experience challenges in maintaining milk supply and finding the time and space to express breast milk or feed their babies in workplace settings. Changing attitudes and culture within the workplace may be accomplished in conjunction with ensuring compliance with state and federal laws regarding breastfeeding to improve breastfeeding rates after return to work. Employee wellness programs can be 1 avenue to promote breastfeeding and human milk donation as healthy behaviors.

Martin, C. A., Ahmad, I., Klingseisen, A., Hussain, M. S., Bicknell, L. S., Leitch, A., et al. (2014). Mutations in PLK4, encoding a master regulator of centriole biogenesis, cause microcephaly, growth failure and retinopathy. *Nature Genetics,*

Centrioles are essential for ciliogenesis. However, mutations in centriole biogenesis genes have been reported in primary microcephaly and Seckel syndrome, disorders without the hallmark clinical features of ciliopathies. Here we identify mutations in the genes encoding PLK4 kinase, a master regulator of centriole duplication, and its substrate TUBGCP6 in individuals with microcephalic primordial dwarfism and additional congenital anomalies, including retinopathy, thereby extending the human phenotypic spectrum associated with centriole dysfunction. Furthermore, we establish that different levels of impaired PLK4 activity result in growth and cilia phenotypes, providing a mechanism by which microcephaly disorders can occur with or without ciliopathic features.

Matthews, M., & Fair, D. A. (2014). Research review: Functional brain connectivity and child psychopathology - overview and methodological considerations for investigators new to the field. *Journal of Child Psychology and Psychiatry, and Allied Disciplines,*

BACKGROUND: Functional connectivity MRI is an emerging technique that can be used to investigate typical and atypical brain function in developing and aging populations. Despite some of the current confounds in the field of functional connectivity MRI, the translational potential of the technique available to investigators may eventually be used to improve diagnosis, early disease detection, and therapy monitoring. METHOD AND SCOPE: Based on a comprehensive survey of the literature, this review offers an introduction of resting-state functional connectivity for new investigators to the field of resting-state functional connectivity. We discuss a brief history of the technique, various methods of analysis, the relationship of functional networks to behavior, as well as the translational potential of functional connectivity MRI to investigate neuropsychiatric disorders. We also address some considerations and limitations with data analysis and interpretation. CONCLUSIONS: The information provided in this review should serve as a foundation for investigators new to the field of resting-state functional connectivity. The discussion provides a means to better understand functional connectivity and its application to typical and atypical brain function.

McGregor, J. C., & Furuno, J. P. (2014). Optimizing research methods used for the evaluation of antimicrobial stewardship programs. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 59 Suppl 3*, S185-92.

Antimicrobial stewardship programs (ASPs) are an increasingly common intervention for optimizing antimicrobial therapy in healthcare settings. These programs aim to improve patient care and limit the emergence and spread of multidrug-resistant organisms by supporting prudent antimicrobial use. However, pressure from the current reimbursement climate necessitates that ASPs operate as cost-cutting programs rather than focus on patient outcomes. This has forced the research that is evaluating ASP interventions to concentrate heavily on economic outcomes. As the science of antimicrobial stewardship advances, it is essential that well-conducted evaluations, focused on patient and microbial outcomes, serve as the evidence base that directs optimal ASP intervention design and implementation. In this review, we provide guidance and recommendations for the design of studies to evaluate the impact of ASP interventions on patient and microbial outcomes.

Medler, T. R., & Coussens, L. M. (2014). Duality of the immune response in cancer: Lessons learned from skin. *The Journal of Investigative Dermatology, 134*(e1), E23-8.

Mello, C. V. (2014). The zebra finch, taeniopygia guttata: An avian model for investigating the neurobiological basis of vocal learning. *Cold Spring Harbor Protocols,*

Songbirds are capable of learning their vocalizations by copying a singing adult. This vocal learning ability requires juveniles to hear and memorize the sound of the adult song, and later to imitate it through a process involving sensorimotor integration. Vocal learning is a trait that songbirds share with humans, where it forms the basis of spoken language acquisition, with other avian groups (parrots and hummingbirds), and with a few other mammals (cetaceans, bats). It is however absent in traditional model organisms such as rodents and nonhuman primates. Zebra finches, a songbird species from Australia, are popular pets and are easy to breed. They also sing a relatively simple and stereotyped song that is amenable to quantitative analysis. Zebra finches have thus emerged as a choice model organism for investigating the neurobiological basis of vocal learning. A number of tools and methodologies have been developed to characterize the bioacoustics properties of their song, analyze the degree of accurate copying during vocal learning, map the brain circuits that control singing and song learning, and investigate the physiology of these circuits. Such studies have led to a large base of knowledge on song production and learning, and their underlying neural substrate. Several molecular resources have recently become available, including brain cDNA/EST databases, microarrays, BAC libraries, a molecular brain atlas, a complete genome assembly, and the ability to perform transgenesis. The recent availability of many other avian genomes provides unique opportunities for comparative analysis in the search for features unique to vocal learning organisms.

Mello, C. V., & Clayton, D. F. (2014). The opportunities and challenges of large-scale molecular approaches to songbird neurobiology. *Neuroscience and Biobehavioral Reviews,*

High-throughput methods for analyzing genome structure and function are having a large impact in songbird neurobiology. Methods include genome sequencing and annotation, comparative genomics, DNA microarrays and transcriptomics, and the development of a brain atlas of gene expression. Key emerging findings include the identification of complex transcriptional programs

active during singing, the robust brain expression of non-coding RNAs, evidence of profound variations in gene expression across brain regions, and the identification of molecular specializations within song production and learning circuits. Current challenges include the statistical analysis of large datasets, effective genome curations, the efficient localization of gene expression changes to specific neuronal circuits and cells, and the dissection of behavioral and environmental factors that influence brain gene expression. The field requires efficient methods for comparisons with organisms like chicken, which offer important anatomical, functional and behavioral contrasts. As sequencing costs plummet, opportunities emerge for comparative approaches that may help reveal evolutionary transitions contributing to vocal learning, social behavior and other properties that make songbirds such compelling research subjects.

Mergy, M. A., Gowrishankar, R., Gresch, P. J., Gantz, S. C., Williams, J., Davis, G. L., et al. (2014). The rare DAT coding variant Val559 perturbs DA neuron function, changes behavior, and alters in vivo responses to psychostimulants. *Proceedings of the National Academy of Sciences of the United States of America,*

Despite the critical role of the presynaptic dopamine (DA) transporter (DAT, SLC6A3) in DA clearance and psychostimulant responses, evidence that DAT dysfunction supports risk for mental illness is indirect. Recently, we identified a rare, nonsynonymous Slc6a3 variant that produces the DAT substitution Ala559Val in two male siblings who share a diagnosis of attention-deficit hyperactivity disorder (ADHD), with other studies identifying the variant in subjects with bipolar disorder (BPD) and autism spectrum disorder (ASD). Previously, using transfected cell studies, we observed that although DAT Val559 displays normal total and surface DAT protein levels, and normal DA recognition and uptake, the variant transporter exhibits anomalous DA efflux (ADE) and lacks capacity for amphetamine (AMPH)-stimulated DA release. To pursue the significance of these findings in vivo, we engineered DAT Val559 knock-in mice, and here we demonstrate in this model the presence of elevated extracellular DA levels, altered somatodendritic and presynaptic D2 DA receptor (D2R) function, a blunted ability of DA terminals to support depolarization and AMPH-evoked DA release, and disruptions in basal and psychostimulant-evoked locomotor behavior. Together, our studies demonstrate an in vivo functional impact of the DAT Val559 variant, providing support for the ability of DAT dysfunction to impact risk for mental illness.

Mhawech-Fauceglia, P., Yan, L., Sharifian, M., Ren, X., Liu, S., Kim, G., et al. (2014). Stromal expression of fibroblast activation protein alpha (FAP) predicts platinum resistance and shorter recurrence in patients with epithelial ovarian cancer. *Cancer Microenvironment,*

The microenvironment plays an important role in tumorigenesis. Fibroblast activation protein alpha (FAP) is overexpressed by fibroblasts present in the microenvironment of many tumors. High FAP expression is a negative prognostic factor in several malignancies, but this has not been investigated in epithelial ovarian cancer (EOC). The aim of this study is to define the value of FAP in EOC. Immunohistochemical staining using an anti-FAP antibody was performed on 338 EOC tissues. mRNA levels in cancer cell lines and FAP silencing using siRNA was also done. FAP immunoexpression by tumor stroma was a significant predictive factor for platinum resistance ($p = 0.0154$). In survival analysis of days to recurrence, FAP stoma+ was associated with shorter recurrence than those with FAP− stroma ($p = 0.0247$). In 21.8 % of tumors, FAP protein was expressed by the tumor epithelium, and FAP mRNA was more highly expressed in tumors ($n = 489$) than in normal tissues ($n = 8$) ($p = 3.88 \times 10-4$). In vitro, addition of FAP to EOC cells induced a 10–12 % increase in cell viability both in the presence and absence of cisplatin. Conversely, siRNA silencing of FAP resulted in ~10 % reduction in EOC cell proliferation. We have shown that FAP expression in EOC is associated with poorer clinical outcomes. FAP may have novel cell-autonomous effects suggesting that targeting FAP could have pleiotropic anti-tumor effects, and anti-FAP therapy could be a highly effective novel treatment for EOC, especially in cisplatinum-resistant cases.

Milas, M. (2014). The genomic medicine paradigm shift. *Journal of Surgical Oncology,*

Minko, I. G., Earley, L. F., Larlee, K. E., Lin, Y. -., & Lloyd, R. S. Pyrosequencing: Applicability for studying DNA damage-induced mutagenesis. *Environmental and Molecular Mutagenesis, 55*(8), 601-608.

Site-specifically modified DNAs are routinely used in the study of DNA damage-induced mutagenesis. These analyses involve the creation of DNA vectors containing a lesion at a pre-determined position, DNA replication, and detection of mutations at the target site. The final step has previously required the isolation of individual DNA clones, hybridization with radioactively

labeled probes, and verification of mutations by Sanger sequencing. In the search for an alternative procedure that would allow direct quantification of sequence variants in a mixed population of DNA molecules, we evaluated the applicability of pyrosequencing to site-specific mutagenesis assays. The progeny DNAs were analyzed that originated from replication of N6-(deoxy-D-erythro-pentofuranosyl)-2,6-diamino-3,4-dihydro-4-oxo-5-N-methylformamidopyrimidine (MeFapy-dG)-containing vectors in primate cells, with the lesion being positioned in the 5′-GCNGG-3′ sequence context. Pyrosequencing detected ~8% G to T transversions and ~3.5% G to A transitions, a result that was in excellent agreement with frequencies previously measured by the standard procedure (Earley LF et al. [2013]: Chem Res Toxicol 26:1108-1114). However, ~3.5% G to C transversions and ~2.0% deletions could not be detected by pyrosequencing. Consistent with these observations, the sensitivity of pyrosequencing for measuring the single deoxynucleotide variants differed depending on the deoxynucleotide identity, and in the given sequence contexts, was determined to be ~1-2% for A and T and ~5% for C. Pyrosequencing of other DNA isolates that were obtained following replication of MeFapy-dG-containing vectors in primate cells or Escherichia coli, identified several additional limitations. Collectively, our data demonstrated that pyrosequencing can be used for studying DNA damage-induced mutagenesis as an effective complementary experimental approach to current protocols.

Mohamed, A. S., Yoo, J., Hart, R., Ragel, B. T., Hiratzka, J., Hamilton, D. K., et al. (2014). Posterior fixation without debridement for vertebral body osteomyelitis and discitis. *Neurosurgical Focus, 37*(2)

Object. The authors evaluated the efficacy of posterior instrumentation for the management of spontaneous spinal infections. Standard surgical management of spontaneous spinal infection is based on debridement of the infected tissue. However, this can be very challenging as most of these patients are medically debilitated and the surgical debridement requires a more aggressive approach to the spine either anteriorly or via an expanded posterior approach. The authors present their results using an alternative treatment method of posterior-only neuro-decompression and stabilization without formal debridement of anterior tissue for treating spontaneous spinal infection. Methods. Fifteen consecutive patients were treated surgically by 2

of the authors. All patients had osteomyelitis and discitis and were treated postoperatively with intravenous antibiotics for at least 6 weeks. The indications for surgery were failed medical management, progressive deformity with ongoing persistent spinal infection, or neurological deficit. Patients with simple epidural abscess without bony instability were treated with laminectomy and were not included in this series. Fourteen patients were treated with posterior-only decompression and long-segment rigid fixation, without formal debridement of the infected area. One patient was treated with staged anterior and posterior surgery due to delay in treatment related to medical comorbidities. The authors examined as their outcome the ambulatory status and recurrence of deep infection requiring additional surgery or medical treatment. Results. Of the initial 15 patients, 10 (66%) had a minimum 2-year follow-up and 14 patients had at least 1 year of followup. There were no recurrent spinal infections. There were 3 unplanned reoperations (1 for loss of fixation, 1 for early superficial wound infection, and 1 for epidural hematoma). Nine (60%) of 15 patients were nonambulatory at presentation. At final followup, 8 of 15 patients were independently ambulatory, 6 required an assistive device, and 1 remained nonambulatory. Conclusions. Long-segment fixation, without formal debridement, resulted in resolution of spinal infection in all cases and in significant neurological recovery in almost all cases. This surgical technique, when combined with aggressive antibiotic therapy and a multidisciplinary team approach, is an effective way of managing serious spinal infections in a challenging patient population.

Monteys, A. M., Spengler, R. M., Dufour, B. D., Wilson, M. S., Oakley, C. K., Sowada, M. J., et al. (2014). Single nucleotide seed modification restores in vivo tolerability of a toxic artificial miRNA sequence in the mouse brain. *Nucleic Acids Research,*

Huntington's disease is a fatal neurodegenerative disease caused by polyglutamine-expansion in huntingtin (HTT). Recent work showed that gene silencing approaches, including RNA interference (RNAi), improve disease readouts in mice. To advance RNAi to the clinic, we designed miHDS1, with robust knockdown of human HTT and minimized silencing of unintended transcripts. In Rhesus macaque, AAV delivery of miHDS1 to the putamen reduced HTT expression with no adverse effects on neurological status including fine and gross motor skills, no immune activation and no induction of neuropathology out to 6 weeks post injection. Others showed

safety of a different HTT-targeting RNAi in monkeys for 6 months. Application of miHDS1 to Huntington's patients requires further safety testing in normal rodents, despite the fact that it was optimized for humans. To satisfy this regulatory requirement, we evaluated normal mice after AAV.miHDS1 injection. In contrast to monkeys, neurological deficits occurred acutely in mice brain and was attributed to off-target silencing through interactions of miHDS1 with the 3'UTR of other transcripts. While we resolved miHDS1 toxicity in mouse brain and maintained miHDS1-silencing efficacy, these studies highlight that optimizing nucleic acid-based medicines for safety in humans presents challenges for safety testing in rodents or other distantly related species.

Munk, M. R., Jung, J. J., Biggee, K., Tucker, W. R., Sen, H. N., Schmidt-Erfurth, U., et al. (2014). Idiopathic multifocal Choroiditis/punctate inner choroidopathy with acute photoreceptor loss or dysfunction out of proportion to clinically visible lesions. *Retina (Philadelphia, Pa.),*

PURPOSE:: To report acute/subacute vision loss and paracentral scotomata in patients with idiopathic multifocal choroiditis/punctate inner choroidopathy due to large zones of acute photoreceptor attenuation surrounding the chorioretinal lesions. METHODS:: Multimodal imaging case series. RESULTS:: Six women and 2 men were included (mean age, 31.5 +/- 5.8 years). Vision ranged from 20/20-1 to hand motion (mean, 20/364). Spectral domain optical coherence tomography demonstrated extensive attenuation of the external limiting membrane, ellipsoid and interdigitation zones, adjacent to the visible multifocal choroiditis/punctate inner choroidopathy lesions. The corresponding areas were hyperautofluorescent on fundus autofluorescence and were associated with corresponding visual field defects. Full-field electroretinogram (available in three cases) showed markedly decreased cone/rod response, and multifocal electroretinogram revealed reduced amplitudes and increased implicit times in two cases. Three patients received no treatment, the remaining were treated with oral corticosteroids (n = 4), oral acyclovir/valacyclovir (n = 2), intravitreal/posterior subtenon triamcinolone acetate (n = 3), and anti-vascular endothelial growth factor (n = 2). Visual recovery occurred in only three cases of whom two were treated. Varying morphological recovery was found in six cases, associated with decrease in hyperautofluorescence on fundus autofluorescence. CONCLUSION:: Multifocal choroiditis/punctate inner choroidopathy can present with transient or permanent central

photoreceptor attenuation/loss. This presentation is likely a variant of multifocal choroiditis/punctate inner choroidopathy with chorioretinal atrophy. Associated changes are best evaluated using multimodal imaging.

Muppidi, J. R., Schmitz, R., Green, J. A., Xiao, W., Larsen, A. B., Braun, S. E., et al. (2014). Loss of signalling via Galpha13 in germinal centre B-cell-derived lymphoma. *Nature,*
Germinal centre B-cell-like diffuse large B-cell lymphoma (GCB-DLBCL) is a common malignancy, yet the signalling pathways that are deregulated and the factors leading to its systemic dissemination are poorly defined. Work in mice showed that sphingosine-1-phosphate receptor-2 (S1PR2), a Galpha12 and Galpha13 coupled receptor, promotes growth regulation and local confinement of germinal centre B cells. Recent deep sequencing studies of GCB-DLBCL have revealed mutations in many genes in this cancer, including in GNA13 (encoding Galpha13) and S1PR2 (refs 5,6, 7). Here we show, using in vitro and in vivo assays, that GCB-DLBCL-associated mutations occurring in S1PR2 frequently disrupt the receptor's Akt and migration inhibitory functions. Galpha13-deficient mouse germinal centre B cells and human GCB-DLBCL cells were unable to suppress pAkt and migration in response to S1P, and Galpha13-deficient mice developed germinal centre B-cell-derived lymphoma. Germinal centre B cells, unlike most lymphocytes, are tightly confined in lymphoid organs and do not recirculate. Remarkably, deficiency in Galpha13, but not S1PR2, led to germinal centre B-cell dissemination into lymph and blood. GCB-DLBCL cell lines frequently carried mutations in the Galpha13 effector ARHGEF1, and Arhgef1 deficiency also led to germinal centre B-cell dissemination. The incomplete phenocopy of Galpha13- and S1PR2 deficiency led us to discover that P2RY8, an orphan receptor that is mutated in GCB-DLBCL and another germinal centre B-cell-derived malignancy, Burkitt's lymphoma, also represses germinal centre B-cell growth and promotes confinement via Galpha13. These findings identify a Galpha13-dependent pathway that exerts dual actions in suppressing growth and blocking dissemination of germinal centre B cells that is frequently disrupted in germinal centre B-cell-derived lymphoma.

Nannini, M., Astolfi, A., Urbini, M., Indio, V., Santini, D., Heinrich, M. C., et al. (2014). *Integrated genomic study of quadruple-WT GIST (KIT/PDGFRA/SDH/RAS pathway wild-type GIST)* BioMed

Central Ltd.

Background: About 10-15% of adult gastrointestinal stromal tumors (GIST) and the vast majority of pediatric GIST do not harbour KIT or platelet-derived growth factor receptor alpha (PDGFRA) mutations (J Clin Oncol 22:3813-3825, 2004; Hematol Oncol Clin North Am 23:15-34, 2009). The molecular biology of these GIST, originally defined as KIT/PDGFRA wild-type (WT), is complex due to the existence of different subgroups with distinct molecular hallmarks, including defects in the succinate dehydrogenase (SDH) complex and mutations of neurofibromatosis type 1 (NF1), BRAF, or KRAS genes (RAS-pathway or RAS-P).In this extremely heterogeneous landscape, the clinical profile and molecular abnormalities of the small subgroup of WT GIST suitably referred to as quadruple wild-type GIST (quadrupleWT or KITWT/PDGFRAWT/SDHWT/RAS-PWT) remains undefined. The aim of this study is to investigate the genomic profile of KITWT/PDGFRAWT/SDHWT/RAS-PWT GIST, by using a massively parallel sequencing and microarray approach, and compare it with the genomic profile of other GIST subtypes.Methods: We performed a whole genome analysis using a massively parallel sequencing approach on a total of 16 GIST cases (2 KITWT/PDGFRAWT/SDHWTand SDHBIHC+/SDHAIHC+, 2 KITWT/PDGFRAWT/SDHAmut and SDHBIHC-/SDHAIHC- and 12 cases of KITmut or PDGFRAmut GIST). To confirm and extend the results, whole-genome gene expression analysis by microarray was performed on 9 out 16 patients analyzed by RNAseq and an additional 20 GIST patients (1 KITWT/PDGFRAWTSDHAmut GIST and 19 KITmut or PDGFRAmut GIST). The most impressive data were validated by quantitave PCR and Western Blot analysis.Results: We found that both cases of quadrupleWT GIST had a genomic profile profoundly different from both either KIT/PDGFRA mutated or SDHA-mutated GIST. In particular, the quadrupleWT GIST tumors are characterized by the overexpression of molecular markers (CALCRL and COL22A1) and of specific oncogenes including tyrosine and cyclin- dependent kinases (NTRK2 and CDK6) and one member of the ETS-transcription factor family (ERG).Conclusion: We report for the first time an integrated genomic picture of KITWT/PDGFRAWT/SDHWT/RAS-PWT GIST, using massively parallel sequencing and gene expression analyses, and found that quadrupleWT GIST have an expression signature that is distinct from SDH-mutant GIST as well as GIST harbouring mutations in KIT or PDGFRA. Our findings suggest that quadrupleWT GIST represent another unique group within the family of gastrointestintal stromal tumors.

Nazi, K. M., Turvey, C. L., Klein, D. M., Hogan, T. P., & Woods, S. S. (2014). VA OpenNotes: Exploring the experiences of early patient adopters with access to clinical notes. *Journal of the American Medical Informatics Association : JAMIA,*

OBJECTIVE: To explore the experience of early patient adopters who accessed their clinical notes online using the Blue Button feature of the My HealtheVet portal. METHODS: A web-based survey of VA patient portal users from June 22 to September 15, 2013. RESULTS: 33.5% of respondents knew that clinical notes could be viewed, and nearly one in four (23.5%) said that they had viewed their notes at least once. The majority of VA Notes users agreed that accessing their notes will help them to do a better job of taking medications as prescribed (80.1%) and be better prepared for clinic visits (88.6%). Nine out of 10 users agreed that use of visit notes will help them understand their conditions better (91.8%), and better remember the plan for their care (91.9%). In contrast, 87% disagreed that VA Notes will make them worry more, and 88.4% disagreed that access to VA Notes will be more confusing than helpful. Users who had either contacted their provider or healthcare team (11.9%) or planned to (13.5%) primarily wanted to learn more about a health issue, medication, or test results (53.7%). CONCLUSIONS: Initial assessment of the patient experience within the first 9 months of availability provides evidence that patients both value and benefit from online access to clinical notes. These findings are congruent with OpenNotes study findings on a broader scale. Additional outreach and education is needed to enhance patient awareness. Healthcare professionals should author notes keeping in mind the opportunity patient access presents for enhanced communication.

Nelson, J. W., Young, J. M., Borkar, R. N., Woltjer, R. L., Quinn, J. F., Silbert, L. C., et al. (2014). Role of soluble epoxide hydrolase in age-related vascular cognitive decline. *Prostaglandins & Other Lipid Mediators,*

P450 eicosanoids are important regulators of the cerebral microcirculation, but their role in cerebral small vessel disease is unclear. We tested the hypothesis that vascular cognitive impairment (VCI) is linked to reduced cerebral microvascular eicosanoid signaling. We analyzed human brain tissue from individuals formerly enrolled in the Oregon Brain Aging Study, who had a history of cognitive impairment histopathological evidence of microvascular disease. VCI subjects had significantly higher lesion burden both on premortem MRI and postmortem

histopathology compared to age- and sex-matched controls. Mass spectrometry-based eicosanoid analysis revealed that 14,15-dihydroxyeicosatrienoic acid (DHET) was elevated in cortical brain tissue from VCI subjects. Immunoreactivity of soluble epoxide hydrolase (sEH), the enzyme responsible for 14,15-DHET formation, was localized to cerebral microvascular endothelium, and was enhanced in microvessels of affected tissue. Finally, we evaluated the genotype frequency of two functional single nucleotide polymorphisms of sEH gene EPHX2 in VCI and control groups. Our findings support a role for sEH and a potential benefit from sEH inhibitors in age-related VCI.

Nitsche, U., Müller, T. C., Späth, C., Cresswell, L., Wilhelm, D., Friess, H., et al. (2014). The evidence based dilemma of intraperitoneal drainage for pancreatic resection - A systematic review and meta-analysis. *BMC Surgery, 14*(1)

Background: Routine placement of intraperitoneal drains has been shown to be ineffective or potentially harmful in various abdominal surgical procedures. Studies assessing risks and benefits of abdominal drains for pancreatic resections have demonstrated inconsistent results. We thus performed a systematic review of the literature and meta-analyzed outcomes of pancreatic resections with and without intraoperative placement of drains. Methods. A database search according to the PRISMA guidelines was performed for studies on pancreatic resection with and without intraperitoneal drainage. The subgroup 'pancreaticoduodenectomy' was analyzed separately. The quality of studies was assessed using the MINORS and STROBE criteria. Pooled estimates of morbidity, mortality and length of hospital stay were calculated using random effects models. Results: Only two randomized trials were identified. Their results were contradictory. We thus included six further, retrospective studies in the meta-analysis. However, with I2 = 68% for any kind of complication, the estimate of inter-study heterogeneity was high. While overall morbidity after any kind of pancreatic resection was lower without drains (p = 0.04), there was no significant difference in mortality rates. In contrast, pooled estimates of outcomes after pancreaticoduodenectomy demonstrated no differences in morbidity (p = 0.40) but increased rates of intraabdominal abscesses (p = 0.04) and mortality (p = 0.04) without intraperitoneal drainage. Conclusion: Although drains are associated with slightly increased morbidity for pancreatic resections, routine omission of drains cannot be advocated, especially after pancreaticoduodenectomy. While selective drainage seems reasonable, further efforts to generate

more reliable data are questionable because of the current studies and the presumed small differences in outcomes. Trial registration. Systematic review registration number CRD42014007497.

Olson, C. R., Wirthlin, M., Lovell, P. V., & Mello, C. V. (2014). Proper care, husbandry, and breeding guidelines for the zebra finch, taeniopygia guttata. *Cold Spring Harbor Protocols,*
The zebra finch Taeniopygia guttata castanotis is a songbird commonly used in the laboratory, particularly for studies of vocal learning, neurobiology, and physiology. Within the laboratory, it is important to adopt careful husbandry practices that allow for normal development of the birds. For example, their song is a learned trait, passed culturally from adult males to juveniles, and thus its learning can be influenced by the health and social conditions of the birds present in the laboratory. Here we present guidelines for the successful maintenance and breeding of captive zebra finches.

O'Rourke, R. W., Meyer, K. A., Neeley, C. K., Gaston, G. D., Sekhri, P., Szumowski, M., et al. (2014). Systemic NK cell ablation attenuates intra-abdominal adipose tissue macrophage infiltration in murine obesity. *Obesity, 22*(10), 2109-2114.
Objective: Natural killer (NK) cells are understudied in the context of metabolic disease and obesity. The goal of this study was to define the effect of NK cell ablation on systemic inflammation and glucose homeostasis in murine obesity. Methods: A transgenic murine model was used to study the effect of NK cell ablation on systemic inflammation and glucose homeostasis in the context of diet-induced obesity using flow cytometry, QRTPCR, and glucose tolerance and insulin sensitivity testing. Results: NK cell ablation achieved a three to fourfold decrease in NK cells but had no effect on T-cell levels in adipose tissues and spleen. NK cell ablation was associated with decreased total macrophage infiltration in intra-abdominal adipose tissue, but macrophage infiltration in subcutaneous adipose tissue and spleen was unaffected. NK cell ablation was associated with modest improvement in insulin sensitivity but had no effect on tissue transcript levels of inflammatory cytokines. Conclusions: NK cells play a role in promoting intra-abdominal adipose tissue macrophage infiltration and systemic insulin resistance in obesity.

Ostrogorsky, T. L., Raber, A. M., McKinley Yoder, C., Nielsen, A. E., Lutz, K. F., & Wros, P. L. (2014). Becoming a nurse: Role formation among accelerated baccalaureate students. *Nurse Educator,* To understand nursing role formation for students enrolled in an accelerated baccalaureate nursing program, end-of-term narrative reflections from 34 students were analyzed over the course of the 15-month program. Using thematic analysis, 4 major themes were identified: evolving role perception, extending nursing student-patient interaction, engaging with health care team and systems of care, and expanding clinical thinking.

Ozcan, U. A., Isik, U., Ozpinar, A., Baykan, N., & Dincer, A. (2014). Assessment of sedated pediatric brain with 3D-FLAIR sequence at 3T MRI. *Brain & Development,* Background and purpose: In sedated pediatric brains, 2D-FLAIR causes increased signal intensity of the cerebrospinal fluid (CSF) leading to false-positive diagnoses. Our aim is to determine whether increased CSF signal intensity is observed on 3D-FLAIR images. Methods: In this institutional review board-approved study, a 2-year retrospective analysis of our MRI database was conducted which revealed 48 sedated pediatric patients with normal cranial MRI findings and 3D-FLAIR sequence. One adult volunteer was imaged before and after O2 inhalation with 2D and 3D-FLAIR sequences. The hyperintensity in the subarachnoid spaces and basal cisterns were quantified as follows: 0: artifact free; 1: homogeneous minimal CSF signal; 2: abnormal CSF signal. Inter-observer agreement was assessed with kappa agreement analysis. Results: Grade 0 and grade 1 signals were observed at inferior to Liliequist membrane (LLQ) in 48/48 and 0/48 cases; prepontine cistern 47/48 and 1/48; superior to LLQ 26/48 and 22/48; 4th ventricle 16/48 and 32/48; 3rd ventricle 34/48 and 14/48; lateral ventricle 3/48 and 45/48; subarachnoid space 36/48 and 12/48, respectively. No patients showed grade 2 signal. Inter-observer agreement was 0.81-1. In the volunteer, after O2 inhalation, grade 2 signal intensity was evident on 2D-FLAIR however; 3D-FLAIR did not show any signal increase. Conclusions: In sedated pediatric brains, 3D-FLAIR suppresses CSF signal, and enables reliable assessment free from CSF artifacts.

Palejwala, N. V., Lauer, A. K., & Weleber, R. G. (2014). Choroideremia associated with choroidal neovascularization treated with intravitreal bevacizumab. *Clinical Ophthalmology, 8*, 1675-1679. Purpose: To report a rare case of central vision loss in a patient with choroideremia. Patients and

methods: A retrospective, interventional case report. Results: A 13-year-old male with history of choroideremia presented with subacute loss of central acuity in his left eye. Examination and diagnostic testing revealed subretinal fibrosis secondary to a choroidal neovascular membrane (CNVM). A trial of anti-vascular endothelial growth factor (VEGF) therapy with the injection of intravitreal bevacizumab was attempted. Mild improvements in acuity and anatomy were noted. Conclusion: Choroideremia is a rare hereditary choroidal dystrophy that predominantly affects males in the first and second decades of life. Visual acuity is usually spared until later in life. CNVM is a rare manifestation of choroideremia with only a handful of case reports presented in the literature. This case is unique in that it is the first reported case that received treatment with intravitreal anti-VEGF therapy.

Palghat Udayashankar, A., Kössl, M., & Nowotny, M. (2014). Lateralization of travelling wave response in the hearing organ of bushcrickets. *Plos One, 9*(1)

Travelling waves are the physical basis of frequency discrimination in many vertebrate and invertebrate taxa, including mammals, birds, and some insects. In bushcrickets (Tettigoniidae), the crista acustica is the hearing organ that has been shown to use sound-induced travelling waves. Up to now, data on mechanical characteristics of sound-induced travelling waves were only available along the longitudinal (proximal-distal) direction. In this study, we use laser Doppler vibrometry to investigate in-vivo radial (anterior-posterior) features of travelling waves in the tropical bushcricket Mecopoda elongata. Our results demonstrate that the maximum of sound-induced travelling wave amplitude response is always shifted towards the anterior part of the crista acustica. This lateralization of the travelling wave response induces a tilt in the motion of the crista acustica, which presumably optimizes sensory transduction by exerting a shear motion on the sensory cilia in this hearing organ.

Park, G. Y., Lee, J. Y., Himes, R. A., Thomas, G. S., Blackburn, N. J., & Karlin, K. D. (2014). Copper-peptide complex structure and reactivity when found in conserved his-xaa-his sequences. *Journal of the American Chemical Society, 136*(36), 12532-12535.

Oxygen-activating copper proteins may possess His-Xaa-His chelating sequences at their active sites and additionally exhibit imidiazole group δN vs εN tautomeric preferences. As shown here,

such variations strongly affect copper ions coordination geometry, redox behavior, and oxidative reactivity. Copper(I) complexes bound to either δ-HGH or ε-HGH tripeptides were synthesized and characterized. Structural investigations using X-ray absorption spectroscopy, density functional theory calculations, and solution conductivity measurements reveal that δ-HGH forms the CuI dimer complex [{CuI(δ-HGH)}2]2+ (1) while ε-HGH binds CuI to give the monomeric complex [CuI(ε-HGH)]+ (2). Only 2 exhibits any reactivity, forming a strong CO adduct, [CuI(ε-HGH)(CO)]+, with properties closely matching those of the copper monooxygenase PHM. Also, 2 is reactive toward O2 or H2O2, giving a new type of O2-adduct or CuII-OOH complex, respectively.

Peterson-Besse, J. J., Walsh, E. S., Horner-Johnson, W., Goode, T. D., & Wheeler, B. (2014). Barriers to health care among people with disabilities who are members of underserved racial/ethnic groups: A scoping review of the literature. *Medical Care, 52*(10 Suppl 3), S51-63. BACKGROUND: Understanding barriers to health care access experienced by people with disabilities who are members of underserved racial/ethnic groups is key to developing interventions to improve access. OBJECTIVE: To conduct a scoping review of the literature to examine the published literature on barriers to health care access for people with disabilities who are members of underserved racial/ethnic groups. DATA SOURCES: Articles cited in MEDLINE, PsycINFO, and CINAHL between the year 2000 and June 19, 2013. In addition, table of contents of 4 journals and the reference lists of the included article were reviewed for potentially relevant titles. STUDY SELECTION AND EXTRACTION: Studies examining barriers to health care access among adults aged 18-64 with disabilities who are members of an underserved racial/ethnic group were included. Two reviewers screened abstracts, screened each full-text article and extracted data, and discrepancies were resolved by consensus. RESULTS: Ten studies were identified that met all inclusion criteria. The most frequently described barriers were uninsurance, language, low education level, and no usual source of care. Barriers to health care access related to race or ethnicity (6 studies) and disability (1 study) were observed less often than those related to socioeconomic status or health care systems factors (9 studies). CONCLUSIONS: Our findings reflect a critical gap in the literature. Greater attention is needed to subgroup differences including race, ethnicity, and culture within the population of people with disabilities.

Phillips, R. L.,Jr, Pugno, P. A., Saultz, J. W., Tuggy, M. L., Borkan, J. M., Hoekzema, G. S., et al. (2014). Health is primary: Family medicine for america's health. *Annals of Family Medicine, 12 Suppl 1*, S1-S12.

PURPOSE: More than a decade ago the American Academy of Family Physicians, American Academy of Family Physicians Foundation, American Board of Family Medicine, Association of Departments of Family Medicine, Association of Family Practice Residency Directors, North American Primary Care Research Group, and Society of Teachers of Family Medicine came together in the Future of Family Medicine (FFM) to launch a series of strategic efforts to "renew the specialty to meet the needs of people and society," some of which bore important fruit. Family Medicine for America's Health was launched in 2013 to revisit the role of family medicine in view of these changes and to position family medicine with new strategic and communication plans to create better health, better health care, and lower cost for patients and communities (the Triple Aim). METHODS: Family Medicine for America's Health was preceded and guided by the development of a family physician role definition. A consulting group facilitated systematic strategic plan development over 9 months that included key informant interviews, formal stakeholder surveys, future scenario testing, a retreat for family medicine organizations and stakeholder representatives to review strategy options, further strategy refinement, and finally a formal strategic plan with draft tactics and design for an implementation plan. A second communications consulting group surveyed diverse stakeholders in coordination with strategic planning to develop a communication plan. The American College of Osteopathic Family Physicians joined the effort, and students, residents, and young physicians were included. RESULTS: The core strategies identified include working to ensure broad access to sustained, primary care relationships; accountability for increasing primary care value in terms of cost and quality; a commitment to helping reduce health care disparities; moving to comprehensive payment and away from fee-for-service; transformation of training; technology to support effective care; improving research underpinning primary care; and actively engaging patients, policy makers, and payers to develop an understanding of the value of primary care. The communications plan, called Health is Primary, will complement these strategies. Eight family medicine organizations have pledged nearly $20 million and committed representatives to a multiyear implementation team that will coordinate these plans in a much more systematic way

than occurred with FFM. CONCLUSIONS: Family Medicine for America's Health is a new commitment by 8 family medicine organizations to strategically align work to improve practice models, payment, technology, workforce and education, and research to support the Triple Aim. It is also a humble invitation to patients and to clinical and policy partners to collaborate in making family medicine even more effective.

Piper, B. J., Gray, H. M., Corbett, S. M., Birkett, M. A., & Raber, J. (2014). Executive function and mental health in adopted children with a history of recreational drug exposures. *PloS One, 9*(10), e110459.

Adoptive children are at increased risk for problematic behaviors but the origin of these individual differences in neurobehavioral function is unclear. This investigation examined whether adopted children with prenatal exposure to a wide variety of recreational drugs exhibited higher scores (i.e. more problems) with executive function and psychiatric symptomology. Caregivers of children ages 5 to 18 completed an online survey with items about use of alcohol, nicotine, or methamphetamine during pregnancy followed by the Behavior Rating Inventory of Executive Function (BRIEF, N = 437 including 59 adoptive parents) or the Child Behavior Checklist (CBCL, N = 549 including 54 adoptive parents). Relative to a comparison group of children raised by their biological parents, adoptive children that were polysubstance exposed during prenatal development exhibited higher rates of academic difficulties and were behind their classmates in math and reading. Adoptive children had statistically and clinically significant higher BRIEF ratings and this pattern was similar for boys and girls. CBCL ratings were significantly increased in adoptive children, particularly for Externalizing and Attention problems. Adoptive children with a history of polysubstance exposures including alcohol, nicotine, and methamphetamine are at heightened risk for difficulties with executive function as well as various psychopathologies. These findings suggest that increased monitoring to identify and implement remediation strategies may be warranted for adopted children with a history of in utero drug exposures.

Pittman, A., Lindau, R., Andersen, P., & Wax, M. K. (2014). Stomal recurrence: Salvage surgery and reconstruction utilizing microvascular free tissue transfer. *Head and Neck, 36*(10), 1431-1434.

Background. Stomal recurrence in patients after laryngectomy has a poor prognosis. Studies

performed using sternal resection with pectoralis flap reconstruction report <25% 2-year survival. The purpose of this study was to ascertain whether the use of larger resection with free flap reconstruction improves survival. Methods. Thirteen cases of stomal recurrence that underwent extended sternal resection and free flap reconstruction were identified and classified according to Sisson criteria. Postoperative morbidity, mortality, and survival were assessed. Results. Median survival was 10 months in patients with Sisson types I and II, with 37.5% 1-year and 25% 2-year survival. Median survival was 6 months in patients with Sisson types III and IV, with 40% 1-year and 0% 2-year survival. There were 2 perioperative deaths and a major morbidity rate of 45%. Conclusion. Salvage surgery using free flap reconstruction did not show improved survival rates compared with previously described techniques.

Protopsaltis, T., Schwab, F., Bronsard, N., Smith, J. S., Klineberg, E., Mundis, G., et al. (2014). The t1 pelvic angle, a novel radiographic measure of global sagittal deformity, accounts for both spinal inclination and pelvic tilt and correlates with health-related quality of life. *The Journal of Bone and Joint Surgery.American Volume, 96*(19), 1631-1640.

BACKGROUND: Adult spinal deformity is a prevalent cause of pain and disability. Established measures of sagittal spinopelvic alignment such as sagittal vertical axis and pelvic tilt can be modified by postural compensation, including pelvic retroversion, knee flexion, and the use of assistive devices for standing. We introduce the T1 pelvic angle, a novel measure of sagittal alignment that simultaneously accounts for both spinal inclination and pelvic retroversion. The purpose of this study was to investigate the relationship of the T1 pelvic angle and other established sagittal alignment measures and to correlate these parameters with health-related quality-of-life measures. METHODS: This is a multicenter, prospective, cross-sectional analysis of consecutive patients with adult spinal deformity. Inclusion criteria were adult spinal deformity, an age of greater than eighteen years, and any of the following: scoliosis, a Cobb angle of >/=20 degrees , sagittal vertical axis of >/=5 cm, thoracic kyphosis of >/=60 degrees , and pelvic tilt of >/=25 degrees . Clinical measures of disability included the Oswestry Disability Index (ODI), Scoliosis Research Society (SRS)-22, and Short Form-36 (SF-36) questionnaires. RESULTS: Five hundred and fifty-nine consecutive patients with adult spinal deformity (mean age, 52.5 years) were enrolled. The T1 pelvic angle correlated with the sagittal vertical axis (r = 0.837), pelvic

incidence minus lumbar lordosis (r = 0.889), and pelvic tilt (0.933). Categorizing the patients by increasing T1 pelvic angle (30 degrees) revealed a significant and progressive worsening in health-related quality of life (p 30 degrees) revealed a significant and progressive worsening in health-related quality of life (p 40), and the meaningful change in T1 pelvic angle corresponding to one minimal clinically important difference was 4.1 degrees on the ODI. CONCLUSIONS: The T1 pelvic angle correlates with health-related quality of life in patients with adult spinal deformity. The T1 pelvic angle is related to both pelvic tilt and sagittal vertical axis; however, unlike sagittal vertical axis, it does not vary on the basis of the extent of pelvic retroversion or patient support in standing. Since the T1 pelvic angle is an angular and not a linear measure, it does not require calibration of the radiograph. Thus, the T1 pelvic angle measures sagittal deformity independent of many postural compensatory mechanisms, and it can be useful as a preoperative planning tool, with a target T1 pelvic angle of <14 degrees . LEVEL OF EVIDENCE: Diagnostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Quittner, A. L., O'Donnell, A. E., Salathe, M. A., Lewis, S. A., Li, X., Montgomery, A. B., et al. (2014). Quality of life questionnaire-bronchiectasis: Final psychometric analyses and determination of minimal important difference scores. *Thorax,*

BACKGROUND: The Quality of Life-Bronchiectasis (QOL-B), a self-administered, patient-reported outcome measure assessing symptoms, functioning and health-related quality of life for patients with non-cystic fibrosis (CF) bronchiectasis, contains 37 items on 8 scales (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden). METHODS: Psychometric analyses of QOL-B V.3.0 used data from two double-blind, multicentre, randomised, placebo-controlled, phase III trials of aztreonam for inhalation solution (AZLI) in 542 patients with non-CF bronchiectasis and Gram-negative endobronchial infection. RESULTS: Excellent internal consistency (Cronbach's alpha >/=0.70) and 2-week test-retest reliability (intraclass correlation coefficients >/=0.72) were demonstrated for each scale. Convergent validity with 6 min walk test was observed for Physical and Role Functioning scores. No floor or ceiling effects (baseline scores of 0 or 100) were found for the Respiratory Symptoms scale (primary endpoint of trials). Baseline Respiratory Symptoms scores discriminated between patients based on baseline FEV1% predicted in only one trial. The minimal

important difference score for the Respiratory Symptoms scale was 8.0 points. AZLI did not show efficacy in the two phase III trials. QOL-B responsivity to treatment was assessed by examining changes from baseline QOL-B scores at study visits at which protocol-defined pulmonary exacerbations were reported. Mean Respiratory Symptoms scores decreased 14.0 and 14.2 points from baseline for placebo-treated and AZLI-treated patients with exacerbations, indicating that worsening respiratory symptoms were reflected in clinically meaningful changes in QOL-B scores. CONCLUSIONS: Previously established content validity, reliability and responsivity of the QOL-B are confirmed by this final validation study. The QOL-B is available for use in clinical trials and routine clinical practice.

Raber, J., Olsen, R. H. J., Su, W., Foster, S., Xing, R., Acevedo, S. F., et al. (2014). CD44 is required for spatial memory retention and sensorimotor functions. *Behavioural Brain Research, 275*, 146-149.

CD44 is a transmembrane receptor for the glycosaminoglycan hyaluronan, a component of the extracellular matrix. CD44 is expressed by neural stem/progenitor cells, astrocytes, and some neurons but its function in the central nervous system is unknown. To determine the role of CD44 in brain function, we behaviorally analyzed CD44-null (KO) and wild-type (WT) mice. KO mice showed increased activity levels in the light-dark test and a trend toward increased activity in the open field. In addition, KO mice showed impaired hippocampus-dependent spatial memory retention in the probe trial following the first hidden-platform training day in the Morris water maze: WT mice showed spatial memory retention and spent more time in the target quadrant than any other quadrant, while KO mice did not. Although there were no genotype differences in swim speeds during the water maze training sessions with the visible or hidden platform, sensorimotor impairments were seen in other behavioral tests. In the inclined screen and balance beam tests, KO mice moved less than WT mice. In the wire hang test, KO mice also fell off of the wire faster than WT mice. In contrast, there was no genotype difference when emotional learning and memory were assessed in the passive avoidance test. These data support an important role for CD44 in locomotor and sensorimotor functions, and in spatial memory retention.

Ramachandran, D., Mulle, J. G., Locke, A. E., Bean, L. J., Rosser, T. C., Bose, P., et al. (2014). Contribution of copy-number variation to down syndrome-associated atrioventricular septal defects. *Genetics in Medicine : Official Journal of the American College of Medical Genetics,* Purpose:The goal of this study was to identify the contribution of large copy-number variants to Down syndrome-associated atrioventricular septal defects, the risk for which in the trisomic population is 2,000-fold more as compared with that of the general disomic population.Methods:Genome-wide copy-number variant analysis was performed on 452 individuals with Down syndrome (210 cases with complete atrioventricular septal defects; 242 controls with structurally normal hearts) using Affymetrix SNP 6.0 arrays, making this the largest heart study conducted to date on a trisomic background.Results:Large, common copy-number variants with substantial effect sizes (OR > 2.0) do not account for the increased risk observed in Down syndrome-associated atrioventricular septal defects. By contrast, cases had a greater burden of large, rare deletions ($P < 0.01$) and intersected more genes ($P < 0.007$) as compared with controls. We also observed a suggestive enrichment of deletions intersecting ciliome genes in cases as compared with controls.Conclusion:Our data provide strong evidence that large, rare deletions increase the risk of Down syndrome-associated atrioventricular septal defects, whereas large, common copy-number variants do not appear to increase the risk of Down syndrome-associated atrioventricular septal defects. The genetic architecture of atrioventricular septal defects is complex and multifactorial in nature.Genet Med advance online publication 23 October 2014Genetics in Medicine (2014); doi:10.1038/gim.2014.144.

Ramaker, M. J., Strong-Kaufman, M. N., Ford, M. M., Phillips, T. J., & Finn, D. A. (2014). Effect of nucleus accumbens shell infusions of ganaxolone or gaboxadol on ethanol consumption in mice. *Psychopharmacology,* RATIONALE: Allopregnanolone (ALLO) is an endogenous neuroactive steroid thought to alter the reinforcement value of alcohol (ethanol) due to its actions as a positive modulator of the GABAA receptor (GABAAR). Extrasynaptic GABAARs may be a particularly sensitive target of ethanol and neuroactive steroids. Previous work showed that systemic injections of an ALLO analog, ganaxolone (GAN), or an extrasynaptic GABAAR agonist (gaboxadol; THIP) decreased ethanol intake in male mice with limited access to ethanol. OBJECTIVES: The present studies tested

whether activation of GABAARs in the nucleus accumbens (NAc) shell by GAN or THIP was sufficient to reduce ethanol intake. C57BL/6J male mice had 2-h access to 10 % ethanol (10E) and water, and 10E intake was measured following site-specific infusions of GAN or THIP. RESULTS: Decreases in limited-access 10E consumption were observed following site-specific bilateral infusions of either drug into the NAc shell. Significant changes in intake were absent when the drugs were infused in a region dorsal to the target site (GAN) or into the lateral ventricle (THIP). Locomotor data confirmed that the decreases in intake were not due to a sedative effect of the drugs. CONCLUSIONS: These data demonstrate the sufficiency of GABAAR activation by a positive allosteric modulator or an agonist with selectivity for extrasynaptic GABAARs to decrease ethanol consumption in mice. Importantly, more refined GABAAR-active targets that decrease ethanol intake may enhance our understanding and ability to treat alcohol use disorders.

Rauch, B. J., Gustafson, A., & Perona, J. J. (2014). Novel proteins for homocysteine biosynthesis in anaerobic microorganisms. *Molecular Microbiology,*

The metabolic network for sulfide assimilation and trafficking in methanogens is largely unknown. To discover novel proteins required for these processes, we used bioinformatics to identify genes co-occurring with the protein biosynthesis enzyme SepCysS, which converts phosphoseryl-tRNACys to cysteinyl-tRNACys in nearly all methanogens. Exhaustive analysis revealed three conserved protein families, each containing molecular signatures predicting function in sulfur metabolism. One of these families, classified within clusters of orthologous groups (COG) 1900, possesses two conserved cysteine residues and is often found in genomic contexts together with known sulfur metabolic genes. A second protein family is predicted to bind two 4Fe-4S clusters. All three genes were also identified in more than 50 strictly anaerobic bacterial genera from nine distinct phyla. Gene-deletion and growth experiments in Methanosarcina acetivorans, using sulfide as the sole sulfur source, demonstrate that two of the proteins (MA1821 and MA1822) are essential to homocysteine biosynthesis in a background lacking an additional gene for sulfur insertion into homocysteine. Mutational analysis confirms the importance of several structural elements, including a conserved cysteine residue and the predicted 4Fe-4S cluster-binding domain.

Reed, D., Block, R. G., & Johnson, R. (2014). Creating an adolescent and young adult cancer program: Lessons learned from pediatric and adult oncology practice bases. *Journal of the National Comprehensive Cancer Network : JNCCN, 12*(10), 1409-1415.

Driven by reports of unmet clinical needs and lack of survival improvement, programs for adolescents and young adults (AYAs) with cancer have become increasingly common across the United States during the past 10 years. Programs generally originate from existing pediatric or adult hospitals, serve all or a subset of patients between 15 and 39 years of age at the time of cancer diagnosis, and aim to work collaboratively with other branches of their institution to deliver superior care for AYAs. Until recently, programs responded to local needs and evolved without an established framework for growth. Over the past several years, organizations including NCCN have published guidelines for AYA cancer care and for the development of clinical AYA programs. This article reviews these publications, describes the growth and development of 2 nationally recognized AYA centers-Seattle Children's Hospital and Moffitt Cancer Center-and offers practical suggestions to assist developing AYA programs. AYA oncology is entering a new era of increasing public recognition and nationally coordinated growth, as evidenced by the recent establishment of the Change it Back's Centers of Excellence Program that codifies criteria for excellence in AYA cancer care. AYA programs have the potential to improve care for a vital and underserved patient population, stimulate collaborative research, and enhance relationships with patients, the local community, referring physicians, and donors.

Reiss, L. A., Ito, R. A., Eggleston, J. L., Liao, S., Becker, J. J., Lakin, C. E., et al. (2014). Pitch adaptation patterns in bimodal cochlear implant users: Over time and after experience. *Ear and Hearing,*

OBJECTIVE:: Pitch plasticity has been observed in Hybrid cochlear implant (CI) users. Does pitch plasticity also occur in bimodal CI users with traditional long-electrode CIs, and is pitch adaptation pattern associated with electrode discrimination or speech recognition performance? The goals of this study were to characterize pitch adaptation patterns in long-electrode CI users, to correlate these patterns with electrode discrimination and speech perception outcomes, and to analyze which subject factors are associated with the different patterns. DESIGN:: Electric-to-acoustic pitch matches were obtained in 19 subjects over time from CI activation to at least 12

months after activation, and in a separate group of 18 subjects in a single visit after at least 24 months of CI experience. Audiometric thresholds, electrode discrimination performance, and speech perception scores were also measured. RESULTS:: Subjects measured over time had pitch adaptation patterns that fit one of the following categories: (1) "Pitch-adapting," that is, the mismatch between perceived electrode pitch and the corresponding frequency-to-electrode allocations decreased; (2) "Pitch-dropping," that is, the pitches of multiple electrodes dropped and converged to a similar low-pitch; and (3) "Pitch-unchanging," that is, the electrode pitches did not change. Subjects measured after CI experience had a parallel set of adaptation patterns: (1) "Matched-pitch," that is, the electrode pitch was matched to the frequency allocation; (2) "Low-pitch," that is, the pitches of multiple electrodes were all around the lowest frequency allocation; and (3) "Nonmatched-pitch," that is, the pitch patterns were compressed relative to the frequency allocations and did not fit either the matched-pitch or low-pitch categories. Unlike Hybrid CI users which were mostly in the pitch-adapting or matched-pitch category, the majority of bimodal CI users were in the latter two categories, pitch-dropping/low-pitch or pitch-unchanging/nonmatched-pitch. Subjects with pitch-adapting or matched-pitch patterns tended to have better low-frequency thresholds than subjects in the latter categories. Changes in electrode discrimination over time were not associated with changes in pitch differences between electrodes. Reductions in speech perception scores over time showed a weak but nonsignificant association with dropping-pitch patterns. CONCLUSIONS:: Bimodal CI users with more residual hearing may have somewhat greater similarity to Hybrid CI users and be more likely to adapt pitch perception to reduce mismatch with the frequencies allocated to the electrodes and the acoustic hearing. In contrast, bimodal CI users with less residual hearing exhibit either no adaptation, or surprisingly, a third pattern in which the pitches of the basal electrodes drop to match the frequency range allocated to the most apical electrode. The lack of association of electrode discrimination changes with pitch changes suggests that electrode discrimination does not depend on perceived pitch differences between electrodes, but rather on some other characteristics such as timbre. In contrast, speech perception may depend more on pitch perception and the ability to distinguish pitch between electrodes, especially since during multielectrode stimulation, cues such as timbre may be less useful for discrimination.

Rich, N. E., Sanders, C., Hughes, R. S., Fontana, R. J., Stravitz, R. T., Fix, O., et al. (2014). Malignant infiltration of the liver presenting as acute liver failure. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association,*

There have been few reports of acute liver failure (ALF, with encephalopathy and coagulopathy) due to infiltration of the liver by malignant cells. We describe a case series of 27 patients with ALF caused by malignancy. We examined a large, multi-center ALF registry (1910 patients; mean age, 47.1+/-13.9 years) and found only 27 cases (1.4%) of ALF attributed to malignancy. Twenty cases (74%) presented with abdominal pain and 11 with ascites. The malignancies included lymphoma or leukemia (33%), breast cancer, (30%), and colon cancer (7%); 90% of the patients with lymphoma or leukemia had no history of cancer, compared to 25% of patients with breast cancer. Overall, 44% of the patients had evidence of liver masses by imaging. Diagnosis was confirmed by biopsy in 15 (55%) and autopsy for 6 cases. Twenty-four patients (89%) died within 3 weeks of ALF.

Richardson, A. S., Meyer, K. A., Howard, A. G., Boone-Heinonen, J., Popkin, B. M., Evenson, K. R., et al. (2014). Neighborhood socioeconomic status and food environment: A 20-year longitudinal latent class analysis among CARDIA participants. *Health & Place, 30C*, 145-153.

Cross-sectional studies suggest that neighborhood socioeconomic (SES) disadvantage is associated with obesogenic food environments. Yet, it is unknown how exposure to neighborhood SES patterning through adulthood corresponds to food environments that also change over time. We used latent class analysis (LCA) to classify participants in the U.S.-based Coronary Artery Risk Development in Young Adults study [n=5,114 at baseline 1985-1986 to 2005-2006] according to their longitudinal neighborhood SES residency patterns (upward, downward, stable high and stable low). For most classes of residents, the availability of fast food and non-fast food restaurants and supermarkets and convenience stores increased ($p<0.001$). Yet, socioeconomically disadvantaged neighborhood residents had fewer fast food and non-fast food restaurants, more convenience stores, and the same number of supermarkets in their neighborhoods than the advantaged residents. In addition to targeting the pervasive fast food restaurant and convenient store retail growth, improving neighborhood restaurant options for disadvantaged residents may reduce food environment disparities.

Roark, B., Allauzen, C., & Riley, M. (2013). Smoothed marginal distribution constraints for language modeling. *51st Annual Meeting of the Association for Computational Linguistics, ACL 2013,* Sofia. *, 1.* pp. 43-52.

We present an algorithm for re-estimating parameters of backoff n-gram language models so as to preserve given marginal distributions, along the lines of wellknown Kneser-Ney (1995) smoothing. Unlike Kneser-Ney, our approach is designed to be applied to any given smoothed backoff model, including models that have already been heavily pruned. As a result, the algorithm avoids issues observed when pruning Kneser-Ney models (Siivola et al., 2007; Chelba et al., 2010), while retaining the benefits of such marginal distribution constraints. We present experimental results for heavily pruned backoff ngram models, and demonstrate perplexity and word error rate reductions when used with various baseline smoothing methods. An open-source version of the algorithm has been released as part of the OpenGrm ngram library. © 2013 Association for Computational Linguistics.

Rodriguez-Contreras, D., Aslan, H., Feng, X., Tran, K., Yates, P. A., Kamhawi, S., et al. (2014). Regulation and biological function of a flagellar glucose transporter in leishmania mexicana: A potential glucose sensor. *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology,*

In Leishmania mexicana parasites, a unique glucose transporter, LmxGT1, is selectively targeted to the flagellar membrane, suggesting a possible sensory role that is often associated with ciliary membrane proteins. Expression of LmxGT1 is down-regulated approximately 20-fold by increasing cell density but is up-regulated approximately 50-fold by depleting glucose from the medium, and the permease is strongly down-regulated when flagellated insect-stage promastigotes invade mammalian macrophages and transform into intracellular amastigotes. Regulation of LmxGT1 expression by glucose and during the lifecycle operates at the level of protein stability. Significantly, a lmxgt1 null mutant, grown in abundant glucose, undergoes catastrophic loss of viability when parasites deplete glucose from the medium, a property not exhibited by wild-type or add-back lines. These results suggest that LmxGT1 may function as a glucose sensor that allows parasites to enter the stationary phase when they deplete glucose and that in the absence of this sensor, parasites do not maintain viability when they run out of

glucose. However, alternate roles for LmxGT1 in monitoring glucose availability are considered. The absence of known sensory receptors with defined ligands and biologic functions in Leishmania and related kinetoplastid parasites underscores the potential significance of these observations.-Rodriguez-Contreras, D., Aslan, H., Feng, X., Tran, K., Yates, P. A., Kamhawi, S., Landfear, S. M. Regulation and biological function of a flagellar glucose transporter in Leishmania mexicana: a potential glucose sensor.

Rodriguez-Contreras, D., & Hamilton, N. (2014). Gluconeogenesis in leishmania mexicana: Contribution of glycerol kinase, phosphoenolpyruvate carboxykinase and pyruvate phosphate dikinase. *The Journal of Biological Chemistry,*

Gluconeogenesis is an active pathway in Leishmania amastigotes and is essential for their survival within the mammalian cells. However, our knowledge about this pathway in trypanosomatids is very limited. We investigated the role of glycerol kinase (GK)1, phosphoenolpyruvate carboxykinase (PEPCK) and pyruvate phosphate dikinase (PPDK) in gluconeogenesis by generating the respective L. mexicana Deltagk, Deltapepck and Deltappdk null mutants. Our results demonstrated that indeed GK, PEPCK and PPDK are key players in the gluconeogenesis pathway in Leishmania, although stage-specific differences in their contribution to this pathway were found. GK participates in the entry of glycerol in promastigotes and amastigotes, PEPCK participates in the entry of aspartate in promastigotes, and PPDK is involved in the entry of alanine in amastigotes. Furthermore, the majority of alanine enters into the pathway via decarboxylation of pyruvate in promastigotes, whereas a pathway redundancy is suggested for the entry of aspartate in amastigotes. Interestingly, we also found that L-lactate, an abundant glucogenic precursor in mammals, was used by Leishmania amastigotes to synthesize mannogen, entering the pathway through PPDK. On the basis of these new results, we propose a revision in the current model of gluconeogenesis in Leishmania, emphasizing the differences between amastigotes and promastigotes. This work underlines the importance of studying the trypanosomatid intracellular life cycle stages in order to gain a better understanding of the pathologies caused in humans.

Rosenbaum, B. P., Kshettry, V. R., Kelly, M. L., Mroz, T. E., & Weil, R. J. (2014). Trends in inpatient vertebroplasty and kyphoplasty volume in the united states, 2005-2011: Assessing the impact of randomized controlled trials. *Journal of Spinal Disorders & Techniques,*

STUDY DESIGN:: Retrospective analysis of the Nationwide Inpatient Sample (NIS), 2005-2011. OBJECTIVE:: To identify trends in procedural volume and rates in the time period surrounding publication of randomized controlled trials (RCTs) that examined the utility of vertebroplasty and kyphoplasty. SUMMARY OF BACKGROUND DATA:: Vertebroplasty and kyphoplasty are frequently performed for vertebral compression fractures. Several RCTs have been published with conflicting outcomes regarding pain and quality of life compared to non-surgical management and sham procedures. Four RCTs with discordant results were published in 2009. METHODS:: The NIS provided longitudinal, retrospective data on United States' inpatients between 2005 and 2011. Inclusion was determined by a principal or secondary ICD-9-CM code of 81.65 (percutaneous vertebroplasty) or 81.66 (percutaneous vertebral augmentation; "kyphoplasty"). No diagnoses were excluded. Years were stratified as "pre" (2005-2008) and "post" (2010-2011) in relation to the four RCTs published in 2009. Patient, hospital, and admission characteristics were compared using Pearson's chi-squared test. RESULTS:: The estimated annual inpatient procedures performed decreased from 54,833 to 39,832 in the pre and post periods, respectively. The procedural rate for fractures decreased from 20.1% to 14.7% (P<0.0001). Patient and hospital demographics did not change considerably between the time periods. In the post period, weekend admissions increased (34.2 vs. 12.4%, P<0.0001), elective admissions decreased (21.4 vs. 40.0%, P<0.0001), routine discharge decreased (33.0 vs. 52.1%, P<0.0001), and encounters with three or more Elixhauser comorbidities increased (54.5 vs. 39.1%, P<0.0001). CONCLUSION:: The absolute rate of inpatient vertebroplasty and kyphoplasty procedures for fractures decreased five percent in the period (2010-2011) following the publication of four RCTs in 2009. The proportion of elective admissions and routine discharges decreased, possibly indicating a population with greater disease severity. While our analysis cannot demonstrate a cause-and-effect relationship, the decreased inpatient volume and procedural rates surrounding the publication of sentinel negative RCTs is clearly observed.

Rosenbaum, J. T. (2014). Nibbling away at the diagnosis of idiopathic uveitis. *JAMA Ophthalmology,*

Schillace, R. V., Skinner, A. M., Pommier, R. F., O'Neill, S., Muller, P. J., Naik, A. M., et al. (2014). Estrogen receptor, progesterone receptor, interleukin-6 and interleukin-8 are variable in breast cancer and benign stem/progenitor cell populations. *BMC Cancer, 14*(1), 733-2407-14-733. BACKGROUND: Estrogen receptor positive breast cancers have high recurrence rates despite tamoxifen therapy. Breast cancer stem/progenitor cells (BCSCs) initiate tumors, but expression of estrogen (ER) or progesterone receptors (PR) and response to tamoxifen is unknown. Interleukin-6 (IL-6) and interleukin-8 (IL-8) may influence tumor response to therapy but expression in BCSCs is also unknown. METHODS: BCSCs were isolated from breast cancer and benign surgical specimens based on CD49f/CD24 markers. CD44 was measured. Gene and protein expression of ER alpha, ER beta, PR, IL-6 and IL-8 were measured by proximity ligation assay and qRT-PCR. RESULTS: Gene expression was highly variable between patients. On average, BCSCs expressed 10-106 fold less ERalpha mRNA and 10-103 fold more ERbeta than tumors or benign stem/progenitor cells (SC). BCSC lin-CD49f-CD24-cells were the exception and expressed higher ERalpha mRNA. PR mRNA in BCSCs averaged 10-104 fold less than in tumors or benign tissue, but was similar to benign SCs. ERalpha and PR protein detection in BCSCs was lower than ER positive and similar to ER negative tumors. IL-8 mRNA was 10-104 higher than tumor and 102 fold higher than benign tissue. IL-6 mRNA levels were equivalent to benign and only higher than tumor in lin-CD49f-CD24-cells. IL-6 and IL-8 proteins showed overlapping levels of expressions among various tissues and cell populations. CONCLUSIONS: BCSCs and SCs demonstrate patient-specific variability of gene/protein expression. BCSC gene/protein expression may vary from that of other tumor cells, suggesting a mechanism by which hormone refractory disease may occur.

Schmid, M., Steinlein, C., Tian, Q., Hanlon Newell, A. E., Gessler, M., Olson, S. B., et al. (2014). Erratum to: Mosaic variegated aneuploidy in mouse BubR1 deficient embryos and pregnancy loss in human. *Chromosome Research,*

Secher, A., Jelsing, J., Baquero, A. F., Hecksher-Sørensen, J., Cowley, M. A., Dalbøge, L. S., et al. (2014). The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *Journal of Clinical Investigation, 124*(10), 4473-4488.

Liraglutide is a glucagon-like peptide-1 (GLP-1) analog marketed for the treatment of type 2 diabetes. Besides lowering blood glucose, liraglutide also reduces body weight. It is not fully understood how liraglutide induces weight loss or to what degree liraglutide acts directly in the brain. Here, we determined that liraglutide does not activate GLP-1-producing neurons in the hindbrain, and liraglutide-dependent body weight reduction in rats was independent of GLP-1 receptors (GLP-1Rs) in the vagus nerve, area postrema, and paraventricular nucleus. Peripheral injection of fuorescently labeled liraglutide in mice revealed the presence of the drug in the circumventricular organs. Moreover, labeled liraglutide bound neurons within the arcuate nucleus (ARC) and other discrete sites in the hypothalamus. GLP-1R was necessary for liraglutide uptake in the brain, as liraglutide binding was not seen in Glp1r-/- mice. In the ARC, liraglutide was internalized in neurons expressing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). Electrophysiological measurements of murine brain slices revealed that GLP-1 directly stimulates POMC/CART neurons and indirectly inhibits neurotransmission in neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) via GABA-dependent signaling. Collectively, our findings indicate that the GLP-1R on POMC/CART-expressing ARC neurons likely mediates liraglutide-induced weight loss.

Seol, S. H., & Lindner, J. R. (2014). A primer on the methods and applications for contrast echocardiography in clinical imaging. *Journal of Cardiovascular Ultrasound, 22*(3), 101-110. Contrast echocardiography is broadly described as a variety of techniques whereby the blood pool on cardiac ultrasound is enhanced with encapsulated gas-filled microbubbles or other acoustically active nano- or microparticles. The development of this technology has occurred primarily in response to the need improve current diagnostic applications of echocardiography such as the need to better define left ventricular cavity volumes, regional wall motion, or the presence or absence of masses and thrombi. A secondary reason for the development of contrast echocardiography has been to expand the capabilities of echocardiography. These new applications include myocardial perfusion imaging for detection of ischemia and viability, perfusion imaging of masses/tumors, and molecular imaging. The ability to fill all of these current and future clinical roles has been predicated on the ability to produce robust contrast signal which, in turn, has relied on technical innovation with regards to the microbubble contrast agents

and the ultrasound imaging paradigms. In this review, we will discuss the basics of contrast echocardiography including the composition of microbubble contrast agents, the unique imaging methods used to optimize contrast signal-to-noise ratio, and the clinical applications of contrast echocardiography that have made a clinical impact.

Shah, M. M., Steele, E. A., White, K. P., & Wilson, D. J. (2014). Syringoid eccrine carcinoma of the eyelid presenting as cicatricial entropion. *International Journal of Ophthalmology, 7*(5), 912-913.

Shim, C. Y., Kim, S., Chadderdon, S., Wu, M., Qi, Y., Xie, A., et al. (2014). Epoxyeicosatrienoic acids mediate insulin-mediated augmentation in skeletal muscle perfusion and blood volume. *American Journal of Physiology.Endocrinology and Metabolism,* , ajpendo.00216.2014.

Skeletal muscle microvascular blood flow (MBF) increases in response to physiologic hyperinsulinemia. This vascular action of insulin may facilitate glucose uptake. We hypothesized that epoxyeicosatrienoic acids (EETs), a family of arachadonic acid-derived endothelium-derived hyperpolarizing factors, is a mediator of insulin's microvascular effects. Contrast-enhanced ultrasound (CEU) was performed to quantify skeletal muscle capillary blood volume (CBV) and MBF in wild-type and obese insulin-resistant (db/db) mice after administration of vehicle or tAUCB, an inhibitor of soluble epoxide hydrolase which converts EETs to less active dihydroxyeicosatrienoic acids. Similar studies were performed in rats pre-treated with L-NAME. CEU was also performed in rats undergoing a euglycemic hyperinsulinemic clamp, half of which were pre-treated with the epoxygenase inhibitor MS-PPOH to inhibit EET synthesis. In both wild type and db/db mice, intravenous tAUCB produced an increase in CBV (65-100% increase at 30 min, $p<0.05$) and in MBF. In db/db/ mice tAUCB also reduced plasma glucose by approximately 15%. In rats pretreated with L-NAME, tAUCB after produced a significant approximately 20% increase in CBV indicating a component of vascular response independent of nitric oxide (NO) production. Hyperinsulinemic clamp produced a time-dependent increase in MBF (19+/-36 and 76+/-49% at 90 min, $p=0.026$) mediated in part by an increase in CBV. Insulin-mediated changes in both CBV and MBF during the clamp were entirely blocked MS-PPOH. We conclude that EETs are a mediator of insulin-mediated augmentation in skeletal muscle perfusion and are involved in regulating changes in CBV during hyperinsulinemia.

Shin, A. C., Fasshauer, M., Filatova, N., Grundell, L. A., Zielinski, E., Zhou, J. Y., et al. (2014). Brain insulin lowers circulating BCAA levels by inducing hepatic BCAA catabolism. *Cell Metabolism,* Circulating branched-chain amino acid (BCAA) levels are elevated in obesity/diabetes and are a sensitive predictor for type 2 diabetes. Here we show in rats that insulin dose-dependently lowers plasma BCAA levels through induction of hepatic protein expression and activity of branched-chain alpha-keto acid dehydrogenase (BCKDH), the rate-limiting enzyme in the BCAA degradation pathway. Selective induction of hypothalamic insulin signaling in rats and genetic modulation of brain insulin receptors in mice demonstrate that brain insulin signaling is a major regulator of BCAA metabolism by inducing hepatic BCKDH. Short-term overfeeding impairs the ability of brain insulin to lower BCAAs in rats. High-fat feeding in nonhuman primates and obesity and/or diabetes in humans is associated with reduced BCKDH protein in liver. These findings support the concept that decreased hepatic BCKDH is a major cause of increased plasma BCAAs and that hypothalamic insulin resistance may account for impaired BCAA metabolism in obesity and diabetes.

Shtivelman, E., Beer, T. M., & Evans, C. P. (2014). Molecular pathways and targets in prostate cancer. *Oncotarget, 5*(17), 7217-7259.

Prostate cancer co-opts a unique set of cellular pathways in its initiation and progression. The heterogeneity of prostate cancers is evident at earlier stages, and has led to rigorous efforts to stratify the localized prostate cancers, so that progression to advanced stages could be predicted based upon salient features of the early disease. The deregulated androgen receptor signaling is undeniably most important in the progression of the majority of prostate tumors. It is perhaps because of the primacy of the androgen receptor governed transcriptional program in prostate epithelium cells that once this program is corrupted, the consequences of the ensuing changes in activity are pleotropic and could contribute to malignancy in multiple ways. Following localized surgical and radiation therapies, 20-40% of patients will relapse and progress, and will be treated with androgen deprivation therapies. The successful development of the new agents that inhibit androgen signaling has changed the progression free survival in hormone resistant disease, but this has not changed the almost ubiquitous development of truly resistant phenotypes in advanced prostate cancer. This review summarizes the current understanding of the molecular

pathways involved in localized and metastatic prostate cancer, with an emphasis on the clinical implications of the new knowledge.

Simon, J., Kinkel, R., Kollman, C., O'Connor, P., Fisher, E., You, X., et al. (2014). Ten-year follow-up of the 'minimal MRI lesion' subgroup from the original CHAMPS multiple sclerosis prevention trial. *Multiple Sclerosis (Houndmills, Basingstoke, England),*

BACKGROUND: Patients with clinically isolated syndrome (CIS) and characteristic magnetic resonance imaging (MRI) lesions are at high risk for multiple sclerosis (MS). However, patients with a minimal MRI lesion burden (a low T2-hyperintense [low T2] lesion count) may have borderline formal diagnostic criteria, presenting a clinical management challenge. OBJECTIVE: Compare the 10-year disease progression of patients with low and higher T2 lesion counts treated over most intervals. METHODS: CIS patients from the original CHAMPS MS trial were retrospectively assigned to low-T2 (first quartile; 2-8 lesions) or higher-T2 (second through fourth quartiles; >/= 9 lesions) groups using baseline T2 lesion counts. The 5- and 10-year open-label extension of CHAMPS (CHAMPIONS) evaluated conversion to clinically definite MS (CDMS), MRI activity, relapses, and disability. RESULTS: The vast majority of patients showed new disease activity by MRI and/or clinical criteria at 10 years (low-T2 86%; higher-T2 98%). Fewer low-T2 than higher-T2 patients developed CDMS (40% vs. 63%; p = 0.013); low-T2 patients also had fewer new brain lesions, less brain volume loss, and less disability progression. CONCLUSION: CIS patients with low T2 lesion counts show continued disease activity. However, all assessments of disease progression over 10 years indicated a significantly less severe disease course for low-T2 patients.

Simpson, E. L., Chalmers, J. R., Hanifin, J. M., Thomas, K. S., Cork, M. J., McLean, W. H., et al. (2014). Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *The Journal of Allergy and Clinical Immunology, 134*(4), 818-823.

BACKGROUND: Atopic dermatitis (atopic eczema) is a chronic inflammatory skin disease that has reached epidemic proportions in children worldwide and is increasing in prevalence. Because of the significant socioeconomic effect of atopic dermatitis and its effect on the quality of life of children and families, there have been decades of research focused on disease prevention, with

limited success. Recent advances in cutaneous biology suggest skin barrier defects might be key initiators of atopic dermatitis and possibly allergic sensitization. OBJECTIVE: Our objective was to test whether skin barrier enhancement from birth represents a feasible strategy for reducing the incidence of atopic dermatitis in high-risk neonates. METHODS: We performed a randomized controlled trial in the United States and United Kingdom of 124 neonates at high risk for atopic dermatitis. Parents in the intervention arm were instructed to apply full-body emollient therapy at least once per day starting within 3 weeks of birth. Parents in the control arm were asked to use no emollients. The primary feasibility outcome was the percentage of families willing to be randomized. The primary clinical outcome was the cumulative incidence of atopic dermatitis at 6 months, as assessed by a trained investigator. RESULTS: Forty-two percent of eligible families agreed to be randomized into the trial. All participating families in the intervention arm found the intervention acceptable. A statistically significant protective effect was found with the use of daily emollient on the cumulative incidence of atopic dermatitis with a relative risk reduction of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; P = .017). There were no emollient-related adverse events and no differences in adverse events between groups. CONCLUSION: The results of this trial demonstrate that emollient therapy from birth represents a feasible, safe, and effective approach for atopic dermatitis prevention. If confirmed in larger trials, emollient therapy from birth would be a simple and low-cost intervention that could reduce the global burden of allergic diseases.

Smith, K. A., Smith, T. L., Mace, J. C., & Rudmik, L. Endoscopic sinus surgery compared to continued medical therapy for patients with refractory chronic rhinosinusitis. *International Forum of Allergy and Rhinology, 4*(10), 823-827.

Background: The decision to continue medical therapy or recommend endoscopic sinus surgery (ESS) can be challenging in patients with refractory chronic rhinosinusitis (CRS). The objective of this study was to evaluate continued medical therapy vs ESS for patients with refractory CRS who have severe reductions in baseline disease-specific quality of life (QoL). Methods: This was a prospective longitudinal crossover study between August 2011 and June 2013. All patients were >18 years old, diagnosed with CRS based on guideline recommendations, failed initial medical therapy and elected ESS. While waiting for ESS, all patients received continued medical therapy.

The preoperative waiting period outcomes (continued medical therapy) were compared to the postoperative outcomes. The primary outcome was change in disease-specific QoL (22-item Sinonasal Outcome Test [SNOT-22]). Secondary outcomes were change in endoscopic grading (Lund-Kennedy score), medication consumption, and work days missed in the preceding 90 days. Results: Thirty-one patients were enrolled. Mean baseline SNOT-22 score was 57.6. After a mean of 7.1 months of continued medical therapy, there was a worsening in SNOT-22 score (57.6 to 66.1; $p = 0.006$). After ESS, with a mean postoperative follow-up of 14.6 months, there was a significant improvement in SNOT-22 score (66.1 to 16.0; $p < 0.001$). There was also a significant improvement in endoscopic grading ($p < 0.001$) coupled with a reduction in both work days lost ($p < 0.001$) and medication consumption ($p < 0.01$). Conclusion: Results from the study suggest that ESS is a more effective intervention compared to continued medical therapy for patients with refractory CRS who have severe reductions in their baseline disease-specific QoL.

Smith, M. E., Chiovaro, J. C., O'Neil, M., Kansagara, D., Quinones, A. R., Freeman, M., et al. (2014). Early warning system scores for clinical deterioration in hospitalized patients: A systematic review. *Annals of the American Thoracic Society,*

Rationale: Early warning system (EWS) scores are used by hospital care teams to recognize early signs of clinical deterioration and trigger more intensive care. Objective: To systematically review the evidence on the ability of EWS scores to predict a patient's risk of clinical deterioration, and the impact of EWS implementation on health outcomes and resource utilization. Methods: We searched MEDLINE, CINAHL, and the Cochrane databases through May 2014. We included English language studies of EWS scores used with adults admitted to medical or surgical wards. We abstracted study characteristics including population, setting, sample size, duration, and criteria used for EWS scoring. For predictive ability, the primary outcomes were model discrimination on 48-hour mortality, cardiac arrest, or pulmonary arrest. Outcomes for impact of EWS implementation included 30-day mortality, cardiovascular events, use of vasopressors, respiratory failure, ventilator days, and resource utilization. We assessed study quality using a modified Quality in Prognosis Studies (QUIPS) assessment tool, where applicable. Measurements and Main Results: Of 11,183 citations reviewed, one controlled trial and 20 observational studies of 13 unique models met criteria. Eight studies addressed the predictive ability of EWS tools and

found a strong predictive value for death (AUROC 0.88-0.93) and cardiac arrest (AUROC 0.74-0.86) within 48 hours. Thirteen studies (one controlled trial and twelve pre-post observational studies) addressed the impact on health outcomes and resource utilization and had mixed results. The one study was a controlled trial was of good quality and found no difference in mortality, transfers to the ICU, and length. The pre-post design of the remaining studies have significant methodological limitations resulting in insufficient evidence to draw conclusions. limitations. Conclusions: EWS scores perform well for predicting cardiac arrest and death within 48 hours although the impact on health outcomes and resource utilization remains uncertaindue to methodological limitations. Efforts to more rigorously assess performance and effectiveness are needed as EWS use becomes more widespread. Primary Source of Funding: The research reported here was supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative project ESP 05-225, and the Portland VA Medical Center.

Snowden, J. M., Cheng, Y. W., Emeis, C. L., & Caughey, A. B. (2014). The impact of hospital obstetric volume on maternal outcomes in term, non-low-birthweight pregnancies. *American Journal of Obstetrics and Gynecology,*

OBJECTIVE: The impact of hospital obstetric volume specifically on maternal outcomes remains under studied. We examined the impact of hospital obstetric volume on maternal outcomes in low-risk women who delivered non-low-birthweight infants at term. STUDY DESIGN: We conducted a retrospective cohort study of term singleton, non-low-birthweight live births from 2007-2008 in California. Deliveries were categorized by hospital obstetric volume categories and separately for nonrural hospitals (category 1: 50-1199 deliveries per year; category 2: 1200-2399; category 3: 2400-3599, and category 4: >/=3600) and rural hospitals (category R1: 50-599 births per year; category R2: 600-1699; category R3: >/=1700). Maternal outcomes were compared with the use of the chi-square test and multivariable logistic regression. RESULTS: There were 736,643 births in 267 hospitals that met study criteria. After adjustment for confounders, there were higher rates of postpartum hemorrhage in the lowest-volume rural hospitals (category R1 adjusted odds ratio, 3.06; 95% confidence interval, 1.51-6.23). Rates of chorioamnionitis, endometritis, severe perineal lacerations, and wound infection did not differ

between volume categories. Longer lengths of stay were observed after maternal complications (eg, chorioamnionitis) in the lowest-volume hospitals (16.9% prolonged length of stay in category 1 hospitals vs 10.5% in category 4 hospitals; adjusted odds ratio, 1.91; 95% confidence interval, 1.01-3.61). CONCLUSION: After confounder adjustment, few maternal outcomes differed by hospital obstetric volume. However, elevated odds of postpartum hemorrhage in low-volume rural hospitals raises the possibility that maternal outcomes may differ by hospital volume and geography. Further research is needed on maternal outcomes in hospitals of different obstetric volumes.

Stecker, E. C., Teodorescu, C., Reinier, K., Uy-Evanado, A., Mariani, R., Chugh, H., et al. (2014). Ischemic heart disease diagnosed before sudden cardiac arrest is independently associated with improved survival. *Journal of the American Heart Association, 3*(5), e001160. BACKGROUND: Sudden cardiac arrest (SCA) is a significant public health problem, and rates of survival after resuscitation remain well below 10%. While several resuscitation-related factors are consistently associated with survival from SCA, the impact of specific comorbid conditions has not been assessed. METHODS AND RESULTS: The Oregon Sudden Unexpected Study is an ongoing, multisource, community-based study in Portland, Oregon. Patients with SCA who underwent attempted resuscitation between 2002 and 2012 were included in this analysis if there were both arrest and prearrest medical records available. Information from the emergency medical services system, medical examiner, public health division, hospitals, and clinics was used to adjudicate SCA, evaluate comorbidities, and identify medical treatments. Univariate and multivariate analyses were performed to investigate the influence of prearrest comorbidities on survival to hospital discharge. Among 1466 included patients, established resuscitation-related predictors (Utstein factors) were associated with survival, consistent with prior reports. When a panel of prearrest comorbidities was evaluated along with Utstein factors, recognized coronary artery disease was significantly associated and predicted higher odds of survival (unadjusted odds ratio 1.5, $P<0.001$; adjusted odds ratio 1.5, $P=0.02$). In multivariable logistic models, prearrest coronary artery disease modified the survival effects of bystander cardiopulmonary resuscitation, but did not modify other Utstein factors. CONCLUSIONS: An established diagnosis of coronary artery disease was associated with 50% higher odds of survival from resuscitated SCA after

adjustment for all arrest-related predictors. These findings raise novel potential mechanistic insights into survival after SCA, while highlighting the importance of early recognition and treatment of coronary artery disease.

Stephenson, L. S., Gorsuch, A., Hersh, W. R., Mohan, V., & Gold, J. A. (2014). Participation in EHR based simulation improves recognition of patient safety issues. *BMC Medical Education, 14*(1), 224-6920-14-224.

BACKGROUND: Electronic health records (EHR) are becoming increasingly integrated into the clinical environment. With the rapid proliferation of EHRs, a number of studies document an increase in adverse patient safety issues due to the EHR-user interface. Because of these issues, greater attention has been placed on novel educational activities which incorporate use of the EHR. The ICU environment presents many challenges to integrating an EHR given the vast amounts of data recorded each day, which must be interpreted to deliver safe and effective care. We have used a novel EHR based simulation exercise to demonstrate that everyday users fail to recognize a majority of patient safety issues in the ICU. We now sought to determine whether participation in the simulation improves recognition of said issues. METHODS: Two ICU cases were created in our EHR simulation environment. Each case contained 14 safety issues, which differed in content but shared common themes. Residents were given 10 minutes to review a case followed by a presentation of management changes. Participants were given an immediate debriefing regarding missed issues and strategies for data gathering in the EHR. Repeated testing was performed in a cohort of subjects with the other case at least 1 week later. RESULTS: 116 subjects have been enrolled with 25 subjects undergoing repeat testing. There was no difference between cases in recognition of patient safety issues (39.5% vs. 39.4%). Baseline performance for subjects who participated in repeat testing was no different than the cohort as a whole. For both cases, recognition of safety issues was significantly higher among repeat participants compared to first time participants. Further, individual performance improved from 39.9% to 63.6% ($p = 0.0002$), a result independent of the order in which the cases were employed. The degree of improvement was inversely related to baseline performance. Further, repeat participants demonstrated a higher rate of recognition of changes in vitals, misdosing of

antibiotics and oversedation compared to first time participants. CONCLUSION: Participation in EHR simulation improves EHR use and identification of patient safety issues.

Sullivan, M. P., Griffiths, G. G., & Sohlberg, M. M. (2014). Effect of posttraumatic stress on study time in a task measuring four component processes underlying text-level reading. *Journal of Speech, Language, and Hearing Research, 57*(5), 1731-1739.

Conclusions: Overall, the results provide evidence for the control theory of attention but suggest that more direct measures of task-irrelevant processing during text-level reading are needed. More important, the results begin to lay a foundation for developing not only diagnostic but also intervention strategies. Purpose: To investigate the effect of combat-related posttraumatic stress disorder (PTSD) on 4 components underlying text-level reading comprehension. Method: A group of 17 veterans with PTSD and 17 matched control participants took part. An experimental task required participants to read and study 3-sentence paragraphs describing semantic features associated with real and unreal objects. Each paragraph was followed by true-false statements that assessed knowledge access, text memory, inference, and integration. Results: The results revealed that the PTSD group took significantly longer than the control group to study the paragraphs. Although there was no group difference in test statement accuracy, the PTSD group also took significantly longer to respond to the test statements.

Sung, J. J., Pardeshi, N. N., Mulder, A. M., Mulligan, S. K., Quispe, J., On, K., et al. (2014). Transmission electron microscopy as an orthogonal method to characterize protein aggregates. *Journal of Pharmaceutical Sciences,*

Aggregation of protein-based therapeutics is a challenging problem in the biopharmaceutical industry. Of particular concern are implications for product efficacy and clinical safety because of potentially increased immunogenicity of the aggregates. We used transmission electron microscopy (TEM) to characterize biophysical and morphological features of antibody aggregates formed upon controlled environmental stresses. TEM results were contrasted with results obtained in parallel by independent methods, including size-exclusion chromatography, dynamic light scattering, microflow imaging, and nanoparticle tracking. For TEM, stressed samples were imaged by negative staining and in the frozen-hydrated state. In both cases, aggregates

appeared amorphous but differed in fine structural detail. Specifically, negatively stained aggregates were compact and consisted of smaller globular structures that had a notable three-dimensional character. Elements of the native IgG structure were retained, suggesting that the aggregates were not assembled from denatured protein. In contrast, aggregates in frozen-hydrated samples appeared as extended, branched protein networks with large surface area. Using multiple scales of magnification, a wide range of particle sizes was observed and semiquantitatively characterized. The detailed information provided by TEM extended observations obtained with the independent methods, demonstrating the suitability of TEM as a complementary approach to submicron particle analysis.

Tanchuck-Nipper, M. A., Ford, M. M., Hertzberg, A., Beadles-Bohling, A., Cozzoli, D. K., & Finn, D. A. (2014). Sex differences in ethanol's anxiolytic effect and chronic ethanol withdrawal severity in mice with a null mutation of the 5alpha-reductase type 1 gene. *Behavior Genetics,* Manipulation of endogenous levels of the GABAergic neurosteroid allopregnanolone alters sensitivity to some effects of ethanol. Chronic ethanol withdrawal decreases activity and expression of 5alpha-reductase-1, an important enzyme in allopregnanolone biosynthesis encoded by the 5alpha-reductase-1 gene (Srd5a1). The present studies examined the impact of Srd5a1 deletion in male and female mice on several acute effects of ethanol and on chronic ethanol withdrawal severity. Genotype and sex did not differentially alter ethanol-induced hypothermia, ataxia, hypnosis, or metabolism, but ethanol withdrawal was significantly lower in female versus male mice. On the elevated plus maze, deletion of the Srd5a1 gene significantly decreased ethanol's effect on total entries versus wildtype (WT) mice and significantly decreased ethanol's anxiolytic effect in female knockout (KO) versus WT mice. The limited sex differences in the ability of Srd5a1 genotype to modulate select ethanol effects may reflect an interaction between developmental compensations to deletion of the Srd5a1 gene with sex hormones and levels of endogenous neurosteroids.

Tarlow, B. D., Pelz, C., Naugler, W. E., Wakefield, L., Wilson, E. M., Finegold, M. J., et al. (2014). Bipotential adult liver progenitors are derived from chronically injured mature hepatocytes. *Cell Stem Cell,*

Adult liver progenitor cells are biliary-like epithelial cells that emerge only under injury conditions in the periportal region of the liver. They exhibit phenotypes of both hepatocytes and bile ducts. However, their origin and their significance to injury repair remain unclear. Here, we used a chimeric lineage tracing system to demonstrate that hepatocytes contribute to the progenitor pool. RNA-sequencing, ultrastructural analysis, and in vitro progenitor assays revealed that hepatocyte-derived progenitors were distinct from their biliary-derived counterparts. In vivo lineage tracing and serial transplantation assays showed that hepatocyte-derived proliferative ducts retained a memory of their origin and differentiated back into hepatocytes upon cessation of injury. Similarly, human hepatocytes in chimeric mice also gave rise to biliary progenitors in vivo. We conclude that human and mouse hepatocytes can undergo reversible ductal metaplasia in response to injury, expand as ducts, and subsequently contribute to restoration of the hepatocyte mass.

Tayyari, F., Yusof, F., Vymyslicky, M., Tan, O., Huang, D., Flanagan, J. G., et al. (2014). Variability and repeatability of quantitative, fourier domain-OCT doppler blood flow in young and elderly healthy subjects. *Investigative Ophthalmology & Visual Science,*

The purpose of this study was to determine the within-session variability and between-session repeatability of spectral Fourier-domain optical coherence tomography (Doppler FD-OCT) Doppler retinal blood flow measurements in young, and elderly subjects. Methods: Doppler FD-OCT blood flow was measured using the RTVue system (Optovue Inc., USA). One eye of each of 20 healthy young (24.7 +/- 2.7 years) and 16 healthy elderly (64.6 +/- 5.1 years) subjects was randomly selected and the pupil was dilated. The double circular scanning pattern of the RTVue was employed. Six Doppler FD-OCT measurements (i.e. each separate measurement comprising an upper, and a lower, nasal pupil scans) were acquired at each session. Measurements were repeated approximately 2 weeks later. Total retinal blood flow was calculated by summing flow from all detectable venules surrounding the optic nerve head. The co-efficient of variation (COV), and of repeatability (COR), were calculated for each individual. Results: The individual COVs for retinal blood flow for young subjects ranged from 0.4 to 20.4% (median 7.5%) and for the elderly subjects ranged from 0.6 to 34.6% (median 9.2%). The group mean CORs for retinal blood flow for young participants were 6.4microl/min (median 5.91microl/min, relative to a mean

effect 39.8microl/min) and for elderly subjects were 10.5microl/min (median 9.2microl/min, relative to a mean effect 46.4microl/min). Conclusions: Doppler OCT gave consistent and repeatable blood flow measurements within retinal venules in normal subjects. Considering the individual variation in blood flow measurements, confidence limits for retinal hemodynamics need to be determined on an individual basis.

Tehrani, S. (2014). Gender difference in the pathophysiology and treatment of glaucoma. *Current Eye Research,* , 1-10.

Abstract Glaucoma is the principal cause of irreversible blindness in the world, the second leading cause of blindness in the United States, and it results in optic nerve head axonal degeneration and corresponding visual field deficits. Intraocular pressure (IOP) is the only known modifiable risk factor in glaucoma. Non-modifiable risk factors for glaucoma include age, ethnicity, central corneal thickness, and family history. While our understanding of the role of gender as a risk factor in glaucoma development and progression remains nascent, multiple observations have shown gender differences in the incidence and prevalence of glaucoma. Depending on the type of glaucoma, hormone therapy, oral contraceptive use and menopausal status have also been associated with glaucoma. In addition, pregnancy leads to changes in IOP, while the treatment of glaucoma must be tailored based on the systemic effects of topical therapeutics on the mother and fetus. This review will focus on the epidemiologic, anatomic and endocrinologic differences in male and female glaucoma patients. In addition, this review will discuss treatment modalities that may be more appropriate for one gender than the other, especially with respect to a woman's pregnancy status.

Teo, A. R., & Kato, T. A. (2014). The prevalence and correlates of severe social withdrawal in hong kong. *The International Journal of Social Psychiatry,*

Thauland, T. J., Koguchi, Y., Dustin, M. L., & Parker, D. C. (2014). CD28-CD80 interactions control regulatory T cell motility and immunological synapse formation. *Journal of Immunology (Baltimore, Md.: 1950),*

Regulatory T cells (Tregs) are essential for tolerance to self and environmental Ags, acting in part by downmodulating costimulatory molecules on the surface of dendritic cells (DCs) and altering

naive CD4 T cell-DC interactions. In this study, we show that Tregs form stable conjugates with DCs before, but not after, they decrease surface expression of the costimulatory molecule CD80 on the DCs. We use supported planar bilayers to show that Tregs dramatically slow down but maintain a highly polarized and motile phenotype after recognizing Ag in the absence of costimulation. These motile cells are characterized by distinct accumulations of LFA-1-ICAM-1 in the lamella and TCR-MHC in the uropod, consistent with a motile immunological synapse or "kinapse." However, in the presence of high, but not low, concentrations of CD80, Tregs form stationary, symmetrical synapses. Using blocking Abs, we show that, whereas CTLA-4 is required for CD80 downmodulation, CD28-CD80 interactions are critical for modulating Treg motility in the presence of Ag. Taken together, these results support the hypothesis that Tregs are tuned to alter their motility depending on costimulatory signals.

Thompson, E. M., Wagner, K., Kronfeld, K., & Selden, N. R. (2014). Using a 2-variable method in radionuclide shuntography to predict shunt patency. *Journal of Neurosurgery,* , 1-4.

Object Radionuclide shuntography interpretation is uncertain when the tracer fails to enter the ventricles but quickly drains distally or when the tracer enters the ventricles but takes longer than 15 minutes to drain distally. The purpose of this study was to aid in the clinical interpretation of a variety of shuntography results and to determine the applicability of shuntography in different patient populations. Methods The results of 259 shuntograms were reviewed. Chi-square analysis was performed to evaluate the relationship between clinical variables and shuntography results. Two-by-two binary classification analyses were performed to determine the sensitivity, specificity, positive predictive value, and negative predictive value for 4 different combinatorial types of shuntography results based on 2 variables: ventricular tracer entry and distal tracer drainage. Results Median patient age was 19 years, and 51% of patients were male. The most common presentation in patients undergoing shuntography was headache (169/254, 66.5%) with radiographically stable ventricle size. Of 227 patients with available imaging data, 163 (71.8%) presented with the same ventricle size as shown on a previous asymptomatic scan, 43 (18.9%) had larger ventricles, and 21 (9.2%) had smaller ventricles. Within 30 days of shuntography, 74 of 259 patients (28.6%) underwent surgical shunt exploration: 65 were found to have an obstructed shunt and 9 were found to have a patent

shunt. Of those patients not undergoing surgery, the median length of benign clinical follow-up was 1051 days. Clinical variables were not significantly associated with shuntography results, including valve type (p = 0.180), ventricle size (p = 0.556), age (p = 0.549), distal drainage site (p = 0.098), and hydrocephalus etiology (p = 0.937). Shuntography results of patients with myelomeningocele were not dissociable from those of the group as a whole. Sensitivity to diagnose shunt failure was lowest (37.5%) but specificity was highest (97.2%) when the definition of a "normal" shuntogram included any tracer movement into the distal site within 45 minutes. Conversely, sensitivity was highest (87.5%) and specificity was lowest (51.4%) when the definition was limited exclusively to tracer entry into the ventricles and distal drainage within 15 minutes. Conclusions Even with a stringent definition of a "normal" shuntogram, sensitivity and specificity were relatively low for a diagnostic test. Clinical variables such as valve type, ventricle size, patient age, distal drainage site, and etiology of hydrocephalus were not associated with shuntography results.

Todd Greene, M., Kiyoshi-Teo, H., Reichert, H., Krein, S., & Saint, S. (2014). Urinary catheter indications in the united states: Results from a national survey of acute care hospitals. *Infection Control and Hospital Epidemiology, 35*, S96-S98.

In a survey of acute care hospitals across the United States, we found that many hospitals use indwelling urinary catheters for reasons that are not medically necessary (eg, urinary incontinence without outlet obstruction and patient/family requests). Our findings highlight an opportunity to reduce unnecessary catheter use through promoting awareness of appropriate use.

Tommaso, C. L., Fullerton, D. A., Feldman, T., Dean, L. S., Hijazi, Z. M., Horlick, E., et al. (2014). SCAI/AATS/ACC/STS operator and institutional requirements for transcatheter valve repair and replacement. part II. mitral valve. *Journal of the American College of Cardiology, 64*(14), 1515-1526.

Topaloglu, A. K., Lomniczi, A., Kretzschmar, D., Dissen, G. A., Kotan, L. D., McArdle, C. A., et al. (2014). Loss-of-function mutations in PNPLA6 encoding neuropathy target esterase underlie pubertal failure and neurological deficits in gordon holmes syndrome. *The Journal of Clinical*

Endocrinology and Metabolism, 99(10), E2067-75.

CONTEXT: Gordon Holmes syndrome (GHS) is characterized by cerebellar ataxia/atrophy and normosmic hypogonadotropic hypogonadism (nHH). The underlying pathophysiology of this combined neurodegeneration and nHH remains unknown. OBJECTIVE: We aimed to provide insight into the disease mechanism in GHS. METHODS: We studied a cohort of 6 multiplex families with GHS through autozygosity mapping and whole-exome sequencing. RESULTS: We identified 6 patients from 3 independent families carrying loss-of-function mutations in PNPLA6, which encodes neuropathy target esterase (NTE), a lysophospholipase that maintains intracellular phospholipid homeostasis by converting lysophosphatidylcholine to glycerophosphocholine. Wild-type PNPLA6, but not PNPLA6 bearing these mutations, rescued a well-established Drosophila neurodegenerative phenotype caused by the absence of sws, the fly ortholog of mammalian PNPLA6. Inhibition of NTE activity in the LbetaT2 gonadotrope cell line diminished LH response to GnRH by reducing GnRH-stimulated LH exocytosis, without affecting GnRH receptor signaling or LHbeta synthesis. CONCLUSION: These results suggest that NTE-dependent alteration of phospholipid homeostasis in GHS causes both neurodegeneration and impaired LH release from pituitary gonadotropes, leading to nHH.

Van Der Fluit, F., & Klein-Tasman, B. P. (2014). A case study of autism spectrum disorder (ASD) symptomatology in a child with 15q13.3 deletion and williams syndrome. *Journal of Developmental and Physical Disabilities,*

A variety of genetic disorders of known etiology present with behavioral profiles similar to that described in autism spectrum disorders (ASDs). Although some of these disorders are more likely to be associated with a comorbid ASD diagnosis, there exist cases in which there is a lack of empirical evidence to support a dual diagnosis. Two disorders, Williams syndrome (WS) and 15q13.3 deletion syndrome, have both been reported in the literature as examples of this phenotypic overlap. We present a case study of a young child with both WS and 15q13.3 deletion syndrome and significant ASD-related symptomatology. The results of a developmental evaluation, specifically the rationale for ruling out a comorbid ASD, are the focus of the present report. Implications for careful diagnostic consideration in cases of patients with known genetic conditions are also discussed.

Varlamov, O., Chu, M., Cornea, A., Sampath, H., & Roberts, C. T.,Jr. (2014). Cell-autonomous heterogeneity of nutrient uptake in white adipose tissue of rhesus macaques. *Endocrinology,* , en20141699.

Phenotypic diversity may play an adaptive role by providing graded biological responses to fluctuations in environmental stimuli. We used single-cell imaging, using the metabolizable fluorescent fatty acid analog 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY)-C12 and fluorescent 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-D-glucose, to explore cellular heterogeneity in nutrient uptake in white adipose tissue (WAT) explants of rhesus macaques. Surprisingly, WAT displayed a striking cell size-independent mosaic pattern, in that adjacent adipocytes varied with respect to insulin-stimulated BODIPY-C12 and 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-D-glucose uptake. Relative free fatty acid (FFA) transport activity correlated with the cellular levels of FFA transporter protein-1 and the scavenger receptor CD36 in individual adipocytes. In vitro the incubation of WAT explants for 24 hours caused partial desynchronization of cellular responses, suggesting that adipocytes may slowly alter their differential nutrient uptake activity. In vitro-differentiated human adipocytes also exhibited a mosaic pattern of BODIPY-C12 uptake. WAT from animals containing a homogeneous population of large adipocytes was nonmosaic, in that every adipocyte exhibited a similar level of BODIPY-C12 fluorescence, suggesting that the development of obesity is associated with the loss of heterogeneity in WAT. Hence, for the first time, we demonstrate an intrinsic heterogeneity in FFA and glucose transport activity in WAT.

Ventres, W., & Haq, C. (2014). Toward a cultural consciousness of self in relationship: From “Us and them” to “We”. *Family Medicine, 46*(9), 691-695.

BACKGROUND AND OBJECTIVES: While skills and techniques can help family physicians and other health professionals achieve basic competence in working across cultural and social boundaries, perhaps their most important tasks are those directed inward toward attitudes, beliefs, and capacities for self-exploration. This essay links the practice and teaching of cross-cultural medicine to clinicians’ and educators’ exploration of their own self-consciousnesses. The more they are willing to explore the unfamiliar within themselves, the more emotionally and psychologically comfortable they can become in dealing with the joys and challenges inherent in

cross-cultural medicine. Several practices can foster this development of a sense of self in relationship with others. As health professionals and medical educators recognize and promote an awareness of self in relationship, they can enhance their personal and professional roles to become more effective advocates of equity and social justice in every clinical encounter.

Westergren, H., Freeman, M. D., & Malmström, E. -. (2014). The whiplash enigma: Still searching for answers. *Scandinavian Journal of Pain, 5*(4), 226-228.

Wiest, K. L., Colditz, J. B., Carr, K., Asphaug, V. J., McCarty, D., & Pilkonis, P. A. (2014). Pain and emotional distress among substance-use patients beginning treatment relative to a representative comparison group. *Journal of Addiction Medicine,*
OBJECTIVES:: A secondary analysis assessed health-related quality-of-life (HRQOL) characteristics (ie, anxiety, depression, fatigue, and types of pain) among patients entering substance-use treatment and identified characteristics specific to treatment modalities relative to a representative comparison group. METHODS:: As part of a larger alcohol bank assessment, substance-use patients (n = 406) beginning methadone treatment (n = 170) or other outpatient treatment (n = 236) and a comparison group representative of the general population (n = 1000) completed a survey measuring anxiety, depression, fatigue, pain interference, and pain in the last 7 days. Previous studies lacked comparable and concurrent assessments across these 3 groups. RESULTS:: Patients entering substance-use treatment had relatively high levels of emotional distress and poorer HRQOL relative to the general population. Among treatment modalities, patients beginning methadone treatment reported the highest levels of pain interference and pain behavior and the poorest physical functioning. Before the potentially modifying effects of methadone maintenance, patients beginning agonist therapy reported the greatest levels of compromised quality of life. CONCLUSIONS:: These data present the magnitude of differences in HRQOL characteristics between treatment and comparison groups using the same assessment rubric and may help inform the design and timing of treatment modalities, thereby enhancing treatment efficacy for patients.

Willer, T., Inamori, K. I., Venzke, D., Harvey, C., Morgensen, G., Hara, Y., et al. (2014). The glucuronyltransferase B4GAT1 is required for initiation of LARGE-mediated alpha-dystroglycan

functional glycosylation. *Elife, 3*, 10.7554/eLife.03941.

Dystroglycan is a cell membrane receptor that organizes the basement membrane by binding ligands in the extracellular matrix. Proper glycosylation of the alpha-dystroglycan (alpha-DG) subunit is essential for these activities, and lack thereof results in neuromuscular disease. Currently, neither the glycan synthesis pathway nor the roles of many known or putative glycosyltransferases that are essential for this process are well understood. Here we show that FKRP, FKTN, TMEM5 and B4GAT1 (formerly known as B3GNT1) localize to the Golgi and contribute to the O-mannosyl post-phosphorylation modification of alpha-DG. Moreover, we assigned B4GAT1 a function as a xylose beta1,4-glucuronyltransferase. Nuclear magnetic resonance studies confirmed that a glucuronic acid beta1,4-xylose disaccharide synthesized by B4GAT1 acts as an acceptor primer that can be elongated by LARGE with the ligand-binding heteropolysaccharide. Our findings greatly broaden the understanding of alpha-DG glycosylation and provide mechanistic insight into why mutations in B4GAT1 disrupt dystroglycan function and cause disease.

Wilson, T., Omelchenko, I., Foster, S., Zhang, Y., Shi, X., & Nuttall, A. L. (2014). JAK2/STAT3 inhibition attenuates noise-induced hearing loss. *PloS One, 9*(9), e108276.

Signal transducers and activators of transcription 3 (STAT3) is a stress responsive transcription factor that plays a key role in oxidative stress-mediated tissue injury. As reactive oxygen species (ROS) are a known source of damage to tissues of the inner ear following loud sound exposure, we examined the role of the Janus kinase 2 (JAK2)/STAT3 signaling pathway in noise induce hearing loss using the pathway specific inhibitor, JSI-124. Mice were exposed to a moderately damaging level of loud sound revealing the phosphorylation of STAT3 tyrosine 705 residues and nuclear localization in many cell types in the inner ear including the marginal cells of the stria vascularis, type II, III, and IV fibrocytes, spiral ganglion cells, and in the inner hair cells. Treatment of the mice with the JAK2/STAT3 inhibitor before noise exposure reduced levels of phosphorylated STAT3 Y705. We performed auditory brain stem response and distortion product otoacoustic emission measurements and found increased recovery of hearing sensitivity at two weeks after noise exposure with JAK2/STAT3 inhibition. Performance of cytocochleograms revealed improved outer hair cell survival in JSI-124 treated mice relative to control. Finally,

JAK2/STAT3 inhibition reduced levels of ROS detected in outer hair cells at two hours post noise exposure. Together, these findings demonstrate that inhibiting the JAK2/STAT3 signaling pathway is protective against noise-induced cochlear tissue damage and loss of hearing sensitivity.

Win, T. T., Venkatesh, B. A., Volpe, G. J., Mewton, N., Rizzi, P., Sharma, R. K., et al. (2014). Associations of electrocardiographic P-wave characteristics with left atrial structure, function and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: The PRIMERI study. *Heart Rhythm : The Official Journal of the Heart Rhythm Society,*

BACKGROUND: Abnormal P-terminal force in V1 (PTFV1) is associated with an increased risk of heart failure, stroke, atrial fibrillation (AF) and death. OBJECTIVE: Our goal was to explore associations of left ventricular (LV) diffuse fibrosis with left atrium (LA) function and ECG measures of LA electrical activity. METHODS: AF-free patients (n=91, mean age 59.5, 61.5% men, 65.9% Caucasian) with structural heart disease (wide spatial QRS-T angle>/=105 degrees +/- Selvester QRS score>/=5 on ECG) but LV ejection fraction >35% underwent clinical evaluation, cardiac magnetic resonance and resting ECG. LA function indices were obtained by multimodality tissue tracking using 2 and 4-chamber long-axis images. T1 mapping and late gadolinium enhancement were used to assess diffuse LV fibrosis and presence of scar. P-prime in V1 amplitude (PPaV1) and duration (PPdV1), averaged P-duration, PR interval and P-axis were automatically measured using 12SL TM algorithm. PTFV1 was calculated as product of PPaV1 by PPdV1. RESULTS: In linear regression after adjustment for demographic, body mass index, LA volumemax index, presence of scar and LV mass index, each decile increase in LV interstitial fibrosis was associated with 0.76mV*ms increase in negative abnormal PTFV1 [(95%CI -1.42 to -0.09), P=0.025], 15.3ms prolongation in PPdV1 [(95%CI 6.9 to 23.8), P=0.001], and 5.4ms widening in averaged P-duration [(95%CI 0.9 to10.0), P=0.020]. LV fibrosis did not affect LA function. PPaV1 and PTFV1 were associated with an increase in LA volumes, decrease in LAEF and LA reservoir function. CONCLUSION: LV interstitial fibrosis is associated with abnormal PTFV1, prolonged PPdV1 and P-duration, but does not affect LA function.

Wong, A. J., Planck, S. R., Choi, D., Harrington, C. A., Troxell, M. L., Houghton, D. C., et al. (2014). IgG4 immunostaining and its implications in orbital inflammatory disease. *PloS One, 9*(10), e109847.

OBJECTIVE: IgG4-related disease is an emerging clinical entity which frequently involves tissue within the orbit. In order to appreciate the implications of IgG4 immunostaining, we analyzed gene expression and the prevalence of IgG4- immunostaining among subjects with orbital inflammatory diseases. METHODS: We organized an international consortium to collect orbital biopsies from 108 subjects including 22 with no known orbital disease, 42 with nonspecific orbital inflammatory disease (NSOI), 26 with thyroid eye disease (TED), 12 with sarcoidosis, and 6 with granulomatosis with polyangiitis (GPA). Lacrimal gland and orbital adipose tissue biopsies were immunostained for IgG4 or IgG secreting plasma cells. RNA transcripts were quantified by Affymetrix arrays. RESULTS: None of the healthy controls or subjects with TED had substantial IgG4 staining. Among the 63 others, the prevalence of significant IgG4-immunostaining ranged from 11 to 39% depending on the definition for significant. IgG4 staining was detectable in the majority of tissues from subjects with GPA and less commonly in tissue from subjects with sarcoidosis or NSOI. The detection of IgG4+ cells correlated with inflammation in the lacrimal gland based on histology. IgG4 staining tissue expressed an increase in transcripts associated with inflammation, especially B cell-related genes. Functional annotation analysis confirmed this. CONCLUSION: IgG4+ plasma cells are common in orbital tissue from patients with sarcoidosis, GPA, or NSOI. Even using the low threshold of 10 IgG4+ cells/high powered field, IgG4 staining correlates with increased inflammation in the lacrimal gland based on histology and gene expression.

Wong, A. J., Planck, S. R., Choi, D., Harrington, C. A., Troxell, M. L., Houghton, D. C., et al. (2014). Lgg4 immunostaining and its implications in orbital inflammatory disease. *Plos One, 9*(10)

Methods: We organized an international consortium to collect orbital biopsies from 108 subjects including 22 with no known orbital disease, 42 with nonspecific orbital inflammatory disease (NSOI), 26 with thyroid eye disease (TED), 12 with sarcoidosis, and 6 with granulomatosis with polyangiitis (GPA). Lacrimal gland and orbital adipose tissue biopsies were immunostained for lgG4 or IgG secreting plasma cells. RNA transcripts were quantified by Affymetrix arrays. Results:

None of the healthy controls or subjects with TED had substantial IgG4 staining. Among the 63 others, the prevalence of significant IgG4-immunostaining ranged from 11 to 39% depending on the definition for significant. IgG4 staining was detectable in the majority of tissues from subjects with GPA and less commonly in tissue from subjects with sarcoidosis or NSOI. The detection of IgG4+ cells correlated with inflammation in the lacrimal gland based on histology. IgG4 staining tissue expressed an increase in transcripts associated with inflammation, especially B cell-related genes. Functional annotation analysis confirmed this. Conclusion: IgG4+ plasma cells are common in orbital tissue from patients with sarcoidosis, GPA, or NSOI. Even using the low threshold of 10 IgG4+ cells/high powered field, IgG4 staining correlates with increased inflammation in the lacrimal gland based on histology and gene expression. Objective: IgG4-related disease is an emerging clinical entity which frequently involves tissue within the orbit. In order to appreciate the implications of IgG4 immunostaining, we analyzed gene expression and the prevalence of IgG4immunostaining among subjects with orbital inflammatory diseases.

Wong, T. E., Brandow, A. M., Lim, W., & Lottenberg, R. (2014). Update on the use of hydroxyurea therapy in sickle cell disease. *Blood,*

Yarris, L. M., Fu, R., Duby, R., Frakes, B., Brooks, H., & Norton, R. L. (2014). Comparison of mailed vs. on-site emergency department patient satisfaction surveys. *The Journal of Emergency Medicine,*

BACKGROUND: Patient satisfaction is one measure of the quality of emergency department (ED) care. The impact of survey delivery method on patient satisfaction in the ED remains unknown. OBJECTIVE: We hypothesized that self-administered surveys in the ED would yield a higher response rate and different satisfaction compared to mailed surveys. METHODS: This observational study was conducted during a 2-month period in an urban, tertiary-care, university-based ED. Eligible patients were randomized to either complete an on-site satisfaction survey in the ED at discharge or to complete an identical survey mailed 1 week after discharge. The primary outcome was the reported overall satisfaction of on-site vs. mail-out surveys. Satisfaction was measured using Likert-type scales and dichotomized outcomes were compared using a chi2 test and logistic regression. RESULTS: Two hundred and forty-two of 457 eligible

patients randomized to the on-site group and 275 of 1152 patients in the mail-out group completed a survey (53% vs. 24%; p < 0.001). Compared with the mail-out group, on-site subjects reported higher overall satisfaction (79.6% vs. 68.9%; p = 0.006), significantly higher satisfaction with their nurses' (p < 0.001) and doctors' listening skills (p < 0.001), and were more likely to recommend this ED to friends or family (71.4%, vs. 56.6%; p = 0.001). CONCLUSIONS: We found that patients who completed satisfaction surveys in the ED reported higher satisfaction than those who received mailed surveys. In addition, measuring patient satisfaction by self-administered on-site surveys at the time of discharge from the ED yields a significantly higher response rate than measuring satisfaction using mailed surveys.

Young, J. M., Nelson, J. W., Cheng, J., Zhang, W., Mader, S., Davis, C. M., et al. (2014). Peroxisomal biogenesis in ischemic brain. *Antioxidants & Redox Signaling,*

Abstract Aims: Peroxisomes are highly adaptable and dynamic organelles, adjusting their size, number, and enzyme composition to changing environmental and metabolic demands. We determined whether peroxisomes respond to ischemia, and whether peroxisomal biogenesis is an adaptive response to cerebral ischemia. Results: Focal cerebral ischemia induced peroxisomal biogenesis in peri-infarct neurons, which was associated with a corresponding increase in peroxisomal antioxidant enzyme catalase. Peroxisomal biogenesis was also observed in primary cultured cortical neurons subjected to ischemic insult induced by oxygen-glucose deprivation (OGD). A catalase inhibitor increased OGD-induced neuronal death. Moreover, preventing peroxisomal proliferation by knocking down dynamin-related protein 1 (Drp1) exacerbated neuronal death induced by OGD, whereas enhancing peroxisomal biogenesis pharmacologically using a peroxisome proliferator-activated receptor-alpha agonist protected against neuronal death induced by OGD. Innovation: This is the first documentation of ischemia-induced peroxisomal biogenesis in mammalian brain using a combined in vivo and in vitro approach, electron microscopy, high-resolution laser-scanning confocal microscopy, and super-resolution structured illumination microscopy. Conclusion: Our findings suggest that neurons respond to ischemic injury by increasing peroxisome biogenesis, which serves a protective function, likely mediated by enhanced antioxidant capacity of neurons. Antioxid. Redox Signal. 00, 000-000.

Yuen, K. C., Roberts, C. T.,Jr, Frystyk, J., Rooney, W. D., Pollaro, J. R., Klopfenstein, B. J., et al. (2014). Short-term, low-dose GH therapy improves insulin sensitivity without modifying cortisol metabolism and ectopic fat accumulation in adults with GH deficiency. *The Journal of Clinical Endocrinology and Metabolism, 99*(10), E1862-9.

CONTEXT: Low-dose GH (LGH) therapy has been reported to improve insulin sensitivity in GH-deficient adults; however, the mechanism is unclear. HYPOTHESIS: Effects of LGH therapy on insulin sensitivity are mediated through changes in cortisol metabolism and ectopic fat accumulation. DESIGN AND SETTING: This was a double-blind, placebo-controlled, parallel, 3-month study. PARTICIPANTS AND INTERVENTION: Seventeen GH-deficient adults were randomized to receive either daily LGH or placebo injections. Fasting blood samples were collected at baseline, and months 1 and 3, whereas hyperinsulinemic-euglycemic clamps, magnetic resonance spectroscopy scans, 24-hour cortisol production rates (CPRs), and sc abdominal fat biopsies were performed at baseline and month 3. MAIN OUTCOME MEASURES: Clamp glucose infusion rate, intramyocellular, extramyocellular, and intrahepatic lipid content, 24-hour CPRs, adipocyte size, and adipocyte 11beta-hydroxysteroid dehydrogenase activity in adults with GH deficiency were evaluated. RESULTS: At month 1, LGH did not alter fasting levels of glucose, insulin, C-peptide, free fatty acid, adiponectin, total IGF-1, IGF-1 bioactivity, IGF-2, IGF binding protein (IGFBP)-2, or IGF-1 to IGFBP-3 molar ratio. At month 3, LGH increased clamp glucose infusion rates ($P < .01$) and IGF-1 to IGFBP-3 molar ratio ($P < .05$), but fasting glucose, insulin, C-peptide, free fatty acid, adiponectin, IGF-1 bioactivity, IGF-2, IGFBP-2, 24-hour CPRs, adipocyte size, adipocyte 11beta-hydroxysteroid dehydrogenase activity, intrahepatic lipid, extramyocellular, or intramyocellular were unchanged. In the placebo group, all within-group parameters from months 1 and 3 compared with baseline were unchanged. CONCLUSIONS: Short-term LGH therapy improves insulin sensitivity without inducing basal lipolysis and had no effect on cortisol metabolism and ectopic fat accumulation in GH-deficient adults. This may reflect an LGH-induced increase in IGF-1 to IGFBP-3 molar ratio exerting insulin-like effects through the abundant muscle IGF-1 receptors, but this hypothesis requires confirmation with further studies.

Zhang, Z., Liu, F., Tsui, H., Lau, Y., & Song, X. (2014). A multiscale adaptive mask method for rigid intraoperative ultrasound and preoperative CT image registration. *Medical Physics, 41*(10),

102903.

PURPOSE: Rigid registration of intraoperative ultrasound (US) and preoperative CT image is important for providing real-time guidance during operations. However, due to the low spatial and temporal resolutions and the dissimilarity between US and CT, accurate registration of CT and US images is still a challenging problem. METHODS: The authors propose an adaptive-mask-based CT and US registration method. The registration is initialized by matching the image regions of CT and US with intensity distinctiveness. The registration is a multistage iterative process in which the US region mask is adaptively updated. Each stage is an interleaving process of optimizing a global similarity energy and updating the mask of US by selecting high saliency and local statistical dependency regions. RESULTS: Performances of their proposed method and mutual information (MI) based method are validated with simulated, in vitro phantom and real patient datasets. Results show that their method has larger capture range in all datasets. The estimated transformation parameters in their method are more accurate than the mutual information based method. CONCLUSIONS: By using an adaptively updated mask of the US image, regions with salient intensity information and high intensity correlation with CT are included in the registration. Regions which have low correlation with CT such as artifacts are excluded in the registration so that the robustness and accuracy of the intensity-based registration method are improved.

Zheng, J. -., Lai, C. -., Parnell, L. D., Lee, Y. -., Shen, J., Smith, C. E., et al. (2014). Genome-wide interaction of genotype by erythrocyte n-3 fatty acids contributes to phenotypic variance of diabetes-related traits. *BMC Genomics, 15*(1)

Background: Little is known about the interplay between n-3 fatty acids and genetic variants for diabetes-related traits at the genome-wide level. The present study aimed to examine variance contributions of genotype by environment (GxE) interactions for different erythrocyte n-3 fatty acids and genetic variants for diabetes-related traits at the genome-wide level in a non-Hispanic white population living in the U.S.A. (n = 820). A tool for Genome-wide Complex Trait Analysis (GCTA) was used to estimate the genome-wide GxE variance contribution of four diabetes-related traits: HOMA-Insulin Resistance (HOMA-IR), fasting plasma insulin, glucose and adiponectin. A GxE genome-wide association study (GWAS) was conducted to further elucidate the GCTA

results. Replication was conducted in the participants of the Boston Puerto Rican Health Study (BPRHS) without diabetes (n = 716). Results: In GOLDN, docosapentaenoic acid (DPA) contributed the most significant GxE variance to the total phenotypic variance of both HOMA-IR (26.5%, P-nominal = 0.034) and fasting insulin (24.3%, P-nominal = 0.042). The ratio of arachidonic acid to eicosapentaenoic acid + docosahexaenoic acid contributed the most significant GxE variance to the total variance of fasting glucose (27.0%, P-nominal = 0.023). GxE variance of the arachidonic acid/eicosapentaenoic acid ratio showed a marginally significant contribution to the adiponectin variance (16.0%, P-nominal = 0.058). None of the GCTA results were significant after Bonferroni correction (P < 0.001). For each trait, the GxE GWAS identified a far larger number of significant single-nucleotide polymorphisms (P-interaction ≤ 10E-5) for the significant E factor (significant GxE variance contributor) than a control E factor (non-significant GxE variance contributor). In the BPRHS, DPA contributed a marginally significant GxE variance to the phenotypic variance of HOMA-IR (12.9%, P-nominal = 0.068) and fasting insulin (18.0%, P-nominal = 0.033).Conclusion: Erythrocyte n-3 fatty acids contributed a significant GxE variance to diabetes-related traits at the genome-wide level.

Zhu, W., Casper, A., Libal, N. L., Murphy, S. J., Bodhankar, S., Offner, H., et al. (2014). Preclinical evaluation of recombinant T cell receptor ligand RTL1000 as a therapeutic agent in ischemic stroke. *Translational Stroke Research,*

Recombinant T cell Receptor Ligand 1000 (RTL1000), a partial human major histocompatibility complex (MHC) molecule coupled to a human myelin peptide, reduces infarct size after experimental stroke in HLA-DRB1*1502 transgenic (DR2-Tg) mice. In this study, we characterized the therapeutic time window of opportunity for RTL1000; we explored the efficacy of a single dose of RTL1000 administration and determined if RTL1000 affords long-term neurobehavioral functional improvement after ischemic stroke. Male DR2-Tg mice underwent 60 min of intraluminal reversible middle cerebral artery occlusion (MCAO). RTL1000 or vehicle was injected 4, 6, or 8 h after MCAO, followed by three daily injections. In the single-dose study, one-time injection of RTL1000 was applied 4 h after MCAO. Cortical, striatal, and hemispheric infarct sizes were measured 24 or 96 h after stroke. Behavioral testing, including neuroscore evaluation, open field, paw preference, and novel object recognition, was performed up to 28 days after

stroke. Our data showed that RTL1000 significantly reduced the infarct size 96 h after MCAO when the first injection was given at 4 and 6 h, but not 8 h, after the onset of stroke. A single dose of 400 or 100 mug RTL1000 also significantly reduced the infarct size 24 h after MCAO. Behavioral testing showed that RTL1000 treatment used 4 h after MCAO improved long-term cognitive outcome 28 days after stroke. Taken together, RTL1000 protects against acute injury if applied within a 6-h time window and improves long-term functional recovery after experimental stroke in DR2-Tg mice.

Zhu, W., Libal, N. L., Casper, A., Bodhankar, S., Offner, H., & Alkayed, N. J. (2014). Recombinant T cell receptor ligand treatment improves neurological outcome in the presence of tissue plasminogen activator in experimental ischemic stroke. *Translational Stroke Research, 5*(5), 612-617.

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

Zubair, M. M., Bailly, D. K., Lantz, G., Sunstrom, R. E., Saharan, S., Boshkov, L. K., et al. (2014). Preoperative platelet dysfunction predicts blood product transfusion in children undergoing cardiac surgery. *Interactive Cardiovascular and Thoracic Surgery,*

OBJECTIVES: Excessive bleeding can be a problem during or after cardiac surgery. While cardiopulmonary bypass-associated platelet dysfunction is an important inducer of coagulopathy, preoperative platelet dysfunction can also contribute to this bleeding. We investigated the relationship between preoperative platelet dysfunction and transfusion of blood products given to children undergoing cardiac surgery. METHODS: The platelet function analyser test measures platelet function in vitro by aspirating blood through a small standard hole (creating high shear) in a collagen membrane infused with a platelet agonist. The time taken to form a platelet plug is known as closure time and prolonged closure time (CT) indicates platelet dysfunction. Three hundred and thirty-eight children who had undergone surgery with cardiopulmonary bypass between 2008 and 2012 were included. The volume of red blood cells and fresh-frozen plasma transfused was recorded. The relationship between closure time and transfusion requirements was analysed using linear and logistic regression. RESULTS: Patients with prolonged closure time had greater odds of getting red blood cells and fresh-frozen plasma transfusions compared with patients with normal closure time ($P < 0.01$). On univariate analysis, age, weight, haematocrit, cardiopulmonary bypass time, Risk Adjustment for Congenital Heart Surgery score and closure time were associated with increased odds of red blood cells and fresh-frozen plasma transfusion in the operation theatre ($P < 0.05$). However, when logistic multivariable regression analysis was applied, only age, cardiopulmonary bypass time and closure time remained as significant predictive factors for transfusion. CONCLUSIONS: In children who have undergone cardiac surgery, when age and cardiopulmonary bypass time are accounted for, a prolonged preoperative closure time is significantly associated with increased odds of red blood cells and fresh-frozen plasma transfusion in the operation theatre. This may have implications for planning and utilization of blood products.