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Contents

Ageing

One size does not fit all, making reasonable adjustment to facilitate people with intellectual disability engage in objective health assessment.

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Aim: This paper aims to describe techniques employed in designing and engaging people with an intellectual disability in a health assessment suite as part of a large research study and, in doing so facilitate researchers, carers and clinicians to more effectively engage people with ID in clinical assessment.

Methods: A multiphase approach was employed in the design of the 8 item objective health measurement suite. The design process, accessible and instructional material were informed and reviewed by independent advocacy groups, expert opinion, a scientific advisory committee and finally a conveniently sampled pilot study was rolled out to further test the design suitability. The model was under pinned by the emancipatory principles of social engagement, reciprocity, gain and empowerment.

Results: Specific techniques were developed to address difficulties and in total 604 participants successfully engaged in the health suite with 51% completing all eight items.

Conclusion: Health screening is an imperative first step in improving the health of people with ID. However one size does not fit all and assessment delivery adaptations are needed to support optimum health for people with ID.

Prevalence and predictors of osteoporosis risk among older adults with intellectual disability in Ireland.

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Aims: The aim of this paper is to describe the objectively measured prevalence of osteoporosis among older adults with intellectual disability (ID) and the contributing risk factors.

Methods: The sample was drawn from the *Intellectual Disability Supplement to The Irish Longitudinal Study on Ageing*. Bone quality was measured by quantitative ultrasound (QUS) as part of an objective health suite of assessments. Multiple variable logistic regression analysis was performed to determine the significance predictors for poor bone quality

Results: In total 575 participants had QUS. The prevalence of osteoporosis was identified at 41%. The logistic regression model explained between 35.9% and 47.9% of variance. Adjusted for age and level of ID the strongest significant predictors to emerge are proton pump inhibitors followed by, in descending order, history of fracture, epilepsy, grip strength and body mass index.

Conclusion: The findings support a need for robust risk assessment and, for clinical practitioners to not only seek the obvious risks but also consider the specifics for ID. Identifying risk factors enables more accurate and targeted preventative strategies to decrease future risk of fragility fractures.

Single and dual task gait speed: Implications for older pedestrians crossing the road.

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Aim: In many countries, including Ireland, a minimum walking speed of 1.2 m/s is required to cross the road at light-controlled pedestrian crossings. Many older adults report having insufficient time to complete the crossing in the time provided. The aims of this study were to examine (i) how many older Irish adults walk slower than the minimum required walking speed and (ii) how walking while completing a cognitive-based dual task affects the ability to walk at this speed.

Method: Data were obtained from the first wave of The Irish Longitudinal Study on Ageing (TILDA), a nationally representative sample of community-dwelling adults aged 50 years and older. 5,035 participants completed a comprehensive centre-based health assessment. Of these, 4,909 participants (mean age 63.3 years, range 50-93 years, 52.2% female) completed usual and dual task gait speed tests, measured using a 4.88 m GAITRite → walkway. The weighted proportion of older adults with walking speeds of less than 1.2 m/s was obtained, stratified by age and sex.

Results: Mean usual gait speed was 1.33 m/s (SD=0.21 m/s) while mean dual task gait speed was 1.09 m/s (SD=0.27 m/s). 31% of Irish adults aged 65-74 years and 61% of the over 75s walked slower than the minimum required walking speed of 1.2 m/s and therefore would have insufficient time to cross the road at pedestrian crossings. 54% of the under 65s and 91% of the over 75s would be unable to cross if they were walking while also carrying out a cognitive-based task.

Conclusion: Pedestrian light settings are not compatible with older adults' walking abilities which may impact on functional independence and quality of life. Dual tasking is associated with reduced walking speed across all age groups, highlighting that an increased awareness about the hazards of dual tasking while crossing the road is required.

Translating Population Health Research Findings into Clinical Tools: Impaired BP Recovery, but not Initial Orthostatic Hypotension, is a Risk Factor for Injurious Falls.

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Aim: Cardiovascular disorders are recognised as important modifiable risk factors for falls. However the association between falls and orthostatic hypotension (OH) remains ambivalent, particularly because of poor measurement methods of previous studies. Our goal was to determine for the first time to what extent OH (and variants) are risk factors for incident falls, unexplained falls (UF), injurious falls (IF) and syncope using dynamic blood pressure (BP) measurements in a population study.

Methods: Community dwelling adults resident in Ireland aged ≥50 years were recruited to waves 1 and 2 of the Irish Longitudinal Study on Ageing (TILDA). Continuous BP recordings measured during active stands were analysed. Persistent OH and variants (initial OH (IOH) and delayed BP recovery OH(40)) were defined using dynamic BP measurements. Associations with the number of falls, UF, IF and syncope reported two years later were assessed using negative binomial and modified Poisson regression.

Results: 4128 participants were studied, mean age 61.5(8.1) years, 52.9% female. OH(40) was associated with increased relative risk of UF (RR:1.51 95%CI:1.02-2.24). Persistent OH was associated with all-cause falls (IRR:1.41 95%CI:1.01-1.97), UF(RR:1.81 95%CI:1.06-3.09), and IF(RR:1.57 95%CI:1.11-2.23). IOH was not associated with any outcome considered.

Conclusion: It is common place in clinical practice to report standing BP measures as soon as possible after standing. However this work indicates that impairments in orthostatic BP recovery, but not initial BP drops, are independent risk factors for injurious falls which affect 10% of the over 65's. Our results emphasise the importance of establishing that postural BP drops are sustained or slow to recover and highlights the clinical perils in assessing OH with misdiagnosis and consequent mismanagement a real possibility if strict measurement protocols are not utilised. Current work is focussed on translating these biomarkers into usable educational information and commercialisable technologies suitable for non-specialist clinical and home environments.

Meta-analysis of Cohort Data: Impact of Palliative Care on Costs for Hospitalised Adults with Serious Illness.

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Aim: This paper analyses the impact of palliative care consultation teams (PCCT) on hospital costs by primary diagnosis, by specific combinations of conditions, and by total number of comorbidities.

Methods: Datasets from three prior multi-site cohort studies of PCCTs in the United States were combined for this analysis. Sociodemographic, clinical and cost data were extracted from databases at 10 hospitals between 2002 and 2011. Adults were eligible if admitted to participating hospitals during study periods with at least one of seven life-limiting conditions: cancer, heart failure, COPD, AIDS/HIV, liver failure, kidney failure and specified neurological conditions. A total of 92,895 patients, of whom 10,015 (11%) were seen by a PCCT, were included. Patients seen by a PCCT were matched on baseline characteristics with those who received usual care only using propensity scores. Cost-effects of PCCTs were estimated using generalized linear models with a gamma distribution and a log link.

Results: PCCTs significantly reduce the cost of hospital costs for seriously-ill adults ($p<0.01$). The cost-effect is larger for patients with a primary diagnosis of cancer than non-cancer ($p<0.01$). The cost-effect varies by total number of comorbidities ($p<0.01$), as well as by primary noncancer diagnosis ($p<0.01$).

Conclusion: Palliative care is associated with lower costs and improved outcomes for patients, but our results emphasize the heterogeneity of treatment effect within a population of adults with serious illness. Palliative care has a larger cost-saving effect than has previously been understood for patients with cancer and for patients with complex multimorbidity, and specific combinations of conditions appear particularly amenable to palliative care cost impact. These results can inform prioritization of palliative care to those patients for whom the impact is greatest.

What is Community? A theoretical model of community for people with intellectual disability.

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Aims: To propose a model of community for people with intellectual disability based on a critical review of the general sociological literature.

Method: Systematic searches explored the meanings of community and the related concepts of social inclusion, cohesion and capital. General sociological literature located were then reviewed and critically assessed in the context of relevant ID literature and policy.

Results: The review revealed that the concept of community has been a contested concept in sociology. Arguments have centred around spatial, relational, symbolic and recent postmodern understandings of community. However, common elements emerging from these different understandings of community supported that interdependent relationships lead to bonding between people and this cultivates the sense of belonging associated with community.

Conclusion: Understandings of community based on a dichotomy of between institutional and community based locations potentially overlooks some of the important processes that inform a better experience of community for people with ID.

Conducting a feasibility study on cognitive training with adults with Down syndrome: Methodology and lessons learned.

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Aim: To assess the feasibility of conducting a cognitive training programme with adults with Down syndrome.

Method: In a quasi-experimental mixed factorial with partial crossover design, 46 participants in the BEADS study (Brain Exercises for Adults with Down Syndrome) completed an 8-week cognitive training programme using an Ipad. Participants were aged 30 to 49 years with a mild or moderate level of intellectual disability. The researcher/instructor met with participants 3 times a week. A weekly questionnaire on satisfaction and perceived difficulty was completed as well as a semi-structured interview when the programme ended.

Results: Acceptability and usability of the cognitive training programme was high; most participants completed the programme, with number of minutes spent ranging from 450-2000 minutes, which compared favourably with a recommended dosage of 800 minutes (based on previous literature). On the weekly questionnaire, most consistently responded they 'really enjoyed' the training programme. Feedback on the length of the programme varied, with some indicating a preference for a longer training period.

Conclusions: While additional supports were needed for some participants, all were able to engage in the programme.

Are there differences in symptom presentation in myocardial infarction patients depending on age.

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Patients with MI need to present as soon as possible after symptom onset to optimise prognosis and reduce morbidity. Many factors have been shown to influence pre-hospital delay especially behavioral and symptom presentation factors.

Aim: The aim of this study is to compare the profile of those <65 and those >65 to elucidate if there is a significant difference in the signs and symptoms known to influence pre-hospital delay time.

Methods: This cross-sectional study is a secondary analysis of a multi-site RCT study examining the impact of an educational intervention on pre-hospital delay time study. MI patients were recruited prior to discharge, completed a detailed questionnaire about their presentation, and clinical details were verified with patient's case notes.

Results: 2111 patients were recruited, 57% were <65, 78% were male and 43 % had a STEMI. The median pre-hospital delay time for MI patients aged <65 and >65 was 2.57 and 3.74 hours respectively, this was a significant difference ($p<0.001$). A logistic regression model finally examining 15 typical and atypical symptoms and presentation features between the age groups was significant ($\chi 2 = 61.33$, $p<0.001$). The presenting features that were singularly significantly associated with the >65 age group were: less sweating, less stomach symptoms, less chest pain, less chest pressure, less left arm pain, less severe symptoms. In addition more patients in the >65 age group phoned their general practitioner.

Conclusions: Pre–hospital delay time was higher in MI patients >65. This study observed that this may be due to differences in symptoms and behaviours known to impact pre-hospital delay. Increased awareness that older patients may present with less severe, less typical symptoms and promoting patients to access the 999/112 services rather than their GP in the face of unresolved MI symptoms is essential to improve prognosis in this cohort.

A comparison of the prevalence of IDF- and ATPIII- defined metabolic syndrome in adults aged 50 and over in Ireland: findings from TILDA.

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Metabolic syndrome (MetS) is described as the clustering of modifiable cardiovascular risk factors including hyperglycaemia, dyslipidaemia, central obesity and hypertension and is a recognised risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Those who meet the criteria for MetS have a potential 1.6-fold increase in risk of early mortality.

Aim: This study aimed to determine the national prevalence of MetS in older adults using data from the first wave of The Irish Longitudinal Study on Ageing (TILDA), a nationally representative cohort of community-dwelling adults aged 50 and over.

Methods: All TILDA participants completed a computer-assisted personal interview (CAPI) and were invited to participate in a comprehensive health assessment. Two sets of criteria were used to calculate prevalence; the Adult Treatment Panel III (ATPIII) and the International Diabetes Foundation (IDF) criteria. Each component of MetS was measured using objective data from the

health assessment, i.e. triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure, waist circumference and glycated haemoglobin (HbA_{1c}), in addition to reported medication usage (n=5026). The prevalence of MetS in the total population and by subgroups of age, sex and educational attainment were generated using the statistical software Stata/MP 12.1.

Results: The mean (SD) age of the sample was 62 (8.5) years; 54.2% were female. The table shows the prevalence of MetS with 95% confidence intervals (95% CI) for the older Irish population and subgroups. The ATPIII-defined prevalence of MetS in the population was 41.6%, while the IDF criteria identified 47.3% as having MetS. MetS was more prevalent in men than women and increased with age, with 55.3% [50.3 - 60.3] and 61.3% [56.6 - 66.1] of those aged ≥75 years having MetS according to ATPIII and IDF, respectively.

Conclusions: This is the first time that MetS has been estimated at a population level in Ireland. These results confirm that MetS is a widespread condition and is more prevalent in men, the elderly and those with lower educational attainment.

Tracking change in health service use following a change in living arrangement – examining the continued role of ID service providers in delivering health care.

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Aim: To examine the health service use by type and setting for a cohort of people with ID who changed residence in Ireland over a 3-year period.

As de-institutionalisation is implemented, it is expected that demand for community based health services will increase. However, such outcomes are not inevitable.

Method: Data form two waves (2010 and 2013) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA) were analysed.

Results: Community based movers continued to rely on ID service providers for specialist health services (social work, psychology, dietician services) and to a lesser extent for general health services (dental, optician, pharmacy).

Conclusion: The continued reliance on ID service providers for health services by community based movers, highlights the need for greater efforts to prepare and expect mainstream health service providers to support the health needs of people with ID.

Prevalence and Typology of Behaviour That Challenges in Older Adults with an Intellectual Disability.

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Aim: The aim was to identify prevalence of BTC in older adults with ID.

Behaviour that challenges (BTC) is a barrier to community integration for adults with intellectual disabilities (ID) and poses management problems for families and service providers. Little is known about prevalence and types of BTC in older adults with ID.

Methods: Data was generated from Wave 2 of the intellectual disability supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a nationally representative sample of 713 persons with ID aged ≥40. Information on presence of four categories of BTC was collected in the pre-interview questionnaire, completed by the person with ID and/or a proxy.

Results: 71.4% (*n*=487) reported getting angry or frustrated when things didn't work out, of those (*n*=485), screaming was most frequently reported (42.8%), followed by hitting out (33.6%), throwing things (24.7%) and self-injury (18.6%). Of those who reported BTC, 60.9 % reported doctor's diagnosis of a mental health condition.

Conclusions: Over half of older adults with ID were reported to have shown at least one type of BTC, which is likely to be detrimental to quality of life.

Drug Burden in Aging Adults with Intellectual Disabilities Living in Residential Facilities in Ireland: A Cross-Sectional Study.

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Aim: Use of drugs with sedative and/or anticholinergic effects have been associated with adverse outcomes such as falls and daytime sedation. Older people with intellectual disabilities (ID) are at increased risk of exposure to these medicines owing to higher prevalence of multimorbidity, particularly psychiatric morbidities. The aims of this study were to determine individuals with ID who live in residential institution's exposure to anticholinergic and/or sedative medication through use of the evidence-based prescribing tool; the Drug Burden Index (DBI), to identify therapeutic classes contributing to burden and to examine associations between higher burden and functional adverse effects.

Methods: Cross-sectional (self-report/proxy report) medication data were drawn from those living in residential institutions from Wave2 of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing, a study on aging of 708 nationally representative people with ID aged over 44 years living in a variety of settings randomly selected from the National Intellectual Disability Database. Medication data were available for 276 participants living in residential institutions.Each individual's exposure to anticholinergic and/or sedative medicines was calculated using the DBI. Bivariate analysis examined associations between functional adverse effects and DBI scores 0, 0-1 and 1+.

Results: In the eligible population of 276 participants (59.4% female, 25.4% 65+ years), 87.3%(241) were exposed to a DBI medicine, a mean (±SD) score of 1.57 (±1.13), 66.3% (114) a DBI score of 1+. Antiepileptics accounted for 28.8% of the cumulative DBI score in the cohort, followed by antipsychotics (23.7%). Higher DBI score >2) was not significantly associated with daytime dozing (p=0.76), falls (p=0.26) or constipation (p=0.05).

Conclusions: Use of medications with anticholinergic and/or sedative properties in older adults with ID is high. Utilisation of the DBI tool may be useful in predicting effects of medication on function in older people with ID and informing development of interventions to improve appropriate prescribing.

Prevalence Of Common Conditions Of Ageing And Frailty: The Irish Longitudinal Study On Ageing (TILDA).

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Aim: Biomarkers have been linked to phenotype frailty in several cross-sectional and fewer longitudinal studies[1-3]. Here we examined the prevalence of common age-related conditions and frailty among older adults in Ireland using clinical biomarker reference ranges.

Methods: Cross-sectional analyses were performed using data from community-living adults aged ≥50 years (n=5463) from Wave 1 of TILDA. Prevalence estimates of diabetes/pre-diabetes (HbA1c), chronic kidney disease (creatinine and cystatin c), hypercholesterolemia (Total, HDL and LDL cholesterol), inflammatory stress (CRP) and micronutrient status (vitamin B12, vitamin D, lutein and zeaxanthin) were calculated using clinical reference values of the relevant biomarkers. by phenotype frailty status. Multinomial logistic regression measured significant differences in prevalence of each condition by phenotype frailty status.

Results: Prevalence estimates of pre-frailty and frailty were 33% and 4% respectively. Among the frail there was a higher prevalence of diabetes (5.9%; $p<0.01$), pre-diabetes (18.1%; $p<0.01$), chronic kidney disease (39.1%; $p<0.01$) and inflammatory stress (70.4%; $p<0.01$) compared to the pre-frail or non-frail. The frail also showed significant deficiencies in micronutrients: lutein (51%; $p<0.01$), zeaxanthin (50%; $p<0.01$), and vitamin D (27%; $p<0.01$), but not vitamin B12 (7%; $p=0.23$). Hypercholesterolemia was significantly lower among the frail (32%; $p<0.01$). The pre-frail exhibited intermediate prevalence estimates of these conditions compared to the non-frail.

Conclusion: The prevalence of treatable age-related conditions is significantly higher among the pre-frail and frail in the community. This illustrates the loss of physiological reserve and complexity of need that exists. It emphasises the requirement for multidisciplinary, integrated care approaches to treatment among this vulnerable group.

Examining frail older people's use and experience of the Irish healthcare system: a mixed methods study.

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Background: Frail older people are vulnerable to adverse outcomes and require a multimodal, integrated package of healthcare services. Planning such care requires robust evidence about the frail population and their current patterns of service utilisation in order to identify the nature and scale of problems in the current model of care. This study describes the community-living frail older Irish population and examines their patterns of service utilisation and their experiences seeking, securing and managing services.

Methods: A sequential explanatory mixed methods design was operationalised. Data was obtained from wave one of the Irish Longitudinal Study on Ageing (TILDA) for those aged ≥65 years (n=3,422). Multivariate regression techniques examined the impact of frailty, measured by the Frailty Index, on utilisation of hospital and community services adjusting for need, predisposing and enabling factors. Latent class analysis identified profiles of service-use among fail TILDA participants (n=745). Data from semi-structured interviews with a qualitative sample of frail older people (n=12) explored why service-use patterns occur.

Results: 24% (95%CI: 23-26) of the Irish older population were classified as frail. In adjusted models, frailty remained a significant predictor of utilisation across many types of services. Four diverse patterns of service use were identified among frail older people. Misaligned referral routes, hospital consultant waiting lists and inadequate budgeting all contributed to impeding access to services. However, the Public Health Nurse service enabled navigation and referral to community services.

Discussion: The findings indicate a supply-constrained, hospital-centric healthcare system which fails to proactively manage the needs of the majority of the frail older population. Receiving community services is a rarity rather than the norm, and these are utilised mainly by the very-frail (FI >0.40, $p<0.01$).

Conclusions: Since the frail older population comprises a diverse set of service users, new models of care should be designed to reflect that diversity.

Does it matter what we measure: How do the number and type of deficits included affect the predictive power of frailty indices?

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Background: Frailty can be measured using a count of health deficits summarised as a frailty index. This method has been found to robustly predict adverse outcomes but the minimum number of deficits needed to optimize prediction is not clear. Here we apply an iterative re-sampling method to explore the predictive relationships with adverse outcomes for frailty indices including different numbers and types of deficits.

Methods: Data were from The Irish Longitudinal Study on Ageing (TILDA) (4,961 participants with a mean age of 61.9 ± 8.4, 54.2% female) and the Survey of Health and Retirement in Europe (SHARE) (18,097 participants with a mean age of 64 ± 10.4, 55.4% female). Adverse outcomes assessed included mortality and disabilities. A bootstrap-by-variables procedure was used to generate 100 random combinations of each type of deficits for frailty indices of different sizes. 5 item increments were used for the frailty indices (TILDA: 66 items; SHARE: 70 items). Area Under the Receiver Operating Characteristic Curve (ROC AUC) statistics were calculated for each iteration of each index for all outcomes.

Results: Across all outcomes, the ROC AUCs increased with the number of deficits in each index up to 20-30 items, above this number of items the increase tended to plateau with only modest improvements up to 50 deficits. For example, using the combined frailty index median ROC AUC for mortality for 5-item indices was TILDA: 0.62; SHARE: 0.67, for 30-item indices: TILDA: 0.70; SHARE: 0.74, for 50-items indices: TILDA: 0.72; SHARE: 0.75.

Conclusions: Predictive ability of the indices generally stabilized around 20-30 deficits. This suggests frailty may be adequately measured using the deficit accumulation approach in any dataset containing at least 20 health related items. Future studies are needed to confirm these findings in older populations with higher rates of adverse outcomes over longer follow up times.

The MISA biomedical engineering lab: A hospital based technology research and innovation unit.

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This poster describes the role, capabilities and activities of the biomedical engineering laboratory hosted by Mercer's Institute for Successful Ageing (MISA) and the Department of Medical Physics and Bioengineering (MPBE) at St. James's Hospital.

The MISA lab provides a space for engineering concepts and skills to be applied to clinical and research problems in medicine. The defining attributes of the lab are its integration with and physical proximity to the working life of a large acute hospital. This disposition allows engineering and medicine to work together close to the point of care. In this way, medical and engineering effort can be combined and focused on identifying and solving problems that are of real concern to patients and clinicians. The MISA biomedical engineering lab is unique in an Irish hospital context.

The lab hosts hospital personnel and visiting postdoctoral, postgraduate and undergraduate students working on clinical projects with a technological or engineering science component. In particular, the lab draws on hospital clinical engineering and medical physics expertise to support individual projects. The lab is equipped to support electronic prototyping, software development, data analytics, optics development, system modelling and 3D printing.

The lab activities include:

Medical Device prototyping: The lab supports the full lifecycle of medical device design, from prototyping concepts, to design for commercialisation.

Technology Assessment: Assessment of technology on the market against clinical and user requirements, e.g. assessment of falls detectors and brain perfusion monitoring devices.

Software Development: Mobile app development and programming.

Physiological modelling: Application of engineering modelling methods to help understand normal and pathological physiology, e.g. neurocardiovascular control, gait and falls.

Clinical research support: Support of scientific and technical aspects of clinical research, such as data analytics, signal processing and device specification and deployment.

Education: Teaching engineering concepts and skills to biomedical engineering and medical device design students.

Cancer

The Influence of Autophagy Inhibitors on Chemotherapeutic Efficacy in Oral Squamous Cell Carcinoma.

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Aim: Oral squamous cell carcinoma (OSCC) is the most common form of oral cancer. Squamous cell carcinomas differ to other cancers by undergoing a precancerous stage known as dysplasia. Autophagy dysfunction has been implicated in most cancers, including oral cancers, and can be tumourgenic or tumour suppressing depending on the cancer and the dysregulation involved. Metabolic stress from chemotherapeutics can activate autophagy and mediate acquired resistance to these compounds. Autophagy inhibition may prevent resistance occurring and prevent tumours from utilizing the autophagic pathway for cancer cell survival. This study aims to understand how chemotherapeutic drugs interact with the autophagic pathway, potentially driving chemoresistance rather than cell death. Autophagy targeting is a potential therapeutic avenue in OSCC.

Materials and methods: The OSCC cell line Ca9.22 was used throughout these experiments. Common chemotherapeutics cisplatin, carboplatin, docetaxel and 5-flourouracil were used in combination with several autophagy inhibitors. IC_{50} values for the chemotherapeutics were determined by Alamar Blue® assay. Inidicative levels of autophagy were determined by acridine orange staining. Apoptosis levels were determined by propidium iodide staining.

Results and discussion: IC_{50} values for all chemotherapeutics in Ca9.22, TR146 and DOK cell lines ranged from 200 pM – 50 µM and were used as the dose concentration for subsequent experiments. Acidic vesicle levels increased in the presence of a number all chemotherapeutics. Treatment of cells with autophagy inhibitors attenuated the levels of acidic vesicle formation and corresponded to the stage of autophagy targeted.

Conclusion: Inhibiting earlier stages of the autphagy pathway reduced the levels of acidic vesicles caused by cisplatin in Ca9-22 cells. Verification by quantitative analysis has yet to be conducted. All chemotherapeutics increased levels of apoptosis, however, It has yet to be investigated whether inhibiting particular stages of autophagy can impact the levels of apoptosis in cells undergoing chemotherapeutic treatment.

Identification and targeting of the DNA repair gene, XRCC6BP1, in cisplatin resistant non-small cell lung cancer (NSCLC).

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Aims: In the absence of specific treatable mutations, platinum-based doublet chemotherapy remains the gold standard treatment for NSCLC patients. However, its clinical efficacy is hindered in many patients due to intrinsic and acquired resistance to these agents, in particular, cisplatin. This study examined alterations in the DNA repair capacity of chemoresistant lung cancer cells *in vitro* and *in vivo*.

Methods: DNA Repair Pathway RT^2 Profiler Arrays were used to elucidate key DNA repair genes in H460 cisplatin resistant (CisR) and corresponding parental (PT) NSCLC cell lines previously generated in our laboratory. DNA repair genes significantly altered in CisR cells were validated using RT-PCR and western blot analysis, respectively. The translational relevance of these genes was examined in a cohort of matched normal and tumour lung tissues (n=20) from

NSCLC patients. Loss of function studies were carried out using siRNA technology. The effect of XRCC6BP1 gene knockdown on apoptosis was assessed by Annexin V/PI staining using the Cytell® Imaging System. To investigate the effects of siXRCC6BP1 on DNA damage and repair in response to cisplatin, the γH2AX foci formation assay was used.

Results: We identified a number of important DNA repair genes differentially regulated between PT and CisR cells. These included XRCC6BP1, TOP3A, XPA, PMS1 and hSSB1. XRCC6BP1 mRNA was significantly increased (19.4-fold) in H460 CisR cells relative to their PT counterparts. Relative to matched normal lung tissues, XRCC6BP1 mRNA was significantly increased in adenocarcinoma tissues, while hSSB1 mRNA was significantly increased in tumour tissues from both tumour histologies. Gene silencing of XRCC6BP1 re-sensitized CisR lung cancer cells to the pro-apoptotic effects of cisplatin and significantly reduced the DNA repair capacity of these cells.

Conclusion: Our data highlight the potential of targeting XRCC6BP1, at least in part, in re-sensitizing chemoresistant lung cancer cells to the cytotoxic effects of cisplatin chemotherapy.

Cisplatin induces the emergence and expansion of a distinct cancer stem cell (CSC) population in NSCLC.

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Aims: Resistance to cisplatin chemotherapy has become a significant clinical challenge in the treatment of non-small cell lung cancer (NSCLC) patients. The root of this resistance is hypothesized to be due to the presence a subpopulation of cancer stem cells (CSCs) within the tumour population, which have the potential to recapitulate a heterogenic tumour. The aim of this study was to examine the effect of cisplatin in promoting the expansion of this inherently resistant CSC population which, in part, may explain tumour recurrence in lung cancer patients following platinum-based chemotherapy.

Methods: RT-PCR gene expression analysis of stemness markers (Nanog, Oct-4, Sox-2, Klf4, cMyc, CD133 and ALDH1) was carried out in a cohort of matched normal and tumour lung tissues from NSCLC patients. Using an *in vitro* model of cisplatin resistance, FACS screening of reported CSC-markers in matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines, identified aldehyde dehydrogenase (ALDH1) as a promising CSC-marker associated with the cisplatin resistance phenotype across all NSCLC histologies. ALDH1 activity was measured using the Aldefluor assay, while $ALDH1^+$ and $ALDH1^-$ subpopulations were identified and isolated by FACS and MoFlo, respectively. Additional stemness parameters were also examined. PT and CisR cell lines were chronically exposed to cisplatin for 2 weeks after which time, stemness parameters were re-assessed.

Results: Stem-like genes were differentially altered in NSCLC tumours relative to their matched normal lung tissues. A significantly greater $ALDH1^+$ subpopulation was identified in all CisR sublines relative to their parental counterparts. Chronic cisplatin treatment induced the expansion of an $ALDH1^+$ CSC subpopulation in PT and CisR cells relative to baseline controls (week 0).

Conclusions: Our data show that prolonged treatment with cisplatin drives the expansion and survival of an $ALDH1^+$ CSC population, which in turn promotes the development of therapeutic resistance in lung cancer.

The Regulation of STAT3 and its role in the adhesion and migration of chronic lymphocytic leukaemia cells.

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Introduction: The bone marrow and lymph node microenvironments are important in promoting cell proliferation and survival in chronic lymphocytic leukaemia (CLL). Chemokines and adhesion molecules including selectins, such as CD62L, allow the transmigration of CLL cells to these niches. The B-cell receptor (BCR) signalling pathway plays a key role in microenvironmental crosstalk and has been shown to interact with the STAT3 signaling pathway in CLL.

Materials and Methods: The role of STAT3 in CLL cell survival and migration was investigated using pharmacological inhibition and siRNA knockdown. Adhesion marker expression and STAT3 phosphorylation (pSTAT3) were assessed by flow cytometry. Gene expression studies were performed using Taqman Assays. CLL cell adhesion under shear flow was investigated using a microfluidics system.

Results: Stimulation of the BCR induced tyrosine pSTAT3 and upregulation of STAT3 regulated genes in CLL cells with unmutated immunoglobulin (IgVH) genes but not in cells with mutated IgVH. This induced tyrosine pSTAT3 was abrogated by pre-treatment with the JAK/STAT3 inhibitor Ruxolitinib and the BCR inhibitors Ibrutinib and Idelalisib. BCR stimulation resulted in a significant increase in CD62L expression, which was inhibited by pre-treatment with Ruxolitinib.

STAT3 inhibition had a divergent effect on CLL cell survival: the STAT3 inhibitor cucurbitacin induced apoptosis in patient samples with high levels of serine pSTAT3, while in samples with low levels of serine pSTAT3 cucurbitacin had a prosurvial effect. siRNA mediated STAT3 knockdown and treatment with STAT3 inhibitors, resulted in a significant decrease in CD62L expression. Treatment of CLL cells with cucurbitacin resulted in a significant decrease in adhesion to endothelial cells under fluid shear flow and in cell migration in response to the chemokine CXCL12.

Conclusion: This study shows a role for the STAT3 pathway in cell survival and CLL cell-microenvironment crosstalk, suggesting therapeutic potential by interfering with the migration CLL cells to protective microenvironments.

Identification of Novel PGE_2 Receptor Antagonists that Modulate Angiogenesis and Inflammation in Oesophageal Adenocarcinoma.

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Introduction: Oesophageal adenocarcinoma (OAC) is the 7th leading cause of cancer deaths worldwide, with its incidence increasing. COX-2 is overexpressed in the progressive sequence from Barrett's oesophagus to OAC. While COX-2 inhibitors hold promise for prevention/treatment, they have been associated with cardiovascular toxicity. Downstream, prostaglandin E_2 (PGE_2) and its corresponding EP receptors are associated with angiogenesis and tumourigenesis in a number of cancers, including OAC.

Aim: This aim of this study was to investigate PGE_2 receptor (EP) antagonism as a novel approach for OAC prevention and/or treatment.

Methods: The effect of selective EP blockade (EP1-4 antagonists) on blood vessel formation was investigated *in-vivo* using a transgenic zebrafish model (*TgEGFP fli-1*). EP receptor expression was assessed by qRT-PCR and western analysis. An *ex-vivo* human 3D-explant model was established by culturing Barrett's and matched control patient tissue to investigate the effects of selected EP antagonists. Angiogenic and inflammatory protein secretions were assessed using multi-plex ELISAs and correlated with PGE_2 expression.

Results: The EP receptor antognists 1-4 all reduced vessel formation *in-vivo* in the zebrafish model. EP2 and EP4 were expressed in endothelial, Barrett's oesophagus and Oesophageal cancer cell lines. Explant culturing revealed significantly higher PGE_2 levels in Barrett's tissue, relative to matched normal and was associated with inflammatory factors IL1-β, IL-2, IL-6, IL-10 (all $p<0.01$), and TNF-α ($p<0.0001$). Significant reductions in secretion of IL-2, IL-10, IL-13, and TNF-α were observed following selective EP2 antagonism ($p<0.05$).

Conclusion: Selective EP antagonism has anti-angiogenic and anti-inflammatory effects *in-vivo*. The ability of selective EP antagonists to reduce inflammatory cytokine secretion suggests they may be promising chemopreventative agents.

Comparison of high-throughput methods for extracellular vesicle isolation to "gold standard" ultracentrifugation.

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Aim: Extracellular vesicles (EVs) represent a unique, enriched source of circulating biomarkers present in a multitude of bodily fluids. Research into EVs is limited however by a lack of consensus on standardised protocols for their isolation and thus analysis. At present the "gold standard" isolation method is ultracentrifugation, which is low-throughput and laborious, so alternative methods that could offer the same yield and purity are highly sought after. Here we aim to assess commercially available methods and compare these with various ultracentrifugation techniques.

Methods: Six EV isolation methods: ultracentrifugation (UC), ultracentrifugation with sucrose cushion (SC), ultracentrifugation with Optiprep density gradient (ODG), size exclusion chromatography columns (SEC), Total Exosome Isolation reagent (TEI) and Exo-spin were assessed using pooled serum specimens. EVs were characterized by transmission electron microscopy, nanoparticle tracking analysis, protein quantification and immunoblotting.

Results: TEI and Exo-spin were found to be inadequate for the isolation of EVs due to large amounts of precipitated protein and larger vesicle size present in samples. EVs isolated using SEC were found to be comparable to UC, but proved to be much more expensive for large scale studies. ODG outperformed UC and SC on EVs yield and purity, as enrichment for EV positive markers and lack of EV negative markers was observed.

Conclusions: We recommend the use of ODG, at least for initial validation of biomarkers, and the use of UC thereafter if ODG is no longer feasible.

HLA-DR is an independent prognostic indicator of patient survival in oesophageal adenocarcinoma.

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Oesophageal adenocarcinoma (OAC) is an aggressive malignancy with a five-year survival of <15%. OAC is an inflammation-driven cancer and incidence is predicted to double in Ireland in the next 20 years. Neo-adjuvant chemoradiotherapy treatment is increasingly used as the standard of care with surgery, but only a minority of patients respond. The clinical challenge is to predict which patients will have favourable clinical outcomes, in order to better tailor therapy.

Measurement of immune cells and markers in tumours has shown to be useful in predicting clinical outcomes, in a manner superior to current staging systems[1]. However, such immune scoring systems have not yet been tested in OAC. The aim of this study was to assess the prognostic potential of the antigen presentation molecule HLA-DR, in OAC tumours. Tissue microarrays (TMAs) were constructed from 3 separate cohorts of patients with OAC tumours, normal adjacent oesophageal tissue or pre-malignant inflammatory disease, e.g. Barrett's oesophagus (BO). TMAs were stained for HLA-DR by immunohistochemistry and average percentage positivity in the tissue epithelium and stroma was graded by 2 independent observers.

HLA-DR expression was elevated from an early stage in the inflammation to cancer progression sequence, with HLA-DR expression being highest in tumour tissue, compared to BO or non-inflamed adjacent normal tissue from matched donors. Kaplan Meier survival analysis demonstrated that high (>/=50%) HLA-DR expression in the tumour epithelium was associated with significantly longer survival time (mean 43.4 months, 95% CI 34.0-52.8 months) compared with low (<50%) HLA-DR expression (mean 29.8 months, 95% CI 17.5-42.2 months), (p=0.013). Cox-regression multivariate analysis demonstrated that low HLA-DR expression in OAC tumour leading edge epithelium was the single independent predictor of poor survival, associated with a 2.8 fold increase in disease associated death (p=0.023).

Future work will include assessment of other immune scoring strategies in the setting of OAC.

CT-based Body Composition Analysis in Pancreatic Cancer; a Feasibility Study.

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Introduction: Cancer Cachexia affects up to 80% of patients with pancreatic cancer, reducing resectability prospects and survival. Skeletal muscle measurement is necessary to allow timely recognition of cachexia, particularly in obese patients where muscle loss may be masked if relying on weight and/or BMI.

Aims: We sought to explore the feasibility of using diagnostic CT scans to assess baseline body composition in patients treated surgically during the first 2 years following centralisation of surgery. We compared baseline body composition in patients with shorter and longer than average post-operative length of stay (LOS).

Methods: Patients admitted for surgery between 2010 and 2012 were identified from a prospective database. Using Slice-O-Matic™, muscularity and adiposity at the level of L3 was measured in patients where pre-operative CT was availability. Baseline demographics and nutritional indices were recorded. Whole body fat free and fat mass were calculated using validated regression equations.

Results: Average post-operative LOS was 21 days. 80 patients with short (<14days) and long (>28 days) LOS were identified for inclusion. 39 patients were excluded due to lack of CT scan availability or poor visualisation at the level of L3. Body composition analysis took approximately 45 minutes per patient. 66% of patients were sarcopenic while 41% were sarcopenic and overweight/obese. There was no difference in skeletal muscle index between LOS groups (45.7 vs. 44.6 cm/m^2), however patients with prolonged LOS had higher baseline adipose levels (p=0.03).

Conclusions: Sarcopenia is prevalent in Irish pancreatic cancer patients with resectable disease, and may be missed due to the majority of patients presenting with normal or elevated BMI at diagnosis. Body composition analysis using diagnostic CT scans is feasible, but requires significant time input.

Characterization of microbubble contrast agents for subharmonic dynamic contrast-enhanced ultrasound imaging of liver tumours.

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Aim: Dynamic contrast enhanced ultrasound (DCE-US) using ultrasound contrast agents (UCA) is a non-invasive method of imaging the microvasculature. Imaging focal liver diseases using DCE-US improves detection and characterisation over conventional ultrasound. UCAs are currently used clinically for qualitative purposes only. They produce subharmonic signals at half of the transmitted fundamental frequency when insonated with ultrasound energy, whereas native tissue does not. Subharmonic imaging (SHI) offers the potential to image the microvasculature with better sensitivity and improved accuracy for use in quantitative measurements. The aim of this study was to develop an acoustic characterization system for SHI of UCAs.

Methods: Various methods for UCA characterization were investigated using single element transducers (Olympus, USA) to transmit and detect ultrasound energy through solutions containing varying concentrations of UCAs. The effects of bubble floatation, bubble concentration, bubble size distribution and reflector type were investigated. Pressure levels, which influence the production of subharmonic signal were investigated using a needle hydrophone (Precision Acoustics, UK) for signal detection.

Results: A broadband reflection-based acoustic characterization system was developed, and the native populations for two UCAs, Definity (Lantheus Medical Imaging, USA) and SonoVue (Bracco, Italy), were successfully acoustically characterized. A through-transmission narrowband system for use in subharmonic characterization was developed. Pressure levels above the subharmonic threshold of 49 kPa were measured.

Conclusion: The developed narrowband through-transmission system will be used to characterize subharmonic signals from both Definity and SonoVue. The results of both the broadband and narrowband investigations will be used to develop an optimized protocol for the acquisition of subharmonic signals using the programmable settings on our research clinical ultrasound scanner, to develop a technique which could be used for liver cancer imaging in a clinical setting.

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Xerostomia in Advanced Cancer: A Clinical Audit.

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Aim: Xerostomia is the subjective sensation of dry mouth. It is the fourth most common symptom in advanced cancer patients and impacts negatively on physical and psychosocial wellbeing. Older age and polypharmacy are risk factors for dry mouth and are common in advanced disease. This study aims to evaluate prevalence of xerostomia, as well as compliance with assessment and treatment practices.

Method: A retrospective chart audit was conducted on 173 admissions from an in-patient palliative care unit. Data were collected pertaining to patient demographics, cancer diagnosis, medications, oral health assessment and xerostomia treatment. Audit standards were based on local policy as follows: Oral Health Assessment Tool (OHAT) completed on all patients; OHAT completed within one day of admission; oral care plan completed if problem diagnosed; xerostomia treatment prescribed where necessary. Descriptive statistics were used to report compliance with standards. Cohen's Kappa and Intraclass Correlation Coefficient were used for inter- and intra-rater reliability based on a 10% sample of the dataset.

Results: Palliative in-patients were significantly more likely than the general population to experience dry mouth ($p<0.001$). 86% of admissions had OHAT completed and 91% of these were on day of admission. Care plans were completed for 76% of patients with oral care needs. Appropriate medications were prescribed for 34% of patients with dry mouth. Inter- and intra-rater reliabilities were high or perfect for all primary outcomes.

Conclusion: Results indicate that oral health is evaluated in the majority of patients, however treatment appears low. This may be partly due to poor instrument design, where non-prescription treatments or 'treatment unnecessary' cannot be documented. Existing tools could be amended to reflect patient care needs more accurately. A change project is currently underway within the care setting to improve practice as a result of the study.

Error quantification in pharmacokinetic parameters derived from DCE-MRI data using a novel anthropomorphic dynamic prostate phantom.

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Aim: Dynamic contrast enhanced (DCE) MRI, in combination with Pharmacokinetic (PK) modelling of the data, has shown considerable promise in the detection of many cancers, including prostate. However, a lack of consistency with published PK parameter values, such as the volume-transfer constant (K^{trans}), coupled with widely varying acquisition protocols and PK modelling approaches, has hindered the clinical implementation of this technique. A method is currently lacking to comprehensively validate the ability of DCE-MRI techniques to accurately measure PK parameters. To address this shortcoming a novel anthropomorphic MRI test device has been developed which is capable of simultaneously producing two MR-measurable contrast time-intensity curves (CTCs), representative of those observed in healthy and tumorous prostate tissue, from which PK parameters can be derived and compared with known 'ground truth' values, allowing for the quantification of any errors in the MRI measurements.

Methods: 'Ground truth' CTCs were measured using a custom-built high spatiotemporal resolution optical imaging system, and ground truth PK parameter values derived from the optical data. DCE-MRI data were acquired using a 3T scanner (Achieva, Philips, Netherlands) and a 16-channel phased array detector coil (3D-SPGR, TR/TE=3.6/1.75ms, α=10°, voxel size=1.1x1.1x4mm^3, FOV=224x224x72mm^3, slices=18). The parallel imaging factor and number of signal averages were varied to give temporal resolutions from 2.3s to 20.3s.

Results: K^{trans} values derived from MR-data from the phantom were compared with the ground truth values and were found to differ by -8.1% to -44.6%, with the lowest variance from ground truth values achieved at a temporal resolution of 6.8s.

Conclusion: The phantom provides a model system for the quantitative validation of new and existing prostate DCE-MRI techniques, and could help contribute to the standardisation of clinical prostate DCE-MRI acquisition protocols.

This work is funded by Irish Cancer Society Research Scholarship CRS13KNI (supported by Movember) and an IAPM Young Investigator Grant.

Nutritional Status of Cancer Patients at Dietitian Referral.

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There is increased emphasis on early recognition of people at risk of malnutrition and in the pre-cachexia stage. Clinical staff report concerns that people with cancer are referred late to a dietitian but literature is sparse.

Aim:
This study aimed to provide a snapshot of current practice in Ireland and describe

1. The characteristics of people with cancer at point of dietitian referral
2. Professional opinion on adequacy of referral timing
3. The utility of the 2011 consensus definition (Fearon et al) to identify cancer cachexia in clinical practice.

Method: This was a prospective observational study. Data was recorded in five Irish hospitals from referrals to dietitian services of people with cancer. Demographic details, barriers to nutrition and timing of referral were noted. Where possible, the dietitian categorised each patient by stage of cachexia.

Results: Interim data from 175 patients was included, 59% males and 57% inpatients. Weight loss was the most common reason for referral (57%). Most (68%) had lost ≥ 5% of body weight. 71% had 2 or more barriers to nutrition were present, most commonly anorexia, nausea and early satiety. In 31%, a clear missed opportunity for earlier referral was identified. Cachexia stage was assigned in 87%. 65% of patients were deemed cachectic or refractory, with only 16% pre-cachectic.

Conclusion: Despite the importance of nutritional care in cancer, most patients with cancer were still referred late to a dietitian, with established weight loss and multiple nutritional symptoms. Only one sixth of patients saw a dietitian at the pre-cachectic stage. One third had missed earlier opportunities for referral. The 2011 cancer cachexia definition appeared feasible in practice but would require validation.

To our knowledge, this is the first study to describe practice in Irish hospitals. It will inform service planning, education and research in malnutrition and cancer cachexia.

miR-134 in breast cancer-derived extracellular vesicles: potential biomarker and therapeutic option.

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Introduction: Extracellular vesicles (EVs) have key roles in breast cancer cell invasion, metastasis, apoptosis and in anti-cancer drug resistance. The aim of this project was to profile the miRNA contents of triple-negative breast cancer (TNBC) cells and their EVs to identify miRNAs which may have therapeutic potential in TNBC and to investigate EVs as therapeutic miRNA delivery vesicles.

Methods: The miRNA content of TNBC isogenic cell line variants and their EVs was investigated using low density arrays representing 384 miRNAs. miR-134 levels in breast tumour vs. normal breast tissue were determined using GEO2R on publically-available datasets Transcriptional silencing at chromosome 14q32.2 was investigated using qRT-PCR for the neighbouring MEG3/DLK1 loci. Functional analysis (proliferation, migration, invasion and apoptosis assays) was performed to investigate the effects of EV-delivery and direct transfection of miR-134 into TNBC cells. The sensitivity of cells to anti-cancer drugs was evaluated acid phosphatase assays.

Results: The most substantially down-regulated miRNAs in aggressive cells and their EVs originated from 14q32. miR-134 was down-regulated in tumour tissue from GSE26659 ($p<0.001$) and GSE40525 ($p<0.001$) datasets. MEG3 was detected in Hs578T cells but its expression was significantly decreased in the Hs578Ts(i)8 variant ($p<0.001$). Directly transfecting miR-134 into Hs578Ts(i)8 cells significantly decreased proliferation ($p<0.001$) and enhanced cisplatin-induced apoptosis ($p<0.05$). miR-134-enriched EVs reduced STAT5B and Hsp90, reduced cellular migration and invasion ($p<0.01$), and enhanced sensitivity to anti-Hsp90 drugs ($p<0.05$).

Conclusions: While the differing effects achieved by transfection or EV delivery are likely to be partly due to specific amounts of miR-134 delivered by these routes, these EV-based studies identified miRNA-134 as a potential biomarker and therapeutic for breast cancer.

A novel role for the complement cascade in chemoradiation therapy resistant oesophageal adenocarcinoma.

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Aim: This project aims to elucidate the role of the complement system in the resistance of oesophageal adenocarcinoma (OAC) to neoadjuvant chemoradiation therapy (CRT).

Methods: OAC tumour biopsies were collected prior to neoadjuvant CRT. Tumour conditioned media was generated by culturing human explants for 72 h. Response to treatment was determined pathologically using the Mandard Grading System. C3 mRNA expression was assessed by qPCR. Secreted C3, C3a and MCP-1 was measured by ELISA. An isogenic model of radioresistant OAC was established by chronically irradiating OE33 cells with clinically-relevant doses of 2 Gy X-ray radiation. C5aR and C3aR expression was determined by flow cytometry.

Results: We demonstrate for the first time that the central component of the complement cascade, complement component 3 (C3), is expressed in OAC tumours and furthermore, is significantly increased in pre-treatment OAC biopsies from patients (n=13) who have a subsequent poor response to neoadjuvant CRT ($p < 0.05$). Importantly, we demonstrate that C3 is secreted

from ex vivo human OAC tumour explants (n=13) and significantly correlates with levels of the monocyte chemoattractant MCP-1 ($p< 0.01$). In vitro, using a novel isogenic model of radioresistant OAC, radioresistant OE33 R cells demonstrated significantly increased levels of C3 mRNA ($p < 0.01$) and significantly elevated levels of secreted C3 and the anaphylatoxin C3a ($p < 0.05$), when compared to radiosensitive OE33 P cells, supporting a role for complement in the radioresistance of OAC. Furthermore, we demonstrate for the first time that the anaphylatoxin receptor C5aR is expressed in OAC cells, suggesting that OAC cells can respond to complement anaphylatoxins.

Discussion: This study highlights for the first time, a novel role for the complement cascade in the resistance of OAC to CRT and highlights C3 as a novel predictive marker of response to CRT in OAC.

Cancer stem cells: targeting aldehyde dehydrogenase 1 (ALDH1) as a novel strategy to overcome cisplatin resistance in NSCLC.

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Aims: Cisplatin is the backbone of chemotherapeutic treatment in NSCLC. Unfortunately, the development of cisplatin resistance has become a major clinical challenge. The survival and expansion of highly resistant cancer stem cells (CSCs) during and following chemotherapeutic treatment are thought to be a contributing factor of resistance and recurrence. This study examined whether specific targeting of key CSC markers, in combination with chemotherapy, could re-sensitize cisplatin resistant lung cancer cells to cisplatin chemotherapy.

Methods: Using an isogenic panel of matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines, aldehyde dehydrogenase 1 (ALDH1) activity was examined in H460, SKMES-1 and H1299 NSCLC cell lines, representing each histological subtype. ALDH1 was inhibited using two ALDH1 inhibitors, diethlylaminobenzaldehyde (DEAB) and Disulfiram (Antabuseä). ALDH1 inhibition was measured FACS analysis. PT and CisR cell lines were treated with inhibitor alone, and in combination with cisplatin. Functional parameters such as cell proliferation, clonogenic survival and apoptosis were assessed relative to cells treated with cisplatin alone.

Results: Cisplatin resistant NSCLC cell lines exhibited a significant increase in ALDH1 activity relative to matched parental counterparts. Both DEAB and the FDA-approved drug, Disulfiram, significantly reduced ALDH1-positive stem-like cells across all CisR sublines. DEAB or Disulfiram, when used in combination with cisplatin, significantly decreased proliferation and clonogenic survival ability of chemoresistant cells, and significantly increased cisplatin-mediated cell death in all three resistant cell lines, relative to cells treated with cisplatin alone.

Conclusions: Our data suggest a role for ALDH1 inhibition as a potential therapeutic strategy in re-sensitizing chemoresistant lung cancer cells to the cytotoxic effects of cisplatin chemotherapy. Further studies are warranted to examine the effects of clinical and/or pharmacological inhibitors targeting ALDH1 and other ALDH1 isoforms *in vitro* and *in vivo*.

Design, synthesis and evaluation of the azetidin-2-ones as novel bioactive compounds.

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Introduction: The African willow tree *Combretum caffrum* Kuntze (Combretaceae) is a very productive source of cancer cell growth (murine P388 lymphocytic leukemia) inhibitory stilbenes, bibenzyls, and phenanthrenes. The synthesis of a series of rigid analogues of combretastatin A-4 is described which contain the four membered β-lactam heterocyclic azetidinone in place of the usual ethylene bridge present in the natural combretastatin stilbene products[1]. The structure-activity relationships of antiproliferative β-lactams, focusing on modifications at the 3- and 4-position of the β-lactam ring, are described.

Methods: Synthesis of this series of compounds was achieved utilizing the Staudinger and Reformatsky reactions. To investigate the importance of the OCH_3 substituent on C-4 of the aryl Ring B moiety for the biochemical activity and potency, a series of thioether S-CH_3 and S-CH_2-CH_3 to replace the oxygen substituent at the C-4 position of the Ring B aryl moiety were synthesized, which were then evaluated for antiproliferative activity against three human cancer cell lines (MCF-7, HT-29, and HL60 cancer cell lines.

Results: Of a diverse range of heterocyclic derivatives (Figure1), 3-phenyl, 3-vinyl and 3-hydroxy analogues displayed the highest potency with nanomolar IC_{50} values, comparable to combretastatin A-4.

Conclusions: a new class of combretastatin A-4 analogues that have thioether substituents at the C-4 position of the Ring B-aryl moiety of the β-lactam ring was successfully synthesized. All thioether S-CH_3 compounds exhibited significant antiproliferative activity equally to -OCH_3 β-lactams which can inhibit the first-pass metabolism pathway (formation of glucuronide metabolite) occurring by -OCH_3 β-lactams.

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Synthesis, characterization and biochemical evaluation of novel heterocyclic stilbene compounds with tubulin targeting activity.

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Drug-like small molecule natural product such as colchicine and the combretastatins provide ideal structural templates for the design of structural scaffolds with improved efficacy as tubulin targeting agents. Combretastatin A-4 originally isolated from *Combretum caffrum*, exhibits strong antitubulin activity by binding to the colchicine binding site[1]. In this work a library of amide conjugates of Combretastatin A-4 and related structures have been synthesized and the biological activity has been investigated. We report our synthetic approaches to stilbene analogues of colchicines, combretastatins and phenstatin together with their *in vitro* biological activity. We also report docking studies and the SAR of these compound classes which have underlined the presence of the 3,4,5 trimethoxy substituted A-ring and the 4-methoxy substituted B- ring separated by a double-bond to be essential for antiproliferative activity. The activity of CA4 is limited by isomerization of the active *cis*-stibene configuration into the inactive *trans* analog.

Introduction of a heterocyclic amide group on the stilbene scaffold may create a stabilized CA4-like compound locked in its *cis*-form. The newly synthesised acrylic acids have then been coupled to a variety of heterocycles using the Mukaiyama reagent as coupling reagent (using appropriate protecting/deprotecting steps) to afford the heterocyclic amide conjugates. The novel compounds synthesised have been characterized (^{1}H-NMR, ^{13}C-NMR, IR, HRMS). The purity of the final products has been evaluated by HPLC and when possible the structure of the compounds was established by single crystal X-ray analysis. The biological activity has been evaluated on the human MCF-7 cell line in an antiproliferative assay and the IC_{50} value for the most active compounds obtained.

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Discovery of potential therapies for lymphomas and leukaemias: Synthesis and antiproliferative action of novel ehanoanthracenes.

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The antidepressant maprotiline and its (*E*)-9-(2-nitrovinyl)anthracene analogues have been identified as potent novel antiproliferative compounds in Burkitt Lymphoma (BL) cell lines MUTU-1 and DG-75.[1,2] This knowledge was translated to CLL (Chronic Lymphocytic Leukaemia) a related B cell malignancy. CLL is the most common leukaemia in the western world, accounting for greater than one third of new diagnoses.

Initial biochemical screening (Alamar Blue) in PGA1 and HG3 CLL cell lines was completed and a number of potent compounds were identified. The results were then compared to BL studies, with compounds being tested at 1 mM and 10 mM concentrations. Activity was determined as percentage of viable cells remaining. The subsequent finding of these studies is presented together with discussion of the rationalisation of the compound SAR in PGA1 and HG3 CLL cell lines. Synthesis of (*E*)-9-(2-nitrovinyl)anthracenes was accomplished through the use of a piperidine catalysed Henry-Knoevenagel condensation reaction, in addition to Grignard and Vilsmeier-Haack chemistry to yield the required 10-substituted 9-anthraldehyde intermediates.

Future work includes the expansion of the current SAR knowledge for the ethanoanthracene-type maprotiline analogues and bioisosteric replacement of the nitro group on the 9-vinyl anthracene substituent with a view to optimising biological activity.

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Maximum Voluntary Contraction and Endurance Time as Objective Measures of Cancer-Related Fatigue.

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Aims: Cancer-Related Fatigue (CRF) is a prevalent, highly debilitating symptom. Current assessment of CRF is by subjective questionnaires (e.g. Brief Fatigue Inventory (BFI)) as no effective objective measures exist. In this study, overall fatigue score was assessed using the BFI, and then compared to objective measures of muscular fatigue. Associations of muscular fatigue, as measured by Maximum Voluntary Contraction (MVC) and Endurance Time (ET), to the subjective measure of BFI were explored. Differences between healthy controls and CRF sufferers were assessed using these measures.

Methods: 10 pre-chemotherapy patients with NSCLC and 10 healthy controls (HC) assessed their fatigue through BFI. They then performed a sustained contraction of the right forearm at 30% maximal level until self-perceived exhaustion. MVC and ET were recorded.

Results: Mean age was 64.1 +/- 11.77 for CRF and 28.1 +/- 7.89 for HC. Gender: CRF: 6F, 4M and HC: 3F, 7M.

BFI was moderately correlated with ET (r= -.57, p=0.01) and MVC (r=-.61, p=.004) for all participants, and strongly correlated with MVC (r=-.743, P=0.01) for cancer patients alone. Other correlations were weak. For participants overall, for HC and for CRF, linear regression analysis with MVC and ET as predictors of BFI resulted in an R2 of .577, .308 and .653 respectively.

CRF patients reported significantly (p=0.02) higher mean fatigue on the BFI (30.2 vs 12.90). The CRF group had a significantly (P=0.006) shorter duration time and a significantly (P=0.05) lower mean MVC (278.19 vs 408.83).

Conclusion: There was strong correlation between MVC and BFI, for CRF suggesting this could be used as an objective measure of fatigue. The notably high R2 value of .653 for MVC and ET as a predictor of BFI suggests that muscular fatigue makes up over half of cancer related fatigue.

Salivary Protein Glycosylation and Biomarker potential in OSCC.

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Aim: Protein glycosylation is a diverse and crucial post-translational modification involved in physiological and pathophisiological conditions. In respect to cancers of the oral cavity very few early diagnostic and prognostic biomarkers exist and their clinical utility remains minimal. Inability of early diagnosis challenges the scientific community to find reliable biomarkers in a suitable biofluid. The aim of this study was to develop and optimize analytical methods enabling the detection of glycans and determining their potential usefulness in biomarker discovery.

Materials & Methods: Due to the complexity of glycosylation, an orthogonal analytical approach was necessary for structural characterization. The release of *N*-glycans from the protein backbone was achieved using the endoglycosidase, PNGase F followed by glycan derivatization with the 2-aminobenzamide (2-AB) fluorophore. Glycans were analysed using hydrophilic interaction liquid chromatography (HILIC) coupled with Ultra low Performance Chromatography (UPLC). Exoglycosidase enzymatic digestions and comparison of pre and post enzymatic digestion chromatographic profiles were used to identify peak shifts in order to determine the presence of a specific residue(s). Weak anion exchange (WAX) Chromatography and Mass Spectrometry (MS) were used to assist in the identification of glycan structures.

Results: Oral biofluids were found to contain a heavily glycosylated protein composition. All types of glycans complex, hybrid and high mannonse structures were present. The main glycans were neutral glycans with smaller levels of mono, di- and tri- sialylated glycans. Furthermore glycans were heavily fucosylated.

Conclusion: Glycosylation changes are the most frequent biochemical alterations associated with cancer, both in terms of specific hypo- and hyper-glycosylation events. Sensitive and reliable diagnostic markers for oral cancers and recurrence of oral cancers remain unavailable. This study demonstrates the applicability of the developed methodology and its potential identification of alterations in the glycoproteome to facilitate the detection of cancers within the oral cavity.

HPV Primary Screening Pilot Study.

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Introduction: HPV testing plays an important role in cervical cancer prevention strategies, in particular in the context of HPV vaccination populations. Primary HPV screening is more sensitive than cytology based screening. However, while HPV DNA testing is more sensitive than cytology for identifying CIN2+, the specificity is lower. Thus, a key challenge with HPV primary screening is to find the optimal balance between sensitivity and specificity, and avoid large numbers of unnecessary follow-ups of HPV-positive women. This can be achieved by using more specific HPV tests and appropriate triage algorithms.

Methods: In partnership with CervicalCheck, The National Cervical Screening programme, CERVIVA are undertaking a longitudinal HPV primary screening pilot study which will evaluate several different triage strategies for management of a HPV-positive primary screening test. Cervical cytology samples from 13,000 women undergoing routine cervical screening will be tested for HPV DNA (cobas 4800 HPV test) and mRNA (Aptima HPV assay). All HPV-positive women will be further assessed with cytology and a panel of molecular tests including HPV16/18 genotyping, p16INK4a/Ki-67, and specific methylation markers. The performance of different triage strategies will be examined both cross-sectionally and longitudinally over two screening rounds for detection of CIN3+.

Results: To date 1700 woman have been recruited into the study. The median age of the population is 39 years. HPV DNA testing, performed on 1170 samples, shows a 12.6% positivity rate. HPV mRNA, performed on 1126 samples, gave an 11.4% positive rate. Both tests have a 92.5% agreement. Biomarker testing has begun and clinical data is currently been collected.

Conclusion: Here we introduce the study concept and design and will provide an update on recruitment and clinical performance to date.

Immunology, Inflammation & Infection

Accuracy of the CLO test versus histology in the diagnosis of *Helicobacter pylori* infection.

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Introduction: The accurate detection of *H. pylori* infection is essential for managing infected patients with gastro-duodenal symptoms. Commonly employed tests for *H. pylori* on gastric biopsies include the *Campylobacter*-like organism (CLO) test, histological examination and culture.

Aim: To determine the accuracy of the CLO test versus histological testing for the detection of *H. pylori* infection.

Methods: Following ethical approval and informed consent, gastric biopsy samples were obtained from patients undergoing endoscopy at Tallaght Hospital. CLO tests were examined and interpreted after 30 minutes in accordance with manufacturer's guidelines. Histological examination for *H. pylori* was by hematoxylin and eosin staining and immunohistochemistry. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the CLO test was compared to histology using Diagnostic Test Evaluation software (www.medcalc.org).

Results: In all, 473 patients mean age 52.7 ± 16.8 years, 45% (*n*=213) male were included. A total of 98 (20.7%) patients were *H. pylori*-positive by histology while 99 (20.9%) patients were positive by the CLO test. Patients infected with *H. pylori* (according to histology) were significantly younger than those who were not (49.4 vs 53.6 years; *p*= 0.03; 95% CI 0.50 to 7.96). Using histological testing as the gold standard, there were 21 false positive and 20 false negative CLO tests. The sensitivity, specificity, PPV and NPV of the CLO test compared to histology were 80%, 94%, 79% and 95% respectively.

Conclusions: The rate of patients infected with *H. pylori* attending for endoscopy at Tallaght Hospital is low (21%). The low sensitivity of the CLO test warrants continued histological testing for *H. pylori*. However, continued use of the CLO test during endoscopy is necessary as it enables rapid diagnosis of infection and same-day prescription of therapy.

Hepatitis C Virus (HCV) induces Suppressor of Cytokine Signaling (SOCS) proteins, revealing a novel immunomodulatory mechanism.

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Patients acutely infected with HCV are often asymptomatic, although 55-85% fail to clear the virus, leading to chronic infection, liver cirrhosis and hepatocellular carcinoma. HCV effectively suppresses host immune responses, although the mechanisms underlying immune modulation are poorly understood. HCV induction of Suppressor Of Cytokine Signaling (SOCS) proteins, (a family of 8 intracellular inhibitors that are negative regulators of cytokine signaling) is one mechanism by which the virus suppresses the immune response.

We have previously demonstrated elevation of suppressor of cytokine signaling 3 (SOCS3) in HCV+ patients. Here, we examined the effect of individual HCV proteins on SOCS induction in vitro. We observed that both p7, an ion channel required for infective HCV particles, and NS2 which is a protease required in the replication cycle, induce SOCS3, SOCS4 and SOCS5 mRNA expression and SOCS3 protein expression. To investigate the molecular mechanism of SOCS induction,

we performed bioinformatic analysis of the promoter regions of SOCS genes, and identified a number of putative transcription factor binding sites, including STAT3, STAT1, NFκB and AP-1. We found that p7 enhanced pSTAT3 and pERK signaling, while inhibited NFκB promoter activity and also basal expression of NFκB dependent genes. In addition, both p7 and NS2 induced CXCL-8 mRNA expression, a chemokine, which has been shown to inhibit anti-viral interferon signaling. Our demonstration that HCV proteins p7 and NS2, modulate innate immune signaling via SOCS induction, identifies a novel mechanism for immunosuppression during HCV infection.

Population pharmacokinetics of teicoplanin and attainment of pharmacokinetic/ pharmacodynamic targets in adult patients with haematological malignancy.

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Aim: Teicoplanin has maintained an important niche in the antibiotic arsenal for the treatment of Gram-positive infections in patients with haematological malignancy. However, inadequate antibiotic exposure in patients with haematological malignancy may result in a considerable increase in infection-related morbidity and mortality. The aim of this study was to describe the population pharmacokinetics (PK) of teicoplanin concentrations in adult patients with haematological malignancy with and determine dosing regimens associated with a high likelihood of achieving optimal teicoplanin concentrations based on the resulting population PK model.

Method: This was a prospective study based in Tallaght hospital, Dublin. Serial serum samples were collected and teicoplanin concentration determined. Population pharmacokinetic analyses and Monte Carlo dosing simulations were undertaken using Pmetrics®.

Results: Thirty adult patients with haematological malignancy were recruited with a mean (SD) age, total body weight and creatinine clearance of 63 (12) years, 69.1 (15.8) kg and 72 (41) mL/min, respectively. A three-compartment linear pharmacokinetic model best described the teicoplanin concentration data. High interpatient pharmacokinetic variability was observed (coefficient of variation for clearance and volume of the central compartment 71% and 26%, respectively). Covariates supported for inclusion in the final pharmacokinetic model were creatinine clearance for clearance and total body weight for volume of the central compartment. The median (IQR) teicoplanin area under the concentration-time curve from 48-72 h (AUC48-72h) was 679 (319) mg.h/L. There was a very strong correlation between the AUC48-72h and trough concentration at 72 h ($P<0.001$). Dosing simulations showed that administering five loading doses 12 h, stratified by total body weight and creatinine clearance, increased the probability of achieving target concentrations within 72 h.

Conclusion: To increase the number of patients achieving optimal teicoplanin concentrations an individualised dosing approach, based on body weight and creatinine clearance, is recommended.

'A novel fluorescent analogue of TUDCA reveals new mechanistic insights into TUDCA cytoprotection'.

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Aim: Molecular chaperones are substances that assist protein folding or reduce protein unfolding and aggregation. They have potential in a wide range of amyloid diseases and ER stress. The taurine conjugate of UDCA which may contribute to the therapeutic effects of UDCA is a chemical chaperone. TUDCA has shown promise in Huntington's and ALS and in models of metabolic syndrome. Notably, the mechanism of its hepatoprotective effects is currently unknown. The aim of this work was to produce reporter compounds related to TUDCA that could be used to investigate its mechanism.

Methods: We used the hepatocarcinoma cell line HUH7 and tunicamycin or DCA as a model of ER stress. We measured mRNA of BIP/GRP78, ATF4, CHOP and XBPu/s and PERK phosphorylation by Western Blotting at 6h. We established an in vitro model of cholestatic cytotoxic effects using DCA and GCDCA (200-300 mM) to stimulate apoptosis/necrosis. Cell viability with or without additional UDCA, TUDCA or fluorescent reporter was assessed using MTT and nuclear cell count on INCELL. The effect of pre and co-treatment on cell viability was assessed. Finally we used confocal microscopy to compare the distribution of the fluorescent analogue and fluorescent but unconjugated UDCA.

Conclusion: The 3-alpha dansyl analog had similar effects to TUDCA on ER stress and it inhibited protein aggregation. In a model of cholestasis using DCA to induce apoptosis, UDCA had no effect but pretreatment with its dansyl TUDCA prevented cell death similarly to TUDCA. The new reporter is suitable for new investigations into UDCA/TUDCA in liver disease and potentially new treatments.

'A new non-absorbable MMP-9 inhibitor modifies disease in the DSS ulcerative colitis model'.

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Aim: Selective inhibition of a matrix metalloproteinase (MMP) by a small molecule inhibitor has remained elusive due to the highly conserved structural conformation of the enzyme family. We proposed that an inhibitor designed to remain confined to the gastrointestinal lumen would allow us to test the hypothesis that disease modifying effects in inflammatory bowel disease (IBD) could be achieved by inhibition of apically secreted gelatinases potentially without side-effects of systemic inhibition of MMPs.

Methods: Of the synthesized candidates, the permanently positively charged compound MP038 was chosen as a suitable candidate for evaluation in a DSS mouse model of colitis. Its limited absorption potential was demonstrated in a Caco-2 cell uptake assay and it is a potent inhibitor of MMP-9 with an IC50 of 5.6 nM determined by fluorogenic assay. It also exhibited favourable drug characteristics of water solubility and crystallinity. Compound MP038 was administered to the treatment group by oral gavage at 10 mg/Kg once daily.

Results: The disease activity index of the treatment group on day 7, a combined score of weight loss, stool consistency and presence of blood, was statistically significantly better than that of the positive control group as determined by a two-tailed t test (p value = 0.0004). Zymographic analysis of the retained colon samples indicates down-regulated MMP-9 and MMP-2 activity in the treatment group in comparison with the positive control group.

Conclusions: Specific local inhibition of MMP activity in the intestinal lumen modifies the disease course in DSS ulcerative colitis. New drug designs can be devised that limit MMP inhibition to the intestine.

An in-depth analysis of an emerging CC1-MRSA-IV/t127 clone in Irish hospitals using whole-genome sequencing.

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Aim: Recently, a community-associated (CA) MRSA clone, CC1-MRSA-IV/t127, was detected in several Irish hospitals, including a protracted hospital outbreak. This study investigated these isolates using whole genome sequencing (WGS).

Methods: Eighty-four CC1-MRSA-IV/t127 isolates recovered between 2013-2016 were investigated, including 50 from a 26 month-long outbreak in hospital H1, 22 isolates from 15 other hospitals and 12 community isolates. All isolates uderwent WGS using an Illumina MiSeq sequencer. BioNumerics 7.6 (Applied Maths, Belgium) was used for assembly and analysis of sequence reads. Whole-genome multilocus-sequence typing was performed on each genome from which a minimum spanning tree (MST) was generated to investigate isolate relationships. Single nucleotide variations (SNVs) were recorded between isolates within MST clusters, using the earliest recovered isolate genome (ERI) as a reference.

Results: A major MST cluster of 67 closely related isolates was identified, 50 from hospital H1, one each from eight other hospitals and nine from the community. Within this cluster, two sub-clusters were evident radiating from the ERI from hospital H1. Sub-clusters 1 and 2 consisted of 55 and 12 isolates, and diverged from the ERI by 75-141 and 70-119 SNVs, respectively. A total of 43/50 of the major MST cluster isolates from the hospital H1 outbreak exhibited high-level mupirocin resistance, harbouring a conjugative ileS2-encoding plasmid. Of the 17 isolates outside the major MST cluster, three were from the community and 14 were from 10 other hospitals and diverged from the reference genome by 203-455 SNVs.

Conclusions: WGS established the close relatedness of CC1-MRSA-IV/t127 isolates from an ongoing hospital outbreak with isolates from other hospitals and the community. The majority of outbreak isolates harboured a conjugative mupirocin resistance plasmid. More distantly related CC1/t127-MRSA-IV isolates were identified elsewhere in Ireland. Ongoing surveillance is required to prevent these and other CA-MRSA becoming more widespread in Irish hospitals.

The oral microbiome in children with Crohn's disease exhibits reduced biodiversity compared to healthy children, revealed by 16s profiling.

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Aims: To identify marker organisms that could identify if a patient is suffering from Crohn's disease. This information may also be used to improve the oral health of patients with Crohn's disease.

Methods: The oral microbiome was examined in a cohort of children diagnosed as suffering from Crohn's disease (n=23, CD), inflammatory bowel disease (n=10, IBD), and ulcerative colitis (n=5, UC) respectively. A cohort of 24 children who were attending DDUH were grouped as a healthy

control (HC) group. Bacterial DNA was extracted from tongue and buccal swabs and the V1-V2 region of the 16s gene was amplified and sequenced using the MiSeq. Sequences were analysed with the Mothur pipeline.

Results: At the phyla level, the tongue of Crohn's patients was found to have significantly lower levels of *Bacteroidetes, Proteobacteria* and *Fusobacteria*. Reduced biodiversity of the tongue was reflected by differences in the inverse Simpson's index for both sites (CD tongue=9.39; HC=12.87). Analysis of species richness by rarefaction showed a significant reduction in species richness in CD tongue samples compared to HC tongue samples, whereas species richness in CD buccal was almost as the same as HC buccal. The number of Operating Taxonomic Units (OTUs) identified per sample ranged from 68 to 210. Analysis of community structure and membership using AMOVA showed that the populations on HC and CD tongues were significantly different ($P < 0.001$). Lefse analysis identified 20 OTUs that were significantly enriched on the tongues of healthy children including *Haemophilus parainfluenzae, Neisseria flavescens, Fusobacterium periodonticum, Streptococcus sp., Porphyromonas sp., Actinomyces sp.*

Conclusion: Children with Crohn's have an altered microflora that may contribute to their oral health problems**.** These data could potentially be used to diagnose a patients overall gastrointestinal health.

Utility of Measurements of Urinary Soluble CD163 & MCP-1 in the Identification of Subtle Renal Flares in ANCA-Associated Vasculitis.

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Aim: Prior work has shown that urinary soluble CD163 (usCD163) displays excellent biomarker characteristics for detection of active renal vasculitis at diagnosis. This study focused on use of usCD163 in the detection of the more clinically relevant state of mild renal flare, and compared the performance of usCD163 directly to urinary monocyte chemoattractant protein 1 (uMCP-1).

Methods: Samples were obtained from patients (n=88) with active renal AAV (n=34) and active non-renal AAV (n=54) in a serially-sampled longitudinal multi-center cohort. Creatinine-normalized usCD163 and uMCP-1 levels were measured simultaneously by ELISA.

Results: Samples were available from 320 study visits including times of active renal vasculitis (n=34), remission (n=278), and active extra-renal vasculitis (n=54).usCD163 levels were higher in patients with active renal vasculitis compared with patients in remission and those with active extra-renal vasculitis, with median values of 5.2 pg/mmol (interquartile range (IQR) 1.5-19.4pg/mmol), 0.8pg/mmol (0.1-2.5pg/mmol) and 0.6pg/mmol (0.1-1.6 pg/mmol), respectively ($p<0.001$). uMCP-1 levels were also higher in patients with active renal vasculitis compared with patients in remission and those with active extra-renal vasculitis, with median values of 12.6pg/mmol (IQR 5.1-25.1), 2.4pg/mmol (4.1-8.5) and 3.1pg/mmol (1.2-5.5), respectively ($p<0.001$, Figure 1).

Using diagnostic cut-offs for usCD163 and uMCP-1 of 1.2pg/mmol and 10.6pg/mmol, the specificity of identifying renal vasculitis flare were 91% and 80% (sensitivities with these cut-offs were 68% and 64%). The addition of uMCP-1 to usCD163 did not further increase the specificity. usCD163 and uMCP-1 levels were moderately correlated ($r^2 = 0.36$, $p<0.001$), suggesting that additional information may be obtained from sequential modelling that incorporates traditional biomarkers.

Conclusion: In the context of subtle renal vasculitis flare, both usCD163 and uMCP1 levels are tightly associated with active renal disease in AAV.

Toll-Like receptor signaling & complement synergy in the pathogenesis of Age Related Macular Degeneration (AMD).

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Aim: Age-related macular degeneration (AMD) is the primary cause of central vision loss in the developed world. Biological signatures include marked deposition of complement factor 3 (C3) sub-retinal pigment epithelium (RPE). It is widely accepted that inappropriate activation of the alternative complement cascade is involved in AMD progression; however, both the cause and outcome of aberrant C3 deposition remain elusive. In AMD the RPE is coated in oxidative stress-related modification, 2-(w-carboxyethyl-pyrrole (CEP), a recently identified TLR2 ligand. We hypothesized that sterile danger associated molecular patterns, such as CEP, found in the degenerating retina activate Toll-like receptor (TLR) signaling pathways to induce C3 expression and deposition.

Methods: Murine bone marrow derived macrophages, human monocytes and human RPE cells were treated with various TLR ligands over time and assayed by qPCR and Western Blot for C3 expression and secretion. Human RPE cells were treated with CEP and 10% normal human serum and membrane attack complex (MAC) formation was detected by immunohistochemistry.

Results: We find C3 expression is significantly induced in response to TLR2, 3, 4, 7, 8 and -9 ligation in macrophages and monocytes and TLR 2, 3 and 4 in the RPE. Furthermore, TLR2 activation results in an increase of C3 secretion from both RPE cells and monocytes in a Mal/MyD88 dependent manner. Moreover, TLR2 ligation induces MAC deposition and synergises with complement anaphylatoxins to induce secretion of IL-1beta, IL-6 and TNF.

Conclusion: Complement and TLRs are critical components of the innate immune response, despite this little is known about the interaction between these two pathways. We have demonstrated that TLR activation can promote the expression, secretion and activation of C3, the key factor in all three complement cascades providing a possible mechanism for C3 deposition observed in AMD.

ANCA stimulation of monocytes leads to an immediate change in their cellular metabolism.

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ANCA vasculitis is a collection of complex multisystem autoimmune diseases resulting in the destruction of the microvasculature. It is characterised by the presence of autoantibodies directed against myeloperoxidase (MPO) or proteinase-3 (PR3). Experimental data indicates that these antibodies are pathogenic. Both neutrophils and monocytes express the MPO and PR3 antigens, however, the role of monocytes has to date been understudied. Changes in cellular metabolism have recently been shown to be important in inflammatory settings and postulated as targets for treatment in autoimmunity. Here we investigated the effect of anti-MPO and anti-PR3 antibodies (ANCA) on the metabolic profile of monocytes isolated from healthy donor blood. Using flow cytometry we show that anti-MPO, but not anti-PR3 antibodies increase glucose uptake by monocytes - indicating increased glucose metabolism. We have shown by ELISA that the ability of monocytes to produce pro-inflammatory IL-1β in response to anti-MPO can be abrogated by blocking glycolysis using 2-deoxyglucose. Conversely, IL-1β is increased when oxidative phosphorylation is blocked. To investigate the effect of ANCA on monocyte metabolism further we used Seahorse extracellular flux analysis and found that ANCA stimulation results in a significantly

upregulated oxidative respiration along with an increase in the overall respiratory capacity of the cells. Interestingly, these changes occur immediately following exposure to ANCA with a different kinetic pattern seen between each ANCA. Studies in other immune cells have found that pro-inflammatory activation leads to a switch from oxidative phosphorylation to glycolysis (Warburg metabolism). However, we have found that ANCA activation of monocytes leads to increased glycolysis which serves to also increase oxidative phosphorylation. Taken together these data indicate an important role for the upregulation of glucose metabolism and oxidative respiration in the activation of monocytes in response to ANCA. This area of research could lead to new targets for clinical intervention in these diseases.

Characterization of arginine catabolic mobile elements (ACME) in *Staphylococcus epidermidis* isolates from patients with healthy and diseased subgingival sites, periodontal pockets and dental implants.

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Aim: The high prevalence of ACME-positive *S. epidermidis* in healthy subgingival sites, periodontal pockets and subgingivally around oral implants suggests a possible role for ACME in these anaerobic environments. ACME has previously been detected in *S. aureus* and *S. epidermidis* adjacent to staphylococcal chromosomal cassette *mec* (SCC*mec*). The genetic organization of ACME in *S. epidermidis* from oral sites is not yet described.

Method: The ACME-*arc* genes were detected in 21 *S. epidermidis* isolates (12 from periodontal patients and 9 from peri-implantitis patients) by DNA microarray profiling (Alere Technologies, Germany). The 21 isolates were subjected to whole genome sequencing using a MiSeq desktop sequencer (Illumina). Reads were assembled *de-novo* using SPAdes version 3.6 (http://bioinf.spbau.ru/en/spades). ACME-associated or SCC-related contigs were annotated using BioNumerics version 7.6 (Applied Maths, Belgium). Reads were mapped to published full genome sequence AE015929.1 of *S. epidermidis* ATCC 12228 (http://www.ncbi.nlm.nih.gov/pubmed/12950922) with Burrows-Wheeler aligner (http://arxiv.org/abs/1303.3997).

Results: Reads from all isolates aligned to approximately 78% of the ACME type II element sequence from *S. epidermidis* ATCC12228, which harbours the ACME-*arc* operon but lacks the *opp3* operon. In all isolates investigated, no reads aligned to a *ca.* 7-kb region 5' to the ACME-*arc* genes in ATCC12228, indicating a truncated ACME type II element. In addition, one isolate also harboured an SCC*mec* type V element. Eight isolates harboured SCC/SCC*mec* remnants including the *ccrAB2* recombinase gene (exhibiting between 83-98% DNA sequence similarity). These eight isolates were from healthy implants (3/8), a diseased implant (1/8), a nasal swab (1/8), periodontal sites (2/8) and an oral rinse (1/8). In the remaining 12 isolates, the ACME element was integrated directly into *orfX*.

Conclusion: The presence of an ACME type II variant in oral *S. epidermidis* isolates from different clonal backgrounds could be important for successful colonization of both healthy and diseased subgingival sites.

Cigarette smoke impairs alveolar macrophage migration to *Mycobacterium tuberculosis.*

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Introduction: Mycobacterium tuberculosis (Mtb) causes one million deaths globally every year. Importantly almost 80% of the world's one billion smokers live in countries of high tuberculosis incidence. With a relative risk of 1.5 for progression from latent tuberculosis infection (LTBI) to active disease, smoking is probably the single largest risk factor driving this epidemic. Alveolar macrophages recognise and phagocytosis the invading bacteria at the lung interface. We have shown that smokers' alveolar macrophages (AMs) have impaired immune responses to Mtb infection (1)such as susceptibility to infection, disease reactivation, mortality, transmission and persistent infectiousness. The mechanistic basis for this remains poorly understood. Objectives: To compare the functional impairment, seen in human alveolar macrophages (AM.

Aim: We sought to investigate the ability of AMs- non-smokers, smokers- to migrate to Mtb *in vitro*.

Methods: AMs were isolated from bronchial washings obtained from patients undergoing routine bronchoscopy under ethical approval. The migration assay was performed in transwell chambers by adding AM (0.5 x 10^5 cells) to upper chambers and Mtb, Tuberculin PPD or medium alone in lower chambers, incubating at 37°C, 5%CO_2 for 2hrs. Migrated cells were counted by fluorescent microscopy.

Results: Smokers' AMs had large vacuolar inclusions, significantly higher percentage of cells (67.75%) with vacuolar inclusions compared to ex-smokers (8%) and non-smokers (1.15%). AMs migrated to Mtb and PPD, however the number of vacuolar cells in the migrated population of smokers AMs was significantly decreased (21.29%).

Conclusion: Smoker's AMs have an impaired ability to migrate adequately to Mtb suggesting a possible mechanism for increased risk of tuberculosis in smokers.

Evaluating the immune-modofying properties of bioengineered inhalable micropaticles targeting alveolar macrophages.

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Mycobacterium tuberculosis (Mtb) infects and resides within alveolar macrophages (AM). Inhalable therapies, used as an alternative or adjunct to conventional chemotherapy for TB, have the potential to reduce systemic toxicity and treatment duration. Inhalable polylactide-co-glycolide (PLGA) microparticles can be loaded with anti-mycobacterial drugs and bioengineered to target AMs. As well as acting as a vehicle for drug delivery, synthetic microparticles may also activate innate bactericidal macrophage responses, however, this could also lead to excessive inflammation. A comprehensive understanding of the consequences of cell-particle interactions is required to evaluate the biocompatibility of PLGA microparticles in the lung. To this end we assessed the effect of drug-free PLGA microparticles in an *in vitro* model of Mtb infection.

Drug-free PLGA microparticles were assessed for uptake and toxicity in human macrophages. The bactericidal properties of microparticles were determined by colony forming assay and immune activation by measuring NFkappaB activity, autophagy induction and inflammatory cytokine secretion.

Uptake of PLGA microparticles reduced the intracellular bacterial load in macrophages in the absence of anti-mycobacterial drugs. Microparticles increased NFkappaB activity and the induction of autophagy but did not affect cytokine secretion or cell death in either uninfected or Mtb-infected macrophages. Inhibitors of NFkappaB and autophagy reversed the bactericidal effect of microparticles.

In conclusion, autophagy and NFkappaB activity contribute to the bactericidal effect of PLGA microparticles and may enhance the efficacy of microencapsulated anti-mycobacterial drugs in the lung. Further *in vivo* studies are being carried out to evaluate the impact of repeated doses of PLGA microparticles in the lung.

Altered Inflammasome activation in preterm infants.

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Aims: Preterm infants have many multiorgan complications many of which are mediated by persistent inflammation. The NLRP3 inflammasome is a caspase-activating complex that plays a major role in innate immune responses and we aimed to examine its role in preterm inflammation.

Methods: Whole blood was sampled from Preterm infants < 29 weeks gestation, term infants' cord blood with or without LPS exposure. mRNA was extracted and the components of the inflammasome (NLRP3, IL1b and ASC) gene expressions were assessed using TaqMan® Real time PCR.

Results: Average gene expression in preterm infants showed no differences in ASC and NLRP3 genes but a significant down regulation of IL1b gene ($p < 0.001$) compared to term infants. LPS significantly increased IL1b and NLRP3 gene expression ($p=0.01$, 0.02 respectively) but not ASC gene expression in term infants. In preterm infants IL1b, NLRP3 and ASC gene expressions were not significantly increased following LPS incubation.

Conclusions: IL1b gene expression is down regulated in preterm infants while measured components of the inflammasome are otherwise intact. LPS-up regulation of the inflammasome did not occur in preterm infants although this was intact in term infants. This may mediate early susceptibility to infection in preterm infants.

Differential modulation of *Helicobacter pylori* lipopolysaccharide-mediated TLR2 signalling by individual Pellino proteins.

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Background: *Helicobacter pylori* infection causes gastritis, gastric and duodenal ulcers and gastric cancer. Eradication rates for current *H. pylori* therapies have fallen in recent years, in line with the emergence of antibiotic resistant infections. The development of therapeutic alternatives to antibiotics requires a more lucid understanding of host-pathogen interactions. Pellino proteins are emerging as key regulators of the immune response.

Aim: to characterise the role of Pellino proteins in the innate immune response to *H. pylori* lipopolysaccharide.

Materials and Methods: Gain-of-function and loss-of-function approaches were utilised to elucidate the role of individual Pellino proteins in the Toll-like receptor 2-mediated response to *H. pylori* LPS by monitoring NF-κB activation and the induction of pro-inflammatory chemokines. Expression of Pellino family members was investigated in gastric epithelial cells and gastric tissue biopsy material.

Results: Pellino1 and Pellino2 positively regulated Toll-like receptor 2-driven responses to *H. pylori* LPS, whereas Pellino3 exerted a negative modulatory role. Expression of Pellino1 was significantly higher than Pellino3 in gastric epithelial cells and gastric tissue. Furthermore, Pellino1 expression was further augmented in gastric epithelial cells in response to infection with *H. pylori* or stimulation with *H. pylori* LPS.

Conclusions: The combination of low Pellino3 levels together with high and inducible Pellino1 expression may be an important determinant of the degree of inflammation triggered upon Toll-like receptor 2 engagement by *H. pylori* and/or its components, contributing to *H. pylori*-associated pathogenesis by directing the incoming signal towards an NF-kB-mediated pro-inflammatory response.

Neuroscience

The roles of glycosylated neural precursors in central nervous system formation.

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In the nervous system, glycans regulate the activity of membrane receptors and mediate cell-cell or cell-matrix interactions. LewisX (LeX) is a glycan motif associated with glycoproteins and glycolipids that are present on neural stem and progenitor cells. SSEA-1 and FORSE-1 identify different regions of the LeX epitope. We report both the correlative and differential expression patterns of SSEA-1 and FORSE-1 in discrete subpopulations of glycosylated neuroepithelial and radial glial cells in the developing and postnatal CNS. Radial glial cells have already shown potential in facilitating axonal growth and are known to give rise to both neurons and glial cells in the brain. In vitro and in vivo LeX glycosylation patterns of neural precursors during key stages of axonogenesis and neurogenesis indicate roles for LeX glycans in white matter formation and cell fate determination. These glycans motifs represent novel biomarkers in determining radial glial and neuroepithelial lineages during brain and spinal cord formation.

A retrospective study of the efficacy and tolerability of Levetiracetam (Keppra) as a first line monotherapy in childhood epilepsy.

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Introduction: Levetiracetam is an anticonvulsant licensed as monotherapy in those over 16 years of age and as add-on therapy in childhood epilepsy since 2005(1). Off-label use of Levetiracetam has increased considerably over the last decade. There have been 4 retrospective studies of Levetiracetam monotherapy use in children naive to anticonvulsants, involving 155 children and documenting seizure freedom in more than 60%(1).

Aims: We aim to report our experience in a national cohort of children prescribed Levetiracetam monotherapy as a first line agent over a 5 year period, outlining treatment success (seizure freedom or > 50 % reduction in seizure frequency) at one year and treatment failure (< 50% reduction in seizure frequency) or discontinuation of Levetiracetam because of side effects.

Methods: We undertook a retrospective analysis of the medical records of children attending 4 tertiary Paediatric Neurology Clinics between January 2009 and December 2014. Inclusion criteria are children aged 3 months – 16 years, with a diagnosis of epilepsy, prescribed Levetiracetam as a first line monotherapy for their epilepsy.

Results: We report findings on 52 children from one centre (age mean 7.5 years (SD 5.4). …..% achieved seizure freedom or > 50% improvement in seizures at one year. The drug was discontinued in 12% because of lack of efficacy or side effects. 37% of patients reported experiencing at least one adverse effect (low mood and irritability most commonly) and 19% of these resulted in discontinuation of medication.

Conclusion: We have found Levetiracetam in monotherapy to be an effective and safe anti convulsant for children with focal and generalised epilepsy aged 3 months to 16 years. Side effects limit tolerance of the drug in 12%.

Weijenberg, A. Brouwer, O.Callenbach, P. (2015) Levetiracetam Monotherapy in Children with Epilepsy: A Systematic Review. *CNS Drugs.* 29, pp371-382.

Tryptophan Pathway Depletion and Hyperactivity of the HPA Axis in Major Depressive Disorder.

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Hypothesised aetiologies of Major Depressive Disorder (MDD) include Kynurenine Pathway (KP) induction and hyperactivity of the hypothalamic pituitary adrenal axis (HPAA). Metabolism of tryptophan into kynurenine is one proposed mechanism of serotonin depletion in MDD. Kynurenine production is induced via tryptophan 2,3-dioxygenase (TDO), which is activated by HPAA activity including increases in cortisol. In this study, the possible relationship between depressive symptoms, tryptophan depletion, and cortisol activity will be investigated in MDD.

Saliva samples collected from patients with first presentation MDD (n=55) and healthy controls (n=49) were analysed by LCMS to capture the Cortisol Awakening Response (CAR) which is an established measure of HPAA activity. Blood samples were collected and High Performance Liquid Chromatography (HPLC) was performed on plasma to determine concentrations of several Tryptophan Pathway metabolites. Several rating scales were utilised to assess mood, suicidality, and sleep.

An independent t-test revealed that depressed patients had significantly lower levels of both Tryptophan (8322.7 vs. 9889.7; p=0.001) and Kynurenine (667.3 vs. 824.6; p=0.001) than healthy controls. The depressed group also exhibited an altered CAR, with a significantly higher cortisol concentration at wakening (10.95 nMol/L vs 7.33 nMol/L; p=0.041). Additionally, the slope of the regression line through the log transformed CAR data was significantly lower in depressed patients than controls (0.0016 vs. -0.0011, p=0.024). A Pearson's correlation revealed a significant relationship between Tryptophan and HAM-D Score (r=-0.344, p=0.003), Kynurenine and HAM-D score (r=-0.310, p=0.008) wakening cortisol and HAM-D (r=0.245, p=0.038), and between Kynurenine and wakening cortisol (r=-0.319, p=0.029). These results indicate that Kynurenine is depleted in conjunction with Tryptophan, and KP induction is not evident despite HPAA hyperactivity.

DNA methylation changes at the CD3E gene promoter in depression.

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Depression is a debilitating mood disorder which affects at least 350 million people worldwide. Unfortunately, the exact biological mechanisms of the disorder are not fully understood and there are short-comings in current treatments available. Therefore, it is important to investigate novel mechanisms underlying this conditions so that improved diagnostic tools are treatments are made available.

It is likely that depression has multiple aetiologies. While much attention has been focused on the innate immune system, less has been directed towards dysregulations in the adaptive immune system in depression. T cells make up a large proportion of the adaptive immune system population and CD3e is a cell surface glycoprotein found on T cells, which is also a component of the T-cell receptor (TCR).

As part of an ongoing depression research study (REDEEM study), DNA methylation analysis was performed on samples collected from those presenting with depression for the first time, those suffering from chronic/recurrent depression and healthy controls. Analysis revealed a significant increase in CD3E gene promoter methylation across the groups (ordinary one-way ANOVA, P=0.0032), with controls having the lowest level of methylation and the chronic depression group having the highest levels. CD3E gene promoter methylation levels also positively correlated with HAM-D (r=0.3172; p=0.0127), CES-D (r=0.3209; p=0.0064), PSQI (r=0.4082; p=0.0003) and CTQ (r=0.3703; p=0.0007) scores. This indicates that there are alterations at the level of the adaptive immune system in depression that require further investigation.

Poster Title: Toll-like Receptor 3 signalling as a cannabinoid target in multiple sclerosis.

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Multiple Sclerosis (MS) is a chronic inflammatory autoimmune condition of the central nervous system (CNS) characterised by inflammatory episodes (relapses) that damage the CNS myelin. A body of literature indicates that cannabinoids, the components of the cannabis plant, have therapeutic efficacy in neuroinflammatory disorders, in particular MS. Indeed, cannabinoids reduce the symptoms associated with murine MS, experimental autoimmune encephalomyelitis (EAE), and a novel oromucosal spray (SativexÓ) and has been shown to palliate symptoms associated with MS in patients. SativexÒ contains a 1:1 mixture of Tetrahydrocannabinol (THC) and cannabidiol (CBD), and despite its clinical development, little is known about its mechanism(s) of action. Toll-like receptors (TLRs) are the sensors of pathogen associated molecules that trigger tailored innate immune intracellular signalling responses. TLR signalling and innate immune responses have been implicated in MS. Evidence exists which suggests that TLR signalling may cross-talk with cannabinoid signalling through recruitment of IFN regulatory factor 3 (IRF-3), and downstream induction of β-Interferons (IFN-β)[1, 2]. This is significant as IFN-β is a first-line treatment for relapsing-remitting (RR) MS. Data herein demonstrate that CBD and THC regulate IRF-3 activation and translocation into the nucleus in both a human monocyte cell line, and in primary human peripheral blood mononuclear cells (PBMCs). The impact of CBD and THC on IRF-3 signalling in PBMCs isolated from RRMS patients is also presented. Finally, evidence is also presented that MS patients have significantly higher levels of the IL-8 chemokine present in their plasma. These findings identify CBD and THC as novel regulators of IRF-3 activation and highlight TLR3 signalling as a possible mechanism to be exploited in the development of new therapeutics for the treatment of MS.

[1] Downer EJ, Clifford E, Gran B, Nel HJ, Fallon PG, Moynagh PN. (2011) *J Biol Chem*. 25; 286(12): 10316-28.

[2] Fitzpatrick JM, Downer EJ. (2016) *Neuropharmacology*. [epub ahead of print]

Maternal depression during pregnancy: An early life stressor for the fetus?

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Background: Maternal antenatal depression activates the HPA axis and leads to high cortisol levels. The resulting fetal overexposure to cortisol *in utero* may programme the fetal HPA axis, leading to alterations in infant stress response and predisposing the infant to mental illness in adult life.

Aims: Measure differences in cortisol output across three groups – clinically depressed pregnant women (Depressed), euthymic pregnant women with a prior history of depression (History), and never-depressed pregnant women (Control); and to measure differences in infant cortisol stress reactivity within these groups.

Method: Maternal saliva samples were collected during pregnancy to assess cortisol awakening response (CAR). Maternal CAR and infant cortisol response to vaccination stressor were assessed at two months (PB1), six months (PB2), and one year post-birth (PB3).

Results: 66 women and 47 infants to date.

Pregnancy: No significant differences.

PB1: The Depressed group had significantly lower AUCi compared to both History (p=0.04) and Control (p=0.001) groups.

PB2: Infants born to the Depressed group had significantly higher mean cortisol values compared to History (p=0.000) and Control (p=0.001) groups, with significantly higher baseline (p=0.005 and p=0.001 respectively) and post-vaccination cortisol levels (p=0.000 and p=0.001 respectively). Infant baseline cortisol levels correlated positively with maternal waking cortisol level at pregnancy (r=0.527, p=0.005) and PB2 (r=0.506, p=0.007).Mean infant cortisol correlated positively with pregnancy mean morning cortisol levels (r=0.390, p=0.049).

Conclusions: Infants born to women who were depressed during pregnancy had significantly higher resting cortisol levels and higher cortisol responses to a vaccination stressor at six months. The relationship between maternal CAR and infant cortisol measures suggests that the state of arousal in the HPA axis during pregnancy is 'transmitted' to infant HPA axis. These findings suggest that maternal depression may constitute a very early life stressor for the fetus through its effects on the HPA axis. The study remains in progress.

Assessment of Surgical Skills Competence using fMRI: A Feasibility Study.

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Aim: Patient safety is fundamental to modern surgical practice. Assuring surgical competence is becoming more important at a time when Surgeons are being trained in fewer hours. Accurate objective assessment of technical skills ability is difficult. Functional Magnetic Resonance Imaging (fMRI) has a long history in neuroscience and cognitive studies; however, little is published on actual rather than perceived motor skill ability. This study sought to assess the feasibility of measuring blood oxygen level dependent signal changes (BOLD) in specific brain regions via fMRI during motor activity.

Methods: fMRI images were acquired in 9 subjects (3 Experts, 3 Intermediates, 3 Novices) whilst performing a basic surgical skill: hand tying of knots which was videoed and photographed. Quantity and quality of knots were independently assessed by subject experts who were blinded to the categorisation of participants. The effect of subject head motion caused by the task itself was assessed.

Results: Voxel-shifts of less than 1 voxel were recorded in all participants. It proved feasible to perform actual motor actions in the scanner whilst recording meaningful data. Experts and Intermediates performed consistently with 100% square knots. Novices had 2 slip knots. Regarding quantity novices ranged from 14 -26 knots, Intermediates 54- 58 and Experts 38-47. A Kruskal Wallace Rank Sum Test revealed the difference between the 3 groups was statistically significant with regard to quantity of square knots tied, $p = 0.147$. There was increased BOLD activity observed in Novices compared to Experts when tieing knots.Specific Regions of Interest identified whilst performing the surgical task concur with previous studies findings during motor activity.

Conclusion: fMRI is a feasible method of assessing actual as well as perceived motor skill. Head motion during performance of a motor skill does not preclude the attainment of meaningful data. Larger numbers are needed to investigate further.

Impairment of Cortico-cortical and Cortico-muscular Communication in Amyotrophic Lateral Sclerosis.

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Aim: To mark the potential disruption of neural communication in motor and non-motor networks due to neurodegeneration in Amyotrophic Lateral Sclerosis (ALS), using non-invasive electrophysiological recordings.

Method: High-density 128-channel electroencephalographic (EEG) and surface electromyographic (sEMG) recordings from ALS patients and healthy controls in three experimental paradigms: first, in resting state, second, during an auditory oddball paradigm, and third during isometric precision grip tasks.

Results: The Auditory Evoked Potentials (AEPs) were suppressed and the Mismatch Negativity (MMN) response was delayed in ALS ($n_{ALS} = 90$, $n_{Control} = 19$), which correlated with neuropsychological performance in colour-word interference (CWI) Stroop test in a subset of patients ($n = 32$). The ALS group ($n_{ALS} = 101$, $n_{Control} = 34$) showed decreased spectral power and reduced cortico-cortical synchrony in motor-region scalp electrodes, which was correlated with disease-specific degeneration in structural MRI. The ALS group also showed increased functional connectivity in non-motor scalp regions, which was correlated with brain-wide degeneration in structural MRI in a subset of patients ($n = 51$). None of the measures were different between the subgroups of the ALS patients (spinal onset, bulbar onset, cognitive onset/ALS-FTD, and C9Orf72 Gene careers).

Conclusion: The changes in AEP and MMN imply that the cognitive networks responsible for discrimination and probably part of the auditory sensory network have been affected in ALS. The cortico-cortical connectivity patterns suggest the disruption of motor, as well as non-motor brain networks. The ongoing study of cortico-muscular communication is expected to further elucidate the altered communication in motor subsystems affected in ALS. The above-mentioned electrophysiological signatures help to understand the underlying disease mechanisms, provide new patient stratification perspectives, and facilitate the development of diagnostic and prognostic biomarkers.

Offset Analgesia: Investigating an Individualised Protocol Using Cerebellar Transcranial Direct Current Stimulation (c-tDCS)

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Offset Analgesia (OA) is an experimentally induced endogenous pain inhibition characterised by a disproportionate analgesic response to a small decrease in noxious thermal stimulation. Assessment of OA is a potential diagnostic tool for pain syndromes. A clear definition of OA characteristics and mechanisms is required in order to assess its clinical potential. Clinical and neuroimaging data suggest a role for the cerebellum in OA. Cerebellar transcranial direct current stimulation (c-tDCS) is a novel technique enabling targeted investigation of cerebellar neurophysiology.

The present study characterised the magnitude, time course and reproducibility of OA using an individualised OA protocol based on heat pain thresholds (HPTs) in 14 healthy participants. Underlying mechanisms of OA were investigated using conventional and high definition (HD) c-tDCS in a single-blind, sham-controlled, repeated measures experiment.

Intraclass correlations coefficients (ICC) were high to very high for intra-session OA trials, however significant differences in OA end-points were reported between sessions. Active conventional c-tDCS significantly increased ΔVAS ($p<.05$) whereas sham conventional c-tDCS increased ΔVAScorrected ($p<.05$) values. There was no significant effect on HD-tDCS on any OA end-point. To investigate differences in the effect of conventional and HD c-tDCS on OA, computational modelling was used to compare the neuroanatomical locations of the electric current induced by the two montages. Conventional c-tDCS induced maximal field intensities in the brainstem whereas the effects of HD c-tDCS were limited to the posterior cerebellar hemisphere.

Enhancement of the OA response between days, combined with comparable effects of active and sham c-tDCS on OA magnitude, indicate susceptibility of OA to expectational influence. This expectation effect may be enhanced by active conventional c-tDCS. Our modelling analysis suggests the effect of conventional c-tDCS of OA may partly be due to stimulation of brain regions not reached by the HD-tDCS montage, including the cerebellar vermis or brainstem analgesic centres.

Prenatal depression: The relationship between gestational cortisol levels and infant neurobehavioural development at 2 months

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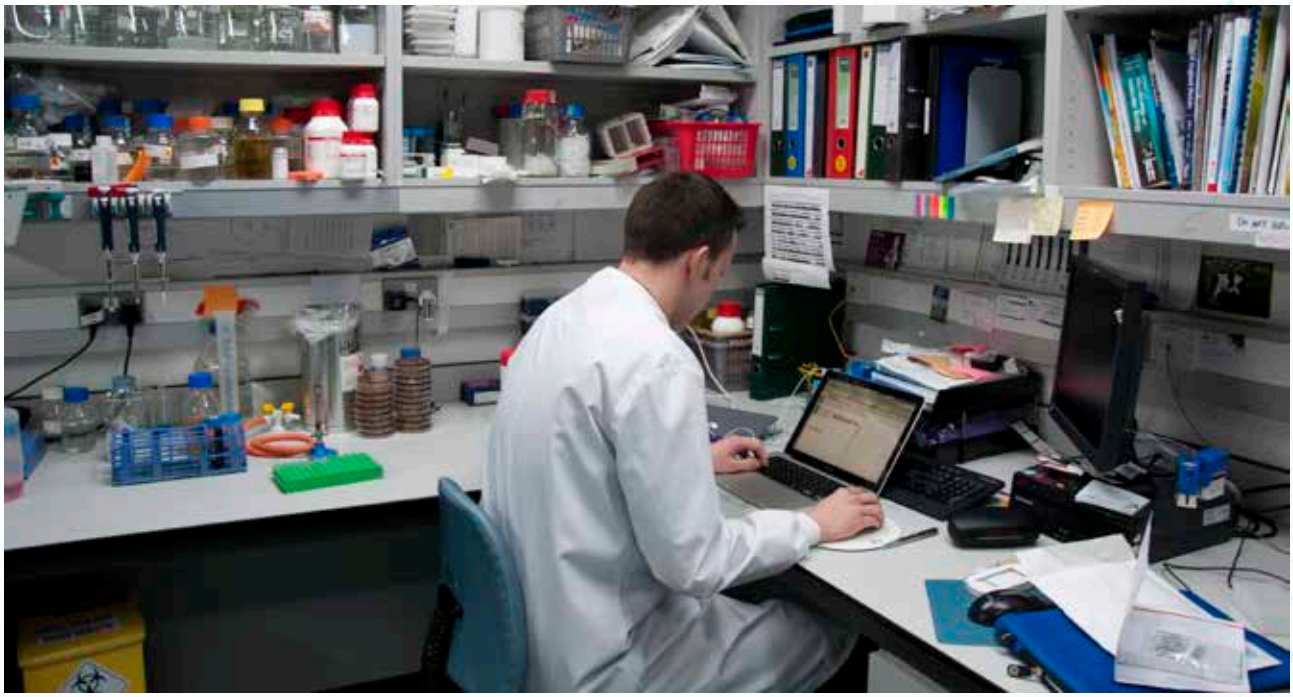
Background: Hypothalamic pituitary adrenal (HPA) axis hyperactivity has been demonstrated in pregnant women with Major Depressive Disorder. Exposure to excess glucocorticoids *in utero* may have a 'programming' effect on the fetus whereby the structure and function of the fetal brain adapts to the intrauterine environment. This study aims to investigate the impact of prenatal depression on infant neurobehavioural development using the NBAS and the relationship between maternal diurnal cortisol during pregnancy, infant cortisol stress reactivity and performance on the NBAS at 2 months.

Methods: Participants were recruited between 20-30 weeks gestation and maternal depression was assessed using the *MINI-SCID* and the *Hamilton Rating Scale for Depression*. Participants were allocated into either depressed (*n=6),* depressed history *(n*=11) or control *(n=9)* groups. Infant stress reactivity was assessed by measuring salivary cortisol levels at baseline and thirty minutes after a scheduled infant inoculation. Maternal diurnal salivary cortisol was measured at 5 time-points across the day preceding the infant inoculation. Infant neurodevelopment was assessed using the NBAS.

Results: There were no significant differences between the 3 groups on the measures of the NBAS. However, across the entire sample there were significant negative correlations between maternal mean evening cortisol levels during pregnancy and the animate visual, (*r*=-.497, *p*=.036), inanimate visual and auditory (*r*=-.522, *p*=.032) and overall alertness (*r*=-.439, *p*=.046) items of the orienting scale of the NBAS implicating a relationship between exposure to higher levels of cortisol *in utero* and performance on this measure. There was also a significant negative correlation between higher infant stress response and infant consolability (*r*=-.926, *p*=.008) and a significant correlation between infant baseline cortisol and irritability (*r*=-.522, *p*=.038).

Conclusions: Within this data set, there is a relationship between higher maternal evening cortisol during pregnancy with poorer scores on orienting items of the NBAS and increased infant irritability.



Population Health

Polish migrants accessing both Irish and Polish health care systems.

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The Polish community is the largest ethnic group living in Ireland. The qualitative phase of this mixed methods study identified that accessing a culturally familiar health service was one of the reasons for visiting private ethnic health care providers and or travelling to Poland for healthcare.

Aim: To identify what health services Polish migrants, living in Ireland reported accessing in the previous 12 months and to identify the variables predicting migrants accessing both Irish and Polish health services?

Methods: This quantitative phase used two modes of data collection, web format using surveymonkey and paper format. Paper copies of the questionnaire were distributed to a convenience sample of Polish migrants after Polish Masses. The surveymonkey link to the Polish questionnaire was posted on Facebook and Polish websites. Data was collected in 2012. Multinomial logistic regression was used to predict use of health services in Poland and in Ireland.

Results: The majority of the participants were female (67.7% (n= 611/903) and 21.9% (n= 134/611) of the women reported that they were pregnant in the previous 12 months. Polish migrants reported accessing Irish GP services less frequently and Irish ED more frequently than the Irish population. The two main predictor variables for accessing both Irish and Polish health services were having a chronic illness and pregnancy in the previous 12 months.

Conclusion: There is a need to foster migrants' trust in the GP services of the host country. Health care staff need to be cognisant of the high percentage of migrants visiting private ethnic healthcare providers resident in the host country and visiting health care professionals in their countries of origin. Implications for practice include the lack of continuity of care and the risk of potential drug interactions.

Combining data from a nutritional database to a national cohort survey using a data mapping protocol.

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Population based public health surveys assess prevalence and determinants of disease outcomes. The Growing Up in Ireland (GUI) infant cohort was investigated to determine associations between dietary intake, dental problems and anthropometric measurements. The Food Frequency Questionnaire (FFQ) from the GUI survey provided a limited list of foods and their consumption frequency. This study explored the augmentation of this limited dietary intake by unidirectional mapping from the more detailed 4-day food diary in the National Preschool Nutrition Survey (NPNS).

The objectives were to: 1) investigate matching of the sample databases, 2) estimate the dietary food intake not covered by the FFQ in GUI and 3) assess the lack of capture of high sugar foods by using a short FFQ.

Data derived from the second wave of the GUI infant cohort (n=9,793) and NPNS (n=126) of 3-year-old children, both sampled in 2010/2011. All of the GUI FFQ categories were mapped in one direction with food groups from NPNS. The population samples were assessed for difference using equivalence tests and the two proportion z- test, $p<0.05$.

Both samples were nationally representative although NPNS had a higher proportion from the 'Professional' social class. The frequency of consumption of all mapped food groups varied considerably. Approximately 43% (SD=13) of the food consumption occasions and approximately 33% (SD=15) of the weight of food consumed in the NPNS survey were not covered by the GUI FFO categories. High sugar foods such as fruit juices, smoothies, RTEBC, puddings and added sugar were not covered by the GUI FFQ and constituted approximately 6% of overall consumptions. This research demonstrates that if a FFQ provides insufficient dietary information for health outcome analysis, it is possible to augment dietary intake values by data-mapping. This highlights the necessity to merge available data to ensure accuracy of data for planning healthcare strategies.

Outcomes Associated with Non-adherence to Anti-hypertensives and Statins.

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Background: Non-adherence to medicines is associated with poorer patient outcomes. As hypertension and dyslipidaemia are asymptomatic, adherence can be an issue due to the lack of perceived treatment benefit.

Aims: To determine the effect of non-adherence in relation to: (i) blood pressure (BP) in anti-hypertensive use and (ii) LDL and total cholesterol levels in statin use.

Methods: A retrospective cohort study with health assessments linked to pharmacy claims data was conducted. The setting was community dwelling participants aged ≥ 50 years from 2009-2011. The exposures were the proportion of days covered (PDC) for each of five classes of antihypertensive medication and all statins during 12 months prior to the health assessment. Adherence was assumed at PDC≥ 80%. The main outcome measures were: (i) Mean systolic and diastolic BP measurement and (ii) total cholesterol (TC) and LDL cholesterol levels. Statistical analysis included multivariable linear and logistic regression, adjusting for covariates including age, gender, smoking status, chronic disease, educational level and BMI. Targets for reaching TC≤ 5mmol/L and LDL≤ 3.5mmol/L were used.

Results: There were n=998 receiving anti-hypertensive medications, with n=567 (56.8%) adherent. The adjusted β coefficient for systolic BP in adherent vs non-adherent was non-significant, but was significant for diastolic BP. There were n=771 receiving statins and having blood lipid data, with 482 (62.5%) adherent. Adherent subjects were more likely to reach target TC (OR=1.79, 95%CI 1.27,2.52) and LDL (OR=1.65, 95%CI 1.12,2.41).

Conclusions: Adherence to anti-hypertensive medication reduced diastolic but not systolic BP and adherence to statins improved targets for TC and LDL cholesterol. The results support improving adherence amongst patients taking anti-hypertensive and lipid lowering therapy for optimal patient outcomes.

Irish National Register for Children with Down Syndrome.

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Aims: We aimed to accurately define the incidence, morbidity and mortality of Down syndrome (DS) in Ireland and to provide parents with evidence based health information e.g. the frequency of associated malformations or illnesses to enhance counseling regarding prevalence in DS.

Methods: A parent information leaflet, consent and data collection form were approved by ethics committees and all 19 maternity hospitals in Ireland were included. Parents of babies born after January 1st 2015 were invited to take part in the study and the data collection form was completed by the health care team and forwarded to the researcher. In addition the maternity centres were requested to record the number of persons who declined to participate. Data will be compared with EUROCAT data of reported cases of DS annually to measure case ascertainment Parents were consented to be contacted by the researcher on an annual basis.

Results: Forty-two children were enrolled on the register over 18months with the following issues: prenatal diagnosis (n=9); cardiovascular (n=26); Haematological (n=1); respiratory (n=7) and 2 babies died. EUROCAT data from 2014 showed an incidence of 1 in 444 live births which gives an estimated 168 babies born with DS per annum and indicates current underreporting to the National Register.

Conclusion: The Down Syndrome National Register will advance our knowledge, enhance and inform the care we provide to those with Down syndrome. It will enable healthcare practitioner's to provide parents and service providers with evidence based estimates regarding prevalence, patient demographics and also health and wellbeing.

National Prevalence of Type 1 Diabetes in Children Aged Under 5 Years – Data to Improve Health Provision to this Vulnerable Population and the National Diabetes Register.

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Aim: Epidemiological monitoring to accurately define disease frequency is key to inform effective and efficient healthcare planning, resource deployment, utilization and support audit. This is vital for management of Type 1 diabetes (T1D) and especially in Ireland, where care may be delivered at multiple sites, with limited integration of data management systems and in the absence of a unique patient identifier. Reliable prevalence data, critical for effective diabetes management, is lacking in Ireland. The aim of this study is to provide a robust baseline measure of national prevalence of T1D in Irish children aged under 5 years and provide key demographic data to inform the New National Model of Care for this vulnerable group.

Method: Prevalent cases of T1D in children aged under 5 years were identified from the prospective Irish Childhood Diabetes National Register (ICDNR*) in 2012 and 2013 and survey of all national centres caring for children with T1D. Cases were verified and capture-recapture methodology applied to estimate ascertainment.

Results: There were 114 cases (59 male) and 123 cases (64 male) with T1D aged under 5 years at

31st December identified in 2012 and 2013 respectively. Three additional cases were identified who were not registered with the ICDNR. One case of non-Type 1 diabetes was excluded. No deaths were recorded. The point prevalence for T1D in those aged under 5 years was 0.31/1,000 and 0.34/1,000 in 2012 and 2013 respectively.

Conclusions: The prevalence of T1D for children under 5 years was 0.31/1,000 and 0.34/1,000 in 2012 and 2013 respectively. The ability to define and target this vulnerable groups of patients with T1D who are especially vulnerable to the damaging effects of hypoglycaemia etc and present significant management challenges is important. Additional demographic data to support care provision to this vulnerable group is provided. Monitoring of prevalence will continue.

Ambulatory Blood Pressure Monitoring as a Community Pharmacy Service.

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Background: Hypertension is an important risk factor for stroke, and the current National Cardiovascular Health Policy has identified the need for more effective detection and management within the primary care setting[1].

Aims: This cross-sectional observational study of patients availing of an ABPM service in community pharmacies was designed to:

- Explore the profile of patients availing of the service, and
- Examine the prevalence of hypertension among the sample.

Methods: All patients > 18 years undergoing 24 hour blood pressuring monitoring service in Boots Ireland community pharmacies were invited to participate in the study. The service consultation gathered information on demographics, past medical history and cardiovascular risk factors. The 24 hour monitoring comprised blood pressure measurements at 30 minute intervals using a Microlife® WatchBP® O3 Afib device. The ABPM reports for consenting patients were screened for validity, and where a patient had availed of the ABPM service repeatedly, only the first valid report was included. Data were anonymized and analysed using SPSS v. 21.

Results: 566 valid records from consenting patients were available for analysis. 46.8% of the participants were male and 53.2% were female. The mean age was 57.29 years (SD 13.33) and the majority (91.8%) had white ethnicity. 58.4% had private health insurance, 17.4% had medical cards, 5.1% had doctor's visit cards, and 4.4% were participants in the Long-term Illness scheme, while 22.3% were covered by none of the above.

64.3% of participants were diagnosed as hypertensive based on ABPM, nocturnal hypertension being more prevalent than daytime hypertension, and males showing higher prevalence than females. The study demonstrated the value of this service as an aid to diagnosis, particularly in patients with 'white coat' phenomena.

1. Department of Health and Children. Changing cardiovascular health: National cardiovascular health policy, 2010-2019. Dublin, 2010.

A scoping review of oral health interventions for children and adolescents with disabilities.

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Aim: The aim of this project was to provide an overview of the types of oral health interventions that have been implemented for children and adolescents with disabilities (CAWD), prior to a Cochrane supported Systematic Review.

Methods: A scoping review is a practical methodological approach to finding relevant literature in a previously unsearched subject area. The purpose of this search was to quantify the elements of the interventions targeting CAWD, and to use this information to develop and refine a systematic review question that would be feasible and have sufficient literature to review.

A search strategy on five databases was developed and carried out. A screening protocol for the articles was piloted and implemented and inter rater (n =2) agreement measured. The bibliographic software Endnote was used to record and manage the articles.

Results: A total of 3,909 articles were identified in the search of the databases. Duplicate articles, non-English language articles and those not meeting the inclusion criteria following the screening by title and abstract, were excluded. Following full text reading of the remaining articles, 112 studies were included in the scoping review.

The number of interventions implemented and evaluated has increase dramatically in the last 15 years (54%).

The usual disability targeted was intellectual. Carers and parents were most commonly involved with the oral health interventions, both as deliverers or supervisors of the care or as the target of the intervention. The most usual types of interventions were therapeutic, which were very diverse, and skills-based interventions, which predominantly focused on tooth brushing skills.

Conclusion: The use of a scoping review to identify the range and type of oral health interventions, targeted at children and adolescents with disabilities, has proved efficient and effective and has helped to focus the objectives of a Systematic Review of the topic.

The role of sun-related behaviour on vitamin D deficiency and analysis of ambient UVB dose in Ireland.

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Aim: Solar UVB radiation is the most important natural source of vitamin D. The aim of this study was to describe the dose of ambient UVB limited to wavelengths that can induce vitamin D synthesis and examine the impact on 25-hydroxyvitamin D (25(OH)D) concentration in older, free-living adults on the island of Ireland.

Methods: Study participants (N=5,138) were recruited to the Trinity, University of Ulster and Department of Agriculture ageing cohort (TUDA) Study (aged over 60 y). This all-Ireland cohort included three groups of patients: those with cognitive impairment, high blood pressure or osteoporosis. All participants filled in a detailed questionnaire that gathered information on

multiple sociodemographic and lifestyle characteristics. The daily dose of vitamin-D-making UVB was retrieved from the Tropospheric Emission Monitoring Internet Service (TEMIS) database. An individual cumulative and weighted UVB (cw-UVB) dose prior to blood draw was calculated for each participant, based on their place of residence and date of sampling. Association between UVB dose and serum 25(OH)D, and modification of this association by sun-related behaviours were investigated.

Results: UVB dose in Ireland varies dramatically, despite the small latitude differential (51°-55°). UVB dose and sun-related behaviours were strongly associated with circulating 25(OH)D concentration ($P<0.001$ for both). When stratified by UVB dose, we consistently observed higher 25(OH)D among those who enjoy sunshine compared to those who avoid sunshine; this was true for all levels of UVB. Very large differences in 25(OH)D of over 20 nmol/L were observed in some instances, particularly with higher ambient UVB radiation among individuals aged 60-75 years who are not taking supplements.

Conclusion: These results suggest that the variation in ambient vitamin-D-making UVB dose in Ireland is greater than previously thought. Sun-related behaviour was strongly associated with vitamin D status at all levels of UVB exposure, even in this older and northerly population.

Other

The MISA biomedical engineering lab: A hospital based technology research and innovation unit.

Boyle, Gerard; Finucane, Ciaran; Foran, Tim; Norkus, Mindaugas; Soraghan, Chris

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This poster describes the role, capabilities and activities of the biomedical engineering laboratory hosted by Mercer's Institute for Successful Ageing (MISA) and the Department of Medical Physics and Bioengineering (MPBE) at St. James's Hospital.

The MISA lab provides a space for engineering concepts and skills to be applied to clinical and research problems in medicine. The defining attributes of the lab are its integration with and physical proximity to the working life of a large acute hospital. This disposition allows engineering and medicine to work together close to the point of care. In this way, medical and engineering effort can be combined and focused on identifying and solving problems that are of real concern to patients and clinicians. The MISA biomedical engineering lab is unique in an Irish hospital context.

The lab hosts hospital personnel and visiting postdoctoral, postgraduate and undergraduate students working on clinical projects with a technological or engineering science component. In particular, the lab draws on hospital clinical engineering and medical physics expertise to support individual projects. The lab is equipped to support electronic prototyping, software development, data analytics, optics development, system modelling and 3D printing.

The lab activities include:

Medical Device prototyping: The lab supports the full lifecycle of medical device design, from prototyping concepts, to design for commercialisation.

Technology Assessment: Assessment of technology on the market against clinical and user requirements, e.g. assessment of falls detectors and brain perfusion monitoring devices.

Software Development: Mobile app development and programming.

Physiological modelling: Application of engineering modelling methods to help understand normal and pathological physiology, e.g. neurocardiovascular control, gait and falls.

Clinical research support: Support of scientific and technical aspects of clinical research, such as data analytics, signal processing and device specification and deployment.

Education: Teaching engineering concepts and skills to biomedical engineering and medical device design students.

Restoration of pharyngeal dilator muscle force in dystrophin-deficient (*mdx)* mice following co-treatment with neutralizing IL-6R antibody and Urocortin-2.

Burns David P, Rowland Jane, Canavan Leonie, Murphy Kevin, O'Malley Dervla, O'Halloran Ken D., Edge Deirdre

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Duchenne Muscular Dystrophy (DMD) is a fatal genetic disorder wherein patients lack the major structural protein dystrophin. DMD is characterised by severe muscle weakness. The *mdx* mouse, a model of DMD has impaired respiratory muscle function. Inflammation is a primary pathological feature of DMD and known to play an integral part in DMD muscle pathology. We hypothesise that co-treatment of anti-IL-6 receptor antibody & CRF receptor-2 agonist will alleviate respiratory muscle dysfunction in *mdx* mice.

Six week old *mdx* (C57BL/10ScSn-Dmd^{mdx}/J; n=24) and wild-type (WT; C57BL/10ScSn; n=23) mice received either saline (0.9% w/v) or a co-treatment of neutralizing IL-6 receptor antibodies (xIL-6R; 0.2 mg/kg) and CRF receptor-2 agonist (Urocortin-2; 30µg/kg). Following treatment, sternohyoid muscle (pharyngeal dilator) contractile function was examined *ex vivo*. Muscle fibre nucleation and inflammatory cell infiltration were histologically examined. Muscle fibre type analysis was determined by myosin heavy chain immunofluorescence.

Peak specific force (Fmax) was significantly reduced in *mdx* compared with WT. Co-treatment restored Fmax for *mdx* to values equivalent to WT. Co-treatment also restored mechanical power production over the load continuum. The percentage of centrally-nucleated muscle fibres was significantly increased in *mdx* compared with WT, and was significantly reduced in *mdx* mice only, following co-treatment. The areal density of inflammatory cell infiltrates was significantly increased in *mdx* mice also, and unaffected by co-treatment. Fibre type transitions were apparent in the *mdx* sternohyoid muscle and were ameliorated by co-treatment.

Co-treatment with xIL-6R and Urocortin-2 had a positive inotropic effect, completely restoring mechanical force and power. Co-treatment reversed fibre transitions in *mdx,* as well as decreasing the proportion central nucleated muscle fibres. Preservation of MHCIIb fibres may underpin, at least in part, recovery of force production in the *mdx* co-treated mice. These data may have implications for the development of pharmacotherapies for DMD with relevance to respiratory muscle performance.

Supported by Muscular Dystrophy Ireland and the Departments of Physiology, Trinity College Dublin and University College Cork. The neutralizing IL-6R antibodies were kindly gifted by Chugai Pharmaceuticals, Japan.

Gender and Neonatal Inflammatory Responses: The role of the oestrogen receptor.

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Background: Females have a well-recognised survival advantage compared to males throughout the entire lifecycle. The superior immune ability of females is noted from birth, with male infants more prone to septicaemia, meningitis and pulmonary disease. Neonatal sepsis is one of the major health problems throughout the world and male gender is associated with an increased risk in the preterm infant. It has long been known that the immune responses of females are more robust than males and these gender differences are largely attributed to oestrogen levels.

Objective: Our aim was to investigate the molecular mechanism of the male survival disadvantage and whether this is mediated by altered sex hormone and receptor levels.

Methods: Patients were recruited from The Coombe Women and Infants University Hospital, Dublin. Ethical consent has been granted and altogether 90 patients will be recruited with results stratified to gender. Umbilical cord blood samples were taken at term following normal pregnancy as our controls (n=3). Samples were treated with LPS (1ng/ml), +/- 17β-estradiol (10nM) and +/- ICI 182,780 (50ng/ml) and compared with vehicle controls. Whole blood flow cytometry was performed to assess neutrophil surface markers CD11B and TLR4 and also the classical oestrogen receptors.

Results: To date this pilot study of one female and two male cord whole blood samples have been analysed using flow cytometry. The results show a trend towards an increased expression of ERα in term males compared to females whereas females have a higher ERβ expression. Treatment with LPS decreased this ERα expression in male term neonates which was ameliorated with the addition of estradiol and the oestrogen receptor antagonist ICI 182, 780.

Conclusions: The expression of the nuclear receptors ERα and ERβ differ between the sexes. The TLR4 agonist LPS decreases the expression of ERα in term males, which is ameliorated with estradiol. This could possibly lead to an explanation of sexual dimorphism in inflammatory related disease in the neonate. Further investigations in preterm neonates are warranted with an increase in sample size across all study cohorts.

Elevated Granulocyte-macrophage colony stimulating factor is associated with low Apgar scores in Preterm infants.

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Introduction: Persistent inflammation and activation of innate immune cells has been associated with neonatal brain injury. Activated neutrophils and monocytes may be a target for treatment of inflammatory disease in preterm infants and cytokines may be biomarkers for neonatal outcomes.

Aim: Our aim was to examine pro- and anti-inflammatory cytokine production over the first week of life in preterm infants.

Methods: In a tertiary referral university neonatal intensive care unit, serial blood samples were analysed from preterm infants (<32 weeks gestation) on day 0, 1, 3 and 7 of life in this pilot study. Serum levels of Vascular Endothelial Growth Factor (VEGF), Granulocyte-Colony Stimulating Factor (G-CSF) and Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) were measured with Cord pH, Cord base excess, pH and Apgar score. Spearman's correlation was used to compare these parameters.

Results: Preterm infants (n=51) enrolled had a gestation of 27.9+/-1.6 weeks and a birthweight of 1.1+/-0.3kg. Serum GM-CSF levels on day 1 statistically correlated with VEGF (p=0.001) and negatively correlated with Apgar score at 5min (p=0.023). There were no significant correlations across the remaining parameters measured.

Conclusions: Elevated GM-CSF correlated with low Apgar scores at 5 minutes may indicate a potent stimulation of innate immunity in preterm infants who require resuscitation.

Design of a protocol for a stepped wedge cluster randomised controlled trial of a complex intervention.

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Aim: Collaborative Pharmaceutical Care at Tallaght Hospital (PACT), a complex intervention, was developed and piloted. The intervention combined medication reconciliation and review in an environment which aligned pharmacists to medical teams. Evidence supported the organisation-wide implementation, involving significant service reconfiguration. The aim of this study was to design a protocol for implementation evaluation.

Method: A comprehensive literature review and sample size calculations were undertaken to support study protocol development.

Results: ***Study design*** was a stepped wedge (SW) cluster randomised controlled trial (CRCT). A cluster was a group of one or more medical or surgical specialities to which a clinical pharmacist

was aligned. Cluster design protects against potential contamination from randomisation at the individual patient level. A SW design facilitates staggered introduction of the intervention and suits organisational change projects where it is planned to sustain the intervention after study completion. Each cluster was randomised to a start date for transition from control to intervention phase. ***Participants*** were adult inpatients using five or more medications before admission, receiving acute medical/surgical care and admitted & discharged alive. The ***intervention*** was PACT with pharmacists aligned to a specialty cluster. The ***comparator*** was standard ward-based clinical pharmacy service. Primary ***outcome*** measure was proportion of patients with one or more significant discharge medication error, defined as an error with a mean potential for harm score $^{3}5$, as measured by at least four assessors using a validated, reliable visual analogue scale (0 no harm – 10 death). Sample size, allowing for cluster effects, was calculated as 215 patients per group to ensure 80% power at a significance level of 0.05, inflated by 20% to allow for attrition.

Conclusion: Evaluation of reconfiguration of the clinical pharmacy service and implementation of the PACT model employed a SW CRCT.

Patients' perspective of self-testing of INR (international normalized ratio) while on warfarin therapy.

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Self-testing of INR has been shown to be reliable and is fast becoming common practice. As we introduce new technologies to this process more research is needed to elicit patients' perceptions of the self-testing process.

Aim: To elicit the perceptions of patients, who self-test their INR and communicate their results via a text or phone messaging system, to determine their satisfaction with the education and support that they receive and to establish their confidence to move to a self-management programme.

Methods: This three site study utilized a cross sectional prospective descriptive survey. Patients who were prescribed Warfarin and using INR self-testing were invited to take part in the study. The anonymous survey examined patient profile, patients' usage, issues, perceptions, confidence and satisfaction with using the self-testing system and their preparedness for self-management of warfarin dosage.

Results: The response rate was 57% (178). The majority of patients were prescribed warfarin for six years or more (77%) and were self-testing for eighteen months or more (80%). Patients confidence in self-testing was high (90%), although 29% did do more tests than required. When asked if they felt confident to adjust their own warfarin levels 73% agreed. Chi squared analysis revealed that none of the patient profile factors examined (age, gender, diagnosis, length of time on warfarin, length of time doing own INR testing, INR levels or having problems with their equipment) were associated with this confidence. The patients cited that the greatest advantages of the service were reduced burden, more autonomy, convenience and ease of use. The main disadvantages cited were cost and communication issues.

Conclusion: Patients were satisfied with self-testing. The majority were ready to move to self-management. Introduction of new technologies need to have adequate support in order to optimize patient satisfaction.

Analysis of uterine Natural Killer cell (uNK) phenotype and pregnancy outcome following Assisted Reproductive Technology (ART) in women with endometriosis.

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Aim: Analysis of uterine Natural Killer cell (uNK) phenotype and pregnancy outcome in women with endometriosis who have undergone Assisted Reproductive Technology (ART).

Method: The phenotype of progenitor and mature uNK were investigated by flow cytometry. Specifically, expression of CD34, CD10, Integrin B7, CD161, CD117, NKp46, NKp44, CD94, CD159A, NKG2C, CD215, CD132, CD221, CD122, NKG2D, CD127, and CD16 was measured by flow cytometry. Serum levels of Stem Cell Factor (SCF) were also measured in these patients. Results were then analysed in order to compare data from those who successfully became pregnant following ART (n=21) and those who did not (n=10).

Results: The percentage of $CD34^+$ NK cell progenitors was increased in those who became pregnant following ART (5% compared to 1% in those who did not become pregnant (p=0.0157)). A similar trend in CD117 expression was also identified although this was not statistically significant (24% compared to 15% in those who did not become pregnant). Similarly, CD94 expression was statistically unchanged in those who became pregnant following ART (81% compared to 68% in those who did not become pregnant).

The proportion of $CD45^+CD56^+$ uNK was marginally decreased in those who become pregnant following ART although this was not statistically significant (23% compared to 38% in those who did not become pregnant). Analysis of the number of peripheral blood NK cells in these patients showed a reverse in this trend although this was not statistically significant (16% compared to 12% in those who did not become pregnant).

Conclusion: Although numbers are small, this study provides some evidence that altered uNK cell differentiation and phenotype may be associated with pregnancy outcome following ART.

Radiation Dose to Eyes for Staff in an Irish Hospital Setting: A 5-Year Review.

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Aim: Interventional Radiology (IR), Interventional Cardiology (IC) and PET can result in occupational radiation doses high enough to warrant concern. There has been a significant focus recently on eye doses, due to the 2011 ICRP statement recommending a reduction in the annual eye dose limit. The revised limit has been adopted into the new EU BSS Directive and will be legally binding in Ireland from early 2018. The goal of our study was to obtain reliable estimates of eye doses using data from typical clinical departments. We have used our findings over five years as evidence in establishing routine eye-dose monitoring programmes.

Method: A dedicated eye dosimeter was used to measure eye dose, $H_p(3)$, in five clinical areas (see Table 1). Eye doses to 40 staff from more than 2,000 Radiology procedures were monitored.

Results: An extract of results is shown in Table 1. Further analysis was carried out to determine eye dose per procedure and per unit KAP.

Clinical Speciality	Annual equivalent dose to the left eye, $H_p(3)$ (mSv)
Gastroenterology	Mean: 11.7 (overcouch X-ray) Mean: 1.3 (undercouch X-ray)
IR	Mean: 24.7 Range: 7.1 – 44.9
IC	Mean: 12.5 Range: 4.2 – 33.3
PET	Mean: 0.87 Range: 0.04 – 2.01
EndoVascular	Mean: 4.54 Range: 1.73 – 7.63

Table 1: Annual equivalent dose to the lens of the left eye for five specialities

Conclusion: We have estimated eye doses to radiation workers in terms of $H_p(3)$ for the first time in an Irish hospital setting. The eye doses quoted for the interventional staff are based on measurements taken over lead glasses, where worn. Recommendations for positioning of eye dosimeters and establishing eye dose monitoring programmes will be presented. **Conclusion:** Occupational eye doses from IR/IC procedures have the potential to exceed the ICRP/BSS dose limit of 20mSv per annum, unless adequate eye protection is worn.

@NESTSJH: A Community of Practice for Clinical Educators in a Large Teaching Hospital.

O Shea, Noreen, Foley, Emer, Hughes, Gerry, Ni Rathaille, Neans, Mullen, Carol, O Shaughnessy, Ide, Part, Siobhan, Soraghan, Christopher, Waugh, Alice

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Aim: To support & prepare clinicians for their educator role. To help them manage their workload, reduce their stress. To improve the quality of clinical education for students and patients in a 1000 bedded teaching hospital.

Methods: An existing Allied Health Professional Group started offering workshops on clinical education topics hospital wide. Workshops were offered at lunchtime in a central location. As the workshops progressed a more diverse group of clinicians offered to participate in the organizing committee. (AHPs, Nurses, Scientists, Engineers, Pharmacy, Radiography) Terms of reference were drawn up and monthly meetings timetabled to plan workshops, inter-professional learning and research.

Results: Over a sample of 10 workshops, there were 70 attendees from nine professions. These professions provided placements for 451 TCD health science students in 2015. The feedback on the workshops was very positive. Marketing the sessions effectively was a key success factor.

Overall the numbers remain very low compared to the number of potential clinical teachers in the hospital, however interest has been growing. The effect on placement availability or quality of placement experience has not been measured.

Conclusion: A strong interdisciplinary community of practice has evolved from these endeavors. Further assessment to measure the impact of this Community of Practice is anticipated.

Investigating the role of Kynurenine on platelet function.

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Kynurenine is a tryptophan metabolite that has been implicated in several physiological and pathological processes. Kynurenine is known to be an endogenous ligand of the Aryl Hydrocarbon Receptor (AHR) which is involved in numerous signalling pathways. It has been recently demonstrated that kynurenine suppresses T-cell effector function by binding to AHR. Those findings prompted us to investigate the potential effect of kynurenine on platelet function. We have previously demonstrated that kynurenine is able to inhibit collagen-induced platelet aggregation, *in vitro,* in the micromolar range.

Aim: To investigate further the effects of kynurenine on platelet function and elucidate its potential mechanism of action through the AHR receptor.

Methods: Blood was collected from healthy volunteers and Platelet-Rich-Plasma (PRP) prepared by centrifugation. Immunoblotting was used to determine the presence of AHR in platelets. A wide range of AHR agonists was evaluated for their effect on platelet function using light aggregometer and phase contrast microscopy.

Results: The presence of the AHR in human platelets was confirmed by immunoblot. Kynurenine was able to inhibit not only collagen- but also ADP- and thrombin-induced platelet aggregation in a concentration dependent manner. Platelet aggregation induced by collagen and ADP was inhibited by agonists of AHR.

Conclusion: Kynurenine is an inhibitor of platelet aggregation probably acting via the AHR. Pharmacological manipulation of the AHR could be used to modulate platelet aggregation and therefore potentially exploited for therapeutic use.

Are normal adult carpal angle ranges applicable to the paediatric population?

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Aim: The aim of this study is to assess the applicability of standard adult carpal angle measurements, specifically the scapholunate and capitolunate angles, in the radiographic assessment of the paediatric wrist.

Method: The study cohort comprised of male and female children and adults who underwent a right or left wrist radiograph for the evaluation of suspected wrist or forearm injuries in the setting of acute trauma. In order to ensure accurate carpal angle measurement, only individuals with a sufficiently ossified carpus and an adequately positioned lateral wrist radiograph were included. Carpal angle measurements were performed on the lateral wrist radiographs of 256 individuals between the ages of 5 and 17 years and a gender-matched adult cohort of 256 patients aged between 18 an 39 years. The scapholunate angle was determined by measuring the angle formed between lines drawn through the axes of the scaphoid and lunate bones. The capitolunate angle was assessed measuring the angle between lines drawn through the axes of the capitate and lunate bones. Patients with an insufficiently-ossified carpus, oblique lateral radiograph, a displaced fracture, or a fracture angulated >10° were excluded.

Results: The mean scapholunate and capitolunate angles in the paediatric cohort were 48° (SD ± 7) and 10° (SD ± 6) respectively. The mean scapholunate and capitolunate angles of the adult cohort were 51° (SD ± 6) and 13° (SD ± 7) respectively. No statistically significant difference was observed between angle measurements in the two groups ($p < 0.05$).

Conclusion: The study data suggests that standard adult assessment techniques and values for scapholunate and capitolunate angle radiographic measurements are applicable to the paediatric population provided the carpus is sufficiently ossified.

Shared understandings of spiritual care among the members of an innovative Spirituality Interest Group in the Republic of Ireland.

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Spirituality is receiving unprecedented attention in the nursing literature (McSherry & Jamieson 2011). Recently the UK has made recommendations for the nurses' role in this area (RCN 2011, 2014). A Spirituality Interest Group (SIG) was set up in in the School of Nursing and Midwifery, Trinity College Dublin, in March 2013. This poster reports the results of the survey regarding the establishment of the SIG and the development of a shared understanding of spiritual care among the members. A 13-item survey was distributed in 2014 containing both closed and open-ended items. A total of 15 members participated. Responses revealed majority agreement with Ramezami et al (2014) dimensions of the concept of spiritual care, which was also confirmed in open responses, after qualitative analysis. As such attributes were identified as the following: healing presence, therapeutic use of self, intuitive sense, exploration of the spiritual perspective, patient-centredness, meaning-centred, therapeutic intervention and creation of a spiritually nurturing environment. There is consensus that the spiritual care in health care settings is a shared responsibility of the whole ought to be an integrated effort across the health care team (Pesut and Sawatzky 2006). However understandings of spirituality and spiritual care are not always clear. By developing shared understandings of spirituality and spiritual care the Spirituality Interest Group hopes to be able to underpin both research and practice with a solid conceptual understanding and foundation.

Assessment of sleep problems in children with Cerebral Palsy.

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Aim: Although sleep disturbances are commonly seen in children with Cerebral palsy, there is not much data to support this.

Our aim was to assess sleep pattern of children with cerebral palsy, using validated sleep questionnaire; Child Sleep Habit Questionnaire (CSHQ).

Methods: Total of 20 children with diagnosis of CP with ages from 3 to 18 years were selected. Their sleep pattern were evaluated using the sleep questionnaires (CSHQ) and compared with the sleep pattern of children with normal development and intelligence (mean age 7.2 years) and with children who had neonatal encephalopathy (NE) and normal development or mild learning difficulty (mean age 4.5 years). The children in the CP group had moderate to severe developmental delay & learning disability and suffered from comorbidities like epilepsy (71.4%) and visual impairment (57%).

Results: We found that majority of children with CP (71%) and NE (53%) had a pathological total sleep score in comparison with 5% of children in the general population. Children with CP demonstrated higher percentage of problems including sleep disordered breathing (SDB) (71%), parasomnias (72%), and excessive daytime sleepiness (EDS) in 62.5% compared to children with normal development. However preschool children with normal development demonstrated increased prevalence of bed time resistance (46%) and sleep anxiety (50%). Children suffering from epilepsy had problems with initiation and maintenance of sleep and around 40% were on melatonin.

Conclusion: Results of our study indicate that children with CP have a high incidence of sleep problems compared to the sleep pattern of children with normal development. Also associated co-morbidities contribute to increase frequency of sleep disturbances in children with CP.

Mission of the Clinical Research Facility

"It is our mission to improve health outcomes and quality of life by leading and enabling high quality, innovative translational clinical research"

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St. James's Hospital and Trinity College Dublin (TCD), with support from the Wellcome Trust and Health Research Board (HRB) operate a state-of-the-art Clinical Research Facility (CRF) within St. James's Hospital.

Come and talk to us about your study

- **Contact** the CRF Nurse Manager at +353 1 410 3919 or reidyde@tcd.ie for an initial discussion of needs
- **Complete** the CRF's Standard Application Form. A copy of the form is available for download from the website at www.sjhcrf.com or by email to reidyde@tcd.ie.
- **Applications** are reviewed by the CRF's Operational Management Team, within a 10 day period in most cases. This results in approval, rejection, or requests for further information from the applicant.
- **Following** its approval the study is initiated and conducted. It is continually reviewed by the Operational Management Team to ensure it is achieving the study objectives.

CRF Contact Information

Those wishing to learn more about the CRF, or with questions on how to bring a study into the CRF are invited to contact one of the following:

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