The Fourth Annual Student Research Symposium

Program & Abstracts

March 20th, 2014

New York State/American Program
Sackler Faculty of Medicine
Tel Aviv University, Israel
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Thursday, March 20th, 2014

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Public Health & Epidemiology, Room 201

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The potential impact of safety-net hospital closure on patients and surrounding emergency departments with the implementation of the Affordable Care Act

Torkan, A
Assessing the implementation and yield of the touchscreen tablet PC patient self-administered ASSIST drug screening tool in community health centers

Snyder, D
The health care system in Argentina: an explanation of its structure and analysis of its strengths and weaknesses

Reissner, H
Factors influencing birthing decisions after previous caesarean section

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Preferences for resuscitation and intubation among patients with do-not-resuscitate/do-not-intubate orders: a one-year follow up study

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Kossar, AP
Moderate pre-operative renal dysfunction improves following orthotopic heart transplantation and does not impact long-term mortality

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Control of hypertension: a survey of Israeli internal medicine departments
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**Pharmacology Presentations, Room 215**

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Zilberstein, N  Activation of complex I of the electron transport chain favors mitochondrial permeability transition pore opening

Glick, M  Characterization and determination of fate of adult progenitor cells in a rat femur fracture model

Sabbah, BS  Extracellular matrix-like substances and leukemia inhibitory factor for culturing early human follicles

Adler, D  Murine whole bone marrow contains various populations of cycling hematopoietic stem cells

8:00-8:10  Break

8:10-8:30  Announcement of Awards and Closing Ceremony, Room 201
Blake Zelickson, Mark Vieyra, and Maxine Stachel
Biomechanical adjuvant therapy: changing the course of total knee arthroplasty

Eytan M Debbi¹, Benjamin Bernfeld², Arnan Greental³, Michael Soudry⁴, Yocheved Laufer⁵, Amir Herman⁶, Alon Wolf⁴

¹ Biorobotics and Biomechanics Lab, Faculty of Mechanical Engineering, Technion Israel Institute of Technology, Israel; ² Department of Orthopedic Surgery, Carmel Medical Center, Israel; ³ Department of Orthopedics, Rambam Medical Center, Israel; ⁴ Division of Orthopedics, Sourasky Medical Center, Israel; ⁵ Department of Physical Therapy, Faculty of Social Welfare and Health Studies, University of Haifa, Israel; ⁶ Department of Orthopedics, Sheba Medical Center, Israel

Background: Total knee arthroplasty (TKA) corrects the mechanical deformities of end-stage knee osteoarthritis (OA). Knee loading patterns, however, have been shown to remain abnormal and have been implicated with prolonging the postoperative recovery, as well as the high rate of implant deterioration and the need for revision surgery in the long-term.

Methods: We conducted a randomized, controlled, double-blind trial involving fifty patients after unilateral TKA for end-stage knee OA. The active group underwent a biomechanical therapy program aimed at gait rehabilitation using a foot-worn device, while the control group received a similar training program with a sham walking sneaker. Patients were evaluated at six weeks, six months and twelve months after surgery. Outcomes included a three-dimensional barefoot gait analysis measuring the kinematic and kinetic movements and loading patterns on the knee joint, as well as self-evaluative questionnaires on pain and function, objective functional tests, and clinical knee scores.

Results: The active group consistently showed significantly better outcomes in VAS pain scores, self-evaluative questionnaires, Time-Up-Go test and Six Minute Walk exams, as well as a greater peak knee extension moment and lower second peak knee adduction moment. Linear mixed effect models over time showed faster improvements in the active group in all clinical parameters, stride, cadence, double-limb-support, step-length, knee range of motion and impulses of the knee flexion and extension moments, as well as slower regression of the knee adduction impulse. The knee varus angle did not differ between groups over time.

Conclusions: The therapy applied in the study altered the postoperative outcomes of TKA, specifically the knee loading patterns. In addition to these mid-term results, it is reasonable to speculate that these findings could considerably alter long-term outcomes as well as implant longevity.
Mitochondrial stress induced by volume overload leads to cardiomyocyte bioenergetic dysfunction

Blake R Zelickson\textsuperscript{1,2,3}, Elena Ulasova\textsuperscript{1,2,3}, James D Gladden\textsuperscript{1,2,4}, Wayne E Bradley\textsuperscript{2,4}, Chih-Chang Wei\textsuperscript{2,4}, Pamela C Powell\textsuperscript{2,4}, Michelle S Johnson\textsuperscript{1,3}, Louis J Dell’Italia\textsuperscript{1,2,4}, Victor M Darley Usmar\textsuperscript{1,2,3}

\textsuperscript{1}Center for Free Radical Biology; \textsuperscript{2}Center for Heart Failure Research; \textsuperscript{3}Department of Pathology; \textsuperscript{4}Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294

Volume overload (VO) in the heart is known to cause the progressive enlargement of the left ventricle (LV), which is associated with cardiomyocyte dysfunction and oxidative stress. Importantly, the mitochondrion is well known to be a major source and target of this oxidative stress. This led us to hypothesize that VO causes mitochondrial damage in cardiomyocytes, which then results in cardiomyocyte dysfunction and heart failure. VO was induced in C57BL/6 mice by creating an aortocaval fistula (ACF) for three days prior to cardiomyocyte isolation. Mice subjected to ACF were studied using echocardiography and high-fidelity pressures; they exhibited a decrease in mean arterial pressure and an increase in both LV end-diastolic (LVED) pressure and LVED dimension as compared to the sham mice. LV tissue was isolated from both sham and ACF mice and evaluated using transmission electron microscopy, which revealed that the ACF mice exhibited both myofibrillar and mitochondrial degeneration. Next, several parameters of mitochondrial function were assayed using an XF24 Analyzer, which measures the oxygen consumption rate (OCR) of intact cells. Using this instrument, the basal, maximal, and non-mitochondrial OCRs of the cardiomyocytes were determined. This data allows for the calculation of the reserve capacity, which represents the amount of mitochondrial function that the cells can call upon under stress. Interestingly, cardiomyocytes isolated from ACF mice exhibited a decrease in the maximal OCR and the reserve capacity as compared to the sham myocytes. Taken together, these data support the concept that VO results in the impairment of mitochondrial function and suggests that novel therapeutics targeted to the mitochondria may attenuate the VO-induced cardiomyocyte dysfunction.
From macro to micro: population studies, genotyping technology and the development of a new therapeutic approach for Huntington disease

ER Fisher\textsuperscript{1,2}, NH Skotte\textsuperscript{1} and MR Hayden\textsuperscript{1}

\textsuperscript{1}Centre for Molecular Medicine and Therapeutics, University of British Columbia, Canada; \textsuperscript{2}Sackler School of Medicine, Ramat Aviv, Israel

Background: Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder affecting both the pyramidal and extrapyramidal systems of the brain. The disorder is caused by a CAG repeat expansion in the huntingtin (\textit{HTT}) gene, resulting in an elongated polyglutamine stretch and a toxic gain of function in the mutant huntingtin (HTT) protein. Individuals with a CAG size of $\geq 36$ will become affected with HD in their lifetime. Symptoms include psychiatric disturbances, cognitive decline, and severe movement disorder such as chorea and dystonia. Average age of onset is 45 years, but symptoms can begin at any age. At this time, there is no treatment to stop or reverse the course of the disease.

Rationale: The pathogenesis of HD is complex and multiple pathways are compromised. Therefore, attacking the problem at its roots, by suppressing mutant HTT expression, may be a promising therapeutic strategy for treating HD. Importantly however, wild-type HTT is important for development, function, and health of the brain. As such, therapies must aim for selective suppression of mutant HTT while sparing the expression of the wild-type form.

Approach: 1) Identify the prevalence and incidence of HD patients in a multi-ethnic community (British Columbia, Canada); 2) Use acquired macro-scale epidemiological data to collect samples for micro-scale genotyping analysis; 3) Evaluate multiple single-nucleotide polymorphisms (SNPs) for heterozygosity and identify targets that differ between the mutant and wild-type alleles of \textit{HTT}; 4) Use anti-sense oligonucleotides (ASOs) to selectively silence mutant \textit{HTT} by targeting relevant SNPs; 5) investigate efficacy and tolerability.

Findings: On a population-level, HD is 10-100 times more prevalent in European descendants as compared to other ethnic groups. Furthermore, genotyping assays have shown that particular SNP-combinations are associated with CAG expansion, and that these combinations are only present in populations in which higher disease prevalence is observed. Based on this knowledge, we selected targets with high population coverage and found that the majority of HD patients may be treatable by targeting HD associated SNPs – SNPs that are significantly enriched in the mutant \textit{HTT} gene. Finally, we demonstrate that our lead ASOs can potently and selectively suppress mutant HTT expression both in vitro and in vivo in the absence of overt toxicity.

Significance: This pipeline provides a compelling example to display the importance of collaboration between disciplines in achieving clinically relevant outcomes. Following successful delivery and long-term toxicity studies in mice, ASOs may represent the most precise therapeutic strategy for the treatment of HD and could be rapidly translated into an analogous approach for humans. Safety and dosage is currently underway in primates, and human clinical trials are expected to begin within two years.
**Increased risk of chest blow induced ventricular fibrillation (Commotio Cordis) in an acquired LQTS model**

Christopher Madias, John Kalin, Sivan Vainer, Alawi A Alsheikh-Ali, Mark S Link

Rush University Medical Center, Chicago, IL, Tufts Medical Center, Boston, MA

**Introduction:** A blunt chest blow that induces ventricular fibrillation (VF) has been observed in young individuals and has been called commotion cordis. Whether pre-existing abnormalities in the heart such as patients with long QT syndrome (LQTS) lead to an increased risk of commotion cordis is not known. Data from recent animal research has suggested that certain individuals may be more susceptible to commotio cordis, with the susceptibility rooting from cardiac repolarization abnormalities such as patients with LQTS. This research project tests the increased susceptibility to chest blow induced VF by inducing QT prolongation from IKr blockade.

**Methods:** Juvenile swine were anesthetized and hung in a sling, while receiving 8 chest wall strikes with a 40 mph lacrosse ball. The ball hit directly over the heart and was timed to do so in the vulnerable period of the heart cycle to induce VF. In this double-blind design, animals were randomly assigned to receive intravenous dofetilide (dose= 30 mcg/kg) (n=12) or a placebo (n=12). Animals were immediately defibrillated if VF was induced. Assessments were made of VF vulnerability (defined as % impacts resulting in VF) and non-sustained polymorphic VT (PMVT).

**Results:** It was found that VF incidence was significantly higher in the group that received dofetilide vs the control group (51% (48/49) vs 27% (27/93), p<0.0001).

**Conclusions:** In this experimental model, IKr blockade caused an increased susceptibility to chest wall induced VF. Acquired and congenital abnormalities of repolarization might be important in the mechanism of VF in commotio cordis. Humans with clinical or subclinical LQTS might be at higher risk of chest blow induced VF.
The role of sodium-coupled neutral amino acid transporters in alveolar fluid homeostasis

Simon Rozowsky, Cécile Chupin, Wolfgang Kuebler

University of Toronto, Toronto, Ontario, Canada

Introduction and Objectives: Alveolar fluid clearance (AFC) is a physiological process by which the lungs remove fluid from the alveolar space by active absorption that is driven by epithelial Na⁺ uptake. In isolated lungs, inhibition of the apical epithelial sodium channel (ENaC) with amiloride blocks AFC, and furthermore can reverse transepithelial ion and fluid transport to induce alveolar fluid secretion (AFS). In vivo, however, the scenario is considered more complex due to the presumed contribution of epithelial Na⁺-cotransporters to AFC. Here, we specifically considered the role of the Na⁺-coupled neutral amino acid transporter (SNAT). We aimed to analyze i) whether SNAT functionally contributes to AFC in the intact lung, ii) whether stimulating SNAT may attenuate AFS, and iii) whether inhibition of SNAT may stimulate AFS.

Methods: AFC was determined by a double indicator dilution technique in an isolated perfused rat lung. Alveolar fluid flux is calculated from the concentration change of a high and low molecular weight fluorescent marker in the alveolar and vascular spaces, respectively, based on a two-compartmental distribution model.

Results: Neither stimulation of SNAT with its substrate L-alanine (5 mM) nor inhibition by HgCl₂ (100 µM) altered AFC in isolated lungs under basal conditions. Yet, when L-alanine was given along with amiloride, it was able to rescue AFC (0.19 ± 0.10 ml/h; p < 0.05 vs. amiloride - 0.11 ± 0.17ml/h) and this rescue was abolished by HgCl₂ (p<0.05 vs. L-alanine and amiloride).

Conclusions: Our findings indicate that SNAT does not critically contribute to AFC under basal conditions, yet provides an important rescue mechanism in scenarios in which ENaC-mediated Na⁺ uptake is impaired or blocked. Stimulation of SNAT may therefore present an attractive novel strategy for reversing pulmonary edema.
Public Health & Epidemiology

The potential impact of safety-net hospital closure on patients and surrounding emergency departments with the implementation of the Affordable Care Act

Ted Clarfield¹, Carol Tang², Christina Sheu², Aisha Lodin², Aparna Desai³, Sophie Terp², Elizabeth Burner⁴, Chun Nok Lam⁴, Michael Menchine⁵,⁶, Sanjay Arora⁵,⁶.

¹Sackler School of Medicine, Tel Aviv, Israel; ²University of Southern California, Los Angeles, CA; ³Touro University College of Osteopathic Medicine, Las Vegas, NV; ⁴Keck School of Medicine, University of Southern California, Los Angeles, CA; ⁵University of Southern California Keck School of Medicine, Los Angeles, CA; ⁶Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, Los Angeles, CA

Background: Medicaid Disproportionate Share Hospital payments will be cut under the Affordable Care Act (ACA), putting safety-net hospitals at risk for closure due to the cost of uncompensated care. The closure of large, safety-net hospital such as LAC+USC would greatly affect the uninsured, and immigrants who do not qualify for expanded insurance coverage under the ACA.

Objectives: To determine what other facilities would be impacted by the closure of LAC+USC based on patient preferences for alternate venues of care.

Methods: Electronic surveys were completed by 1243 ED patients from June to July 2013. Patients were presented with the question: “If LAC+USC (this hospital) was not available, where would you go for emergency care?” Answer choices were: a clinic, another emergency department, I don’t know, other, and out of the county or out of the country. Qualification for ACA coverage was determined by patients’ self-reported socio-economic factors.

Results: Overall, 47.1% of respondents said they would go to another ED, and 39.2% said they did not know where they would seek care if LAC+USC was not available. Among those who indicated they would go to another ED, only 22.8% would go to another publicly funded facility, and 77.2% would go to a private institution. Of those who selected a private ED, 28.4% would go to White Memorial, which is the closest private ED to LAC+USC. When focusing on the patients who will not qualify for coverage under the ACA, there was even higher degree of uncertainty as to where to receive care.

Conclusion: In this study conducted among patients seen in the largest safety-net hospital in California, results show that its closure would result in a large increase in the number of patients seen at private EDs. Although there was a great degree of uncertainty as to which ED they would go to, particularly in those ineligible for coverage under ACA, the most proximate private ED would see the largest influx as opposed to other public facilities located further away.
Public Health & Epidemiology

Assessing the Implementation and Yield of the Touchscreen Tablet PC Patient Self-Administered ASSIST Drug Screening Tool in Community Health Centers

A Torkan, M Vahidi, J Scholtz, M Rico, R Andersen, B Johnson, J Yacenda, L Arangua, S Shoptaw, L Gelberg

UCLA Department of Family Medicine and UCLA School of Public Health

Background: There are clear benefits of screening and brief intervention for drug problems in primary health care. The objective of this study is to assess whether the self-administered Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) is appropriate for screening for drug use in low-income urban community health centers in Los Angeles County.

Method: All adult patients coming in for a primary care visit at five community health centers in Los Angeles, were screened in the waiting room for drug use using a tablet PC patient self-administered version of the ASSIST.

Results: Implementation of ASSIST Screening: 4257/13083 = 33% of patients who were approached in the waiting room were successfully screened for eligibility to complete the ASSIST. Yield of ASSIST Screening: among 3807 patients screened with the ASSIST: (1) 205/3807 = 5% screened positive for dependent use; (2) 498/3807 = 13% screened positive for risky drug use; (3) 3104/3807 = 82% had no or low drug use.

Conclusions: Based on ASSIST screening, we found high rates of drug use (18%) in patients at five community health centers in Los Angeles. Our data suggest the imperative to conduct broad screening of all patients for drug use in community health centers; drug use screening by patient self-administration on a touchscreen tablet may be a feasible method for doing so. The implementation of such a screening tool would allow community health centers to screen for the use of illicit drugs enabling primary care physicians to intervene on such use, which could lead to the prevention of progression of risky use to addiction, as well as lead to identification of patients who might be addicted and in need of substance use treatment. If clinics were to include the ASSIST screening as part of the patient registration process, the respondent refusal rate would be lower because patients would be more willing to complete screening.
The healthcare system in Argentina: An explanation of its structure and analysis of its strengths and weaknesses

Daniel Snyder, Cristina Lucchini

Universidad de Buenos Aires, Buenos Aires, Argentina

Background: Universal healthcare is a popular topic of debate among healthcare providers, politicians and the general population of healthcare patients. Some argue that access to medical care is a basic human right and that a government-run health system can have economic benefits. Others believe that health care is not the government’s responsibility, and privately-run health insurance companies provide higher quality coverage and are more economically efficient. Argentina has a universal healthcare system. This study set out to learn the structure of Argentina’s health system, the fairness of healthcare distribution throughout the country, the economic impact and the quality of medical services.

Methods: The information was learned through interviews with Argentine health professionals, experience working in a rural medical setting, hospital tours, and other sources including the Argentine Congress Library, the Ministry of Public Health, local and international newspapers, and international health websites.

Results: Argentina has the highest life expectancy in South America. The healthcare system is divided into three parts – public sector, obras sociales, and private sector. Obras sociales are the heart of the system. They are obligatory insurance plans paid through work. The public sector has good services so people often choose to use it instead of their obras sociales providers. This behavior overloads the public system and reduces quality of care. A significant piece of the system is “PAMI”, a successful but costly obra social for senior citizens. Private insurance plans became popular in the 1990s and are growing in influence.

Conclusions: Argentina has a high quality healthcare system, but there are economic inefficiencies and disparities in access and quality of care. Only after understanding the actual state of the entire system is it possible to form solutions to problems. This study can be used as a basis through which to guide reform in public policy.
Factors Influencing Birthing Decision After Previous Cesarean Section

Meir Pomeranz, Limor Haddifr, Hana Reissner, Yitshak Romem, Tal Biron

Meir Hospital, Kfar Saba, Israel

Objective: Compare factors influencing women's decision for trial of labor after cesarean (TOLAC) or elective repeat cesarean delivery (ERCD) based on religion and Multidimensional Health Locus of Control (MHLC).

Study Design: Cross sectional study of women at Meir Hospital and Laniado Hospital in Israel who were candidates for TOLAC or ERCD. Women filled out a demographic questionnaire and a questionnaire using Form C of MHLC scale to determine birthing influence from internal and external factors. Statistical analysis using t-tests and chi squared tests.

Results: This study included 197 women, 101 for TOLAC and 96 for ERCD. Women who chose TOLAC were more religious and were influenced more by internal factors and chance. Women who chose ERCD were more likely to be secular and influenced by others, most notably physicians. Women who reported being influenced by physicians were more likely to choose ERCD. Women not influenced by others were more likely to choose TOLAC.

Conclusions: A woman’s decision for TOLAC or ERCD is influenced by her belief of control over her health and religious beliefs. In order to decrease the amount of ERCDs health practitioners should take into account a woman’s individual beliefs. Health practitioners should provide women with the appropriate educational information so they feel empowered to make their own birthing decision. If a woman feels in control over her health and educated about the birthing options then more women might choose TOLAC, thus reducing the rate of unnecessary ERCDs.
Preferences for resuscitation and intubation among patients with do-not-resuscitate/do-not-intubate orders: a 1 year up follow up study.

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Background: The prevalence of do-not-resuscitate (DNR), and do-not-intubate (DNI) orders is increasing. Previous investigators have noted limitations of DNR/DNI orders, including their inability to capture important patient preferences regarding CPR and intubation. In our original study, the majority of patients with DNR/DNI orders desired CPR and/or intubation in specific hypothetical clinical scenarios directly conflicting with their documented DNR/DNI status. This follow up study seeks to compare their original DNR/DNI status with their actual decisions when presented with real life medical conditions.

Objective: Determine the accuracy of DNR/DNI orders in representing patient preferences regarding cardiopulmonary resuscitation (CPR) and intubation.

Design, Setting, Participants: We conducted a prospective survey study of patients with documented DNR/DNI code status at an urban academic tertiary care center that serves approximately 250,000 patients per year. From 2010-2011, research staff enrolled a convenience sample of patients on the inpatient medical service, providing them with a series of emergency scenarios for which they related their treatment preference. We then conducted one year follow up via chart review to examine patient’s clinical course.

Results: 100 patients documented as having a DNR/DNI code status were enrolled in the study, median age 78 (± SD 14). In the one year follow up assessment, 37% (CI 29-46) patients had expired. 30% (CI 22-40) patients changed their code status, of which 3 patients faced illnesses that were immediately life threatening, and subsequently were intubated, treated and survived beyond the 1-year follow up period. No one in the study sample received CPR in the setting of cardiac arrest. When presented with hypothetical scenarios, 60% (CI 50-69%) would prefer CPR and/or intubation in specific clinical scenarios directly conflicting with their documented code status. In one-year follow up, 27% (CI 19-36) were intubated and/or cardioverted for real life medical conditions that threatened life, limb or quality of life.

Conclusions: DNR/DNI patients frequently reversed their code status and expressed a desire for interventions intended to prevent cardiac and/or respiratory arrest, including intubation and electrical cardioversion.
Advanced age is not a risk factor for poor functional outcome in patients with ulcerative colitis treated with restorative proctocolectomy

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Background: Restorative Proctocolectomy (RPC) is the most commonly performed procedure for patients with Ulcerative Colitis (UC). There is concern that functional outcome may be suboptimal in patients over age 55 due to age-related changes in the pelvic floor musculature. Therefore, our purpose was to determine the functional outcome for RPC in patients age 55 and over at the time of surgery and compare this group to those under age 55 at the time of surgery.

Methods: We queried our prospectively maintained database of patients undergoing RPC for UC and identified those age 55 and over at the time of surgery. We then matched the study group with a control group under age 55 at the time of surgery. Patients were administered the validated Fecal Incontinence Severity Index (FISI) and Cleveland Global Quality of Life Score (CGQOL) to determine functional outcome. Groups were compared using chi square and t-test. P<0.05 was considered significant.

Results: Of the 1050 patients in our database, 54 patients were over age 55 at the time of RPC and completed FISI and CGQOL scores. The study patients were matched with 108 patients under age 55 at the time of RPC. Other than age, there were no significant differences between groups. The mean FISI score for the study group was 8.7 and for the control group was 15.8 (p=0.003). The mean CGQOL score for the study group was 0.79 (range: 0.47-1.00) and for the control group was 0.80 (range:0.17-1.00) (p=NS).

Conclusions: Fecal continence was significantly better in patients over age 55, accounted for by better control of gas, mucus, and liquid stool. CGQOL scores were not different between the two groups. These findings may be attributed to stringent selection criteria for older patients undergoing RPC. In properly selected patients with UC, age over 55 should not be a contraindication to RPC.
Determinants of effort intolerance in patients with heart failure: combined echocardiography and cardio-pulmonary stress protocol

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Objectives: To determine the mechanisms responsible for the reduced effort capacity observed in patients suffering from heart failure with preserved (HFP EF) or reduced ejection fraction (HFR EF).

Background: Combined stress echocardiography and cardio-pulmonary stress tests are able to divide effort into four well-defined activity levels (rest, unloaded cycling, anaerobic threshold [AT], and peak exercise). Such testing allows non-invasive assessment of cardiac function, hemodynamics, and oxygen content difference at each stage.

Methods: Echocardiographic parameters were measured at rest and during three stages of exercise-stress. 45 subjects were evaluated for effort intolerance.

Results: In heart failure, the change in VO\textsubscript{2} and peak heart rate during exercise was attenuated compared to controls, as were other parameters. End diastolic volume to E/e' ratio (measure of compliance) was superior in HFR EF and controls when compared to HFP EF at baseline but worsened in HFP EF and HFR EF at peak exercise. HFP EF and HFR EF patients had higher peak SVR, but similar peak A-VO\textsubscript{2} difference. Determinants of effort intolerance for controls were: SVR, A-VO\textsubscript{2} diff, heart rate and stroke volume, for HFP EF were: worse compliance, heart rate, A-VO\textsubscript{2} diff, and stroke volume and for HFR EF patients were: A-VO\textsubscript{2} difference, heart rate, lower MR volume, and stroke volume. The combined cardio-pulmonary and echo stress protocol facilitated recognition of several unique etiologies for effort intolerance, allowing individualized therapy for each patient.

Conclusions: Combined cycle cardio-pulmonary and stress echocardiography tests allow non-invasive, comprehensive and individualized evaluation of effort intolerance. Despite similarities between HFP EF and HFR EF patients, HFP EF patients mostly fail to increase LV diastolic volume, whereas HFR EF fail to increase LV emptying, and develop functional mitral regurgitation to a greater extent. Nevertheless, in both HFR EF and HFP EF groups, heart rate, compliance and contractility are reduced compared to controls. Peripheral non cardiac factors play a prominent role in limiting exercise performance in all subjects.
Cardiovascular Abstracts

**Aortic pulse wave velocity as a marker of cardiovascular risk in patients with FM**

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**Background:** This project is looking at central blood pressure's correlation to atherosclerosis and peripheral artery disease in patients with Familial Mediterranean Fever. Central blood pressure is that of the aorta, the central artery, rather than peripheral blood pressure in peripheral arteries, normally measured from a cuff on a person's arm. Central aortic BP minimizes the effect of wave reflection from the branching points off the peripheral arteries. This 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 is a novel technique that has recently been introduced into clinical practice and is considered a stronger prognostic technique than the conventional blood pressure cuff. This allows the analyzer to record the force being applied to the arterial wall. This project aims to determine the clinical significance of aortic blood pressure in the prognosis of patients with Familial Mediterranean Fever, a chronic disease that flares up periodically and induces systemic inflammation. The aim is to find out whether these periodic bouts of inflammation contribute to arterial stiffness long-term.

**Methods:** We employed the Sphygmocor device to calculate the central aortic pressure in our patients. It calculates arterial stiffness by measuring the pulse wave velocity, the speed at which the maximum pressure of each pulse, travels from the carotid artery to the femoral artery. Arterial stiffness is a measure of the loss of elasticity in one's arteries and is greater in patients with atherosclerosis, a disease that thickens the walls of arteries causing them to be less flexible. The stiffer an artery, the faster the pulse wave travels down it. We first recorded the brachial BP of our patients with the conventional blood pressure cuff seated, and immediately proceeded by taking his/her orthostatic BP. Then, we recorded the pulse wave velocity from the radial artery to the femoral artery. The computer analyzed the data and compared the results to the standard methods. Our aim was to see if there is a significant difference between one’s central BP and peripheral BP.
Moderate pre-operative renal dysfunction improves following orthotopic heart transplantation and does not impact long-term mortality

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Background: Although chronic kidney disease (CKD) is a common complication following orthotopic heart transplantation (OHT), the long-term effect of OHT on estimated glomerular filtration rate (eGFR) is not well-defined. We evaluated the effect of CKD on outcomes and the dynamic changes in eGFR that occur after OHT.

Methods: We retrospectively reviewed 844 patients who underwent OHT between 1998 and 2010. Patients were divided into 3 groups based on pre-transplant eGFR. Primary outcomes were to investigate changes in eGFR after OHT, and overall survival within groups.

Results: Before OHT, eGFR in the normal kidney function, moderate CKD, and severe CKD groups was 86.38±19.66, 45.59±8.47, and 23.26±6.84 ml/min/1.73m², respectively. Patients with moderate and severe CKD demonstrated initial improvement in eGFR at 2 months post-transplantation (both p<0.001 vs. pre-transplant eGFR). Conversely, patients with normal kidney function displayed a progressive decline in eGFR over 6 months following OHT; thereafter, eGFR remained stable throughout the 5-year-follow up period in all groups (p<0.001 vs. pre-transplant eGFR). Moderate CKD did not predispose OHT recipients to decreased survival when compared to the normal group (68.7% vs. 71.33%; p=0.481) at 5 years post-OHT. However, the severe group compared to all others (normal and moderate CKD) had significantly lower 5-year survival (69.9% vs. 54.1%; p=0.043).

Conclusions: Changes in eGFR occur after OHT in all cohorts dependent on pre-transplant renal function. Our data suggest that patients with moderate CKD should expect improvement in renal function after OHT and the presence of moderate CKD alone should not preclude transplant.
New evidence that elevated concentrations of angiogenesis inhibitors drive endothelial-to-mesenchymal transition in the CKD population

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Background: Sudden cardiovascular (CV) death is increased in chronic kidney disease (CKD). Animal models suggest that high concentrations of angiogenesis and nitric oxide inhibitors induce myocardial fibrosis and microvascular dropout in CKD thereby facilitating arrhythmogenesis, but human evidence is limited.

Methods: We performed autopsy, serologic, and in vitro studies to compare individuals with and without CKD. Left ventricular fibrosis, capillary density, and endothelial to mesenchymal transformation (EndMT) were quantified in post-mortem samples. Circulating asymmetric dimethylarginine (ADMA), endostatin (END), angiopoietin-2 (ANG), and thrombospondin-2 (TSP) and proliferation and apoptosis of human coronary artery endothelial cells (HCAEC) grown in subject serum were measured.

Results: Fibrosis increased 12% and 77% in stage 3-4 CKD and ESRD (P_trend=0.003) and microvascular density decreased 12% and 16% (P_trend=0.04) vs. preserved renal function. EndMT-derived fibroblast proportion was 17% higher in stage 3-4 CKD and ESRD (P_trend=0.02). ADMA, ANG, TSP, and END concentrations were increased in CKD. CKD serum increased HCAEC apoptosis (P=0.02) and decreased proliferation (P=0.03).

Conclusions: CKD is associated with an increase in circulating angiogenesis and nitric oxide inhibitors, which impact proliferation and apoptosis of cardiac endothelial cells and promote EndMT, leading to cardiac fibrosis and capillary rarefaction. These processes may play key roles in CKD-associated CV disease.
Cardiovascular Abstracts

**Hind limb ischemia-reperfusion analysis in ApoE knockout mice**

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**Background:** Apolipoprotein E (apoE) is an important lipid transport molecule associated with cholesterol metabolism and atherogenic plaque formation. It was demonstrated that surgically induced hindlimb ischemia in apoE knockout mice have impaired collateral vessel development and thus decreased hind limb perfusion. However, preliminary data from our research group indicated that the heightened inflammatory state associated with the apoE knockout genotype may be important for generating a pro-angiogenic environment, which could actually enhance perfusion. Our goal was to test this hypothesis by performing a follow up study that would confirm an increased rate of perfusion amongst apoE knockout mice.

**Methods:** The two arms of the study included apoE (-/-) and C57Bl wild type mice. At 6 weeks of age, apoE (-/-) mice were begun on a “western” diet to accelerate atherosclerosis. Following a 10-week period of “western” diet feeding, apoE mice were confirmed to have developed a highly atherogenic state via serum blood measurement of cholesterol levels in all mice. The study groups were then anesthetized using isoflurane, and surgical induction of hindlimb ischemia was performed using previously established techniques. Hind limb blood flow was measured via laser Doppler perfusion imaging (LDPI) one day prior to surgery and at days 1, 7, 9, 15, and 22 following.

**Results:** There was no statistically significant difference in perfusion rates or overall perfusion levels noted in either arm of the study.

**Conclusions:** hind limb ischemia is useful method for evaluating
Control of hypertension: a survey of Israeli internal medicine departments

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Background: Control of hypertension has been shown, if detected early enough and managed, to decrease morbidity and mortality related to myocardial infarction, stroke, and renal failure.

Objective: A questionnaire regarding various aspects of hypertension treatment and management among patients hospitalized in various departments was sent to 127 heads of department, senior physicians, residents, and interns.

Results: 127 surveys were returned. The results were subsequently divided into 3 sections concerning background of hypertensive patients on wards, technique of blood pressure measurement, and finally the protocol used on wards for hypertensive treatment. The study results highlight the prevalence of hypertension on the ward, the lack of uniformity in the technique of blood pressure measurement, and varying approaches to follow-up care. The survey respondents estimated that over half of the patients hospitalized on their ward had hypertension. These figures are consistent with the high percentage (>50%) of various groups of hospitalized patients with hypertension as reported in several European and U.S. studies in the past 15 years.

Conclusion: It is of vital importance to address the inconsistent attitudes regarding the control of hypertensive patients on medical wards. Further evaluation for a defined protocol is necessary in order to attain an effective, practical approach for the treatment of hypertension.
A small molecule DNA synthesis inhibitor modulates protein homeostasis and increases healthspan in *Caenorhabditis elegans*

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The DNA synthesis inhibitor 5-fluoro-2-deoxyuridine (FUdR) has been used for decades in the study of the roundworm *Caenorhabditis elegans* to prevent reproduction in study populations. It has been shown previously that mutant strains with the inability to produce sperm or oocytes have normal lifespans. However, it has also been shown that mutants that are sterile due to loss of germ line precursor cells have increased protein homeostasis and lifespan. We have shown that inducing sterility with the compound FUdR induces increased protein homeostasis, increased lifespan, and decreased rate of aging in *C. elegans* independently of previously described germline signaling pathways. FUdR is an analog of the commonly used cancer medication 5-FU, and these findings may implicate a new use for DNA synthesis inhibitors in the future.
Amantadine as an augmentation therapy to sildenafil for sexual dysfunction caused by risperidone

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Patients with schizophrenia are managed with long-term regimens of antipsychotic medication, thus drug adherence plays a critical role in improving disease prognosis. One of the main causes for medication non-compliance in patients with schizophrenia is the drug side effect profile. Accordingly, sexual dysfunction is highly prevalent among patients taking antipsychotics and can be a precipitating cause of treatment failure. We present the case of a 36-year-old male patient with a five-year diagnosis of schizophrenia, paranoid type, who presented to medical professionals with the complaint of sexual dysfunction since starting Risperidone atypical antipsychotic. An initial trial of Sildenafil was attempted, but failed in remedying the patient’s anorgasmia. We then turned to the dopamine-elevating medication Amantadine as a potential treatment for the undesirable side effects of Risperidone. Over the course of a six-week trial period of Amantadine as add-on medication to Sildenafil, we tracked the patient’s response with routinely scheduled surveys. At the conclusion of the trial, the patient reported significantly improved sexual function when compared to his preliminary baseline. Since dopamine has been implicated as a probable factor in the pathogenesis of sexual dysfunction, Amantadine supplementation may be one of many dopamine-elevating agents that should be considered as a potential therapeutic option.
Sponsorship, antidepressant dose, and outcome in major depressive disorder: meta-analysis of randomized controlled trials

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Objective: Differences in dosing may influence results of pharmaceutical industry–sponsored medication trials. This study aims to determine the relationship between sponsorship and antidepressant dosing and efficacy in randomized controlled trials for major depressive disorder. Data Sources: Trials were identified through English-language searches of MEDLINE and PsycINFO (January 1996–June 2010) using specific drug names and classes and depressive disorder or major depression and double blind or double-blind method. Other limitations included human subjects and treatment study designs using the clinical queries option. Other sources were also searched following a strict set of inclusion and exclusion criteria. Study Selection: Randomized controlled trials were included if they examined antidepressant treatment for major depressive disorder, reported mean final medication dosages, acknowledged an association with industry, and included study arms of medications produced by the associated manufacturer and a competitor (“sponsor” and “nonsponsor” arms) (58 trials involving 15,026 patients from 101 citations identified). Data Extraction: Data on dosing, efficacy, baseline severity, and adverse events were extracted by 2 of the authors. Results: Meta-analyses were used to examine dosing and efficacy data. Using consensus guidelines for medication dosing, we determined that sponsor medication was dosed relatively higher than nonsponsor medication, in 37% (22/60) of comparisons as opposed to 5% (3/60) in which the nonsponsor medication was dosed higher ($\chi^2 = 25.9, P < .001$). Trials in which sponsor drugs were dosed higher than nonsponsor drugs demonstrated higher remission rates for the sponsor drug (OR = 1.28, 95% CI = 1.11–1.47, P < .001). These results were confirmed using regulatory dosing guidelines. There was no significant correlation between dosing or outcome with baseline severity or adverse events. Conclusions: Sponsor drugs are dosed higher than nonsponsor drugs in antidepressant randomized controlled trials, and higher dosing is associated with better sponsor drug outcomes in some cases.
Pharmacology Abstracts

The role of intranasal ketamine analgesia in acute orthopedic trauma injuries

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Ketamine, an NMDA-receptor antagonist has been widely used in anesthesia. Recently, there has been increased interest in using ketamine in analgesia due to its safety profile as a non-opioid analgesic. Ketamine’s unique properties of (a) maintaining blood pressure, (b) maintaining respiratory drive, and (c) increasing cerebral blood flow, make it an ideal drug in an acute trauma setting when compared to opioids. The current study is designed to elucidate whether ketamine, administered intranasally, is effective in reducing moderate-severe musculoskeletal pain. This novel administration of ketamine is being compared to the current standard of care, intravenous or intramuscular morphine.

Patients recruited to the study were randomly assigned to either the study group (receiving 1mg/kg IN Ketamine), or one of two controls (0.1 mg/kg IV MO or 0.15 mg/kg IM MO). Patients were required to meet certain inclusion criteria including: (1) orthopedic pain described as between 8 and 10, (2) between the ages of 18 and 65, and (3) systolic blood pressure between 90 mmHg and 160 mmHg. Major exclusion criteria included (1) pregnancy, (2) psychiatric illness, (3) allergy to morphine or ketamine, and (4) nasal/septal anatomical abnormality. Pain (measured on a 100mm VAS scale), as well as vital signs, were measured before administration of analgesia and at 5 minutes intervals for one hour. Patients completed an opiate side-effect survey as well as a satisfaction measurement at the end of the study.

At 58 patients, results showed (1) “Time To Onset” of IN Ketamine was not statistically different than IV MO bolus, but both were statistically shorter than IM MO. (2) All groups showed statistically indistinguishable efficacy with approximately 50mm in “Total Pain Reduction”, (3) There is no statistical significance yet for “Time to maximum pain reduction,” and (4) There is an apparently reduced sense of satisfaction using the IN Ketamine, but this has not achieved statistical significance yet.
ED11, a biologically feasible Caspase-6 inhibitor is a potential therapy for Alzheimer disease

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Background: There is currently no treatment available for Alzheimer’s disease (AD). Through decades of research, insights regarding the underlying pathology have been obtained; however, physicians and affected families still await valid therapeutics. Shortcomings associated with many trials relate to the development of drug targets that are insufficiently upstream. For example, amyloid beta (Aβ) plaques, believed for many years to play a key role in causing AD, were targeted in a recent human trial that did not produce distinguishable results. Therefore, Aβ plaques may be the result of upstream events rather than the underlying cause itself.

Rationale: Caspase-6 (C6) may be a suitable upstream target for AD therapeutics. A number of studies have shown that C6 is up regulated in regions of the brain associated with neurodegeneration in AD. C6 has also been shown to precede plaque and tangle formation, and thus may be involved early in AD pathogenesis. C6-inhibitors have shown promise in reducing AD associated pathologies in vitro, however, to our knowledge, in vivo evidence to support C6-inhibition has yet to be established. Biologically feasible C6 inhibitors to date have fallen short due to toxic effects, nonspecific caspase binding, or insufficient permeability. Our group has developed ED11, a biologically feasible C6-inhibitor. In mice with human Huntington’s disease, ED11 has successfully and specifically down-regulated C6, and may have rescued HD-associated pathologies in these mice. Overlap has been observed between the pathological mechanisms associates with AD and HD. This suggests, along with evidence showing the participation of C6 in AD pathology, that ED11 may be a promising therapy for reducing the pathological progression of AD.

Methods & implications: Triple transgenic AD mice (3xTg) as well as control (C57) mice will be used for this project. ED11 will be administered via slow-release pump implantations over a six-month period. After the treatment period, a combination of imaging, behavioral testing and chemical analysis will be conducted in order to observe the efficacy of ED11 on treating lesions commonly associated with AD.
Effect of vitamin E and memantine on functional decline in Alzheimer disease

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Objective: To determine if vitamin E (alpha tocopherol), memantine, or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor.

Design, Setting, and Participants: Double-blind, placebo-controlled, parallel-group, randomized clinical trial involving 613 patients with mild to moderate AD initiated in August 2007 and concluded in September 2012 at 14 Veterans Affairs medical centers.

Interventions: Participants received either 2000 IU/d of alpha tocopherol (n = 152), 20 mg/d of memantine (n = 155), the combination (n = 154), or placebo (n = 152).

Main Outcomes and Measures: Alzheimer’s Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory score (range, 0-78). Secondary outcomes included cognitive, neuropsychiatric, functional, and caregiver measures.

Results: Data from 561 participants were analyzed. ADCS-ADL Inventory scores declined by 3.15 units less in the alpha tocopherol group compared with the placebo group. In the memantine group, these scores declined 1.98 units less (95% CI, −0.24 to 4.20; adjusted P = .40) than the placebo group’s decline. This change in the alpha tocopherol group translates into a delay in clinical progression of 19% per year compared with placebo. Caregiver time increased least in the alpha tocopherol group. All-cause mortality and safety analyses showed a difference only on the serious adverse event of “infections or infestations,” with greater frequencies in the memantine and combination groups compared with placebo.

Conclusions and Relevance: Among patients with mild to moderate AD, 2000 IU/d of alpha tocopherol compared with placebo resulted in slower functional decline. There were no significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol. These findings suggest benefit of alpha tocopherol in mild to moderate AD by slowing functional decline and decreasing caregiver burden.
Neurology Abstracts

**Corpus callosum DTI metrics correlate with MRI lesion load in active relapsing-remitting multiple sclerosis patients**

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**Background:** The corpus callosum is one of the heavily myelinated fiber tracts known to be involved in multiple sclerosis. Brain MRI lesion load as well as diffusion tensor imaging (DTI) metrics measurements that signify myelin and axonal loss are frequently used to assess disease progression.

**Objectives:** To elucidate the relationship of microstructural damage in the corpus callosum as measured by brain DTI and quantitative MRI lesion measurements in patients with relapse-remitting multiple sclerosis (RRMS).

**Materials and Methods:** Active RRMS patients with more than 0.5 relapses per year, 32 of which treated with immunomodulatory drugs, were enrolled in the study. MRI sequences were obtained on a 3.0T scanner (GE, Signa HDX). MS lesion number and volume on T1 and T2 scans were measured using semi-automated segmentation software. Corpus callosum DTI analyses were performed with Tract-Based Spatial Statistics (TBSS). Fractional anisotropy (FA) and radial diffusivity (RD) were obtained in the splenium, body, and genu regions of the corpus callosum. Spearman correlation test was used for analysis.

**Results:** Forty active RRMS patients, 28 females, 12 males, age 34.9±1.3 years, disease duration 7.2±0.5 years and Expanded Disability Status Scale (EDSS) 2.0±0.2 were studied. Corpus callosum FA and RD DTI metrics correlated with the volume of T1 and T2 brain lesions. Negative correlations were found between lesion volume and FA in the splenium (T2 lesion: r= -0.84, p=1.7*10^-11, T1 lesion: r=-0.78, p=2.5*10^-08), body (T2 lesion: r= -0.80, p=7.4*10^-10, T1 lesion: r= -0.78, p=1.5*10^-08) and genu (T2 lesion: r= -0.73, p=1.5*10^-07, T1 lesion: r= -0.72, p=6.3*10^-07). Positive correlations were demonstrated between lesion volume and RD of splenium (T2 lesion: r=0.80, p=5.6*10^-10, T1 lesion: r=0.78, p=1.5*10^-08), body (T2 lesion: r=0.74, p=1.7*10^-11, T1 lesion: r=0.75, p=1.9*10^-07), and genu (T2 lesion: r=0.58, p=0.0001, T1 lesion: r=0.63, p=4.4*10^-05).

**Conclusion:** The correlation of regional corpus callosum abnormalities with brain MRI lesion load in active MS patients was demonstrated. In addition, differential changes were noted to exist between different subsections of the corpus callosum, most probably relating to the density and diameter of axons within these areas. These findings signify the occurrence of myelin loss together with Wallerian degeneration in the corpus callosum of active RRMS patients.
Exposure to female pheromones stimulates a specific type of neuronal population in the male but not female magnocellular division of the medial preoptic nucleus of the Syrian hamster

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The magnocellular division of the medial preoptic area (MPN mag) integrates pheromonal and hormonal signals to play a critical role in the expression of male typical sex behavior. The MPN mag contains two morphologically distinct neuronal populations; the percentage of each type within the nucleus is sex specific. Males have more neurons with a single nucleolus whereas females have more with multiple nucleoli. To determine which neuronal subtype mediates pheromonal induction of copulation, tissue from male and female hamsters exposed to female pheromones was immunolabeled for the immediate early protein (EGR-1). Subsequently the tissue was counterstained and the number of ERG-1 neurons with one or two nuclei was determined. The results indicate that pheromones stimulate neurons with single nucleoli in males but fail to stimulate either neuronal subtype in females suggesting that synaptic input to the MPN mag is sexually differentiated.
Pelvic nerve injury leads to increased Rho-kinase mediated adrenergic vasoconstriction of the distal vagina

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Introduction: Female sexual responses rely on innervations from the pelvic plexus which may become damaged during radical hysterectomy. We demonstrated that bilateral pelvic nerve injury (BPNI) leads to increased vaginal adrenergic contractions and impaired vaginal blood flow in rats. This study examined the role of Rho–kinase (ROCK) in the elevated vaginal contractions after BPNI.

Methods: Female Sprague–Dawley rats (12 wks) were divided into sham or BPNI in which nerves from the pelvic plexus were bilaterally crushed. Animals were examined 3, 7, 14, 30 days following BPNI. Distal vaginal strips were contracted to norepinephrine (NE) in the presence/absence of ROCK inhibitor Y–27632. ROCK1, ROCK2, RhoA, and α–smooth muscle actin (ASMA) protein and gene expression were assessed by Western blot and qtPCR. Vaginal segments were stained with Masson’s trichrome to assess smooth muscle and collagen.

Results: An increase in vaginal contraction to NE was evident 3, 7, 14 days following BPNI (\textit{p}<0.05). ROCK inhibition normalized NE–induced vaginal contractions after BPNI (\textit{p}<0.05). Gene expression of ROCK1, ROCK2 was increased 14 days after BPNI and its activator RhoA was also increased at 3 and 14 days compared to sham (\textit{p}<0.05). Protein expression of ROCK1, ROCK2 and activated RhoA were elevated 3, 14 days after BPNI (\textit{p}<0.05). A significant decrease in ASMA protein was evident at 7, 14 days after BPNI. Increased collagen in the vaginal wall and a decrease in vaginal epithelium were evident14 days after BPNI.

Conclusions: Pelvic nerve injury leads to increased adrenergic, rho–kinase mediated tone, and structural changes to the vagina. These findings parallel the phenotype in the penis after cavernous nerve injury and provide us with a possible therapeutic target for neuropraxia–induced vaginal dysfunction.
The undiscovered link

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Through the advancements in genetic testing we have been able to determine the unidentified gene tying together three separate individuals. As the three unrelated patients separately visited the genetics clinic, we noticed a distinctive similarity amongst them. Due to comparable abnormal facial and body anomalies that all the patients’ possessed as well as characteristically distinct developmental delays, we concluded that the disease these individuals suffer from might in fact be somehow connected. Via thorough histories on all three individuals; analyzing pedigrees, brain scans, milestone achievements, and physical features, it was determined there was enough similarities to proceed with further studying. PCR’s were then done on all three individuals and it was found that in fact they all possessed the same gene mutation. The gene of interest is found to be a transcriptional co-activation, which is required and used in majority of the RNA polymerase II dependent genes. By being able to determine this gene, we will be able to diagnose and treat future patients with this same mutation.

* Process of being published so unable to state name of gene.
Sarcopenia and geriatric depression are prevalent diseases that consume substantial health care funds in the elderly population. If this study finds significant results we will have established clinically significant cutoff points for treating elderly individuals with depression and sub-threshold depression. Early prevention and treatments may reduce healthcare cost associated with limited mobility in the elderly population. Furthermore, clinically significant cutoff points of energy expenditure may be established. Those cutoff points could affect recommended activity levels in the elderly population. The participants of the study were chosen from the Osteoperotic Fractures in Men Study (MrOS) study based on only two criteria, to avoid as much selection bias as possible. Study subjects needed to have had Geriatric Depression Scale assessments at visit two and three of the MrOS study and subjects were required to have had activity monitor data assessed at visit three of the MrOS study. Depressive symptoms were evaluated at visit two and visit three using the 15-item Geriatric Depression Scale short form (GDS) to screen for Major Depression Disorder. Participants were instructed to wear the SenseWear Pro Armband (Body Media, Inc; Pittsburgh, PA) over the right triceps muscle at all times, including while sleeping, over a typical 7-day period. Data were sampled in 1-minute epochs from several sensors: a heat flux sensor, a galvanic skin response sensor, a skin temperature sensor, a near body sensor and body movement sensor (2-axis accelerometer). These data were used in proprietary algorithms (Innerview Professional 5.1 software) along with height, weight, handedness and smoking status to estimate energy expenditure in kilocalories per day. Participant characteristics will be compared across categories of GDS using ANOVA for normally distributed continuous variables, Kruskal Wallis for non-normal continuous variables, or chi-square tests for categorical variables. We await results and will subsequently discuss the implications of the data findings.
An investigation of bovine intracranial endothelial cell behavior through isolation and characterization including response to shear stress

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Endothelial cells play a vital role in vascular physiology and pathophysiology. The region of the cerebrovasculature is populated by endothelial cells with distinct structures and functions. To study how cerebrovascular endothelial cells differ in comparison to other vascular beds it is necessary to use cells from specific cerebrovascular regions. The first part of this investigation describes a method for culturing primary endothelial cells from bovine cerebral arteries. Endothelial identity was confirmed by the ability to uptake low-density lipoprotein and the expression of Factor VIII and eNOS. Cell-line suitability was confirmed by the ability to form confluent monolayers. The second part of this study directly compares the newly characterized primary endothelial cells with endothelial cells from extracranial sources. As reactive oxygen species (ROS) modulate endothelial functions through intracellular signaling, ROS generation was measured between cell populations under conditions of normal and elevated wall shear stress. Under chronic application of either regimen, intracranial endothelial cells generated significantly greater ROS compared with similarly treated aortic endothelial cells. This confirms the presence of fundamental differences in cerebrovascular endothelial cells, and may be indicative of important signaling mechanisms specific to the cerebral vasculature.
Biochemical, functional, and clinical implications of PP6C mutations in melanoma

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Recent whole genome melanoma sequencing studies have identified recurrent mutations in the gene encoding the serine/threonine phosphatase PP6C. However the biochemical, functional, and clinical significances of these mutations are unknown. To address the impact of PP6C mutations in melanoma, we first sequenced PP6C from DNA extracted from 310 melanoma samples linked to extended prospective clinical follow up, and found 50 mutations in 33 patients. There was no association between PP6C mutations and BRAF/NRAS mutational status. Although PP6C mutations were seen equally in stage I-IV melanomas, only a subpopulation of cells within a tumor contained PP6C mutations, suggesting PP6C mutation is an early, but non tumor-initiating event in melanoma. Those mutations resulting in stop codons predicted a worse prognosis compared to other mutations. Biochemically, PP6C mutations could be divided into two classes: those that bound to PP6C regulatory subunits, and those that did not. Mutations that did not bind to PP6C regulatory subunits were associated with increased phosphorylation of Aurora Kinase A, a PP6C substrate, and resulted in mitotic defects. However, both classes of PP6C mutations led to increased sensitivity to Aurora Kinase inhibition. Together, our data support for the first time that PP6C mutations are molecularly, biochemically, and clinically heterogenous, and may have therapeutic implications.
Biomarker Use is Associated with Reduced Clinical Trial Failure Risk in Metastatic Melanoma

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Background: Metastatic melanoma is associated with a high morbidity and mortality, with many treatments failing during clinical trials and never being approved by the FDA.

Objectives: Here, we investigate the risk associated with clinical trial testing of treatments for metastatic melanoma.

Methods: A systematic analysis of all trials evaluating metastatic melanoma treatments was conducted. Trial data were obtained from ClinicalTrials.gov until July 1, 2013. Online searches were included to supplement these findings. The success rate was calculated for each phase of development with medical and commercial failures identified. Drug candidates were excluded if they began the Phase I program prior to 1998, did not focus on unresectable metastatic melanoma, contained topical or reformulated therapies, or were not industry sponsored.

Results: Out of 197 drugs that entered Phase I and met the inclusion criteria, only four treatments obtained FDA approval. The cumulative success rate was 17% compared to the industry average (16%). The cumulative success rates were observed to be similar between biologics (20%) and small molecules (21%). Candidates that used biomarkers for patient selection increased success rates by nearly eight times to 47% compared to non-biomarkers (6%). Only 48% of the biomarkers examined were validated and had received FDA approval.

Conclusions: Overall, the cumulative success rate for metastatic melanoma was similar to the industry average. The high relative success rate for compounds using predictive biomarkers could suggest an advantage to targeted therapy in this heterogeneous population and provide a clinical rationale for patient recruitment and resource allocation during clinical trials.
Hematology & Oncology Abstracts

Use of liver SUL\textsubscript{mean} in FDG PET/CT: reader variability and effect of volume of interest placement

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Positron emission tomography (PET) is valuable for staging and treatment assessment of various solid tumors. Using fluorine 18 fluordeoxyglucose (FDG) as a biomarker, radiologists compare uptake in potential tumor foci to normal tissue like the liver. This comparison, called lesion-to-liver standardized uptake value (SUV) ratio, is useful in localizing benign and malignant tumors of various cancers. Recent studies have normalized the liver SUV to lean body mass (SUL\textsubscript{mean}) as a quality control measure for targeting lesions in FDG PET/CT studies. However, if the SUL\textsubscript{mean} varies because different readers measure the parameter at different locations (volume of interest, VOI) within the liver, target selection may be compromised. Variability in SUL\textsubscript{mean} is problematic in tumors with low FDG uptake, like bronchioalveolar lung carcinoma. This retrospective study evaluates the impact of VOI placement and interreader agreement on the reliability and variability of liver SUL\textsubscript{mean}. We reviewed PET/CT images in 116 randomly selected patients who had normal livers and had received a baseline PET/CT. A 30-mm-diameter spherical VOI was placed within the right liver lobe above, below, and at the level of the main portal vein. Two readers performed all measurements independently. Analysis of variance and intraclass correlation coefficient (ICC) analysis were performed. The mean SUL\textsubscript{mean} was between 2.11 and 2.17 at upper, portal, and lower levels of the right liver lobe. Coefficient of variance was between 21.0% and 23.1%, without significant differences for location. The ICC of the two readers varied between 0.98 and 0.99 (95% confidence interval [CI]: 0.97, 0.99; \( P = .0001 \)) at each level. The goal was to understand mistakes in measuring liver SUL\textsubscript{mean} that can affect standardization and quantitative PET imaging in oncology. The results demonstrate that liver SUL\textsubscript{mean} at FDG PET/CT has excellent interreader agreement, with similar values when measured at different levels within the right liver lobe.
Efficacy and safety of bevacizumab for recurrent glioblastoma multiforme: a systematic review and meta-analysis

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**Background:** There has been limited direct comparison of how the safety and efficacy of bevacizumab regimens compare to other therapeutic approaches for recurrent glioblastoma multiforme. The aim of this meta-analysis is to estimate the safety and efficacy of bevacizumab treatment in comparison to cytotoxic chemotherapy for the treatment of recurrent GBM.

**Methods:** We conducted a meta-analysis of clinical trial data, pooling bevacizumab study outcomes and compared them to outcomes from clinical trials of cytotoxic chemotherapy for recurrent GBM.

**Results:** For analysis of efficacy, we found that bevacizumab regimens associate with a longer duration of disease control, as measured by progression free survival at 6 months (38\% versus 30\%, \( p = 0.001 \)). When adjusted for patient age and KPS, we estimate an increase of 10.5\% in PFS6 (\( p = 0.124 \)). We found that bevacizumab regimens associate with a 10.5 month median survival versus 8.9 months for cytotoxic chemotherapy regimens (\( p = 0.52 \)). When adjusted for age and KPS we estimate the difference in median survival as 2.44 months (\( p = 0.451 \)).

For analysis of safety we estimate that 10.5\% of patients on bevacizumab regimens and 7.1\% patients on cytotoxic regimens discontinued because of toxicity (\( p = 0.209 \)). When adjusted for age and KPS, we estimate that bevacizumab associates with a 4.2\% increase in the cumulative incidence of treatment stoppage related to toxicity (\( p = 0.139 \)). We estimated the cumulative incidence of fatal adverse events at 2.1\% in patients on bevacizumab trials and 0.12\% in patients on cytotoxic chemotherapy (\( p < 0.005 \)). With adjustment for age and KPS, we found that bevacizumab treatment associated with a 1.7\% increase in fatal toxicity event (\( p = 0.01 \)).

**Conclusions:** These findings suggest that bevacizumab regimens have important increases in treatment efficacy and toxicity, both of which should be considered in making treatment decisions.
Specialized geriatric care in head and neck surgical oncology

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Background: The Geriatrics Service at Memorial-Sloan Kettering’s Department of Medicine was established in 2009. The service offers medical consultations with fellowship-trained geriatricians during the treatment of older patients with cancer. The elderly have unique health concerns in addition to their cancer including multiple health conditions, increased risk of drug reactions, different response to treatment, increased caregiver strain, and growing financial burdens. They are often receiving treatment from multiple physicians and need a comprehensive evaluation by those with an expertise in geriatrics. Such an evaluation is critical due to the importance of assessing their symptoms in the context of their overall condition. The Geriatrics Service consists of geriatric physicians and a nurse practitioner that consult with the patients’ oncologists to help determine how well the patients may tolerate cancer treatment and what precautions should be taken due to their age.

Methods: A pilot study was performed that aimed to describe the implementation and feasibility of a novel intervention designed to improve perioperative care in geriatric head and neck surgery. Elderly patients over the age of 75 with head and neck cancer that received perioperative evaluation by the geriatrics service between 2010 and 2011 were assessed.

Results: A total of 168 patients requiring head and neck surgery were seen, of which 94% subsequently underwent surgery. In addition to preoperative medical optimization, geriatricians assisted in decision-making regarding indications for cancer therapy. Postoperatively, geriatricians were instrumental in preventing and treating delirium and poly-pharmacy. They facilitated planning for patient discharge and rehabilitation. Consequently, 87% of the patients were discharged home postoperatively, and only 13% required placement in skilled nursing facilities. Overall survival at 24 months was 80%.

Conclusion: Geriatric preoperative and postoperative support for elderly head and neck cancer patients has promising potential. The impact and direct benefits of this pilot initiative require additional study.
Immunology & Ophthalmology

Vitamin D supplementation and upper respiratory tract infections in adolescent swimmers: a randomized controlled trial

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Upper respiratory infections (URI) in athletes might hinder performance in training and in competition. Observational studies have identified an elevated risk of developing a URI when serum Vitamin D (25(OH)D) concentrations are insufficient (<30ng/ml). Intervenional trials have only been conducted in the general population, and have yielded contradicting results.

The aim of the study was to examine if supplementation with Vitamin D₃ reduces the URI burden in competitive adolescent swimmers with Vitamin D insufficiency. Fifty-five competitive adolescent swimmers with Vitamin D insufficiency were randomized to receive Vitamin D₃ (2,000IU/d) or placebo for 12 weeks during the winter months. Serum 25(OH)D concentration was measured before and after supplementation and participants completed a URI symptoms questionnaire weekly. The relationship between the change in 25(OH)D concentrations and the frequency, duration and severity of colds was analyzed by linear modeling. Mean serum 25(OH)D concentrations were significantly higher in the Vitamin D₃ group compared with the placebo group at the end of the study period (29.6±6.5ng/ml vs. 20.3±4.2ng/ml, respectively). Twenty-two participants reported URI events, 11 from each group. There were no between-group differences in the frequency, severity or duration of URIs. Baseline 25(OH)D concentration did not correlate with the duration or severity of colds. Exploratory analyses revealed that the duration and severity of colds in the placebo group were closely correlated with the change in 25(OH)D concentrations during the study period (r= -0.90, p<0.001 and r= -0.65, p= 0.043, respectively). We conclude that Vitamin D₃ supplementation in adolescent swimmers with serum 25(OH)D <30ng/ml does not reduce URI burden during the winter months. However, larger decreases in 25(OH)D concentration were associated with longer and more severe colds.
Caspase-1 dependent IL-1β secretion is critical for host defense in a mouse model of Chlamydia pneumoniae lung infection

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Chlamydia pneumoniae (CP) is an important human pathogen that causes atypical pneumonia and is associated with various chronic inflammatory disorders. Caspase-1 is a key component of the ‘inflammasome’, and is required to cleave pro-IL-1β to bioactive IL-1β. Here we demonstrate for the first time a critical requirement for IL-1β in response to CP infection. Caspase-1−/− mice exhibit delayed cytokine production, defective clearance of pulmonary bacteria and higher mortality in response to CP infection. Alveolar macrophages harbored increased bacterial numbers due to reduced iNOS levels in Caspase-1−/− mice. Pharmacological blockade of the IL-1 receptor in CP infected wild-type mice phenocopies Caspase-1-deficient mice, and administration of recombinant IL-1β rescues CP infected Caspase-1−/− mice from mortality, indicating that IL-1β secretion is crucial for host immune defense against CP lung infection. In vitro investigation reveals that CP-induced IL-1β secretion by macrophages requires TLR2/MyD88 and NLRP3/ASC/Caspase-1 signaling. Entry into the cell by CP and new protein synthesis by CP are required for inflammasome activation. Neither ROS nor cathepsin was required for CP infection induced inflammasome activation. Interestingly, Caspase-1 activation during CP infection occurs with mitochondrial dysfunction indicating a possible mechanism involving the mitochondria for CP-induced inflammasome activation.
Prevalence of acute otitis media and acute mastoiditis with and without complications in the pre and post-Prevnar era

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Background: Acute Otitis Media and Complications are a major cause of morbidity in children. Complications are mostly associated with pneumococcal disease. The Ministry of Health in Israel instituted mandatory immunizations with the PCV7 vaccine starting in July 2009. After two years, the PCV7 was replaced with the PCV13 vaccine, which allowed for more pneumococcal bacteria serotypes to be covered.

Objective: To see if the introduction of the pneumococcal conjugate vaccine (PCV) in our study population resulted in a decrease in complicated acute otitis media and mastoiditis.

Methods: We conducted a retrospective study to examine the effect of the pneumococcal conjugate vaccine (PCV) on the incidence of acute mastoiditis and severe acute otitis in the pediatric population in our hospital. Patients were selected from the Tel Aviv Sourasky Medical Center database over an eight-year period, from January 2006 to March 2013. Patients that met the inclusion criteria were divided into three time periods: pre-Prevnar (Jan. 2006 to June 2009), post-PCV7 (July 2009-Dec. 2010), and post-PCV13 (Jan. 2011-April 2013). We further investigated the patients for correlations in age, gender, comorbidities, serum levels of leukocytes and C-reactive protein, immunizations records, imaging, bacteriology, and hospital admission.

Results: Of the cases reviewed, two hundred thirty-nine children met the inclusion criteria. Our results displayed a significant 24% drop in acute mastoiditis admissions in the post-PCV7 era, and an even more dramatic 43% reduction in acute mastoiditis admissions once the subsequent vaccine was utilized in the post-PCV13 era.

Conclusion: The introduction of PCV resulted in less cases of complicated AOM in our cohort.
Comparison of early experience with intraoperative wavefront aberrometry IOL power calculations in laser-assisted versus conventional cataract surgery

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Purpose: To compare the preoperative IOL calculations with intraoperative IOL power measurements made by ORA on eyes pretreated with a femtosecond laser and those that were not.

Methods: This was a retrospective study of aphakic intraoperative wavefront IOL power calculations in eyes that underwent conventional cataract surgery (n=45) and laser assisted cataract surgery with either a B+L Victus or LenSx femtosecond laser (n=53). Each eye had a postoperative target of Plano and received a B+L MI60L lens. Preoperative IOL calculations were compared to ORA measurements.

Results: The mean difference between preoperative and intraoperative IOL calculations in the femtosecond group was -0.37D ± 0.53D (p=0.013). For the conventional surgery group there was a mean difference of -0.1D ± 0.67D (p=0.32). Postoperative manifest refraction showed the mean spherical equivalence of the femto group to be -0.251D ± 0.39D and the non-femto group to be -0.248D ± 0.41D (p=0.48). Using the implanted power, the ORA suggested power, and the POMR, the mean postoperative spherical equivalences were 0.66D ± 0.62D in the femto group and -0.47D ± 0.60D for the non-femto group (p=0.058).

Conclusions: Preoperative and intraoperative IOL calculation differ significantly when the eye were pretreated with a femtosecond laser. Relying heavily on intraoperative measurements for lens selection may lead to a higher rate of postoperative myopia in femtosecond laser assisted cataract surgery.
Corneal sensitivity after application of four NSAIDs in volunteers: a randomized clinical trial

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Non-steroidal anti-inflammatory drugs (NSAIDs) are often administered topically for a variety of ophthalmologic conditions. However, NSAIDs may be associated with topical anesthetic effects that could limit their safety. We performed a prospective, blinded, comparative trial comparing the topical anesthetic effects of four commercially available ophthalmologic NSAIDs (Diclofenac, Nepafenac, Ketorolac, Bromfenac). We compared the anesthetic effects and duration of anesthesia of several commercially available topical NSAIDs. Corneal sensitivity profiles over time were measured and while all four NSAIDs significantly reduced corneal sensitivity, the anesthetic effect of Diclofenac was greater than that of Nepafenac. Time to recovery of corneal sensitivity was similar among the four agents.
SOX9 and Wnt signaling in human fetal pancreatic development

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Disturbances in glucose homeostasis due to either β-cell destruction or insulin resistance result in Type 1 and 2 diabetes, respectively. Pancreatic β-cells perform the essential function of blood glucose regulation. Currently, β-cell replacement offers an attractive therapy for treatment of diabetes; however, no sufficient β-cell source is available. In vitro generation of β-cells from alternative cell types [e.g. ESC, MSC and BMSC] could provide a source for islet cell transplantation but a complete understanding of the developmental process is required. SOX9 is an important transcription factor in pancreatic progenitor maintenance as well as endocrine differentiation; however, pathways regulating its expression are unclear. In the present study, co-localization of WNT3A, frizzled receptor (FZD), and nuclear β-catenin (nβ-catenin) were examined in human pancreatic development. The majority of insulin+ cells expressed WNT3A, FZD and nuclear β-catenin (nβ-catenin). Half of SOX9+ cells expressed WNT3A in early development decreasing throughout. nβ-catenin expression in SOX9+ cells remained stable. To examine Wnt signaling in progenitors, human islet-epithelial clusters were cultured and treated with recombinant mouse WNT3A in dose and time dependent trials. After 48h treatment with WNT3A, an increase in SOX9 expression and differentiation of progenitors was observed associated with mature β-cell proteins ISL1 and insulin. Differentiation was time-dependent and found to be mediated through both FZD and non-FZD pathways. This evidence highlights an active role for Wnt signaling in promoting endocrine differentiation.
Activation of complex I of the electron transfer chain favors mitochondrial permeability transition pore opening

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Introduction: In mitochondria, ROS are mainly produced in complex I, into the matrix, and in complex III, mostly in the inter-membrane space. Increase in ROS generation has been implicated in ischemia/reperfusion injury. On the other hand, ROS production increases in cardio-protection by preconditioning and it has been speculated that ROS can act as second messenger for pro-survival signaling.

Objective: We investigated whether the dual role of ROS (cardio-damaging and cardio-protecting) can be related to their site of production in the electron transfer chain (ETC). In addition we investigated whether ROS production in complex I or in complex III that may cause the inhibition or facilitation of the mitochondria permeability transition pore (mPTP) opening.

Methods: In heart isolated mitochondria we measured 1. ROS generation using amplex red and 2. mitochondria viability by the calcium-retention-capacity (CRC) which is the amount of added Ca2+ required to induce the mPTP opening. Extra mitochondrial Ca2+ was measured with calcium green. Specific substrates for complex I (glutamate/malate), complex II (succinate), the ETC inhibitors (rotenone or antimycin-A) and Mg2+(mPTP opener) were used. Mitochondria were isolated in untreated animals (sham) and in animals 10 minutes after subjected to 18 min of ischemia reperfusion.

Results: We found that, the calcium-retention-capacity was greatly reduced in mitochondria treated with succinate (2 mM)+glutamate/malate (3 mM) compared to succinate alone (2 mM): values were 132±13succinate+glutamate/malate and 212±14succinate nmoles/mg of mito protein (n=3), respectively. Further, Mg2+ 3 mM decreased ROS production in succinate alone (3 mM) (1422±61succinate pmol.min-1mg-1 vs. 905±55succinate+Mg pmol.min-1mg-1) while no effect was observed in glutamate/malate (127±45 glutamate/malate pmol.min-1mg-1 vs. 120±38 glutamate/malate+Mg pmol.min-1mg-1), suggesting a better mitochondria state in succinate. Also, mitochondria from hearts after ischemia/reperfusion and non-ischemic mitochondria treated with ETC inhibitors produced more ROS than control (sham) and preconditioned groups when using glutamate/malate. Values are 482±26I/R, 396±4preconditioning, and 320±46non-ischemic pmol.min-1mg-1 of mitochondria protein, n = 4). In sham, and sham+rotenone (2 mM) or antimycin-A (20 mM) values are 232±15sham, 482±18sham+rotenone, and 891±70antimycin-A pmol.min-1mg-1 of mitochondrial protein (n = 4, p< 0.001 n= 4/group). In contrast, succinate produced less ROS in mitochondria from hearts after ischemia/reperfusion and in non-ischemic mitochondria treated with ETC inhibitors than in normal and preconditioned groups. Nod decreased ROS production when using succinate, while it increased ROS production when using glutamate/malate.
Characterization and determination of fate of adult progenitor cells in a rat femur fracture model

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Background: Impaired fracture healing remains a significant clinical obstacle in orthopaedics. Cell-based therapy (CBT) has been explored as one possible adjunct to current methods. CBT is the isolation, expansion, and reapplication of progenitor cells from the adult body to aid healing. Previous animal models have detailed the ability of mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) to enhance fracture healing. MSCs are precursors to bone cells and EPCs contribute to post-natal vasculogenesis, giving insight into possible mechanisms.

Objectives: (1) To extensively characterize isolated MSCs and EPCs, relating these to bone healing (2) To determine the fate of MSCs and EPCs in a segmental defect model (3) To relate these populations to fracture healing

Methods: (1) EPCs and MSCs are characterized by analysis of cell surface marker expression through flow cytometry, morphological assays, functional assays, differentiation assays, and quantitative real-time PCR. (2) Fate is determined by the implantation of GFP-expressing EPCs/MSCs on a gelfoam scaffold into a segmental defect created in femurs of Fischer 344 rats. Histology is examined at two and four weeks after surgery to examine location of GFP-expressing cells. Concurrently, immunohistochemistry details the identity of the implanted cells. (3) Fluorescent microangiography is performed two weeks after surgery to assess changes of the vasculature.

Results: A majority of cells isolated for fracture-healing experiments resemble EPCs/MSCs as described by the literature. Differences in EPC/MSC potential to heal bone are quantified. Post-implantation, EPCs and MSCs remain in the callus exerting influence over healing mechanisms. Impact on healing is inconclusive at the time points investigated. The EPC implanted rats have a non-significant increased vessel content compared to both the MSC and control groups.

Conclusions: Isolated populations of EPCs/MSCs contribute to the healing of bone through elucidated mechanisms. This contributes to the development of a viable CBT for fracture repair.
Extracellular matrix-like substances and leukemia inhibitory factor for culturing early human follicles.

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Introduction: The ability to mature human primordial follicles in vitro would assist fertility restoration without reseeding malignancies. The development of a culture technology is still at its infancy. Various extracellular matrices might improve the culture system. LIF activated primordial follicles in rodents and goats might promote activation also in the human.

Aim: To compare culture of human primordial follicles on human recombinant vitronectin (hrVit) and on swine small intestine submucosa (SIS) and to investigate if LIF supplementation activates these follicles.

Material & Methods: Fourteen frozen-thawed ovarian samples from girls/women (ages 6-35) were used for the study. Thick (1-2mm) slices were cultured for six days on either hrVit or on SIS. Samples were cultured with: basic culture medium only; basic culture medium with two concentrations of LIF (10ng/ml and 100ng/ml) and basic culture medium with LIF (10ng/ml) + LIF neutralizing antibody (1mg/ml). Growth evaluation consisted of follicular counts and classification, Ki67 immunohistochemistry, 17b-estradiol (E2) and antimullerian hormone (AMH) measurements in spent media samples.

Results: There were higher, albeit non-significant, primordial and developing follicles without LIF or its neutralizing antibody on both matrices with a parallel non-significant decrease in atretic follicles. In all other groups the levels of the atretic follicles were relatively high (~50%). E2 secretion was higher (almost at significant values) from slices cultured with LIF (100ng/ml) on hrVit than on SIS. AMH levels were detected but did not yield conclusive results. Ki67 immunostaining was identified in all growing follicles beyond the primordial stage, regardless of treatment or matrix.

Conclusions: Of the two extracellular-like matrices, hrVit seems to slightly improve the results. However, further efforts should be made to develop more beneficial matrices. Unlike studies in other mammals, LIF does not enhance human primordial follicular growth. Therefore, studies investigating the effects of other growth factors should be attempted.
Murine whole bone marrow contains various populations of cycling hematopoietic stem cells

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Background: According to the hierarchical model of stem cell biology, hematopoietic stem cells exist primarily in a dormant state. However, an alternative theory exists that views hematopoietic stem cells as dynamic entities rather than quiescent. In the continuum model, it is believed that hematopoietic stems cells are fluxing through cell cycle, continuously shifting their surface epitopes as well as their phenotypes. Currently, the focus of traditional stem cell isolation procedures is on highly purified populations of hematopoietic stem cells. However, we argue that such isolation procedures do not account for cycling cells located within unseparated bone marrow and its various sub-fractions.

Methods: Whole bone marrow was extracted from B6.SJL mice. This marrow was density depleted and lineage depleted. Throughout the lineage depletion, unseparated whole bone marrow (WBM), lineage-positive cells (Lin+), lineage-negative cells (Lin-), and highly purified long-term hematopoietic stem cells (LT-HSC; Lin-/-c-kit+/Sca-1+/CD150+/CD41-/CD48-) were collected. These cell populations were individually incubated with thymidine, tritiated thymidine, or no thymidine, and competitively engrafted into lethally irradiated C57BL/6J mice. Since thymidine is selectively incorporated into growing DNA strands, any stem cell going through S-phase during incubation with the tritiated thymidine would be killed, leading to a concomitant reduction in engraftment within that group. Post-transplant, peripheral tail vein blood was collected, stained with antibodies, and subjected to flow cytometry.

Results: Statistically significant decreases in engraftment were observed within the WBM, Lin+, and Lin- groups when they were incubated with tritiated thymidine. There was no statistically significant difference in engraftment within the LT-HSC group.

Conclusions: There are populations of cycling hematopoietic stem cells that exist within unseparated whole bone marrow as well as its sub-fractions. These cycling stem cells are lost with conventional stem cell isolation techniques. We suggest that stem cell isolation procedures performed in the future account for these populations of cycling stem cells.
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