The Third Annual New York State/American Program
Sackler Faculty of Medicine
Research Symposium on Basic and Clinical Science

Scientific Program and Abstract Book

March 3rd, 2013
Ramat Aviv, Tel Aviv, Israel
The Third Annual New York State/American Program
Sackler Faculty of Medicine
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New York State/American Program Administration in Tel Aviv

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The Third Annual New York State/American Program
Sackler Faculty of Medicine
Research Symposium on Basic and Clinical Science

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The Third Annual New York State/American Program
Sackler Faculty of Medicine
Research Symposium on Basic and Clinical Science

March 3rd, 2013

Schedule of Events

4:00-4:15  
Arrival and Refreshments

4:15-4:30  
Welcome and Opening of Symposium, Room 201
Prof. Arnon Afek, M.D., M.H.A.
Justin Karlin

4:30-5:00  
Keynote Presentations, Room 201
Louis Shenkman, M.D., Meir Hospital, Kfar Saba
Gilad Twig, M.D., Ph.D., Sheba Medical Center, Ramat Gan

5:00-5:15  
Break

Parallel Sessions: Group 1

5:15-6:15  
Cardiology Presentations
Chairperson: Prof. Arnon Afek

Setareh-Shenas, S.  
Efficacy of Anti-Thymocyte Globulin Induction Therapy After Heart Transplantation

Mizrahi, I.  
A Retrospective Comparison of Infection in Contemporary Left Ventricular Assist Devices

Zelickson, B.R.  
Hypoxia alters mitochondrial bioenergetics in endothelial cells

Murinson, M.A.  
Significance of T-wave amplitude and dynamics at the time of reperfusion in patients with acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention.

Setareh-Shenas, S.  
Safety and Efficacy of Blood Pressure Management in Bicuspid Aortic Aneurysm
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<td>Zucker, D.</td>
<td>Amyloid-Binding Compounds Maintain Protein Homeostasis During Aging and Extend Lifespan</td>
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<td>Schwartz, J.</td>
<td>Quantitative MRI in Benign Multiple Sclerosis</td>
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<td>Kossar, A.P.</td>
<td>Elucidating a Putative Neurosteroid Binding Site on the GABAA Receptor via Glycine Receptor Homology</td>
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<td>Simsoło, E.</td>
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<td>Statins may improve the outcome of Erlotinib as second line treatment in patients with metastatic non small cell lung cancer</td>
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<td>Blumenfeld, P.</td>
<td>The lag-time in initiating clinical testing of new-drugs in combination with radiation therapy, a significant barrier to progress in radiation oncology</td>
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<td>Preclinical Evaluation of Tumor Angiogenesis with Contrast Enhanced Digital Breast Tomosynthesis</td>
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<td>Markers of radiation nephropathy: Albuminuria and azotemia are associated with histologic damage in a mouse model of radiation nephropathy</td>
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5:15-6:15  **Biomechanics, Orthopedics and Biophysics Presentations**
Chairperson: Prof. Karen Avraham

Debbi, E.M.  Knee Biomechanics After Total Knee Arthroplasty: Early Outcomes

Nouri, A.  “See Me Move and Groove.” National Science Foundation Engineering Design Projects to Aid Persons with Disabilities

Kenan, S.  Long term outcomes of subcapital hip fractures reduced by cannular screw internal fixation in the young using the Harris Hip Score.

Debbi, E.M.  Mechanics of the Non-Operated Knee Before and After Total Knee Arthroplasty


6:15-6:30  **Break**

6:30-7:30  **Parallel Sessions: Group 2**

6:30-7:30  **Cardiology and Nutritional Science Presentations**
Chairperson: Prof. Arnon Afek

Stachel, M.W.  A human model of human disease: investigation of dystrophic cardiomyopathy using human dystrophin-deficient induced pluripotent stem cells

Halleluyan, R.  Hyaluronic Acid Receptors RHAMM and CD44 Reprogram Myocyte Mechano- sensitivity

...  Aortic Pulse Wave Velocity as a Marker of Cardiovascular Risk in Patients with FMF and Amyloidosis

Helfand, A.M.  Circulating Endoglin Concentration Is Not Elevated in Chronic Kidney Disease

Choleva, L.  The Effect of *Salvia hispanica* L. (Salba) on Weight Loss in Overweight and Obese Individuals with Type 2 Diabetes Mellitus
6:30-7:30  **Neuroscience, Ophthalmology, Endocrinology, and Dermatology Presentations**  
Chairperson: Dr. Blake Zelickson

Kaplan, M.  
Man from Meat: Medicine, Music and the Generation of Pain

Vieyra, M.  
Possible association of Revatio (sildenafil) and optic nerve stroke

Feidi, R.  
The Effect of Inflammation on EMP2 Expression in Proliferative Vitreoretinopathy

Weiss, M.  
Cochlear Structure and Hearing in Murine Congenital Hypothyroidism Caused by Targeted Gene Mutations in the Mouse Dual Oxidase A1 and A2 Genes

Warshauer, E.  
Regulation and mechanisms of action of RBM28, a protein deficient in ANE syndrome

6:30-7:30  **Molecular Biology and Biophysics Presentations**  
Chairperson: Prof. Karen Avraham

Dallalzadeh, K.L.  
The effects of glycerol kinase deficiency on mitochondrial energy metabolism and morphology

Barlow, S.  
Fezf2-GFP and FoxA2-GFP Tagged Stem Cells Shed Light on In Vitro Developmental Patterns

Singer, D.D.  
The Effects of Rat Mesenchymal Stem Cells on Injury Progression in a Rat Model

Rubin, J.  
Glowing Worms: The Protein-Protein Interactions of par-Associated Genes in *C. elegans* Embryogenesis.

Gura, Y.  
Creation of the H-+ Atom
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Background: Left ventricular assist devices are mechanical pumps that are attached between the heart and the aorta. They function to circulate a person’s blood when the normal heart cannot do so. Left ventricular assist device related infections persist as a major life threatening complication in the use of this technology. In order to provide more qualitative and quantitative clinical data on survival outcome and safety of these devices we propose to update this body of knowledge with a retrospective review of all patients given either the HeartMate II or the HeartWare left ventricular assist device at the Washington Hospital Center between 2006-2010.

Methods: Data collected includes demographics, device type, implant/explant dates, incidence and cause of death, site of infection, incidence of infection, and microbiology of infection. Once abstracted from medical records this data was analyzed using the appropriate statistical tests.

Results: Our results demonstrate that the HeartMate II and the HeartWare have very similar epidemiological and microbiological profiles. Incidence of infection is high in both cohorts, with approximately 50% of patients acquiring at least one infection during treatment. Microorganisms responsible for infection are also exhaustively uniform, with a broad spectrum of organisms leading to infection. In both devices there is a temporal distribution between acquiring blood and driveline infections: with bloodstream infections occurring early and driveline infections occurring later in treatment. Differences between devices lay in timeline to first driveline infection and death due to pump-pocket infections. The HeartWare cohort experienced their first driveline infection twice as fast as the HeartMate II cohort (226.5 days for the HeartMate II vs 99.5 days for the HeartWare). Also, our data demonstrated pump-pocket infections to be a rare but significant source of mortality. Considering the severity of these infections (all of which resulted in mortality) the preclusion of a pump-pocket is a striking advantage in the HeartWare model.

Conclusions: There are many exciting avenues in LVAD technology that may prove to have lasting effects in the realm of mechanical support. The possibility for heart recovery is an avenue that is gaining much steam in recent years. Heart failure causes a number of structural, functional, and molecular alterations collectively known as cardiac remodeling (Terraciano et al., 2010). There has been a collection of evidence in recent years to prove that VADs induce “reverse remodeling.” Unfortunately, there is a paradoxical reality to these observations. To date, an average of only 5%-10% of patients who undergo VAD placement demonstrate adequate ventricular function to allow device explantation (Terraciano et al., 2010). In addition, the observed clinical improvement is fleeting as the pathological condition returns after prolonged support (Terraciano et al., 2010). The speculated cause of this phenomenon is that VAD placement, specifically its prolonged mechanical unloading, also induces aspects of negative remodeling. The most prominent negative change induced by VADs is myocardial atrophy, due to excessive unloading of the heart (Terraciano et al., 2010). Future therapies in using VADs as a bridge-to-recovery must balance these positive effects with adjunctive therapies to directly treat the causes of disease.

Concurrently, advances in wireless power generation provide an exciting avenue to create VADs that no longer require external drivelines. As a prevalent cause of morbidity, a potential cause of mortality, and a source of extreme financial cost in the use of LVADs, driveline infections have become known as “the Achilles’ heel of prolonged left ventricular assist device support” (Zierer et al., 2007).
Hypoxia alters mitochondrial bioenergetics in endothelial cells

Zelickson BR¹², Diers AR¹², Landar A¹², Darley-Usmar VM¹².

¹Center for Free Radical Biology, ²Department of Pathology, University of Alabama at Birmingham, Birmingham, AL 35294-0022

Cardiovascular pathologies such as ischemia/reperfusion injury and atherosclerosis cause decreased oxygen delivery to affected ischemic tissues, resulting in localized hypoxia. Hypoxia in the vasculature has been shown to cause an increase in oxidative stress and lipid peroxidation, which can result in the accumulation of reactive lipids, such as 4-hydroxy-2-nonenal (HNE). These reactive lipids, through their electrophilic nature, can covalently modify proteins and change their function. Importantly, the mitochondrion has been demonstrated to be both a source and target of oxidative stress. Furthermore, multiple mitochondrial proteins are known to be modified by HNE. Protein modification by HNE has been shown to depress bioenergetic function in both isolated mitochondria and whole cells. However, the effect of HNE on the bioenergetics of vascular cells during hypoxia is not known. Under normoxia, treatment of bovine aortic endothelial cells (BAEC) with HNE (20μM) caused a decrease in the oxygen consumption rate (OCR). However, when exposed to HNE (20μM) in hypoxia (1% O₂), OCR in BAEC was transiently depressed at oxygen tensions above 18 mm Hg. At oxygen tensions below 18 mm Hg, no effect of HNE on OCR was observed. Exposure to HNE under hypoxic conditions did not affect protein-HNE adduct formation. Interestingly, when re-equilibrated to room air, cells treated with HNE showed an inhibition of OCR compared to cells treated with vehicle control and then re-oxygenated. Taken together, these data suggest that the shift in metabolic control of the mitochondria which occurs as a result of hypoxia leads to attenuation of the HNE-induced decrease in OCR. However, upon re-oxygenation, the bioenergetic dysfunction caused by HNE is once again apparent. These results provide important insight into the mechanisms by which lipid peroxidation products cause damage in ischemic cardiovascular pathologies.
Efficacy of Anti-Thymocyte Globulin Induction Therapy After Heart Transplantation.

**Saman Setareh-Shenas**, Lawrence Czer, Anita Phan, Matthew Rafiei, Andrea Ruzza, James Mirocha, Mick DeRobertis, Alfredo Trento, (2012)

Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center.

Background: Survival, cellular (CR) and antibody-mediated (AMR) rejection rates were evaluated in immunologically low and high risk patients who received intravenous anti-thymocyte globulin (ATG) induction therapy after heart transplantation (HTx).

Methods: All patients (pts) who underwent HTx from 2000 through 2010 who received ATG induction therapy were divided into two groups based on risk of rejection and were prospectively followed. High risk pts (age<60 yrs, multiparous female, African American race, panel reactive antibody > 10%, positive crossmatch) received ATG (1.5mg/kg) for 7 days (ATG7), and remaining lower risk pts received ATG for 5 days (ATG5), all followed by calcineurin, mycophenolate and prednisone. Endomyocardial biopsies were performed according to standard protocol for up to 3 years post HTx, and for suspected rejection.

Results: In 253 HTx recipients (mean age 56.4±11.8 years, 24% female) receiving ATG5 (n=87) or ATG7 (n=166), clinical characteristics were similar (48% hypertension, 27% diabetes mellitus). Baseline creatinine (creat) was 1.3±0.8 mg/dL before HTx, maximal creat post-HTx 1.8±0.9, with discharge creat 1.0±0.4 (p<0.01 compared to pre-HTx). Of 3667 biopsies, 33 (0.90%) had grade 3A/2R or greater CR. Of 3599 biopsies, 16 (0.44%) had AMR. At 5 years, freedom from rejection for 3A/2R or greater CR (94.4% vs 82.8%) and freedom from AMR (95.1 vs. 89.5%) were similar between ATG5 and ATG7. At one year, survival rates for ATG5 and ATG7 were 94.3% and 93.3% and at 7 years were 60.9% and 61.1% respectively (Log-Rank P = 0.88). Absolute lymphocyte count <200 was achieved within 10 days in 88% of ATG5 and 86% of ATG7. At 5 years, ATG5 and ATG7 were similar in freedom from infection (28.5% vs 41.8%), CMV disease (92.3% vs 94.3%), and pneumonia (83.8% vs 82.1%). The percentage of patients developing malignancies during follow up was 8.0% in ATG5 and 6.0% in ATG7 (p=NS).

Conclusions: Use of ATG induction therapy (prospectively dose-adjusted for immunologic risk) is associated with a similar low rate of cellular and especially antibody mediated rejection (<1% of >3000 biopsies) and similar survival up to 7 years after HTx in low and high risk pts. A randomized clinical trial is warranted.
Background: Bicuspid Aortic Aneurysm patients are prone to aortic dissection and rupture and premature death if untreated. Appropriate systolic blood pressure control combined with annual imaging follow up, under strict guidelines of a thoracic aortic surgery center and its potential advantages has been observed but not reported. Blood pressure management under strict thoracic aortic surgery center protocol could potentially decrease incidence of aortic dissection or rupture.

Methods: 150 bicuspid aortic valve patients were placed on twice daily systolic blood pressure monitoring via home purchased arm cuff fully digital automatic blood pressure monitor. Target systolic blood pressure in a sitting up rest position was aimed at 105-110 mm Hg with exercise systolic blood pressure of 130-140 mm Hg. 150 patients were placed on Beta Blocker and or ACE or ARB and or Calcium Channel Blockers. Sodium Nitroprusside was used intra-operatively with a target mean arterial pressure of 50-60 mm Hg. Oral medications were resumed and Sodium Nitroprusside was weaned post extubation. Further follow up and adjustments were made on an outpatient basis.

Results: In a 10 year period (2000-2010) 150 patients with bicuspid aortic valve aneurysm, 117 (78%) males and 33 (22%) females, average age 55.3±14.8 years were studied on this protocol. 35 patients in non-operative group with ascending aneurysms of less than 4.5 cm in diameter are being followed to this date without a need for surgery. One patient died as a result of severe smoking related COPD and emphysema. 115 patients in operated group with ascending aneurysm of more than 4.5 cm (Avg 4.81 cm in diameter) had no cases of dissection or aortic rupture. 2 (2.32%) patients died, one secondary to pulmonary embolism 14 days post operatively and the second due to multi-organ failure 47 days post operatively. For the operative group, operative and mid-term results were analyzed. Variables including ascending aortic resection, total circulatory arrest with hemi arch anastomosis, aortic valve replacement ± valve sparing ± CABG reviewed.

Conclusions: Blood pressure control in bicuspid aortic aneurysm patients in conjunction with annual imaging follow up under strict thoracic aortic surgery center protocol could potentially prevent dissection and or rupture.
Significance of T-wave amplitude and dynamics at the time of reperfusion in patients with acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention.

Sørensen JT, **Murinson MA**, Kaltoft AK, Nikus KC, Wagner GS, Terkelsen CJ (2009)

Aarhus University Hospital, Skejby, Aarhus N, Denmark.

Background: Peri-interventional T-wave changes may reflect the microvascular reperfusion status and potentially carry early independent, prognostic information in patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Methods: The first available electrocardiogram (ECG) (index ECG) and the ECG recorded immediately post-PCI were analyzed for T-wave morphology in 207 patients with STEMI. Absolute T-wave amplitude was recorded and any change in T-wave amplitude from index ECG to post-PCI ECG was calculated. Continuous ST monitoring was performed from hospital arrival until 90 minutes after PCI. Maximum troponin level and left ventricular ejection fraction were evaluated before discharge. Final infarct size was assessed by myocardial perfusion imaging after 1 month.

Results: Large, positive T-wave amplitude in the index ECG and the post-PCI ECG was associated with delayed ST resolution after PCI. In the post-PCI ECG, T-wave amplitude was positively associated with troponin-T value (P < .001) and final infarct size (P = .036), and inversely associated with left ventricular ejection fraction (P < .001). However, T-wave amplitude in the post-PCI ECG was also associated with procedural increase in ST elevation (P < .001) and inversely associated with spontaneous ST resolution (P < .017). A net decrease in T-wave amplitude during reperfusion therapy was associated with faster microvascular reperfusion as evaluated by time to ST resolution.

Conclusions: Large T-wave amplitudes in static pre- and post-PCI ECGs are associated with delayed microvascular reperfusion, whereas the dynamic development of more negative T waves during PCI is associated with earlier microvascular reperfusion. However, in the acute setting, T waves provide little incremental information when compared to ST parameters available in the per-interventional phase.
A human model of human disease: investigation of dystrophic cardiomyopathy using human dystrophin-deficient induced pluripotent stem cells.

**Stachel, MW** Lei Bu, Emil Hansson, Kenneth R. Chien. (2012).

Cardiovascular Research Center, Massachusetts General Hospital; Boston, MA, USA
Department of Stem Cell and Regenerative Biology, Harvard University; Cambridge, MA, USA

Background: Duchenne muscular dystrophy (DMD), caused by the loss of dystrophin, constitutes the most common X-linked recessive disease worldwide. In addition to skeletal muscular dystrophy, many DMD patients develop cardiac dysfunction in adolescence, and up to 40% of DMD patients eventually die from heart failure. There is no cure for DMD and no therapy to halt its progress to heart damage. Due to the inadequacy of existing animal models, the pathophysiology underlying dystrophic cardiomyopathy remains poorly understood.

Methods: To investigate the effect of dystrophin mutations on human cardiomyocytes (CMs), we generated induced pluripotent stem cell (iPSC) lines from the fibroblasts of DMD and control patients. Using genetic modification and FACS methods, we were able to isolate GFP+ CMs from human cTNT:eGFP transgenic iPSC lines with >95% purity. Immunochemical studies confirm dystrophin protein is absent in DMD iPSC-derived CMs. To uncover disease-related phenotypes, we measured size, electrophysiological properties and viability of iPSC-derived CMs at baseline, and recorded their responses to stretch, osmotic shock and isopreteronol-induced hypertrophy assays.

Results: In separate experiments, we used membrane sealant P188 and modified microdystrophin mRNA to restore function to dystrophin-deficient iPSC-derived CMs, as measured by histochemical and phenotypic assays.

Conclusions: This work illuminates molecular and cellular aspects of dystrophin-deficient cardiomyopathy in humans and may facilitate development of a feasible platform for testing drug cardiotoxicity as well as new agents to treat this disease.
Background: Hyaluronic Acid (HA) is a ubiquitous polysaccharide which plays a major role in heart development and cardiac disease. The elastic modulus of bioengineered materials strongly influences the phenotype of many cell types, including cardiomyocytes. On polyacrylamide (PAA) gels laminated with ligands for integrins, cardiac myocytes develop well organized sarcomeres only when cultured on substrates with elastic moduli in the range 10 kPa–30 kPa, near those of healthy heart tissue. Previous research in our lab has shown that cardiomyocytes can spread significantly, as well as develop organized myofibrillar networks, when grown on low-rigidity HA gels, despite the lack of the proper mechanical cues. The two most widely researched HA receptors, RHAMM and CD44, have been shown to mediate important cellular and physiological processes such as migration and differentiation in many different cell types.

We hypothesized that cardiomyocyte mechanosensitivity through integrin adhesion receptors is reprogrammed by RHAMM and CD44 activation on HA.

The aim of our research was to determine if myocyte response to HA is integrin type specific. Also, to determine if the HA receptors RHAMM and CD44 are involved in reprogramming the myocyte response to gel stiffness.

Methods: Neonatal rat ventricular myocytes (NRVM), or neonatal mouse ventricular myocytes (NMVM) were plated onto gels made from hyaluronic acid. Cells were grown for 24 to 48 hours, with inhibitors added as required by the experiment. Cells were stained and imaged for α-actinin and f-actin to visualise myocyte morphology and myofibrillar organization, as well as RHAMM and CD44 antibodies to assay receptor expression. Quantification of cell spread area was made using ImageJ and Axiovision analysis software.

Results: • Cardiomyocyte growth on HA is ligand type specific.
• Cardiomyocytes require the RDG-binding integrins α5β1 and/or αVβ3 to attach and respond to HA differentially.
• The HA receptors RHAMM and CD44 reprogram cardiomyocyte mechanosensitivity on HA, but each of these is responsible for different aspects of myocyte growth; CD44 mediates sarcomeric organization, while RHAMM activation drives myocyte spreading.

Conclusions: These results have implications for the use of injectable ECM-protein-functionalized hyaluronan gels for cardiac repair. Functionalizing hyaluronan gels with adhesion proteins and/or growth factors can have added benefits of recruiting/differentiating stem cells and enhancing angiogenesis at the site of myocardial injury.
Background: My project is looking at central blood pressure's correlation to atherosclerosis and peripheral artery disease in patients with familial mediterranean fever and/or amyloidosis. This is a novel technique that has recently been introduced into clinical practice and is considered a stronger prognostic technique than the conventional method. Central blood pressure is that of the aorta, the central artery, rather than peripheral blood pressure in peripheral arteries, normally measured from a person's arm. Central aortic BP minimizes the effect of wave reflection from the branching points off the peripheral arteries. Our project utilizes the process of pulse wave analysis, which involves applanation tonometry: a noninvasive, simple, accurate method of measuring the velocity of the pulse while partially compressing the artery against a bone. This allows the analyzer to record the force being applied to the arterial wall. Our project aims to determine the clinical significance of aortic blood pressure in the prognosis of patients with familial mediterranean fever or amyloidosis.

Methods: We are employing the Sphygmocor device to calculate the central aortic pressure in our patients. It calculates arterial stiffness by measuring the pulse wave velocity. Arterial stiffness is a measure of the loss of elasticity in one's arteries and is found in patients with atherosclerosis. The greater the stiffness of an artery, the greater the pulse wave velocity. We will first record the brachial BP of our patients with the conventional blood pressure cuff seated, and immediately proceed by taking his orthostatic BP. Then, we will have the patient lie down and record his pulse wave velocity in his radial artery with the Sphygmocor device. The computer will analyze the data and compare the results to the standard methods. We will track these patients over a certain period of time and record their changes in quality of life.
Circulating Endoglin Concentration Is Not Elevated in Chronic Kidney Disease.

Charytan DM, **Helfand AM**, MacDonald BA, Cinelli A, Kalluri R, EM Zeisberg. (2011) Renal Division, Brigham and Women's Hospital, Boston, MA

(PLoS ONE 6(8): e23718. doi:10.1371/journal.pone.0023718)

Background: Soluble endoglin, a TGF-β receptor, plays a key role in cardiovascular physiology. Whether circulating concentrations of soluble endoglin are elevated in CKD or underlie the high risk of cardiovascular death associated with chronic kidney disease (CKD) is unknown.

Methods: Individuals with and without CKD were recruited at a single center. Estimated glomerular filtration rate (eGFR) was estimated using the modified MDRD study equation and the serum creatinine at the time of recruitment, and patients were assigned to specific CKD stage according to usual guidelines. Serum endoglin concentration was measured by ELISA and univariate and multivariable regression was used to analyze the association between eGFR or CKD stage and the concentration of soluble endoglin.

Results: Serum endoglin was measured in 216 patients including 118 with stage 3 or higher CKD and 9 individuals with end stage renal disease (ESRD). Serum endoglin concentration did not vary significantly with CKD stage (increase of 0.16 ng/mL per 1 stage increase in CKD, P = 0.09) or eGFR (decrease -0.06 ng/mL per 10 mL/min/1.73 m2 increase in GFR, P = 0.12), and was not higher in individuals with ESRD than in individuals with preserved renal function (4.2±1.1 and 4.3±1.2 ng/mL, respectively). Endoglin concentration was also not significantly associated with urinary albumin excretion.

Conclusions: Renal function is not associated with the circulating concentration of soluble endoglin. Elevations in soluble endoglin concentration are unlikely to contribute to the progression of CKD or the predisposition of individuals with CKD to develop cardiovascular disease.
Nutritional Science Abstracts
The Effect of *Salvia hispanica* L. (Salba) on Weight Loss in Overweight and Obese Individuals with Type 2 Diabetes Mellitus.

**Choleva, L**, Vuksan, V, Jovanovski, E, Jenkins, A (2011) University of Toronto; Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, ON

Background: Canadian statistics indicate that the incidence of obesity is rising, and that the prevalence of type 2 diabetes mellitus (T2DM) within this group is significantly higher than those of a healthy weight. Preliminary evidence has shown that the oil-rich grain, *Salvia hispanica* L. (Salba), improves glycemic control, suppresses appetite, and affects additional cardiovascular disease (CVD) risk factors.

Methods: This study followed a randomized, double-blind, placebo-controlled, parallel design in a subset population of twenty individuals who were overweight or obese and had T2DM. Participants received supplements of Salba, or an energy- and fibre-matched control, and followed a hypocaloric diet for 24 weeks.

Results: Findings of this study reveal that Salba does not significantly affect weight loss, glycemic control or other CVD risk factors.

Conclusions: These findings are preliminary and highlight the complexities of weight loss research. Further investigation into the potential health benefits of Salba is currently being carried out.
Quantitative MRI in Benign Multiple Sclerosis

The Chaim Sheba Medical Center at Tel Hashomer

Background: Multiple Sclerosis (MS) is a chronic, venocentric inflammatory demyelinating disease of the central nervous system that may follow several different clinical courses. The term Benign Multiple Sclerosis refers to a clinical subtype of MS characterized by slow disease progression as measured by the Expanded Disability Status Scale (EDSS). MRI imaging is an important paraclinical tool for the diagnosis and monitoring of MS disease progression augmented by the use of quantitative metrics such as lesion number and volume. A subgroup of Benign MS patient show conversion to active disease after the prolonged disease-free period. The current study seeks to determine whether quantitative imaging metrics in combination with clinical variables can distinguish between Benign MS patients who remain disease free or convert to active disease.

Methods: MRI data from twenty-seven patients diagnosed with Benign MS was analyzed using a custom program, the Multiple Sclerosis Evaluation Tool (MSET), to calculate lesion load. Two trained observers blinded to conversion status identified MS plaques using a semiautomatic technique with the MSET program. Imaging modalities included T2-Weighted, FLAIR, and Gadolinium-Enhanced T1-Weighted MRI imaging sequences. Lesion count and total lesion volume were extrapolated from the selected lesions. Additional patient data included the date of MS onset, time to progression, time to second relapse, and basic demographic variables. Discriminant analysis was performed on the data to identify which combination of variables, if any, could discriminate between converting and non-converting Benign MS patients.

Results: Among the Benign MS patients, FLAIR lesion numbers and volumes ranged from 3 to 50 and 0.6 to 16.46, respectively. Data acquisition among the two trained observers is currently in progress.

Conclusions: Quantitative MRI measurements in patients with suspected or diagnosed Benign MS may assist in identifying which patients have a higher risk for conversion to active disease.
**Background:** The GABAA receptor (GABAAR) is a chloride ion-permeant channel responsible for a majority of the inhibitory signaling seen by the central nervous system (CNS). The receptor is a heteropentamer, with each subunit being comprised of four transmembrane (TM) domains flanked by extracellular N and C termini. While homology modeling in different organisms has aided in characterizing binding sites for benzodiazepines and GABA in the N-terminus of the receptor, sites for neurosteroids (NSDs), alcohols, barbiturates, and anesthetics have proven more elusive. The potentiating effects of NSDs can be functionally observed as an increase in GABA-evoked chloride current (IGABA). NSDs thus act as endogenous anxiolytics and/or hypnotics and broadly control neuronal excitability by increasing the overall inhibitory tone of the CNS. Consequently, much attention has been turned towards the clinical and pharmacological implications of rational drug design with respect to such issues as anxiety, depression, post-traumatic stress disorder, and other physiological/cognitive ramifications of NSD dysfunction. Previous studies have identified two amino acids within the first transmembrane domain that putatively participate in NSD binding and/or modulation of IGABA: α1T236 and α1Q241. This research extends the knowledge of the current field to ask whether these amino acids are both necessary and sufficient for NSD sensitivity. Specifically, these efforts aim to better understand NSD binding by resolving a discrete NSD binding site within the first TM domain of the GABAAR alpha subunit.

**Methods:** In order to confirm that TM1 is indeed the sufficient domain for neurosteroid sensitivity within the GABAAR α1 subunit, a chimera will be generated by inserting TM1 of the GABAAR α1 subunit into TMI of the glycine receptor’s (GlyR’s) α1 subunit. Since the GlyR is normally neurosteroid-insensitive, this chimera should, in essence, confer neurosteroid sensitivity to the GlyR. Thus, assuming successful generation of the aforementioned chimera, the integrity of the receptor’s function will be evaluated by testing the ability of glycine, in the presence and absence of neurosteroid, to evoke IGly. The apparent affinity of glycine for the receptor (measured as the EC50 value on a glycine concentration-response curve), as well as the possible change in apparent affinity in the presence of a neurosteroid, will be cross-referenced with literature and my own wild type GlyR values to ensure that the integrity of the receptor’s functionality was not compromised. Furthermore, a neurosteroid-induced current would suggest that the molecular basis of neurosteroid sensitivity within the GABAAR is ultimately localized to TM1.

Subsequently, attention will be focused primarily on the GlyR via site-directed mutagenesis using Stratagene’s QuikChange protocol. Assuming that neurosteroid sensitivity can indeed be isolated to TM1, it will be necessary to seek a more specific site of neurosteroid interaction at the level of the receptor’s amino acid sequence. Initially, amino acid residues will be independently mutated from the GlyR’s amino acid sequence to their GABAAR counterparts until neurosteroid sensitivity is conferred. If a single, discrete amino acid is indeed responsible for neurosteroid binding, then this method will undoubtedly isolate that particular site. Each mutant-containing plasmid will be sent to the University of Pennsylvania for nucleotide sequencing to confirm the presence of the desired mutations following their construction. Upon confirmation, surgical extraction of Xenopus laevis oocytes will provide the cells in which we will inject cRNA coding for receptor. Following RNA expression, receptor sensitivity to neurosteroids will be evaluated using two-electrode voltage clamping.
Conclusions: The most convenient outcome of this work would be one in which the mutation of an individual amino acid provides for formidable evidence suggesting a singular, discrete amino acid site necessary for neurosteroid sensitivity, which we could deem as the putative site of neurosteroid modulation. Alternatively, it is feasible that multiple amino acids will be required for neurosteroid sensitivity. Both of these possibilities will be covered through rigorous screening of GABAAR and GlyR amino acid sequences and consideration of appropriate mutations. If we are unsuccessful in conferring neurosteroid sensitivity – either potentiation or direct activation – at the level of a single amino acid, then we have gained significant information regarding receptor structure and function. This finding would be particularly significant in the sense that the way in which the field viewed the mechanism for neurosteroid binding would be altered. If it turns out that α1Q241 is necessary but not sufficient, we would need to test additional, novel amino acid residues that have not yet been implicated by the neurosteroid literature. Likewise, we could use multiple simultaneous point mutations in order to find a sufficient group of residues capable of conferring sensitivity. For example, it has already been determined that swapping out a glutamine for a tryptophan at site 241 eliminates neurosteroid sensitivity in the GABAAR. Therefore, if swapping a tryptophan for a glutamine at a homologous site 267 in the GlyR does not induce sensitivity, then we know that this glutamine residue is necessary, but not sufficient for binding. This experiment is only considering TM1 of the receptor, and thus additional research may need to be done regarding putative binding sites concerning other TMs.

I am most interested in the pharmaceutical implication of this project. The effectiveness and practicality of drug design is contingent upon an ability to limit side effects. Considering the levels of interest in pharmacological advancement with respect to depression and anxiety disorders, any data purporting a specific region of endogenous ligand interaction would be invaluable to the field. Furthermore, an indication of a discrete area for neurosteroid interaction on the GABAA could suggest a new type of inhibitory signal regulation that has not previously been discussed in neuropharmacological literature.
Background: As an organism ages, many substances accumulate in its cells. The mechanisms to safely dispose of or sequester those products deteriorate with age. This, in short, is the mechanism of some of the most common diseases found in aged populations; Parkinson's Disease, Alzheimer's Disease, Huntington's Disease are just a few. Our hypothesis was that we could prevent or delay the onset of these diseases by preventing the aggregation of their respective aberrant proteins. We started with a simple, well-known amyloid-staining dye called Thioflavin-T that we thought would prevent aggregation of amyloid-beta. What we discovered was far more surprising and significant. We realized that certain small molecules can change the transcriptional profile of an organism and allow old cells to manage their waste the way young cells normally do. In various models of protein misfolding disease in C. elegans, we showed that a single compound can delay the onset of pathology and extend lifespan. One cheap, small molecule may hold the answer preventing disease and extending the healthy years of life in humans.

Methods: All of our experiments were conducted using Caenorhabditis elegans as a model. We compared the mean lifespan of populations with and without treatment of Thioflavin-T and other compounds. We tested other metrics of health in with similar methods. We utilized disease model strains of C. elegans to observe the benefits of treatment. For example, we observed the time it took for amyloid-beta and other proteins to aggregate in treated and untreated groups, and we used fluorescence microscopy to detect and quantify aggregation.

Results: Thioflavin-T increased the lifespan of C. elegans by 60%. Treatment delayed and reduced aggregation of pathogenic protein. These results were dependent on several heat shock factors and lysosomal proteins.

Conclusions: A simple dye extends the lifespan of C. elegans and prevents pathology in several disease models. These results are not from simple structural inhibition of aggregation; rather, Thioflavin-T elicits transcriptional changes that seem to upregulate innate protein homeostatic mechanisms. This response requires several stress-activated genes, suggesting that Thioflavin-T functions as a stress-response inducer. These findings suggest that using small molecule stress mimetics may be a viable way of treating disease and slowing aging in the future.
Lithium as a Modulator of Protein Homeostasis and Lifespan in C. elegans.

Buck Institute for Research on Aging.

Background: It has been previously shown that lithium extends lifespan in the model organism Caenorhabditis elegans. In this work, I investigated the mechanism by which lithium extends lifespan. Lithium, a tiny ion, can be expected to have a plethora of molecular targets. It is important to understand the results of lithium treatment as it is the therapeutic of choice in treatment of bipolar disorder. Furthermore, it may serve as a potent activator of protein homeostasis, and therefore may be used in the future to treat and prevent diseases of aberrant protein folding.

Methods: Mutant populations of C. elegans expressing various aggregation-prone proteins were studied in several assays. Severity and velocity of the pathology of those aberrant proteins were measured using paralysis and movements assays, as well as fluorescent microscopy with software capable of identifying aggregates. A focused screen was undertaken with RNA interference for transcription factors identified from previous microarray data.

Results: Lithium prevents aggregation in all tested mutant strains, and it extends lifespan in all of those strains except for one expressing Q40 (poly glutamine expansion). These effects require many genes involved with chromatin remodeling, stress response, and nutrient metabolism.

Conclusions: Improved protein homeostasis may be one mechanism by which lithium increases lifespan and prevents pathology in mutant strains of C. elegans. Interestingly, one gene that is required by lithium to elicit it's maximal effect, nhr-80, is a regulator of fatty acid metabolism. Other modulators of protein homeostasis also require this gene to function. These data suggest that the fatty acid profile of an organism may have a profound effect on lifespan and disease. Most importantly, this work is helping the scientific community understand all the facets that contribute to age-related disease, and helping to move towards real and practical solutions in the near future.
p75 neurotrophin receptor expression occurs from two alternative start codons.


Background: The p75 neurotrophin receptor (p75NTR) is an important initiator of apoptosis in both the developing nervous system and adult neurodegenerative conditions. Although the p75NTR start codon from a variety of species is consistently annotated to encode a 29 amino acid signal peptide, the mRNA contains a second in-frame start codon that is prefaced by a more highly conserved Kozak sequence. Furthermore, in some species the first methionine is not present. Proteins initiating from this second start codon would produce a p75NTR protein with a 19 amino acid signal peptide. Given the functional importance of transcriptional and translational regulation of expression of the p75NTR ligands, the neurotrophins, we hypothesized that p75NTR might be regulated through the use of the alternative start sites i.e., different translational initiation sequences or signal peptide lengths may lead to the mRNA being transcribed, or the protein being directed, into alternative sub-cellular locations, respectively.

Methods: Two p75NTR constructs were designed: Met1 signal peptide and Met2 signal peptide, including a Kozak sequence (nucleotides -29 – 87). Met1 began at the first start codon, while Met2 began at the subsequent one. Several cell lines were cultured and transfected with the respective receptor constructs. For primary neuronal culture, pregnant mice were sacrificed and the embryos were removed via Caesarian section to retrieve hippocampal tissue, which would be transfected as well. Western blot analysis and immunofluorescence imaging were utilized to analyze the translation and expression of both p75NTR constructs.

Results: Here we found that each start codon allows p75NTR translation when under the control of the CMV promoter and is therefore functional.

Conclusions: Although, no obvious difference was found in apical/basolateral or somatic/neuritic location between p75NTR proteins derived from each start codon, this work raises the interesting possibility that each start codon may be used under different cellular conditions, thereby contributing to the function or regulation of p75NTR. Future experiments designed to investigate whether there is preferential use of the start codons by somatic or neuritic compartments will need to combine the use of Met1 and Met2 mutations with the ability to restrict the location of the mRNA of interest.
Man from Meat: Medicine, Music and the Generation of Pain

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“The real important discovery in science is the Concept; the concept must be elegant and beautiful.”- Dr. Susumu Tonegawa

Background: The brain is no more spectacular in biochemical or anatomical structure than a stomach, spleen or scrotum. This is why it’s strange that the brain is somehow, but absolutely, responsible for the generation of subjective experience (i.e.- the misery of suffering). This fact begs at the question: “What is the physiological mechanism by which the human—the lover, sufferer, the hummus enthusiast—emerges from a ball of biological jelly in a calcified cranium?” (Chalmers, 1994) The question remains one of the most alarming in modern medicine by virtue of its conspicuous neglect; relegated to the realm of philosophical banter. The answer remains elusive.

Synopsis: Integrating concepts across the neural sciences, medical physiology, and music, I have attempted to derive a basic physiological principle of the brain; a mechanism that can possibly account for the union of biological tissue with experience. My approach to this problem was guided by three foundational principles.

First, the brain is meat: no more, no less. It is a natural organ akin to the kidney and the liver, devoid of unique properties and privileges. The neural mechanism underpinning subjectivity must, therefore, be considered through the lens of natural physiology: in the context of the body. Second, organ physiology is understood by considering the talents and physical orientation of their constituent cells. Furthermore, on a macroscopic level, organs hi-jack natural properties of the world to execute their function. Third, when considering that which the brain directly creates (like the heart does pressure), we cannot use the word “consciousness.” It is loaded with ambiguities and mysticism I adopted the word “Quality,” for reasons to be explored in great detail.

After briefly exploring each tenet of the approach, I will turn to actual neural tissue. I will argue here for a unique physiological role for the neuron—a concept yet to be explored, to my knowledge. I will offer support for my claim by considering subtle histological structures called Schmidt Lanterman Clefts.

I will conclude by addressing real life implications of this work. Experimentally, mathematical and musical software have the potential to prove me wrong; one of the greatest strengths of this theory is its potential to be falsified with scientific experiment. I will discuss designs for future experiments to test the merits of this theory. The clinical implications rest on the power afforded by a Concept. If the basic physiology underpinning pain were understood, then we would have a new conceptual paradigm within which we might design novel and effective medical interventions for the treatment of pain.
Ophthalmology Abstracts
Possible association of Revatio (sildenafil) and optic nerve stroke.

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Background: Revatio (Sildenafil) relaxes muscles and increases the blood flow to particular areas of the body. A potential link between Revatio and damage to the optic nerve remains controversial with some studies showing a possible association and others showing no association. The purpose of this study was to measure the effect of Revatio on mouse ocular blood vessels and neuronal tissue.

Methods: Transgenic Thy-1-CFP and C57Bl6 mice underwent Revatio injection intravitreally to the right eye (IVT, n=12) or intraperitoneally (IP, n=20). The left eye with or without saline injection served as a control. Another control group (n=6) was with no intervention. Evaluation included: 1. Retinal fluorescence angiography; 2. Flat mount retinae analysis; 3. TUNEL staining for apoptosis; 4. TTC staining of the nerves for stroke detection; 5. Molecular analysis for the expression of apoptosis and ischemic related genes: SOD , HO-1, GFAP, MBP, Bcl-2 and BAX.

Results: Retinal vessels dilatation and increased choroidal effusion were detected by FA and flat mount retinae immediately following IVT and 30 minutes after IP Revatio injection. No RGC loss was detected in the retina 21 days following IVT injection (n=5) and IP (n=10). None of the 5 optic nerves following direct IVT injection revealed stroke. TTC staining revealed one (out of 20) stroke suspected area in the anterior segment of the nerve following Revatio IP. In the IVT group, gene expression analysis showed an increase in Bel-2 on day 1 which reverted to baseline at day 3; no significant change was detected in the other gene levels. All genes measured in the IP group, increased (2-3 fold) on both days 1 and 3 and every 10th optic nerve tested showed a significant increase in all genes examined, higher than those of other samples.

Conclusions: Revatio increased choroidal perfusion and mildly dilated retinal vessels. Following IP injection, we detected, histological and molecularly, clues towards an optic nerve stroke in a few samples, with an increase in apoptotic and ischemic related gene expression. These marginal examinations should be further investigated in a large number of mice, to validate the possible association of Revatio and optic nerve stroke.
The Effect of Inflammation on EMP2 Expression in Proliferative Vitreoretinopathy.

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Background: Proliferative vitreoretinopathy (PVR) is a common complication of rhegmatogenous retinal detachment. It is believed to be the result of an aberrant wound-healing strategy which leads to abnormal membrane formation and retinal contraction. Epithelial membrane protein 2 (EMP2), a key mediator of PVR, increases collagen gel contraction in cultured retinal pigment epithelial cells (ARPE-19). The purpose of this study was to assess the role of several pro-inflammatory signals associated with PVR on the expression of EMP2 in ARPE19 cells in vitro.

Methods: ARPE-19 cells were treated with various cytokines, growth factors or danger signals including IL-1α, IL-1β, IL-2, IL-15, PDGF, IFN-γ, TNF-α, TGF-β and LPS. Expression of EMP2 was assayed using Western blotting.

Results: Cells treated with pro-inflammatory cytokines IL-1α and IFN-γ showed decreased EMP2 expression by Western blotting. LPS and TNF-α had no effect on EMP2 expression. While TGF-β, IL-15, IL-2 showed no dose-dependence on EMP2 expression but was not confirmed in a repeat assay. It was also found that EMP2 overexpressing cells expressed higher levels of PDGF receptor α (PDGFRα).

Conclusions: Pro-inflammatory cytokines like IL-1α and IFN-γ may play a role in the regulation of EMP2 expression. Thus, these cytokines may potentially represent therapeutic targets for the treatment of PVR. Likewise, PDGFRα may also be a potential therapeutic target in the treatment of PVR.
Cochlear Structure and Hearing in Murine Congenital Hypothyroidism Caused by Targeted Gene Mutations in the Mouse Dual Oxidase A1 and A2 Genes.


Background: Congenital hypothyroidism is the most common class of human congenital endocrine disorders estimated to affect 1 in every 4000-5000 neonates. Hearing loss as a result of hypothyroidism accounts for 1-10% of all hereditary deafness. Previous hypothyroid animal models studied include PAX8, hyt/hyt, and Pit1, which have demonstrated substantial hearing impairment as well as abnormal development of the organ of corti, cochlea, and the tectorial membrane.

Our new mouse model:

Human dual oxidase (DUOX) genes, DUOX1 and DUOX2, are expressed in a variety of tissues including thyroid follicular cells and epithelial cells in the respiratory and gastrointestinal tracts. The genes encode surface proteins that act as reduced nicotinamide adenine dinucleotide phosphate dependent oxidases. They are involved in the synthesis of hydrogen peroxide, which acts as the final electron acceptor for the oxidation of iodine. Our new mouse model is not a spontaneous mutation, but a targeted deletion (DUOXA1/2 KO mice) disrupting two genes simultaneously. The newly discovered, dual oxidase maturation factors DUOX A1 and A2 have been shown to be essential for the maturation and translocation of the DUOX enzyme to the apical cell membrane. Knockout mice provide a model for complete functional deficiency of the dual oxidases. Since these mice display a severe hormonogenesis defect we would expect sequelae of congenital hypothyroidism, such as hearing impairment.

Methods: The two arms of the study included analysis of hearing impairment and cochlear histopathology. Hearing impairment: Twenty-two mice (7 knockout, 15 wild type), age 65-155 days, were anesthetized (isofluorane and ketamine) prior to undergoing auditory brainstem evaluation at 2000-4000 Hz. Cochlear histopathology: Twenty-five mice (19 knockout, 6 wild type), age 14-30 days, were anesthetized (isofluorane) and perfused with Bouins fixative solution prior to cochlear harvest and histopathologic analysis.

Results: There was no significant difference noted between wild type and knock out mice of varying ages with regards to cochlear histopathology and auditory brainstem response.

Conclusions: The targeted deletion used is a new mouse model and functions by disrupting two genes simultaneously: Dual oxidase maturation factor 1 and 2. The knock-out mice developed provide a model for complete functional deficiency of the dual oxidases. Such mice display essentially no iodide organification within the thyroid and subsequently undetectable serum T4. Since such a severe defect in hormonogenesis would occur, we expect to encounter sequelae of congenital hypothyroidism, such as hearing impairment. From this study, we have noted no significant difference between wild type and knock out mice with regards to auditory brainstem response testing and cochlear histopathology. These results differ from previously reported data murine hypothyroid models. Future direction and improvement in analysis include larger sample size and performing auditory brainstem response at higher frequencies. There may also be a role in biochemical analysis of the etiology of hearing impairment associated with congenital hypothyroidism.
Dermatology Abstracts
Regulation and mechanisms of action of RBM28, a protein deficient in ANE syndrome

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We previously showed that a rare hair disorder termed Alopecia-Neurological defects-Endocrinopathy (ANE) syndrome (MIM612079) results from defective function of the RNA binding motif protein 28 (RBM28). In the present study, we attempted to delineate the molecular pathology of this disorder. To obtain direct evidence for RBM28 involvement in hair growth, we used RNAi to down-regulate RBM28 expression in human hair follicle (HF) organ cultures, and observed catagen induction and HF growth arrest. Given the fact that an RBM28 homolog was recently found to regulate miRNA biogenesis in C. elegans and given the known pivotal importance of miRNA for proper hair follicle development, we performed a global correlative analysis of mRNA and miRNA expression profiles in primary keratinocytes transfected with either RBM28-specific siRNA or an siRNA control in an attempt to identify the targets of the miRNA network differentially perturbed in the absence of RBM28. We also used miRNA transfection and luciferase promoter activity assays to validate our data. This analysis revealed that RBM28 regulates the expression of miR-203, which in turn modulates the expression of SCG5, whose expression was found to depend upon RBM28. Since SCG5 encodes a protein with a known role/expressed in neuroendocrine cells and HFs, these data are of direct relevance to the phenotypic consequences of RBM28 deficiency in humans. Furthermore, bioinformatics analysis predicted the presence along RBM28 promoter of multiple binding sites for SP1 which mir-203 regulates. Deletion analysis of the RBM28 promoter revealed a 230 bp fragment containing multiple SP1 sites, critical for RBM28 promoter activity. Addition of an SP1 specific inhibitor abolished the activity of this promoter sequence. Taken altogether, the present set of data sheds light upon the mechanisms of action of RBM28 and upon the pathogenesis of ANE syndrome.
Hematology and Oncology Abstracts
Statins may improve the outcome of Erlotinib as second line treatment in patients with metastatic non-small cell lung cancer.

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Background: The EGFR inhibitor erlotinib is a standard second line treatment for metastatic non-small cell lung cancer (mNSCLC). Statins are used in the treatment of hyperlipidemia. Pre-clinical and clinical studies in several cancer types have shown that they may inhibit tumor growth. Their effect on the outcome of erlotinib as second line treatment in mNSCLC is poorly defined. We aimed to study the effect of statins on the outcome of erlotinib as second line treatment for mNSCLC.

Methods: We performed a retrospective study of an unselected cohort of patients with mNSCLC, who were treated continuously with 150mg of oral erlotinib. Pts were divided into 2 groups: (1) statins users and (2) statins naive. The effect of statin use on objective response, progression free survival (PFS) and overall survival (OS), was tested with adjustment of other known confounding risk factors using a chi-square test and partial likelihood test from cox model.

Results: Between 2005-2011, 107 pts with mNSCLC were treated with second line erlotinib. There were 51 statins users (group 1) and 56 nonusers (group 2). All users started statins before erlotinib treatment initiation. The groups were balanced regarding the following known clinical prognostic factors: female gender, ECOG performance status, active smoking, anemia, adenocarcinoma histology type, EGFR mutation (positive vs negative + unknown). Objective response in group 1 vs 2 was partial response (PR) 41% vs 29% (p=0.15), stable disease (SD) 41% vs 25% (p=0.11), and progressive disease (PD) 18% vs 46% (OR=2.5, p=0.07). Median PFS was 12 vs 3 ms (HR 0.44 in statins users, p=0.02). Median OS was 35 vs 19 ms (HR 0.63, p=0.1).

Conclusions: Statins may improve the outcome of patients with mNSCLC that are treated with erlotinib as second line treatment. This should be investigated prospectively, and if validated, applied in clinical practice and clinical trials.
Screening for Lynch Syndrome: Predictive Models

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Background: Lynch syndrome is the most common cause of inherited colorectal cancer (CRC) and is due to germline mutations in mismatch repair (MMR) genes. Early Lynch syndrome diagnosis and appropriate CRC surveillance improves mortality. Traditional qualitative clinical criteria including Amsterdam and Bethesda guidelines may miss mutation carriers. Recently, quantitative predictive models including MMRPredict, PREMM(1,2,6), and MMRPro were developed to facilitate diagnosis. However, these models remain to be externally validated in the United States. Therefore, we evaluated the test characteristics of Lynch syndrome predictive models in a tertiary referral group at two US academic centers.

Methods: We retrospectively collected data on 230 consecutive individuals who underwent genetic testing for MMR gene mutations at the University of Chicago and University of California at San Francisco's Cancer Risk Clinics. Each individual's risk of mutation was examined using MMRPredict, PREMM(1,2,6), and MMRPro. Amsterdam and Bethesda criteria were also determined. Testing characteristics were calculated for each of the models.

Results: We included 230 individuals in the combined cohort. In all, 113 (49%) probands were MMR mutation carriers. Areas under the receiver operator characteristic curves were 0.76, 0.78, and 0.82 for MMRPredict, PREMM(1,2,6), and MMRPro, respectively. While similar in overall performance, our study highlights unique test characteristics of these three quantitative models including comparisons of sensitivity and specificity. Moreover, we identify characteristics of mutation carriers who were missed by each model.

Conclusions: Overall, all three Lynch syndrome predictive models performed comparably in our multi-center US referral population. These results suggest that Lynch syndrome predictive models can be used to screen for MMR mutation carriers and can provide improved test characteristics compared with traditional clinical criteria. Identification of MMR mutation carriers is paramount as appropriate screening can prevent CRC mortality in this high-risk group.
The lag-time in initiating clinical testing of new-drugs in combination with radiation therapy, a significant barrier to progress in radiation oncology

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Purpose: The development of new drugs with radiation appears to be limited. We hypothesized that phase I clinical trials with radiation therapy (RT) are initiated late into a new drug’s lifetime, hence limiting the ability to complete RT-drug development programs prior to patent expiration.

Methods and Materials: We identified novel drug-radiation phase I combination trials performed between 1980 and 2012 from the PubMed and Clinicaltrials.gov databases. For each pharmacological agent we then identified when the initial Phase I trial without RT was published. Other parameters collected included date of published positive Phase III trials (if any), and patent-expiration dates. 'Lag-time' was defined as the number of years between publishing the 'initial phase I trial without RT' and the 'initial phase I trial with RT'. Linear-regression was used to model how ‘lag-time’ has changed over time.

Results: An initial 'phase I trial with RT' was identified for 66 drugs: 20 chemotherapeutic agents, 11 monoclonal antibodies, 35 targeted small molecules and 5 biological modifiers. The initial ‘non-RT phase I trials’ for these agents were published between 1983 and 2011. The median time between the ‘opening of the phase I trial without RT’, and the ‘opening of the phase I with RT’ was 6 years. It took an average of 5 years to progress from the ‘1st published Phase I without RT’ to the first published ‘phase III trial without RT’. The ‘phase I with RT’ was typically published soon after the first published positive phase III trial (median 2 years), and 11 years prior to patent expiration. Using a best-fit linear model, the lag-time (time from ‘publication of Phase I trial without radiation’ until the ‘opening of a phase I trial with radiation’) was shown to have decreased from 9 years for phase I trials published in 1990 to 2 years for trials published in 2005, (slope significantly non–zero, p<0.001).

Conclusion: Clinical drug development with RT commences late in the life cycle of anti-cancer agents, a median 11 years prior to patent expiration. Taking into account the additional time required for late-phase clinical trials, the delay in initiating clinical testing of drug-RT combinations produces a considerable disincentive for drug companies to pursue drug development with RT.
Preclinical Evaluation of Tumor Angiogenesis with Contrast Enhanced Digital Breast Tomosynthesis.


Background: Contrast enhanced digital breast tomosynthesis (CE DBT) is a quasi-3D mammographic imaging technique that provides valuable vascular information at increased sensitivity compared to traditional digital mammography. CE DBT is still under clinical trial investigation, and work still needs to be done to optimize the acquisition parameters for the most relevant clinical information. A key step in the process of tumor development is angiogenesis - the recruitment of additional vasculature to provide nutrients. The goal of this work is to directly correlate CE DBT image properties with underlying histopathological markers.

Methods: Eight New Zealand White Rabbits were inoculated in their hind leg with VX2 sarcoma. At time points from two to three weeks post-inoculation, a 60 second contrast-enhanced CT scan was performed with a full-volume acquisition every 1 second. Subsets of the full CT data were used to simulate DBT volumes. As an immunohistochemical (IHC) marker for vessel permeability, a 70kDa biotinylated dextran was injected intravenously prior to rabbit sacrifice. Fiducial markers were inserted into the tumor and imaging was performed again to allow for registration between the tissue sections and CE DBT. Both the tumor and normal muscle tissue from the contralateral hind leg were excised and embedded in paraffin wax. Serial whole-mount sections were made and stained for histologic markers. For the initial work, the IHC markers stained for included H&E, CD31, and biotinylated dextran, but further work will test other markers as well. The stained whole-mount sections were digitized and compared with image enhancement properties and contrast kinetics from the CE DBT reconstructions.

Results: A statistically significant correlation was found between image-enhancement and dextran, but not with CD31. The correlation was significant at the 30 second mark, corresponding to the tumor washout-phase. This correlation strengthened at later time points up to the end of the 60 second acquisition. CD31 is an endothelial cell adhesion marker in vascular endothelium.

Conclusions: We believe this study provides the first direct evidence of the relationship between vascular permeability and image signal in contrast-enhanced breast imaging. Future directions include the additional examination of other immunohistochemical markers such as VEGF, and microvessel density (MVD), as well as further optimization of DBT acquisition and reconstruction parameters for individual tissue features.
Markers of radiation nephropathy: Albuminuria and azotemia are associated with histologic damage in a mouse model of radiation nephropathy.

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Background: Ionizing radiation has long been known to cause kidney damage. Total body irradiation, used for bone marrow transplant, has become the leading cause of radiation-induced kidney damage. There are no available clinical markers to non-invasively predict which patients’ kidneys will be affected.

This study sought to demonstrate an association between the histologic evidence of renal damage and common biomarkers of kidney damage. This could lead to improved detection of renal damage in patients undergoing TBI and obviate the need for renal biopsies and provide for earlier intervention.

This study is novel in two ways. First, it provides a meticulous microscopic examination of the effects of radiation on the mouse kidney over time. Second, it shows that easily obtainable markers of kidney injury can be used to monitor development of radiation nephropathy.

Methods: Male and female mice were subject to total body irradiation, and subsequently received a T-Cell depleted bone marrow transplant. Urine and blood were collected for assessment. Mice were eventually sacrificed and nephrectomized. Kidneys were sliced and subsequently stained with H&E, Masson's Trichome or Periodic acid-Schiff.

Results: Results varied with time between TBI and sacrifice. A longer time frame correlated with increased injury. The mice with moderate to significant glomerular, or tubulo-interstitial injury showed elevated levels of urine albumin and BUN.

Histopathology of irradiated mice showed glomerular damage, including glomerular congestion, sclerosis, collapse or evidence of thrombotic microangiopathy. Tubulointerstitial damage was also found which included tubular cell lysis, injury or atrophy, and vascular injury. Of the 26 specimens, 11 demonstrated at least some evidence of glomerular damage, whereas 15 were categorized as having histologically normal glomeruli. 13 animals showed tubulointerstitial changes and 13 did not. Only three kidney specimens demonstrated abnormal collagen deposition.

Conclusions: This study characterized both tubular and glomerular histopathology, both at the light and electron microscopic level, and found a worsening of damage over time with increases in both albuminuria and BUN. These markers correlated with histologic damage much better than serum creatinine, and suggest that they may be valuable clinically to monitor progression of radiation-induced renal pathology in humans.
Biomechanics Abstracts
Knee Biomechanics After Total Knee Arthroplasty: Early Outcomes

1 **Eytan M. Debbi***, 2Benjamin Bernfeld, Michael Soudri3, 3Mazen Falah, 3Arnan Greental, 3Amit Sigal, 4Ronen Debi, and 1Alon Wolf (2012)
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Background: Total knee arthroplasty (TKA) is the most common treatment for end-stage knee OA, with approximately 500,000 procedures performed each year in the United States. Several studies have examined the long-term effects of TKA on the biomechanics of the operated knee and have found that most patient still demonstrate poor gait patterns that are similar to their gait patterns preoperatively. Most of these abnormalities have been found in the sagittal plane. Specifically, there is limited knee flexion-extension range of motion postoperatively as well as poor flexion-extension moments. Studies have related these findings to “stiff knee” muscle activation patterns due to habits developed preoperatively, as well as proprioceptive deficiency, instability and quadriceps weakness leading to a “quadriceps avoidance gait”. In the frontal plane, researchers have found that KAM is improved at 6 months after surgery, but slowly regresses back to higher, preoperative levels after 1 year. In the long-term, KAM is not significantly different from preoperative levels. This finding is noteworthy since high KAM may result in prosthetic degradation and failure in the long term.

There is a lack of information on the biomechanical postoperative results of surgery in the period earlier than six months, as well as adequate comparisons to gait patterns preoperatively. The purpose of the present study was to determine if gait patterns of the knee are improved in the early postoperative period. This would help determine what, if any, changes can be made to therapy protocols to prevent regression to preoperative gait levels with time. Furthermore, outcomes were examined across different knee prosthetics to determine if differences exist between prosthetic types.

Methods: Fifty patients were examined before and two months after TKA. Patients underwent a 3D gait analysis using the Vicon Motion Analysis system (Oxford Metrics Ltd., Oxford, UK). Patients completed a VAS scale for pain and functional tests. Knee prosthetics included either PCL-retaining or PCL sacrificing, and custom fit design or not.

Results: Results are presented in Table 1. Knee flexion-extension range of motion decreased significantly by 22% (p<0.001). Knee flexion angle and moment did not change significantly postoperatively (p=0.231 and 0.169, respectively). Knee extension angle, moment and impulse were significantly worse postoperatively than preoperatively (all p<0.01), and extension impulse showed a significant positive correlation of 0.4 with BMI (p<0.05).

Peak knee varus angle during gait showed a significant reduction and improvement of 3.1° postoperatively (p=0.001). After surgery, first and second peak KAM decreased to 71% and 77% of preoperative values, respectively (both p=0.001), and knee adduction impulse decreased by 30% postoperatively (p<0.001) and VAS pain scores decreased by 21% (p<0.001).
Spatiotemporal parameters and functional tests did not yet show significant improvements by two months. No significant differences were found between outcomes in patients undergoing PCL retaining TKA or PCL sacrificing TKA, or between patients undergoing custom fit TKA and those not. Changes were consistent across BMI, age, gender and pain scores.

Conclusions: Knee biomechanics in the sagittal plane worsen significantly in the early postoperative period after TKA. TKA results in high improvement in kinematic and kinetic parameters in the frontal plane early in postoperative recovery. The results also suggest that there is an absence of differences between types of knee prostheses. When compared to the findings of previous studies, the results suggest that early after surgery, TKA patients will show decreased, improved KAM, but these improvements are slowly lost over the first and second year postoperatively. When considering long-term postoperative studies, these results suggest that the knee biomechanics of gait in the sagittal plane will improve with time, but they will not reach the levels of function of healthy individuals. This highlights the importance of early intervention postoperatively aimed at maintaining the low levels of KAM and joint loading. This may help reduce the risk of prosthetic failure and surgical revision in the long-term.
Mechanics of the Non-operated Knee Before and After Total Knee Arthroplasty

Eytan M. Debbi, 2Benjamin Bernfeld, 3Moshe Salai, 3Aviram Gold, 3Aharon Menachem, 3Yadin D. Levy 1Alon Wolf (2012)

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Background: Total knee arthroplasty (TKA) is the most common treatment for end-stage knee OA, with approximately 500,000 procedures performed each year in the United States. The number of procedures is expected to rise to over three million by 2030 due to population growth, increasing longevity and a rise in obesity. There have been numerous studies on the operated knee before and after unilateral TKA, but there have been fewer studies on the non-operated knee. There is evidence of non-random progression of OA in the other lower limb joints after unilateral TKA, with the non-operated knee being at the greatest risk for OA progression and another TKA.

Recent biomechanical studies suggest one reason for the higher rate of OA progression may be limb asymmetry postoperatively, in which the non-operated knee bears greater loads postoperatively than the operated knee. It is unclear, however, whether this is a result of gait changes due to the surgery itself. The present study aimed to examine the preoperative and postoperative biomechanics of the non-operated knee to determine if gait patterns worsen after surgery.

Methods: Fifty patients were examined before and two months after TKA. Patients underwent a 3D gait analysis using the Vicon Motion Analysis system (Oxford Metrics Ltd., Oxford, UK) and completed a VAS scale for pain. Data from both the operated and non-operated knees were analyzed and compared. Data were compared to a healthy control group using findings from previously published studies.

Results: The non-operated knee did not show significant changes in knee varus angle (KVA), knee adduction moment (KAM), knee flexion angle or knee flexion moment after surgery (all p>0.05). Pain in the non-operated knee did not improve significantly after surgery (p=0.066). Changes were not found in spatiotemporal parameters unique to the non-operated knee after surgery.

In the coronal plane, the non-operated knee showed similar KVA and KAM preoperatively in comparison to the operated knee, but higher KVA and KAM postoperatively because the both KVA and KAM in the operated knee were reduced by surgery while the non-operated knee remained unchanged. The limb differences in peak 1 and 2 of KAM were significant (p=0.0028 and 0.005, respectively). Both before and after surgery, the non-operated knee did not differ significantly from healthy control in KVA or KAM. The knee was significantly worse than controls in pain scores and spatiotemporal parameters (all p<0.0001).

In the sagittal plane, the operated and non-operated knee show similar gait patterns preoperatively. Postoperative deterioration in the operated knee leads to significant limb differences in kinematic and kinetic knee parameters in the sagittal plane after surgery. The operated knee showed significantly lower extension at terminal stance and flexion in swing, as well as a significantly lower knee extension moment compared to the non-operated knee. Regardless of limb differences, loading patterns in the non-operated knee are significantly worse than controls preoperatively and postoperatively (all p<0.0001).
Conclusions: The study’s findings suggest that gait patterns in the non-operated knee may not change after surgery. The study confirms that there is a limb asymmetry after surgery, with the non-operated limb bearing greater loads than the operated limb, but suggests that the asymmetry likely results from improvements in the operated knee rather than deterioration in the non-operated knee. As a whole, the findings indicated that the surgery itself might not be the catalyst for higher loading patterns postoperatively. Nevertheless, the non-operated knee may still be at risk for OA after surgery due to the limb asymmetry and the persistent higher levels of KAM. Clinicians should consider this when prescribing therapy to patients postoperatively. There should be a focus on caring for the non-operated knee in addition to the operated knee.
See Me Move and Groove.

**Nouriel, Ariella** and Kuai Yu. 

Background: Our client is a 9-year-old girl with spastic quadriplegia cerebral palsy and cortical visual impairment. While she has severe cognitive impairment, she has normal hearing and demonstrates a positive response to simultaneous audio and visual signals. She wears a brace for trunk support, and manages switch controls with her hands, though their movements still remain highly limited. Due to her visual impairment, she is unable to see peripherally and her right eye is dominant. She also does not detect all colors and therefore prefers brighter shades such as red and yellow against a dark background.

Our first goal is to improve our client’s ability to use her vision together with hearing as stimuli. The second goal is to encourage more targeted and controlled hand movements.

Methods: The device is intended for home use while in a wheelchair, stander, or in bed. When the client presses a switch, the device responds with musical and/or visual feedback, as well as a shaking toy. The caregiver, parent, or therapist can select the desired feedback.

A PIC18F4520 microcontroller controls the logic for this device. Electroluminescent wires were used for visual feedback and can be configured to light in sync with the music that the device is currently playing. The music can also be customized to the client's preferred music via the SD card.

Results: We successfully developed a device for a young client with cerebral palsy which allowed her to work on upper extremity strengthening and visual training through play. This resulted in more targeted and controlled hand movements, first experience of active participation in play from her bed, and first time the client was able to see her hands and face during play.

Conclusions: We expect that the client will likely use the device often and it will increase her ability to rely on her vision and hearing as a stimulus, as well as create more targeted and controlled hand movements.
Background: Nanotechnology is an exploding field which is producing new possibilities for the advancement of medicine and health. In our research, we utilized the sensitivity of nanostructures to create a lab-on-a-chip (LOC) for real-time detection of cancer cells. This chip is the first step towards obtaining accurate and comprehensive results in a shorter amount of time using a smaller sample size. By combining the physicochemical properties of nanowires modified with biological components, our research works to open up a new approach to address the clinical issues of cancer detection that patients and doctors face today.

Methods: We designed and built a nanochip using silicon nanowires modified with anthraquinone and several biological antibodies. This chip is connected to a system with wells for testing pH, H2O2 and lactate concentrations. When a suspension of cancer cells (Jurkat) are sent through, signals are generated based on these concentrations, which are recorded electronically. Based on recent observations made in cancer cell metabolism, the sensor used the information to detect the presence of Jurkat cells in a complex biological solution. The signals detected by the nanowire sensor were compared with standard measurements for pH, H O (DCF assays) and lactate.

Results: We found that the signals detected by the nanowire sensor were not significantly different from those detected by the standard tests.

Conclusions: Our findings are only the conceptual base for the eventual development of a practical and useable application for the detection of cancer cells in a clinical setting.
Background: Our goal is to create, detect and study an exotic atom made up of an H- ion along with a positron. Production of this atom will open the door to precise spectroscopic measurements of this atom and may provide greatly improved understanding of the H- ion core. The H- ion plays a critical role for all forms of life as an antioxidant and is one of the strongest bases known due to its highly exothermic reaction to produce hydrogen gas. Due to this exotic atoms structural resemblance to antihydrogen, it can also be used to provide insight and motivation for focused experimentation on the latter. Both have a positron in a bound state with a core that has a net negative charge of one unit and approximately of similar size. Relatively speaking, antihydrogen is much more expensive to produce and so clues from H-+ experiments can save precious time and money and provide new ideas when planning and designing an antihydrogen experiment.

Methods: The beam of H- ions will be directed towards a cloud of positrons that will be waiting in a particular potential well in an electrode stack. The positrons are accumulated from radioactive sodium (Na-22). The H- ions will undergo some process emerging with a positron orbiting at an excited state. Further down the electrode stack the H-+ atom will encounter a strong electric field gradient created by the electrodes. This will strip the positron from the H-+ atom which will allow us to accumulate and detect the stripped positrons. The detection of the positrons in this ionizing potential well will be evidence of the production of H-+ atoms.

Results: Extensive optimization of this apparatus has led to a record number of 6.5 million positrons accumulated in 120 seconds. Optimization of the ion source parameters has lead to increased H- currents of 10nA within the 0.5 inch radius of the trapped e+ target and with H- ion kinetic energies of 900eV.

Conclusions: Future directions: Successfully produce H-+. Antihydrogen is the simplest form of antimatter and can be used to test current theories of particle physics.
Molecular Biology Abstracts
The effects of glycerol kinase deficiency on mitochondrial energy metabolism and morphology

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Background: Glycerol kinase (GK) is an X-chromosome-encoded, multifunctional enzyme that catalyzes the phosphorylation of glycerol to glycerol-3-phosphate, working at the interface between fat and carbohydrate metabolism. Glycerol kinase deficiency (GKD) is an inborn error of metabolism that has a wide range of phenotypic variability and demonstrates a lack of genotype-phenotype correlation. Severe GKD leads to hyperglyceroluria, CNS depression, metabolic acidosis, and possibly death. In addition to its role in metabolism, previous research has shown that GK binds to the voltage-dependent anion channel located on the outer mitochondrial membrane. This allows GK direct access to the electron transport chain and therefore oxidative phosphorylation. We hypothesize that GKD affects mitochondrial function leading to decreased mitochondrial ATP production and eventually the cellular energy loss seen in humans and mice with GKD.

Methods: The effects of GKD on mitochondrial energy metabolism will be determined through ATP determination, mitochondrial quantification, and studies of energy expenditure. Glycerol kinase knock out (Gyk KO) mouse livers were harvested on day of life 3 and subjected to mitochondrial fractionation (Actif Motif) and ATP quantification (Molecular Probes) using bioluminescence. ATP values were normalized according to the protein concentration of the sample. Sections were obtained from the right lobe of the liver in day of life 1 mice and then fixed and plastic embedded for analysis via transmission electron microscopy (CM 120). Confocal microscopy was used to quantify the differences in active mitochondria between KO GyK and WT GyK cultured cell lines using MitoTracker Red CMXRos staining.

Results: ATP quantification revealed that KO mouse livers had significantly less total mitochondrial ATP, p-value=0.008, (0.36 nM ATP per μg protein +/- 0.33, n=7) compared to WT (0.885 nM ATP per μg protein +/- 0.38, n=16). Consistent with these results the concentrations of mitochondria in Gyk KO liver was significantly reduced when compared to WT. Gyk KO mitochondrial concentrations had 18.9 +/- 5.5 mitochondria/μm2 (n=2 mice, 10 sections per mouse) compared to WT which had 25.3 +/- 4.5 mitochondria/μm2 (n=2 mice, 10 sections per mouse), p-value=0.006. In addition, preliminary studies have shown that Gyk KO cells had a bloated appearance with larger cell diameters as compared to wild type cells, which may be due to increased apoptosis from stress.

Conclusions: Mitochondrial concentrations and ATP production are significantly decreased by glycerol kinase deficiency. Therefore, GK not only has a role at the interface between fat and carbohydrate metabolism, but also in mitochondrial energy metabolism. Future studies will lead to further characterizing this role.
Fezf2-GFP and FoxA2-GFP Tagged Stem Cells Shed Light on In Vitro Developmental Patterns

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Background: Studies in embryonic development have helped to elucidate the steps that cells progress through as they develop from the inner cell mass (ICM) into a fully formed fetus. The cells composing the ICM, termed embryonic stem cells (ESCs), can be isolated from the embryo and cultured in vitro while retaining their pluripotency. Unfortunately, the potential of ESCs is currently tempered with problems of low yield and specificity. One possible key to progressing ESC research involves identifying and isolating cells primed for specific lineages at their earliest stage. Several studies of ESCs have corroborated this view by showing in vitro variability of several markers of pluripotency, and suggest that ESCs exist in the petri dish in several developmental stages that span from the ICM through the epiblast/hypoblast. Here we present our work with two transcription factors expressed in early forebrain and floor plate tissues, FezF2 and FoxA2 respectively, that further contributes to the study of in vitro ESC heterogeneity.

Methods: We generated two transgenic ESC cell lines by coupling green fluorescent protein (GFP) with the FezF2 and FoxA2 promoters in an extrachromosomal transgene (BAC), and nucleofected the BACs into the mouse R1 ESC line. We then took our GFP tagged lines, and nucleofected them with a mCherry plasmid. This gave us four cell lines: FoxA2-GFP, FoxA2-GFP-mChry, Fezf2-GFP, and Fezf2-GFP-mChry. Our ESCs lines were cultured in mouse embryonic serum (mES) with Leukemia Inhibiting Factor (LIF) on irradiated mouse embryonic fibroblasts (mEFS), passaged every 2 days, and transferred to gelatin plates 2 days before Fluorescence Activated Cell Sorting (FACS). We used the FACS on both our GFP and GFP-mChry lines to select for groups of cells with high, middle, and low GFP fluorescence. These cells were then used to collect RNA for qPCR, subjected to embryoid body (EB) and monolayer differentiation, and immunostaining.

Results: Our Fezf2 and FoxA2 reporters generated selectable populations with notable differences in characterization and differentiation. The colonies formed from Fezf2-GFP(+) cells were more numerous, round, and pluripotent-like, than Fezf2-GFP(-) cells, which generally formed flatter, more spread out colonies, indicative of differentiating ESC morphology. Broad gene qPCR analysis of our Fezf2-GFP and FoxA2-GFP lines also revealed differences in gene expression associated with GFP fluorescence. Blastocyst implantation of our GFP-mChry lines confirmed pluripotency and normal differentiation in vivo.

Conclusions: Fezf2 and FoxA2 variability in ESCs leads to two distinct populations. Both Fezf2-GFP(+) and FoxA2-GFP(+) cells develop colonies with pluripotent-like characteristics, while GFP(-) cells develop into colonies similar to differentiating ESCs. The transcriptional differences of these two cell lines further suggest that these isolated groups of cells express unique characteristics, and represent two separate pluripotent subpopulations in our ESC colonies. Further, the Fezf2 and FoxA2 genes are both known to be expressed in the early neural lineages of organizer and early forebrain tissues, respectively. Our results suggest that in vitro ESC heterogeneity extends into early neural lineages, and that isolating FezA2 and FoxA2 expressing cells may offer an avenue to increase neural differentiation yield.
The Effects of Rat Mesenchymal Stem Cells on Injury Progression in a Rat Model.
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Background: Burns are common injuries that can result in significant scarring leading to poor function and disfigurement. Unlike mechanical injuries, burns often progress both in depth and size over the first few days after injury, possibly due to inflammation and oxidative stress. A major gap in the field of burns is the lack of an effective therapy that reduces burn injury progression. Since stem cells have been shown to improve healing in several injury models, we hypothesized that species-specific mesenchymal stems cells (MSC) would reduce injury progression in a rat comb burn model.

Methods: Using a brass comb preheated to 100 degrees C, we created 4 rectangular burns, separated by 3 unburned interspaces on both sides of the backs of male Sprague-Dawley rats (300g). The interspaces represented the ischemic zones surrounding the central necrotic core. In an attempt to reduce burn injury progression, 20 rats were randomized to tail vein injections of 1 ml rat specific MSC $10^6$ cells/ml (n=10) or normal saline (n=10) 60 minutes after injury.

Results: We found that at a concentration of $10^6$ rat MSC, burn progression surface area was reduced by 20%. This supported our hypothesis.

Conclusions: We conclude that intravenous injection of rat MSC reduced burn injury progression in a rat comb burn model. Future research is still needed to determine the exact mechanism by which stem cells can reduce burn progression. Dosing and the method of injecting stem cells also needs to be further specified and refined before this kind of treatment can be extended into humans.
Glowing Worms: The Protein-Protein Interactions of par-Associated Genes in *C. elegans*  
Embryogenesis. New York University

Background: In order for a single cell division to occur during *C. elegans* embryogenesis, a vast collection of essential cellular pathways must be coordinated and properly completed. Systems-level studies in *C. elegans* have generated network representation models of accumulated phenotypic, expression, protein-gene interaction, and protein-protein interaction data. However, in order to fully understand these instructive yet static models, it is necessary to decipher the temporal and spatial details involved in early embryogenesis by isolating the localization patterns of every active protein in the dividing cell. To date, only a small fraction of the *C. elegans* proteome has been described along such dynamic dimensions, and an even smaller fraction of this valuable temporal and spatial data has been organized in a systematic and accessible manner.

This study aimed to pioneer such a database by determining and archiving the localization patterns of 24 proteins predicted to exhibit protein-protein interaction with PARs 1-6 and PKC-3, which are significant in polarity establishment during embryogenesis.

Methods: Localization patterns are generated by designing green fluorescent protein (GFP) fusion clones of each protein-encoding gene. The final gene expression clones are transfected into *C. elegans* worms via microparticle bombardment. Embryos containing the GFP fusion are imaged in vivo under a spinning disc confocal microscope. Images of the developing embryo are captured every 10 seconds, yielding a dynamic map of discernable localization routes as each marked protein engages in its cellular pathway. When combined, these routes generate a record of spatial and temporal data that reveals how protein-protein associations change over the course of two cell divisions.

Results: Out of the original 24 proteins I aimed to study, 15 were successful in yielding final expression clones and distinct localization patterns. Proteins can be visually categorized as cytoplasmic, nuclear, cortical, centriolar, ER, or midzone microtubular.

Conclusions: These studies allow us to postulate about functional molecular relationships and the cellular networks involved in the formation of embryonic polarity. Future goals include creating a digital signature for each localization pattern to systematically capture and catalog the spatial-temporal data.
Orthopedics Abstracts

Kenan, Shachar*, "Gold, Aviram, MD", "Chechik, Ofir, MD", "Professor Moshe Salai, MD" (2013)
Long term outcomes of subcapital hip fractures reduced by cannular screw internal fixation in the young using the Harris Hip Score. Ichilov Medical Center.

Background: -Understanding various femoral neck fracture patterns along with treatment options- from nonoperative to various surgical techniques, depending on severity, age, and other options. Discussion of pros and cons of these surgical procedures will be reviewed.
-The Garden and Pauwel classifications of hip fractures will be explained.
-Various outcome measures including the Charnley Score, the Harris Hip Score, and the Oxford Hip Score will be discussed.

All patients in this study have undergone fixation using 3 parallel screw method.
Question: Was the 3 parallel screw method optimal in all fracture patterns? Was there a better option? What factors will influence whether this fracture pattern is optimal? Age? Fracture severity?

Hypothesis: Nondisplaced Hip fractures (Garden 1 and 2) will have better HHS outcomes than displaced hip fractures (Garden 3 and 4).

Methods: Retrospective cohort study of patients who are "young" (under 60) and have had femoral neck fractures that have been fixated using 3 parallel screw method between 7-15 years ago.

Patients were contacted by phone and were administered the Harris Hip Score questionnaire. Following this, they were invited for physical exam and x-ray.

Patients were selected from a database at Ichilov Hospital who had various types of hip fractures. 67 patients who had undergone fixation using parallel screws were selected. Of those, 35 patients were reached and agreed to answer the HHS questionnaire. Of those, 10 patients agreed to come in for physical exams.

Results: Of those patients who both answered the HHS questionnaire and also came in for physical exams, Garden I hip fractures had the best HHS outcome. There was no difference between Garden II and III. Garden IV hip fractures had the worst HHS outcome, and were also associated with a higher revision rate.
This partially supported our hypothesis. (Official final results are still pending.)

Conclusions: In the young patient population, patients who have undergone fracture patterns that are severe (garden 4) should not be offered fixation using the 3 parallel screw method, as this will likely result in a poor outcome. Instead they should be offered other options such as sliding hip screw, cephalomedullary device, or arthroplasty (hemi or total). In less severe cases (garden 2 and 3) it is debatable which is the best option. In the mildest fracture pattern (garden 1), treatment with 3 parallel screw is the optimal treatment. We cannot say compare this to nonop because we didnot have access to these patients, which would be a good study for the future.
**Allergy, Infection and Immunology Abstracts**

*Chlamydia pneumoniae* Infection-Induced Allergic Airway Sensitization Is Controlled by Regulatory T-Cells and Plasmacytoid Dendritic Cells

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**Background:** Asthma is characterized by an inappropriate immune response that results in bronchoconstriction, mucus secretion, and eosinophilic airway inflammation, and is thought to develop in two stages. The first stage, known as sensitization, encompasses the exposure to a normally innocuous antigen in the lungs during some type of inflammatory response that leads to the development of Th2 type memory cells. Later, upon re-exposure to the same antigen, these memory cells are activated, resulting in an inflammation of the lungs. There are many possible mechanisms for antigen sensitization to occur, and one increasingly important scenario involves respiratory infections. It is known that respiratory viral infections among young children can lead to a much greater risk of asthma development. Experimental studies using murine models have also shown that pulmonary viral infections can enhance antigen sensitization or lead to exacerbation of asthma, depending on the timing and severity of infection. However, much less is known about the interactions of bacterial infections and asthma.

**Methods:** C57BL/6 mice 8 to 12 weeks of age were used throughout the study. Mice previously infected with *C. pneumoniae* received 100 µg of human serum albumin (HSA) in PBS (sensitization) intranasally. Mice were sacrificed on day 21 and sera and lungs were harvested. The right lobes of the lungs were fixed in 10% formalin, and paraffin-embedded and hematoxylin and eosin-stained sections were evaluated. Total lung cell preparations from mice infected with *C. pneumoniae* and sensitized with HSA were also analyzed by flow cytometry. Serum HSA-specific immunoglobulins and cytokine levels were measured using ELISA.

**Results:** In this study, we now provide additional mechanistic insights on the specific roles of Treg cells and plasmacytoid DCs in the temporal and dose-related allergic sensitization induced by CP infection. We show that TLR4 signaling is required for antigen sensitization, but TLR2 is not, and that Tregs are involved in both phenotypes. Additionally, we find that during a severe CP infection, which is normally non-permissive for allergic sensitization in this murine model, both Tregs and plasmacytoid dendritic cells (pDCs) are increased in the lung and that the depletion of either cell type results in the reversal of the phenotype and allows development of allergic sensitization. In further mechanistic investigations we observed that in addition to a live CP infection, UV killed CP (CPUV) can also induce allergic sensitization and we show that this observation is not specific to pulmonary CP infection but can occur with other bacteria as well, as UV killed *Bordetella bronchiseptica* was also able to induce allergic sensitization to HSA. Indeed, we show that bacterial ligands, such as a TLR2 ligand, in addition to the TLR4 ligand LPS, are able to induce the allergic sensitization.

**Conclusion:** Collectively these data now provide strong evidence that killed CP, or other bacteria such as *Bordetella bronchiseptica*, as well as TLR2 ligands can induce allergic sensitization, and that during a live CP infection, both Tregs and pDCs critically regulate the temporal and dose-dependent induction of allergic airway sensitization. Additionally, TLR2 and TLR4 signaling during CP infection may play...
a regulatory role though the modulation of Tregs.
Treatment of isoniazid-resistant tuberculosis in children: a literature review

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**Jonathan Eisenberg**

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Background: To identify effective regimens for the treatment of children sick with or exposed to isoniazid-resistant tuberculosis and to better understand the scope of this problem. We aim to summarize the literature describing the risk of Isoniazid resistance as an obstacle to the treatment of tuberculosis disease and latent tuberculosis.

Methods: A literature review (systematic) was undertaken of published reports of children with tuberculosis disease who had isolates tested for susceptibility to isoniazid. PubMed, Embase, and LILACS online databases were searched (dates up to January 12, 2012).

Results: Our search identified 3,403 citations, of which 95 studies met inclusion criteria. These studies evaluated 8351 children with TB for resistance to isoniazid. The median proportion of children found to have resistance was 8%.

Conclusions: High proportions of isoniazid resistance has been reported among pediatric TB patients suggesting that drug susceptibility testing should be more widely used in deciding treatment regimens and that rifampin only testing is insufficient. Many children are likely receiving sub standard treatment with empirical isoniazid based regimens and this is both costly and ineffective. Work is needed to identify cost and safety effective testing and treatment for children who are sick or who have been exposed to isoniazid resistant TB.
The Relative Contribution of Toll Like Receptors 2,4 & 9 to Systemic Inflammation and Immune Dysfunction Following Peripheral Tissue Injury.

The University of Pittsburgh

Background: Toll-like receptors (TLRs) detect endogenous ligands released after trauma and contribute to the proinflammatory response to injury. Post-traumatic mortality correlates with the extent of the immuno-inflammatory response to injury and this response comprises both proinflammatory and immunosuppressive components. Although TLRs are known to modulate adaptive immunity, the role of TLRs in the adaptive immune dysfunction following traumatic tissue injury is unclear.

Methods: This study used a murine model of severe peripheral tissue injury to evaluate the role of toll-like receptors 2,4 & 9 through transgenic mice and inhibitory CpG oligonucleotides. Post-traumatic immune dysfunction was tested through ex-vivo assessment of splenocyte proliferation and Th1 cytokine release. Flow cytometry was used to identify iNOS induction within splenic MDSC. Confirmation of systemic inflammation and remote organ damage was obtained through circulating interleukin-6 levels and assessment of hepatocellular injury.

Results: This study shows that TLRs 2,4 & 9 play selective roles in both the early proinflammatory and sustained immune dysfunction after sterile tissue trauma. Suppression of splenocyte responses after injury was dependent on TLR4 & 9 signaling as was post-traumatic iNOS upregulation in splenic MDSC. TLR2 was found to have only a partial role by contribution to splenocyte proliferation. This study also identifies the involvement of TLRs 2 & 4 in the initial systemic inflammatory response to traumatic tissue injury, however, this response was found to be TLR9-independent.

Conclusions: These findings demonstrate the previously unidentified role of TLRs 2,4 and 9 in the T-cell mediated adaptive immune dysfunction following traumatic tissue injury. Importantly, this study also illustrates that TLRs play differing roles in both the initial proinflammatory response and adaptive immune response after trauma. These results suggest a potential for targeted therapies that could limit the immune dysfunction through selective inhibition of receptor function following injury.
Pharmacology and Toxicology Abstracts
Hidden Manifestations of Camphor’s Neurotoxic Effects: Febrile Seizures

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Background: Background:  Camphor, a well-known neurotoxin, is the cause of many pediatric emergencies annually.  It is found in over-the-counter health products, products used in religious practices, unregulated imported products, and in items used for insect and rodent control.  Ingestion, inhalation, and topical application have been linked to seizures, respiratory problems, coma, and death in pediatric patients.

Objective: The goal of our study was two-fold.  First, we aimed to determine the types, frequency, and methods of use of camphor-containing products in pediatric patients 6 years of age and under.  Second, we hypothesized that a link between use of camphor products and febrile seizures exists.

We posit that camphor products are used more frequently when children are ill, and that a portion of seizures occurring with fever are due to camphor’s neurotoxic effects.  We aim to determine if the incidence of febrile seizures in users of camphor products is greater than in the general population.

Methods: Parents of patients 6 years of age and younger were surveyed with a questionnaire that was read aloud by a volunteer student.  Parents were surveyed at St. Barnabas Hospital in Bronx, NY in the waiting areas of three affiliated ambulatory clinic sites and the pediatric emergency room.  All questionnaires were coded and kept confidential.

Results: This cross-sectional study ended up telling us more about camphor use habits in the community than it did about it's link to febrile seizures. We did determine that camphor is used more frequently and in dangerous ways when children were  ill. We also discovered that many adults in the community use camphor in their homes in ways that could be toxic to children without realizing it.  However, few cases of febrile seizures at all were found, not enough to determine if more seizures occur with camphor use than without.

Conclusions: Past papers have posited that camphor is a neurotoxin and has been linked to febrile seizures in the pediatric community (Khine H et al, 2009). Examining habits of use in communities can help identify potential high risk groups for this and other types of neurotoxic effects. A broader study examining camphor use habits in a population of pediatric febrile seizure patients would be more adequate to test the part of our hypothesis that was not proven.
A Double-Blind Controlled Trial of a Single Dose Ibuprofen and an Amino Acid Medical Food Theramine for the Treatment of Low Back Pain.

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Targeted Medical Pharma.

Background: The diagnosis and management of back pain is a challenge for health care providers. It has been established that increased nutrient requirements associated with pain syndromes, and the consequent reduced production of neurotransmitters contributes to maladaptive pain responses. Enhancing neurotransmitter production associated with pain syndromes is limited by multiple factors, specifically unavailability of adequate essential amino acids in the diet and increased turnover rates of amino acids needed to produce neurotransmitters under such conditions. Theramine is a proprietary prescription Medical Food that both enhance several neurotransmitters that are involved in pain modulation and sensation by providing neurotransmitter precursors in the form of amino acids. Medical foods are specially formulated compounds for the specific dietary management of a disease or condition that has distinctive nutritional requirements. This study examined the efficacy and tolerability of Theramine alone in patients with chronic back pain in comparison to the NSAID, Ibuprofen, and the co-administration of Ibuprofen with Theramine in patients with low back pain.

Methods: The study involved 122 patients between the ages of 18 and 75 in a double blind, randomized, three-armed trial, with approximately 40 patients in each group comparing Ibuprofen alone (400 mg daily), Theramine alone (2 capsules twice daily), or the combined use of Ibuprofen (400 mg daily) and Theramine (2 capsules twice daily) for the duration of 28 days.

Results: Of the 3 groups, none of the efficacy and safety variables assessed in this study were statistically different between groups at baseline. At Day 28, both the Theramine group and combined therapy group (Theramine with ibuprofen) pain assessment indices showed a statistically significant improvement compared to the group that was administered Ibuprofen alone (P < 0.05).

Conclusions: The data in this study indicate that the provision of amino acid precursors in a formulation to facilitate neurotransmitter production results in improving the efficiency of pharmaceutical therapy. We postulate that the mechanism is related to improving intracellular metabolic function rather than having any effect on the efficiency of pharmaceuticals. This may be a new approach to a long-standing pain therapy. Additionally reduction in C-reactive protein (CRP) with Theramine use has been demonstrated in this study, as well as in a previous study using naproxen and Theramine. With CRP’s association with inflammation, and subsequent involvement as a marker for heart disease, a question arises as to whether Theramine may have a cardio protective application. Further investigation into this possible protective effect of Theramine is warranted.