Daniel Turnberg

The Daniel Turnberg Memorial Fund was established by Edna and Leslie Turnberg following the loss of their son Daniel in a plane crash in Africa at the age of 37. Daniel had already made a mark as a bright young doctor and as a medical researcher and was destined for a future full of promise. A graduate of Leeds University, he trained first in hospitals in Yorkshire before starting his specialist training in renal medicine in a series of London teaching hospitals. He went on to obtain his PhD for his research into the role of the immune system in kidney disease at Imperial College and the Hammersmith Hospital before taking up a lectureship in renal medicine at the Royal Free Hospital in 2006.

But above all his academic achievements it was the universal view of his kind and gentle nature, his compassion for others and his sense of fun and enthusiasm for everything that life had to offer that earned him the love, respect and admiration of his patients, colleagues and wide circle of friends. In setting up this fund his parents hope to continue a keen interest he had in international medicine and in encouraging greater understanding between Israel, the Middle East and the UK.

The Academy *of* Medical Sciences

The Academy of Medical Sciences is the independent body in the UK representing the diversity of medical science. Our mission is to promote medical science and its translation into benefits for society. The Academy's elected Fellows are the UK's leading medical scientists from hospitals, academia, industry and the public service. We work with them to promote excellence, influence policy to improve health and wealth, nurture the next generation of medical researchers, link academia, industry and the NHS, seize international opportunities and encourage dialogue about the medical sciences.

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The Academy of Medical Sciences
41 Portland Place
London W1B 1QH

+44 (0)20 3141 3200

@acmedsci

info@acmedsci.ac.uk
www.acmedsci.ac.uk

The Academy *of* Medical Sciences

Daniel Turnberg Travel Fellowship Scheme

Alumni Conference

9 – 11 November 2016

Hilton Cyprus, Nicosia

www.acmedsci.ac.uk

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Daniel Turnberg Travel Fellowship Scheme

The Daniel Turnberg Travel Fellowship Scheme is a unique scheme that encourages scientific interchange and international understanding between the UK and Israel and the Middle East. The programme offers travel Fellowships that provide wonderful opportunities for young medical researchers to meet experts in their field and plan research collaborations.

Turnberg grants provide airfare and a subsistence allowance of up to £3,500 for a period of one month or up to £9,000 for three months. To date 190 researchers have been awarded Travel Fellowships through the scheme since 2009.

The Scheme is made possible by the support of many generous donors to the Daniel Turnberg Memorial Fund and we are very grateful to them for that.

We will be taking photographs at the conference and posting on social media. If this is of concern to you and you do not wish to have your photograph taken, or be referenced in social media please make yourself known to an Academy staff member at the start of the meeting.

Welcome

We are delighted to welcome you to this first Daniel Turnberg Travel Fellowship Scheme Alumni Conference.

During the last eight years the scheme has supported over 190 Fellows from across the Middle East. This is the first occasion when it has been possible to bring together a large number of you to tell us about the research in which you have been engaged since your Fellowship.

We have had the privilege of meeting many of you over the years and hearing about your exciting work and now we have a marvelous opportunity to hear more.

I hope that you too will be able to take advantage of the occasion to meet Fellows from other countries, to hear about the work of others and perhaps to think about ways in which collaboration may be enhanced.

Thank you for joining us and we wish you a fruitful and enjoyable couple of days.

Leslie and Edna Turnberg
Lord and Lady Turnberg of Cheadle

Daniel Turnberg Memorial Fund

Agenda

Wednesday 9 November 2016

Arrivals and registration		
19:00	Welcome reception and dinner	Poolside restaurant
	Welcome address Lord Turnberg of Cheadle FMedSci, Chair Daniel Turnberg Memorial Fund and Daniel Turnberg Travel Fellowship Scheme Selection Panel	

Thursday 10 November 2016

07:30	Breakfast	Main restaurant
09:00	Welcome and introduction to the conference Lord Turnberg of Cheadle FMedSci, Chair	Ballroom A
09:05	Introduction to the Academy of Medical Sciences Dr Helen Munn, Executive Director, Academy of Medical Sciences	
09:15	Keynote Address: Challenges in Translational Medicine Sir Keith Peters FRS FMedSci FLSW	
09:45	Oral Plenary Session 1 *Speakers will give a 10 minute presentation followed by 5 minutes of discussion and questions*	
09.45	Christopher Adams Keele University Abstract 44 *Multimodal Magnetic Nanoparticles for Regenerative Neurology*	
10.00	Iyad Ali An-Najah National University Abstract 18 *Influence of processing and storage conditions on the antioxidant properties of fruit juices*	
10.15	Sharon Anavi Goffer Ariel University Abstract 54 *A role for the cannabinoid CB2 receptor in schizophrenia*	
10.30	Azmy Faisal Alexandria University Abstract 85 *Effective Bronchoscopic Lung Volume Reduction Accelerates Exercise Oxygen Uptake Kinetics in COPD*	
10.45	Yuval Ramot Hadassah – Hebrew University Medical Center Abstract 20 *Neuroendocrine regulation of keratin expression and stem cell biology: a novel therapeutic strategy for skin and hair disorders*	
11.00	Tea and coffee break	
11.30	Poster Session 1	Ballroom B
12.30	Lunch	Main restaurant
13.30	Oral Plenary Session 2	Ballroom A
13.30	George Daoud American University of Beirut Abstract 76 *Transcriptomic profiling of trophoblast fusion using BeWo and JEG-3 cell lines*	
13.45	Mario Giardini University of Strathclyde Abstract 78 *Optical power transfer for the powering of active brain implants*	
14.00	Rula Abdul Ghani Al-Quds University Abstract 71 *Overcoming Resistance to the CDK4/6 Inhibitor Palbociclib in ER+ Breast Cancer*	
14.15	Michal Bernstein Tel Aviv University Abstract 64 *Neural Model of Dynamic Face Processing*	
14.30	Nancy Hakooz University of Jordan Abstract 72 *CYP4F2 Genotyping in Jordanian Population*	
14.45	Mohamed Mandour Suez Canal University Abstract 37 *NK cell activation mediates protection against mesothelioma in a mouse model of viral infection*	

Agenda

15.00	Benyamin Ladeuix Weizmann Institute of Science Abstract 81 *Oxygen cycles synchronize clock on a Hif1a dependent manner*	
15.15	Tea and coffee break	
15.30	Poster Session 2	Ballroom B
16.30	Working together *Case study on the Arava Institute for Environmental Studies* Maya Negev, University of Haifa	Ballroom A
16.50	Closing remarks Lord Turnberg of Cheadle FMedSci	
17.00	Break	
18.00	Drinks Reception	Akamas Room
18.15	Presentation	Akamas Room
19.00	Dinner Dinner speaker Professor Raymond Tallis FMedSci	Akamas Room

Friday 11 November 2016

07:30	Breakfast Breakfast runs from 07.30-09.00	Main restaurant
10.00	Check out of hotel bedrooms	
10.00	Conference closes	
Departures		

Speaker biographies

Lord Turnberg of Cheadle FMedSci

Leslie Turnberg was Professor of Medicine at the University of Manchester from 1973 to 1997, and consultant gastroenterologist at Hope Hospital, Salford and Dean of the Faculty of Medicine from 1986 to 1989. He was President of the Royal College of Physicians (1992 to 1997) and Chairman of the Academy of Medical Royal Colleges (1994 to 1996). He was President of the Medical Protection Society (1997 to 2007) and Chair of the Board of the National Centre for Replacement, Reduction and Refinement of Research in Animals (2004 to 2007). He was Vice President of the Academy of Medical Sciences (1998 to 2004) and served on the House of Lords Select Committee on Science and Technology (2001 to 2005).

Lord Turnberg is Chair of the Daniel Turnberg Memorial Fund and Travel Fellowship Scheme Selection Panel. He acts as Scientific Advisor to the Association of Medical Research Charities and is a Trustee of The Wolfson Foundation, The Foulkes Foundation, Ovarian Cancer Action, and a number of other charities. He was knighted in 1994 and raised to a Peerage in 2000.

Dr Helen Munn

Dr Helen Munn is the Executive Director of the Academy of Medical Sciences – the UK's national academy representing the full spectrum of medical science, from basic research through clinical application to healthcare delivery. The Academy's 1200 elected Fellows are the UK's most talented biomedical and health researchers, working to promote medical science and its translation into benefits for society. The Academy of Medical Sciences is a committed member of the Federation of European Academies of Medicine.

Helen joined the Academy's policy team in 2004, becoming Executive Director in 2009. Since then she has overseen a major expansion in the Academy's resources, profile and impact, including a successful £5 million fundraising appeal to establish the Academy's first headquarters in 2010, influential policy reports, leading-edge public dialogue exercises, and a portfolio of innovative grant and mentoring schemes to support early career researchers in the UK and overseas. Prior to joining the Academy, Helen worked at the UK Parliamentary Office for Science & Technology and in the BBC Science Team. She followed her undergraduate degree from The Queen's College, Oxford with a PhD in molecular endocrinology from the University of Edinburgh.

Sir Keith Peters FRS FLSW FMedSci

Emeritus Regius Professor of Physic, University of Cambridge; Consultant in Clinical Science and Translational Medicine to the Francis Crick Institute, and Senior Consultant in R&D to GlaxoSmithKline.

Sir Keith has been a notable exponent of clinical science in the UK, and Cambridge, under his leadership, became a major centre for clinical research. As Interim Director of the MRC's National Institute for Medical Research he initiated discussions which led to the establishment of the UK Centre for Medical Research and Innovation, the Francis Crick Institute, and has been involved in Singapore medicine in various ways. He was a founder Fellow of the Academy of Medical Sciences and its second President, is a Fellow of the Royal Society and a Foreign Member of the National Academy of Medicine of the USA.

His research has been on elucidation of immunological mechanisms underlying diseases of kidney and blood vessels, in particular on the roles of the complement and clotting pathways in glomerulonephritis. His research on antibody mediated crescentic nephritis led to the introduction of plasma exchange and immunosuppression in autoantibody mediated diseases, and plasma exchange remains an established therapy in severe autoimmune disorders.

Professor Raymond Tallis FMedSci

Raymond Tallis is a philosopher, poet, novelist and cultural critic, and a retired physician and clinical neuroscientist.

For the last decade Raymond has been a full-time writer. He has published fiction, poetry, and 25 books on the philosophy of mind, philosophical anthropology, literary and cultural criticism The Black Mirror. Fragments of an Obituary for Life – has been widely praised and Aping Mankind (2010) is being reissued in 2016 as a Routledge Classic. The Mystery of Being Human: God, Free Will and the NHS has just been published.

He is a Fellow of the Academy of Medical Sciences and has honorary degrees of DLitt and Litt.D. for contributions to the humanities and DSc for contributions to medicine.

Speaker biographies

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Ordered by abstract number

Abstract: 0018 Oral Presentation

Influence of processing and storage conditions on the antioxidant properties of fruit juices

Iyad Ali, Qamar Mohamed, Dua'a Dwaik, Ghosson Aqel
Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine

BACKGROUND: The food composition tables, which are necessary tools for epidemiological and nutritional studies, are really only representative of foodstuffs consumed in their raw state. They cannot take into consideration the fact that concentration of nutrients and their biological activity may be changed by environmental variables as well as by processing. This aspect is of great importance considering that only a small amount of fruit and vegetables are consumed in their raw state, whilst most of them need to be processed for safety, quality and economic reasons.

METHODS: Fully matured and high-quality fruits of tomato, lemon, orange, grapefruit, and guava were used. Fresh fruits were thoroughly washed, peeled, cut into small pieces (tomato and guava were not peeled). The freshly squeezed juice was obtained by careful hand-squeezing of fruits. The collected juices were filtered through 4-fold muslin cloth, and the pulp free juice was stored in clean containers.

The radical scavenging ability of fruit juices was tested on the basis of the radical scavenging effect on the DPPH free radical. The fruit juices (12.5 µL to 100 µL/mL) were prepared in methanol. In clean and labeled test tubes, 2 mL of DPPH solution (0.002% in methanol) was mixed with 2 mL of different concentrations of fruit juices separately. The tubes were incubated under different experimental conditions and the optical density was measured at 517 nm. The scavenging activity of the juices was calculated using the formula: Scavenging activity (%) = [(A – B) / A] x 100, where A is absorbance of DPPH and B is absorbance of DPPH and fruit juice combination.

Results: Free radical scavenging activity of juices of citrus fruits was determined by DPPH free radical scavenging assay. In this assay, the antioxidants reduce the DPPH radial (purple color) to a yellow colored compound, Diphenylpicrylhydrazine. A dose dependent scavenging of free radical was observed, and different types of fruit juices showed different scavenging activity. After various fruit juices were incubated at 4 oC for 4 days, it was found that the highest radical scavenging activity was shown by lemon juices followed by orange juices, grapefruits, and mandarin. After 4 days of incubation under sun light, orange juices retain their antioxidant activity after incubation under sunlight. Lemon juices, mandarin and grapefruits lost more than 70% of their antioxidant activity. Finally, the effect of temperature on the antioxidant activity of different juices was evaluated. Even after 60 minutes of incubation in boiling water (90 oC) all juices retain their antioxidant activity.

Conclusions: Domestic and commercial food storage typically has drastic effects on the structural integrity of fruits and vegetables. The health-promoting capacity of fruit strictly depends on their processing history and storage conditions. These aspects has been generally neglected or scarcely considered in present nutritional and epidemiological studies. It is believed that the implications of this challenging and rapidly advancing area may contribute to enhanced industrial competitiveness as well as consumer health and well-being.

Abstract: 0020 Oral Presentation

Neuroendocrine regulation of keratin expression and stem cell biology: a novel therapeutic strategy for skin and hair disorders

Yuval Ramot
Department of dermatology, Hadassah - Hebrew University Medical Center, Jerusalem, Israel

BACKGROUND: Keratins are intermediate filaments that provide mechanical stability to epithelial cells, and, thus, are crucial as key components of the epidermal barrier function. However, keratins have many additional functions, such as the control of epithelial cell proliferation, differentiation, migration, apoptosis, wound healing, carcinogenesis, hair follicle cycling, and even immunomodulation. Therefore, understanding the hormonal controls of keratin expression is essential in epithelial biology and pathology and in the skin and hair. The skin and hair are known to be a source and target of numerous neurohormones, neuropeptides, and neurotransmitters. Nevertheless, little is known about the neuroendocrine control of human keratin expression. Such controls can be harnessed to treat a large number of skin and hair conditions.

METHODS: Microdissected human hair follicles, human scalp skin, outer root sheath keratinocytes and HaCaT keratinocytes were treated in serum-free organ culture for 12 hours to 6 days with different concentrations of thyrotropin-releasing hormone (TRH), thyroid stimulating hormone (TSH), prolactin and arachidonoyl-chloro-ethanolamide (ACEA), a cannabinoid receptor 1 (CB1)-specific agonist. Additionally, prolactin receptor and CB1-specific antagonists were also added to the culture media. The effects of these neurohormones were assessed using microarray analyses, quantitative immunohistomorphometry and quantitative PCR.

RESULTS: Prolactin, TRH and TSH strongly regulate the gene and protein expression of selected keratins in the outer root sheath of the hair follicle and hair keratins. Some of these changes can explain the hair shaft growth-promoting effects of TRH and the hair growth inhibitory effects of prolactin. Both neurohormones also change expression of selected keratins in the epidermis. Of special interest is the upregulation of the epithelial stem cell-associated keratins K15 and K19 by prolactin, a finding that suggest a hitherto unrecognized role for prolactin in human epithelial stem cell biology. ACEA decreased expression of K6 and K16, markers for hyperproliferative conditions of the skin, at the gene and protein levels, suggesting a role for the endocannabinoid pathway in inflammatory skin conditions and wound healing.

CONCLUSIONS: This study shows that TRH, TSH, prolactin, and endocannabinoids profoundly modulate human keratin gene and protein expression in human keratinocytes in situ and that some neurohormones, such as prolactin, even modulate human epithelial stem cell-associated signature keratins. These effects could be harnessed for different clinical applications, such as improvement of wound healing, amelioration of inflammatory skin conditions (e.g. psoriasis), treatment of keratin-related hereditary skin disorders, enhancement of hair growth and protection of stem cells from inflammation- or chemotherapy-induced damage, which might result in permanent hair loss. These findings make the neuroendocrine-keratin connection an exciting research frontier located at the interface of neuroendocrinology, epithelial biology, and dermatology.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0037 Oral Presentation

NK cell activation mediates protection against mesothelioma in a mouse model of viral infection.

Mohamed Ahmed Fouad Mandour[1], Jean Paul Coutelier[2]
[1]Department of Clinical Pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
[2]Unit of Experimental Medicine, De Duve Institute, Université Catholique de Louvain, Brussels, Belgium

INTRODUCTION: Lactate dehydroganase-elevating virus (LDV) is a mouse nidovirus, usually non-pathogenic, but that can deeply modulate the mouse immune microenvironment. Acute LDV infection is followed by a burst in secretion of pro-inflammatory cytokines (i.e. IL-6 and IL-12). This results in NK cell activation responsible for strong, but transient IFN- γ production. Through interaction with Toll-like receptor 7, LDV also triggers production of type I IFNs by plasmacytoid dendritic cells. So, LDV infection provides a unique model to analyse the consequences of infection on alterations of the host immune microenvironment.

Malignant mesothelioma (MM) is an asbestos-related aggressive tumor developed from the mesothelium lining the serosal cavities (pleura, pericardium and peritoneum). This malignancy has a very poor prognosis with a mean survival time of 9 months from diagnosis. Different therapeutic strategies have not improved the prognosis. Recently, several data aroused the notion that MM is susceptible to immunotherapy with a proposed role for innate immune effector cells such as natural killer (NK) cells in tumor surveillance. Our objective was to determine the effect of virally-triggered modulation of the immune microenvironment on mesothelioma development, by using a mouse model.

METHODS: MM was induced in Balb/C mice by intraperitoneal injection of AB1 mesothelioma cell line. The tumor growth and survival was investigated in mice infected by lactate dehydrogenase-elevating virus (LDV). The viral induced immunomodulation of the host microenvironment and the underlying mechanisms were investigated using a panel of antibodies. Furthermore, survival was investigated in mice challenged with some TLRs ligands.

RESULTS: Acutely infected animals were significantly protected against tumor development. The protection by viral infection was attributed to the activated NK cells. However, increased NK cells cytotoxicity was not the underlying mechanism for this protection. The tumor cells were highly sensitive to direct cytolytic effect of IFN- γ in culture. Additionally, TLRs stimulation significantly protected the mice.

CONCLUSIONS: Our results indicated that modulation of the mouse immune microenvironment (specially innate immune system) following a non-pathogenic viral infection could protect the mouse against mesothelioma through non- specific stimulation of NK cell activation. TLRs stimulation along the course of infections might play also an important role.

Abstracts

Abstract: 0044 Oral Presentation

Multimodal Magnetic Nanoparticles for Regenerative Neurology

Christopher Adams[1], Liron Limor Israel[2], Stella Ostrovsky[2], Arthur Taylor[3], Harish Poptani[3], Jean Paul Lellouche[2], Divya Chari[1]
[1]Institution for Science and Technology in Medicine, Keele University, Newcastle-under-Lyme, UK
[2]Department of Chemistry, Bar-Ilan University, Tel-Aviv, Israel
[3]Centre for Pre-Clinical Imaging, University of Liverpool, Liverpool, UK

BACKGROUND: Magnetic nanoparticles (MNPs) offer considerable benefit as multimodal tools for cell transplantation as they can (1) genetically engineer cells to produce repair enhancing proteins and (2) act as labels for non-invasive and post-mortem cell detection enabling researchers to track biodistribution and survival of cells. Despite this promise, there is a critical clinical, commercial and scientific gap in the development of multimodal MNPs (which can achieve genetic engineering and cell labelling) for neural cell applications.

METHODS: To identify multimodal MNPs with potential for use in neural cells, we used a systematic screen to test MNPs of varying chemistries for their multifunctionality in neural stem cells (NSCs; a cell population of high clinical relevance for central nervous system disorders). These particles were all based on a magnetic core previously shown to cause contrast for magnetic resonance imaging (MRI), a widely available non-invasive medical imaging platform. Six different surface coatings (which surround the core) were tested using chemistries known to be able to bind nucleic acids for cell delivery.

RESULTS: We proved for the first time that MNPs (specifically those coated with polyethylenimine and a novel oxidised polyethylenimine/alginic acid hybrid) could safely genetically engineer NSCs whilst also facilitating MRI detection of labelled cells. Engineered NSCs can still generate their daughter cells (crucial for cell replacement strategies) and retain expression of the introduced gene (green fluorescent protein; shown in Figure 1).

CONCLUSIONS: Our results indicate the potential of employing multimodal MNPs as bioengineering tools for neural cell therapies (for simultaneous gene delivery and cell tracking). Importantly, the particles were designed with materials that are routinely used in the clinic already, such as iron oxide (used as a contrast agent for lymph node and bowel MRI) and Cerium salts (widely used in the clinic as an anti-emetic) indicating their translational relevance.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0054 Oral Presentation

A role for the cannabinoid CB2 receptor in schizophrenia

Alex Naftaly[1], Jürg Gertsch[2], Ester Fride[1], Sharon Anavi Goffer[3]
[1]Department of Behavioral Sciences, Ariel University, Ariel, Israel
[2]Institute of Biochemistry and Molecular Medicine, University of Bern, Bern, Switzerland
[3]Department of Behavioral Sciences, Ariel University, Ariel, Israel; School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, UK

Schizophrenia is one of the most important forms of psychiatric illness, affecting young people. This disease is associated with deficits in cognitive function, and with anxiety and depression. These symptoms are enhanced by the consumption of cannabis, suggesting the involvement of a signalling system in the brain which is sensitive to cannabis and cannabis-mimicking (cannabinoid) drugs. Alterations in some components of the endogenous cannabinoid system have been observed in schizophrenic patients. Recent studies have focused on the contribution of the 'non-psychoactive' cannabinoid CB2 receptor to disease aetiology. The inhibition of the glutamate NMDA receptor in mice induces impairment of emotional and cognitive functions, and alterations in the sensorimotor gating which resembles human schizophrenic behaviour. We have shown that postnatal administration of phencyclidine (PCP), an NMDA antagonist, leads to behaviour paradigms that are associated with schizophrenia. Our study is focused around the effects of CB2 selective ligands in the PCP model of schizophrenia. The results of this study further support a role for the cannabinoid CB2 receptor in schizophrenia. Identifying the role of CB2 receptor in the pathophysiology of the disease may generate a new class of drugs to treat schizophrenia.

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Abstracts

Abstract: 0064 Oral Presentation

Neural Model of Dynamic Face Processing

Michal Bernstein[1], Yaara Erez[2], Idan Blank[3], Galit Yovel[1]
[1]Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel
[2]Cognition and Brain Sciences Unit, Medical Research Council, Cambridge, UK
[3]Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA

Introduction: The current dominant neural face processing model (Haxby et al., 2000, 2007) includes three 'core areas': the fusiform face area, FFA, the occipital face area, OFA, and the posterior superior temporal sulcus face area, pSTS-FA. This model suggests that the FFA processes invariant facial aspects, such as identity or gender, whereas the pSTS-FA processes changeable aspects such as facial expression. While this model focuses on static face processing, recent studies using dynamic face stimuli reveal that the FFA shows similar responses to dynamic and static faces while the pSTS-FA shows a much stronger response to dynamic than static faces (Fox et al., 2009, Pitcher et al., 2011, 2014). Given the dynamic nature of changeable as opposed to invariant facial aspects, and in light of the recent findings showing differential sensitivity to motion in the different face areas, the aim of the current study was to propose a comprehensive model which accounts for both the sensitivity to changeable and invariant aspects and the sensitivity to motion and form in the dorsal and ventral face areas, respectively (for a recent review see Bernstein and Yovel, 2015).

Methods: In this fMRI experiment we presented static and dynamic faces while subjects performed a task that examines an invariant aspect (gender) or a changeable aspect (expression). The same stimuli were used for both tasks, counterbalanced between subjects. We assessed the fMRI responses in the face areas, as well as the motion sensitive area MT. We also examined functional connectivity between these areas.

Results and Conclusions: Univariate and multivariate analyses revealed sensitivity to motion in area MT and pSTS-FA, but not in the OFA and FFA, for both tasks. MT and pSTS-FA also showed a similar higher response to the expression than the gender task. Since MT is not a face-selective area, and is not expected to be involved in the processing of one facial aspect more than another, the similar pattern of response between MT and pSTS-FA suggests that the response of the pSTS-FA to facial expression reflects sensitivity to motion rather than expression per se.
Connectivity results showed that the OFA and FFA are strongly correlated with each other, and much less with the pSTS-FA, suggesting different systems for motion and form processing. Area MT was correlated with pSTS-FA, but also with the OFA and FFA, possibly allowing for 'form-from-motion' analysis (O'Toole et al., 2002).

Our results suggest an integrated model of face processing, in which the pSTS-FA is primarily processing facial motion, and responds strongly to changeable facial aspects as a result of their dynamic nature. The FFA and OFA on the other hand are sensitive to face form, regardless of whether the face is moving or not and regardless of task. This is the first work that integrates the two main properties of the dorsal and ventral face areas, their sensitivity to motion or form and to changeable or invariant aspects, and therefore provides a more comprehensive understanding of the functional architecture of the face processing system in the human brain.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0071 Oral Presentation

Overcoming Resistance to the CDK4/6 Inhibitor Palbociclib in ER+ Breast Cancer.

Katia Bouchekioua Bouzaghou[1], Rula Abdul Ghani[2], Catherine Lenihan[1], Alice Shia[1], Juliette Chupin[1], Peter Schmid[1]
[1]BARTS Cancer Institute, Queen Mary University of London, London,UK
[2]Department of Biochemistry, Faculty of Medicine,AL-Quds University.Jerusalem,Palestine: BARTS Cancer Institute,London,UK

Dysregulation of the cyclin D-CDK4/6-Rb axis occurs in a substantial proportion of ER-positive (ER+) breast cancers and has been linked with endocrine resistance. Adding the CDK4/6 inhibitor palbociclib to endocrine treatment has led to a substantial improvement of the outcome of patients with ER+ metastatic breast cancer. However, with the increasing clinical use, acquired resistance to palbociclib is merging as a new major clinical challenge and understanding of resistant mechanisms will be crucial. We aimed to characterise the mechanisms of resistance using an in vitro model of acquired resistance to palbociclib in ER+ breast cancer cell lines. The present work addresses whether palbociclib still has target effects and/or residual activity in resistant cells and to study if palbociclib resistance might be associated with a more aggressive phenotype.
Using long-term culture with palbociclib, we have established MCF7 and T47D cell lines with 8-10 fold increased IC50 values as a model of acquired resistance. Characterization of resistant cell lines revealed that resistant cells have an altered morphology and upregulate the Rho/Rac pathway indicating changes in cytoskeletal organisation and potentially a more invasive phenotype. Palbociclib resistant cells have developed a more aggressive phenotype with increased migration and invasion Whilst palbociclib has sustained target effects and anti-proliferative activity during early stages of resistance, these effects gradually diminish during later stages of acquired resistance. Resistant cells have multiple signalling alterations, including upregulation of alternate cell cycle pathways, inhibition of ER signalling and activation of PI3K/AKT. In palbociclib resistance, the PI3K/AKT/mTOR pathway can be targeted therapeutically by co-treatment with CDK4/6 inhibitors and PI3K/AKT inhibitors

Abstract: 0072 Oral Presentation

CYP4F2 Genotyping in Jordanian Population

Nancy Hakooz[1], Said Ismail[2]
[1]Faculty of Pharmacy-University of Jordan, Faculty of Pharmacy-Zarqa University
[2]Faculty of Medicine-University of Jordan

Background/OBJECTIVES: Warfarin is one of the most used oral anticoagulants for the treatment of both arterial and venous thromboembolitic diseases (1). Many genetic and environmental factors influence warfarin dose, such as age; height and polymorphism of CYP2C9 and VKORC1 (2). More recently CYP4F2 polymorphism has been reported to affect warfarin dose (3). The objective of this study was to investigate the frequency of the CYP4F2 (rs2108622) genotypes in Jordanian population.

METHODS: Blood samples were used from healthy Jordanian subjects (n=241; 123 male and 119 female). DNA was extracted from blood using EZNA Blood DNA kit (Omega Bio-Tek). All DNA samples were amplified by PCR. The amplification product was digested using PVUII.

Results and DISCUSSION: Genotype and allele frequency were matched to expectation by Hardy-Weinberg Equilibrium. The frequency of subjects with wild-type CYP4F2 (CC) was 24.9% while the most frequent genotype was the heterozygous (CT) with a frequency of 55.2%. Conversely, the frequency of the homozygous (TT) was 19.9%.
To our knowledge, this is the first study to investigate the CYP4F2 genotypes in the Jordanian population. The frequencies obtained in this study are similar to Turkish, Egyptian and Indians. Conversely, the frequency of the homozygous (TT) was much higher (19.9%) than that reported in Malays, Chinese, African American and Hispanic (2.2, 4.6, 1.3 and 5.3% respectively).

CONCLUSION: As many studies report that the CT/TT genotype carriers require a significantly higher dose of warfarin than the CC genotype groups (4), the results of this study suggest that the CYP4F2 genotyping can be used in the genetic testing to determine the warfarin dose as most of the Jordanian population (80.1%) are carriers of these genotypes.

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Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0076 Oral Presentation

Transcriptomic profiling of trophoblast fusion using BeWo and JEG-3 cell lines.

Georges Daoud[1], Manu Vatish[2]
[1]Department of Anatomy, Cell Biology and Physiological Sciences
[2]Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, UK

The human placenta, or afterbirth, is an organ that establishes, maintains, and regulates pregnancy. The trophoblast cells form a specialized barrier characterized by extensive placental villi that allow communication between the maternal and fetal circulation. They serve many functions, including implantation, nutrient and waste exchange and endocrine function. During pregnancy, trophoblast cells differentiate into two layers: an inner mononuclear cytotrophoblast and an outer multinuclear syncytiotrophoblast. Through intercellular fusion, the undifferentiated mitotically active cytotrophoblast fuse and form the syncytiotrophoblast. The intercellular fusion and replenishment of syncytiotrophoblast is continuous throughout pregnancy and crucial for placentation and appropriate fetal growth. Different systems were used to study trophoblast differentiation including placental explants, trophoblast cell lines and freshly isolated cytotrophoblast from early and term placenta. In culture, freshly isolated cytotrophoblast fuse and form syncytium in the presence of fetal bovine serum. Unfortunately, the drawback of these cells is their short lifespan in culture. Therefore, multiple immortalized trophoblastic cell lines were established and used to study trophoblast function and differentiation. The most commonly used cellular in vitro model is BeWo cell line since it shares morphological and biochemical characteristics of villous trophoblasts, including syncytial fusion and secretion of hormones such as hCG, hPL, progesterone and estradiol. Having a low spontaneous fusion rate, BeWo cells fusion can be triggered by treatment with cyclic adenosine monophosphate (cAMP), its analogue 8-bromo-cAMP, or the differentiation forcing agent forskolin. In contrast to BeWo cells which undergo fusion following forskolin treatment, JEG-3 and JAR cell lines fail to undergo substantial fusion following forskolin treatment. Therefore, BeWo and JEG-3 cells were used to study the fusion process in BeWo cells under forskolin treatment. Using microarray analysis, our results identified a list of 32 genes in fused BeWo cells compared to JEG-3 after forskolin treatment. Among these genes, 4 were validated by real time PCR. This study identified new target genes implicated in trophoblast fusion; a process implicated in the etiology of many pregnancy related diseases such as preeclampsia, intra-uterine growth restriction and gestational diabetes.

Abstract: 0078 Oral Presentation

Optical power transfer for the powering of active brain implants

Gabor Kósa[1], Yehuda Fass[1], Mario Ettore Giardini[2], Abraham Kribus[1]
[1]School of Mechanical Engineering, Tel Aviv University, Tel Aviv, Israel
[2]Department of Biomedical Engineering, University of Strathclyde, Glasgow, United Kingdom

Medical microrobotics shows great promise in reducing the invasiveness of brain microsurgical procedures, in particular when an interventional or diagnostic device needs to remain inserted into the brain tissue. For example, in deep brain stimulation (DBS) for the treatment of Parkinson's disease and epilepsy, the efficiency of the stimulating electrodes is impaired by their static placement. The possibility to deploy DBS devices on an implantable microrobot would allow changing the electrode location after implantation, enabling both the optimisation of the stimulation site as the patient evolves, and the re-instatement of electrical contact with the tissue when the tissue reaction insulates it.

Yet, in order not to cause critical damage while moving within brain tissue, a microrobotic capsule must be as small as possible, and not tethered to wires. In minimizing the size of a wireless medical robot, a major difficulty lies in finding a suitable power source.

Throughout the last years, the University of Tel Aviv, in Israel, has developed technology to enable microrobotic capsules to swim in the cerebrospinal fluid and within brain tissue itself [1, 2]. Such capsules could be navigated to specific brain sites, carrying electrodes and delivering drugs. In this framework, a Daniel Turnberg Travel Fellowship has supported a visit to Tel Aviv of a researcher from the United Kingdom, now at the University of Strathclyde, to explore concepts related to powering a microcapsule in the brain by shining infrared light through the skull and the brain tissue onto miniature photovoltaic panels [3].

Throughout this visit, an optically-compliant phantom of the brain has been built, using 3D printed polylactic acid-based plastics and a Laponite-water hydrogel. An optical power panel has been inserted within the phantom, and infrared light has been injected from the outside, thus simulating non-invasive optical powering through the scalp, skull and tissue. Such electrical power has been harnessed for the powering of a small radio transmitter that has emitted a presence signal outside the phantom.

The activity has been followed up by a reciprocal visit from Tel Aviv University to the University of Strathclyde, funded by the Royal Academy of Engineering, UK. Further miniaturisation of the technology, adding sensing capabilities to the radio transmitter, will be pursued in oncoming activity, to demonstrate useful communication between the implant and the outside world, with the ultimate vision of reaching a miniaturised and untethered robotic vector capsule for brain diagnostics and treatment.

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Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0081 Oral Presentation

Oxygen cycles synchronize clock on a Hif1a dependent manner

Benjamin Ladeuix[1], Yaarit Adamovich[1], Marina Golik[1], Maarten Koeners[2], Gad Asher[1]
[1]Biochemistry department, Weizmann Institute of Science, Rehovot, Israel
[2]School of Physiology and Pharmacology, University of Bristol, Bristol, England

BACKGROUND: Organisms from bacteria to human being possess circadian clocks. They are time keeper systems that maintain daily rhythms in behavior, physiological and biochemical processes with a rhythmicity of about 24 hours. Higher organism possesses a central clock located in a specific part of the brain called suprachiasmatic nucleus, and peripheral clocks located virtually in every cells of the organism. Those clocks are based on a negative transcription-translation feedback loop. BMAL1 and CLOCK proteins heterodimerize and drive the expression of many clock controlled genes, including cryptochrome and period genes. A negative feedback loop is formed once PER and CRY proteins accumulate and inhibit CLOCK/BMAL1 mediated activation, thereby inhibiting their own transcription. Since uncoupling between our circadian clocks and external time is linked to a lot of pathologies (metabolic diseases, cancer…), it become of interest to understand how clocks are synchronized every day. Both feeding rhythms and body temperature cycles are known to synchronize peripheral clocks. Nutrients assimilation and maintenance of body temperature are tightly linked to oxygen consumption. Because oxygen is available for every cell, it appears to be a good signaling molecule for clocks synchronization. In order to function as a resetting cue for circadian oscillators, oxygen needs to fulfill two requirements: (i) it should exhibit daily rhythms and (ii) peripheral oscillators must be sensitive to variation of oxygen levels.

METHODS: Animals were maintained under a 12 hrs light/dark cycle. Oxygen consumption was measured in metabolic cages. Blood samples were collected around the clock to determine blood oxygen concentration. Oxygen concentration in tissue was followed through several days in awake and unrestraint animals. In vitro, cells were exposed to 12 hours low oxygen and 12 hours high oxygen concentration cycles (within the physiological range) and clock genes expression was determined.

RESULTS: In vivo, animals present daily oxygen variations in oxygen consumption, blood oxygen concentration and oxygen concentration in tissue such as kidney, with a maximum occurring during the dark phase when animals are active. Those oxygen variations occur with variation of HIF1a expression through the day. In vitro, exposition of cells to cycles of low and high oxygen concentration results in the synchronization of clocks. This synchronization is realized in a HIF1a dependent manner.

CONCLUSION: Physiological oxygen variation through the day appears to be a good cue to synchronize clocks via HIF1a activation. Oxygen modulation could be a good therapy for pathologies involving uncoupling of clocks.

Abstract: 0085 Oral Presentation

Effective Bronchoscopic Lung Volume Reduction Accelerates Exercise Oxygen Uptake Kinetics in COPD

Azmy Faisal[1], Zaid Zoumot[2], Nicholas S Hopkinson[3], Michael I Polkey[3]
[1]Faculty of Physical Education for Men, Alexandria University, Alexandria, Egypt.
[2]Respiratory and Critical Care Institute, Cleveland Clinic Abu Dhabi, UAE
[3]Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, UK

BACKGROUND: Improved exercise capacity is a key objective of therapeutic interventions in patients with chronic obstructive pulmonary disease (COPD). Impaired oxygen uptake ($\dot{V}O_2$) kinetics during the rest-to-exercise transition are characteristically related to lung hyperinflation in COPD. Swift changes in lung volumes occurring after effective bronchoscopic lung volume reduction (e-BLVR) should allow examination of the impact of mitigating lung hyperinflation on $\dot{V}O_2$ kinetics. We tested the primary hypothesis that lung deflation induced by e-BLVR would accelerate $\dot{V}O_2$ kinetics in patients with COPD. We also postulated that these beneficial findings would be associated with improved cardiovascular adjustments to exercise and greater exercise tolerance.

METHODS: Thirty-one patients (FEV1: 36±9% predicted; residual volume (RV): 219±57% predicted) underwent a constant intensity exercise test at 70% peak work rate to the limit of tolerance before and after treatment bronchoscopy (n=24) or sham bronchoscopy (n=7). Physiological responses in e-BLVR patients (n=16) were compared with controls (ineffective BLVR or sham bronchoscopy; n=15). A reduction in residual volume >350 mL was chosen as the threshold for defining e-BLVR based on the accepted minimal clinically important difference for RV reduction in COPD patients following BLVR. To precisely characterize $\dot{V}O_2$ kinetics following the onset of exercise, patients who were able to perform a constant work rate test on a cycle ergometer (CWR) for at least 4 min at a minimum of 5 W were included in this study. Breath-by-breath $\dot{V}O_2$ data were fitted by a least-squares gradient algorithm to a three-parameter first-order exponential model: $[\dot{V}O_2](t) = [\dot{V}O_2](b)+A * (1-\exp[-(t-TD)/\tau])$
where b is the baseline unloaded cycling, and A, TD, and τ are the amplitude, time delay and time constant of the exponential response, respectively.

RESULTS: e-BLVR was associated with improvements in pulmonary functions. In addition to decreased RV (-0.36 to -2.32 L), total lung capacity (TLC) also fell albeit to a lesser extent, such that RV/TLC decreased and vital capacity increased. e-BLVR was also associated with increases in FEV1 (0.25±0.18 L, p<0.001) and lung diffusing capacity (DLCO) by 12% (1.2±1.4 mL/min/mmHg, p=0.001). The e-BLVR group had significant improvements in: St. George's Respiratory Questionnaire (58±17 vs. 45±21, p=0.01), CWR exercise tolerance (355±99 vs. 537±213s, p=0.004) and 6-minute walk distance (342±89 vs. 418±105m, p=0.001). $\dot{V}O_2$ kinetics were accelerated in the e-BLVR group but remained unchanged in controls (Δ mean response time: -20±29% vs. 1±25%, p=0.04). Acceleration of $\dot{V}O_2$ kinetics was associated with reductions in heart rate and O_2-pulse response half-times by 8% (84±14 to 76±15s, p=0.04) and 20% (49±16 to 34±16s, p=0.01), respectively. Faster $\dot{V}O_2$ kinetics in e-BLVR group were significantly correlated with reductions in RV (r=0.66, p=0.005), and improvements in inspiratory reserve volume (r=0.56, p=0.024) and exercise tolerance (r=0.63, p=0.008).

CONCLUSION: e-BLVR is associated with enhanced cardiovascular adjustments to exercise leading to improved $\dot{V}O_2$ kinetics and exercise tolerance in patients with advanced COPD. Our results suggest that negative cardiopulmonary interactions secondary to lung hyperinflation may impair muscle O_2 availability during exercise. This may help to develop novel pharmacological and non-pharmacological approaches to improving patients' exercise capacity and quality of life.

Abstract: 0010 Poster

Evolving classification of intensive care patients: do more data lead to better predictions?

Zisis Kozlakidis1, Tiziano Gallo Cassarino2, Jonathan Edgeworth3, Olga Tosas3, Mark Last4
1Department of Infection and Immunity, University College London, United Kingdom
2Farr Institute of Health Informatics Research, University College London, United Kingdom
3Department of Infectious Diseases, Guy's and St. Thomas' NHS foundation Trust, London, United Kingdom
4Department of Information Systems Engineering, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Background: Over the recent years, the nature, the scale and the speed of data collected within healthcare has changed dramatically, creating new challenges and opportunities. For example, we may be interested to utilize data mining techniques for estimating the probabilities of various discharge outcomes on each day of a given hospital episode. The current work aims to predict the patient discharge outcome on each hospitalization day by introducing a new paradigm—evolving classification of event data streams.
Most classification algorithms implicitly assume the values of all predictive features/data points to be available at the time of making the prediction. This assumption does not necessarily reflect real-life settings or hold true in the evolving classification setting (such as an intensive care patient monitoring environment). In the latter case we may be interested in classifying the monitored entities as early as possible, based on the attributes initially available to the classifier, and then keep refining our classification model at each time step (e.g., on daily basis) with the arrival of additional attributes.

Methods: An oblivious read-once decision-tree algorithm, called information network (IN), is extended to deal with evolving classification. The new algorithm, named incremental information network (IIN), restricts the order of selected features by the temporal order of feature arrival. The IIN algorithm is compared to six other evolving classification approaches on an 8-year dataset of adult patients admitted to two Intensive Care Units (ICUs) in the United Kingdom.

Results: The retrospective study involved the analysis of 3452 episodes of adult patients (≥ 16 years of age) admitted to the ICUs of Guy's and St. Thomas' hospitals in London between 2002 and 2009. Random partition (66: 34) into a development (training) set n = 2287 and validation set n = 1165. Episode-related time steps: Day 0—time of ICU admission, Day x—end of the x- th day at ICU. The most accurate decision-tree models, based on the area under curve (AUC): Day 0: IN (AUC = 0.652), Day 1: IIN (AUC = 0.660), Day 2: J48 decision-tree algorithm (AUC = 0.678), Days 3–7: regenerative IN (AUC = 0.717–0.772). Logistic regression AUC: 0.582 (Day 0) —0.827 (Day 7).

Conclusions: Our experimental results have not identified a single optimal approach for the evolving classification of ICU episodes. On Days 0 and 1, the IIN algorithm has produced the simplest and the most accurate models, which incorporate the temporal order of feature arrival. However, starting with Day 2, regenerative approaches have reached better performance in terms of predictive accuracy. The availability of more data with time progression did not add predictive power to the models tested or accuracy to the outcome prediction beyond that achieved at the initial stages post-admission.

Abstract: 0011 Poster

Nano-theranostics with plasmonic nanoparticles

Dror Fixler
Faculty of Engineering and the Institute of Nanotechnology and Advanced Materials, Bar Ilan University, Ramat Gan, 5290002, Israel

Light and tissue-cells interaction is common in clinical treatments and bio-medical researches; therefore the resolution limit due to diffraction as well as the investigation of light path in irradiated tissue is of high importance. In our talk we will describe three biological application using nano-photonics techniques: in medicine; food industry; molecular and functional imaging.
(1) Identification and treatment of inflamed, unstable atherosclerotic lesions is challenging. Recent studies have shown that gold nanoparticles (GNPs) are uptaken by macrophages, and that high density lipoprotein (HDL) attenuates atherosclerotic vascular disease by exerting anti-inflammatory effects. In our talk we will present a new method that use GNPs coupled with HDL to enable both detection and treatment targeted directly to macrophage-rich plaques.
(2) Recent developments in the field of optical biosensors make them very attractive to the food industry. We will present a system that aimed to detect the possibility of lactose and milk proteins' quantitative signature by an iterative optical tool, en route to the design of a novel milk-content-monitoring tool. The technique combines an iterative optical algorithm called Gerchberg–Saxton with an experimental setup for estimating the reduced scattering coefficient of a substance and detecting changes in the passing light as a result of the scattering particles within the substance.
(3) We will present a new method that we developed for highly sensitive dual modal imaging system designed for GNPs conjugated to various fluorophores. The system consists of fluorescence lifetime imaging microscopy (FLIM) for surface imaging, diffusion reflection (DR) for deep tissue imaging (up to 1cm), and metal enhanced fluorescence (MEF). This promising dual modal imaging technique enables efficient and sensitive molecular and functional imaging.

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Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0012 Poster

Larger osteotomies result in larger ostia in external dacryocystorhinostomies.

Guy Jonathan Ben Simon[1], Chris Brown[2], Alan Angus Mcnab[2]
[1]goldschleger eye institute, sheba medical center, tel hashomer, israel
[2]royal victorian eye and ear hospital, melbourne, australia

OBJECTIVE: To evaluate whether final ostium size is determined by the osteotomy created during dacryocystorhinostomy (DCR).

DESIGN: Prospective nonrandomized study. Intraoperative measurements of bony osteotomy were taken during external DCR. Endonasal endoscopy with functional endoscopic dye testing and internal ostium photography were performed 3 months after surgery.

RESULTS: Fifty patients (mean age, 63 years) underwent 55 DCRs. Postoperative nasal endoscopy with functional endoscopic dye testing was performed in 27 cases (49%), and measurements of intranasal ostia were feasible in 24 of them (86%). The mean follow-up time was 7 months (range, 3-12 months). Surgical success was achieved in 25 of 27 patients (93%) who underwent postoperative nasal endoscopy. There was no difference in either the intraoperative osteotomy size or the postoperative ostium size between failed and successful cases. The mean (SD) intraoperative osteotomy size was 256.3 (89.0) mm(2), and the mean (SD) postoperative ostium size was 9.6 (6.7) mm(2). The intraoperative osteotomy size correlated positively with the postoperative intranasal ostium size (r = 0.45; P =.03, Pearson bivariate correlation).

CONCLUSIONS: Larger osteotomies created during external DCR are correlated with larger postoperative ostia as measured by endonasal endoscopy and image analysis software. There is a trend toward greater success with larger osteotomies; however, failed cases in this series were not associated with smaller-sized intraoperative osteotomies.

Abstracts

Abstract: 0013 Poster

Integrating the impact of cigarette and waterpipe tobacco use among adolescents in the Eastern Mediterranean Region: a cross-sectional, population-level model of toxicant exposure

Mohammed Jawad1, Paul Roderick2
1Imperial College London
2University of Southampton

Background: Waterpipe smoking is more prevalent than cigarette smoking among adolescents in the Eastern Mediterranean Region (EMR); however, simple prevalence masks complex waterpipe smoking patterns and makes uncertain its contribution to risk of tobacco-related harm. This study aimed to integrate the impact of cigarette and waterpipe tobacco use on toxicant exposure among EMR adolescents.

Methods: A cross-sectional model made equivalent individual-level toxicant exposure data for cigarettes and waterpipes, and aggregated it to 23 countries in the EMR using the Global Youth Tobacco Survey. The waterpipe model adjusted for estimated frequency of use, session duration and sharing behaviours. The final model included 60 306 12–17-year olds, and modelled as outcomes nicotine, carbon monoxide (CO) and 14 carcinogens. Sensitivity analyses substantially reduced session duration and proportion of solo use.

Results: Our model suggests waterpipe use may contribute a median of 36.4% (IQR 26.7–46.8%, n=16) of the total toxicant exposure from tobacco, and may reach up to 73.5% and 71.9% of total CO and benzene exposure, respectively. Sensitivity analyses reduced all values by 4.3–21.0%, but even the most conservative scenarios suggested over 50% of benzene and CO exposure was from waterpipe use. Between 69.2% and 73.5% of total toxicant exposure derived from dual cigarette and waterpipe users, who smoked cigarettes and waterpipe more frequently and intensely than single users.

Conclusions: More research is warranted to refine our model's parameters. Tobacco control researchers should consider a move towards a single unit of measure for cigarette and waterpipe tobacco exposure in order to better inform health policy.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0015 Poster

Comparison of first trimester to second trimester fetal heart examination in detection of cardiac anomalies in a tertiary fetal medicine teaching unit

Sahar Sheta1, Mona Abou El Ghar2, Alaa El Ebrashy2, Mohamed El Hodeiby2
1Cairo University Childrens Hospital,Pediatric cardiology Department, Faculty of Medicine, Cairo,EGYPT
2Fetal Medicine Unit, Obstetrics and Gynecology Department, Cairo University, Faculty of Medicine, Cairo, Egypt

OBJECTIVES: To study the detection rate of congenital fetal heart anomalies in first trimester scanning compared with second trimester scanning and to postnatal exam and neonatal echocardiography.

METHODS: This is a prospective observational study performed at a tertiary Fetal Medicine Unit. Patients had a first trimester scan from 11–14 weeks which included screening for Down's syndromeby measurement of the NT thickness, detection of Nasal bone, measurement of DV flow and tricuspid valve flow. Full anatomyexam was performed with special interest in the heart. Examination of the heart included; the four chamber view, intact inter-venticular septum, correct outflow tract and the three vessel view in the mediastinum. Pulsed Doppler was done at level of tricuspid valve to exclude regurgitation. A similar examination of the heart was performed at 20–24 weeks with full anatomy survey for other congenital malformations. Comparison of the two fetal heart examinations was done compared to final neonatal examination and neonatal echocardiography when indicated.

RESULTS: A total of 300 pregnant females were examined. The mean age of the patients were; 29.9±6.3. Mean BMI was 32.5. The mean GA at the first trimester was 12.9±0.9 and the mean GA at the second trimester was 20.4±1.4. A total of 11 congenital heart anomalies were confirmed postnatal (3.7%).Seven were diagnosed and 4 were missed at the first trimester and one was falsely diagnosed as having an anomalygiving a detection rate of 63.6%, specificity 99.7%, PPV 87.5%, NPV 98.6% and agreement reached 98.3% (kappa 0.728). In the second trimester scan 9 cases were diagnosed, 2 cases were missed giving a detection rate of 81.8%, specificity 99%, PPV 75%, NPV 99.3% agreement 98.3% (kappa 0.774).

CONCLUSIONS: First trimester heart examination has a good detection rate for congenital heart anomalies and should be done as a routine during first trimester screening for Down's syndrome.

Abstract: 0016 Poster

Surveillance for highly pathogenic H5N1 avian influenza viruses in duck and poultry from Bangladesh

Mohamed Ezzat El Zowalaty1, Wahedul Karim Ansari2, Md. Shafiullah Parvej2, Stephen A Bustin3, Nitish Debnath4, Graba Ahmed4, Md. Bahanur Rahman2
1School of Health Sciences, University of KwaZulu Natal, Durban, South Africa
2Department of Microbiology and Hygiene, Bangladesh Agricultural University, Mymensingh, Bangladesh
3Postgraduate Medical Institute, Anglia Ruskin University, Chelmsford, UK
4Emergency Center for Transboundary Animal Diseases (ECTAD), Food and Agriculture Organization (FAO) of the United Nations, Bangladesh

Avian influenza viruses (AIVs) continue to pose a global threat. Waterfowl are the main reservoir and are responsible for the spillover of AIVs to other hosts. This study was conducted as part of routine surveillance activities in Bangladesh and it reports on the serological and molecular detection of H5N1 AIV subtype. A total of 2169 cloacal and 2191 oropharyngeal swabs as well as 1725 sera samples were collected from live birds including duck and chicken in different locations in Bangladesh between the years of 2013 and 2014. Samples were tested using virus isolation, serological tests and molecular methods of RT-PCR. Influenza A viruses were detected using reverse transcription PCR targeting the virus matrix(M)gene in41/4360(0.94%) samples including both cloacal and oropharyngeal swab samples, 31 of which were subtyped as H5N1using subtype-specific primers. Twenty-one live H5N1 virus isolates were recovered from those 31 samples. Screening of 1,868 blood samples collected from the same birds using H5-specific ELISA identified 545/1603 (34%) positive samples. Disconcertingly, an analysis of 221 serum samples collected from vaccinated layer chicken in four districts revealed that only 18 samples (8.1%) were seropositive for anti H5 antibodies, compared to unvaccinated birds (n = 105), where 8 samples (7.6%) were seropositive. Our result indicates that the vaccination program as currently implemented should be reviewed and updated. In addition, surveillance programs are crucial for monitoring the efficacy of the current poultry vaccinations programs, and to monitor the circulating AIV strains and emergence of AIV subtypes in Bangladesh.

Abstract: 0019 Poster

Use of Systematic Reviews When Adapting Guidelines

Andrea Darzi1, Elie Akl1, Manale Harfouche1, Holger Schünemann2, Jasvinder Singh3, Peter Tugwell4, Thurayya Arayssi5, Robin Christensen6
1AUB GRADE Center, Clinical Research Institute, American University of Beirut, PO Box 11-0236, Riad El Solh, Beirut, 1107 2020, Lebanon
2Department of Medicine, McMaster University, Hamilton, ON, Canada
3University of Alabama at Birmingham 510 20th Street South Faculty Office Tower 805B Birmingham, AL 35294
4Centre for Global Health, University of Ottawa Bruyère Research Institute, Ottawa, Ontario
5Weill Cornell Medicine-Doha, Qatar
6Faculty of Health Science, University of Southern Denmark, Denmark

BACKGROUND: Adaptation of health practice guidelines to the local setting is expected to improve their uptake and implementation. One of the challenges of adaption is to keep it efficient while ensuring it is sufficient in terms of the need for updates and remaining evidence-based.

OBJECTIVE: The objective of this paper is to showcase the advantage of published systematic reviews (SRs) to increase efficiency of the process of adaptation of health practice guidelines.

METHODS: We are using the GRADE-Adolopment methodology to adapt the recently published American College of Rheumatology (ACR) Rheumatoid Arthritis (RA) guidelines to the Eastern Mediterranean Region. The methodology builds on the advantages of adaptation, adoption, and de novo guideline development. We searched for published SRs on the topic of interest and selected those that would contribute to evidence to support the guideline recommendations.

RESULTS: In the context of adapting the ACR RA guidelines, these three characteristics of published SRs were important when evaluating their potential use: Relevance, Quality and Up-to-date-ness. First, we assess the relevance of identified SRs by matching their PICO to that of the guideline questions. The minimum requirement is for the Population, Intervention and Control elements to match to a reasonable degree, i.e. not have serious indirectness for more than one of the three elements. Then, we assess the quality of relevant SRs. If we identify more than one SR, we prioritize based on the scoring on the ROBIS tool. Finally, we assess the up to date-ness of the chosen SR. When that SR is not up to date, we proceed with updating it. At the time of the meeting, we will present the descriptive statistics relating to the number of guideline questions, SRs identified, how many were considered relevant and of high quality and how many required updating.

CONCLUSION: It is anticipated that this GRADE-Adolopment methodology will inform guideline groups by applying a sufficient ‘rapid review’ format. This format may influence the way in which a subset of guidelines using this methodology are undertaken to accommodate condensed timelines for urgent decision-making.

Abstract: 0022 Poster

Varied utilisation of health provision by Arab and Jewish residents in Israel

Jo Southern1, Hector Roizin2, Mohannad Daana2, Carmit Rubin3, Samantha Hasselton2, Adi Cohen2, Aviva Goral3, Galia Rahav4, Meir Raz2, Gili Regev Yochay4
1Immunisation Department, Health Protection, Public Health England, 61 Colindale Ave, London NW9 5EQ, UK.
2Jerusalem-Hashfela District, Macabbi Healthcare Services, Modiin, Israel
3Infectious Disease Epidemiology Section, The Gertner Institute, Tel Hashomer, 52621, Israel
4Infectious Disease Unit, Chaim Sheba Medical Center, Ramat Gan, 52621, Israel

Background: The Palestinian-Israeli Research Collaboration (PICR) studied the impact of the pneumococcal conjugate vaccination (PCV) programme in 2009-2010. This sub-analysis assessed wider utilisation of healthcare in 16 clinics across East Jerusalem (EJ) and central Israel (IL).

Methods: With parental consent, information was collected about children aged 5 years or under attending participating primary care clinics, using a standardised questionnaire with reference to GP notes, including: • vaccination status –primary and influenza immunisations; • antibiotic use; • GP/ hospital visits; • lifestyle – smoking, breastfeeding, household size. Analyses compared areas using chi square tests, univariate and multiple logistic regression.

Results: 1. Lifestyle factors - Household size [≥7 people] was larger in EJ 18.2% vs IL 5.3%. Tobacco smoking was higher in EJ 49.5% vs IL 26.2%. Breastfeeding was more common in EJ 94.6% than IL 63.3% and continued to 6 months more frequently [55.6% vs 18.3% respectively].
2. Consultations – Within the prior three months hospitalisation was higher in EJ 11.5% vs IL 7.2%, though there were more primary care visits in in IL 94.2% vs EJ 82.3%. Causes of the current primary care visit differed, with more upper respiratory tract infections (URTI) in EJ 65.9% vs IL 49.0%, though other infections were higher in IL 30.0 % vs EJ 17.6%. The incidence of urinary tract infections (UTI), gastroenteritis, skin infections, viral infections and other non-infectious issues were similar between areas. 3. Antibiotics - Antibiotic use in the previous three months was higher in EJ 28.2% vs IL 11.9% and even higher for the current visit [36.4% vs 12.7%]. An interesting observation was the proportion of macrolides used, which can be bought in some places, 29.7% EJ vs 15.4% IL. 4. Vaccinations - Completion of primary immunisations was similar between areas EJ 98.9%, IL 97.9%, though influenza vaccination was much lower IL 11.8% vs EJ 4.7%. Younger children (≤2 years old) and those form larger households (≥4 people) were less likely to be vaccinated. Before PCV was included in the national immunisation programme (pre-2009), it could be bought privately and uptake was significantly higher in IL 30.7% vs EJ 2.6%. This reversed on inclusion in the national schedule in 2010, EJ 55.6%vs IL 62.5%, p=0.04. Again younger children from larger households were less likely to be vaccinated, as were those with a parent smoker in the 2009 study, and the 2010 study showed those with multiple clinic visits were more likely to receive PCV.

Conclusion: Routine immunisations, bar influenza, are effectively delivered across the population. However, household structures and behaviours vary greatly between the two areas with different patterns of interaction with healthcare services despite provision through same HMO. These are multifactorial and rooted in complex cultural and socioeconomic differences which required further in depth study.

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Abstract: 0026 Poster

Improving Antibiotic Prescribing in Palestinian Hospital: A new Antimicrobial Stewardship Program

Maher R Khdour1, Mowafq Nassif3, Alia Khalili3, Mohammad Jaradat3, James Mcelnay2, Fiona Gallagher4
1Department of Pharmacy, Al-Quds University, Jerusalem, Palestine.
2Department of Pharmacy, Queen's University Belfast, UK.
3ICU. Palestinian Medical Complex, Ramallah, Palestine.
4Department of Pharmacy, Queen's University Hospital, Antrim, UK.

BACKGROUND: High rates of antimicrobial use and increasing antimicrobial resistance make intensive care units (ICUs) ideal wards to implement antimicrobial stewardship program (ASP) efforts. The purpose of this study was to determine if the implementation of a pharmacist-led ASP in a community hospital ICU decreased antimicrobial utilization and improved antimicrobial susceptibilities.

METHODS: An ASP was established at a community teaching hospital in April 2015, with 12 ICU beds. The program was led by an infectious diseases-trained pharmacist who worked daily with a clinical pharmacist rounding with the ICU care team to make ASP interventions. Prospective audit with intervention and feedback began in Sep, 2015. We chose to compare 4 months of pre-ASP data with 4-months of post-ASP data. Data collected included clinical and demographic data; included utilization of antimicrobials which was calculated using Defined Daily Doses DDD/100 bed, hospital stay, intervention Type, acceptance rate and susceptibility trends.

RESULTS: A total of 376 antimicrobial prescriptions for 157 patients were revised during a 4 month period. There were 8 drugs in the DU 90% segment out of 21 drugs prescribed in the ICU. In all, 166 prescriptions (44.1%) were considered inappropriate in 93 patients. The majority of interventions were de-escalating or discontinuing antimicrobial therapy (68.7%), intravenous to oral conversion (16.8%). and dose optimization (12.7%) and with acceptance rate of (80.7%),Overall Utilization Reduced By 33.0% (95.4 DDD/100 bed. vs 63.9 DDD/100 bed p<0.001). Carbapenems Utilization decreased by 39% (11.3 DDD/100 vs 6.9 DDD/100 bed p<0.001) and Pip/Taz Utilization decreased by 30.1% (9.9 DDD/100 bed vs 6.7 DDD/100 p<0.001). there was a non-significant reduction in the average hospital stay (7.4 day Vs 6.3 day; p=0.17). The acceptance rate of recommended changes by stewardship team was high (80.7%).

CONCLUSIONS: A pharmacist-led ASP in a community teaching hospital ICU significantly impacted antimicrobial prescribing, reduced antimicrobial utilization and hospital stay with high acceptance rate.

Abstract: 0027 Poster

Health aspects of adaptation to climate change in England and the Mediterranean

Maya Negev1, Sari Kovats2, Shlomit Paz1
1University of Haifa, Israel
2London School of Hygeine and Tropical Medicine

BACKGROUND: Climate change is expected to result in more intense and frequent extreme events such as heatwaves and floods, as well as scarcity of fresh water, outbreaks of communicable diseases and additional risks to human health. Therefore, access morbidity and mortality are expected, as well as a negative impact on wellbeing and mental health. Nations and cities worldwide are starting to adapt for climate change, including preparedness of health systems and adaptation of urban planning and infrastructure. The Mediterranean and England are vulnerable to climatic changes.

METHODS: The presentation includes an integration of three policy studies. In England, a qualitative research included in-depth interviews with seniors in the health system at the regional and local level, and a thematic analysis was conducted. In the Mediterranean, at the country level, a comparative policy assessment was conducted in six representative countries regarding preparedness to outbreaks of vector-borne diseases. In Mediterranean-climate regions globally, at the city level, a policy assessment was conducted in five representative cities.

RESULTS: In England, public health seniors at the local and regional level recognize that climate change is a risk to health in England, but do not prioritize it. While they are not clear about the particular long-term risks or appropriate solutions, they are positive regarding implementation of localized long-term adaptation policy. In the Mediterranean, countries started preparing for emergence of vector-borne diseases, but the preparation levels differ among countries, and policy mechanisms are limited and basic. Furthermore, cross-border cooperation is not stable and depends on temporary international frameworks. Also at the city level, Mediterranean-climate cities with adaptation plans address most of the fundamental climate change-related drivers of risks to human health, including rising temperatures, flooding and drought, but the policy measures to reduce negative impacts vary across cities.

DISCUSSION: While public health systems worldwide are starting to prepare for climate change, the integrated results of the current studies show that currently adaptation is not a priority. Many countries and cities in climate-sensitive areas do not have an adaptation plan. When adaptation plans exist, they vary greatly in scope and quality. In England, a heatwave plan is successfully implemented, but long-term public health adaptation is lacking. In the Mediterranean, among the several countries and cities that have comprehensive adaptation plans, there is great variety in adaptation measurements. We suggest recommendations for Mediterranean climate countries and cities in various aspects, depending on their local needs and vulnerability challenges. Recommendations include assessment of health risks, extreme events management, long-term adaptation, enhancing collaboration and learning across cities and countries, and utilizing a stable and neutral framework in the Mediterranean basin that should address the characteristics and needs of African, Asian and European countries.

Abstract: 0028 Poster

A novel Optineurin truncation mutation identified in an adult onset consanguineous Palestinian family with Amyotrophic lateral sclerosis confirms loss of function as a disease mechanism

Marc Gotkine1, Martina De Majo2, Chun Hao Wong2, Simon Topp2, Rachel Eigess4, Rachel Michaelson Cohen4, Silvina Epsztejn Litman4, Moein Kanaan3, Agnes Nishimura2, Bradley Smith2, Christopher Shaw2
1Hebrew University-Hadassah Medical Center P.O. Box 12000 Jerusalem 91120 Israel
2Maurice Wohl Clinical Neuroscience Institute 125 Coldharbour Lane, Kings College London. Camberwell, SE5 9NU United Kingdom.
3Hereditary Research Lab Director POB 9 Bethlehem University POB 54866 Jerusalem
4Medical Genetics Institute Dept. of Obstetrics & Gynecology Shaare Zedek Medical Center Hebrew University of Jerusalem

The genetic factors involved in the majority of ALS cases remain to be elucidated. Optineurin (OPTN) mutations have been described in open angle glaucoma and more recently, in ALS- with recessive mutations found in consanguineous Japanese, Turkish and Moroccan Jewish kindreds; dominant Caucasian cases with variable penetrance have also been reported. Here we describe the genetic and functional characterization of a novel recessive mutation in OPTN found in a consanguineous Palestinian family with an aggressive, adult form of ALS. This study is the first to characterize endogenous OPTN from primary fibroblast lines cultured from carriers of OPTN mutations.
OPTN is a 577 amino acid protein involved in a variety of cellular pathways, including autophagy, which seems to be the most important in ALS pathogenesis. OPTN acts as autophagy receptor and it is involved in the clearance of protein aggregates through the autophagy-lysosome pathway in an ubiquitin dependent and ubiquitin independent manner. Within the same pathway OPTN is phosphorylated on Ser177 by tank binding kinase 1 (TBK1), a protein linked to ALS.
A novel homozygous truncation mutation in OPTN (S174X) was identified in this family, via exome sequencing from genomic DNA of the affected family member; this results in removal of both the Ubiquitin binding in ABIN and NEMO (UBAN) domain and the TBK1 phosphorylation site, as well as other important protein interaction sites. Notably, the truncated protein retains the TBK1 binding region of OPTN. The unaffected mother was confirmed to be a heterozygous carrier, and sequencing of three unaffected siblings of the proband showed two of them to be heterozygous carriers and one to harbor a homozygous S174X change.
Fibroblast primary lines were obtained from homozygous and heterozygous family members and compared to wild-type controls. Mutation status was confirmed by Sanger sequencing. Interestingly, Western blot analysis of fibroblast lysates, probing for endogenous OPTN, revealed OPTN expression for the wild type and heterozygous carriers but no expression of the truncated S174X OPTN allele. These observations support the hypothesis that early truncation results in an unstable protein; this was also confirmed by immunocytochemistry. However, transcript analysis revealed that full length and truncated OPTN message was produced from both the heterozygous and homozygous carriers. Further investigation with quantitative PCR will identify the level of OPTN mRNA transcription, and whether the mutation promotes nonsense mediated decay in homozygous and heterozygous individuals.
The absence of the mutated copy of OPTN suggests that the pathogenic mechanism could be associated with a loss of function, which could result in a knock on effect abolishing interaction with TBK1. Further research will aim to characterise the mechanism behind the pathogenicity of this truncation mutation in OPTN and how this affects its interaction with TBK1.

Abstract: 0029 Poster

Perceptions of Arab Medical Students on Supporting Clinical Pharmacology Learning in English by Flashcards Prepared in Arabic

Yasin I. Tayem1, Marwan F. Abu Hijleh2, Reginald P. Sequeira1
1Department of Pharmacology and Therapeutics, College of Medicine and Medical Sciences, Arabian Gulf University, Manama, Bahrain
2Department of Anatomy, College of Medicine, Qatar University, Doha, Qatar

OBJECTIVES: The vast majority of medical schools in the Arab World use a foreign language for teaching medicine for students whose first language is Arabic. This practice has resulted in creating a significant language barrier. In this study, we supplemented pharmacology teaching materials in English by flashcards prepared in Arabic then we explored the perceptions of medical students on this approach.

METHODS: This study targeted third-year medical students at the Arabian Gulf University in Bahrain (n= 183). During the endocrine and metabolism part of the basic medical sciences phase of the curriculum, the handouts of each lecture were divided into blocks. At the beginning of each block, an Arabic flashcard which contained focused information on the block, was followed by regular detailed English slides. At the end of this sub unit, students` perceptions were explored by using a self-administered structured questionnaire.

RESULTS: the number of students who accepted to answer the questionnaire was 124 (response rate: 67.8%). Most participants reported that this intervention improved their clinical pharmacology learning in general (85.5%), made it easier (82.9%) and enjoyable (81.3%). Students also noticed improved confidence in drug selection for patients (71.5%) and knowledge of adverse reactions of medications (79.8%). Most students supported continuing this approach for learning pharmacology in other units (78.8%) and for helping students learn other basic medical sciences (60.5%). The majority of respondents agreed that this approach would help them during the clinical phase of their study (83.9%) and in communicating with Arab patients in their future practice (94.3%). In response to the open-ended item of the questionnaire, some of the students expressed concerns that adding Arabic material may increase their reading load although they thought that the Arabic flashcards made studying pharmacology faster.

CONCLUSIONS: Supporting pharmacology learning in a foreign language by materials prepared in native language improved students self-reported learning and satisfaction.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0031 Poster

The Use of Economic Evidence to Inform Drug Pricing Decisions in Jordan

Eman Hammad
Department of Biopharmaceutics and Clinical Pharmacy, University of Jordan, Amman, Jordan

BACKGROUND: Drug pricing is an example of a priority setting in a developing country with official requirements for the use of cost-effectiveness (CE) evidence.

OBJECTIVE: To describe the role of economic evidence in drug pricing decisions in Jordan.

METHODS: A prospective review of all applications submitted between November 2013 and May 2015 to the Jordan Food and Drug Association's drug pricing committee was carried out. All applications that involved requests for CE evidence were reviewed. Details on the type of study, the extent, and whether the evidence submitted was part of the formal deliberations were extracted and summarized.

RESULTS: The committee reviewed a total of 1608 drug pricing applications over the period of the study. CE evidence was requested in only 11 applications. The submitted evidence was of limited use to the committee due to concerns about quality, relevance of studies, and lack of pharmacoeconomic expertise. There were also no clear rules describing how CE would inform pricing decisions.

CONCLUSIONS: Limited local data and health economic experience were the main barriers to the use of economic evidence in drug pricing decisions in Jordan. In addition, there are no official rules describing the elements and process by which the CE evidence would inform drug pricing decisions. This study summarized accumulated observations for the current use of economic evaluations and evidence-based decision making in Jordan. Recommendations have been proposed to applicants and key decision makers to enhance the role of economic evidence in influencing health policies and evidence-based decision making across priority settings.

Abstracts

Abstract: 0032 Poster

Nebulizable nanosystems for treatment of pulmonary cancer: a promising approach

Maha Nasr1, Ramy Said El Bahr1, Mohamed A. Alhnan2, Omaima Amin Sammour1
1Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Egypt
2Department of Pharmaceutics, School of Pharmacy and biomedical sciences, University of Central Lancashire, UK

The administration of therapeutic agents through the pulmonary route can provide both local and systemic actions for treatment or prophylaxis of lung diseases. Particulate delivery systems such as polymeric nanoparticles and nanoemulsions seem to be a promising approach for such purpose; upon optimization of their aerodynamic properties.

Apart from dry powder inhalers, nebulizers are commonly employed to generate therapeutic aerosols for pulmonary application and are especially advantageous for reaching the distal region of the lungs. The objective of our work was to formulate two anticancer molecules (one of herbal and the other is non herbal in origin) in suitable nanocarrier systems and their optimization to allow deep deposition in the lung for treatment of lung cancer. These formulations were administered through the pulmonary route to benefit from the large absorptive surface area of the lung and reduce the systemic side effects.

A challenging disease such as lung cancer requires the combination of different modalities to achieve beneficial therapeutic outcomes. In our work, PLGA nanoparticles and lipidic nanoemulsions were chosen as colloidal carriers for two drugs with reported anti-lung cancer activity; naringin and celecoxib. Nanoparticles were prepared and characterized for their particle size, zeta potential, entrapment efficiency, in vitro release, stability, morphology, cytotoxicity, as well as aerosolization and nebulization behaviours. Their biodistribution pattern upon pulmonary aerosolization, and safety on healthy lung tissues were determined as well.

Results showed that the described system displayed a particle size < 260 nm with unimodal distribution, entrapment efficiency for celecoxib and naringin reaching 96% and 62% respectively and a controlled release profile for the two drugs. The selected formulae displayed favourable nebulization properties with high drug deposition percentages in lower impinger and impactor stages; denoting in vitro deep lung deposition potential. They also exhibited higher cytotoxic activity on A549 lung cancer cell lines compared to the free drugs, while displaying considerable safety on healthy lung tissues. Biodistribution studies delineated the high lung deposition potential of the nanoparticles accompanied with high distribution to the bones, brain and liver which are common metastatic sites of lung cancer, proving their promising nature in the treatment of lung cancer.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0033 Poster

Rapid and low cost biosensor for the detection of Prostate Specific Antigen biomarker

Ghadeer Abdul Rahman Suaifan1, Mohammed Zourob2
1Department of Pharmaceutical Sciences, The University of Jordan, Amman, Jordan
2Department of Chemistry, Alfaisal University, Riyadh, Saudi Arabia

Cancer is the second most common cause of death in the United States which is exceeded by heart disease only. In males, prostate carcinoma is the most common leading cause of cancer-related deaths, aside from lung cancer. Prostate specific antigen (PSA) is a serine protease produced by both normal prostate epithelial and prostate cancer cells. There are two types of PSA in the body fluids, proteolytically-active PSA and inactive PSA, of which the proteolyticcally-active type is found to be a useful diagnostic serological marker for the early diagnosis and monitoring of prostate cancer.

In the past years, researchers executed a lot of research to increase the utility and applicability of several PSA detection methods. However, these methods were usually frustrated by limitation in sensitivity, specificity, times constrains and ease of on-site application and analysis. Thus, a call for a direct and highly sensitive colorimetric detection method for the evaluation of protealytically-active PSA level was a challenging issue for scientist. Thus, in this work, we developed a novel, facile and inexpensive lab-on-a-chip (LOC) PSA biosensor without the use of any chromophoric label. The biosensor probe was constructed by covalently binding PSA specific peptide substrate with magnetic –nano particles (MNPs) through its N-terminus and to a gold sensing platform via thiol moiety at the C-terminal. A black color layer of the MNPs-peptide complex would then be placed over the gold sensor surface masking its golden color. Upon proteolysis of the probe MNPs-peptide moiety by PSA, the physical link between the MNPs-peptide moiety and the gold sensor platform will be abolished. An external magnetic field would then collect the cleaved MNPs-peptide moiety away from the gold sensing platform. This would in turn reveal the golden color of the sensor platform to become observable by naked eye as shown in scheme 1. This biosensor was capable of detecting PSA in buffer and spiked urine samples with a lower detection limit of 100 pg/mL and 0.5 ng/mL, respectively. This approach permits the development of a cost-effective lab-on-a-chip device suitable for point-of-care diagnostic.

Abstract: 0034 Poster

Adherence to antidepressants and all-cause mortality – a nation-based cohort study

Amir Krivoy1, Ran D Balicer2, Moshe Hoshen2, Becca Feldman2, Gil Zalsman1, Abraham Weizman1, Gal Shoval1
1Geha Mental Health Center, Petach Tikva, Israel; Tel-Aviv University, Ramat-Aviv, Israel
2Clalit Research Institute, Tel-Aviv, Israel

BACKGROUND: antidepressant medications (AD) are among the most prevalent prescribed drugs across the world. They are prescribed in many conditions, such as depression, anxiety and obsessive compulsive disorder, and all across age groups. However, although their beneficial effect requires long-term use, there was no study exploring the effect of adherence to these drugs on the long-term outcome measures such as all-cause mortality.

METHODS: we used a large dataset, using Israel's biggest health provider electronic medical records (53% of the nation population, representative of the general population) to follow-up a cohort of 429,457 individuals who were prescribed AD between 2008-2011. We measured adherence as the ratio between the length of period the drug was purchased and the prescription period. The main outcome measure was all-cause mortality. We also were able to control for other covariates that may affect mortality.

RESULTS: overall, of the total population, 251,745 purchased at least one prescription, with a 9.3% mortality rate. Although crude mortality rates showed association with increased adherence, adjusting for covariates reversed that association completely. In a multivariate analysis, adherence of 50% and above was associated with significantly less mortality (HR 0.83, 0.87) compared to non-adherence (<20%) in the general population. Further analysis revealed the same pattern of association in sub-populations such as patients with ischemic heart disease, stroke or Parkinson's disease. Surprisingly, in cancer patients there were mixed results.

CONCLUSIONS: This is the first study to demonstrate the inverse association between adherence to AD and all-cause mortality in a general-population-based large sample cohort (N=251,745) for a period of 4 years. These findings are vital for clinicians' practice. The beneficial effect of adherence (even partial) on increasing survival should encourage clinicians of all disciplines, particularly general physicians, to upgrade their efforts to sustain and enhance their patients' adherence to AD, eventually leading to increased life-expectancy.

Depression is projected to become the second leading cause of disability worldwide by the year 2020. Since suboptimal duration and inadequate dosing of AD treatment increase the risk for relapse, chronicity and – as shown here- mortality, low adherent behavior is of considerable clinical, economic and public health concern. This study contributes new data for health policy decision-makers to evaluate the effects and correlates of adherence to AD on mortality rate.

Abstract: 0035 Poster

Are serotonin metabolite levels related to bone mineral density in patients with neuroendocrine tumours?

Maralyn Druce1, Simona Grozinsky2, Sen Gupta Piya1
1Barts and the London School of Medicine and Dentistry, QMUL, London, UK
2Hadassah Hospital, Jerusalem, Israel

BACKGROUND: Bone mineral density (BMD) is influenced by multiple factors. Recent studies have highlighted a possible relationship between serotonin and BMD. Patients with neuroendocrine tumours (NET) frequently have elevated urinary 5-hydroxy-indoleacetic acid (5HIAA) levels, a serotonin metabolite. Evaluation of the relationship between 5HIAA and BMD in NET patients may provide insights into the relationship between serotonin and BMD.

METHODS: One-year prospective audit of consecutive NET patients (UK and Israeli institutions). Relationships between urinary 5HIAA and dual X-ray absorptiometry (DEXA)-scan-measured BMD were investigated by group comparisons, correlation and regression.

RESULTS: Of 65 NET patients, 18 did not participate or were excluded. Of 47 subjects evaluated (48.9% males, 63.8±10.5 years, BMI 26.6±4.4kg/m2) with 32 gastrointestinal, 10 pancreatic, 3 pulmonary and 2 ovarian NETs, 72.3% had the carcinoid syndrome. Median interval from diagnosis was 4.0 years (IQR 2.0-6.0); 42.6% had osteoporosis and 31.9% osteopaenia (WHO definition). There was no significant difference between the high and normal urinary 5HIAA groups' hip or spine BMD (standardised BMD, total T-score or total Z-score). There was a weak inverse correlation between urinary 5HIAA and hip BMD; urinary 5HIAA was an independent predictor (linear regression) for low hip BMD.

CONCLUSION: These data do not demonstrate that NET patients with high serotonin metabolites have lower BMD but a weak inverse correlation between urinary 5HIAA and hip BMD warrants further evaluation. A larger cohort with prospective design including fractures as a clinical outcome will aid these data in determining if NET patients should be subject to targeted osteoporosis prevention.

Abstract: 0036 Poster

Novel Glycosylated Sulfonylurea`s Anti diabetic drug candidates

Ghadeer Abdul Rahman Suaifan1, Mayadah B Shehadeh1, Vincenzo Abbate2
1Department of Pharmaceutical Sciences, The University of Jordan, Amman, Jordan
2Institute of Pharmaceutical Science, King's College London,, London, UK

Diabetes mellitus (DM) is a lifelong metabolic disease with an increased prevalence over the world. According to the International Diabetes Federation reports, one in every eleven adults had diabetes and one in every ten adults will have diabetes by 2040. DM is divided into three main types: Type I, Type II and Gestational diabetes. Type II DM accounts for more than 90% of all diabetic cases and is commonly treated with any of the two oral hypoglycemic medications (sulfonylureas and biguanides) available in the market despite the extensive research efforts done up to date. Sulfonylureas medication. However, these therapies have a number of side effects due to their poor selectivity. Therefore, the discovery of new hypoglycemic scaffolds with minimum side effects is still a challenge to medicinal chemists. Streptozocine is an anticancer drug commonly used to generate type II DM animal model due to its selective uptake by pancreatic cells. This selectivity was attributed to the presence of glucosamine moiety in its structure. Therefore, novel glycosylated sulfonylurea derivatives were synthesized. These compounds were designed to integrate the glucosamine moiety with the reactive sulfonylurea pharmacophoric features essential for the anti-diabetic activity. Glucosamine moiety is proposed to promote selective drug uptake by pancreatic β islets cells, hence, reducing drug cardiotoxic adverse effect and enhancing drug potency. Accordingly, several derivatives were synthesized and evaluated in vivo on streptozocine induced diabetic mice model. The 2-deoxy-2-(4-chlorophenylsulfonylurea)-d-glucopyranose showed higher potency among the derivatives at different doses (60 mg/kg, 30 mg/kg and 7.5 mg/kg). In conclusion, these novel glycosylated sulfonylurea derivatives are potential anti-diabetic drug candidates.

Abstract: 0038 Poster

Occupational exposure of pharmaceutical workers to drug product ingredients and their effect on Staphylococcus spp. nasal carriage and antibiotic resistance

Randa Nayef Haddadin1, Suhair Saleh2, Manal Ayyash2, Phillip Collier3
1Faculty of Pharmacy, The University of Jordan, Amman, Jordan
2Faculty of Pharmacy, University of Applied Sciences, Amman, Jordan
3School of Contemporary Sciences, University of Abertay Dundee, Dundee, UK

BACKGROUND: Pharmaceutical manufacturing workers are exposed to significant amounts of product ingredients, including antibiotics. Such exposure could affect their nasal microflora.

OBJECTIVE: To assess the effect of exposure to various unidentified pharmaceutical ingredients in cephalosporin-manufacturing and non-cephalosporin plants on the nasal carriage of Staphylococcus spp. and their antibiotic resistance.

METHODS: Nasal swab samples were collected from 39 workers in both plants on three different occasions. Staphylococci were isolated and identified to species level. Antibiotic resistance profiles were determined.

RESULTS: There was complete absence of S. aureus in the samples collected from workers in both facilities. Multiple drug resistant coagulase-negative staphylococci (MDR CONS) prevalence rates were higher in the non-cephalosporin plant than in the cephalosporin plant, with resistance towards six classes of antibiotics.
S. epidermidis was the prevalent species in the non-cephalosporin plant and S. haemolyticus prevailed in the cephalosporin-producing plant.

CONCLUSION: The observed prevalence of CONS in both production plants was the same. However, exposure to intermittent non-cephalosporin pharmaceuticals results in higher prevalence of MDR CONS compared to continuous exposure to cephalosporin.

Abstract: 0041 Poster

Levels of metabolic markers in drug-naive prediabetic and type 2 diabetic patients

Amal Akour1, Violet Kasabri1, Yasser Bustanji1, Dana Hyasat2, Nahla Khawaja2, Ayman Zayed3, Munther Momani3
1Department of Biopharmaceutics and Clinical Pharmacy, Faculty of Pharmacy, The University of Jordan, Amman, Jordan.
2National Center of Endocrinology and Genetics, Amman, Jordan.
3Endocrinology and Diabetes Unit, Jordan University Hospital, Amman, Jordan.

OBJECTIVE: Type 2 diabetes mellitus (T2DM) and prediabetes (Pre-DM) are associated with changes in levels of metabolic markers. The main aim of this study was to compare the levels of omentin, irisin, endothelin-1, nesfatin, hepatocyte growth factor (HGF), Fibroblast growth factor (FGF21) and oxytocin (OXT) between normoglycemic and preDM/T2DM obese Jordanian patients.
METHODS: One hundred and ninety eight adult Jordanian subjects were recruited. Demographic data, clinical parameters, were collected. The serum levels of biomarkers were measured by enzymatic assay procedure.

RESULTS: Compared to normoglycemic subjects (95 subjects), pre-DM/T2DM (103 subjects) displayed higher HGF (ng/mL) = 78.8 (71.4-104) vs. 55.9 (45.3-66.6), p <0.0001; and Nesfatin (ng/ml)= 0.5 (0.4-0.7) vs. 0.2 (0.1-0.4), p <0.0001; betatrophin (ng/ml)= 1.2 (0.8-1.6) vs. 0.22 (0.15-0.41), p<0.0001. On the other side, they had lower levels of omentin (ng/ml)= 2.1 (0.9-3.3) vs. 3.6 (2.0-6.4), p<0.0001, irisn (ng/ml)= 113.7 (88.9-142.9) vs. 132.6 (110.7-147.8), p<0.0001; and oxytocin (pg/ml) =1077.9 (667.3-1506.0) vs. 2180.1 (1464.5-2795.6), p<0.0001; respectively. Incomparably, FGF-21 (ng/ml) = 0.3 (0.2-0.5) vs. 0.2 (0.1-0.4), and Endothelin (pg/ml) = 2.7 (1.3-5.2) vs. 2.8 (1.6-5.6) did not prove any substantial difference among two groups (p>0.05).

CONCLUSION: In the present study, patients with pre-DM and T2DM have higher serum levels of metabolic HGF, Nesfatin, betatrophin and lower levels of omentin, irisin and OXT. Future interventional studies are required to confirm the potential utilization of these markers as novel progression or therapeutic targets in the pharmacotherapy of diabetes.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0043 Poster

Lower levels of placental protein 13 (PP13) in the extracellular vesicles (EVs) of preeclampsia patients at delivery

Marei Sammar1, Dionne Tannetta2, Manu Vatish3, Ian Sargent3
1Ephraim Katzir Dept. of Biotechnology Engineering, ORT Braude College, Karmiel, IL
2Department of Food and Nutritional Sciences, PO Box 226, Whiteknights, Reading RG6 6AP
3Nuffield Department of Obstetrics & Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, UK.

INTRODUCTION: Extracellular vesicles are an important cell-derived component in communicating various pathological conditions and pregnancy disorders. Preeclampsia (PE) is one of the most life threatening pregnancy disorders. A hallmark of PE is elevated placental shedding of syncytiotrophoblast extracellular vesicles (STB-EV) into the maternal circulation. Previous studies have implicated increased shedding of STB-EV expressing one of the putative placental biomarkers galectin 13 (also known as PP13) from placental villi in established PE. Other studies have shown reduced PP13 RNA in both the placenta and in maternal serum. In this study we explored PP13 in STB-EV collected by dual placental lobe perfusion in order to assess the differences in STB-EV PP13 levels in PE compared to normal placentae.

METHODS: Placentae were obtained at caesarean section and the STBEVs were collected by the dual placental lobe perfusion model, using sequential centrifugation and filtration. Two populations were isolated: a 10,000×g pellet (10 KP) that was enriched for STB micro-vesicles (STB-MVs) and a 150,000×g pellet (150 KP) enriched for STB exosomes (STB-EX). The purity and size distribution were assessed by Nanoparticle Tracking Analysis (NTA). Western blot analyses was used to verify the enrichment of the 10 KP (STB-MVs) and 150 KP (STB-EX) by their respective proteomic cargo. PP13 expression was determined by Western blotting and quantified in the STB-EVs by ELISA immunoassay. Statistical analyses were performed using a t-test ($p<0.05$ as significant).

RESULTS: Placentae were collected at the time of delivery from 10 normal and 10 PE cases, and the presence of PP13 was determined on the 10k (STB-MV) and 150 k (STB-EX) pellets and quantified in STB-EVs. Western blot analyses revealed that the STB marker placental alkaline phosphatase (PLAP) was present in both the 10KP and the 150 KP preparations by immunoblotting with the MAb NDOG2, whereas the 150 KP samples uniquely expressed the exosome specific markers Alix, and CD9. Accordingly, PP13 was present in both of the vesicle populations. The PP13 load in the total STBEVs (10+ 150 KP) derived from PE patients was significantly lower compared to normal placentas (300.5+166.4 vs 637.8+160.8 pg/μg protein, p= 0.00016). PP13 was localized to both the inside and displayed on the surface of STBEVs derived from normal and preeclamptic placentas.

CONCLUSIONS: This study has shown for the first time the expression of PP13 in both STBMVs and STBEXs isolated by placental lobe perfusion. Our study indicates that the levels of PP13 in STB-EV (10K P and 150KP) preparations are significantly reduced during established PE. This reduction correlates with the previously reported lower level of PP13 mRNA detected in both the placenta and in maternal blood. It remains to be seen how of the reduced level of PP13 in STB-EVs is utilized in communicating the development of PE within the placenta and how these fractions are involved in the secondary organ response of PE and in the pathogenesis of the disorder.

Abstracts

Abstract: 0045 Poster

Human liver sinusoidal endothelial cells promote intracellular crawling of lymphocytes during recruitment- a new step in migration.

Daniel Adam Patten1, Chris Weston1, Sirpa Jalkanen2, Marko Salmi2, Antal Rot3, David Harvey Adams1, Shishir Shetty1
1Centre for Liver Research, Institute of Immunology and Immunotherapy, University of Birmingham, United Kingdom
2MediCity Research Laboratory, University of Turku, Turku, Finland
3Department of Biology, University of York, United Kingdom

BACKGROUND: Endothelial cells (ECs) play a key role in the homing of leukocytes to different sites within the body. Endothelial heterogeneity is a evolutionary conserved property of ECs and influences their morphological and functional properties. These properties allow ECs to adapt to their environment within specific organs but also contribute to organ specific homing of immune cells.
Chronic liver disease is rising in incidence globally and there are limited treatments for end stage disease. The recruitment of lymphocytes via the hepatic sinusoidal channels and positioning within liver tissue is a critical event in the development and persistence of chronic inflammatory liver diseases. The hepatic sinusoid is a unique vascular bed lined by hepatic sinusoidal endothelial cells (HSEC), a functionally and phenotypically distinct sub-population of endothelial cells.

METHODS: We isolated primary human HSEC from liver tissue obtained from surgical resection specimens. These cells were incorporated into flow based adhesion assays which recapitulate the environment of the hepatic sinusoids. We used immunofluorescent markers to study the migration of lymphocytes across primary human HSEC.

RESULTS: We found that lymphocytes enter into HSEC, confirmed by electron microscopy demonstrating clear intracellular localization of lymphocytes in vitro and by studies in human liver tissues. Stimulation by interferon gamma (IFNγ) increased intracellular localization of lymphocytes within HSECs. To determine whether this was a specific feature of HSEC we tested the ability of IFNγ to promote this route of migration in vascular endothelial cells isolated from human umbilical veins (HUVEC). We found that whilst total adhesion was similar between HSEC and HUVEC, intracellular migration in HUVEC occurred significantly less frequently compared to HSEC. Furthermore, using confocal imaging and time-lapse recordings we demonstrated ‘intracellular crawling’ of lymphocytes entering into one endothelial cell from another. This required the expression of ICAM-1 and stabilin-1 and was facilitated by the junctional complexes between HSEC. Microarray analysis, validated by qPCR and ELISA, confirmed that HUVEC and HSEC are characterised by significant differences in junctional formation.

CONCLUSION: We demonstrate a new step in lymphocyte migration which is facilitated by the unique structure of HSEC. During chronic inflammatory diseases lymphocyte recruitment increases often leading to ‘ infiltrates’ around portal vessels. Our findings suggest that lymphocytes crawl intracellularly from endothelial cell to endothelial cell towards the portal regions.The fact that we saw a marked increase in intravascular crawling in HSEC treated with IFN-γ supports a particular role in inflammation. We therefore believe this novel finding provides a new insight into lymphocyte migration and could lead to new treatments for inflammatory liver diseases.

Abstract: 0046 Poster

Anti-cancer and Anti-inflammatory activities of plant extracts used against hematological tumors in traditional medicine of Jordan.

Areej M Assaf1, Randa N Haddadin2, Nedhal A Aldouri3, Mohammad K Mohammad2, Sundos Al Alawi1, Reem Alabassi1, Yasser Bustanji1
1Department of Biopharmaceutics and Clinical Pharmacy. Faculty of Pharmacy, The University of Jordan, Amman, Jordan.
2Pharmaceutics and Pharmaceutical Technology. Faculty of Pharmacy, The University of Jordan, Amman, Jordan.
3Faculty of Pharmacy, Al-Zaytoonah Private University, Amman, Jordan.

Ethnopharmacological relevance: Mercurialis annua L., Bongardia chrysogonum L. and Viscum cruciatum Sieb have been traditionally used by local herbalists in Jordan for the treatment of hematopoietic neoplasms.

Aim of the study: To determine the anti-cancer and anti-inflammatory potentials of the three extracts against two of the most common hematopoietic malignancies in the Jordanian populations; Burkitt’s lymphoma and Multiple myeloma.

MATERIALS-METHODS: The anti-cancer activity was tested against the two cell lines (BJAB Burkitt’s lymphoma and U266 Multiple myeloma) using the MTT and trypan blue assays. The pro-inflammatory cytokines interleukin (IL) -1β, IL-8 and tumor necrosis factor-α (TNF-α) were measured in the pretreated cell lines using ELISA assay to determine the anti-inflammatory activity of Viscum cruciatum Sieb against the two cell lines.

RESULTS: The results show no evidence of stimulation of tumor growth by any of the three extracts comprising cell lines from hematological malignancies, but Viscum cruciatum Sieb showed a selective anticancer activity against BJAB cells, with IC50 value of 14.21 µg/mL Viscum cruciatum Sieb extract showed an inhibitory effect on the pro-inflammatory cytokine IL-8, but it increased TNF-α and IL-1β secretions in BJAB cells. Whereas, it had an inhibitory effect on TNF-α and IL-1β cytokines while it enhanced IL-8 secretions in U266 cells.

CONCLUSION: Among the three tested herbal extracts used in the traditional medicine in Jordan, only Viscum cruciatum Sieb showed high anti-cancer potentials. They also had an anti-inflammatory effect. These observations raise the prospects of using Viscum cruciatum Sieb for treatment of imbalanced cytokine production and for enhancing cancer and other immunotherapies.

Abstract: 0048 Poster

Bovine serum albumin-loaded nanoemulsion using spontaneous emulsification: A potential drug delivery system for protein therapeutics.

Rania Hamed1, Harmesh Ajoula2
1AlZaytoonah University of Jordan
2University of Manchester

Objective. To develop a protein loaded nanoemulsion without employing high energy to avoid the denaturation of proteins. Such an approach has a lot of potential to formulate protein therapeutics in stable form. Toward this aim, bovine serum albumin (BSA), a water-soluble model protein, was incorporated into water in oil in water (w/o/w) nanoemulsion drug delivery system using spontaneous emulsification method.

Methods. BSA w/o/w nanoemulsion formulations were obtained by screening the type and concentration of the oil phase, surfactant, and cosurfactant. Coarse BSA emulsion (w/o) was prepared at a concentration of 25 mg/mL (Table 1). Different volumes of BSA emulsion were spontaneously emulsified in an aqueous phase of surfactant, cosurfactant and water to form w/o/w nanoemulsions (Table 2). The optimized BSA nanoemulsion formulations were selected based on mean droplet size, miscibility, clarity, flowability, and storage stability at room temperature.

Results. BSA-loaded nanoemulsions were composed of oil (oleic acid), combination of surfactant (Tween 20) and co-surfactant (Transcutol P) at a ratio of 1: 2, respectively, and water. The concentration of BSA in BSA-loaded nanoemulsion ranged from 4 to 11.1 mg/mL. The average droplet diameter was about 191 nm. BSA-loaded nanoemulsions showed no turbidity, phase separation, and precipitation, and were stable at room temperature for 20 days (Fig. 1).

Conclusions. W/o/w nanoemulsions of the model protein BSA were prepared by spontaneous emulsification to enhance the stability of BSA protein. The results showed that w/o/w nanoemulsion could be employed as a potential drug delivery system for water-soluble protein drugs.

Future work. Thermodynamic stability (turbidity, phase separation, precipitation, and flowability) at room temperature and 37ºC, and BSA bioactivity in the optimized BSA-loaded nanoemulsion will be investigated. Extrapolating the nanoemulsion developed method to produce a stable liquid formulation of Interleukin-1 receptor antagonist and a nanoemulsion of the biologically active IgG, as test cases to show proof of concept for protein delivery.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0049 Poster

Identification of high-penetrance rare genetic variations among Israeli patients manifesting early severe Age-related Macular Degeneration

Eran Eran1, Nadav Shoshany1, Chen Weiner1, Noam Shomron2
1The Matlows Ophthalmo-genetics Laboatory, Assaf Harofeh Medical Center,Sackler Faculty of Medicine, Tel Aviv University, Israel
2Functional Genomics Laboratory, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

PURPOSE: To identify rare genetic variations in Israeli patients with severe, early-onset Age-related Macular Degeneration (AMD).

METHODS: We performed Whole Exome Sequencing (WES) on eight patients (four sib pairs from four families – two from Tunisian ancestry and two from Ashkenazi ancestry) manifesting early-onset AMD, and searched for disease-causing genetic variants in previously identified macular degeneration related genes. Validation studies of the variants included bioinformatics tools, segregation analysis of mutations within the families, and an estimate on variant prevalence in an ethnically matched cohort of AMD patients.

RESULTS: All index patients were in their 6th to early 7th decade when diagnosed, with severe visual impairment due to extensive geographic atrophy and/or choroidal-neovascularisation common by the age of 75 years. Approximately, 400,000 genomic variants for each DNA sample were included in the downstream bioinformatics analysis, which ended in the discovery of four rare variants: a single base-pair deletion (c.4162delC) in the Hemicentin (HMCN1) gene; a missense variant (p.V412M) in the Complement Factor-I (CFI) gene; a missense variant (R735W) in Complement Factor 3 (C3) gene; and a missense variant (R1210C) in Complement Factor-H (CFH) gene. Screening for these variants in ethnically matched cohorts confirmed their rarity (<0.05%), and identified another family with the CFI variant.

CONCLUSIONS: Our study identified four rare genetic variants including two novel ones (CFI p.V412M; and HMCN1 c.4162delC) in a cohort of aggressive AMD patients. These results further support the significance of rare pathogenic variants in the complement system components in AMD pathogenesis.

Abstract: 0050 Poster

Longitudinal effects of lesions on functional networks after stroke

Smadar Ovadia Caro1, Kersten Villringer2, Jochen Fiebach2, Gerhard Jan Jungehulsing3, Elke van der Meer4, Daniel S Margulies5, Arno Villringer6
1Berlin School of Mind and Brain, The Mind-Brain Institute, Humboldt University, Berlin, Germany; Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; Institute of Psychology, Humboldt University, Berlin, Germany
2Center for Stroke Research, Charité University, Berlin, Germany
3Center for Stroke Research, Charité University, Berlin, Germany; Department of Neurology, Charité University, Berlin, Germany
4Institute of Psychology, Humboldt University, Berlin, Germany; Berlin School of Mind and Brain, The Mind-Brain Institute, Humboldt University, Berlin, Germany
5Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; Berlin School of Mind and Brain, The Mind-Brain Institute, Humboldt University, Berlin, Germany
6Berlin School of Mind and Brain, The Mind-Brain Institute, Humboldt University, Berlin, Germany; Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; Center for Stroke Research, Charité University, Berlin, Germany

While ischemic stroke reflects focal damage determined by the affected vascular territory, clinical symptoms are often more complex and may be better explained by additional, indirect effects of the focal infarct. Assumed to be structurally underpinned by anatomical connections, supporting evidence has been found using alterations in functional connectivity of resting-state fMRI data in both sensorimotor and attention networks. However, stroke commonly results in a multi-faceted neurological deficit involving more than one modality. Heterogeneity of lesions poses an additional experimental challenge to study plasticity in this population. In the current study we investigated the distal effects of lesions on a global level. We present a methodological approach to study plasticity at the multi-network level, allowing the exploration of heterogeneous lesions in a unified model. Longitudinal resting-state fMRI scans were acquired at three consecutive time points, beginning in the acute phase (day 1, 7, and 90 after stroke) in 12 patients following ischemic stroke. Changes in functional connectivity over time were computed for eight pre-defined networks, excluding the lesion area. We found a preferential functional change in affected networks (i.e. networks containing lesions changed more during recovery when compared to unaffected networks). Since the lesion area was excluded from the analysis, these results reflect indirect effects of focal infarcts on structurally intact, interconnected regions. The degree of change in functional connectivity within affected networks was significantly correlated with clinical changes assessed with the National Institute of Health Stroke Scale (NIHSS). Our results provide evidence that the functional architecture of large-scale networks is critical to understanding the clinical effect and trajectory of post-stroke recovery.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0052 Poster

Knowledge, awareness, and attitudes toward antibiotic use and antimicrobial resistance

Mohamed Ezzat El Zowalaty1, Tatiana Belkina2, Jurjen Duintjer Tebbens3, Safaa Daghriry4, Ayman Noreddin5
1School of Health Sciences, University of KwaZulu Natal, Durban, South Africa
2Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University, Prague, Czech Republic
3Department of Biophysics and Physical Chemistry, Faculty of Pharmacy, Charles University, Prague, Czech Republic
4Faculty of Applied Medical Sciences, Jazan University, Jazan, Saudi Arabia
5Faculty of Pharmacy, Chapman University, Irvine, California, USA

Inappropriate use of antibiotics is a public health problem of great concern. The objective of the present study was to evaluate knowledge of antibiotics, race, gender and age as independent risk factors for self-medication. Residents and population from different regions of Saudi Arabia were randomly selected and we conducted a cross sectional survey study among residents. Data were collected between June 2014 to May, 2015 from 1,310 participants and data were recorded anonymously. The questionnaire was randomly distributed by interview of participants and included sociodemographic characteristics, antibiotics knowledge, attitudes and behavior with respect to antibiotics usage. Main outcome measure: Population aggregate scores on questions and data were analyzed using univariate logistic regression to evaluate the influence of variables on self-prescription of antibiotics. The response rate was 87.7%. A cumulative 63.6 % of participants reported to have purchased antibiotics without a prescription from pharmacies; 71.1% reported that they did not finish the antibiotic course as they felt better. The availability of antibiotics without prescription
was found to be positively associated with self-medication (OR 0.238, 95% CI 0.17- 0.33). Of those who used prescribed or non-prescribed antibiotics, 44.7% reported that they kept left-over antibiotics from the incomplete course of treatment for future need. Interestingly, 62% of respondents who used drugs without prescription agreed with the statement that antibiotics should be access-controlled prescribed by a physician. We also found significant association between storage, knowledge/attitudes and education.
The overall level of awareness on antibiotics use among residents in Saudi Arabia is low. This mandates public health awareness intervention programs to be implemented on the use of antibiotics. The impact on practice of the present study is that (i) residents in Saudi Arabia reported low level of awareness on the use of antibiotics and antimicrobial resistance, as there was a significant association between storage, knowledge/attitudes and education and use of antibiotics, (ii) there is an urgent need for public health intervention programs to increase the awareness on use and knowledge towards antimicrobial resistance in Saudi Arabia, and (iii) interestingly, respondents who used antibiotics without prescription agreed with the statement that antibiotics should be access-controlled drugs prescribed by a physician Implementation of strict legislatures on the dispensing of antibiotics without prescription in local pharmacies will reduce the uncontrolled access to antibiotics in Saudi Arabia.

Abstracts

Abstract: 0053 Poster

Characterization of Novel Antimicrobial Peptides from the Venom of Egyptian Scorpions

Mohamed A Abdel Rahman1, Patrick L Harrison2, George R Heath3, Benjamin R Johnson3, Mohamed M Tawfik2, Stephen D Evans3, Keith Miller2, Peter N Strong2
1Zoology Department, Faculty of Science, Suez Canal University, Ismailia 41522, Egypt
2Biomolecular Research Centre, Sheffield Hallam University, Sheffield, UK
3Department of Physics and Astronomy, Leeds University, Leeds, UK

There is an urgent need for the discovery of new antimicrobial agents as evidenced by the recent dramatic increase in the numbers of pathogenic bacteria that have become resistant to front-line antibiotics. Antimicrobial peptides (AMPs) have been found in both vertebrates and invertebrates, existing in the skin, epithelial cells, blood or haemolymph, as well as the venoms of various animals including scorpions. Because of their selectivity for prokaryotes and their membrane-disruptive mechanisms for which microbes have little natural resistance, AMPs offer an attractive approach to the development of novel antibiotics. Using a cDNA cloning strategy, four new AMPs (Smp-13, Smp-24, Smp-43 and Smp-76) were characterized from the venom gland of the Egyptian scorpion Scorpio maurus palmatus (Abdel-Rahman et al., 2013). Smp-24 and Smp-43 have broad spectrum antimicrobial activity with MICs (ug/ml) ranging from 2-8, 64-128 and 32-64 for Gram-positive bacteria, Gram-negative bacteria and fungi, respectively. Toxicity assays showed that Smp-24 exhibited mild hemolytic activity against sheep red blood cells while no hemolytic activity was detected for Smp-43. Moreover, Smp-24 and Smp-43 were cytotoxic (ATP release assay) toward mammalian HepG2 liver cells. In order to elucidate the mechanism of action of these peptides, we have used various biophysical and molecular techniques, including atomic force microscopy (AFM), quartz crystal microbalance-dissipation (QCM-D), intracellular bioreporter genes and liposomal leakage assays. Both Smp-24 and Smp-43 exhibited a membrane disruptive mechanism of action, however Smp-24 showed evidence of interference with DNA synthesis. Also, our AFM and QCM-D data provide direct evidence that Smp-24 has multiple mechanisms of action, dependent on lipid composition. Smp-24 forms toroidal pores in model prokaryotic membranes but induces hexagonal, non-lamellar phase structures and causes phase segregation in model eukaryotic membranes. Our findings suggest that both Smp-24 and Smp-43 can be successful scaffolds for future therapeutic AMPs.

Abstract: 0055 Poster

A minority of cells causing a major problem? - The emergence of fluconazole resistance in Cryptococcal meningitis

Neil Stone1, Tihana Bicanic1, Judith Berman2
1Institute of Infection and Immunity, St. George's, University of London, United Kingdom
2Department of Molecular Biology and Biotechnology, Tel Aviv University, Israel

BACKGROUND: Cryptococcal meningitis (CM) is caused by the fungal pathogen Cryptococcus neoformans (Cn). Symptoms include severe headache, seizures and reduced consciousness. CM is always fatal if left untreated. Advanced immunosuppression due to HIV is the major risk factor for developing CM, and is most often seen in sub-Saharan Africa, due to the high prevalence of HIV in that region. Mortality from CM is estimated at 500,000 people per year. The most effective CM treatment is a combination of two antifungals, amphotericin B and flucytosine (5FC), neither of which is available in most parts of Africa. Instead, patients are treated with fluconazole (FLU) despite poor clinical outcomes with this treatment. The phenomenon of heteroresistance, in which a minor subpopulation of cells are drug resistant, in an otherwise susceptible strain, has the potential to play a major role in the rapid appearance of FLU resistance. Recent in vitro studies have described the role of aneuploidy (an imbalanced number of chromosomes), as contributing to heteroresistant Cn isolates. However, the role of heteroresistance in the clinical setting has not been reported for CM. We are investigating the role of FLU heteroresistance in patients receiving treatment for CM, and the molecular basis of this type of drug resistance.

METHODS: A clinical cohort of patients in Tanzania presenting with a first episode of CM is being prospectively studied. Patients are treated with FLU at a dose of 800mg or 1200mg daily, or in combination with 5FC. Lumbar punctures are performed on days 1, 7 and 14 to relieve symptoms and to collect cerebrospinal fluid (CSF) for culture. CSF is plated onto plain and FLU-containing agar, to determine total CFU/ml in CSF as well as the FLU-resistant subpopulation. Cn isolates will be analyzed by whole genome DNA sequencing to investigate the role of aneuploidy and drug target site mutation in the emergence of resistance. Additionally, drug efflux and upregulation of drug resistance genes will be evaluated in vitro.

RESULTS: 25 patients have been recruited - 18 receiving FLU monotherapy and 7 receiving FLU/5FC combined. Heteroresistance, defined as a resistant subpopulation, was found at baseline in all isolates, comprising 0.01–25% of the total population of Cn cells in the CSF. By day 7, the proportion of resistant cells in the population increased (“amplification”). In patients on the combination arm of 5FC/Fluconazole, the resistant subpopulation apparently disappeared by day 14. 3 patients to date, all in the FLU monotherapy group and with high level heteroresistance at baseline, have confirmed clinical relapse with highly resistant Cn.

CONCLUSION Our results suggest that heteroresistance is a common feature of Cn isolates in Tanzania. Furthermore, amplification of the resistant subpopulation at day 14 was observed in 83% of patients during fluconazole monotherapy and in no patients treated with the fluconazole/5FC combination. This may be an underappreciated factor in the inferior activity of fluconazole as monotherapy for CM. The addition of 5FC appears to prevent amplification of resistance in these patients, and provides a promising path to improved CM treatment in sub-Saharan Africa.

Abstract: 0056 Poster

The miltiple faces of the TMEM231 gene

Elena Chervinsky1, Ronen Spiegel2, Stavit Shalev1, Juan Chemke1, Tamar Ben Josef3
1The Genetic Institute, Emek Medical Center, Afula, Israel
2Pediatric Department B', Emek Medical Center, Afula, Israel
3Rappaport Faculty of Medicine, Technion, Haifa, Israel

The ciliopathies are a group of heterogeneous inherited diseases, affecting multiple organ systems, mainly renal, retinal, and hepatic, together with skeletal malformations and central nervous system developmental defects.TMEM231 is a part of the protein complex "transmembrane proteins" (TMEMs) which linked to defects in cilia assembly and function, and has been shown to be associated with a spectrum of phenotypes, including Joubert syndrome (JBTS), Meckel-Gruber syndrome (MKS), and Oro-facial-digital 3 syndrome (OFD3).

Given the facial gestalt of the probands (IV4) included mild downslanting palpebral fissures, convex and high nasal bridge, short philtrum and prominent incisors, as well as slender palms, truncal obesity, short stature, hypogonadism and pigmentary retinopathy (RP), the diagnosis of Cohen syndrome was highly suspected. His two sisters (IV3 and IV5) were presented with early onset RP as well. However the other clinical features were different between three siblings to a great extent. His older sister had severe developmental delay and profound intellectual disability, and his younger sister had very mild-borderline learning disabilities and nephronophthisis diagnosed later in adolescence.

We used whole-genome homozygosity mapping as well as exome sequencing and targeted gene sequencing to identify novel TMEM231disease-causing mutation c.511T>G (p.L171V) in three affected individuals originating from one consanguineous family of Arabic Muslim origin. Chromosomal microarray analysis (Affymetrix&Cytoscan 750K) did not detect any clinically significant genomic imbalances in patients IV3 and IV4.

Seeing that JBTS had been associated with several dysmorphic facial characteristics we compared the data to our patients and found only partial overlap. Given the overlapping of the phenotypes of our patients and Cohen syndrome, and the existence of VPS13 gene pathogenic variants in approximately 88% Cohen's syndrome individuals, the genetic analysis of these patients has to take in to account the possibility of ciliopathies genes involvement.

Allelic heterogeneity can explain the variability of clinical presentation of TMEM231 gene. However, non-typical malformation of MKS, as showed by Roberson et al (2015) and emphasized in our study, including heterotaxy, spleno-pancreatic fusion, cortical dysplasia etc., suggests the presence of additional syndromes due to involvement of the gene and its wider impact in biological processes. The family presented in our study shows a wide range of intra-familial phenotypic variability in subjects carrying the same mutations, both in terms of target-organs and in terms of severity of the disease, which might be explained by influence of epigenetic protective factors. Isolated RP, as presented in our study, could be due to genetic defect in ciliopathies syndromic genes. This work adds an example of the contribution of exome sequencing, not only in the discovery of new genes but also in expanding the phenotypic spectrum of known disease-associated genes, using reverse phenotyping, and supports the growing appreciation of the overlap in the molecular pathogenesis between different types of ciliopathies.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0057 Poster

Leptin and insulin up-regulate miR-4443 to suppress NCOA1 and TRAF4, and decrease the invasiveness of human colon cancer cells.

Ari Meerson, Hila Yehuda
Department of Molecular Biology of Chronic Diseases, MIGAL Galilee Research Institute, Kiryat Shmona, Israel

Obesity is a risk factor for colorectal cancer (CRC). Normal and tumour cells respond to metabolic hormones, such as leptin and insulin, and may react to obesity-associated resistance to these hormones by modifications in gene expression and alterations in tumourigenesis. The mechanisms affected by leptin and insulin signaling in CRC cells remain mostly unknown.

We hypothesized that microRNAs (miRNAs) are involved in the regulation of tumourigenesis-related gene expression in CRC cells by leptin and insulin. To test this hypothesis, miRNA levels in the CRC-derived cell lines HCT-116, HT-29 and DLD-1 were profiled, following leptin and insulin treatment. Validation by QRT-PCR confirmed that leptin at 100 ng/ml significantly up-regulated miR-4443, concomitantly with a significant decrease in cell invasion ability. Transfection with miR-4443 mimic decreased invasion and proliferation of HCT-116 cells. Moreover, leptin and miR-4443 transfection significantly down-regulated endogenous NCOA1 and TRAF4, both predicted targets of miR-4443, with known roles in cancer metastasis. miR-4443 was found to directly regulate TRAF4 and NCOA1, as validated by a reporter assay. The up-regulation of miR-4443 by leptin or insulin was attenuated by the inhibition of MEK1/2.

Our findings suggest that miR-4443 acts in a tumour-suppressive manner by down-regulating TRAF4 and NCOA1 downstream of MEK-C/EBP-mediated leptin and insulin signaling, and that insulin and/or leptin resistance (e.g. in obesity) may suppress this pathway and increase the risk of metastatic CRC.

Abstract: 0058 Poster

Identification and classification of the malaria parasite blood developmental stages, using imaging flow cytometry

Elya Dekel, Anna Rivkin, Meta Heindrich, Yotam Nadav, Yifat Ofir Birin, Ziv Porat, Neta Regev Rudzki
Department of Biomolecular Sciences, The Weizmann Institute of Science, Rehovot, Israel

Malaria is the most devastating parasitic disease of humans, caused by the unicellular protozoa of the Plasmodium genus, such as Plasmodium falciparum (Pf) and is responsible for up to a million deaths each year. Pf life cycle is complex, with transmission of the parasite between humans via mosquitos involving a remarkable series of morphological transformations. In the bloodstream, the parasites undergo asexual multiplications inside the red blood cell (RBC), where they mature through the ring (R), trophozoite (T) and schizont (S) stages, and sexual development, resulting in gametocytes (G). All symptoms of malaria pathology are caused by the asexual blood stage parasites. Flow cytometry methods were previously used to detect malaria infected (i) RBCs, in live or fixed cells, using DNA (Hoechst) and RNA (Thiazole Orange) stains. Here, by using imaging flow cytometry, we developed improved methods of identifying and quantifying each of the four parasite blood stages (R, T, S and G). This technique allows multi-channel, high resolution imaging of individual parasites, as well as detailed morphological quantification of Pf-iRBCs cultures. Moreover, by measuring iRBC morphological properties, we can eliminate corrupted and extracellular (dying) parasites from the analysis, providing accurate quantification and robust measurement of the parasitemia profile. This new method is a valuable tool in malaria molecular biology research and drug screen assays.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0059 Poster

Measuring Peak Oxygen Uptake using Perceptually-Regulated Exercise Test in Arm Cranking Exercise

Harran Al Rahamneh1, Craig Williams2
1Faculty of Physical Education, the University of Jordan, Amman, Jordan
2Children's Health and Exercise Research Centre, Sport and Health Sciences, College of Life and Environmental Sciences, University of Exeter, Exeter, UK

INTRODUCTION: Peak oxygen uptake (VO2peak) is the highest amount of oxygen that a person can take, transport and utilise while exercising at high intensities. Arm exercise is a justified mode of exercise testing and training for paraplegic persons and for those who use their arms predominantly during exercise such as rowing, swimmers and kayaking. Therefore, measuring VO2peak in arm cranking exercise is essential for these persons and athletes especially when considering that VO2peak is the gold standard of measuring cardio respiratory system. O2peak is also used as a predictor for deaths in cardiac patients and healthy-normal individuals.

METHODS: 15 participants (27.7 ± 4.7 years; 177 ± 6 cm; 79.9 ± 12.7 kg) volunteered for the study. Each participant completed two exercise tests; 1) Graded Exercise Test (GXT) to measure VO2peak, 2) perceptually-regulated exercise test (PRET) to measure VO2peak and to compare VO2peak values elicited in the PRET to the GXT. These two exercise tests were conducted in counterbalanced order in order to prevent the effect familiarisation on the test results. The GXT starts at 30 watts and increased by 15 watts each 2 minutes until exhaustion. In the PRET participants were asked to exercise at rating of perceived exertion (RPE) of 9, 11, 13, 15, 17 and 20 for 3 minutes at each RPE level. In the PRET test participants were asked to change the resistance until they feel that the resistance is equal to the given RPE.

RESULTS: paired sample t-test showed no significant difference in peak power output between the two exercise tests (GXT: 114 watt, PRET: 109 watt). There was also no significant difference in VO2peak between the two exercise tests (GXT: 27 ml.kg.min-1, PRET: 25 ml.kg.min-1). However, heart rate and pulmonary ventilation were significantly lower during the PRET compared to the GXT (159 b.min-1 & 144 b.min-1; 109 L.min-1 & 97 L.min-1, respectively). Participants rated the GXT to be more negative compared to the PRET (-3.9 & -3.5, respectively).

DISCUSSION: PRET can be used as an alternative for the GXT especially when considering that there were no significant differences in VO2peak and peak power output between the two exercise tests. Lower heart rate and pulmonary ventilation values in the PRET compared to the GXT can be attributed to the fact that participants increased power output in the last minute of the last stage of the PRET (i.e., RPE 20) which in turn did not give enough time for the heart rate and pulmonary ventilation to increase. However, in the GXT power output was increased at the beginning of each stage which gave at least one minute for the heart rate to increase.

Abstracts

Abstract: 0061 Poster

Diagnostic concordance of breast pathologists: lessons from the National Health Service Breast Screening Programme Pathology External Quality Assurance Scheme

Emad Rakha1, Mohamed Ahmed2, Mohamed Ahmed1, Mohammed Aleskandarany1, Zohlt Hodi1, Andrew Lee1, Sarah Pinder3, Ian Ellis1
1Department of Histopathology, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK
2Department of pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
3Cancer Studies, King's College London, Guy's Hospital, London, UK

Purpose of the study: Some recent studies have reported an unexpectedly high level of diagnostic discordance among breast pathologists which have raised concerns (JAMA.2015;313(11): 1122-32). This study aims to assess the diagnostic agreement among breast pathologists in the UK.

METHODS: 240 cases of breast lesions included in the UK NHSBSP breast pathology interpretive external quality assurance (EQA) scheme in the last ten years were reviewed. In this scheme one representative H&E stained slide from each case is circulated to an average of 600 participants, which resulted in 144,000 readings in total. Data on diagnostic categories (benign, and malignant; in-situ and invasive) were collected. Slides from cases with diagnostic discordance >=5% were reviewed by 3 pathologists.

RESULTS: Out of the 240 cases, 35 cases (14.6%) were identified. The reasons for diagnostic discordance included one or more of the following: 1-Scheme methodology limitations including i) lack of guidelines on coding of certain lesions namely phyllodes tumours and lobular neoplasia (n=7 cases), and ii) use of glass slides with variable representation of the same lesion on the different slides, an average of 75 slides per paraffin block are circulated per case (n=12 cases). iii) inclusion of certain morphologically challenging lesions that can't be interpreted without the aid of ancillary techniques or consultation. These included papillary lesions; benign with sclerosis, epithelial proliferation, and/or atypia (n=6) and malignant papillary lesions (n=6), complex sclerosing lesions (n=3) and intraductal epithelial proliferative lesions (n=5). 2-Pathologist--related factors: reviewing expert pathologists identified over and under-diagnosis in 8 cases (3.3% of all cases) including 5 papillary lesions.

CONCLUSIONS: The performance of breast pathologists is extremely high. Limitations of the EQA system should be addressed to assess the true performance. More complex papillary, proliferative and sclerosing lesions often require additional diagnostic work-up and difficult cases should trigger consensus opinion or expert referral.

Daniel Turnberg Travel Fellowship Scheme, Alumni Conference Cyprus 2016

Abstract: 0062 Poster

Identification and validation of biomarkers associated with acute and chronic graft versus host disease

Ebtesam Mahmoud El Gezawy1, Shaheda Ahmed2, Xiao Wang2, Jean Norden3, Kim Pearce3, Sadaf Atarod3, Ilona Hromadnikova4, Matthew Collin3, Ernst Holler5, Anne Dickinson2
11Haematological Sciences, Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK; 3 Clinical Pathology Department,Faculty of Medicine, Assiut University, Assiut, Egypt.
21Haematological Sciences, Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK;
2Alcyomics Ltd, Newcastle-upon-Tyne, UK
31Haematological Sciences, Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK
4Third Faculty of Medicine, Charles University, Prague, Czech Republic
5Regensburg University Hospital, Department of Hematology and Oncology, Regensburg, Germany

BACKGROUND: Graft versus host disease (GVHD) remains one of the major causes of morbidity and mortality in Hematopoietic stem cell transplantation (HSCT). Cytokines and chemokines and their receptors play a pivotal role in all phases of GVHD. These molecules provide an important signaling pathway for activation and recruitment of effector cells into sites of inflammation and have been implicated in the rejection of allogeneic transplants. Such chemokines, which have been reported to play a role in transplant rejection are CXCR10 and CXCR11. These chemokines share a single receptor, CXCR3, which is expressed by T lymphocytes and NK cells. They are inducible by IFN-alpha and IFN-gamma mediated signals and are expressed at sites of inflammation. They attract and activate cells bearing the CXCR3 receptor which results in trafficking and proliferation of T lymphocytes and NK cells at the site of inflammation. Recent studies have reported increased serum CXCL10 levels and increased epidermal expression in acute GVHD skin biopsies.

METHODS: In this study, we analyzed candidate inflammatory biomarkers (B-cell activating factor (BAFF), interleukin 33 (IL-33), CXCL10 and CXCL11) in a two-centre study. Biomarkers were evaluated pre-transplant and at serial time points post transplant in acute and chronic GVHD patient sera with time-matched control samples from patients without GVHD. Further validation was performed using the human skin explant assay, clinical GVHD biopsies and mRNA expression analysis.

RESULTS: BAFF was significantly increased pre-transplant. BAFF, IL-33, CXCL10 and CXCL11 showed increased levels in acute GVHD patient sera and high protein expression in grades II-III of the in vitro skin explant graft versus host reaction (GVHR) group. BAFF, CXCL10 and CXCL11 also showed increased mRNA expression levels in clinical biopsies compared with the no/low-grade GVHD group. BAFF, CXCL10 and CXCL11 levels were increased in chronic GVHD patient sera. We observed significantly increased levels of CXCL10 and CXCL11 in acute GVHD patient sera (CXCL10 day 14 $p<0.0003$ and day 28 $p<0.0001$, CXCL11 day 14 $p<0.001$ and day 28 $p<0.003$) and in chronic GVHD patient sera (CXCL10 6 months $p<0.02$, CXCL11 6 months $p<0.02$ and 12 months $p<0.0001$) compared to controls.

CONCLUSIONS: The results identify BAFF and CXCL10 as predictive biomarkers for acute GVHD and BAFF, CXCL10 and CXCL11 as useful diagnostic biomarkers for acute GVHD and chronic GVHD. Also, these results indicate a prominent role of CXCL10 and CXCL11 in the pathogenesis of GVHD.

Abstracts

Abstract: 0063 Poster

Changes in the abuse and misuse of prescription and Over-The-Counter (OTC) drugs: perceptions from community pharmacists in Jordan

Mayyada Wazaify1, Ebtesam Abood2, Linda Tahaineh3, Abla Al Bsoul1
1Department of Biopharmaceutics and Clinical Pharmacy, Faculty of Pharmacy, The University of Jordan (UJ), Amman, Jordan
2Department of Clinical Pharmacy, Faculty of Pharmacy, Lebanese International University (LIU), Aden, Yemen
3Department of Clinical pharmacy, Faculty of Pharmacy, Jordan University of Science & Technology (JUST), Irbid, Jordan

BACKGROUND: Prescription and nonprescription (or the so-called over-the-counter) drug misuse and abuse is a relatively under-researched area globally. For such medications, misuse has been identified as the use of the medicine for a genuine medical reason but in an incorrect manner in terms of dosage or duration, while abuse has been identified as the use of such medicines for non-medical reasons (e.g to lose weight or to experience high).1 Previous research has shown that most community pharmacists worldwide deal with this issue by refusing sales.1,2 However, community pharmacists should adopt a more positive role as health care professionals in dealing with suspected abuse / misuse and harm-minimisation may be a possible strategy.

OBJECTIVES: The aim of this study was to investigate the change in the patterns of abuse/misuse (if any) of prescription Over-The-Counter (OTC) drugs in community pharmacies in Jordan during the past 7 years.

METHODS: This was a cross-sectional survey using a drop-and-pick technique. A structured questionnaire based on one used previously in 2008, was sent to a stratified random sample of 320 community pharmacies in Amman, Zarka and Irbid. Data were managed and analyzed in SPSS. Descriptive frequencies and X2 tests of association are reported. Responses were compared across the two cohorts.

RESULTS: A total of 290 questionnaires were completed (response rate= 90.6%). The pharmacists named 727 OTC and 372 prescription-drugs as being suspected of abuse, each classified into 6 categories. The most important change was the appearance of new products on the list of abuse/misuse, that were not previously reported in 2008, such as: ophthalmic drops (cyclopentolate, chlorpheniramine, antazoline and naphazoline; n=39, 13.4%) and the anti-epileptic; Lyrica (pregabalin; n=19, 6.5%). Other drugs previously on the 2008 list like misoprostol have retracted in 2015 (from 7.1% to 1.3%).

CONCLUSION: Patterns of suspected prescription and OTC drug abuse/misuse have slightly changed in Jordan over time, with new drugs emerging and previous ones disappearing from the list. Legislations have resulted in such shifts. Current methods employed for dealing with this problem are still inadequate and a more active role of inspection is recommended.

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3 Albsoul-Younes et al., 2010 Abuse and misuse of prescription and non-prescriptions drug sold in community pharmacies in Jordan.Substance use and misuse;45: 1319-1329.

Abstract: 0065 Poster

A role for cannabinoid CB2 receptor in Tourette syndrome?

Tamar Harpaz1, Natali Shamir2, Merav Hajbi2, Efrat Sasson3, Iain Greig4, Ester Fride2, Sharon Anavi Goffer5
1Department of Behavioral Sciences, Ariel University, Ariel, Israel; The Mina and Everard Goodman Faculty of life Sciences, Bar-Ilan University, Ramat-Gan, Israel
2Department of Behavioral Sciences, Ariel University, Ariel, Israel
3Wise-Image, Israel
4School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK
5Department of Behavioral Sciences, Ariel University, Ariel, Israel; School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK

Attention-deficit hyperactive disorder (ADHD) is a common disorder, affecting 3-9% of children and 2-5% of adults around the world. About 50% of the patients with Tourette syndrome are also diagnosed with ADHD. ADHD is characterised with attention deficit, hyperactivity and impulsivity. The therapeutic effects of Cannabis Sativa in patients with either or both Tourette syndrome and Attention-Deficit Hyperactivity Disorder (ADHD) suggest the core involvement of the endogenous cannabinoid system in these disorders. The goal of our research is to study the effect of cannabinoid CB2 receptor selective ligands on tics. Our data suggest that CB2 receptor is involved in both ADHD-like behaviour and vocal tic-like behaviour. A quantitative MRI measurement revealed that compared with the brain structure of vehicle-treated mice, the tissue density of several brain areas was significantly higher in the ADHD-like mice. Identifying a role for the CB2 receptor in the aetiology of tic disorders will give rise to a new class of drugs to treat TS/ADHD patients.

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Abstract: 0066 Poster

Paraoxon-Induced BBB Dysfunction: A Triple Arm Mechanism Investigation

Itzik Cooper1, Orly Ravid1, Shirin Elhaik Goldman1, David Macheto1, Yael Bresler1, Fabien Gosselet2, Lucie Dehouck2, Michal Beeri3
1BBB-Group, The Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel
2Univ. Artois, EA 2465, Blood-brain barrier Laboratory (LBHE), F-62300 Lens, France
3The Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel

Organophosphorus compounds (OPs) are highly toxic chemicals widely used as chemical warfare nerve agents (e.g. soman, sarin) and as pesticides (e.g. paraoxon). Pesticide poisoning is one of the most common poisonings worldwide, estimated at one million cases each year with several hundred thousand deaths.
The blood–brain barrier (BBB) is a selective barrier formed by the endothelial cells that line cerebral capillaries, together with perivascular elements such as the closely associated astrocytic end-feet processes, perivascular neurons and pericytes. Physiologically, the BBB protects the brain from the compositional fluctuations of compounds that occur in the circulation and plays a major role in maintaining the constant environment required for normal brain function i.e. neuronal homeostasis. Under normal physiological conditions, the presence of continuous strands of tight junctions between adjacent endothelial cells of brain capillaries significantly prevents transport of polar solutes and macromolecules from circulation into the brain through the paracellular pathway. On the other hand, under pathological conditions, the leakage of intravascular substances through the disrupted BBB to brain parenchyma occurs mainly by increased function of transcellular pathway i.e., vesicular trancytosis malfunctioning of various transporters and efflux pups such as the P-glycoprotein (Pgp) and/or paracellular pathway (the opening of the intercellular tight junctions).
We are investigating the cellular mechanisms involved in BBB reaction after exposure to paraoxon. We have focused our investigation in three directions: 1) Barrier disruption at the paracellular (between cells) route i.e. alterations in tight junction (TJs) proteins expression and patterns- thus enabling paracellular permeation of paraoxon and other native blood circulating compounds which might disrupt brain chemical homeostasis. 2) Barrier disruption at the intracellular (through cells) route i.e. changes in the efflux pump P-glycoprotein (Pgp) activity after exposure to paraoxon, which can alter brain homeostasis by changing the brain concentrations of its multitude substrates and 3) Paraoxon-induced inflammation-like phenotype at the BBB surroundings which will suggest an indirect mechanism that can lead to both para and intracellular disruption pathways. State of the art, stem-cell derived, human in-vitro BBB system that closely mimic the in-vivo BBB is used as the key methodological platform.
Our initial results show that paraoxon directly affect the BBB in-vitro both at toxic and non-toxic concentrations by attenuating junctional protein expression as well as the expression levels of Pgp. At toxic concentration brain endothelial cells exhibit a morphological coping mechanism in which they enlarge their cell area thus preventing the formation of meaningful paracellular gaps and maintaining barrier properties for a large extent. At sub-toxic concentrations of paraoxon, a secretion of pro-inflammatory molecules occurs- promoting the transmigration of immune cells across the barrier. Lastly, we show that inhibition of caspases can abolish paraoxon-induced deleterious effects, opening a door for a potential therapeutic opportunity in the field of OPs poisoning.

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Abstract: 0067 Poster

Analysis of poisoning in children less than 6 years old reported to the poison control center in Palestine

Ansam Sawalha, Waleed Sweileh, Saed Zyoud, Samah Jabi
Department of Pharmacology and Physiology, Annajah University, Nablus, Palestine

BACKGROUND: Poisoning in children remains one of the most common reasons of emergency room visits and mostly in children less than 6 years old. The objective of this study was to analyze the inquiries reported to the poison center for children less than 6 years old and provide enlightenment regarding this topic.

METHODS: All data received by the poison control and drug information center (PCDIC) in Palestine were analyzed since its establishment in 2006 till now. The analysis include all cases in which the age was less than 6 years old. Analysis was performed using SPSS 16.

RESULTS: A total of 628 inquiries were received regarding children less than 6 years old. The average age was 2.7± 1.3 years. More than half of the calls (63.2%) were received from health care provider, and the rest was from families. More than two thirds (77.2%) of the inquiries were regarding males, and the majority (89.4%) of the calls were regarding poisoning, the rest were about medication dosage, or drug interactions, or side effects. Medications were encountered in the majority (328, 52.0%) of cases, followed by cleaning products (107, 17%). The rest were pesticides, plants, self care items, and others. Most (98.9%) of cases were due to single agent. Calls were received all day long, but mostly from 12: 00-18: 00 (45%), followed by 18: 00-24: 00 (37.3%). Regarding days of the week, Sunday, which is the first day of the week, had the most calls, but the number was not significantly higher than other days. The amount ingested ranged from one tablet to 8 tablets, and from few drops to full bottle. There were many cases where the amount was not known. Most families brought their children with within few hours of poisoning, and the route of poison entry was oral in 93.3%. In most cases, the poison center was contacted before any symptoms develop (63.4%). In the rest of the cases varied symptoms has developed from vomiting, abdominal pain, to tachycardia, bronchorreaha, to CNS depression, and one child developed coma. At the hospital, and before calling the poison center, 87 children (13.8%) received gastric lavage, and only one child received activated charcoal. After the poison center was contacted, charcoal was advised in 22 cases, while lavage in only 4 cases. The rest received no treatment, or antidotes, or were kept under monitoring for symptomatic treatment. Calls were received through out all months, especially May, June, and July (11.1%, 10.6%, 10.6%), and to a lesser extent in other months.

DISCUSSION: Poisoning of children in Palestine is common, and more attention should be given to parent and children education to avoid poisoning. Chemicals should be safely stored at home, and away from reach and sight of children. Continuous medical education is needed to health care providers regarding the management of acute poisoning cases. The use of gastric lavage should be decreased and limited to life-saving cases, while the utilization of activated charcoal should be encouraged.

Abstract: 0068 Poster

The detection of flunitrazepam in beverages using portable Raman spectroscopy

Esam M A Ali1, Howell Gm Edwards2
1Department of Forensic Medicine and Clinical Toxicology, Sohag Faculy of Medicine, Sohag University, Sohag, Egypt
2Division of Chemical and Forensic Sciences, University of Bradford, Bradford BD7 1DP, UK

Introduction: Flunitrazepam is a well known date rape drug commonly known as Rohypnol, roofies, or the ‘forget pill’.The detection of drugs of abuse in drinks residue has a high evidential value in cases of alleged DFSA. Portable Raman spectroscopy can be applied in these cases as a screening technique for the detection of drugs of abuse in spiked drinks. In these instances, the non-destructive and non-contact character of the technique offers a special role for portable Raman spectroscopy in the first-pass evaluation screening of materials of forensic relevance. Portable Raman spectroscopy has been used for the detection of the date-rape drug flunitrazepam in spiked beverages that may be involved in cases of drug-facilitated sexual assault. Solutions of flunitrazepam with different concentrations were prepared in water and for each beverage type. Definitive evidence for contamination of the spiked drink concerned can be acquired within 10 s. The data can be acquired in-situ and sample extraction and/or preparation steps are unnecessary.

Material and Methods: Solutions of flunitrazepam with different concentrations were prepared in water and for each beverage type. For the limit of detection (LOD) study, water and vodka were chosen.

Instrumentation: The Raman spectra of the drug solutions were recorded using a Delta Nu Inspector Raman FSX(Laramie, WY, USA). The Inspector Raman instrument is equipped with a diode laser emitting at a wavelength of 785 nm, a thermoelectrically cooled (1 x 1024 pixels) CCD detector, and a custom 25mm focal length lens in a nose piece.

Results and Discussion: Raman spectra were obtained from flunitrazepam solutions (concentrations from 0.01 to 0.04% w/v) in spiked beverages. In each case the spectra from each drink were compared with the reference spectra of flunitrazepam to evaluate the identification of the drug spectral band signatures. All the characteristic Raman bands of the drug can be clearly identified in all samples in the range of concentrations studied here. Each solution in this work was measured in triplicate and processed using GRAMS software to calculate the area of the peak at 1335 cm1.These measurements were then averaged to give the mean peak area and a calibration curve plotted.These curves show that flunitrazepam can be detected down to the lowest concentration of the drug studied here (0.01% w/v), demonstrating the ability of portable Raman spectroscopic instrumentation to detect the drug in spiked beverages in-situ.

Conclusions: Portable Raman spectroscopy can be applied efficiently as a screening technique for the identification of the date rape drug flunitrazepam spiked in water and in several alcoholic beverages.

Abstract: 0069 Poster

Deep Brain stimulation in child with genetic dystonia- a story of multi-diciplinary collaboration

Hilla Ben Pazi1, Reeval Segel2, Manju Kurian3
1Pediatric Neurology, Shaare Zedek Medical Center
2Clinical Genetics, Shaare Zedek Medical Center
3Pediatric neurology, Great Ormond Street Hospital London UK

This is a story about a family with two children with different movement disorders. Both were included in a genetic study since the cause of their clinical picture was unknown. Genetic testing of one child revealed a known gene that matched the clinical picture while the other brother had a large deletion on chromosome 19 that was unknown at the time. Deep- brain-stimulation (DBS) was performed to treat the dystonia of the child with the chromosomal deletion. The surgery was performed in parallel to a collaborative genetic research with dramatic results of both. This case had led to 2 new research projects.

The child's outcome following DBS and the genetic results will be presented. Future research progress emerging from this case will be discussed.

Abstract: 0070 Poster

A comparative study of the effects of three Moringa species on obesity –induced oxidative stress state in liver tissue.

Elham Mohamed Youssef1, Ferial Abass Zaher2, Hamdy Abd El Hady Zahran2, Aboelfetoh Mohamed Abdalla3
1Biochemistry department, National Research Center, Giza, Egypt.
2Fats and Oils Department, National Research Center, Giza, Egypt.
3Horticulture Technology Department, National Research Center, Giza, Egypt.

Excessive consumption of diet rich in fat and/or carbohydrates leads to obesity and progressive forms of liver abnormalities due to oxidative stress. The current study was designed to compare the effect of three types of seed oil extracted from three species of Moringa plant, Moringa peregrina, Moringa stenopetala,and Moringa oleifera, on weight gain and liver oxidative stress induced by high fat diet (HFD).

Four groups of male albino rats were fed on HFD for 8 weeks to produce a diet –induced obesity model, then three of them were treated with the three types of oil for 8 weeks more, control group was fed on normal diet for 16 weeks. Histology and serum activity of hepatic enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipid profile, and glucose have been recorded. Malondialdehyde (MDA) as indicator of oxidative stress, glutathione peroxidase, catalase, and superoxide dismutase as antioxidant defense were also estimated using liver homogenate. Moreover, analysis of antioxidant activity and total phenolic content of studied seed oil was carried out.

The study showed that both M.peregrina and M. stenopetala have higher levels of phenolic compounds and diphenylpicrylhydrazyl (DPPH)scavenging activity than M. oleifra. It also showed a significant ($P < 0.05$) increase in body weight, MDA, liver enzymes and a significant ($P < 0.05$) decrease in antioxidant enzyme levels in rats fed on HFD compared with those fed on normal diet ($P < 0.05$). After treatment with the three Moringa seed oil, the body weight, liver enzymes, MDA significantly ($P < 0.05$) decreased and the antioxidant enzyme levels significantly ($P < 0.05$) increased. Two of the three types of Moringa seed oil, M. peregrina and M. stenopetala, were found to cause the level of antioxidant enzymes, MDA, and body weight to approach more the control level than moringa oleifera. However, histopathological studies showed that only one of them, M.stenopetala seed oil, exhibited best effect in restoring the liver tissue against oxidative damage as it showed no histopathological changes except slight hydropic degeneration of hepatocytes.

Our data provided further evidence about the antioxidant activity of Moringa plant and better understanding about the variations in curative antioxidant effect of some of its species against weight gain and oxidative damage caused by HFD.

High-fat diet (HFD) contributes to the increase in oxidative stress and responsible for hepatic alterations and inflammation through the production of inflammatory cytokines and lipid peroxidation.

Abstract: 0077 Poster

Red Blood Cell Alloimmunization Among Egyptian Patients with Transfusion Dependant β Thalassemia

Mohamed Roshdy El Masry1, Amal Mohamed Ibrahim Elbeshlawy1, Asmaa Mohammad Abdelhameed Mohammad1, Alshymaa Ahmed Fouad Salama Kinawy2
1Faculty of Medicine, Cairo University
2El-Sahel Teaching Hospital

BACKGROUND and OBJECTIVE: The development of haemolytic alloantibodies and erythrocyte autoantibodies complicates transfusion therapy in thalassemia patients. These antibodies ultimately lead to increased need for blood and to intensified complications resulting from frequent transfusions in these patients. There is a scanty data on the incidence of RBC alloimmunization and autoimmunization in Egyptian thalassemia patients as pretransfusion antibody screening is not routinely performed. We studied the frequency of alloimmunization and erythrocyte autoimmunization among thalassemia patients who received regular transfusions. We also investigated factors possibly affecting the antibody formation.

METHODOLOGY: This cross-sectional study was carried out on 200 transfusion-dependent thalassemia patients

RESULTS: Of the 200 patients in the study, 94 were males and 106 females, with the age range of 2 - 37 years. Alloantibodies were detected in 36 (18%) of the patients, while autoantibodies were detected in 33 (16.5%). The dominant alloimmunization types in the study were antibody against Kell groups (33%) and against Rh subgroups (24.4%). Alloimmunization had a significant relationship with treatment duration and the frequency of transfusion ($P = 0.007$, 0.014 respectively). The presence of autoantibodies was significantly related to Age ($P = 0.001$), total number of transfused units ($P = 0.000$) and splenectomy ($P = 0.000$).

CONCLUSIONS: The high prevalence of alloimmunization in the study population showed the need for RBC antigen typing, especially Kell and Rh subgroups, in thalassemia patients before starting blood transfusion, and for transfusion of blood compatible with the blood subgroups to reduce risk of alloimmunization and increase the efficiency of blood transfusion.

Abstract: 0079 Poster

Cholinesterase Gene Expression and Serum cholinesterase activity Predict 6 Year Major Adverse Cardiac Events Following Coronary Angiography

Shani Shenhar Tsarfaty1, Ilan Freidson2, Ariel Finkelstein1, Shlomo Berliner1, Gad Keren1, Shmuel Banai1, Hermona Soreq2, Yaron Arbel1
1Departments of internal medicine E" &Cardiology, Tel Aviv Medical Center, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
2Dept of Biological Chemistry, The Life Sciences Institute and the Edmond and Lily Safra Center of Brain Science, The Hebrew University of Jerusalem, Jerusalem 91904, Israel.

BACKGROUND: Parasympathetic activity influences long-term outcome in patients with cardiovascular disease, but the underlying mechanism(s) linking parasympathetic activity and the occurrence of major adverse cardiovascular events (MACE) are incompletely understood.

METHODS: Deposited microarray gene expression datasets from blood samples of patients with and without MI were evaluated to study cholinergic pathway regulators using machine learning logistic regression. Next, we recruited 1000 consecutive patients presenting for angiography for chest pain (acute coronary syndrome and stable angina) and checked the serum capacity to hydrolyze acetylcholine as a biomarker for cholinergic balance. Finally we evaluated the relationship between parasympathetic activity (Cholinesterases activities) and long-term outcome.

RESULTS: A significant predictive model enabled us to diagnose a MI patient from matched control based on 20 cholinergic genes. The Acetylcholinesterase and Choline dehydrogenase genes were found to be the best predictors for MI (beta=0.455, p=0.04 and 0.761, p=0.01 respectively). In 1000 consecutive patients, those with AChE activity above 80 nmol/min*ml presented with less MACE over 6 years of follow up (HR=0.49, p<0.001, CI95% 0.35-0.69) (Figure 1). In a Cox multivariate regression model accounting for risk factors, biomarkers and clinical presentation, low parasympathetic activity was associated with less MACE (HR=0.65, p=0.027, CI95% 0.45-0.95).

CONCLUSIONS: Patients presenting with MI have unique cholinergic gene expression profile, this cholinergic signature can be evaluated by cholinesterases activity, and parasympathetic dysfunction (expressed as increased serum AChE) has been shown to predict increased MACE for up to 6 years of follow up.

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Abstract: 0080 Poster

Investigating Gβγ regulation of cardiovascular Kv7 channels

Jennifer B Stott, Oleksandr V Povstyan, Vincenzo Barrese, Iain A Greenwood
Molecular and Clinical Sciences, St George's University of London, London, UK

The Kv7 family of voltage gated potassium channels (Kv7.1-Kv7.5) are widely expressed with key roles in cardiac and vascular systems. In the heart the Kv7.1 channel underlies the late repolarisation of the cardiac action potential, whilst in the vasculature Kv7.4 and Kv7.5 are important in normal vascular functioning. Consequently, deciphering the regulatory mechanisms which govern cardiovascular Kv7 channel activity is crucial to understanding how these channels behave in health and disease.

Our findings demonstrate that the Kv7.4 channel require G-protein βγ subunits for their voltage dependent activity. Using HEK293 cells transfected with Kv7.4 we show that addition of exogenous Gβγ subunits increases the current and its' rate of activation, whilst application of a number of Gβγ inhibitors abolishes Kv7.4 currents. CHO cells expressing Kv7.5 channels and Kv7.4/Kv7.5 heteromers also display enhanced currents upon stimulation with Gβγ, whilst subunit inhibition impairs Kv7.4/Kv7.5 currents demonstrating that these heteromers also require Gβγ for their basal activity. In arterial myocytes isolated from renal arteries the Kv7 dependent current was isolated pharmacologically, and these currents were enhanced in the presence of Gβγ with an increase rate of activation. These native Kv7 currents were also diminished by Gβγ subunit inhibition. In renal myocytes and HEK293 Kv7.4 cells proximity ligation assay detected protein-protein interactions to within 40nm for Kv7.4 and Gβ which were markedly reduced after treatment with a Gβγ inhibitor.
With such a crucial role in the regulation of vascular Kv7 channels, we next investigated the role of Gβγ subunits in the regulation of the cardiac Kv7 channel – Kv7.1. Intriguingly, Kv7.1 currents were significantly decreased by intracellular perfusion of βγ subunits, and currents increased when Gβγ subunits were inhibited. This suggests that Kv7.1 channels are regulated by Gβγ in a manner contrary to the Kv7.4 and Kv7.5 isoforms, a most extraordinary occurrence in channels from the same family. Overall these findings demonstrate the crucial and diverse role of G-protein βγ subunits in the regulation of Kv7 channels, which could have profound implications for our understanding of the physiological roles these channels play in the cardiovascular system.

Abstract: 0083 Poster

Blocking HCN Ion Channels Arrests the Cell Cycle and Molecular Clock of Adult Neural Stem Cells

Randa Abu Youssef
Department of Clinical Pharmacology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Stem cells are tightly regulated by an as-of-yet incompletely resolved machinery, dictating their cell cycle entry/exit, proliferation, and neurogenesis patterns. Previous studies have shown the proliferative activity of adult neural stem cells (NSCs) to be characterized by periodical cycling, hinting at an integral link between the molecular clock, the so-called temporal orchestrator of animal and plant life, and cell cycle progression. A purported underpinning to this clock-regulated proliferation is the Hyperpolarization-activated Cyclic Nucleotide-gated ion Channels (HCNC) present in many organisms and cell types, including the mammalian brain. In parallel, HCNC have a central role in intracellular calcium oscillations (ICC), which could be their mode of regulating cell cycle and circadian clock activity. To investigate a possible pathway link in NSCs between HCNC, the molecular clock, and cell cycle regulation, NSCs isolated from adult Per2: : Luc knockin reporter mice were cultured and treated with the HCNC inhibitor ZD7288 for 24 hours. FACS analysis revealed an arrest in the G1/G0 phase compared to control (88% vs. 57% respectively, $p<0.05$). ZD7288 also delayed circadian clock cycling and prolonged clock duration, detected by photomultiplier tube bioluminescence recordings of Per2 promoter circadian activity (Per2 is a clock gene). In parallel, live-cell calcium imaging revealed an ICC decrease/inhibition in a ≈five-fold greater number of ZD7288-treated cells than control cells (84% vs. 17%, respectively, $p<0.0001$). We conclude that ICC is controlled, at least partially, by HCNC, and that their manipulation can switch on or off NSC cell cycle progression (and other stem cells) possibly by molecular clock disruption. Moreover, ZD7288 and other HCNC blockers have proven their candidate potential for further investigation on the path to developing cytoprotective agents, with an ultimate aim to shield NSCs from long-term cognitive effects by radio- and chemotherapy toxicity on cycling neural stem cells in brain cancer patients, by inducing neural stem cell quiescence.

This project has been conducted at the Department of Physiology and Pharmacology, Karolinska Institute, Sweden.

Abstract: 0084 Poster

Congenital myasthenic syndrome in Israel: Genetic and clinical characterization

Sharon Aharoni1, Menachem Sadeh2, Yehuda Shapira3, Simon Edvardson3, Muhannad Daana3, Talia Dor Wollman3, Aviva Mimouni Bloch4, Ayelet Halevy1, Rony Cohen1, Ronen Spiegel5, Andrew G. Engel6, Yoram Nevo1
1Institute of Child Neurology, Schneider Children's Medical Center of Israel, Petach Tikva, Israel;Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
2Department of Neurology, Wolfson Medical Center, Holon, Israel.
3Neuropediatric Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
4Pediatric Neurology and Developmental Unit, Loewenstein Rehabilitation Hospital, Raanana, Israel
5Genetic Institute, Emek Medical Center, Afula, Israel
6Department of Neurology and Neuromuscular Research Laboratory, Mayo Clinic, Rochester, MN, USA

OBJECTIVE: To evaluate the epidemiology of patients with Congenital myasthenic syndrome (CMS) in Israel.

METHODS: Targeted mutation analysis performed based on the clinical symptoms and electrophysiological findings for known CMS. Additional specific tests were performed in patients of Iranian and/or Iraqi Jewish origin. All medical records were reviewed and clinical data, genetic mutations and outcomes recorded.

RESULTS: Forty-five patients with genetic mutations in known CMS genes from 35 families were identified. Mutations in RAPSN were identified in 13 kinships in Israel. The most common mutation was c. -38A>G detected in 8 patients of Iranian and/or Iraqi Jewish origin. Four different recessive mutations in COLQ were identified in 11 kinships, 10 of which were of Muslim-Arab descent. Mutations in CHRNE were identified in 7 kinships. Less commonly detected mutations were in CHRND, CHAT, GFPT1 and DOK7.

CONCLUSIONS: Mutations in RAPSN and COLQ are the most common causes of CMS in our cohort. Specific mutations in COLQ, RAPSN, and CHRNE occur in specific ethnic populations and should be taken into account when the diagnosis of a CMS is suspected.

Abstract: 0086 Poster

Ex-Corporeal Tumor Ablation Using High Intensity Focused Ultrasound - Laboratory Characterization of the Thermal Ablation Fields

Ghanem F Oweis
Mechanical Engineering Department; American University of Beirut; Beirut; Lebanon

High intensity focused ultrasound (HIFU) is a growing thermal ablation modality for the destruction of tumors and abnormal masses such as uterine fibroids and prostate cancer. Due to its non-invasive ex-corporeal application, the hospitalization time is significantly reduced compared to other procedures, while the side effects are often minimal.

Any two HIFU transducers from the same manufactured batch can have significantly different performance characteristics. This creates an key technical challenge for their widespread use. A need arises to individually test and characterize the output and performance of each transducer before it can be commissioned for clinical use. Acoustic characterization using hydrophones or fiber-optic pressure probes is often considered the gold standard. However, this approach can be limited to low HIFU power levels to prevent damage to the hydrophone, or the system and testing costs can be prohibitive.

In addition, no reliable and accurate temperature measurement method currently exists for laboratory testing, let alone for clinical monitoring of thermal dose delivery. Such laboratory tool would be a significant addition for improved assessment of the treatment protocol in vitro. This is a pre-requisite for improved clinical quality assurance of the surgical procedure.
We describe the development of a novel, laser-based thermometry lab method that is very well suited for the characterization of HIFU devices and measurement of its temperature field with high spatial and temporal resolutions. The operating principle exploits the changes in the refractive index of the HIFU target spot; and thus when a laser ray is shone at the heated spot it will deflect by an amount dependent on its temperature. One experimental variation of the setup is shown where a bundle of laser beams probes the HIFU target, and a fast camera observes the variations in the bundle due to heating. Computer analysis is used to convert the information in the images into temperature. Comparison between the image-based temperature measurements and the common thermocouple method demonstrates the superiority of the current method in its temporal and spatial resolutions. This technique would be useful in other thermal therapies such as from focused lasers and from RF catheters. Moreover, it carries promise to fill a gap in physics and engineering.

Methods: A HIFU transducer targets with heat deposition a tissue phantom placed in the middle of a water bath (for ultrasound coupling). A bundle of laser rays coming from the right probes the heated spot; and as the rays leave the heated region a fast camera registers their thermal deflections towards the right side.

Results: The black curve depicts the measured temperature with the laser based optical method upon heat deposition by a HIFU pulse 5 ms wide The blue curve is simultaneous measurement with a traditional thermocouple which fails to capture the thermal behavior from the HIFU shot and exhibits significant viscous heating bias.

Abstract: 0087 Poster

Activation of protease-activated receptor 2 (PAR2) and release intracellular calcium by mast cell tryptase

Mogibelrahman Khedr1, Andrew F Walls2
1Department of Clinical Pharmacology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
2Clinical and Experimental Sciences Academic Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

INTRODUCTION: Mast cell tryptase is secreted in substantial quantities at sites of allergic inflammation. Pro-inflammatory actions mediated through PAR2 have been proposed, but mechanisms of receptor activation are unclear. Our aim is to investigate the intracellular mechanisms following tryptase activation of PAR2.

METHODS: Kirsten Murine Sarcoma Virus transformed rat kidney epithelial cells transfected with human PAR2 (KNRKt-PAR2) were employed. Expression of PAR2 was investigated using immunoflorescent staining. Following addition of tryptase or other agents, calcium flux was measured using a fluorescence based microplate procedure.

RESULTS: Trypsin and the PAR2 peptide agonist (SLIGKV-NH2) were able to stimulate marked release of intracellular calcium in the KNRKt cells. Addition of tryptase was associated with a concentration-dependent increase in the intracellular calcium. Pre-treatment of the cells with pertussis toxin (an inhibitor of G protein-coupled receptors) abolished the effect on calcium mobilisation of all agents under investigation. Incubation of cells with trypsin was found to prevent the effect of tryptase and vice versa. The responsiveness of PAR2 receptors to the peptide agonist was greatly reduced following trypsin treatment as compared to tryptase.

CONCLUSIONS: Mechanism of tryptase activation to PAR2 may involve mobilisation of calcium in target cells, an effect that mimics that of trypsin but with less potency.

Abstract: 0088 Poster

Fertility preservation in cancer-affected prepubertal boys: comparing the effectiveness of human testicular tissue cryopreservation methods

Doron Kabiri1, Michal Gropp2, Ariel Revel1, Benjamin Reubinoff2
1Department of Obstetrics and Gynecology, Hadassah University Medical Center, Ein Kerem
2The Sidney and Judy Swartz Embryonic Stem Cell Research Center of The Goldyne Savad Institute of Gene Therapy, Hadassah University Medical Center, Ein Kerem

Due to remarkable advances in cancer treatments, we are witnessing a growing population of long-tern survivors of childhood malignancies. However, fertility in adult life may be severely impaired by gonadotoxic therapies. Since prepubertal boys cannot produce spermatozoa, banking of testicular tissue prior to gonadotoxic treatment is a crucial step towards fertility preservation for this population. Several centers around the world are now cryopreserving testicular tissue for prepubertal boys in anticipation that future technologies will allow the utilization of the banked samples for fertility restoration. The key barriers to restoration of fertility are the small amount of testicular tissue, and accordingly, spermatogonial stem cells that can be preserved. The objective of the study was to compare three methods of testicular cryopreservation (Controlled Slow Freezing, Uncontrolled Slow Freezing and Vitrification), in order to develop efficient protocols for cryopreservation of viable prepubertal human testicular tissue. Histological evaluation of fresh and thawed tissues demonstrated no significant differences in tissue architecture, structural integrity and cellular morphology between fresh and cryopreserved fragments. This research demonstrates the feasibility of those three methods for adult human testicular tissue cryopreservation, and significantly contributes to the potential future utilization of the frozen samples for sperm production and fertility preservation. The results of this study also enabled the establishment of a clinical program for the cryopreservation of testicular tissue samples from pre-pubertal boys undergoing gonadotoxic cancer treatments at Hadassah Hebrew Medical Centre.

Abstract: 0089 Poster

Everolimus (RAD001) sensitises prostate cancer cells to docetaxel by downregulation of hypoxia-inducible factor-1α and sphingosine kinase 1

Heba Alshaker1, Tawfiq Arafat2, Dmitri Pchejetski3
1Department of Pharmacology and Biomedical Sciences, Faculty of Pharmacy and Medical Sciences, University of Petra, Amman, Jordan
2Department of Pharmaceutical Medicinal Chemistry and Pharmacognosy, Faculty of Pharmacy and Medical Sciences, University of Petra, Amman, Jordan.
3School of Medicine, University of East Anglia, Norwich, UK

BACKGROUND: Resistance to docetaxel is one of the key problems in current prostate cancer management. One potential solution is to identify molecular targets that might sensitise prostate cancer cells to taxane therapies. Sphingosine kinase 1 (SK1) and phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathways have been implicated in prostate cancer growth and chemoresistance, and here we investigated whether their combined targeting may re-sensitise prostate cancer cells to docetaxel.

METHODS: Cell viability and caspases assays were used to investigate the combined effects of everolimus (RAD001) and docetaxel in prostate cancer cells. SK1 activity was measured by radiolabelling and alterations in cell signalling and gene expression were measured by Western blotting and qRT-PCR. Mouse prostate cancer xenografts were used to confirm " in vitro" findings.

RESULTS: In hormone-insensitive PC-3 and DU145 prostate cancer cells RAD001 alone did not lead to significant cell death, however, it has strongly sensitised these cells to a low (5nM) dose of docetaxel. Here we show for the first time that this sensitisation was achieved through inhibition of mTOR/hypoxia-inducible factor-1α (HIF-1α)/SK1 pathway that was not affected by docetaxel. Both HIF-1α accumulation by CoCl2 and SK1 overexpression have protected prostate cancer cells from RAD001 effects. In human prostate tumours established in nude mice single RAD001 and docetaxel therapies induced only a 23% and 15% tumour volume reduction, respectively, while their combination has led to a staggering 58% reduction. RAD001 alone or in combination with docetaxel has also suppressed mTOR and SK1 signalling, however as evidenced by tumour size, it required docetaxel for clinical efficacy. Combination therapy was well tolerated and had similar levels of toxicity to docetaxel alone.

CONCLUSION: Our data provide a mechanistic basis that underlies the chemosensitizing properties of RAD001 in prostate cancer cells and mouse models. These findings support further clinical application of RAD001/docetaxel combination in prostate cancer therapy.

Abstract: 0090 Poster

Multilocus sub-genotyping and phylogenic analysis of ""Giardia intestinalis"" isolates from stool of Egyptian children

Ayman A El Badry1, Dina M. Salah1, Hebat Allah S. Yousof1, Marwa A. Ghieth2, Nadia A. El Dib1, Kevin M. Tyler3, Maha Abuzid3, Azza Kamal4, Jose M. Rubio5
1Medical Parasitology, Kasr Al-Ainy Faculty of Mdicine, Cairo University, Cairo, Egypt
2Medical Parasitology, Beni-Suef Faculty of Mdicine, Beni-Suef University, Beni-Suef, Egypt
3Biomedical Research Centre, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ, UK
4Department of Pediatrics, Kasr Al-Ainy School of Medicine, Cairo University, Egypt
5Malaria & Emerging Parasitic Diseases Laboratory, Parasitology Department, National Microbiology Center, Carlos III Health Institute, Cra. Majadahonda Pozuelo Km. 2,5 Majadahonda, 28220 Madrid, Spain

""Giardia intestinalis"" (""G. intestinalis"") is a common human and animal enteric protozoan parasite with high diversity. There is very little information available on the diversity of ""Giardia"" sub-assemblages and multi-locus genotypes infecting people in Egypt. Due to allelic sequence heterogenicity and single nucleotide polymorphism found in ""Giardia"" spp, multi-locus genotyping is highly recommended. This study aimed to identify the assemblages and sub-assemblages of ""G. intestinalis"" isolated from the stool of Egyptian children using PCR based on 3 genetic loci: ""β""-giardin (bg), glutamate dehydrogenase (gdh), and triose phosphate isomerase (tpi)]. Further sub-genotyping phylogenic analysis of DNA sequences was done at these loci using PCR-based sequencing and the phylogenetic trees were constructed using the neighbor-joining method. Related sociodemographic and clinical features of patients infected with ""G. intestinalis"" were also analysed. Two assemblages, A and B, were identified in isolates from stool of Egyptian children with significant predominance of assemblage B. Sequence analysis showed that assemblage B (BIII/BIV) isolates have a higher genetic polymorphism than assemblage A (AII) isolates. BIV was the most prevalent genetic variant of ""G. intestinalis"" found in stool of population studied. Among the studied variables, only flatuelence was significantly associated with ""Giardia"" infection and assemblage. The obtained results may support anthroponotic transmission of ""Giardia"" and occurrence of genetic exchange within assemblages in studied individuals.

Abstract: 0091 Poster

Mapping the brain response to phantom taste

Sally Eldeghaidy1, Martha Skinner2, Rebecca Ford2, Joanne Hort2, Susan Francis1
1Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, UK
2Sensory Science Centre, School of Biosciences, Sutton Bonington Campus, University of Nottingham, Loughborough, UK

INTRODUCTION: Thermal taster status refers to a new taste phenotype in which thermal stimulation of the tongue elicits a “phantom” taste in individuals. The mechanism behind thermal taste is not yet known, but hypothesised to arise from cross-wiring between taste and temperature receptors co-innervating papillae on the tongue. Here, we use fMRI to perform the first study to investigate whether cortical areas respond to phantom taste.

METHODS: 21 subjects were screened for thermal taster status (8 male, 26± 4yrs). 9 subjects (3 male, 27± 4yrs) were classified as thermal tasters (TTs) and took part in the fMRI study. Thermal Taster screening was performed using an intra-oral thermode (Medoc Pathway) to deliver warming and cooling thermal stimuli to the anterior tongue tip. Subjects were asked whether they perceived a taste during heating and/or cooling thermal stimulation, and if so, to describe the taste quality, and to indicate and rate the taste intensity they perceived. TTs were classified as those who perceived a taste during warming or cooling trials. fMRI data was acquired on a Philips 3T Achieva scanner with 32-channel receive coil using 36 transverse dual-echo GE-EPI images (TE: 20/45ms, TR: 2.5s, 3x3x3mm3, SENSE 2). During fMRI scanning, blocks of warming and cooling trials, with 10 repetitions of each trial were delivered, and TTs indicated and rated the intensity of the perceived taste. Weighted fMRI data were analysed using SPM12. A GLM was formed for each subject to identify cortical activation to phantom taste. For each individual, the onset and duration of the phantom taste was determined from the continuous taste intensity ratings collected during the fMRI acquisition. Thermal tasters who responded to warming or cooling trials were pooled, with maps combined, at the 2nd level RFX group analysis.

RESULTS: Thermal tasters reported a sweet taste as the taste most prevalent during warming/cooling trials. The intensity of the “phantom” taste reported was between weak and strong on the gLMS, with an average intensity rating of above moderate. Behavioural data collected during the fMRI session indicated consistency in onset of the perceived phantom taste across the 10 repetition. RFX maps from TTs showed that phantom taste perceived during thermal stimulation of the tongue activated taste areas including anterior insula [(-36, 16, 4), T=5.12, P<0.001], frontal operculum [(-48, 14, 8), T=5.52, P<0.001] and ACC [(4, 26, 44), T=4.83, P<0.001].

CONCLUSION: The results show that thermal stimulation applied to the anterior of the tongue can elicit a clear “phantom” taste response in TTs generating a cortical response in primary gustatory cortex including anterior insula and ACC.

Abstract: 0092 Poster

Arterial stiffening across multiple length scales

Riaz Akhtar
School of Engineering, University of Liverpool, Liverpool, United Kingdom

It is well established that aortic stiffness increases with age, and as a result of a number of risk factors including diabetes. Most quantitative measurements of arterial stiffness involve the use of in vivo techniques such as pulse wave velocity or ex vivo techniques such as tensile testing. However, the aorta has a complicated and intricate structure, governed by the properties and composition of the microstructural components of the vessel wall. Hence, these methods provide an average macroscopic response of the material properties and little is known about the effects of ageing and disease on individual components of the aorta.

In this study, data obtained with novel materials science techniques such as atomic force microscopy (AFM) and scanning acoustic microscopy (SAM) is presented. These techniques allow us to localise mechanical property changes at the microstructural and molecular scale in the aorta. AFM provides ultrastructural and nanomechanical information for aortic tissue. SAM, when operated at frequencies close to 1 GHz, can provide quantitative measurements of acoustic wave speed (related to tissue stiffness) with a spatial resolution around 1 µm. These methods have been used to determine changes in the aorta due to ageing and diabetes. We have found that the inter-lamellar regions of the media have been found to be a key determinant of the overall mechanical and structural properties of the aorta. At the molecular level, we examine the role of fibrillin microfibrils on aorta properties. These data are compared with the in vivo and macroscopic response of the vessel.

Abstract: 0093 Poster

Epidemiology and genotypic characteristics of Staphylococci isolated from diabetic foot ulcer

Amal Al Bakri1, Ghadeer Othman1, Nidal Younis2, Nailya Boulatova3
1The University of Jordan-School of Pharmacy Department of Pharmaceutics and Pharmaceutical Technology
2The University of Jordan Department of General Surgery
3The University of Jordan-School of Pharmacy Department of Biopharmaceutics & Clinical Pharmacy-School of Pharmacy

With the increasing number of diabetic patients, it is likely that the number of diabetic foot infections will increase in upcoming years. Foot complications are common in diabetic patients; foot ulcers are among the more serious consequences. These ulcers frequently become infected, and if not treated promptly and appropriately, diabetic foot infections can lead to septic gangrene and amputation. Data from many countries in the last decade demonstrated that S. aureus predominates (prevalence 28–76%) among the Gram-positive bacteria in patients with infected diabetic foot ulcers. The methicillin resistant S. aureus (MRSA) has been reported to cause infections within DFU in addition to the multidrug resistance isolates. Although historically coagulase negative staphylococci (CONS) have been classified as non pathogenic, currently it is one of the major nosocomial pathogens and many isolates are resistant to commonly used antibiotics including methicillin. Methicillin resistance is determined by the presence of the Staphylococcal Cassette Chromosome "SCCmec" element. Different types and subtypes of SCCmec element have been identified.

Results demonstrated that Gram positive are the most common isolates predominated by Staphylococci spp. High percentage of the isolates were phenotypically and genotypically methicillin resistant. SCCmec type IV predominated among MRSA and MRCONS isolates from healthy volunteers and diabetic foot infected ulcers.

Abstract: 0094 Poster

The Impact of consanguinity on the increase of incidence of rare genetic diseases among Palestinian population

Ayman S Hussein
An-Najah University

The rate of consanguinity among Palestinian population is very high. About 44 % of the marriages are between relatives (22 of them between first cousins). The effect of consanguinity on different genetic disorders was studied. The consanguinity rate in families with dominant or X-linked disorders and chromosome aberrations was similar to the one observed in the general population. No significant differences in the rate of consanguineous marriages between the parents and grandparents of children affected with polyploidy and the general population. With regard to the rare autosomal recessive disorders among the parents of patients, the consanguinity rate was much higher than the one of the general population (90% Among the autosomal recessive disorders. Genetic factors in various congenital malformations and the most frequent rare disorders are also studied. For example we have found that 100 out of 987 (10.1%) patients studied are having Down syndrome. Other genetic disorders studied on our study population will be discussed in the presentation.

Abstract: 0095 Poster

Adiponectin Attenuates Hypertension-Induced Vascular Remodeling through NHE-1 Activity and LKB1/AMPK Signaling

Crystal Ghantous1, Rima Houri1, Nancy Chaaya1, Ramzi Sabra2, Asad Zeidan1
1Department of Physiology, American University of Beirut, Beirut, Lebanon
2Department of Pharmacology, American University of Beirut, Beirut, Lebanon

INTRODUCTION: Hypertension leads to vascular remodeling, affects circulating levels of leptin and adiponectin (APN), and is associated with increased sodium hydrogen exchanger isoform-1 (NHE-1) activity. The aim of this study is to investigate the vascular protective effects of APN during hypertension.

Hypothesis: Hypertension-induced vascular smooth muscle cell (VSMC) remodeling is mediated by NHE-1 activity, LKB1/AMPK signaling and attenuated by high APN/leptin ratio.

METHODS: In order to study the effect of hypertension on VSMC remodeling, the in vivo rat model of angiotensin II (Ang II)-infusion for 14 days and the in vitro model of mechanically stretching the rat portal vein (PV; with 1.2 gr weights due to the force-length relationship normalized to the human force of stretch during hypertension and the longitudinal orientation of its VSMC) were used. APN (10 µg/ml) and the selective NHE-1 inhibitor cariporide (10 µM) were added to blood vessels. ERK1/2, AMPK and LKB1 activation in VSMC was evaluated by Western blot. Leptin and APN expression was studied by Western blot, while ROS production was assessed by DHE staining.

RESULTS: Stretching the PV for 10 min increased p-ERK1/2 by 2.10 ± 0.25 fold (n=6, $p<0.05$) in VSMC, while cariporide and APN attenuated p-ERK1/2 in stretched PV by 1.09 ± 0.15 and 0.96 ± 0.31 fold respectively (n=6, $p<0.05$). Mechanical stretch for 10 min decreased LKB1 and AMPK activation by 0.44 ± 0.14 and 0.34 ± 0.07 fold respectively (n=6, $p<0.05$). This effect was attenuated by cariporide (p-AMPK: 0.70 ± 0.21 fold, $p<0.05$), while APN increased p-LKB1 and p-AMPK in stretched PV to 1.0 ± 0.11 and 0.60 ± 0.04 fold respectively (n=6, $p<0.05$).
Ang II-infusion for 14 days increased leptin (1.48 ± 0.12 fold, $p<0.05$), decreased APN (0.87 ± 0.06 fold), and increased ROS (3.46 ± 0.07 fold, $p<0.05$) in PV. Similar results were observed in the aortas of Ang II-infused rats (leptin: 1.83 ± 0.36 fold; APN: 0.79 ± 0.06 fold; ROS: 1.54 ± 0.12 fold, $p<0.05$) compared to sham-operated rats.

CONCLUSION: APN attenuates mechanical stretch-induced VSMC remodeling by activating LKB1/AMPK and inhibiting ERK1/2 pathways, which are mediated by NHE-1 activity. Moreover, hypertension-induced vascular remodeling is associated with higher leptin and lower APN synthesis.