

Hepatic Site-1-Protease knockdown improves diet induced hyperlipidemia and steatosis

Nonalcoholic fatty liver disease is regarded as the most common chronic liver disease worldwide. Pathogenesis of NAFLD starts with accumulation of triglycerides, and progresses hepatocellular injury and inflammation. Numerous studies have implicated elevated hepatic de novo lipogenesis (DNL) in the pathogenesis of nonalcoholic fatty liver disease. Particularly upregulation of SREBP1c, the major transcription factor controlling DNL, has been documented under conditions of hyperinsulinemia and nutrient overload. Deficiency in cyclic AMP binding protein H (CREBH) or Activating transcription factor 6 (ATF6) also influences the development of hepatic steatosis. **Site-1-Protease (S1P)** activates lipogenic master transcription factor SREBP (Sterol Regulatory Element Binding Protein), and is also a candidate protease for the processing of two other membrane-bound master transcription factors involved in lipid metabolism; ATF6 and CREBH. Using conditional gene knockout approach, we have generated two models of hepatic S1P knockdown (KD), one with adenoviral vector-mediated liver transduction of Cre (S1P Cre) and the other by crossing with liver specific albumin cre mice (S1P L-KD) both of which are defective in activation of SREBP and downstream target genes. S1P Cre mice had lower hepatic triglycerides accumulation and lower hepatic free fatty acids in comparison to control mice when challenged with a 60% high fat diet for 8 weeks. Plasma lipids were lower in S1P Cre mice. De novo TG and FA synthesis rates were reduced in S1P Cre mice and there was a trend towards lower fatty acid oxidation. Surprisingly, hepatic S1P deficiency reduced adiposity and body weight gain. Similar results were obtained in the S1P L-KD mice model. In summary, hepatic S1P deficiency confers resistance to high fat diet-induced steatosis and obesity. These studies provide evidence that pharmacological inhibition of hepatic S1P is a potential drug target for treating these metabolic diseases.

Community Dwelling Lebanese Elders: Phase 1: Teaching the Basics of Geriatric Care and the Use of Geriatric Health Screening Tools to Social workers of the Ministry of Social Affairs.

Introduction: Of the world's growing geriatric population, 75% resides in developing countries, including Lebanon. With only 7 geriatricians in all of Lebanon, and a culture of underutilization of primary care physicians, many elderly have been denied ideal care. Training social workers (SW) to bridge the gap between elders and their physicians is a step to improving Lebanon's fragmented healthcare system.

Aims: With the aid of the Ministry of Social Affairs (MoSA), the authors invited 56 mid-level SW to participate in a one-day workshop aimed at increasing their knowledge of normal aging, Alzheimer's disease (AD), dementias, geriatric depression and elder abuse. Authors addressed psychosocial elder care, safety, common geriatric scales, working with families of AD patients, and improving Quality of Life (QOL) of community dwelling elders.

Methods: Authors used mixed methods to collect demographic data, administered a 6-question pre and post test, and 2 questions assessing the perceived success of the workshop. Quantitative data analysis was conducted using SPSS 17, and qualitative analysis evaluated feedback themes.

Results: 23 SWs attended on Days 1 and 2 (total 56). Age distribution was as follows: 25-34(65.8%), 35-44(17.1%), 45-54(7.3%), and 55-64(9.8%). 100% were women. 71.8% had 2-3 elder cases/week, and 28.1% had 4-6 elder cases/week. Older SW tended to have more elder cases and felt the workshop helped them gain a deeper knowledge of elder care and AD, increased their sense of responsibility towards elders. Younger SW felt the workshop was useful in understanding AD, defining SW responsibilities, and instating radical change.

Conclusions: Phase 2 of the initiative will involve monthly training of highly skilled SW to increase competency in working with the elderly. The authors hope to guide MoSA in choosing eligible SWs using the data presented. Older SW with experience dealing with the elderly and younger SWs who felt they benefited from training may be ideal candidates.

Towards a real-time interface between an *in vivo* neurophysiological data source a biomimetic brain model and a robotic arm

Towards a real-time interface between an *in vivo* neurophysiological data source, a biomimetic brain model and a robotic arm Computational models are an essential tool for making sense of neurophysiological data and for inferring the complex dynamics underlying brain function. New systems are being developed that interface biomimetic models of the brain with *in vivo* data acquisition devices and prosthetic/robotic limbs. These systems provide a test-bed for neuroprosthetic rehabilitative solutions and medical devices for the repair and enhancement of neuronal networks. Additionally, utilizing biomimetic neuronal modeling in brain-machine interfaces offers the possibility of for finer control of prosthetics, and the ability to better understand the brain's own electrical signals. These closed-loop systems require real-time communication among an *in vivo* neurophysiological data source, a simulator-based biomimetic model, and a robotic arm. Here we propose a network-based architecture for that purpose, currently implemented as separate subsystems. Our biomimetic model (BMM) is a detailed neocortical simulation implemented in NEURON software. This biomimetic mode interacts with a Plexon MAP Server, a commercial tool to collect signals from the electrodes implanted in a macaque. Our implementation successfully delivered monkey spiking activity to the BMM via UDP, respecting real-time constraints.

We have also provided communication between the BMM and a Barrett Technology WAM robotic arm. The model is able to drive the robot arm in a motor task requiring trial-and-error convergence on a single target. A visualization tool in the remote computer displays a representation of the moving robotic arm in real time. Future work will include a closed-loop brain-machine-interface which will acquire signals from primate brain, pass to the BMM which will provide motor commands for the robotic arm. The interfaces will then pass haptic feedback in the other direction from robot to BMM to primate to modulate primate brain state and close the loop.

Towards a proper estimation of phase-amplitude coupling from time series.

It is hypothesized that phase-amplitude coupling (PAC) might play role in a multitude of brain functions including routing the flow of information, memory processing, the selection of attention and decision making. It is therefore important to develop robust numerical analytical tools to quantify PAC. To date, several methods for PAC estimation have been proposed, however more effort is necessary for understanding the limitations of PAC estimation as well as the prior assumptions about the input data. In this study we define boundary conditions for the general PAC algorithm including filter settings for phase and amplitude estimation and time-frequency resolution of the method. Second, we explore the effects of noise and common electrophysiological artifacts on PAC estimation. Finally, we propose a new data-driven approach for unbiased parameter estimation for the PAC algorithm as well as a new method for high-resolution PAC estimation from data in short time windows. The new methods are validated and their utility for characterizing differences in brain function is demonstrated with a variety of data sets from EEG and local field potential recordings.

Hexim1 haplodeficiency enhances skeletal muscle regeneration by promoting satellite cell post-injury expansion

The native capacity of adult skeletal muscles to undergo regeneration offers a vital potential for attaining morphological and functional recovery from physical injuries and dystrophic diseases. However, the complex regulatory network underlying the process of muscle regeneration poses a challenge to the design of therapeutic interventions. We previously demonstrated that hexamethylene bis-acetamide inducible 1 (HEXIM1), an inhibitory component of the positive transcription elongation factor b (P-TEFb) complex which promotes transcription elongation of RNA polymerase II, regulated C2C12 myoblast differentiation. Here, we identify HEXIM1 as a pivotal regulator of skeletal muscle regeneration using a skeletal muscle post-injury regeneration model in mice. Hexim1 haplodeficient muscles exhibit greater mass and preserved function compared to wild type muscles after injury as a result of enhanced proliferation of satellite cells. Transplanted Hexim1 haplodeficient satellite cells expand and improve muscle regeneration more effectively than wild type satellite cells. Conversely, HEXIM1 overexpression restrains satellite cell proliferation and impedes muscle regeneration. Mechanistically, dissociation of HEXIM1 from and subsequent activation of P-TEFb are required for satellite cell proliferation and the prevention of early myogenic differentiation, and blockade of P-TEFb activation reduces satellite cell proliferation both *in vitro* and *in vivo*. In conclusion, our findings suggest a crucial role of HEXIM1/P-TEFb pathway in the regulation of satellite cell-mediated skeletal muscle regeneration and offer HEXIM1 as a potential therapeutic target for degenerative muscular diseases.

Clefting in China Over the Last Decade: 205 679 Smile Train Patients

Background: It is widely accepted that the incidence of orofacial clefts is highest among Asians. To date, there are no exact statistics in China on how many individuals with cleft deformity are present or have been surgically treated. This study reports the epidemiology and surgical procedures performed on the largest reported cohort of Chinese individuals treated for clefting. **Methods:** We conducted a retrospective review of Chinese patients who received cleft repair from 2000-2011 through the charity organization, Smile Train.

Results: Over the last decade, 205,679 patients underwent 209,169 cleft repairs through Smile Train in China. Cleft lip and palate (CLP) (42.7%) was the most common cleft type treated followed by cleft palate (CP) (32.4%) and cleft lip (24.9%). Among each cleft type, males were more commonly affected. Associated anomalies occurred in 12.8% of patients, most commonly CLP patients, and mandibular abnormalities were most frequent. The average age at surgery was 6.12 years. By 2011 the average age for primary repair decreased to 1.8 years for lip repair and 5.9 years for palate repair. The preferred unilateral lip repair technique was rotation advancement (55%) and the preferred palate repair techniques were the Von-Langenbeck (36%) and pushback (39%).

Conclusion: This study provides insight into the current epidemiology and treatment of clefting in China. Our results generally follow previously reported trends. However, more males than females presented with CP in this cohort and associated anomalies were found more commonly in CLP patients. The rate of associated anomalies fell within the previously reported range, although heart defects were most common in other studies. A small percentage of surgeons surveyed in prior reports chose the Von-Langenbeck repair. In the present study, surgeons still favored standard cleft repair techniques and although higher than generally performed, the ages at primary repair appear to be decreasing.

Analysis of CT Perfusion Parameters to Determine Thresholds for Infarct Core Ischemic Penumbra and Benign Oligemia in Patients Undergoing Endovascular Revascularization Therapy (ERT)

CT Brain Perfusion (CTP) is a powerful tool in guiding stroke therapy. In this study, we attempt to determine CTP parameters (CBF, CBV) thresholds that differentiate infarct core, penumbra, and benign oligemia in patients undergoing ERT.

Retrospective review for patients receiving ERT was performed from 05/01/07-09/30/10. Ten patients with complete datasets who underwent CTP, and delayed non-contrast CT (NCT) or MRI, >24 hrs after stroke were divided into the persistently occluded group (n=4) and the revascularized group (n=6), based on catheter angiography. CTP source images were processed by Philips. MATLAB was used to co-register perfusion maps with delayed NCT or MRI. For both groups, final infarct was outlined as ROI on the NCT or MRI. For the occluded group, the region that survived (n ROI=32) was defined as benign oligemia (BO) while infarcted tissue (n ROI=35) represented penumbra (P) plus infarct core (IC). For the revascularized group, survived tissue (nROI=35) encompassed the original BO and P while the final infarct (nROI=22) was defined as IC. Pixel-by-pixel data were graphed in histograms to show distribution of survival and infarcted pixels for the two groups in different CBV and CBF intervals (Figure 1).

In the occluded group, the number of pixels of infarcted tissue peak at CBF of 10 while the peak for survived tissue is CBF of 17 (Figure 1A & B). For the revascularized group, histograms of infarcted tissue peaks at CBF of 2 and CBV of 0.4 while the peaks for survived tissue is at CBF of 8 and CBV of 2.5, suggesting that threshold of CBF and CBV are between 2 and 8, and between 0.4 and 2.5 respectively (Figure 1C & D). Significant tissue survival was observed below CBV of 2.5 (Figure 1D).

Our histograms suggest that potentially salvageable tissue may be found below CBV values of 2.5, and as low as 0.4. Further study of these parameters in patients experiencing successful revascularization will be required to further refine these thresholds.

Restoration of Recurrent-Laryngeal-Nerve Function after Injury in a Rat Model

Outcome Objectives: Recurrent laryngeal nerve (RLN) injury occurs in 4-10% of thyroid surgeries. Spontaneous RLN regeneration takes months and is often incomplete. Lithium promotes neuronal growth *in vitro*. We developed methods to objectively detect vocal-fold impairment in the rat and tested whether systemic lithium enhances recovery after RLN injury.

Methods: The right RLN was crushed in eight adult rats, and osmotic pumps releasing either lithium or water were implanted. Eight sham-operated animals were also implanted with either lithium or water pumps. Vocal-fold motion was captured by microsuspension laryngoscopy and was measured quantitatively by image analysis at the time of surgery and at one and four weeks. Vocalizations, breathing patterns, and laryngeal electromyography were assessed at four weeks.

Results: Cessation of unilateral vocal-fold motion was observed simultaneously with every RLN crush. One week after surgery, 50% of "Crush/Water" animals exhibited full vocal-fold motion, compared to 75% of "Crush/Lithium" and 100% of the sham-operated animals. In animals with unilateral vocal-fold immobility, the quantitative analysis also revealed a subtle decrease of vocal-fold movement on the non-operated side. At four weeks after surgery, vocalizations, breathing patterns, vocal-fold motion, and electromyograms were indistinguishable amongst all groups. Lithium-treated animals weighed 5% less than water-treated controls.

Conclusion: Quantitative endoscopy is a sensitive and efficient tool for detecting vocal-fold impairment in rats. While our results might suggest enhanced recovery in lithium treated animals, all animals showed a rapid return of vocal-fold motion. Perhaps more severe nerve injury is necessary to uncover an effect of lithium on nerve regeneration.

Adherence Risk Patterns in Adult Patients with Asthma in an Inner City Cohort Over a 25 Month Period

Rationale: Non-adherence to therapy may contribute to the high prevalence and significant morbidity and mortality of asthma in inner city adults. The Adherence Estimator (AE) (Merck) is a 3 question survey assessing perceived views of medication concern, commitment and cost. We investigated patterns of adherence over a 25-month period as measured by the AE.

Methods: The AE cross-sectional survey and follow-up was conducted with outpatient adults with persistent asthma treated according to NHLBI EPR-3 guidelines. The AE is scored based on concern regarding medication harm, commitment based on perceived need of medications, and perceived financial burden due to out of pocket expenses. Scores were assessed in July 2010 and August 2012.

Results: At baseline, median total AE score for all patients surveyed was 7.81, indicating a medium risk for adherence problems (32%-75% probability of adherence). Mean scores for concern, commitment and cost were 5.61, 1.35 and 0.84 respectively, indicating mild to moderate risk per parameter for adherence problems. At follow-up, the mean total AE score was 4.10, indicating a medium risk for adherence problems. Mean scores for concern, commitment and cost were 2.65, 0.87 and 0.58 respectively, indicating mild to moderate risk per parameter for adherence concerns.

Conclusions: The risk for adherence problems did not change with standard asthma care over a 25 month period from 2010 to 2012. These findings suggest that new strategies are warranted to address adherence concerns. Increased adherence to therapy may improve morbidity and mortality in the inner city population.

Waqas Shaikh

Research Advisors: Michael Joseph; Stephen W. Dusza Susan A. Oliveria
Allan C. Halpern; Alan C. Geller; and Martin A. Weinstock

Melanoma thickness and survival trends in the United States 1989 to 2009

Melanoma is the 5th most common cancer in the US. Given thickness is the key factor in melanoma prognosis, we sought to characterize trends in thickness and survival in order to provide insight into impacting the two decade long stubbornly stable melanoma mortality. We conducted a retrospective cohort analysis of invasive melanomas in the SEER-9 registries from 1989 to 2009. 98,498 melanomas were identified. Incidence per 100,000 person-years increased (13.9 to 21.9, $P < 0.001$), ultimately fatal incidence remained stable (2.3 to 2.1, $P = 0.20$), and 5-year relative survival increased (87.9 to 90.6%, $P < 0.001$). Incidence rose across all thickness groups. Geometric mean thickness decreased from 0.77 to 0.65 mm with an average 3.05% (95% confidence interval [CI]: 2.72-3.37%) decrease every 3 years. In subgroup analysis, thickness significantly decreased among thin tumors (0.01-1.00 and 1.01-2.00 mm), both genders, all age groups, non-Hispanics, whites, all body sites and most histologic subtypes. However, thickness significantly increased among thick tumors (2.01-4.00 and > 4.00 mm) and nodular melanoma. No change was observed among minorities, Hispanics and acral lentiginous melanoma. Melanoma-specific survival significantly improved (hazard ratio 0.89, 95% CI: 0.88-0.91) per 3-year time period in multivariable analysis. Improvements in survival occurred across all subgroups except among minorities, facial tumors, and the nodular, lentigo maligna and acral lentiginous subtypes in which there was no significant change. Melanoma incidence across all thickness groups is increasing. Thinner lesions are getting thinner but thicker lesions are getting thicker. Melanoma survival is improving independent of thickness with possible explanations including increased detection of indolent disease or improvements in therapeutics. Positive trends in thickness and survival have not been experienced by minorities and those with nodular and acral lentiginous histologic subtypes.