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FOREWORD

The School of Pharmacy and Pharmaceutical Sciences, Cardiff University, is the only school of pharmacy in Wales and is one of the top schools of pharmacy in the UK. Our students graduate well-prepared and satisfied, as seen by the consistently high pass rate in the pharmacist registration examination and high ranking in the National Student Survey respectively.

In addition to supporting individual pharmacists in their initial and ongoing education and development, the School is active in research that has been independently judged to be predominantly of international standing, more than half of which is recognised as world-leading or internationally excellent and with many interdisciplinary and external collaborators. Research at the School encompasses medicinal chemistry, drug delivery and microbiology, pharmacology and physiology, and pharmacy practice and clinical pharmacy, and it impacts on healthcare and pharmaceutical sciences throughout the UK and the world. Further information on the School's research activities and degree programmes, along with contact details for academic staff can be found at http://www.cardiff.ac.uk/phrmy.

At the Cardiff School of Pharmacy and Pharmaceutical Sciences, the combination of these strengths allows us to successfully deliver research-led learning and teaching. All of our MPharm students undertake a significant, independent Masters level research project in the final year of the four year degree, and present and defend their research. The large numbers of well-qualified UK, EU and international students that we attract to our postgraduate diplomas and degrees also contribute significantly to our research output.

This is the 14th year in which we have published the abstracts of our students' research. Within this publication the student is the first named author, and collaborators and supervisors follow. An alphabetical list of authors appears in the index.

Many thanks to my colleagues for their assistance in collating this book.

Rebecca Price-Davies
July 2014

Reflection in research: a thematic analysis

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At the Cardiff School of Pharmacy and Pharmaceutical Sciences, significant weighting is put on the research project that students undertake in their final year, the main aim of which is to understand the process of research. The aims of this project were to explore the views of the students to find what themes arise from learning in the fourth year research project.

In order to achieve this, students' reflections on learning were thematically analysed to identify the common and essential themes. This allowed key features of the data to be summarised whilst still offering a detailed description. They were then mapped to identify relationships between them. Lastly results were discussed as to whether the learning students reflected upon had any relevance to pharmacy or the aims of the module.

Research processes was a strong theme. This included the understanding of research and suggested students felt they now appreciated how research is carried out. Skills gained were also a strong theme, of the skills mentioned, organisation and communication were those that the majority of students identified that they had learnt or developed. They also felt many of these skills would greatly benefit them in the future.

Student's ability to reflect varied greatly; many lacked the ability to go beyond listing what practices they had been involved with in their projects. The importance of being able to reflect upon negatives of an experience is a key step of effective learning from practice in healthcare but mentioning what was challenging during the experience was not common amongst the students. This led to the possibility of students lacking confidence and the honesty of writing a true reflective account as literature suggests reflection is done poorly when it is to be assessed as well as without any facilitation [2,3].

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A-level results as an indicator of academic success for undergraduates in healthcare degree programmes

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Evidence in the literature suggests that students work in different ways, with for example, some students better engaging with didactic material and therefore are more successful at passing "traditional" exams, such as A-levels, while others may develop more strongly when exposed to experiential learning [1]. Despite A-levels being the predominant selection criteria by which most students are accepted onto degree programmes, once enrolled on the course, A-level results are largely ignored [2]. This project seeks to understand whether A-level results are important to academic success on the Cardiff MPharm programme, by looking at the number of A's and subject studied at A-level and degree classifications awarded to 571 MPharm students by the Cardiff School of Pharmacy and Pharmaceutical Sciences over a period of 5 years.

Student results submitted to Cardiff University through UCAS were liaised with the Cardiff officer and confirmed that anonymised student data can be used under the Data Protection Act, were put onto Cardiff University Business Objects Online. Data was extracted of students enrolling between years 05-06 and 09-10 onto the MPharm Degree at Cardiff. Inclusion Criteria was A-levels upon entry and awarded degree classification. Tables were made in Excel spreadsheet and the SPSS programme was used to determine correlations between A-levels and degree outcomes.

The results suggest that there is a correlation between A-level results and degree classification. Despite all 4 science subjects being the most popular to study for this degree, there is no correlation between subjects studied at A-level and degree outcome.

Over 50% of the MPharm degree is contributed by exams for which learning by rote is required to pass well, these are in many ways similar to A-levels [3]. Therefore, students who are particularly skilled at taking these sorts of exams will thrive in the MPharm degree at Cardiff.

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An evaluation of interprofessional learning: vital signs

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Interprofessional education (IPE) can be defined as when “two or more professions learn with, from and about each other to improve collaboration and the quality of care" [1]. Exposure of students to IPE is a requirement of both the medical and pharmacy degrees [2,3]. Sessions with fourth-year pharmacy students and first-year medical students involved the reading and interpretation of vital signs. The aim of this project was to evaluated students' views on the session, their views on IPE at Cardiff University, as well as their general views on the concept of IPE

Anonymous questionnaires were distributed to 156 students, with eight 5-point Likert items and a written comments box. Ethics approval was obtained. Answers from medics and pharmacists were compared, as well as medics who had worked solely with medics against medics working with pharmacists. Data from these forms were analysed by Mann-Whitney U test to determine significance of answers. Questionnaire data were used to drive discussion in semi-structured interviews. Three pharmacy students were recruited by convenience sampling for interview.

Students responded positively overall, with statistically significant differences found including pharmacists being more negative to statements involving learning from the session, and learning specifically from students of the other profession. Most agreed that IPE could help working relationships after qualification, and that more IPE should be implemented between the two Schools. Interviews with pharmacy students provided insight into feedback. Repetition of previous work and inexperience of the medical students contributed to negative feedback.

Feedback was positive, more from medics than pharmacists. Reasons for this included repetition of topics, and inexperienced colleagues, although workshop facilities and staff were praised. Future study into the attitudes of medical students when exposed to other healthcare professionals is suggested. Suggestions for improvement from pharmacists include moving session earlier in the degree.

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Simulation of the mechanical properties of topical microneedles of different geometries

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Microneedles (MNs) need to puncture viscoelastic skin without bending or breaking. Usefulness of sugar MNs, commonly used in topical applications, is therefore limited by structural strength and susceptibility to mechanical failure [1]. Stronger materials can achieve equal penetration without failing under large stress [2], however they cannot dissolve in skin. Using computer simulations, this study aims to characterize the relationship between geometry of dissolving sugar MNs and their subsequent predicted failure through buckling or fracture.

Using COMSOL Multiphysics software, a series of carboxymethyl cellulose and trehalose dihydrate (CMC/TRD 1:1) single MNs and 3x3 MN arrays were designed with a range of regular base shapes (vertices n=3,4,5,6,7,8 and ∞) and array spacings. Epidermal and dermal skin layers were simulated using known Young’s modulus, Poisson’s ratio and density values [3]. Failure by buckling and fracture upon insertion into

skin were simulated for each MN and array using Structural Mechanics module, yielding critical load factors and Von Mises stresses.

Conical MNs (vertices n=∞) had greatest critical load factors as expected, followed by shapes with decreasing vertices. Single conical MNs had lowest Von Mises stresses upon skin insertion, followed by hexagonal MNs then shapes with vertices n=8,7,5,4,3. Conical MNs showed greater critical load factors in 3x3 arrays than hexagonal equivalents. Larger array spacing yielded bigger critical load factors, however placed more stress on skin upon insertion. 400µm spacing exerted the least stress on skin however stress increased at denser 200µm spacing.

Conical MNs were mechanically strongest and therefore most resilient to failure by buckling and fracture. Hexagonal bases may yield the best performing MNs in reality due to having sharp edges and good mechanical strength. Increasing MN array spacing causes a decrease in array failure by buckling. Decreasing MN array spacing causes less skin stress on insertion, until spacing becomes too close and MNs act as one structure due to 'bed of nails' effect [4], increasing skin stress.

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Determining the effect of excipient particle size on the properties of direct-compression paracetamol tablets

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Tablet manufacture through direct-compression is the leading form of solid oral dosage form manufacture. This is attributable to the ease of manufacture and low cost [1,2]. For powders to display compatibility for direct compression, they must have a number of key characteristics to enable compression and formation of a solid mass [3]. Pure paracetamol powder is known to have poor compression properties, which leads to capping upon compression [4]. The aim of this project was to investigate what effect excipient particle size has on direct-compression paracetamol tablets. A series of formulations with varying active:excipient ratios were tested to determine the most suitable composition to obtain robust tablets. The compression excipient chosen for this experiment was Pearlitol.

Tablets were manufactured on a Riva MiniPress. The prepared tablets were subjected to a range of tests from the British Pharmacopoeia (BP) to determine their respective properties and to establish a relationship between tablet performance and excipient particle size. Table hardness (non-BP test), tablet weight uniformity and thickness uniformity were investigated; this gave an indication of powder flow. A tablet dissolution method was adapted from the BP; this investigated the porosity and solubility of the tablet. Scanning electron microscopy was used to investigate particle morphology, relative size and surface topography.

An active:excipient ratio of 15:85 produced tablets with suitable properties. However, powder flow was poor with all formulations, resulting in manual filling during tabletting. Tablet dissolution data revealed that excipient particles of smaller size achieved higher levels of dissolution at 45 minutes compared with their larger counterparts; the same was observed with tablet disintegration testing after 15 minutes of testing.

These findings indicate that excipient particle size does affect tablet properties. However, all tablets failed to comply with all the BP requirements; this may be attributable to the poor flow and compressibility of the pure paracetamol powder.

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Factors affecting delivery from elastomeric ambulatory devices

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The I-Flow Homepump® Eclipse is a type of disposable Elastomeric Ambulatory Device (EAD). Its use in the delivery of continuous infusions of medications such as chemotherapeutic agents, antibiotics and analgesics has increased over the last decade [1]. The benefits of using the device are well known, particularly its portability which enables patients to be treated at home, however there still remains uncertainty over their accuracy and reliability [2]. The aim of the study is to identify and assess whether the conditions encountered by the device will have an effect on its flow rate. Objectives for achieving this are to investigate a range of temperatures, viscosities of infusates and fill volumes.

Eclipses® were exposed to different temperatures that could be encountered during storage and use (15°C, 24°C, 31°C and 37°C) and flow rate determined. The flow rate was also assessed when filled with infusates of varying viscosities (normal saline, water for injection, glucose 5%, 20%, 35% and 50%) and when filled to different volumes (33mL, 66mL, 100mL and 125mL). Flow rate was calculated by measuring the volume of dispensed fluid collected for a given time.

All of the factors tested had an effect on the device's flow rate, as they deviated from the optimal conditions stated in the manufacturer's guidelines [3]. The viscosity of the infusate had the greatest effect, with the device failing to exhaust its fluid reservoir when filled with glucose 35% and 50%.

Every effort should be made to ensure that the manufacturer's guidelines are followed and that both healthcare practitioners and patients are made aware of the effects that deviations can have on the delivery performance of the device.

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The role of clathrin-independent endocytosis in Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disease caused by beta-amyloid protein (Aβ), formed from the cleavage of APP (amyloid precursor protein) by β- and γ-secretase [1]. Uptake of material into a cell is mediated via clathrin-dependent or –independent endocytosis [2]. Caveolin and flotillin, which mediate forms of clathrin-independent endocytosis, are upregulated in AD [3,4]. The aim was to examine the effects of reduced caveolins and flotillins on the intracellular location of proteins involved in AD.

MOG-G-UVW cells were transfected with siRNA to reduce caveolin-1, flotillin-1 and flotillin-2 levels. Immunocytochemistry was performed to label caveolin-1, flotillin-1, flotillin-2, APP, BACE1 (β-secretase) and presenilin 1 (γ-secretase). Primary antibodies were detected with biotinylated secondary antibodies and avidin FITC. Filipin was used to stain free cholesterol. Coverslips were mounted onto slides and viewed under a fluorescent microscope.

Results showed knockdown of all three proteins. No significant changes were observed in APP location in siRNA-treated cells. In caveolin 1 siRNA-treated cells, presenilin 1 had greater accumulation around the nucleus than controls. In flotillin-1 siRNA-treated cells, there was less BACE1 accumulated near the plasma membrane compared to controls. There was reduced cholesterol staining in caveolin-1, flotillin-1 and flotillin-2 siRNA-treated cells.

Caveolin-1 reduction may result in less presenilin1 trapped in caveolin-mediated endocytic vesicles. This allows more presenilin 1 to transport to late endosomes, located close to the nucleus, where it cleaves APP which increased Aβ levels. Flotillin-1 reduction may reduce raft-mediated endocytosis of BACE1 and result in less available to cleave APP in early endosomes, located near the plasma membrane, decreasing Aβ levels. Reduction of caveolins and flotillins may disrupt cholesterol-rich lipid rafts on the plasma membrane. In conclusion, caveolin- and flotillin-mediated endocytosis may contribute to AD pathogenesis through effects on presenilin 1 and BACE1 location.

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Evaluating interprofessional education for pharmacy and medicine undergraduates at Cardiff University

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Interprofessional health education is the collaboration between members of two different healthcare professions in order to share knowledge and develop a professional relationship [1]. IPE is a required feature of both the pharmacy and medicine undergraduate degree programmes [2,3]. An IPE session involving clinical cases was conducted with pharmacy and medical students in the first semester of the 2013/14 academic year. Students were either 3rd year medical students or 3rd/4th year pharmacy students. This project aimed to evaluate these IPE sessions by exploring the views of both the students and facilitators that attended the IPE sessions.

A Likert-scale questionnaire, also containing a small number of open questions for students to provide written feedback, was distributed to the students at the end of the IPE session. Likert-scale responses provided quantitative data, which was inputted into SPSS. A Mann-Whitney U test was used to compare responses from pharmacy and medicine students. Semi-structured interviews were conducted with facilitators, to explore their views and compare them to students, as facilitators views are often overlooked [4]. An interview schedule, information sheet and consent form were prepared. Ethical approval was obtained from Cardiff School of Pharmacy and Pharmaceutical Sciences.

Four hundred and fifty students were provided with a questionnaire and a response rate of 95.6% was achieved. Students from both professions enjoyed (83.4%) the sessions and found them useful (89.3%). However medical students found the session to be more useful. Students from both courses (n=170) identified a need for more IPE in the curriculums. The area requiring most improvement was organisation of the session (n=97), in particular the partner pairing procedure. Both groups of students commented that the most useful aspect of the session was working with another healthcare professional.

Overall, students were positive about the session, and expressed that they should be continued in the future. This evaluation will be submitted to the school of pharmacy to inform and improve future sessions.

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Cardiff MPharm graduates' preparedness for pharmacy practice measured against learning outcomes for undergraduate pharmacy education in the UK: perceptions of employers

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In the UK, there is no published literature regarding the level of graduate preparedness for pharmacy practice using the perceptions of employers, however, there is one study concerning such preparedness based on the perceptions of final year students from pharmacy schools across the UK [1]. The General Pharmaceutical Council (GPhC) published educational outcomes for MPharm and pre-registration students in 2011, which have never been used to measure the level of graduate preparedness [2]. The aim of this study is to explore the perceptions of employers with regard to preparedness of Cardiff University graduates for pharmacy practice using the learning outcomes outlined by the GPhC.

Ethical approval was obtained from the School's Research Ethics Committee. Non-probability purposive then snowball sampling recruited fourteen participants who have been involved in the training of pre-registration pharmacists from both hospital and community pharmacies across South Wales. Each participant took part in a semi-structured interview after consent; each interview was subsequently transcribed *ad verbatim [3]*. The transcriptions were then coded and thematic analysis undertaken from the codes [4].

Participants perceived Cardiff University pharmacy graduates to be prepared for most of the GPhC outcomes. All participants thought Cardiff graduates were prepared for pharmaceutical calculations with other areas of preparedness including team working and CPD. Participants perceived graduates to be least prepared for leadership, communicating with other healthcare professionals and multidisciplinary team working. The perceptions of hospital and community pharmacists were comparable in most areas. Suggestions for improvement to the Cardiff MPharm degree were provided, the most common being the need for a greater exposure to practice especially more experiential placements.

Overall, employers thought Cardiff University graduates were prepared for pharmacy practice with some elements stronger than others. The need for changes to the Cardiff MPharm degree would ensure that graduates are equally prepared for all areas of pharmacy practice.

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Profiling CD44 isoforms (CD44s and CD44v6) in novel models of endocrine resistant breast cancer

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CD44 and its variant isoforms have a controversial status in breast cancer, and are largely unexplored in endocrine resistance [1]. CD44s is overexpressed in short-term tamoxifen resistance in vitro, [2] but little is known about expression in other endocrine resistant states, especially taking longer treatment duration and genotype into consideration. This study will establish CD44s and CD44v6 expression in novel endocrine resistance models to determine any relation between these isoforms and oestrogen receptor (ER) status, aggressive behaviour, and endocrine treatment type and duration, considering whether any findings show genotypic parity.

ER, CD44s and CD44v6 expression were examined in acquired tamoxifen resistant (TamR), Faslodex resistant (FasR) and oestrogen deprived resistant (X/SFCSR) cells modelling shorter (2 year) and longer (3 year) treatment in MCF7 and T47D genotypes, using immunocytochemical analysis. Aggressiveness of the cell lines was examined by modified Boyden chamber migration assays.

MCF7-derived TamR, FasR and X models expressed significantly higher levels of CD44s and CD44v6 versus parental cells, irrespective of anti-hormone, but there was a significant decrease in longer-term resistant models versus shorter-term resistance. T47D-derived longer-term models also expressed relatively low levels of CD44s and CD44v6 in tamoxifen and Faslodex resistance. There was no consistent association between CD44 expression, ER status and aggressiveness, although substantial CD44s and CD44v6 were retained in ER^-, highly migratory, T47D-derived SFCSR cells.

Overexpression of CD44s and CD44v6 in MCF7-derived resistant models indicates these isoforms may have a role in early acquisition of endocrine resistance. Their contribution to endocrine resistant behaviour may vary, with contextual cues determining whether this is beneficial or detrimental. In general, their contribution to resistance may diminish with increasing treatment, irrespective of genotype. If any functional contribution to endocrine resistance can be confirmed, monitoring CD44 levels or targeting the molecule may have clinical utility in overcoming resistance.

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Patient experience: satisfaction with their medicines management during their hospital stay and satisfaction with information about their medicines provided on discharge from hospital

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Medicines Management is a standard of care [1] that involves the pharmacy teams ensuring patients' medicines are being dealt with correctly and that patients are educated about their medicines. The aim of this study is to evaluate these aspects of pharmaceutical care so areas of improvement can be identified and patients can received the best care.

Recently discharged medical patients from two hospitals; (Ysbyty Gwynedd (YG) and Wrexham Maelor (WM)) were identified, basic demographics noted and an anonymised questionnaire incorporating a validated tool to assess satisfaction with information about medicine [2] was mailed to them. Responses were analysed using SPSS. Mann-Whitney U, Kruskal-Wallis and Chi-squared statistical tests were performed to compare quantitative data against patient demographics, hospital and other answers. Any comments were thematically analysed to identify areas where services can be improved.

Of 380 patients contacted, 151 (40%) responded, evenly distributed between hospital and gender. Mean age was 71 years old (SD 15.09) on a mean number of medicines 8 (SD 4.48). Overall satisfaction was 92%. More patients experienced problems with their medicines in YG than in WM ($p=0.016$) due to delays with discharge medicines and issues with administering medicines. Patients were more satisfied with the management of their medicines if they had contact with pharmacy staff ($p=0.002$) and the opportunity to discuss their medicines with them ($p<0.001$). Fewer patients were satisfied with information related to side effects compared to information related to drug actions and uses. From patients' comments, problems identified related to long delays in dispensing medicines on discharge, incorrect doses and insufficient information provision. Positive comments related to the advantages of speaking with a member of the pharmacy team.

Although satisfaction was high, there are several recommendations that can be implemented in order to further improve satisfaction and ensure standards of care are being met for all patients.

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MMP expression and activation in drug-sensitive versus drug-resistant breast cancer

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The majority of ER+ breast cancers treated with endocrine agents develop resistance. Resistant forms are more aggressive and behave more invasively [1]. Evidence suggests matrix metalloproteinase (MMP) involvement in pro-invasive pathways due to their ability to degrade the extracellular matrix, facilitating invasion and metastasis [2]. MMP-2 and -9 correlate with poorer prognosis and have potential therapeutic applications [3,4]. Since MMPs are linked with aggressive forms of breast cancer we hypothesised that they are up-regulated in resistant forms which are inherently more aggressive. We aimed to investigate expression of MMP-2/-9 in drug-resistant versus drug-sensitive breast cancer models.

PCR was used to investigate MMP expression at gene level and to confirm ER status of the cell lines. Gelatin zymography was used to highlight MMP-2/-9 activity via a gelatin-containing gel which was physically degraded. A uPA activity colorimetric assay was run to elucidate information about MMP activity generally since it is a common regulator of MMPs.

All cell lines were ER+ except for the FasR cells, which were ER-. MMP-9 expression was higher in TamR and X cells compared to MCF-7, and negative in FasR cells. MMP-9 expression at both gene and protein level were consistent. The uPA assay detected the highest activity in the drug-sensitive model. MMP-2 was not detected in any experiment.

MMP-9 expression appeared to correlate with ER status since it was only expressed by the ER+ models. Increased expression in TamR and X cells suggests that MMP-9 is important to their resistant phenotypes, but not FasR. Data therefore suggests that different forms of resistance associate with different MMPs. MMP-9 expression did not correlate with in vitro aggressiveness, or the uPA activity assay, which appeared inconclusive due to low activity levels. Further investigation of MMPs in drug-resistant breast cancer may highlight a target up-regulated in all forms to exploit clinically.

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An evaluation of the measurement of equivalence of electronic versions of paper-based patient-reported outcome measures

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The transfer of patient reported outcome (PRO) instruments from paper-based to electronic formats confers benefits to both clinicians and patients [1]. However, any new version should be validated before use, which can be done by demonstrating measurement equivalence between the formats [2]. This review aims to examine studies investigating format measurement equivalence in order to identify the methodologies used and the results achieved.

A search was undertaken of three bibliographic databases (PubMed, OvidSP and Web of Science) using an identical set of keywords. The abstracts and, if available, the full text of results were examined for compliance with inclusion criteria. Articles or abstracts were included if they directly compared a screen-based electronic PRO instrument with its paper-based original on the basis of measurement equivalence. Papers published before 2007 were excluded as a previous meta-analysis examined papers published before this time [3]. Data were extracted from studies using a template.

55 publications were identified, investigating 79 different PRO instruments. 75% were full text journal articles, 60% investigated only one instrument per study and 75% used a population of adult patients. 85% used a crossover study design and the most commonly used formats for the electronic version were Internet formats. The most common correlation measure used was the intraclass correlation coefficient. Of the 30 studies that provided preference data, 87% found that overall patients preferred the electronic format. 78% of studies suggested that the different formats showed evidence of equivalence, as judged by the study authors.

From the literature examined, it appears that generally the process of transferring PRO instruments between formats is successful, resulting in electronic versions that produce equivalent results to the paper originals. Patients appear to prefer electronic versions, supporting their implementation, and it seems likely that as technology improves, the use of electronic PRO instruments will increase.

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Effects of nitric oxide donors in myocardial ischaemia reperfusion injury: a review of the human studies using a systematic approach

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Nitric oxide donors have shown beneficial cardio-protective effects in reducing myocardial ischaemia-reperfusion injury. Following an ischaemic event, due to a myocardial infarction or unstable angina, reperfusion techniques used to restore blood flow can cause further myocardial damage. Nitric oxide can exert various protective mechanisms and therefore, targeting these in a clinical setting has the potential to limit injury and improve myocardial outcomes [1,2]. The aim of this project was to undertake a comprehensive review of human studies, using a systematic approach, to investigate the effects of exogenous nitric oxide donors as an adjunct to reperfusion and whether these therapies are beneficial to the myocardium.

A comprehensive search strategy was developed, using search terms based around keywords within the project title. Using these terms, *Medline*, *Web of Science, Cochrane* and *Embase* were searched, and results from each database were uploaded into Endnote Web and the duplicates were removed. All literature was screened at title level for initial relevance and then at abstract level, using strict inclusion/exclusion criteria that had been developed. Identified articles were assessed at full-text using a specific critical appraisal tool. Following discussion with an independent reviewer, the studies deemed fully appropriate were analysed and discussed.

The initial database search identified 3,771 human studies. Of these, 185 were deemed appropriate for abstract level screening and 32 studies were further assessed at full-text level using the critical appraisal tool. Seven clinical studies were regarded as high quality and relevance and were analysed, interpreted and reviewed.

Studies showed that nitric oxide donors have no effect on reducing infarct size, when determined by enzyme markers. However, there is significant reduction of inflammation, incidence of post-operative atrial fibrillation and highly improved clinical outcomes reported. These achieved outcomes demonstrate the potential of nitric oxide donors to improve and protect the myocardium from ischemia-reperfusion.

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Assessing the quality of life of families of patients with renal disease using the FROM-16

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The symptom and treatment burdens of end-stage renal disease are large, and the impact on both patient and family member quality of life is common and significant [1]. The purpose of this study was to assess the impact of ESRD on family member quality of life.

This was a case-controlled, single site study using four different patient treatment groups- Unit Haemodialysis (UHD), healthy Transplant patients (Tx), Continuous Ambulatory Peritoneal Dialysis (CAPD) patients and stage 4 and 5 ESRD pre-dialysis (PRED) patients. The study included 17 pairs of patients and their family members. Family member quality of life was scored using the first generic family quality of life assessment tool, the Family Reported Outcome Measure (FROM-16) [2]. Patient quality of life scores were measured using the Renal Quality of Life Profile [3].

Family member quality of life was found to be lowest in the UHD group followed closely by PRED, then by CAPD. Family members of the Tx patient group had the highest quality of life scores.

Family member quality of life showed correlation with patient quality of life (R=0.473) but did not reach significance (P=0.055) using spearman's rank correlation. Significant findings using this test were a decreasing family member quality of life with a reduction in the ability of the patient to join in with leisure activities and go on holiday (R=0.527, P=0.030). Family member quality of life was found to significantly

correlate with decreasing patient physical ability (R=0.493, P=0.044) and increasing hours of care (R=0.844, P=0.001). However; decreasing patient physical ability did not significantly correlate with increasing hours of care (R=0.628, P=0.07) which leads us to conclude that family member quality of life is affected by their perception of the patient's quality of life.

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MMP expression and activation in breast cancer subtypes

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Breast cancer is the most common cancer among females and is a heterogeneous disease characterised by four major subtypes including Luminal A, Luminal B, HER2+ and triple negative breast cancer [1]. A limitation in regards to cancer therapy is the lack of success in treating metastatic disease [1]. This led to the possible targeting of matrix metalloproteases (MMPs). These are endopeptidases capable of degrading the extracellular matrix (ECM), an essential step in the metastatic cascade [2]. Therefore this project aimed to identify the expression of gelatinases (MMP-2 and 9) in a range of cancer cell lines representative of the dominant clinical subtypes. We hypothesised that the breast cancer subtype with the poorest prognosis would express the highest level of MMPs.

MMP gene and protein expression were assessed using PCR and zymography respectively. Expression of urokinase-type plasminogen activator (uPA), a major activator of MMPs, was determined using a colourimetric ELISA-based assay. MMP/uPA expression was investigated in a panel of breast cancer cell lines reflecting major breast cancer subtypes. These were: MCF7 (Luminal A), BT474 (Luminal B), SKBR (HER2+) and MDA231 (triple negative). Experimental data was statistically analysed using SPSS and t-testing where replicates allowed.

Our data showed that SKBR cells, a model of HER2+ breast cancer that has a poor prognosis, expressed the highest level of MMP9 gene product which MMP9 gene expression was low or absent across the other models. MMP9 protein expression was again seen at relatively high levels in SKBR3 and MCF7 cells. No MMP2 was detected at either the gene or protein level in any of the cell lines used. uPA expression was detectable in all cell lines but at a low level.

These data suggest a potential role for MMP9 in Her2+ breast cancer although there was a general lack of correlation between MMP expression at either gene or protein level and the inherent aggressive ness of the breast cancer cell lines.

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The puncture properties and shedding of particles of capsules in dry powder inhaler, effect of capsule type and moisture content

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The use of gelatin and HPMC hard shell capsules in dry powder inhalers (DPIs) is well established. However, there have been complaints about throat irritation caused by inhaled particles produced from gelatin capsules due to their brittleness at low moisture contents [1]. This project was designed to compare the puncturing properties of inhalation grade gelatin and HPMC hard shell capsules. The dimensional characteristics of particle fragments produced after capsules had been punctured by Zwick® machine and Plastiape® 2-pin DPI were investigated.

Capsule samples were conditioned in normal and low relative humidity conditions. They were then punctured using the DPI and Zwick® machine. The puncture and force-displacement profiles were recorded using the

Zwick® machine [2,3]. The visible fragment pieces produced were analysed quantitatively using the ImageJ software from the images captured with the AmScope Microscope. The particles were also assessed with a scanning electron microscope (SEM).

The study demonstrated that gelatin capsules required significantly greater puncture forces compared to the HPMC ones and the pin had to move a greater distance (an extra 70%) from the shell end wall at their lower moisture content. Gelatin capsules also produced significantly greater numbers of fragment pieces: no visible particles were seen with the HPMC capsules. Analysis using the SEM managed to identify fragments from both capsules that were not visible to the naked eye.

The results show that gelatin capsules stored in low humidity conditions have a higher tendency to produce more and larger sized fragments, because of their brittleness. It is clear from this work that HPMC capsules have superior puncturing properties compared to gelatin capsules. This work contributes to knowledge of the characterization of fragment particles produced during capsule puncturing.

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An evaluation of how ‘Quality Information’ training is implemented in NHS production areas

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In NHS production areas today, ‘Quality Information’ training has become essential for the continuous improvement of medicinal product quality. This concept is used to provide a basic understanding and some hands-on activities around Aseptic Principles, Good Manufacturing Practice (GMP), Preparation of CIVAS, Parenteral Nutrition and Cytotoxic – a must for any grade of staff linked to these services [1,2]. In 2006, online learning for healthcare was launched, providing a way by which quality training could be delivered to NHS workforce [3]. The aim was to identify how ‘Quality Information’ training is currently implemented in NHS production areas in Wales and England, additionally; to explore the perceptions of the personnel regarding the need to develop or use online learning tools in NHS production areas.

An anonymous, self-completion questionnaire, including 5-point Likert scale, open-ended and close-ended questions, was sent to all production area personnel in Wales and England via email (n=400), giving participants two weeks to respond. A reminder email was sent one week after the initial invitation. Quantitative data were analysed using Microsoft Excel. Qualitative data were entered into Microsoft Word.

A questionnaire response rate of 25% was achieved. Over 70% stated that pharmacy technicians are the most important staff group with regards providing production area training to all grades of staff; 95% indicated that this current method was delivered informally. The majority of participants found online learning useful in NHS production areas, especially when it was supported by alternative learning formats.

This study shows the need for ‘Quality Information’ training to be implemented for all pharmacists and technicians. Specialist training should also be available for pharmacy managers and senior technicians. Online learning was beneficial and should be developed in NHS production areas. It should however be supported by other learning formats and countermeasures to provide more equal opportunities, especially for employees who are relatively new to online learning [4].

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What are the factors that motivate final year undergraduate students in relation to the MPharm degree?

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Academic motivation plays a crucial role in student learning and there are various factors influencing the academic motivation of undergraduate students in university [1]. To date, no research has been reported in the UK in relation to pharmacy undergraduates. Thus, the present study sought to explore, understand and identify what factors motivated final year Cardiff students in relation to the MPharm degree.

One-to-one semi-structured interview were used following a favorable opinion from the Cardiff School of Pharmacy and Pharmaceutical Sciences research ethics committee. Pre pilot and pilot interviews were conducted to provide practice in interviewing and to test the interview guide. A mixture of purposive and convenience sampling was employed. Recruitment emails were sent to the potential interviewees with participant information sheet and consent form. Interviews were then conducted, captured via audio recorder and transcribed *ad verbatim* and anonymised. The results were analyzed thematically using inductive and deductive analysis [2]. Data were coded and arranged into themes and subthemes.

Through the interviews, factors that were found to potentially affect students' academic motivation were classified into four major themes, a total of eleven subthemes and six sub-subthemes. The four major themes were self-motivation (eg., interest), motivation from others (eg., lecturers), academic factors (eg., grades) and other factors (eg., weather). They could be further classified into intrinsic and extrinsic motivation. Students who are intrinsically motivated engage in an activity because he/she is interested and enjoy the activity [2] whereas extrinsic motivation relates to the engagement in activities for instrumental or other external reasons [3,4].

These results suggest there were a number of factors affect students' academic motivation. There is much to learn about academic motivation and thus, additional studies need to be done. In particularly, increase the number of students and get students from other years involved to explore further academic motivation.

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The development of a peracetic acid and spore germinant mixture as an environmentally friendly decontaminant to eliminate bacterial spores from hospital surfaces

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This study demonstrates the feasibility of utilizing peracetic acid as an environmentally friendly decontaminant to eliminate bacterial spores from hospital surfaces. Problems arise with current methods of decontamination against selective bacterial strains namely the *bacilli* and *clostridia*. This is due to the formation of dormant spores by the bacteria. Spores formed have unique endospore structure that is able to resist antimicrobial agents [2,3]. Thus, the developments of new techniques are required to eradicate the bacteria. In 2008, Wheeldon *et al.* demonstrated that germination of dormant spores to vegetative cells showed a reduce resistance to antimicrobial agents. Based on the approach, we hypothesized that co-administration of germinants will improve the efficacy of peracetic acid as an antimicrobial agent to eliminate bacterial spores.

Two treatments were tested - Treatment 1 (0.039% Peracetic Acid) and Treatment 2 (0.039% Peracetic Acid, 100mM L-alanine and 5mM Inosine) with different suspension time (5, 30 and 60 minutes). 1mL of spore suspension was placed into 9mL of treatment. Solutions were vortex mixed and kept at room temperature at 5, 30 and 60 minutes. Next, the solutions were vortex mixed again. 1mL of aliquot of the solution was removed and added to 9mL of neutraliser. The resulting mixture was vortex mixed again and left to stand for another 5 minutes. Lastly, 100µL was removed, and spore enumeration was performed. Remaining solution

in the centrifuge was subjected to heat shock treatment in a water bath. Spore enumeration was performed once more after.

Treatment 1 was found to be ineffective in reducing the counts of *bacilli* spores at all standing times. Furthermore, different *Bacilli spp.* reacted differently towards the germinants used – *Bacillus cereus* G9241 did not show signs of germination. However it was found in the *Bacilli thuringiensis* strains that germinants used effectively germinate spore and increased peracetic acid's efficacy as an antimicrobial agent in Treatment 2.

In conclusion, the addition of germinants to peracetic acid enhanced its efficacy as an antimicrobial agent. The study supports the hypothesis that preceded the study. The cause of ineffectiveness of germinant found with *Bacillus cereus* G9241 remains inconclusive. It is hoped that the study will stimulate further investigations in this field.

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Is age a factor in the use of non-motor medication antidepressants in Parkinson's patients?

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Parkinson's disease (PD) is considered a motor disorder however patients experience a range of non-motor symptoms, including depression [1]. Many are linked to neurological damage from Lewy body inclusions, spreading in a predictable sequence detailed by the Braak staging system [2]. Aging increases the risk of PD however relationships between non-motor symptoms and age are unclear. This study aimed to analyse the influence of age on antidepressant use in Parkinson's patients.

Data was extracted from a database of movement disorders patients in South Wales, separating patients with PD from benign essential tremor (BET) used as a control. A list of search terms was used to separate those with antidepressants, those with untreated depressive symptoms and those without depression. Age of diagnosis was calculated as was time from diagnosis to initiation of antidepressants. Ethics approval was obtained.

Incidence of depression was higher in PD, affecting 49.25% compared to 27.88% in BET. BET showed no relationship with age however incidence in PD peaked at 45-49 years and decreased with age. In both groups depression was most commonly pre-existing and age did not affect results. BET showed no trend after diagnosis whereas in PD 10.19% were diagnosed in the same year as antidepressant prescribing and rate declined with time.

Depression affects 20% of chronic condition patients due to reduction in quality of life [3]. This is significantly increased in Parkinson's to 30-50% and is likely related to degeneration in mood regulating brain regions [1, 4]. This damage precedes degeneration in movement centres and hence depression affects patients prior to diagnosis [2]. Importantly, this was also seen in BET patients implying an unrecognised premotor phase to this condition. In conclusion, this study shows that age of onset clearly impacts upon depression in PD and younger patients have a greater use of antidepressant medication.

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Profiling CD44s and CD44v3 in novel models of endocrine resistant breast cancer

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Acquired endocrine resistance is a major obstacle in the treatment of oestrogen receptor (ER) positive breast cancer, and is linked to aggressiveness and ER loss in approximately 20% of patients with tamoxifen relapse [1]. Isoforms of adhesion glycoprotein CD44 may contribute: CD44s has previously been linked to ER negativity [2] and CD44v3 to poor clinical response to tamoxifen [3]. However, these findings are controversial and knowledge of their role in endocrine resistance is relatively unknown. This study aimed to determine CD44s and CD44v3 profiles to compare with ER status and aggressiveness in new models of acquired resistance considering different types and duration of anti-hormonal therapy.

A novel *in vitro* panel comprising MCF7 cells previously grown with tamoxifen, Faslodex or oestrogen deprivation to produce 2-year shorter-term (TamR, FasR, X) and 3-year longer-term (TamRLT, FasRLT, XLT) models of acquired resistance, and an equivalent T47D–derived panel of 3-year resistant models (T47DTamRLT, T47DFasRLT, T47DSFCS) were used. CD44s and CD44v3 levels and ER status were determined by immunocytochemistry with H-scoring. Aggressiveness was determined by monitoring migration with a modified Boyden Chamber assay.

The MCF7 and T47D model panels showed a link between ER loss and increased migration in resistance. While increased in all earlier-resistant models, both panels had decreased CD44s and CD44v3 with longer-term resistance, although there was no clear relationship to ER loss or aggressiveness. Interestingly, long-term oestrogen-deprived T47D SFCS retained high levels of CD44 alongside ER loss and being highly migratory, contrasting MCF7-derived XLT.

The lack of apparent link to ER loss or aggressiveness suggests CD44 contribution to resistance is complex, functioning differently between different resistant cell types, involving additional CD44 isoforms or other context-related factors [4]. Its role also appears time-dependent. CD44 expression in T47D SFCS shows CD44 may play a role in some aggressive endocrine resistant tumours which would be interesting to study further.

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Patient experience: satisfaction with their medicines management during their hospital stay and satisfaction with information about their medicines provided on discharge from hospital

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Patient satisfaction is an essential component for achieving high-quality care. Standards for Health Services in Wales stated that: ‘’there is timely, accessible and appropriate medicines advice and information for patients’’ [1]. This study will be part of an All-Wales project requested and supported by the NHS Wales hospital pharmacy services. The aim of this study was to assess in-patient satisfaction with their experience relating to their medicines and the information provided to them about their medicines on discharge.

This study was conducted in Hywel Dda University Health Board. A questionnaire was used as a research tool to target a specified population of recently discharged patients from an acute hospital site. Part of the questionnaire used the validated instrument, the Satisfaction with Information about Medicine Scale (SIMS) to assess patient satisfaction with medicines information [2]. The inclusion criteria consisted of adult patients discharged home on at least one prescribed drug. Full ethical approval was obtained.

A questionnaire response rate of 39.5% was achieved. The results indicate that respondents are more likely to be satisfied with information given at discharge when they have had the opportunity to interact with pharmacy staff, receive clear written information and receive verbal information. The opportunity for discussion with pharmacy staff was a significant find in the results. When a patient had the opportunity to interact with pharmacy staff their total satisfaction with medication information, calculated by the SIMS questionnaire, was statistically significantly improved.

These results support the findings that whilst patients were generally satisfied with the information provided at discharge regarding medication, it was evident that there were inconsistencies in relation to potential problems they might experience. This information gap will possibly have a negative impact on their adherence to medicines.

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Measuring the general public's views about the community pharmacist

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Contractual changes in 2005 [1] expanded the role of the community pharmacist to increase their involvement in public health. Recent studies indicate the utilisation of these additional services by the general public is poor [2]. In order to determine what barriers exist to service uptake the public's perception of the community pharmacist must be explored. The aim of this study was to establish public perception of the role of the community pharmacist.

A combination of purposive and snowball sampling was implemented to recruit participants. Phase 1 (qualitative); one-to-one interviews following a semi-structured interview schedule based on themes derived from a previous study [3]. Phase 2 (quantitative): data collected and analysed informed the design of a structured questionnaire. This consisted of attitudinal (measured by a Likert scale) plus factual questions (with categorical response options). This was piloted and redrafted to achieve the final draft.

Nine individuals took part. Phase 1 data revealed similar themes to previous work in that the public were aware of the traditional role of the pharmacist: dispensing and minor ailment advice, but little knowledge existed of the expanded role. Pharmacists were recognised as highly trained professionals, but the connection to available expertise was not apparent. Preference towards independent and small chain pharmacies was expressed, with distrust shown towards supermarkets. Two new themes emerged: the frustration of GP time constraints, and the inability to differentiate between the pharmacist and pharmacy support staff.

These findings generally concurred with previous studies [4]. The main limitation was sample size, indicating the need for more diversity in socio-economic groups and ethnic minorities. Further qualitative research is required with wider sampling for potential identification of new themes. The profound lack of awareness of services available suggests the need for greater promotion. The questionnaire will be used in future projects to capture the views of the public on a larger scale.

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Development and evaluation of a computer-assisted learning (CAL) package on angina management

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Computer assisted learning (CAL) is a teaching method which employs the use of a computer to improve the users academic learning through explanation and testing of a subject matter, often without the involvement of a human teacher [1]. The aim was to develop and evaluate an informed and interactive computer assisted learning package, on the management of angina to be used by pharmacy students within the United Kingdom.

The CAL package was built using Microsoft Powerpoint® and contained accurate, up-to-date and reliable evidence based information on the management of angina [2,3]. Aspects of the package such as structure, length, visual appearance and interactivity were taken into consideration [4]. A questionnaire was developed using a 5 point Likert scale and free text box for comments, assessing the package presentation/layout, content and overall impression/use of CAL.

A total of 21 online questionnaires were completed by MPharm II students: eight (38%) from males and thirteen (62%) by females, producing a response rate of 18%. The mean, mode, standard deviation and frequency were obtained. All students felt that the package was well presented. 86% of students (n=18) agreed that the package was engaging and interactive and the package content was felt to be relevant and beneficial to MPharm II. The majority disagreed that CAL should replace lectures (52% n=11) and would prefer to attend a lecture rather than complete a CAL package (71% n=15). However 95% (n=20) agreed that the package would be useful as a revision aid and 86% (n=18) would use CAL in the MPharm degree.

This CAL package on the management of angina has been shown to be an effective learning tool in the MPharm II year group, and provides a valuable insight into the views and opinions of the students regarding CAL.

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Can food affect 5-HT receptor pharmacology in the gastrointestinal tract?

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5-hydroxytriptamine (5-HT) is responsible for an extensive range of actions within the body. The diversity of its role can be attributed to the abundance of different receptor subtypes. 5-HT has long been implicated in disorders of the gastrointestinal (GI) tract involving gut motility. Excessive amounts of 5-HT increase peristalsis leading to diarrhoea [1,2]. Conversely a reduction in 5-HT leads to decreased gut transit and subsequently constipation [1,3]. Although 5-HT has been a focal point of research for decades, there is much to be learned of its function.

Non-cumulative concentration response curves (CRC's) were performed using the ileum of two sets of Dunkin Hartley guinea pigs (350-800g). One set had free access to food, the other set were food deprived for twelve hours. CRC's were performed in response to 5-HT ($1x10^{-9}$ – $3x10^{-4}$M), 5-HT + LY 266097 hydrochloride (5-HT_{2B} antagonist, $1x10^{-7}$M), 5-HT + Y25130 hydrochloride (5-HT_3 antagonist, $1x10^{-5}$M), 5-HT + GR 113808 (5-HT_4 antagonist, $1x10^{-7}$M) and 5-HT + GR 113808 + LY 266097.

No differences were seen in the mean EC50 values or the EC50 value shifts between the two sets of guinea pigs with the exception of Y25130, which produced a large rightward shift suggesting an increase in receptor affinity. GR113808 antagonised the relaxant response at high 5-HT concentrations in food deprived guinea pigs which suggests the 5-HT_4 subtype is involved in mediating relaxation following food deprivation but not in fed guinea pigs. In every instance a higher mean maximum contractile response (g) was produced in food deprived guinea pigs indicating a change in intercellular coupling.

Following a series of unpaired, two-tailed t-tests, none of the differences gained statistical significance (P >0.05) indicating no change in 5-HT receptor pharmacology. However, this was probably because the study was underpowered. Further investigations need to be performed to ascertain any differences.

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Evaluating the reliability and validity of a contextualised numeracy diagnostic for undergraduate students at a school of pharmacy

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Pharmacy students in the UK must uphold a standard of core transferable pharmaceutical numeracy skills to comply with the General Pharmaceutical Council's accreditation requirements [1]. First year students at Cardiff School of Pharmacy and Pharmaceutical Sciences (CSPPS) sit a numeracy diagnostic to identify if they have the adequate skills to endure the numeracy demands of the course. This project aims to establish if the diagnostic is valid, reliable and able to discriminate.

Ethical approval was granted from CSPPS ethics committee. Data was collected from 4 cohorts who had taken the test at CSPPS. Item analysis was carried out by measuring item difficulty and item discrimination. Reliability was measured by test-retest analysis and by measuring internal consistency using Cronbach's Alpha. Validity was measured by analysing written feedback and conducting interviews with first year students.

The distribution of overall scores was skewed to the right. This is desirable as the diagnostic aims to discriminate the weakest performers and therefore distribution needs to be widest amongst the lowest scores. Test-retest analysis found the diagnostic to decrease in reliability between years one and three. Internal consistency was 0.77, this is over the critical value of 0.7 [2], meaning the test is reliable. Interviews found items 4 and 8 to be ambiguous, therefore lacking validity and these are proposed for review.

Overall the diagnostic was found to be reliable, valid and able to discriminate. The items are difficult enough to produce the desired discrimination to fit the purpose of the diagnostic. All items are reliable. All items are valid except for 4 and 8, which are recommended for review.

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Validation of the 'FfraMedd': a framework for conducting patient consultations through the medium of Welsh

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The Medication-Related Consultation Framework (MRCF) is a framework designed to evaluate the consultation skills of pharmacists [1]. It is based on the Calgary-Cambridge model [2] but with more emphasis on medication issues. The MRCF was translated to Welsh and is known as the 'FfraMedd'. It is a support tool for pharmacists who wish to provide additional services for Welsh speaking patients [3]. The aim of this study was to determine if the 'FfraMedd' is fit for purpose in pharmacies in Wales.

Pharmacy undergraduates from Cardiff University along with pharmacists (plus one General Practitioner) from across Wales were asked to participate. Semi-structured interviews were conducted which were audio recorded. Practitioners either participated in one-to-one interviews or telephone interviews depending on their location. Students were also asked to complete a written feedback form before the interview to encourage them to review the 'FfraMedd'. The interviews were transcribed verbatim before two separate thematic analyses were performed.

Ten students plus eleven practitioners participated in the study (n=21). Similar themes emerged from both students and practitioners; however there were varying sub-themes and an additional theme appearing from the student data. Participants believe that the 'FfraMedd' is a vital support tool which encourages practitioners to conduct Welsh language consultations. Participants were pleased with the 'FfraMedd', however minor changes are required before the 'FfraMedd' is fit for purpose.

The minor changes required regard the length of the 'FfraMedd' and the translation of certain words. A shorter version of the 'FfraMedd' exists which may be more suitable for practitioners. Overall, the translation was easily understood. The participants believed that certain words were wrongly translated such as the word '*colli*' for missed doses. Practitioners were eager for more support tools in Welsh; therefore making the 'FfraMedd' available would only encourage more consultations through the medium of Welsh.

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Predicting the efficacy of local vs. systemic delivery of antibiotics for the treatment of respiratory tract infections

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The potential for local delivery of antibiotics by inhalation is of therapeutic interest as the respiratory tract has several favourable characteristics for local deposition, such as achieving higher drug concentrations [1]. With recent advances in device technology, new aerosol production systems allow for more effective delivery of pharmaceuticals into the respiratory tract [2]. The aim of this study was to use systemic dosing to predict the efficacy of local delivery of antibiotics to the respiratory tract, and consequently consider if current systemic antibiotics could be inhaled.

Primary data on plasma concentrations seen after systemic dosing of antibiotics used in the respiratory tract was gathered by performing an electronic article search. The results, along with various pharmacokinetic (PK) factors, were used to predict what inhaled daily dose would achieve the same concentration unbound of an antibiotic in the lung fluid. The predicted doses were then compared with reported doses of inhaled antibiotics to find correlations.

Thirty-five readings of plasma concentrations were obtained for twelve systemic drugs. Seventeen readings of plasma concentrations were obtained for four of these drugs following inhalation. The estimated inhaled daily doses were accurate for all four drugs. The method of predicting the inhaled daily dose was therefore effective. All four drugs shared certain pharmacological and PK properties: reasonable inhaled dose, high fraction unbound (Fu) and moderate half-life ($t_{1/2}$). Of the systemic antibiotics, Temafloxacin met all these PK targets, with a Fu of 0.75, $t_{1/2}$ of 8 hours, and predicted daily dose of 127-177 mg to achieve therapeutic concentrations.

The method of predicting the inhaled daily dose was proven to be effective. Temafloxacin met all the predetermined PK targets and was therefore identified as a viable candidate for local delivery via inhalation. Future work should focus on lung PK and bioequivalence studies for pharmacological and clinical benefits.

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ZIP7 and breast cancer: use of phosphorylated ZIP7 as a biomarker

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Zinc transporter ZIP7 (SLC39A7) is differentially expressed in anti-hormone resistant breast cancers [1]. ZIP7 mediates zinc release into the cytosol from intracellular compartments, leading to activation of tyrosine kinases which promote cellular proliferation, thus contributing to the aggressive nature seen in breast cancer cells [1,2]. ZIP7 is activated through phosphorylation by protein-kinase CK2 at $Ser^{275-276}$ residues [3]. This study evaluated whether an antibody which detects phosphorylated ZIP7 (pZIP7) could be used as a biomarker in anti-hormone resistant breast cancers. Downstream phosphorylation of MAPK and AKT was additionally investigated.

Wild-type MCF-7, tamoxifen-resistant (TamR), long-term tamoxifen-resistant (TamRL), Faslodex-resistant (FasR) and long-term Faslodex-resistant (FasRL) breast cancer cells were treated with or without exogenous zinc then probed with antibodies against pZIP7, ZIP7, pAKT and pMAPK by Western blot with data normalised to β-actin. Immunofluorescence was also carried out on the cells to determine pZIP7 activation.

Here TamR cells had the greatest ZIP7 activation along with 94% of cells positive for pZIP7, corresponding with a previous study [1]. TamR cells additionally demonstrated the greatest AKT and MAPK activation as anticipated. TamRL cells showed greater ZIP7 activation compared to MCF-7 cells but this was not as pronounced as TamR cells. FasR and FasRL cells showed similar activity to MCF-7 overall. Interestingly, FasRL cells displayed higher MAPK and AKT activation compared to FasR cells.

The present study implies a pZIP7 antibody would be a valuable biomarker in tamoxifen-resistant breast cancers along with the potential to be a good indicator of long-term tamoxifen-resistance. Although pZIP7 may not be as valuable in Faslodex-resistance, it may be a good marker of disease progression. Our findings bring us closer to a better understanding of mechanisms involved in anti-hormone resistance along with a possible clinical use of a ZIP transporter antibody in the detection of anti-hormone resistant breast cancer.

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Variability in delivered dose from collapsible infusion containers

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Infusion containers act as a reservoir for drug solution for infusions, usually containing at least 50ml liquid. Manufacturers provide different types of containers, which may behave differently. While it is usual for a small volume of liquid to be retained at the end of an infusion, there have been reports of significant volumes remaining in some Ecoflac® semi-rigid collapsible infusion containers (BBraun) [1]. Ecoflac® are available containing sodium chloride 0.9%, commonly used as a diluent, and prefilled with metronidazole solution. We investigated whether the total volume retained from the infusions was likely to be clinically significant, and possible reasons for the retention.

Containers and giving sets from finished infusions were collected from the wards and the date, time, ward, drug name and dose were recorded. The liquid in the giving set was extracted using a 60ml syringe, and the container was sliced open, drained and the fluid measured.

All containers tested retained some liquid. The average retention in the sodium chloride containers was 8.91ml, with approximately half (64/124) of the containers with >5ml retention. The greatest retention was seen for Tazocin solution, where the potential average under-dose of a 4g/500mg dose was 884mg/110.5mg (22.1%). For the metronidazole (pre-filled) containers the potential average under-dose was much less; 29.8mg of a 500mg dose (6.0%).

The study showed that there was a potential clinical problem with the retention of liquid and that there was a difference between the volume retained in the pre-filled containers and containers of sodium chloride with added drug.

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Pharmacists' views about intra- and inter-professional learning

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Traditional models of acute care are inadequate for today's prevalent chronic, multi-pathological health problems, requiring healthcare practitioners to work collaboratively together in providing seamless treatment across services. Inter and intra professional learning, two forms of collaborative learning designed to prepare individuals for collaborative practice, have become important areas for discussion and research. Inter-professional learning involving individuals from more than one profession, and intra-professional from specific disciplines within the same profession, learning together and about each other: the aim being to develop functional teams in order to improve patient outcomes. Information from those taking part in these learning initiatives informs education providers when making decisions on education practice.

This explorative study investigates pharmacists' perspectives on collaborative learning initiatives run by Cardiff University. Twelve semi-structured interviews were conducted with a purposive sample of twelve pharmacists. An interview guide was framed around topics of interest generated from a literature review and questions relevant to Kirkpatrick/Barr's education typology [1]. An iterative approach to data collection [2] allowed for emergent themes. All interviews were transcribed and analysed using a simple thematic analysis involving constant comparison [3].

Data highlighted the need for interaction to be guided through purposeful and planned integration for quality learning. The whole group benefitted when participants were like-minded in their goals, balanced to allow two-way learning and the heterogeneity of groups was acknowledged in terms of activities and topic choice. Courses had positive effects in relation to participants' confidence when interacting with healthcare practitioners. Participants felt that although wider organisational changes had not occurred, improved consultation skills had resulted in better patient-centred care [4].

Implications for practice and improvement are made around the need for collaborative learning opportunities to capitalise on the heterogeneity of learner groups, and the need for a variety of teaching approaches.

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SK2 channel is a promising target for blocking cancer cell proliferation

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Breast cancer is the most common type of cancer in women, current treatments, e.g. tamoxifen show problems with resistance and inefficiency against TNBC [1]. A renowned and established hallmark of cancer is limitless proliferation. Reported was a correlation between the cell cycle and V_m, cells with a high hyperpolarised potential showed little or no mitotic activity [2]. It is known that K^+ channels govern the resting potential; hence in this study we seek to investigate pharmacological modulation of SK channels and their potential role in controlling cell cycle progression. SK channel expression has been studied in neurons in controlling electrical excitability however, little is known about their expression in non-excitable cells [3]. This research aims to; (i) determine the presence of mRNA transcripts encoding SK channels in FasR cells, (ii) determine the presence of SK channel protein by western blotting (iii) investigate the effects of pharmacological modulation by specific SK modulators, NS8593, NS6180 and UCL1684. This project will determine the suitability of potential SK blockers as future perspective therapies in inhibiting breast cancer proliferation.

RT-PCR and microarray data were carried out to determine the presence of the message encoding SK1-4 channels. Furthermore a western blot was used to establish the presence of a functional channel protein. MTS cell proliferation assays were carried out using NS8593 and UCL1684 and NS6180 to determine effects of pharmacological blockade on SK channels and effects on cell growth

Microarray data and RT-PCR confirmed the presence of expression of SK2 and SK4 genes. Western blotting showed the functional expression of the SK2 channel. MTS proliferation assays revealed that NS8593 and UCL1684 induced cell inhibition.

In conclusion, the SK2 channel may be a potential target for inhibiting cell proliferation, however more selective blockers should be sought to block the target more efficiently and minimise off target binding.

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Can food affect adrenoceptor pharmacology in the gastrointestinal tract?

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Adrenoceptors are a super-family of G-protein coupled receptors expressed within tissue smooth muscle and at nerve terminals [1]. Stimulation of adrenoceptors initiates a range of effects in the gastrointestinal tract, including ileum smooth muscle relaxation [2-4]. The aim of the present study was to discover if food alters adrenoceptor pharmacology in the gastrointestinal tract.

Ileum extracted from fed and food restricted guinea-pigs were suspended in 50ml organ baths filled with Tyrode's solution. Histamine was used to induce ileum smooth muscle contraction before noradrenaline cumulative concentrations were added in the presence or absence of antagonists. The response produced by noradrenaline addition in fed and food restricted ileum experiments were compared to determine if food affected adrenoceptor pharmacology in the gastrointestinal tract.

ICI 118,551 (β_2-adrenoceptor antagonist) incubation produced a significant antagonist effect on the response to noradrenaline in fed ileum experiments but not in food restricted ileum experiments. Prazosin (α_1-adrenoceptor antagonist) incubation produced a significant antagonist effect on the response to noradrenaline in food restricted ileum experiments but not in fed ileum experiments. Yohimbine incubation (α_2-adrenoceptor antagonist) did not produce a significant antagonist effect on the response to noradrenaline in either fed or food restricted experiments.

From the results it can be concluded that β_2-adrenoceptors were responsible for ileum smooth muscle relaxation when food was present in the ileum, but not when food was absent from the ileum. Furthermore α_2-adrenoceptors were responsible for ileum smooth muscle relaxation when food was absent from the ileum, but not when food was present in the ileum. Therefore α_1- and β_2-adrenoceptor pharmacology is affected by food since their contribution to ileum smooth muscle relaxation varied according to the presence or absence of food.

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Molecular imprinting of prostaglandin E2 using 1-(4-vinylphenyl)-3-(3,5-bis(trifluoromethyl)phenyl)-urea

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Prostaglandin E2 (PGE2) is a lipid implicated in various conditions, for example inflammatory pain. Lipid analysis is challenging, due to the complexity and diversity of these biomolecules [1]. Sample clean-up is often essential in order to obtain clear, accurate analysis. It is hypothesised molecularly imprinted polymers (MIPs) could be used for selective sample extraction to improve reproducibility, sensitivity and reliability of analysis [2]. The aim of the project is to develop MIPs capable of selectively binding PGE2.

A urea monomer (1-(4-vinylphenyl)-3-(3,5-bis(trifluoromethyl)phenyl)-urea) [3] was selected to facilitate interaction with the carboxylate group of a tetrabutylammonum salt of PGE2 (PGE2-TBA). A NMR titration was performed to determine the affinity of the interaction. MIPs were subsequently synthesised using PGE2-TBA (0.011mmol), 1-(4-vinylphenyl)-3-(3,5-bis(trifluoromethyl)phenyl)-urea (0.011mmol), and ethyleneglycol dimethacrylate (0.22mmol). Polymerisation was initiated at 80°C using 1,1′-azobiscyclohexanecarbonitrile (1% w/w). Rebinding assays were performed to establish time to equilibrium and to generate isotherms to allow parameters such as MIP capacity and affinity to be established.

Interaction between the amidic protons of the monomer and the carboxylate group of PGE2 resulted in a maximum shift of 3.55ppm during the NMR titrations. This translated to an average Ka of 25,617 M^{-1}. The equilibrium assay demonstrated that all PGE2-TBA bound to the MIP within 5 minutes, with little non-specific binding observed. Although the MIP bound more than the control in the full rebinding assays, conventional isotherms could not be generated and therefore it was not possible to determine capacity and affinity data.

The urea monomer shows a strong association with the template and equilibrium studies have shown that the imprinted polymer demonstrates selective, efficient and rapid binding. These features are desirable and confirm the potential for molecular imprinted polymers as tools in lipidomics. The full rebinding results were somewhat disappointing and could be due to an inefficient washing protocol / incomplete template removal.

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Determining whether VGLL1 and GBP1 are associated with acquired endocrine resistance in breast cancer cells that lose oestrogen receptor (ER)

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Anti-hormones are effective breast cancer treatments; however 40% of patients acquire resistance [1]. Loss of oestrogen receptor (ER) is one cause of acquired endocrine resistance but signalling driving such disease is unknown. Cardiff University has developed novel models of acquired endocrine resistance. Preliminary Affymetrix arrays suggested VGLL1 and GBP1 are overexpressed in acquired resistant models which have lost ER. We aimed to further establish whether these genes are associated with ER loss and any associated aggression in acquired endocrine resistance.

Resistant models were previously derived from responsive MCF-7 and T47D cells cultured with anti-hormones for 2-3 years. RT-PCR was used to profile ER, VGLL1 and GBP1 expression. Modified Boyden chamber assays assessed cell migration. Bioinformatic tools used public clinical breast cancer transcriptomes to measure gene interdependence and related expression with survival outcome. Ontology sources were searched regarding gene function.

Three MCF-7-derived resistant models showed significant ER loss and increased migration. Significant ER loss was found in two T47D-derived models, with one showing substantially increased migration. VGLL1 and GBP1 expression was significantly increased in models which lost ER and were aggressive, but this was

more apparent in MCF-7-derived models. Bioinformatic analysis revealed weak inverse correlations between both genes and ER in untreated clinical disease, while higher intrinsic expression correlated with aggressive earlier relapse. Both were signalling genes contributing to multiple cancers, although GBP1 had reported stimulatory and anti-tumour properties.

Some association between ER loss and increased aggression was established in acquired resistance as in de novo ER-ve disease [2]. VGLL1 and GBP1 associated with ER loss and migration in acquired resistance but this was dependent on genotypic background. These findings were supported by bioinformatics and ontology suggesting both signalling genes related to ER negativity [3,4]. These associations could underpin discovery of therapeutic targets for resistance but confirmatory mechanistic studies are needed.

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A systematic review of health-related quality of life and patient preferences in patients with urinary stone disease

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Urinary stone disease is a common, painful and often recurrent condition that can affect kidney function, require surgical treatment and has significant impact on patients' health-related quality of life (HRQoL) [1]. There is limited information on the impact of stone disease or its treatment on patient's HRQoL and the preferences of patients of these treatment options. The primary outcome of current therapy is to achieve a high stone free rate (SFR). Improving patient's HRQoL is often a secondary gain [2]. The aim of this study is to examine the evidence from all studies including an element of HRQoL measurement and patient treatment preference in patients with this disease.

Ovid MEDLINE® 1946 to present, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, EMBASE 1947-Present, SCOPUS, EconLit and Web of Science 1900-2014 with no language restriction were searched. All study designs with adult participants were included. 2 independent authors individually assessed the studies and extracted the data. Narrative data synthesis was performed.

Nine abstracts and 28 full-text articles were assessed. 24 studies met the inclusion criteria (4 RCTs and 20 observational studies) from 10 countries, including 3591 patients.11 studies showed that stone formers had worse HRQoL than the general population or controls and 1 study showed stone formers were more likely to suffer with depression. Women have significant lower HRQoL than men. No studies showed better HRQoL scores in women. 18 studies used a generic HRQoL measure and 6 a disease-specific, none of which have been validated (one is in the process of validation). Studies with regard to patient preference were heterogeneous.

There is a need to shift the paradigm of treatment outcome for urinary stone disease from achieving high SFR to a more patient-centric view [3]. A well-constructed, validated, disease-specific outcome measure is required for urinary stone disease.

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What motivates fourth year pharmacy undergraduates in relation to their MPharm degree?

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Motivation is a complex concept which underlies the actions and behaviours of an individual. It is linked with academic performance with high levels of motivation producing positive academic outcomes [1]. The aims of this study were to identify some of the influences that motivate MPharm IV undergraduates and suggest ways for the school to facilitate motivation.

A qualitative investigation using semi-structured, face-to-face, audio recorded interviews with MPharm IV students was conducted. Ethical approval was granted and the study design, sampling and piloting were undertaken by collaboration between four student researchers and supervisor. A topic guide encompassing six topics relating to motivation was developed based on a literature review. Participant recruitment utilised purposive, convenience sampling looking for demographic difference. The transcripts from all four students were shared and were analysed independently using thematic analysis. A deductive approach implementing the self-determination theory (SDT) and a data driven inductive approach were both used as analytic approaches [2].

In total 24 students were interviewed (6 interviews per researcher). Students were motivated by internal and external stimuli demonstrating a consortium of motivation ranging from intrinsic, extrinsic to amotivation [3]. Interest in material, relevance to pharmacy, novelty and optimal challenges resulted in motivation, whilst a lack of relevance, enjoyment and assessment guidance undermined it. Student motivation was determined by three underlying empirical processes of autonomy, competence and relatedness in accordance with SDT [4].

Motivation is a complex concept with both heightening and undermining influences. It is rarely determined by a single aspect and it varies significantly in terms of where it arises from. Intrinsic motivation is observed when interest in a topic is present and this drives a self-determined motivation. Where no such interest is existent, external impetuses begin to govern motivation or a motivational deficit is observed.

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ZIP7 and breast cancer: use of phosphorylated ZIP7 as a biomarker

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Zinc is an essential trace element in humans and is required in over 300 enzymes [1]. ZIP7, a zinc transporter residing on the endoplasmic reticulum and essential for zinc release [2], is included in the top 10% of genes overexpressed in breast cancer with diminished prognosis [3]. Protein kinase CK2 phosphorylates serine residues (275 and 276) to activate ZIP7, causing zinc release. This ZIP7-mediated release of zinc leads to increased cell proliferation and migration as kinases and other downstream signalling pathways are activated [3]. As resistance to anti-hormones often develops as a result of current breast cancer treatments, such as tamoxifen and fulvestrant, new biomarkers of resistance need to be developed [4]. We hypothesised that the concentration of pZIP7 in cells is a good indicator of anti-hormone resistant breast cancer.

Using fluorescent microscopy and Western Blotting the activation of ZIP7 was examined in MCF-7, TamR (tamoxifen resistant), TamRL (long-term tamoxifen resistant), FasR (fulvestrant resistant) and FasRL (long-term fulvestrant resistant) cells. Separated by 10% SDS-PAGE, Western Blotting was used to probe samples for pZIP7$^{S275/276}$ to examine ZIP7 activation. Additionally, pAKT^{S473} and pMAPK$^{T202/Y204}$ measured the level of activation of downstream signalling pathways. Results were quantified by densitometry against β-actin.

TamR cells have a significantly increased activation of pZIP7 while TamRL cells have a lower activation showing how activation decreases over time. FasR and FasRL cells demonstrated lower levels of pZIP7

activation. Increased pZIP7 activation led to an increase in pAKT and pMAPK activation demonstrating the role of ZIP7 in downstream activation.

In TamR cells, pZIP7 is highly activated, consistent with increased expression observed by affymetrix analysis, highlighting the potential use of pZIP7 as a future biomarker. TamRL cells have less pZIP7 activation further emphasising its use as a biomarker and means to monitor the progression of the disease. This study demonstrates pZIP7 as a potential diagnostic marker leading to novel treatment and improved prognosis for patients.

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ZIP6 and breast cancer: role of post-translational modification

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Zinc is essential for human health and has to be tightly regulated. This can be achieved through zinc transporters, including ZIP6 (SLC39A6/LIV-1) [1]. ZIP6 is a potential biomarker of oestrogen-receptor positive breast cancers metastasising to regional lymph nodes [2]. ZIP6 is always present in small amounts suggesting that it may be highly regulated. A number of predicted ubiquitination sites [3] in the ZIP6 sequence have been observed allowing us to hypothesis that ZIP6 may be degraded by post-translational ubiquitination to regulate its level in cells. The project aims to compare whether removal of potential ubiquitination sites in ZIP6 can prevent removal of ZIP6 from cells.

We used MCF-7 cells transfected with ZIP6 and the different mutants in Western Blotting and Fluorescence microscopy. Samples were separated by 12% SDS-PAGE. Immunoreactive bands were visualized by chemiluminescence using West Femto reagent. For fluorescence, cells were probed with the V5 antibody to recognise the V5 tag on the recombinant proteins followed by AlexaFluor®488-conjugated secondary antibody.

Although Western Blot results show no statistical difference between wild-type ZIP6 to each of the mutants, the trends of the graphs show ZIP6 to be more abundant for the mutants, with K467A/K468A ubiquitin mutant having the highest expression of the protein. Fluorescence results confirmed this where K467A/K468A ubiquitin mutant demonstrated twice the amount of transfected cells positive for ZIP6 compared to wild-type ZIP6.

This data suggests the potential importance of the residues K467/K468 for ZIP6 degradation via the ubiquitination-proteosome pathway. Generally, the mutants did not show much difference from the wild-type which, may be due to the low transfection rate of ZIP6. Furthermore, since all mutants suggested some effect, cumulative mutation of all potential ubiquitination sites could be performed in the future to give a better effect [4]. In conclusion, our study provides some evidence that post-translational modification via ubiquitination plays a role in regulation of ZIP6 in cells.

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Cardiff University graduates' preparedness for pharmacy practice measured against learning outcomes for undergraduate pharmacy education in the UK: perceptions of employers and alumni

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The GPhC is the current regulator of pharmacist education and training in the UK [1], they provide learning outcomes which schools of pharmacies must ensure students have completed by graduation [2]. The GPhC offers accreditation to universities who fulfil the criteria set for training of pharmacists. Cardiff University is currently seeking accreditation [3]. This study aims to explore Cardiff University graduates' perceptions of preparedness for practice measures against the GPhC learning outcomes, which will also identify whether the learning outcomes are being met.

Ethical approval was granted for one-on-one interviews with Cardiff University School of Pharmacy graduates from 2013 currently in their pre-registration year. Opportunistic sampling was used to recruit participants by email and telephone. 14 interviews were conducted and recorded with consent. All interviews were transcribed (*ad verbatim*), coded and then analysed using thematic analysis. Six main themes were identified and explored.

Results of the interviews showed a good overall preparedness for practice. Areas were identified where graduates felt they were not adequately prepared for practice and areas where graduates were extremely well prepared for practice. The most common areas which graduates did not feel prepared for practice were topics which were taught theoretically rather than practically. Areas which were assessed and taught yearly led to graduates feeling extremely prepared in these areas namely CPDs and calculations.

Cardiff University provides students with the knowledge and skills needed for practice. More effort is needed to teach areas practically and not just theoretically. More placements throughout the degree in both hospital and community pharmacy would improve preparedness. There is a learning curve from university to pre-registration as with any transition. Suggestions for Cardiff University to improve graduate preparedness for practice were identified from the research.

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ZIP6 and breast cancer: the role of post-translational modification

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Zinc is vital for life and is involved in many cellular processes, thus regulation is crucial as too much is toxic to cells and too little kills cells. ZIP6 belongs to the LIV-1 subfamily of ZIP zinc transporters [1]. It has an established involvement in breast cancer [1] and plays a role in EMT, leading to cell migration [2]. ZIP6 undergoes N-terminal cleavage before moving to the plasma membrane [3] to influx zinc, however, post-translational modifications controlling its levels remain unexplored. ZIP6 is present in low levels leading to the hypothesis that it is degraded by ubiquitination. This study aimed to determine whether removing potential ubiquitin sites in ZIP6 prevents its degradation and whether some residues are more important than others.

MCF-7 cells were transfected with ZIP6 ubiquitin mutants (K456AK457A, K467AK468A and K472A) and compared to wild-type to determine the effects of the ubiquitination sites. Immunofluorescence examined changes in abundance of ZIP6 positive cells by probing for V5, a tag present on all recombinant proteins, while Western blotting, using ZIP6 E20 and ZIP6 Y3 antibodies, examined expression levels and size changes in the mutants.

The results revealed increased ZIP6 positive cells in the mutants, suggesting a role for those sites in ZIP6 degradation, with ZIP6 K467AK468A consistently having the greatest effect.

The ubiquitination sites, confirmed by mass spectroscopy [4], demonstrated a high level of evolutionary conservation suggesting their potential importance. Cells overexpressing ZIP6 mutants K456AK457A and K472A had a preventative effect on ZIP6 degradation, revealing increased ZIP6 levels in cells compared to wild-type. Cells overexpressing ZIP6 mutant K467AK468A however, achieved a ten-fold increase in band density by Western blotting compared to wild-type, suggesting these ubiquitin sites are of greatest importance in preventing ZIP6 degradation. However, as the results were not statistically significant, definitive conclusions cannot be drawn and further research is required to determine whether ZIP6 is degraded by ubiquitination.

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The frequency of antidepressant use in a South Wales cohort of Parkinson's disease and Benign Essential Tremor patients

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Since the initial account of Parkinson's disease (PD) its understanding has progressed to encompass non-motor symptoms (NMS) [1]. Recently, NMS have gained recognition in Benign Essential Tremor (BET) [1]. With a growing acceptance of NMS in the PD and BET disease process the need to further understand their aetiology and impact has been identified. Depression is the most frequent NMS [1,2]. To explore the association of depression in PD and BET the study aimed to establish antidepressant frequency and type in a South Wales cohort of patients.

A retrospective study design was applied. Subjects were PD and BET patients referred by clinicians at The University Hospital of Wales and The Princess of Wales Hospital between 2000 and 2010. Data was inputted into 'The Electronic Clinical Network Parkinson Disease and Related Disorders Database'. Depressed patients were identified based on antidepressant use, extracted and evaluated for the frequency and type of antidepressants used. Comparisons between the two groups were drawn using descriptive statistics. Ethics approval was obtained.

Overall, depression is more frequent in PD patients than BET patients. 37% (n=310) of PD patients and 26% (n=110) of BET patients used antidepressants. Further, PD patients used a greater variety of antidepressants. Antidepressant initiation was frequent over the entire disease course. Selective serotonin reuptake inhibitors (SSRIS) were most prescribed. Examining antidepressant management over the disease course revealed various possible outcomes. 13% (n=111) of PD patients and 4% (n=16) of BET patients exhibit depressive symptoms without current or past antidepressant use.

Overall, there is a spectrum of mild to moderate depression. Antidepressant prescribing reflects prescribing trends of the general population. Evaluating the safety and efficacy of antidepressants specifically for depression in PD and BET is recommended to aid in developing guidelines that will ensure optimal management over the disease course.

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Patient experience: satisfaction with their medicines' management during their hospital stay and satisfaction with information about their medicines provided on discharge from hospital

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Research into patient satisfaction has been conducted for many years and has been of great interest to the NHS [1] and it is regarded as being vital to improving services and providing better healthcare to patients [2]. Over the last 40 years, different hypotheses have been formulated to attempt to explain patient dissatisfaction and these hypotheses include demographics and health status [1,3]. The aim of this study was to determine the level of patient medication information satisfaction within the Aneurin Bevan University Health Board (ABUHB) and determine if any factors influence them.

After obtaining ethics approval, an anonymous two-part questionnaire was mailed to 400 patients who had been discharged between the 27th January 2014 and 14th February 2014 from The Royal Gwent Hospital, Newport or Neville Hall Hospital, Abergavenny. The questionnaire contained a validated tool [4] and sought quantitative responses about patient experiences plus optional explanatory qualitative responses. Responses were input into SPSS and Kruskal-Wallis and Mann-Whitney U tests were conducted as appropriate.

A questionnaire response rate of 34% was achieved. Overall satisfaction levels were high across the Health Board (94% satisfaction overall). Suggestions were made to improve pharmacy services and these mainly surrounded dosing schedules. Almost all patients (99%) felt that they were treated with dignity and respect whilst an in-patient. Furthermore few patients experienced problems with their medication. Information about a patient's medication was viewed to be sufficient for over half of the patients.

Satisfaction levels were high within the ABUHB and most patients felt that their experience had been positive, nevertheless it is hoped the findings can help the staff to further optimise patients' experiences in future.

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The impact of urological conditions on family members using FROM-16; comparison with the HRQoL impact of a urological condition on the patient using SF-36

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The impact of a patient's condition on a family member's quality of life is a widespread yet under-recognised phenomenon [1]. Research into family quality of life has only been conducted in specialities such as dermatology [2], oncology [3] and childhood illnesses [4]. The aim of this study was to assess the impact of urological conditions on family members using a generic family quality of life measuring instrument; the Family Reported Outcome Measure (FROM-16©), and compare this with the impact of urological conditions on patients' quality of life which was measured using a Short Form Health Survey (SF-36); a generic patient quality of life measuring tool.

The study was conducted in the Urology clinic at the University Hospital of Wales over a six week period. Patients were asked to complete the SF-36 (n=47) and family members completed the FROM-16© at two separate time points, 5 days apart (test 1 n=47; test 2 n=17). Test-retest reliability was assessed using Spearman's rank correlation coefficient.

The mean age of patient participants (male, n=35; female, n=12) was 65.58 years (SD=16.01) and the mean age of family member participants (male, n=12; female, n=35) was 63.02 years (SD=14.82). Weak to moderate correlations (-0.326 to -0.494) were seen between the emotional domain of the FROM-16© with

the physical functioning, bodily pain, general health, vitality, social functioning and mental health domains of the SF-36. Correlations were also seen between FROM-16© personal and social life domain with physical functioning, role-physical and role-emotional domains of the SF-36. Test-retest reliability of the FROM-16© was moderate (Spearman's rank correlation coefficient = 0.533, p=0.028).

The findings of the study have demonstrated that a correlation exists between urology patients' quality of life and their family members' quality of life. The test-retest indicates that the FROM-16© is reliable to be used on families of patients with urological conditions.

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The effects of exogenous administration of NO and NOx in myocardial ischaemia-reperfusion injury: a review of *in vivo* animal studies using a systematic approach

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Myocardial reperfusion injury (RI) occurs when abrupt reperfusion follows a period of myocardial ischaemia [1]. A clinical scenario would be when a patient presents with an acute myocardial infarction caused by occlusion of a coronary artery, and is treated to restore blood flow to the ischaemic tissue. Revascularisation can increase the degree of cardiac tissue injury, leading to a decline in cardiac function [2]. Studies in animal models have shown nitric oxide (NO) to reduce ischaemia/reperfusion injury [3]. The aim was to conduct a comprehensive review of the *in vivo* experimental literature on the role of NO donors in myocardial RI, using a systematic approach. We hypothesised that the administration of these compounds as adjuncts to reperfusion is cardioprotective. Objectives were set to comprehensively synthesise relevant experimental literature, assess articles against a set inclusion criteria and critically analyse the data for inclusion.

A thorough exploration of the current literature of experimental animal studies was conducted by performing searches of the Cochrane library, Medline, Embase, Web of Science and the Clinical Trials databases using set search terms. Articles were screened at title and subsequently abstract level using predefined inclusion criteria followed by full text critical analysis using a critical appraisal tool. 20 animal studies using NO donors (inhaled NO, nitroglycerin, sodium nitroprusside, sodium nitrite, peroxynitrite and novel donating agents) as adjuncts to reperfusion were included.

All NO donors except nitroglycerin afforded cardioprotection against RI, including reductions in infarct size, creatinine kinase concentrations, neutrophil accumulation and improved cardiac function. Sodium nitrite and peroxynitrite showed concentration dependant protection, which at higher doses proved detrimental.

NO donors reduce infarct size in experimental *in vivo* models of RI when given at physiological concentrations as an adjunctive therapy to reperfusion. Additional studies are needed to define the most appropriate agent, dose, route and timing of administration.

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Can food affect trace amine responses in the gastrointestinal tract?

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Tyramine, tryptamine, β-phenylethylamine (β-PEA) and octopamine are examples of trace amines (TAs). They are found endogenously at nanomolar concentrations [1]. They are also found in foods such as cheeses and chocolate. They have been described as false neurotransmitters and many of their effects are

indirectly mediated by the biogenic amines [2,3]. TAs have been identified to cause contraction of the ileum by activating trace amine-associated receptors [4]. They are known to produce effects after ingestion e.g. the cheese effect. Therefore the aim of this project was to identify whether TAs produce different effects on fed and food restricted ileum.

Isolated ileum (2cm) was suspended in an organ bath filled with Tyrode's solution that was kept at 37°C and aerated (95%O2, 5% CO2). In order to stimulate contraction the ileum was electrically stimulated (0.2Hz, 5ms pulse width, 10-20 V). Cumulative concentration-response curves (CCRCs) were constructed for all four TAs. CCRCs were also constructed for tyramine, β-PEA and tryptamine with the antagonists, atropine, mepyramine and ICI 118 551.

The results of the study were not statistically significant due to the study being underpowered. However, qualitatively it can be stated that tyramine did not cause an effect. β-PEA caused the opposite response in fed and food restricted ileum and Tryptamine and octopamine produced relaxation. Relaxation was produced by all three TAs in the presence of ICI 118 551 which was unexpected and implies that ICI 118 551 has an ability to antagonise receptors that cause contraction. Atropine and mepyramine inhibited all responses produced by tyramine and β-PEA, and did not affect the responses produced by tryptamine.

This study failed to show that TAs cause contraction as reported in the literature. At concentrations higher than that found endogenously they failed to produce significant responses which imply that targeting them as future treatments would not be of great benefit.

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Patient experience: satisfaction with their medicines management during their hospital stay and satisfaction with information about their medicines provided on discharge within University Hospital of Wales

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Patient satisfaction with medicines management and information provided has been found to increase compliance and adherence [1]. NHS standards [2] discuss the importance of patients receiving information in a timely and appropriate manner. This is important for a patient's treatment and can help prevent drug-related readmission [3]. It is clear that communication is important but little is known about patients' views so this study was designed with the aim of assessing satisfaction and experiences of patients at the University Hospital of Wales.

A research team comprised of University and Health Board staff designed a questionnaire incorporating (with permission) a validated audit tool; the Satisfaction with Information about Medicines Scale (SIMS), to assess satisfaction [4]. The School of Pharmacy and the hospital research and development department granted ethical approval. Questionnaires were sent to eligible patients over a four-week period. Returned questionnaire data was input into a database and analysed with SPSS using descriptive statistics, Mann Whitney U tests, Kruskal Wallis tests and Chi Square tests.

A total of 72 questionnaires were returned which is a response rate of 31%. As inpatients, 56% of patients came into contact with pharmacy staff, and 49% were able to discuss their medicines. The majority of patients (87%) reported no problems with their medicines, and 92% were either satisfied or very satisfied with this way their medicines were dealt with. The majority of patients received written (50%) or verbal (65%) information on discharge. The mean SIMS score was 10.5 out of 17 and a significant relationship between SIMS score and satisfaction with medicines management was found ($p=0.003$).

Although the findings were generally positive, there is still room for improvement. Ideally all patients should be very satisfied. Hospital staff can use the results to attain and maintain an even higher level of patient satisfaction.

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Does infusion container influence the amount of drug delivered by infusion?

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Anecdotal reports were received from a local NHS trust regarding incomplete emptying of Ecoflac® Plus 100ml containers during infusions. The aim of the study was to investigate why Ecoflac® Plus containers may undergo incomplete emptying and compare flow from a semi-rigid Ecoflac® Plus container against a fully collapsible Freeflex® bag.

Methods involved testing height, roller clamp control and additional volumes using a simple intravenous setup under gravity infusion. For height, both containers were hung from varying heights under wide open flow. For roller clamp control, both containers were hung from a fixed height with the roller clamp taped prior to infusion to prevent movement. For additional volumes, fluid from Ecoflac® Plus was delivered from 90cm controlled to an initial flow rate of 4ml/min, based on Tazocin® infusion guidelines [1]. 0ml, 20ml, 40ml, 60ml and 80ml additional liquid was added, with removal of an equivalent volume of air [2].

Increasing infusion height significantly increased flow rate of both containers. With Freeflex®, a 10cm increase in height gave a 10% increase in flow rate, whilst Ecoflac® Plus gave a 15.75% increase per 10cm height. Freeflex® controlled infusion time ran at 16mins 44secs, slower than the expected time (12mins 30secs). Ecoflac® Plus's average infusion time was recorded as 28mins 22 secs, 72% longer than the theoretical infusion time. Percentage volume remaining increased with volume added. For the control 8.5% of initial volume remained, increasing to 43.3% (78ml) in the 180ml container.

Freeflex® containers flow quicker than Ecoflac® Plus, but Ecoflac® Plus's flow is significantly smoother. The semi-rigid structure of Ecoflac® Plus is a limiting factor on flow rate delivered. Ecoflac® Plus containers show significant residual volumes with additional volumes above 20ml. B.Brauns' revised literature states a maximum addition volume of 40ml [3], raising concern that clinically significant under dosing of patients could occur.

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Can food affect muscarinic receptor pharmacology in the gastrointestinal tract?

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Muscarinic receptors throughout the gastrointestinal tract allow smooth muscle contraction. The M3 receptor is responsible for 75% of ileal smooth muscle contraction, with the remaining 25% due to the M2 receptor [1]. Relationships exist between gut muscarinic response and feeding through the hormone release from gastrointestinal cells [2], however no current knowledge exists to show the effect feeding has upon on muscarinic receptor pharmacology. The aim of the study is to assess the shift in concentration response curves (CRCs) seen through agonising the muscarinic receptor subtypes in the guinea pig ileum, when tissues from fed and food-restricted animals are compared.

The muscarinic agonist methacholine was used along with muscarinic antagonists pirenzepine dihydrochloride, (s)-(+)-dimethindene maleate, and zamifenacin fumarate. Cumulative CRCs were constructed with concentrations added in half log intervals. The EC50 value, antagonist shift and antagonist affinity were calculated. Two tailed, unpaired T-tests were used to assess statistical significance.

No statistically significant differences were seen between fed and food-restricted tissues. Qualitative differences show the methacholine CRC for fed tissue is positioned to the right of the CRC for food restricted

tissue, and a larger antagonist shift in food restricted tissue is induced by atropine. Finally the maximum contractile response did not significantly change within the two tissue types.

The qualitative differences could suggest a lower affinity within the fed tissue, and therefore receptor phosphorylation is present. A lack of difference in maximum contractile response shows no change in intracellular coupling [3]. In this study no results were statistically significant, suggesting that food has not been found to affect muscarinic receptor pharmacology within the guinea pig ileum in this particular study. This could be attributed to a low statistical power caused by the small differences seen between the two tissue types, the low n number used, and the large variability within the results.

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Investigations of modified release melatonin dosage forms

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Melatonin is an endogenous hormone mainly secreted by the pineal gland and it is involved in the regulation of the circadian rhythm of several biological functions [1]. Melatonin has been used as a hypnotic in treating patients with insomnia. Modified release formulation of the drug melatonin was investigated in this research project. The aim is to produce novel suppositories in a modified release pattern for rectal delivery.

A fatty base, Witepsol S55 and hydrophilic base, glycerol suppository base were used respectively for extemporaneous preparation of melatonin suppositories. In vitro drug release of suppositories and three different commercial oral tablets was studied. Paddle method was used, with a stirring speed of 50 rpm at 37℃ ±0.5℃ in 400mL of pH 7.4, phosphate buffered saline. Samples were collected at appropriate intervals and the concentration of melatonin was assayed spectrophotometrically at 278nm. Dissolution profiles of the suppositories were compared against that of the different formulated tablets. Time required for 50% release of melatonin and half-life of different formulation were calculated and analysed statistically.

The suppositories prepared by Witepsol S55 did not completely melt at 37℃ and only deformed. The results demonstrated that only 60% of total drug dose was liberated from the suppositories. Whereas, the suppositories prepared by glycerol base have fully dissolved in the medium and released the drug. The results also showed the release behaviours of the three different formulated tablets were corresponded to what they have been claimed on their product labels.

The dissolution method, test conditions, preparation of suppositories and assay method were discussed and evaluated. Complete melting of lipophilic base was found to be essential for total release of drug. Witepsol S55 appeared to be a potential suppository base for producing modified release melatonin suppositories for rectal delivery, but further investigation is needed to ensure its suitability.

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Involvement of canonical Wnt signalling in Alzheimer's disease

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An accumulation of amyloid-beta (Aβ), cleaved from amyloid precursor protein (APP), is thought to drive the neuropathology observed in Alzheimer's disease (AD) [1]. Canonical Wnt signalling is highly involved in neuronal development and synaptic plasticity [2], and may be dysregulated by Aβ toxicity. Whether the pathway is up- or down-regulated in AD is currently unknown [3]. This study explored whether levels of key canonical Wnt proteins are altered in the London APP(V717I) murine model of AD. London APP(V717I) mutation mice overexpress APP, demonstrating progressive accumulation of Aβ with age [4].

Western blotting analysis determined levels of canonical Wnt signalling proteins β-catenin and GSK3β in right cortex samples from transgenic (Tg) and wild type (Wt) mice. Comparisons were made between age-

matched Tg and Wt mice of ages 3, 9 and 18 months. In addition, changes to protein levels with age were explored.

Levels of APP were significantly increased in 9 month and 18 month old Tg mice compared to age-matched Wt mice. β-catenin levels were significantly reduced in 9 month and 18 month old Tg mice compared to age-matched Wt mice. The effect of ageing on the reduction of β-catenin levels was observed earlier in Tg mice compared to Wt mice. A significant reduction in GSK3β levels was observed in Tg mice with age (9 months vs. 3 months).

The age-dependent reduction in levels of β-catenin implies decreased Wnt signalling output, which appears to be enhanced in Tg mice by Aβ pathology. However, reduced levels of GSK3β in 9 month Tg mice suggest the opposite, correlating to increased Wnt signalling output. This study demonstrates that canonical Wnt signalling is altered by Aβ pathology and with age, however further investigation is warranted to elucidate whether the canonical Wnt pathway is up- or down-regulated in AD.

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Molecular modelling studies on CHKV nsP3 as a possible antiviral target

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Chikungunya fever has influenza-like symptoms caused by Chikungunya Virus (CHKV). CHKV is a genus of *Alphavirus* and transmitted via *Aedes* mosquito. It was first described during an outbreak in southern Tanzania, in 1952. It caused epidemic in tropical and subtropical regions. In 2006, one third of La Réunion Island's population was infected and 237 people died during that CHKV outbreak [1]. It is self-limiting but medical attentions is usually required. However, until now no specific drugs and vaccines and treatment remains symptomatic. Four non-structural proteins (nsP1-4) were reported. NsP3 has been reported to involve in the transcription process at an early stage of the infection [2,3]. The first 160 residue of nsP3 N-terminal macro domain were crystallised. Two crystal structures, 3GPG and 3GPQ were used in this project [4].

Virtual screening was used to filter down the SPECS database. Followed by, using Glide docking score, binding pose and visual inspection. 10 compounds were selected for each crystal structure. Compound 1 was the only compound got selected for both crystal structure. After that, molecular dynamics stimulations were used to study the behaviour of the compound with the crystal structure over time.

Compound 1 had a good Glide docking score, fulfil Lipinski's rule of 5 and did not has chiral centre. The ester of compound 1 was mutated to amide, compound 20 to increase the interaction with the protein residues. The trajectories of molecular dynamics stimulations showed the compound 1 had a good interaction with 3GPQ but not 3GPG and *vice versa* for compound 20. The results were supported by the binding free energy of compound 1 and 20 with correspond crystal structure. The different position of the Arg144 caused these results.

This study has demonstrated a potential to identify inhibitors for N-terminal macro domain of nsP3. Compound 1 and compound 20 had a completely different response with both crystal structure. Nevertheless, biological testing and crystallising is required for biochemical, ligand-protein interaction and structural analysis.

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The transurothelial permeability and bladder wall distribution of oxybutynin chloride in an *ex vivo* porcine model

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Oxybutynin is the most commonly used anticholinergic drug for the treatment of the overactive bladder [1]. Intravesical instillation of oxybutynin is an effective alternative to systemic treatment with minimal adverse effects [2]. The mechanism of action of anticholinergic drugs has recently been reviewed; it is proposed that anticholinergics act on bladder mucosal muscarinic receptors to modulate afferent signalling [3]. The exact location of where this occurs is unknown, thus we aimed to quantify concentrations of oxybutynin achieved in the layers of the bladder wall after local application in an *ex vivo* porcine model.

Whole pigs' bladders freshly excised from the animal were used for instillation of drug solution. Tissue samples were serially sectioned by a cryostat and drug quantities analysed using HPLC-MS after chemical extraction. Franz-type diffusion cells were used to investigate drug permeation across the bladder urothelium. Histology of tissues pre and post-treatment with oxybutynin was also performed.

Intravesical instillation of oxybutynin after 60 minutes resulted in highest drug concentrations in the urothelium and declined through the lamina propria and detrusor. Dilution with urine greatly reduced drug quantities achieved in all bladder layers investigated. No histologic alterations of the bladder mucosa were observed.

These drug delivery studies add more weight to the growing argument that antimuscarincs exert their effects on the bladder wall through mechanisms other than direct detrusor inhibition.

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MMP expression and activation in breast cancer subtypes

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Metastasis is a major cause of death in breast cancer. Matrix metalloproteinases (MMPs) are zinc-dependant endopeptidases implicated in the invasion and metastasis of cancer through the degradation of the extracellular matrix [1]. Overexpression of the gelatinases (MMP-2 and MMP-9) has been found to correlate with increased tumour invasiveness in breast cancer [2,3]. The aim of this study was to test the hypothesis that the gelatinases are associated with poorer prognostic subtypes of breast cancer and therefore, may represent a suitable therapeutic target in these cases to prevent further metastatic spread.

MMP-2, MMP-9 and Urokinase Plasminogen Activator (uPA) were evaluated against a panel of four breast cancer cell lines: MCF7 (ER+), BT474 (ER+ and HER2+), SKBr3 (HER2+) and MDA-231 (ER-, PR- and HER2-). Reverse-Transcription Polymerase Chain Reaction (RT-PCR) and gel zymography were performed to analyse the mRNA and protein expression of the gelatinases whereas the enzymatic activity of urokinase was screened using an uPA assay.

In summary, the four cell models expressed varying levels of gelatinases, Strong expression of MMP-2 and MMP-9 mRNA was identified in the SKBr3 cells, whilst low protein activity was detected in the same cells. In contrast, high MMP-9 protein expression was found in the MCF7 cells. Additionally, MDA-231 cells demonstrated strong uPA activity.

It is concluded that there is no definitive relationship between gelatinase activity and aggressive breast cancer subtypes. As the data suggest a role for MMP-2 and MMP-9 in HER2+ breast cancer, this observation may be significant in the development of novel MMP-2 and MMP-9 inhibitors for HER2-mediated metastasis. In addition, serum levels of uPA may be a prognostic marker for Triple Negative Breast Cancer (TNBC). Further studies are warranted to evaluate the regulatory mechanisms underlying the activation of these gelatinases and their implications in breast cancer progression to aid the development of successful MMP-targeted therapies.

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Community pharmacist's information needs when completing a Discharge Medicine Review, for a patient when they are discharged from hospital

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Discharge from hospital presents as the time where there is the greatest potential risk for the breakdown in the continuity of care for the patient. In Wales a Discharge Medicine Review [1] service has been established where community pharmacists review a patient's medicines on discharge. There has been debate on whether patient's Discharge Advice Letter (DAL) should be provided to community pharmacists. NHS Wales Informatics Service and Cardiff University wanted to identify whether all information on a DAL is required. The aim of this project was to identify the information required by community pharmacists to complete a Discharge Medicines Review for a patient recently discharged from hospital

A questionnaire was developed using the Royal Pharmaceutical Society (RPS) [2] and Royal College of Physicians (RCP) [3] guidance on the content of Discharge Advice Letters. Following a pilot, a copy was sent to all 709 registered pharmacies in Wales, along with a cover letter and a pre-paid envelope. Participants were invited to complete the hard copy or the online version.

A 54.0% response rate was achieved. 269 participants stated they wanted to receive a DAL when patients are discharged from hospital. Preference of delivery of information was split between electronic means and fax. 74.3% wanted to receive information within 48 hours of discharge. Participants' views reinforced the recommendations by the RPS and RCP for the essential content of information in letters. Thematic analysis highlighted patient eligibility and service awareness as additional areas of requirement. Lack of communication and documentation of medication information, and compliance aids patients were mainly linked to medicine-related incidents.

Deficiencies in these practices lead to patient harm and this study identifies suggestions for improvement. It can be used to support the case for the implementation of access for community pharmacists to patients' health care records to improve patient safety and continuity of care.

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Exploring the Welsh sponge *Halichondria panicea* as a source of novel compounds for antibacterial treatment

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Antibacterial resistance is becoming a major health concern [1,2]. It is further aggravated by the uncontrolled and improper use of antibiotics [2]. There is an urgent demand for new antibiotics to combat this issue. Marine sponges provide rich resources for structurally novel compounds, many of which exhibited a wide array of bioactivities [3,4]. The aim of the study was to investigate antibacterial activity of natural compounds isolated from *Halichondria panicea* collected from the Welsh coast.

Halichondria panicea was extracted with solvents of increasing polarity. The compounds in each extract were isolated using analytical TLC and screened for inhibitory activity against *Staphylococcus aureus* and *Escherichia coli* by TLC-direct bioautographic method. The active compounds were then purified using preparative TLC. Preliminary identification of the active components was conducted by low-resolution mass spectrometry and followed by high-resolution mass spectrometry.

Among the three extracts, hexane extracts showed the most successful extraction profile. A total of 12 fractions were obtained from hexane extracts and only two fractions that exhibited the highest antibacterial activity against *S. aureus* were selected for further investigation. No inhibition against *E. coli* was observed. The high-resolution MS spectrum revealed three principal peaks with majority of their empirical formulae did not match any of the literature values or contaminants and therefore, suggested to be novel. One of the compounds was identified as a purine derivative.

The poor yield of acetone extracts and no good separation of compounds in methanol extracts in addition to the negative inhibition against the bacteria have resulted in further analysis of hexane extracts only. No inhibition against *E. coli* suggested that the antibacterial properties of the fractions were less active towards Gram-negative bacteria. Purine compounds are commonly found in marine sponges. Based on the findings, *Halichondria panicea* is a potential source of research on novel compounds for antibacterial treatment.

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Design and synthesis of novel inhibitors of Coxsackie viruses

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Coxsackie viruses account for 16.4% to 24.3% out of the yearly 10 million symptomatic Enteroviral infections [1]. Coxsackie virus B3 can cause life threatening diseases such as pancreatitis and myocarditis [2,3]. A novel non-nucleoside inhibitor, GPC-N114, has been discovered which competes with the RNA primer template primer for the active site of the Coxsackie virus 3D polymerase blocking the replication of the viral genus. Its binding in turn stops the elongation of the RNA. Due to the high lipophilicity of the molecule, the aim of the project is to design novel analogues of GPC-N114 with a better solubility and, ideally, improved activity.

Three main modifications of the lead compound were carried out. Validation of the compounds were undertaken by flexible alignment and docking procedures to observe the binding within the pocket and determine their total energy strain compared to the lead compound. The synthesis involved a one-step nucleophilic substitution reaction to form sulphonamido and amido derivatives. Fischer esterification reaction was used to produce ethyl ester functional groups.

Flexible alignment showed that the compounds had a good total energy strain which demonstrated good alignment. The docking readings showed that the compounds maintained the same essential binding interaction with the amino acids of the 3D polymerase as the lead compound. In total twenty-six designed compounds were successfully synthesised with acceptable yields.

To conclude, modifications to the linker group and lateral functional groups showed an improvement in overall binding compared to the lead compound. The yields of the compounds depend on their structure and also their polarity. Biological evaluation is ongoing with single-cycle assay and multicycle CPE-reduction assay in BGM cells. It is hoped that these results will lead to further research into novel non-nucleoside inhibitors of Coxsackie virus 3D polymerase and possibly other Enteroviruses.

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Study of the dopaminergic pharmacology of the guinea pig ileum

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Dopamine receptors, D_1-D_5, are found throughout the entire GI tract [1] with evidence suggesting varied distribution of receptors between different regions [2]. The role of dopamine and its receptors is unclear but there is a potential for neuronal adaptations to occur with food withdrawal [3] and links between dopamine and GI disorders [4]. The aim of this study was to determine a difference in the dopamine pharmacology of the proximal and distal guinea pig ileum and the effects of food restriction.

Two identical 50ml capacity (overflow system) organ baths were used and average dose-response curves of each individual agonist recorded for each tissue type. The tissues were also incubated for 30 minutes with a specific antagonist before the agonist was re-tested. Acetyl-β-methylcholine was used to test tissue sensitivity and all responses were standardised as a percentage of this control. Student paired and unpaired t-tests were used for analysis.

Proximal food restricted tissue was less sensitive to apomorphine (non-selective dopamine agonist) and bromocriptine (D_2 and D_3 agonist) but more sensitive to SKF 38393 (D_1 and D_5 agonist). Distal food restricted tissue was less sensitive to bromocriptine but more sensitive to apomorphine and SKF 38393. The overall responses of proximal free food and food restricted tissue were reduced in the presence of the antagonists. Distal free food produced an increased response in the presence of raclopride (D_2 antagonist) and distal food restricted tissue produced an increased SKF 38393 response in the presence of SCH 23390 (D_1 and D_5 antagonist). The difference between proximal and distal tissue response to bromocriptine gave a p value of 0.002 whilst all other p values were > 0.05.

The different sensitivities seen between the tissues suggest a change in receptor composition when food is restricted with variations found between the different regions of the ileum. However, the lack of statistical significance indicates more work is needed to establish a true difference between the tissues and further understand the role of dopamine in the gut.

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ABM Health Board patient experience: satisfaction with their medicines management during hospital stay and satisfaction with medicine information provision on discharge

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Patients discharged from hospitals can be vulnerable and susceptible to readmission due to complications, adverse drug reactions or medical errors. It is estimated that between 3-11% of patients are readmitted within the first 28 days after being discharged [1]. It is essential patients are given appropriate information regarding their medications during their stay in hospital and at discharge. Our aim was to assess patient satisfaction regarding their experiences with medicines and information provision while in hospital and at discharge.

A bilingual questionnaire was designed which assessed patient satisfaction and included the SIMS tool [2]. Patients were selected based on specific selection criteria. Patient discharge forms were studied and their information was entered into a database. Questionnaires were coded and packed with a cover letter which was mailed to each patient. 396 questionnaires were sent. SPSS was used to record and analyse returned questionnaires.

119 questionnaires were returned. Mean age of responding participants was 64.5 years. Mean number of medicines taken was 7.16. 83.2% of participants stated that they were in contact with pharmacy staff while only 62.2% specified that they had a chance to discuss their medicines. 78.2% did not experience any medical issues. 56.3% were very satisfied and 36% were satisfied with the management of their medicines. Overall participant satisfaction is highlighted with a mean SIMS score of 10.06 out of 17.

It is encouraging that very few participants had a negative experience whilst in hospital. Most were satisfied with their care. However, there is room for further improvement. Pharmacists can introduce themselves to patients and ensure they have no medical issues. Direct interviews can also be considered for more personal and detailed insight [3]. Further research using adaptations of this questionnaire and the SIMS tool can be used to establish a standard in assessing patient satisfaction with pharmacy services.

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Investigating the relationship between drug polar surface area and skin penetration of topical medications

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In recent years, predicting the efficacy of drug candidates has become the main approach of many researchers over trial and error. This is where polar surface area (PSA) become an attractive descriptor to pharmaceutical companies in recent years. Literatures have shown Literatures have shown that consideration of PSA contributes in improving cellular potency, intestinal absorption [1], oral absorption, bioavailability, blood-brain barrier permeation and restriction to the peripheral circulation. The overall aims of this project are to investigate whether such a correlation can also be observed between polar surface area and skin penetration ability of topical medications.

A quantitative meta-analysis approach was applied where loads of journals were being looked at and analysed for datasets containing skin penetration data for topical medications. Due to the complexity and the need of special software packages in order to calculate the classic PSA, the method proposed by Ertl et al. (topographical PSA) [2] was used in this study. This method did away with the need of generation of 3D geometries, and hence it is a much faster calculation method but with a comparable quality. Three different software packages were used for calculation of TPSA: ChemDraw, Molinspiration and MarvinSketch. Scattered graphs were then plotted with Microsoft Excel 2013 and equations and R^2 values were analysed.

A total of twenty eight datasets were analysed. A wide range and generally low R^2 values were observed. Results from some datasets were categorised as poor studies due to insufficient data and the fact that TPSA is not affected by altering non-polar side chains and molecular sizes.

In conclusion, this research proved that there is no good correlation between PSA and skin penetration ability of topical medications. The wide range and inconsistent R^2 values produced shows that using TPSA as a predictive tool in this area is unlikely. Furthermore, the difficulty in finding datasets with enough structural variety suggests that this method is not fruitful for pharmacophore optimisation.

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Understanding intra- and inter-individual differences in capsule puncture following actuation of a Dry Powder Inhaler

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Hard-shell capsules are used as containers for powdered drug for use in single dose Dry Powder Inhalers (DPIs) [1]. Capsules are punctured by the DPI, creating openings to allow powder release upon inhalation. [2,3] Hard-shell capsules are made from gelatin or hypromellose [2]. Previous studies show that moisture loss affects the puncturing properties of gelatin capsules [1]. There has been little investigation into the puncture of gelatin and hypromellose capsules by a single dose DPI in the hands of patients. This study aimed to investigate intra/inter-individual differences in capsule puncture following actuation of a single dose DPI by a user.

Gelatin and hypromellose capsules were stored in two different conditions; to maintain their moisture contents within their standard specified range (13-16% and 4.5-6.5% respectively) [2] and below this range. Participants (n=34) were recruited, to puncture 3 of both types of capsule (gelatin and hypromellose), each stored in two different conditions (standard and below standard moisture content) using a DPI. Capsules were analysed using light microscopy and punctures were characterised by size, shape, zone, and presence of flap, using a newly developed methodology.

The coefficient of variation in puncture size was greater in gelatin capsules with lower moisture content (33.96%) than both types of hypromellose capsules and gelatin capsules with standard moisture content (12.05-16.27%). Mean puncture size was significantly smaller in gelatin with lower moisture content than hypromellose with lower moisture content (Mann-Whitney U, $p=0.005$).

The punctures formed by DPI users were reproducible for hypromellose capsules, irrespective of moisture content. Lower moisture content reduced the consistency of the DPI punctures in gelatin capsules. Capsules can lose moisture during storage [2], therefore appropriate storage is important to ensure reproducible patient puncture of gelatin capsules by a DPI. Further studies are required to investigate the effect of puncture size on powder release from capsules.

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Developing a novel solid phase extraction method for the isolation of natural products

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With recent decline in drug development, industrial focus is reverting back to biological sources for the identification of new chemical entities. Marine sponges are hugely unexploited and increasingly acknowledged for their pharmaceutical potential. Sponges' sedentary nature has resulted in evolutionary development of extensive chemical defence mechanisms enabling the synthesis of biologically active and structurally diverse compounds [1]. Limitations in efficient isolation strategies exist and innovative approaches are required [2]. The focus of this project is to develop a novel solid phase extraction method to isolate marine sponge compounds based on covalent bonding mechanisms carried out by chemoselective electrophilic resins.

Two sponge species (*Aplysina aerophoba* and *Halichondria panicea*) were prepared for exposure to an isothiocyanate coated polymer, which targeted nucleophilic functional groups of compounds within crude extracts. Polymer bound compounds were subject to traceless cleavage conditions and collected for further investigation. Method development was driven by review of thin layer chromatography and mass spectrometry. Additional antibacterial activity of isolated compounds was investigated.

Method development proved successful. The most optimised extraction procedure resulted in a di-brominated compound in sufficient quantity and purity for further analysis. High-resolution MS confirmed findings, and de-replication strategies suggest a novel compound has been isolated. Additional testing of

antibacterial activity was also positive. Considerable contamination and difficulties in obtaining sufficient purity and yields proved difficult to over-come. However, mixtures of compounds were successfully isolated in various quantities, with a range of molecular weights.

Initial hypothesis focused on the probable isolation of low molecular weight compounds which could act as precursors in fragment based drug design, but deviation of hypothesis occurred as larger drug-like molecules were isolated. Successful isolation of marine sponge compounds was proven. This research highlights the potential of a functional-group targeted approach and provides sufficient evidence for the continual investigation of this novel solid phase extraction method.

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Evaluation of recent molecular and target-based trends in approved cancer drugs

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Natural and synthetic products had both contribute different scope to overall drug discovery and development process. However, it was believe that there is a substitution of synthetic products to replace natural products and its derivatives in drug discovery. Hence, my project was aim to critically evaluate the recent molecular and target-based trend in approved cancer drugs and identify the similar chemical motifs in each cancer drugs.

A list of approved cancer drugs between 2009 to 2014 was identified from FDA and drugs were categorized into small molecules (180g/mol MW) vs. biologics (150,000 g/mol MW)), old drugs vs. new drugs, and the origin of each approved cancer drugs [1]. Old drugs are drugs that approved previously by FDA >5 years. A montage structure was generate using ACD/Chemsketch and sorted by year of approval. Tables and figures are used to further illustrate the drug classes, indication, and chemical motifs to improve understanding of researchers and readers.

According to my research, the amount of small molecules drugs approved was almost twice the amount of biologics approved by FDA. Besides, there are total 37 small molecule drugs that were approved by the FDA and 14 of them were old drugs. Out of these 37 small molecule drugs, protein kinase inhibitors had occupied 57%, followed by 8% of androgen receptor antagonists. Interestingly, out of the 57% of protein kinase inhibitor, 32% were VEGFR kinase inhibitor, followed by 18% of Bcr-ABL kinase inhibitor and EGFR kinase inhibitor.

Despite the fact that synthetic products stands the majority of approved cancer drugs, natural products and its derivatives have actually occupied 44% of total approval and some of the synthetic compounds structure were actually inspired by natural products. Therefore, this fall into the grey area that cause undervalue of natural products and its derivatives in drug discovery. Hence, natural products still serve as a novel foundation of anticancer drug discovery and development.

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Does the TRPM7 channel play a significant role in breast cancer cell proliferation?

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The TRPM7 channel is a member of the TRP superfamily, specifically the TRPM sub-family. There are hints that these channels have a role in governing cancer progression and survival [1], however little is known about their precise role in cell proliferation. The aim of this research is to assess the role the TRPM7 plays in breast cancer cell proliferation; this is achieved by confirming that the cells possess the relevant mRNA for the TRPM7 channel, ensuring they express the protein channel and establishing growth assays to determine if inhibition of the channel affects proliferation.

RT-PCR was conducted to confirm that the relevant mRNA is expressed in FasR cells; RNA was extracted, then transcribed to form cDNA, which was amplified using primers. Ethidium bromide gels were run to confirm the product size of the desired gene. This was quantified by consulting the Affymetrix database. Protein extraction was also conducted, and using TRPM7 antibodies Western Blotting was undertaken to assess expression of the channel protein. An MTS fluorometric cell proliferation assay was used to assess cell viability using a control and treatment with NS8593, a TRPM7 channel blocker [2].

RT-PCR showed that the TRPM7 channel mRNA was expressed in this cell line, this being confirmed by the Affymetrix results. Western Blotting also confirmed that the channel protein for TRPM7 was expressed. MTS assay demonstrated that 10μM and 30μM NS8593 produced a significant decrease in cell number after 3 days.

Intriguingly, results show that the TRPM7 channel does play a significant role in breast cancer cell proliferation in FasR cells, as blocking of the channel causes a significant reduction in cell numbers. Future work must focus on the specific role of this channel in cancer cell growth with a view to assessing its target value for prospective development of new anti-cancer agents.

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The general public's view about patient registration with a community pharmacy

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Patient registration can be described as the process by which new patients register their personal information at a healthcare practice which is used to either update or generate clinical health records [1]. In community pharmacy it has been implemented in two services, the minor ailments service (MAS) and chronic medication service (CMS). A review of the Scottish NHS pharmaceutical care in 2013 envisioned person centred care upheld by a patient registration system [2]. As a new concept to the profession there is limited information available to how this could be employed to a wider scale. The aim of this study was to explore the general public's view on registering with a community pharmacy.

A total of twelve participants engaged in one-to-one audio recorded interviews. A semi-structured interview schedule divided into four sections was used to explore the views on the community pharmacy, registration with them and views on a proposed patient registration model involving the use of patient health records. Interviews were transcribed verbatim and thematic analysis applied to analyse the data which derived four main themes: 1) The community pharmacy, 2) Views on the community pharmacist, 3) General understanding of 'patient registration, 4) Views about registering with community pharmacy. Feedback on proposed model was categorised into themes.

There was overall support for registering with community pharmacy. One finding suggested patient registration could be used to provide a service for the management of minor illnesses as pharmacists were recognised as suitably trained and accessible for this role.

These initial findings support the Welsh minor ailments service using a registration system currently being piloted and can be further implemented to the design of large scale study via a questionnaire However further qualitative research with a larger sample size would be beneficial to obtain more representative views of the general public.

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Early experience with paliperidone: a novel, long-acting antipsychotic injection

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Schizophrenia is a neurodevelopmental disorder, characterized by symptoms including delusions, hallucinations, grossly disorganized behaviour, catatonic behaviour and negative symptoms. It is managed by a variety of medications, including atypical antipsychotics such as risperidone and paliperidone. Paliperidone, also known as 9-hydroxyrisperidone, is one of the active metabolites of risperidone [1]. The main aim of the study was to assess the effectiveness of paliperidone long-acting injection (PLAI) in the treatment of schizophrenia over its first year of use, by establishing characteristics associated with continuation or discontinuation of treatment.

The records of PLAI dispensed from Whitchurch Hospital Pharmacy were used to identify patients who had received treatment. A naturalistic, retrospective case note review was then conducted in a six week period by use of the P.A.R.I.S system. A data collection tool was designed based on previous studies and used to obtain information on PLAI use 12 months prior to initiation up until present day [2,3].

Out of a total of 28 patients, six (21.4%) discontinued treatment due to side effects (P=0.0237), the most prevalent being insomnia. Five patients who discontinued treatment had previously been treated with clozapine (83.3%), an indicator of treatment resistance (P<0.0001).(4)

Factors that contributed to treatment continuation included licensed use (i.e. in schizophrenia or schizoaffective disorder) and those who were not treatment resistant. The presence of side effects suggested a stronger likelihood that treatment would be discontinued. Further investigations, with a larger sample, are needed in order to evaluate the time spent as an inpatient with PLAI use.

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Using meta-analysis to shed some light on the imprinting of proteins

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Molecular imprinting is the process that is used to create artificial receptors by forming an interlinked polymer around a template. Essentially the polymer is a snapshot of the interactions between the various monomers and cross linkers and the template at the moment of polymerisation. This has led to a great deal of research into their use in sensors and as separation media. The aim of this study is to use meta-analytical processes to evaluate the current state of protein molecular imprinted polymers utilising the ever increasing number of published articles, isolate trends in the field of work to inform on future research.

The research papers that have been selected and analysed in this study were derived from a broad literature search of the Imprints dBase. Where useful rebinding data was recoverable from the paper, it was converted into the form of µM concentration in free solution against nmoles/mg bound.

Of the initial sample, 83 papers in size, 30 papers were found to contain useable data for comparison, allowing accurate K_d and B_{max} values to be calculated. It was observed that the proteins most commonly imprinted were lysozyme, bovine serum albumin and haemoglobin.

It is seen that differing molecular weight of proteins does not impact on the ability to create an imprint of the protein. Polymers that have been constructed using dopamine as the monomer make them suited for sensor usage. The reporting of protein polymers on the whole is poor. This lack of available data has hampered this study's ability to come to conclusions about trends in imprinting. It is problematic that such similar polymers seen in this study generate such contrasting isotherms. The lack of reproducibility between researchers implies that the field of protein imprinting is still in its early phases which further work and publication may improve upon.

Development and evaluation of a computer-assisted learning (CAL) package on hepatitis C

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Computer Assisted Learning (CAL) is an effective and supplementary learning aid which provides an interactive learning environment [1]. In addition CAL can also be useful for healthcare professionals when completing their Continual Professional Development (CPD) [2]. This study aimed to evaluate the potential of a CAL package on the topic of hepatitis C for teaching and CPD within the MPharm III year.

The CAL package was based upon current guidelines and evidence based management for hepatitis C. Information was presented in a manner to retain students' interest and attention, through the use of animation, colour and diagrams. A chapter set out to clearly explain the role of the pharmacist in hepatitis C aiming to make the package relevant to pharmacy as a profession. A questionnaire-based survey was conducted on the MPharm III cohort to obtain feedback on the presentation, content and impressions of CAL. Quizzes were included at the end of each chapter to test the students' understanding of the concepts taught. The questionnaire was presented on GoogleDocs®, with a 5-point Likert Scale and a free space for comments was present at the end of the questionnaire.

Fifteen questionnaires were completed and received (11%). Feedback obtained was generally positive; participants agreed that the package was presented well (73% n=11) and that the content included was relevant and easy to understand, particularly with the use of diagrams (100% n=15). Further positive comments were obtained regarding the role of the pharmacist. However, use of CAL for CPD showed a varied response.

The majority believed that the package would be an effective revision aid but nor a replacement for traditional learning methods. Several improvements were suggested including the use of audio, video and case studies. The value of CAL for CPD needs to be further analysed using a sample of postgraduate pharmacists.

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Ease of use and reproducibility of nasal sprays

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Currently the majority of nasal preparations are delivered via metered-dose spray pumps which allow administration of a defined dose with high accuracy in comparison to older systems [1]. However there is doubt around the reproducibility of nasal sprays left unused for a period of time, non-compliance of storage instructions and improper use and technique handling devices. The aim of this study was to determine reproducibility and ease of use for the following nasal sprays; Rhinocort, Nasobec, Flixonase and Avamys in an attempt to address the issues.

The study was split into two main areas; storage and reproducibility. Shot weight was assessed by weighing the spray pumps prior to and after each actuation. Thereafter consistency of sprays were evaluated by high performance liquid chromatography. Colleague's opinions on understanding of patient instructions and overall ease of use of sprays was also assessed.

Results revealed the average mass/spray prior to and after storage for the four sprays was fairly consistent. Inconsistency arose when bottles of Rhinocort and Nasobec were stored on their side or when doses were fired at a 45 degrees, with certain values greater than the +/-10% margin. The reproducibility study displayed consistent mass/spray when a differing number of sprays were fired, with only two exceptions outside the 10% margin. However there was larger variation in actual drug content of sprays than mass fired, but majority of values were still inside the +/- 10% margin.

In conclusion change in mass or percentage variation just outside +/-10% margin are likely to have no clinical implications on the patient. A number of parameters may have affected spray characterization, most importantly acceleration and force of actuation [2] could have affected the reproducibility of results. This study also highlighted the importance of storage instructions and patient instructions to ensure reliable doses are administered.

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The views of the pharmacy and pharmaceutical based sectors on the viability of drug repurposing

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Drug repurposing is a method of drug discovery by which established drugs are re-looked at to find new indications. It is an alternative form of drug development, and it seeks to avoid the problems of traditional drug design, such as high time and money cost. The area is relatively new, but as of the last few years there has been an increasing amount of research into the field. However, there were few papers discussing perception of repurposed drugs. Without a positive perception of drug repurposing, it is unlikely that industry will invest heavily into it to produce new therapeutic advantages. Hence, this project was devised with the objective of exploring people related to the pharmaceutical sector's opinions on drug repurposing.

The participants in the project were recruited by the student and the supervisor, and consisted of teacher practitioners, academics, students, and personnel related to other pharmacy – linked areas. In all, ten participants were recruited. Participants were asked questions in interviews regarding their opinions of drug repurposing, it's strengths, and it's weaknesses. The interviews took a semi – structured format and followed a script, although questions additional to the script were also asked depending on opportunity.

The project found that 90% of participants had a positive outlook towards drug repurposing. There were slight differences between the groups interviewed, as most of them generated the same themes. The most common positive snoted were the decrease in cost and time as well as the advantage of safety data, while the most common negative encountered was legal and patenting issues.

The study found that despite the profile of drug repurposing being fairly low, most members of the pharmaceutical sector were looking forward to the possibility of drug repurposing and despite this knowledge being difficult to generalise, the area warrants further research.

What are the factors that motivate fourth year pharmacy undergraduate students in relation to the MPharm degree?

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Motivation has been defined as “what moves people to act, think and develop” [1]. The aim of this study was to gain understanding into the factors which motivate students in relation to the Master of Pharmacy (MPharm) degree at Cardiff University. This was established as an unexplored area, thus qualitative study methods were used.

Ethics approval was granted by the School’s ethics committee. A sample of fourth year pharmacy students was recruited by four researchers in collaboration by means of purposive and convenience sampling [2]. A topic guide was developed together by the researchers, to aid the conduction of audio-recorded one-to-one, semi-structured interviews with participants. Interviews were anonymously transcribed by each investigator alone, the transcripts shared, and individually thematically analysed [3] using an inductive approach. Analysis involved repeated reading of transcripts, development of codes, identification of themes, and then theme refinement and subsequent naming [3] as to accurately reflect the data set.

Eight main themes were identified together with a number of associated sub-themes. Themes "Assessments" and "Lecture Attendance" were discussed in detail to depict the factors which motivated students to complete assessments and attend lectures. Word constraints meant that other themes could be commented upon in brief. Considerations for the school were suggested and tabulated e.g. increasing guidance for assessments, and giving positive feedback. The study was conducted with one cohort from one UK school of pharmacy, limiting the research. Future work may thus include cohorts from other universities. The addition of quantitative research in this area e.g. questionnaires may be an additional prospect.

The findings of this study unveil a number of factors which motivate some students in relation to the MPharm degree at Cardiff University, and that individual beliefs varied. As a previously unexplored area, this research enables further investigation into the topic of motivation regarding students and the MPharm degree.

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Development of an interactive e-Book to support communication skills for pharmacy students at Cardiff University

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As effective communication skill is a skill that many healthcare professionals and students struggle to learn and develop [1], it is only fitting to find a learning approach that will help them achieve it to satisfactory standards. Since the integration of e-Books into education is a growing trend [2], this study focuses on creating an interactive e-Book to aid the learning and development of communication skills, posing as a learning tool to complement lectures and workshops. The three key objectives were to explore the students' perceptions on a previously developed e-Learning package to determine what aspects are necessary to aid their learning and development, create an interactive e-book based on their feedback and evaluate it and lastly, make the necessary improvements.

Participants that were purely first year pharmacy students at Cardiff University were obtained and via focus group interviews, introduced to a computer-based e-Learning package to bring to light the key aspects that would enrich their learning experience based on a technology derived tool. Using the results from the interview, an interactive e-Book was created by means of the iBooks author on a Mac platform, which enabled the interactive e-Book to be viewed via an Apple iPad. The same participants were called back for a second focus group interview, this time to evaluate the interactive e-Book.

Overall, the participants enjoyed learning through this method; especially the interactive aspect of it was well received including tap-commanded animations, videos and multiple-choice questions. They found the device easy to use and navigation wasn't an issue.

The main limitation is that it is available on iPads and not every student owns one and many still prefer the traditional textbook approach to education [3]. Despite these drawbacks, the e-Book era is rapidly drawing close and it is only sensible to start incorporating them into education.

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Optimising patient care: exploring stakeholders' perceptions of the Common Ailments Scheme (CAS) in community pharmacies

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Common ailments place a huge demand on primary care, accounting for around 75% of A&E admissions and 40% of GPs time [1]. Since October, the Welsh Government has been piloting the All Wales CAS in two health boards. The scheme allows patients to consult their pharmacist who can provide, free of charge,

treatment or advice for a range of 26 conditions [2]. This study aims to explore the perceptions of stakeholders involved in the implementation of the All Wales CAS.

Ethical approval was obtained from CSPPS Ethics Committee. Semi-structured interviews were conducted with stakeholders in Cwm Taf UHB. The sampling frame was defined as any individual involved in the CAS development or delivery. Purposive and snowball sampling were used to identify stakeholders. Interviews were audio-recorded and transcribed verbatim. Resulting transcripts were thematically analysed using codes and the principles of constant comparison.

11 interviews were conducted, with stakeholders comprising 7 pharmacists, 2 practice managers and 2 key informants. Data analysis identified 11 key themes. Pharmacists are perceived to benefit from an improved professional image, GPs from time saved and patients by increased access to medicines. A number of issues were identified concerning referral pathways, formulary limitations and time. Other themes that emerged include remuneration, IT systems, inter-professional relationships and promotion of self-care.

This study has acted as the first qualitative evaluation of the All Wales CAS. Stakeholders perceive the scheme to be working towards its intentions to make community pharmacy the first port of call and promote self-care. A number of suggestions were made that could be considered to help develop the service. These include improved training to support GP receptionists, allowing non-pharmacist staff to help implement the service and revised service advertisement. Further research should explore the perceptions of patients who continue to consult their GP for minor ailments despite the presence of a pharmacy-based ailments scheme.

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Delivery of plasmid DNA to skin cells via coated microneedles

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Microneedles (MNs) are an attractive proposition for the delivery of plasmid DNA (pDNA) and other therapeutics. Advantages of their small size include pain-free administration [1]. pDNA's negative charge prevents effective skin cell uptake, consequently a cationic liposome was used in this study to complex pDNA for cell delivery. Previous studies have successfully delivered functional MN-coated pDNA to skin cells [2,3]. This project investigated the feasibility of delivering functional MN-coated liposome-pDNA complexes (lipoplexes) to the skin for gene therapy applications. A secondary aim was to investigate gold nanoparticles as a potentially novel transfection agent.

To determine the optimum complexing procedure and lipoplex ratio, different methods were designed to complex a fixed quantity of pDNA encoding EGFP reporter with various liposome amounts. The resulting complexes were compared using gel electrophoresis and zeta potential analysis. Transmission electron microscopy (TEM) was used to assess MN-coated and non-coated lipoplex properties. MNs were coated with lipoplexes and functionality assessed by performing a cell transfection in HaCaT keratinocyte cells using fluorescent microscopy and flow cytometry to determine gene expression. Different ratios of nanoparticle-pDNA complexes were compared using electrophoresis and zeta potential analysis. Functionality was assessed by performing cell transfection in HaCaT cells.

Electrophoresis showed changes to complex migration following preparation by both methods, suggesting complexes were negatively charged or had condensed to exclude ethidium bromide. Zeta potential was affected by the complexation method employed. The optimum method was chosen to determine the optimum Lipofectamine: pDNA ratios; found to be 4:1 and 6:1 w/w. TEM images of MN-coated and non-coated lipoplexes were morphologically dislike. MN-coated lipoplex-treated cells did not express EGFP. Cell transfection by nanoparticle-pDNA complexes was unsuccessful.

Evidence from TEM indicates that the MN-coating procedure destroys lipoplexes, resulting in unsuccessful cell transfection. Results from electrophoresis and zeta potential analysis indicated that it is also likely that lipoplex complexation did not fully occur; refinement of the complexation method is required to confirm this. Supplementary work is required to optimise nanoparticle-pDNA complex properties.

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Optimisation of the expression and purification of recombinant protective antigen from *Escherichia coli*

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Protective antigen (PA) is the principal immunogen of current vaccines against anthrax [1]. Recent efforts have focused on developing a subunit vaccine based on recombinant PA (rPA) which can better safeguard the public against the biological threat of *Bacillus anthracis* [2]. The bacterium *Escherichia coli* has been established as a suitable expression host for rPA production [3, 4]. This study aims to produce an optimised high-level expression system for rPA production using *E. coli* to obtain sufficient amounts of purified rPA for use in further studies.

E. coli M15 and SG13009 cells were transformed with pQE30 plasmid containing a codon-optimised PA gene. rPA was expressed as a fusion protein with a 6xhistidine affinity tag. High-level expression yielded insoluble protein aggregating to form inclusion bodies. Inclusion bodies were solubilised in buffer containing 8 M urea and purified under denaturing conditions using immobilised metal ion affinity chromatography (IMAC). Four different IMAC resins (cobalt, copper, nickel and zinc) were compared for single-step purification of rPA. The yield and purity of the rPA recovered by each resin was determined by Bradford assay, SDS-PAGE and Western blot analysis.

E. coli strain M15 expressed the highest amounts of rPA. Purification with the copper resin yielded the highest quantity of rPA (approx. 14 mg per litre of culture) but this contained substantial impurities. The cobalt resin yielded rPA with the highest purity but in a lesser amount (approx. 3 mg per litre of culture).

The aim of the study was achieved as a sufficient quantity of high-purity rPA for potential use in toxin challenge studies in animals was yielded. This was achieved by expressing rPA with *E. coli* strain M15 and purifying the protein using cobalt IMAC resin. Further optimisation of this expression system and specifically the purification procedure is required to further improve the yield and purity of rPA.

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Anti-cancer activity of disulfiram combinations in breast cancer cells

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Cancer cells are showing resistance to anti-cancer therapy and thus the need for more effective treatments is imperative [1]. The thiocarbamate drug, disulfiram, has been known to have anti-cancer activity since the 1960s. Disulfiram is a good drug for anti-cancer therapy as it is safe in the human body, achieving high concentrations in the blood without toxicity. Many studies have also proven that disulfiram has synergistic abilities when used in combination with other anti-cancer drugs [2,3]. The aim for this project is to explore the effects of disulfiram in combinations with other drugs on MCF-7 breast cancer cells. From this it can be determined which combination has the most potential for further exploration.

The drug treatments used a serial dilution of disulfiram or metformin or cyclophosphamide and the cells were then incubated for 24 hours. The cell titre-blue assay was used to determine the extent of cyctotoxicity after drug treatment. In the assay, the viable cells produce a fluorescence from the reduction of resazurin to resorufin and so the extent of fluorescence produced is proportional to the extent of viable cells.

The results show that cytotoxicity of the cancer cells were dose related. The greatest toxicity observed was at the highest drug concentrations used. There were statistically significant (p=<0.05) synergistic results with the use of disulfiram with metformin or cyclophosphamide. Additionally, observed in several experiments was an increase in cell viability. From the assumption that it was autophagy, chloroquine was used to stress the cancer cells. However, this did not potentiate anti-cancer activity, but showed disulfiram to have protective properties due to the increase in cell viability.

The data is encouraging, confirming with literature that disulfiram has synergistic activity when used in combination with other anti-cancer drugs. However, results also showed that disulfiram had protective properties, causing an increase in cell viablilty.

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Identification of antibacterial factors within Welsh honey with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and the bee pathogen *Paenibacillus larvae*

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Honey has been used medicinally for thousands of years. Modern medicine veered away from using honey with the advent of antibiotics. However, in recent years there has been a resurgence of interest in its antimicrobial potential due to growing problems of antimicrobial resistance [1]. Honey has a wide spectrum of antimicrobial effects including some derived from phytochemicals. The aim was to investigate honey samples from three different origins (Manuka, Southampton and Wales) and to study their antimicrobial activity against MRSA and *P. larvae*, a bee pathogen and causative agent of American Foulbrood (AFB) [2].

Organic solvent extractions of honey of varying polarities (n-hexane, ethyl acetate, methanol) were used to perform thin layer chromatography. Amberlite XAD-2 resin was used to further extract any potential phytochemical components in the methanol extractions. Thymol was used as internal control to validate results. Direct and indirect bioautography was used to overlay MRSA (~10^6 CFU/ml) and *P. larvae* respectively to assess activity of the honey samples. Identification of factors responsible for potential antimicrobial activity were additionally analysed using mass spectrometry (MS).

Honey solvent extracts of hexane (excluding Southampton honey) and ethyl acetate exhibited activity against MRSA (10mg/ml). Hexane extractions exhibited activity against *P. larvae* (10mg/ml). Amberlite XAD-2 extracts displayed no activity against MRSA or *P. larvae* though potentially active components may have been present at sub-threshold concentrations [2]. The antimicrobial flavonoids chrysin and a derivative of quercetin were ubiquitous in all MS samples [3].

Further studies are warranted using MS coupled with other spectroscopic techniques (e.g. UV and NMR) for a detailed elucidation of the flavonoid content [4]. The phytochemical content could represent novel leads in drug development as well as providing a better understanding of the role of honey in the preservation of bee brood against bee diseases such as AFB.

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Profiling VGLL1 and MID1, genes associated with ER loss in novel models of endocrine resistant breast cancer

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Relapse on endocrine treatment remains a clinical problem in breast cancer. 20% of these patients with acquired resistance lose oestrogen receptor (ER) resulting in poorer prognosis [1]. Lack of acquired resistant models has made it difficult to study this resistance. MCF7-derived and T47D-derived acquired anti-hormonal resistant models have been recently developed representing different treatments and genetic contexts. Affymetrix mRNA array profiling of the MCF7-derived lines suggested two genes, VGLL1 (vestigial 1) and MID1 (midline1) expression increased where ER loss was seen. This studied aimed to further investigate VGLL1 and MID1 relationship to ER loss and aggressiveness in resistance, using the MCF7 and T47D-derived model panels.

PCR was used to examine expression of VGLL1, MID1 and ER in the resistant model panels.Aggressiveness of the cells was assessed using 2D Boyden chamber migration assays. KM Plotter, GenExMiner and GOBO were used to assess MID1 and VGLL1 in online clinical transcriptomes, while their biology was explored using Genecard and Pubmed.

Five models showed ER loss as well as increased migration although, there was some variation seen according to model panel. VGLL1 and MID1 expression was increased, where ER was lost and appeared to relate to aggressiveness particularly in MCF7-derived models. Tumours with inherently-higher VGLL1 or MID1 showed earlier relapse and weakly-correlated with ER negativity in patients. Both were signalling genes linked to growth or progression in some cancer types.

As seen in the clinic, models that lost ER had a more aggressive phenotype in acquired resistance [2]. VGLL1 and MID1 relate to ER-ve and aggressive behaviour in acquired endocrine resistance but this is dependent on genetic context. Clinical and ontology data supported that these genes can have adverse functions [3,4]. Continued research to understand how these genes relate to the biology of tumours losing ER may reveal new therapeutic avenues to improve patient outcome.

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End product testing of parenteral nutrition (PN) admixtures – exploration of current thoughts and practices in the NHS

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Parenteral nutrition (PN) is the supply of daily nutrient needs to patients who are unable to use their gastro-intestinal system [1]. This complex mixture, administered via intravenous infusion into the blood [2], needs to be sterile and of appropriate composition. The aim of this project was to understand the current testing procedures used to avoid errors and pharmacist's views on end product testing of PN admixtures in the hospital setting.

Using Survey Monkey, an online survey tool, a list of questions was constructed into a survey, accompanied by a cover letter; to send out to an email list containing 411 addresses of hospital pharmacists dealing with PN in the NHS. The responses were collated and handled using spreadsheet (MS-Excel) and database (MS-Access) software.

49 surveys were successfully completed by a variety of hospital staff from all across the UK. Most commonly dispensed PN to adults and neonates, the majority of PN was unlicensed and made by hand. Hospitals experienced errors in PN due to labelling, formulation and compounding processes. Popular testing parameters of PN included visual inspection (98%) and sterility (62%) whereas electrolyte and trace element

content were less common. 62% of the respondents stated that the testing currently carried out is sufficient however constraints on quality testing include time taken and cost burden. The general consensus was that end product testing of PN admixtures is a good idea and a useful tool, though it is unrealistic as it is a retrospective process producing delayed results following the need for immediate use. A few opinions stated it to be irrelevant.

Errors have occurred compromising patient safety, however the views are plausible. Other robust systems like GMP need to ensure quality throughout the entire manufacture process. Basic standard physical tests need to be made mandatory to spot potential errors.

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Evaluating the numeracy skills of undergraduate students using a contextualised formative diagnostic numeracy tool

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The importance of numeracy, especially in healthcare, is irrefutable. However, the numeracy skills of entry level pharmacy undergraduates have raised concern [1,2]. Little is known about changes in the numeracy skills of pharmacy students as they progress through the MPharm programme. The aim of the study was to characterise the inherent numeracy skills of a cohort of undergraduate pharmacy students between entry to and the final year of the MPharm.

Ethics approval was obtained from the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee. A contextualised diagnostic numeracy test was administered to a single cohort of MPharm students in the first week of MPharm 1 (2010) and again in MPharm 4 (2013) without prior notification. The test contained 25 medicines-based calculations questions to be completed in 45 minutes without a calculator, with a confidence assessment after each question. An accompanying questionnaire was administered to collect demographic data and obtain data on students' feelings. The data was analysed using nonparametric tests with SPSS.

Only students who sat the test in both the first year (Y1) and fourth year (Y4) were analysed (n=104). The students performed significantly better (p=0.000) in Y4 (mean 22.13/25) than in Y1 (mean 20.13/25). Students' mean confidence increased from 20.51/25 in Y1 to 23.83/25 in Y4 (p=0.000). Students were least competent in unit conversion despite being highly confident in both years. Students with an A-Level scored significantly higher in first year than those without (p=0.002). Forty-four (42.3%) students had incorrectly gauged their numeracy skills to have improved, worsened, or remained the same. While students expressed a mix of feelings towards numeracy, the responses were generally positive.

The increase in students' competence and confidence may be attributed to effective teaching and learning strategies. Students' incompetence in unit conversion and inaccurate perceptions of their skills echo previous studies [2,3,4] and could potentially cause errors in practice. The numeracy diagnostic test should be used by entry-level undergraduates to identify areas of weakness and tailor interventions accordingly.

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Synthesis of a novel precursor for ^{18}F-labelled gemcitabine

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Gemcitabine is a potent anticancer drug used in the treatment of various solid tumours. However, its treatment efficacy is often compromised due to the poor treatment response and severe side effects [1]. With the use of ^{18}F-labelled gemcitabine as positron emission tomography (PET) radiotracer, responders and non-responders to gemcitabine can be distinguished, potentially personalised gemcitabine treatment, resulting in better treatment outcome. Objectives of this project include the synthesis and characterisation of an advanced precursor for ^{18}F-labelled gemcitabine; first trial on late-stage fluoride introduction using novel precursor (cold fluorination).

Two different routes are used to synthesise novel gemcitabine precursor. Route 1 involves intra-molecular cyclisation of N^4-acetylcytidine, followed by acetylation of 3'- and 5'-hydroxyl groups. Then, hydrolysis and Dess-Martin periodinane (DMP) oxidation at 2'-position of nucleoside furnished gemcitabine precursor [2]. Route 2 involves protection of 3'- and 5'-position of N^4-acetylcytidine using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$) protecting group, followed by DMP oxidation at 2'-hydroxyl group. Then, deprotection and acetylation at 3'- and 5'-position of nucleoside furnished gemcitabine precursor. Using gemcitabine precursor as starting material, novel late-stage deoxofluorination with 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead^{TM}), followed by deacetylation is proposed to furnish radioactive ^{18}F-labelled gemcitabine [3]. Proof of principles with non-radioactive ^{19}F-labelled gemcitabine was carried out prior to translation to radiosynthesis. Several purification and characterisation techniques were used in between steps.

A stable 2'-activated gemcitabine precursor with 98% purity was successfully synthesised via both routes in similar yield, which is 7.24% and 6.1%. Whereas characterisation of reaction mixture after fluorination showed that starting material has decomposed; gemcitabine intermediate was not detected.

After comparison, route 1 is preferred because it is cost-effectiveness and less time-consuming. The failure in the first trial of late-stage fluorination is possibly due to inadequate Fluolead^{TM} used. In summary, this project provides a good base for the development of an efficient synthetic route towards ^{18}F-labelled gemcitabine.

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An evaluation of interprofessional education (IPE) between pharmacy and medical students: basic life support

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IPE has been defined as '...occasions when two or more professionals learn with, from and about each other to improve collaboration and the quality of care' [1]. With the support of the General Medical Council (GMC) and the General Pharmaceutical Council (GPhC), IPE is now a required element of both medicine and pharmacy undergraduate degrees [2-4]. The Basic Life Support (BLS) session was introduced for the first time in 2013 between 1st year medicine students and 4th year pharmacy students of Cardiff University. The aim of this study was to evaluate the views of students who participated in the IPE session.

An anonymous two-part questionnaire, consisting of questions with Likert-item responses, and a free-text response section, was distributed using total population sampling at the end of a 2.5-hour session where participants worked through BLS scenarios in interprofessional groups of 3. Responses to quantitative data were analysed using the IBM SPSS programme, while qualitative responses were analysed using thematic analysis. The Mann-Whitney U statistical test was also used to compare student groups. Ethics approval was obtained from the Cardiff School of Pharmacy and Pharmaceutical Sciences.

A questionnaire response rate of 87% (n=383) was achieved. More than 90% of all respondents strongly agreed or agreed that the session was helpful and well conducted, with constructive feedback. More than 90% of medical and pharmacy students also exhibited positive attitudes about the IPE component. However, the positive attitudes expressed were not translated into positive changes in behaviour, and this was shown by the significant difference between the two student groups in response to IPE, with medical students showing a higher level of disagreement that they have learnt something from the other profession during the session. 92% of medical students and 90% of pharmacy students agreed more IPE should be conducted in the future. The most commonly stated benefit was 'working with another healthcare professional in a hands-on session' while 'timing of session for pharmacy students' was the component most students thought could be improved on.

Overall, students found the session beneficial and should be continued. Evaluation of future IPE sessions using a pre-post test questionnaire will identify changes in attitudes and knowledge that have occurred as a direct result of it.

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Trace element precipitaton in parenteral nutrition (PN) admixtures – is it a risk?

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Parenteral nutrition (PN) provides nutrients in the form of amino acids, glucose, lipid, electrolytes such as phosphate, vitamins, trace elements (TEs) and water via the intravenous route when oral or enteral feeding cannot be given [1,2]. However, addition of TEs to PN admixtures may result in physical incompatibility. Formation of iron phosphate precipitates had been reported [3]. Many factors could influence both the occurrence and extent of precipitation [3,4]. The objectives of this study are to establish the presence of iron phosphate precipitation, determine precipitation curves to propose a safety margin for iron and phosphate concentrations and examine the main factors that affect precipitation.

To establish formation of iron phosphate precipitates, iron chloride solution was tested with three different phosphate solutions. Concentrations of iron (1 to 140µmol/l) were prepared with Addiphos® (5 to 80mmol/l), potassium dihydrogen phosphate (KDP) 13.6%w/v (0.3 to 10mmol/l) and Glycophos® (0.4 to 80mmol/l) respectively. Various components include water, glucose 50%w/v and Aminoven® 25 were added either separately or together with iron phosphate complexes to make up 100ml solutions in five sets of regimens. Investigations were tested at either room temperature, 37°C or 2-8°C. At 0 and 24 hours, samples were visually inspected with illumination, turbidity and pH readings were also measured.

Based on the precipitation curves, maximum concentrations of iron with Addiphos®; KDP and Glycophos® should be 20µmol/l and 60mmol/l; 70µmol/l and 5mmol/l and 140µmol/l and 20mmol/l respectively to ensure no precipitates form and hence safe for patient use.

In general, increases in iron and phosphate concentrations increase the risk of precipitation. Organic phosphates including Glycophos® are least likely to form precipitates compared to inorganic phosphates including KDP and Addiphos® which are not recommended. The presence of glucose and/or amino acid reduces the risk. Samples at room temperature had a greater risk compared to 37°C and 2-8°C which was the safest. However, no single factor should be used in isolation to predict compatibility.

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Welsh marine sponge as a potential source of novel antibacterial lead compounds

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Marine sponges are well known for producing novel metabolites for various pharmaceutical uses [1-2]. Being grown in a temperate region, and scarcely explored, investigation into Welsh marine sponges provides a greater opportunity to isolate a novel drug candidate especially for the pressing need of antibacterial treatment [3-4]. This study aimed to isolate and characterise a novel antibacterial lead compound from a Welsh marine sponge, and investigate the effect of sponge growing conditions on the production of active compounds.

Sponge materials of *Halichondria panicea* collected from competitive and non-competitive environments were extracted in solvents of increasing polarity to yield three crude extracts (hexane, acetone and methanol). Antibacterial activity for each extract was determined using a thin layer chromatography-direct bioautography technique against *S. aureus* (Gram-positive) and *E. coli* (Gram-negative). Active compounds were isolated and further purified into simpler fractions. Isolated fractions were finally subjected to high resolution electrospray ionisation-mass spectrometry (HRESI-MS) for compound identification.

Results showed that sponges growing in a non-competitive environment separated into more bands/compounds compared to those in a competitive environment. Six out of ten compounds isolated from hexane extracts displayed significant inhibition against both *S. aureus* and *E. coli*. Upon identification, one isolated fraction from hexane extract of a non-competitive sponge (1N4.6) was found to be a monobrominated compound, with isotope peaks of *m/z* 669/671 in HRESI-MS.

Database screening of empirical formulae suggested for the peak at *m/z* 669 had resulted in no known marine natural product, which proved the compound's novelty. However, full structural elucidation of the novel isolated compound was not possible due to a very low yield being recovered. In conclusion, this study demonstrated the promising potential of a Welsh marine sponge as a reservoir of novel antibacterial lead compounds, since most compounds isolated had shown significant antibacterial activities. This study also suggested evidence of possible variation in compounds produced in the sponges of different growing conditions.

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What are the factors that motivate MPharm IV pharmacy undergraduate students in relation to the MPharm degree?

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Motivation is a driving force that causes an individual to act towards a goal [1]. It is an important predictor of academic achievement, sometimes considered more important than intelligence [2]. The paucity of available research means little is known about UK pharmacy student motivation. The aim of this study was to determine the factors that motivate MPharm IV students at Cardiff University in relation to their on-going studies, the type of motivation (intrinsic or extrinsic), how students perceive their motivation to have changed and the reason(s) for such change(s). This could help develop strategies to improve motivation.

An interview topic guide was developed through literature review and research team discussion and tested using mock interview and pilots. Non-probability (purposive and convenience) sampling was used to recruit a sample of MPharm IV students. Audio-recorded, semi-structured one-to-one interviews were anonymously transcribed ad verbatim. The transcripts were shared with the other three student researchers of this study. The transcripts were analysed by deductive thematic analysis [3] using self-determination theory (SDT) [4] as theoretical framework.

Twenty-four interviews were conducted on MPharm IV students. Many factors were reported including assessment weighting, perceived relevance, task interest, personal goals, placements, university staff, peers and family. Three main themes were identified; “student factors affecting motivation”, “non-staff MPharm factors affecting motivation” and “the effect of others on motivation”. Pharmacy undergraduate motivation is not constant throughout the degree and is influenced by a variety of factors including gaining a pre-registration position.

Students are motivated by a combination of intrinsic and extrinsic factors although extrinsic factors appear to prevail. Extrinsic motivation appears to increase as undergraduates near completion of the degree. Future research using quantitative methods and expanding the scope of the study to other year groups and/or UK universities may be useful. Suggestions have been made to help improve undergraduate motivation.

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The potential link between ageing, endocytosis and Alzheimer’s disease

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Alzheimer’s disease (AD) is a neurodegenerative disorder and ageing is the greatest risk factor [1]. The amyloid hypothesis states the accumulation of β-amyloid (Aβ) in the brain causes neuronal loss and dementia [1]. APP is synthesised in the cell, then transported to the cell surface. Clathrin-mediated endocytosis (CME) is implicated in internalising APP into the endocytic pathway [1,2]. Aβ is cleaved from amyloid precursor protein (APP) by secretases in the endocytic pathway [1,2]. This study aimed to determine how ageing affects the expression of proteins involved in CME and how AD pathology influenced the expression of proteins involved in CME.

Mice aged 3, 9 and 18 months represented the ageing process. Cortices were extracted from wild-type (Wt) and transgenic (Tg) London mutation mice; which overexpress APP and consequently Aβ with increasing age. The levels of APP, PICALM, and clathrin were compared across the age range in both genotypes. These proteins, and also dynamin I, were compared between genotypes of the same age. Western blotting was used to quantity protein expression and appropriate statistical analysis was conducted.

Unlike the Wt mice, Tg mice showed increased APP expression after 3 months. PICALM expression decreased in ageing Wt mice, but increased in ageing Tg mice. Clathrin expression decreased in ageing Wt mice only. No significant differences in dynamin I expression were observed in any group.

Tg APP results correspond with other research.[3] Decreased PICALM and clathrin expression with ageing in Wt mice suggests reduced CME. Decreased CME in ageing Wt mice suggests reduced APP internalisation and Aβ production which contradicts established AD pathology. In Tg mice, increased PICALM expression with ageing suggests increased CME. This indicates increased conversion of APP to Aβ which corresponds with AD pathology. Alterations in CME protein expression were observed with ageing in both genotypes, which suggests CME may be crucial to AD pathology.

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Investigating automated methods for inhaler testing

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Inhaled therapy is the mainstay of treatment for many respiratory diseases, especially asthma and chronic obstructive pulmonary disease (COPD). Asthma is a chronic condition affecting 5 million patients within the UK [1], which makes it harder for the patient concerned to breathe normally. Asthma is currently costing the UK £752.6 million pounds a year [2]. With inhaled medication being the cornerstone of the pharmacological treatment of patients with asthma and COPD, it is essential that we are able to test the inhalers to maintain a high standard for individual inhalers. This study aimed to analyse factors affecting delivered dose to the patient, from inhaler technique to the valve used on the canister.

Shot weights were studied using an MDI FD10. Shot weight was used to analyse the delivered dose of drug. A number of different inhalers were used with 2 main types of valve being used, one a fast fill fast empty valve (Vari valve) and a dose retention valve. The inhalers also varied in composition of drug and excipients.

The results from analysis of the Vari valves and dose retention valves showed the Vari valves had a decreased shot weight percentage, as well as being more variable than the dose retention valve per actuation. The variables in inhaler technique were all found to be significantly different.

The results indicated that the excipients were having an effect on the way that the metering chamber was filling within the Vari valves which caused the variability and the decreased shot weight percentages. However, observations made in the study, show the benefits of the Vari valves with drug delivery to the lungs [3]. Overall this study suggests the possibility of improved drug delivery to patients with the new Vari valves, but more research is needed to improve reliability with volume of drug delivered.

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The dopaminergic pharmacology of the guinea pig ileum

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Dopamine is catecholamine neurotransmitter with function throughout the Central Nervous System (CNS) and Enteric Nervous System (ENS) [1]. Dopamine acts on G-protein coupled receptors to exert its action [2]. The gastrointestinal tract (GIT) is the body system responsible for digestion. It is innervated by a large number of stimuli. Dopamine is known to have certain effects within the GIT and five receptor subtypes have been identified [3]. The aim of this study was to examine the effect of dopamine within the proximal and distal ileum and to test if restriction of food altered contractile responses [4].

The experimental procedure used guinea pig ileum (GPI) to determine the pharmacological effects of dopamine agonists and antagonists on contractile response. GPI was suspended within an organ bath of Tyrode's solution. Dopamine agonists and antagonists were added and the contractile response was measured. Statistical analysis was employed to test for differences between proximal and distal ileum and between free food and food restricted animals.

The dopamine agonists all produced a dose-dependent contractile response. When comparing the free food and food restricted animals, none of the results were found to be statistically significant ($P>0.05$). For comparisons between proximal and distal ileum, the agonist, bromocriptine, produced statistically significant results in free food ($P=0.0016$) and food restricted ($P=0.0470$) tissues. In most cases, antagonists decreased the contractile response of agonists. In distal, food restricted animals the agonist, SKF 38393, produced the highest average contractile response.

In conclusion, the data demonstrate that there was a difference in responses of the proximal and distal ileum to dopamine agonists and antagonists. However, despite there being a difference between free food and food restricted results, these were not statistically significant. Moreover, there is evidence of an increased activation of D_1 receptors in the proximal ileum and of D_2 receptors within the distal ileum.

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The development of an effective computer assisted learning package on Lyme disease

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Computer Assisted Learning (CAL) is an independent or supplementary method of self-teaching with many possible applications. One proposed application is its use in Continued Professional Development (CPD) [1]. The aim of this research project is to develop an effective CAL package on Lyme disease to be used by both pharmacy undergraduates and postgraduate pharmacists as a CPD entry.

An up-to-date CAL package was designed using Microsoft PowerPoint 2010. The package contained information on Lyme disease relevant to its prevalence, diagnosis, prevention and treatment. The role of the pharmacist was also discussed and various teaching methods such as; animations, diagrams, self-testing and case studies were employed. A questionnaire was also designed in order to test the usefulness of the package, using GoogleDocs and a link was incorporated onto the final slide. A hard copy was also made available using Microsoft Word 2010. Both were then distributed amongst MPharm I at Cardiff University.

Overall feedback on the package was positive. 100% (n=20) agreed it was well presented and easily legible. Respondents also said it was well supplemented with diagrams and a manageable length. 85% (n=17) responded that the content was pitched at an appropriate level and 100% (n=20) agreed it was relevant to pharmacy. 100% (n=20) found CAL to be a useful learning tool with mixed responses as to whether it should replace other methods. The package was said to be useful for CPD entry with 80% (n=16) in agreement.

Participants found the package to be beneficial and useful but would appear to view CAL as a supplementary tool [2]. However interactive, self-teaching aspects were viewed positively [3] and such packages appear to be promising for CPD fulfilment. As well as the suggested improvements, it may be effective to use slides in a more supplementary role, for example by incorporating audio for further expansion.

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The effect of the presence of food on cannabinoid pharmacology in the guinea-pig ileum

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Cannabinoids have shown potential therapeutic benefit in treating gastro-intestinal (GI) conditions such as Irritable Bowel Disease (IBD) [1]. One of these benefits is relaxation of the GI smooth muscle; thought to be mediated via cannabinoid receptors (CB_1 and CB_2) located presynaptically, that reduce acetylcholine release when activated [2]. This study aimed to investigate whether fed or fasted states could alter cannabinoid pharmacology in the isolated guinea-pig ileum.

The ilea of fed and fasted guinea-pigs were cut into 2 cm strips and suspended in an organ bath containing Tyrode's buffer, aerated with carbogen and maintained at 37°C. Electrical field stimulation [3] induced regular ileal contractions and the mean of force of tension was recorded. (+)-WIN (cannabinoid agonist) was dosed alone cumulatively up to 30µM initially, then dosed in the presence of 1µM AM 281 (CB_1 selective

antagonist). A 50% ethanol vehicle was used for (+)-WIN based on preliminary experiments that showed 100% ethanol vehicles significantly suppressed twitch height.

In fed guinea-pig ileum: (+)-WIN suppressed twitch height by up to 71±6.24%. AM 281 shifted the concentration-response curve (CRC) of (+)-WIN to the left (0.23 mean log shift), thus potentiated the (+)-WIN-induced inhibition of twitch height. In fasted guinea-pig ileum: The (+)-WIN effect was abolished due to the ethanol vehicle alone substantially suppressing twitch height (65.7±11.51%) and preventing any (+)-WIN effect. AM 281 had no effect on (+)-WIN in fasted guinea-pig ileum.

This study shows (+)-WIN has cannabinoid-like effects on smooth muscle of the guinea-pig ileum. AM 281 potentiates (+)-WIN-induced suppression of twitch height suggesting potentiation via CB_1 receptors, or possible involvement of non-CB_1 targets. AM 281 enhanced (+)-WIN affinity (shown by a CRC shift left) for its receptors. Fasted guinea-pig ileum is more sensitive to the effects of high vehicle concentrations; highlighting the practicality difficulties when assaying the highly lipophilic cannabinoids.

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The design and synthesis of Bcl3 inhibitors as anti-metastatic agents

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Metastatic cancer is cancer that has spread from the primary tumour to the other part of the body through either the bloodstream or the lymph system. Approximately 90% of cancer-associated deaths are caused by cancer metastasis and breast cancer has been identified as the most common cancer in the UK, despite the fact that it is rare in men [1-3]. Through a recent series of studies by researchers in Cardiff University, researchers confirmed that a potential cancer causing gene, which is Bcl3, plays a critical role in the development of metastatic breast cancer. They revealed that the spread of cancer was reduced by more than 80% if Bcl3 gene is suppressed in mice with metastatic disease [4]. Hence, the main aim of this investigation was to design and synthesis small chemical inhibitors of Bcl3 that might have potential therapeutic value in metastatic breast cancer.

The synthetic pathway provides 2–step synthesis pathways that have similar mechanism, which is the nucleophilic substitution. Step 1 is the synthesis of intermediates while Step 2 is the synthesis of final compound where the heterocyclic is substituted by either morpholine or phenyl ring. Purification techniques such as filtration, extraction, silica gel column chromatography and crystallisation were used to ensure the pureness of our compounds. H-NMR, C-NMR, F-NMR, mass spectrometry and melting point were used to characterize the final compounds obtained.

12 putative Bcl3 inhibitors were prepared and fully characterised. It was justified by the results obtained from the NMR spectrometry. Good yield for all the compounds have been obtained. These final compounds were sent for biological evaluation to test for biological activities and toxicity.

In conclusion, all the Bcl3 inhibitors have been successfully synthesised and its potential therapeutic value will be discovered in later stage. The exact mechanisms of how Bcl3 inhibitors work in metastatic breast cancer are not fully understood at this stage. However, researchers are working hard in finding more therapeutic options in order to reduce the mortality rate and improve the quality of life of patients with metastatic diseases.

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Investigating the potential link between ageing, endocytosis and Alzheimer's disease

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Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases of our ageing population. It is characterised by accumulation of amyloid-beta (Aβ) plaques formed from the cleavage of amyloid precursor protein (APP) [1]. Abnormalities in endocytic pathways have been implicated in the early stages of AD, with evidence of enlarged endosomes leading to increased amyloidogenesis resulting in neurotoxicity [2,3]. This study was undertaken to explore the potential link between ageing, endocytosis and AD - in particular to look at proteins involved in non-clathrin-mediated endocytosis; caveolin-1, caveolin-2, flotillin-1 and flotillin-2. The primary aims were to investigate whether these proteins were up or down-regulated with age and compare their expression within the brain tissue of transgenic London mutation mice (overexpressing human mutated APP V717I) and wild-type mice.

Western blotting was used to establish levels of proteins within the cortex of 3, 9 and 18 month wild-type and transgenic mice. Results were normalised against levels of β-actin to produce semi-quantitative data which were analysed using unpaired t-tests or one-way ANOVA and Tukey's post-hoc tests.

Results confirmed an over-expression of APP in transgenic animals at all ages. A significant decrease in levels of caveolin-1 was seen in transgenic animals compared to the wild-type animals at 9 and 18 months, with p values of 0.019 and 0.0054 respectively. There were no significant differences observed between the levels of caveolin-2, flotillin-1 or flotillin-2 in the wild-type and transgenic animals and no significant differences observed with increasing age.

Further experimentation in different animal models and repetition of this study are necessary in order to draw any firm conclusions. However, findings suggest that a decrease in caveolin-1 levels may be linked to an increase in amyloidogenesis and hence could be implicated in the pathology of AD – presenting a potential target for drug treatments.

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Development of HIV RT model to be included in NAOMI

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Scientists have been trying to reduce the cost and speed up the drug discovery process of nucleoside analogues by using computational techniques. NAOMI, which is a computer program for prediction the activation, and metabolism of nucleoside analogues, has developed [1]. In order to improve the current functions of NAOMI, viral targets were aimed to be included for future novel nucleoside predictions. HIV reverse transcriptase (HIV RT) was chosen, as it is one of the most popular viral targets with Wildtype and mutant (M184V and K65R) structures. A consensus score system of each HIV RT structure was aimed to build based on the present inhibitors and ligands activities.

Computational molecular modeling strategies were used to validate binding and interactions between ligands and the target protein pocket. The differences in docking conformations and molecular behaviours of substrates, non-active inhibitor and inhibitors were identified for building the scoring functions. Meanwhile, the pharmacophores for each viral structure (Wildtype, M184V mutant, K65R mutant) were built and the molecular docking patterns between Wildtype and mutants were investigated for scoring functions. The scoring criteria for pharmacophore searches, docking and rescoring were developed.

The models of 5 scoring functions were developed for the consensus score system. The overall results of Wildtype and M184V mutant showed that the activity data matched the consensus score results with minimal errors. However, K65R mutant showed less correlation between the activity data and the consensus score results because the consensus score system is restricted to conformational binding without "conformational restriction" mechanism resistance [2].

In conclusion, the consensus score system for HIV RT wildtype and M184V mutant was successfully built to distinguish inhibitors and non-active inhibitors. The consensus score system needs to be modified and improved for K65R mutant due to the lack of accuracy on discrimination.

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MMP expression and activation in drug-sensitive versus drug-resistant breast cancer

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The majority of breast cancers express the oestrogen receptor (ER) and antihormone therapies such as tamoxifen, faslodex and aromatase inhibitors have been clinically successful in ER-positive patients. However, tumours can acquire resistance to this treatment which is associated with disease relapse at distant sites. In vitro models of acquired resistance have demonstrated that resistance is accompanied by a significant gain in invasive capacity [1]. Matrix Metalloproteinases (MMPs) are proteolytic enzymes involved in many physiological processes, however their expression can become deregulated and this subsequently implicates them in cancer spread with MMP2 and 9 particularly involved in the latter [2]. The aim of this project was to investigate the hypothesis that acquired antihormone resistance in breast cancer is associated with an increase in pro-invasive pathways that rely on the expression of MMP 2 and/or 9.

Antihormone-sensitive MCF7 cells and their tamoxifen and faslodex-resistant counterparts along with a model of oestrogen deprivation resistance (used to model aromatase inhibitor resistance) were examined for MMP2 and 9 at the gene and protein level by RT-PCR and zymography respectively. A colorimetric assay was also performed to investigate the expression of urokinase-plasminogen activator (uPA), an upstream MMP activator.

Our results show that neither MMP2 nor uPA appear to be involved in acquired resistance as MMP2 was absent in every cell line, and uPA concentration was very low across all cell lines. Contrary to published observations, no relationship between MMP and ER status was observed [3]. A statistically significant increase of the MMP9 gene was seen in tamoxifen-resistant cells compared to MCF7 which was reflected at the protein level, however the most aggressive faslodex-resistant cells exhibited the least MMP9 signal.

In summary, the data suggests that MMP9 overexpression is implicated in acquiring resistance to tamoxifen but not to faslodex. Conversely, neither MMP2 nor uPA appeared to correlate with invasive behaviour.

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Patient experience: satisfaction with their medicines management during their hospital stay and satisfaction with information about their medicines provided on discharge from hospital

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Satisfaction is the 'fulfilment of ones wishes, expectations or needs' [1]. Satisfaction with medicines information is a key determinant in influencing adherence. The study aim was to assess in-patient satisfaction within the Cwm Taf Health Board, with their medicines and information provided on discharge. The main objectives were to assess if providing patients with sufficient information with regard to their medicines management and on discharge affected overall satisfaction. Furthermore, if receiving clear written

and verbal information affected satisfaction and evaluating information provided to patients using the satisfaction with information about medicines scale (SIMS) [2].

The study was conducted at the Royal Glamorgan and Prince Charles Hospitals after ethical approval was obtained. Patients aged over 18 discharged a week prior to data collection, on one or more medications were eligible for participation. An anonymously coded, two part bilingual questionnaire (English and Welsh) incorporating a validated tool[2] was distributed with a covering letter and free-post envelope. Patient demographics were inputted into an Excel spreadsheet. Kruskal-Wallis and Mann-Whitney U statistical tests were used to compare variables to overall satisfaction.

There were 366 eligible patients and 118 participated. Overall, 95% (n=112) of patients were satisfied with the way their medicines were dealt with during their hospital stay and the information provided on discharge. Only 39% (n=46) of the study population received clear written information and 60% (n=71) received clear verbal information. Verbal information did not impact on satisfaction however, not sufficiently receiving clear written information did. The SIMS tool showed that more information about the actions and usage of medications was provided compared to their potential problems.

Information gaps were seen with the formatting of information on discharge and the potential problems of medications. However, this did not affect patient satisfaction ratings as it may have not been relevant to patients a week after discharge.

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The following abstracts have been withheld as they have been or will be published elsewhere, and/or due to intellectual property or confidentiality issues:

Studies on the depletion of PAK1 as a marker for macropinocytosis in drug delivery research

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Developing novel oro-dispersible tablet formulations: service evaluation, formulation development and tablet performance

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Design and synthesis of acyclic nucleoside phosphonate prodrugs as potential antiviral agents

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Design and preparation of pharmaceutical gels and evaluation of their permeation characteristics across model membranes

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Design and synthesis of 25-hydroxyvitamin D-24-hydroxylase (CYP24A1) inhibitors

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e-Books to enhance learning in the pharmaceutical sciences

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Determination of hydrogen peroxide in pomegranate rind extract with luminol chemiluminescence assay

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Identification and characterisation of methicillin-resistant *Staphylococcus aureus* (MRSA)

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A novel complex with potential as a new topical microbicide

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The effect of bile salts on the ability of the spore of hypervirulent strains of *C. difficile* to adhere to clinically relevant surfaces

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Probing interactions between tannins with metal ions

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Novel 6-modified-5-fluorouridine phosphoramidate prodrugs: design, synthesis and biological evaluation as potential anticancer drugs

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Design and synthesis of 25-hydroxyvitamin D-24-hydroxylase (CYP24A1) inhibitors

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The design and synthesis of novel inhibitors of *Mycobacterium tuberculosis* CYP121

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Is caveolin-1 a possible cancer stem cell marker in renal cell carcinoma?

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Kinetic study of nanoparticle transport across porcine mucus barrier

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An investigation into the efficacy of detergent wipes in controlling microbial bioburden on surfaces

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Fabrication and evaluation of a novel microbicide-loaded gauze as a wound healing aid

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Synthesis and characterisation of silica pH-responsive nanomaterials

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Synthesis and characterisation of antimicrobial releasing silica pH responsive nanomaterials

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Development of CYP121 inhibitors as potential tuberculosis therapeutics: docking study and synthesis

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Use of an ex-vivo test method to assess the efficacy of wash cloth in incontinence-associated dermatitis

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Design and synthesis of novel anti-DENV nucleoside analogues

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Antimicrobial activity of silica-based nanoparticles conjugated with antibiotics against *Staphylococcus epidermidis*

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Testing antimicrobial effect of silica-based nanoparticles conjugated with antibiotics against *Staphylococcus aureus*

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The production of fluorescently labelled exosomes, visualisation of their interactions with cells and optimisation of their cellular uptake

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The Role of Cav 1 in CAKI – 1 cells in renal cell carcinoma

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Synthesis and biological evaluation of 5-azacytidine ProTides as anticancer drugs

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Developing an ex-vivo test method to assess efficacy of chlorhexidine washcloth

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An evaluation of the scatter of Indium-111 (^{111}In) photons in to the Technetium-99m (^{99m}Tc) energy window during the measurement of gastric emptying studies using radiolabeling scintigraphic techniques

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During dual isotope gastric emptying studies it has been observed that the higher energy radioisotope can scatter down into the lower energy radioisotope window, giving a misleading count rate for the low energy radioisotope. One example of this is when a ^{99m}Tc radiolabeled meal is administered, followed by an ^{111}In dosage form in a gastric emptying study. This scatter is particularly problematic for pharmaceutical gamma scintigraphic studies where accurate quantification of each isotope is necessary. The objective of this study was therefore to estimate subject specific scatterdown values (in to the ^{99m}Tc energy window) in order to correct for the interaction of ^{111}In with soft tissues during gastric emptying studies. In addition, the relationship between subject BMI and % scatter was evaluated.

Subject thickness was estimated from transmission scans, in this process an image of an external radioactive flood source (^{57}Co) was acquired in the presence and absence of the test subject. The reduction of signal in the presence of the subject provided a transmission factor related to the subject's total body thickness. A source of ^{111}In source was placed on an appropriate stand in-between the gamma camera heads (180° orientation) and imaged using a standard pre-set Tc/In window in the presence of 0-16 1cm thick Perspex sheets.

15 Subjects with a BMI range of 21.3-26.9 were evaluated and % scatter values of 66.25 – 75.25 calculated from the results of experimental testing. When accounting for the % scatter and applying these values to the ^{99m}Tc geometric mean counts as a percentage of the ^{111}In counts (following ^{111}In administration), a more appropriate emptying profile was observed. In addition, it was found that subject BMI is related to % scatter. In general, the larger a subject's BMI, the greater is the percentage scatter of the higher energy isotope.

I suggest that in future studies, it may be beneficial to evaluate the scatter from anterior and posterior images separately, as the anterior and posterior images obtained during a scintigraphy study will result in different attenuation of the radioisotope.

A system search to investigate similarities and differences between genetic and environmental risk factors to determine the cause of multiple sclerosis.

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Background- Multiple Sclerosis (MS) is a disease which effects millions of people all around the world. There are several variations such as Relapsing Remitting Multiple Sclerosis (RRMS), Primary Progressive Multiple Sclerosis (PPMS) and Secondary Progressive Multiple Sclerosis (SPMS). The common identifier of MS is the sclerotic plaque, which essentially is the demyelination of myelin. In a healthy individual, the myelin provides a covering which insulates and protects the nerves, this keeps them healthy and aids the conduction of impulses along the nerves. In MS, inflammation causes the myelin to disappear.

There are several risk factors which cause this disease of the central nervous system (CNS). Genetics and the environment are well known factors that cause the disease, for example ethnicity, familial links, the Epstein-Barr Virus and location/vitamin D. Most people with MS are able to live a normal, or near normal life, however, there is no known cure for MS or for demyelination. MS sufferers can receive treatments to help manage the disease and reduce their symptoms.

Aims- The aim is to compare the significance of genetic factors and environmental factors.
Objective – The objective is to search multiple systems for papers investigating the causes of multiple sclerosis to find out which factor is more likely to be the main cause of MS.
Methods – An extensive search of databases such as PubMed, EMBASE, Cochrane library and Scopus to find papers on case control studies, epidemiology studies and reports on the risk factors of Multiple Sclerosis.

Conclusion – Both genetic and environmental factors play a huge part in the onset of multiple sclerosis. Genetics have a dominant role when it comes to gender and familial links amongst siblings, however, evidence suggested that MS can lay dormant until triggered by an environmental factor. There is no one predominant factor that has proved to be a cause, but a combination of different contributory factors is the most plausible pathogenesis.

A critical analysis of the publication of randomised controlled trials: the use of the CONSORT statement

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It has been widely noted that clinical trial reporting is suboptimal. The CONSORT statement 2010 and its preceding versions were introduced to try and improve the situation. The aim of this dissertation was to assess the current use of and adherence to the CONSORT statement 2010 checklist. In addition, any changes that could be made to the CONSORT checklist in order to enhance both its impact and its prevalence were examined and explored.

A PubMed search identified 12 biomedical journal articles of Randomised Controlled Trials for analysis. All were published in 2013 in peer reviewed journals. The CONSORT statement 2010 checklist was used, and each of the 37 subcategory items were marked as reported or not reported for each article. In addition the recording of a number of other items were noted, such as ethical approval, informed consent and conflict of interest.

The number of CONSORT items reported ranged from as little as only 14 (approximately 41%) per article up to 30 (approximately 81%). No article reported all CONSORT checklist items thus showing that clinical trial reporting remains suboptimal. In addition, some of the other topics looked at were also incompletely and inconsistently reported.

As a result of looking at the current reporting of the CONSORT 2010 checklist items and other salient information that could and should be included in clinical trial reports, a revised CONSORT checklist was produced. More work is needed to improve the publication of all clinical trials, their methodology, results and hopefully in the not too distance future, raw data. The amended CONSORT checklist may just be one small step towards making this happen.

The role pharmacovigilance and spontaneous reporting play in healthcare system

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Healthcare professionals have long been concerned about adverse drug reactions reporting mechanisms. The aim of this thesis is to review and analyse some of the current methodologies used for monitoring drug safety during post marketing authorization, an essential step when considering the limited awareness of the safety profile of new licensed medicinal products. Strengths and weaknesses of some of the current methodologies available together with future developments in pharmacovigilance are here discussed. This introduction is followed by a deeper analysis about attitudes towards adverse events reporting among general practitioners in Wales.

Nowadays, the Yellow Card Scheme is well recognized for being the most common Spontaneous Adverse Drug Reaction (ADR) system within the United Kingdom (UK). Despite its importance, one of the biggest drawbacks this system presents is underreporting. There are many of controversies about the reasons why healthcare professionals are not reporting ADRs to Medicines and Healthcare products Regulatory Agency (MHRA).

UK is currently on leading positions within respect to ADR reporting rates. Apart from the number of structured databases which systematically monitors healthcare events, surveys like the one here aim to evaluate General Practitioners (GPs) knowledge about pharmacovigilance and their attitudes towards ADR reporting, data obtained from a multiple-choice survey questionnaire carried out by Welsh Medicines

Resource Centre (WeMeReC) has been analysed. The survey questionnaire was part of a distance-learning module launched by WeMeReC targeting all healthcare professionals registered on its website in May 2013. However, only answers given by GPs who had completed the 5-year post graduate studies were taken into account in this thesis. In total, the distance learning module was sent out to 411 GPs. Out of this only 364 properly answered the questionnaire which reflects a response rate of 87%.

As a result of the analysis performed, this resource aims to reinforce the importance of pharmacovigilance on the protection of public health. To ensure a successful pharmacovigilance system, this should be effectively used and its importance is to be continually highlighted.

Assessment of quality of life in gastroesophageal reflux disease using generic and disease-specific measures

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Gastroesophageal reflux disease (GERD) is a common and costly condition affecting between 10-30% of the Western population, and is becoming increasingly more common worldwide. One area of GERD which is often overlooked or underappreciated is the affect it can have on a patient's quality of life (QOL). However, using standardised questionnaire/instruments such as the generic Short Form – 36 (SF-36) or disease specific Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaires, QOL of such patients can easily be measured.

Using the SF-36 questionnaire, QOL data was collected from 86 subjects who were split into 2 cohorts; 43 healthy patients, and 43 subjects suffering with GERD. Subjects for the 'healthy' cohort were recruited through friends, family and colleagues, whilst subjects for the 'GERD' cohort were recruited via self help and support groups on the social networking site, Facebook. The data collected from both cohorts was then used to determine whether GERD affects QOL, and if the effect differs based on age/gender. Comparisons were also made to identify whether certain areas of daily life are affected more than others. In addition to the SF-36 questionnaire, the GERD cohort were also asked to complete the QOLRAD questionnaire in order to test for internal and construct validity of responses.

Data processing was carried out using Microsoft Excel. Data was analysed using Mann-Whitney analysis testing, student T-Test, Pearson's correlation coefficient, and Cronbach's alpha. The highest mean SF-36 score was observed in the Emotional Well-being domain in the GERD cohort (66.9) and Role Limitation – Physical for the healthy cohort (98.3). The lowest scores were observed in General health domain (42.5) and Energy / Fatigue (66.9) respectively. Overall, the results showed that GERD does significantly affect the QOL. When testing for internal consistency reliability, a score of ≥0.8 was considered desirable and the majority of SF-36 domains scored this or greater, with the greatest score (0.94) being achieved in the physical functioning domain of the GERD cohort. The lowest score (0.40) was seen in the role limitations – emotional domain of the healthy cohort. All scores for the QOLRAD questionnaire were ≥0.90. The correlation between the SF-36 and QOLRAD scores for the GERD cohort was also calculated using Pearson's correlation coefficient and a iv score of ≥0.30 was considered significant and demonstrating positive correlation. All scores calculated were above this.

In conclusion, patients suffering with GERD have a significantly reduced QOL, with different areas of daily life being affected to differing extents, in comparison with healthy individuals. Its impact is affected by the patient's age however, gender does not affect its impact.

Childhood eczema: do parents and children suffer similar levels of stress?

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Atopic eczema is an inflammatory skin condition that is common among children; it can be a debilitating condition that can have widespread implications for both the child and their family. Much research has been carried out on the effect of this illness on families but little comparing the actual implications felt by both the child and the parent/main carer. The primary objectives of the research: to assess the level of stress

experienced by parents caring for a child with atopic eczema. To assess the level of stress experienced by children suffering from atopic eczema and then compare the results.

Method was by means of a qualitative questionnaire distributed to both adults and children. Families were recruited through private day care nurseries, playgroup and pre-school and parent and child groups. Word of mouth also accounted for some of the returns. Before completing the questionnaires parents were asked to read an information sheet and sign a consent form. The questionnaires used were FDLQI and CDLQI. The questionnaire distributed to children was a modification of the adult questionnaire presented in cartoon form. A demographic information sheet was also circulated to these parents in order to meet secondary objectives of comparing the following: age of diagnosis; duration of disease; perceived disease severity; and family history of allergies.

Other questions such as age, gender, number of children and whether they would be willing to pay for better disease control were also included on the demographic data sheet. These questionnaires were then checked for accuracy and the scores were calculated. Higher scores represent greater impairment of QoL. Primary outcome measure showed that in terms of mean scores, children scored higher than their parent's equivalent. Secondary outcome showed that in terms of the CDLQI score vs severity, these two were not related. The CDLQI did not always correlate with the severity of the child's eczema. Furthermore, the use of a demographic data sheet allowed further comparison of variable such as age of diagnosis, previous medical conditions and socio-economic status.

Complete comprehension of the impact of eczema on children and their parents could not be established, further research into this area needs to be carried out, a larger sample population may show the differences/similarities between parent and child. Introduction of a control group would be of benefit in comparing a 'healthy' child's responses against those with more complex health needs.

MPhil

The identification of therapeutic targets and virulence factors of Clostridium difficile

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Clostridium difficile, a Gram-positive spore forming bacteria, is the leading cause of healthcare-associated diarrhoea in the UK and represents a major healthcare challenge. The vegetative form of the bacterium colonises the gut mucosa and produces two exotoxins, which are responsible for the pathology associated with the bacterium. We thus sought to characterise the host immune response directed against the surface of the bacterium and toxins A and B.

Our studies revealed that the vegetative form of the pathogen is capable of altering its physiology in vitro to produce two distinct colony morphotypes. The differences observed in the cell surface, autolytic activity and bile salt sensitivity; suggest that the M2 morphotype may be better equipped to survive in the hostile conditions encountered in the gut. The mechanisms by which these changes are mediated are as yet unclear; however given the characteristics of the morphotypes it may involve one or more phase variable proteins. The identification of immunogenic proteins, including pyruvate-flavodoxin oxidoreductase, an anaerobic metabolism enzyme associated with oxidative stress warrants further investigation. To be effective, a future immuno-therapeutic should target the form of bacteria which is most often encountered during infection.

Toxins A and B remain the primary virulence factors of C. difficile, with toxin neutralising antibodies targeting the receptor binding domains conferring protection and reducing recurrent infection. To characterise the antibody response directed against toxins A and B, the cell binding and translocation domains of each toxin were expressed in Escherichia coli. To identify immunogenic regions, the native, recombinant and toxoided proteins were subjected to enzymatic digestion with clostripain and probed with toxin neutralising animal sera and sera from C. difficile infected patients. The immune sera consistently identified two fragments of 40 and 60 kDa within both toxins A and toxin B, which may contain toxin neutralising epitopes and thus warrant further investigation.

Computer-aided design, synthesis and evaluation of potential anti-HCV agents

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Hepatitis C virus (HCV) is a major cause of chronic liver disease, leading to hepatic steatosis, fibrosis, cirrhosis and hepatocellular carcinoma. A vaccine is currently not available, while the standard of care is effective in only 50% of treated patients. The first specific anti-HCV drugs have been recently approved, and new classes of targeted agents are under clinical trials/investigation. Nevertheless, improved treatment strategies are needed, in order to bypass the rapid emergence of resistance. All the viral non-structural proteins are a possible target for the identification of novel and selective antivirals. Among them, the NS3 helicase is still underexploited, with no known inhibitor under pre-clinical or clinical development. This enzyme plays a crucial role in the virus life cycle: it catalyses the separation of double-stranded RNA strands, which is necessary for genome amplification and translation. Due to its essential function, the NS3 helicase was chosen as a target for the identification of new, specific anti-HCV compounds.

Different computer-aided techniques were employed to identify potential small molecule inhibitors of the enzyme. Two structure-based virtual screenings of commercially available compounds were performed on the main nucleic acid binding site. A series of candidate inhibitors was evaluated in the HCV replicon assay, yielding two primary hits with low µM activity. Secondly, the model of the one known inhibitor co-crystallised with the enzyme was used as a starting point for a shape-comparison screening of small molecule libraries. A new series of compounds was selected and evaluated for anti-HCV activity, and one of them was found to inhibit the viral replication at a low µM concentration. Several new derivatives of the initial hits were synthesised, belonging to four main structural families: bis-aromatic piperazine derivatives, symmetrical phenylendiamine compounds, differently substituted thieno-pyrimidines, and triphenyl-pyrrolone analogues. Inhibition of HCV replication in the replicon assay was evaluated for the new compounds prepared and several structures showed a range of activity from low-µM to nM.

Viral infection in a murine model of allergic airways inflammation: actions of corticosteroids

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Viral respiratory infection exacerbates asthma symptoms in almost all patients with allergic asthma. Asthma symptoms in viral associated asthma exacerbation are often severe and require urgent care as well as hospitalisation. Corticosteroids are the mainstay treatment for asthma. However, they are less effective in treating virus associated asthma exacerbation. The main aim of the thesis is to determine the role of virus infection in airway allergic inflammation and then define the effects of corticosteroids in virus associated exacerbations of airway allergic inflammation.

Mice sensitised and challenged with ovalbumin demonstrated most of the main features of asthma including lung cellular inflammation with eosinophilia, early phase asthmatic responses (EAR), late phase asthmatic responses (LAR), and airway hyperresponsiveness (AHR) to methacholine provocations. Treatment with either systemic (dexamethasone: DEX) or inhaled (fluticasone propionate: FP) corticosteroids in the murine ovalbumin allergic airways inflammation model attenuated inflammatory cells influx and eosinophilia, LAR, and the AHR.

Influenza A (H1N1/PR8) is the most infective to mice compared to human parainfluenza virus type 3 (HPIV3), and a synthetic dsRNA, poly (I:C). Influenza infection in mice caused a significant increase of inflammatory cell influx in the airways with marked neutrophilia, and AHR. Ovalbumin challenge in the acute course of influenza infection on a murine model of allergic airways inflammation exacerbated the inflammatory cells influx, LAR, and AHR. Treatment with either DEX or FP attenuated the airway cellular inflammation, LAR, but not the AHR. Mice only infected with influenza were resistant to the corticosteroids (DEX and FP) treatment. DEX but not FP showed antiviral activity against HPIV3 and influenza A in vitro.

These data suggest that influenza infection in a murine model of allergic airways inflammation exacerbates the inflammation and alters the sensitivity toward corticosteroids. It is also suggested that some elements in the influenza associated exacerbation of murine model of allergic airways inflammation are refractory or not regulated by corticosteroid treatment.

Examination of viral and bacterial exacerbations of airways inflammation and function

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Chronic obstructive pulmonary disease (COPD) is an umbrella term that encompasses chronic bronchitis, emphysema and airway obstruction. COPD patients are also prone to acute exacerbations (AECOPD) caused primarily by viral and bacterial infection, which leads to an increase in inflammation, a worsening of symptoms and can lead to death. There is an unmet clinical to better understand and treat AECOPD as well as COPD in general, but this is hindered by unreliable animal models of COPD and AECOPD. The aim of this thesis was to establish an animal model of COPD that could be exacerbated by an infectious agent.

Firstly an LPS model of COPD was established in the guinea pig, which resulted in a macrophage and neutrophil inflammatory profile, emphysematous changes, a decrease in lung function and partial steroid insensitivity that could be partially reversed with low dose theophylline. Human parainfluenza 3 virus failed to cause any infection in the guinea pig, so a model of AECOPD could not be established in this model.

A chronic cigarette smoke model in the mouse was established, which again demonstrated a similar phenotype to COPD. This model was able to be exacerbated by the bacteria nontypeable *Haemophilus influenza* (NTHi) with increases in neutrophils and the neutrophil chemoattractant CXCL1. However, it was also observed that while NTHi could exacerbate the model, responses to NTHi in cigarette smoke challenged mice compared to sham challenged animals were impaired, with significant decreases in CXCL8, TNF-a, IFN-γ and IL-10. This impairment was also observed in monocyte derived macrophages (MDMs) challenged with cigarette smoke extract (CSE) with significant impairment of IL-1ß, while chronic LPS challenge also impaired IL-6 and phagocytosis.

The data in this thesis highlights a possible increase in steroid responses by low dose theophylline in an LPS model in the guinea pig. It has also demonstrated chronic cigarette smoke exposure in the mouse can be exacerbated by NTHi, however the inflammatory response is impaired compared to sham challenged animals suggesting that cigarette smoke impairs the innate immune response. MDMs also demonstrated an impaired response to NTHi after CSE or LPS challenge.

Development and validation of a generic instrument for assessing the quality of decision-making

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Decision-making per se can be regarded as part art and part science in the development of new medicines. In the area of pharmaceutical development, decision-making plays a pivotal role in the continuation or the termination of further development or withdrawal of medicinal products. The decisions made at each stage have a direct impact on all stakeholders namely, pharmaceutical companies, regulators, payers and patients. What is lacking at present is a qualified understanding of the subjective decision-making approach, influences, behaviours and other factors which impact the decision-making of individuals and organisations involved in the delivery of new medicines. The aim of this study was, therefore, to develop and validate a generic instrument for appraising the quality of decision-making.

Semi-structured interviews were carried out with 29 key decision-makers from the pharmaceutical industry, regulatory authorities and contract research organisations (CROs). They were invited to discuss all aspects, including their perception of decision-making and its role in drug development and regulatory review; decision making within their organisation; awareness and use of decision-making techniques; and impact and monitoring of decisions. Thematic analysis was carried out using NViVO 8©software. A preliminary 94-item instrument was developed from the themes and the sub-themes that emerged from the interviews. Content validity was assessed using qualitative and quantitative data from an expert panel involving six key decision makers. A separate international cohort of 120 individuals working in the pharmaceutical industry, regulatory authority or CROs was recruited for factor analysis to reduce items. A further 78 individuals completed the final version of the QoDOS for construct validity and reliability.

Most individuals interviewed were male (55% -n=16) and their level of experience ranged from 7 to 35 years. 32 themes and 90 sub-themes of aspects of decision-making were identified from the interviews. The median numbers of themes reported by experts was 6 (range = 1-10). The key themes included: quality and validity of the data; political, financial, competitor and reward influences; analytical and logical approach; overconfidence in own judgement; plunging in or procrastinating with decision-making; impact analysis of decisions; education and awareness of evolving decision-making techniques; and SWOT and alternate outcome planning. Relationships between the themes were identified.

A 94-item generic instrument for assessing the quality of life decision-making, Quality of Decision-Making Orientation Scheme (QoDOS)©, with a 5-point Likert response scale was developed. The content validity panel's rating of each item on a 4-point scale for the 4 attributes showed "strongly agreed" or "agreed" (88%) with an ICC value of .89 (CI = 0.56 –0.99) suggesting a high agreement between the panel members' responses. This led to the reduction of 20 items and addition of two items as a result of cross-referencing with the qualitative data. Thus, the 76 items (version 2) emerged from content validation. Factor analysis produced a 47-item measure with four factors. The QoDOS showed high internal consistency (n = 120, Cronbach's alpha = 0.89), high reproducibility (n = 20, ICC = 0.77) and a mean completion time of 10 minutes. 10 hallmarks of "Good Decision-Making Practice" (GDMP) were identified.

The QoDOS is a valuable addition to the decision-making tool box of drug developers and regulators and has the potential to fill the missing gap of the entire process which is building quality into the lifecycle of medicine. The identification of ten hallmarks and generation of a framework for GDMP are also important contributions of this study to the field.

An evaluation of the contribution of pharmacy sales data for purposes of public health

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The contribution of over-the-counter (OTC) medicines sales data from pharmacies for public health has previously attracted interest in the UK. In this study, data for several OTC medicines were utilised to explore their contribution to (a) understand the impact of medicine reclassification or increased regulation on supply and (b) the surveillance of infectious diseases in the community in Wales.

Following the reclassification of ophthalmic chloramphenicol (June 2005) an increase in primary care supply (OTC and via prescription) of 54% (47,026 units) in eye drops and 29% (15,657 units) in eye ointment were observed (2004 to 2010). Despite this increase the items of eye drops prescribed were similar 12 months before and five years after the reclassification. The impact of regulatory changes concerning the non-prescription sale of opioid-containing analgesics was studied. In the 12 months following September 2009 legislative changes there was a significant fall in sales of codeine- and dihydrocodeine-containing solid oral dosage forms ($p<0.05$). Similarly, following the pack size restriction of non-prescription pseudoephedrine and ephedrine products (April 2008), significant ($p<0.05$) year-on-year reductions in the total weight of pseudoephedrine sold were observed. Sales of non-prescription ophthalmic chloramphenicol were monitored on a small area basis in two areas with known outbreaks of infective conjunctivitis. In both areas sales data did not demonstrate the required sensitivity. When monitoring seasonal influenza, significant positive correlations were observed between cough/cold/flu medicines sales and indicators of influenza activity in Wales.

In alignment with the professional standards for public health practice for pharmacy produced by the Royal Pharmaceutical Society, the work undertaken demonstrated a number of potential uses of medicines sales data for public health. Routine data collection, particularly if captured at time/point of sale, would further enhance its usefulness in detecting and tracking public health incidents.

Small molecule inhibitors of CYP24A1 for the treatment of various cancers

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In the last three decades vitamin D, or calcitriol, has been found to have important anticancer role in different cancer types. Unfortunately, a therapy using calcitriol remains a challenge due to increased drug resistance as a consequence of the up-regulation of CYP24A1, which metabolises and inactivates calcitriol. Moreover, the hypercalcaemia associated with an elevated dose of calcitriol does not allow the use of vitamin D at a high concentration. Analogues of calcitriol have enhanced anti-tumour activity, reducing the calcaemic undesired effect. The use of CYP24A1 selective inhibitors could be the appropriate strategy to increase the lifetime and thereby the anti-cancer functions of calcitriol and its derivatives. Consequently, the aim of this project is to develop new, potent and selective inhibitors of CYP24A1 that could be used in the treatment of different types of cancer in order to enhance endogenous vitamin D levels and favour its anti-tumour activity.

Through molecular modelling studies, a new CYP24A1 homology model has been prepared and the active site has been characterised examining the disposition of (R)-VID400, a CYP24 inhibitor, (E)-N-(2-(1H-imidazol-1-yl)2-phenylethyl)-4-styrylbenzamide (MCC165), a compound previously synthesised in our laboratory that showed a potent CYP24A1 inhibitory activity (IC50= 0.3µM), and the natural substrate calcitriol. Different series of potential CYP24A1 inhibitors were designed in order to mimic completely the calcitriol disposition in the binding pocket and to interact with the haem iron of the enzyme catalytic site. For each series a synthetic pathway was developed. The synthesis was followed by a CYP24A1/CYP27B1 inhibition assay.

All the compounds occupy the same hydrophobic tunnel as calcitriol and access the active site through the same channel. Moreover the substituents in the lateral chain bind directly to the haem iron via a lone pair of electrons. The different syntheses were obtained after several optimisations of reactions and routes. The CYP24A1/CYP27B1 inhibitory activity (IC50) using a cell-free assay and the value of the Ki (dissociation constant) of the different series of compounds, compared with ketoconazole (Ki= 0.030 µM, IC50= 0.47 µM) as the standard, were evaluated. Selectivity of CYP24A1 over CYP27B1 was also calculated. New potent CYP24A1 inhibitors were found. Selectivity gave a range from poor to moderate results with selectivity improved in some case compared with ketoconazole (selectivity: 1.6).

Characterising response and resistance mechanisms to Faslodex in breast cancer

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In ER+ breast cancer initial responses to antihormones are variable, complete responses are rare and resistance is eventually acquired by many patients. It is important to model these events to discover predictive markers of antihormone outcome and so targeted strategies can be developed to maximise antihormone effectiveness. To date, most studies have employed the MCF-7 cell line which fails to represent the variability of ER+ disease. Focusing on Faslodex (fulvestrant), the thesis objective was to use 4 cell lines in vitro encompassing ER+/HER2- (MCF-7/T47D) and ER+/HER2+ (BT474/MDA-MB-361) disease to (i) characterise the magnitude of initial antihormone response, (ii) monitor the onset of resistance by prolonged treatment and (iii) detail gene expression changes during Faslodex treatment.

All models were initially growth-inhibited by Faslodex, with superior responses in HER2- lines. Microarray analysis revealed gene cohorts affected by Faslodex treatment differed between HER2+ and HER2- models. While MCF-7, BT474 and MDA-MB-361 cells acquired Faslodex resistance, this failed to develop in the T47D line, providing a model of complete response. A filtering process identified genes involved in the varying Faslodex responses and clinical relevance was determined using the NEWEST Faslodex clinical trial dataset.

Of interest was the Faslodex-induction of CXCR4, as a potential mediator of acquired resistance, while suppression of the RET signalling pathway related to improved initial response in the ER+/HER2- setting.

Importantly up-regulation of DCN by Faslodex was associated with improved Faslodex response in T47D cells and also with proliferation (Ki67) fall in the NEWEST clinical trial. shRNA knockdown of DCN reduced the sensitivity of T47D cells to Faslodex and enabled development of resistance.

This thesis has successfully identified novel elements of Faslodex response and resistance and further work is now required to clarify the importance of these mediators and to determine if DCN could prove a useful clinical biomarker of Faslodex response.

Development, validation and clinical application of a patient-reported outcome measure in hyperhidrosis: The Hyperhidrosis Quality of Life Index (HidroQoL ©)

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Consideration of broader outcomes of disease, especially those exclusively experienced and reported by the patient, such as HRQOL, is not only consistent with the 'whole person' view of health contained in the 1948 WHO definition, but is also a prerequisite to building health-care systems that are responsive to the needs of the patients. For chronic skin diseases, such as hyperhidrosis, these provide a useful indicator of how a patient feels and functions disease for both practical and methodological reasons. The aims of this study therefore were to investigate the impact of hyperhidrosis on patients' HRQoL using a mix of qualitative and quantitative methods. In addition, a further aim was to develop and validate a disease-specific instrument for assessing HRQoL in hyperhidrosis. In pursuing the above aims, the feasibility of applying online social networking sites for outcomes research in dermatology was assessed.

Patients were recruited through online social networking communities related to hyperhidrosis for all stages of the study. Interviews, focus groups and surveys were used for collecting qualitative data from patients (n = 71) to understand quality of life issues of patients, and to provide the content of the new instrument. Dermatologists (n= 5) and patients (n=7) took part in the content validation of the HidroQoL©. Item reduction and the development of the scale's structure was carried out through several field-testing studies (n: USA, 559; UK, 115), using the item response theory (IRT) Rasch model and factor analyses. Further psychometric testing was performed in a separate study (n = 241). Distribution-based methods were applied in establishing minimum clinically important difference (MCID).

A thematic analysis of the qualitative data collected produced 29 quality of life themes and 102sub-themes, forming the content for the initial 49-item HidroQoL©. The two expert panels judged the instrument as content valid, with a few suggestions. The Rasch analysis modelling led to the collapsing of response categories (from five to three) and the reduction in number of items (from 49 to 18), to ensure a perfect model fit. Factor analyses supported both a single- and a two-factor structure. In subsequent construct validation study the HidroQoL correlated with the DLQI (r_s=0.572, $p < 0.01$) and the Skindex-17 (r_s= 0.551, $p < 0.01$). Reliability was high (Cronbach alpha = 0.9; test-retest ICC = 0.93). The scores were sensitive to change in patients' disease severity (standard response mean = 0.8, 95% C.I: 0.34-1.27). The scale banding proposed for the HidroQoL score is as follows: 0 – 1, no effect at all; 2 – 11, small effect; 12 – 22, moderate effect; 23 – 32, large effect; 33 – 36, very large effect. The MCID values were 1.94 – 3.07, for generalised hyperhidrosis, 2.16 – 4.36, for axillary hyperhidrosis, 2.15 – 3.39, for palmo-plantar hyperhidrosis. An MCID of three is currently being proposed for all types of hyperhidrosis.

This study has provided the initial evidence supporting the appropriateness of the content of the HidroQoL and validity of inferences from its scores for assessing HRQoL in hyperhidrosis. In addition, the availability of MCID estimates for the HidroQoL will facilitate its clinical interpretation in both research and routine clinical practice. This study has also demonstrated how CTT and IRT can be integrated in the development and validation of a new generation of HRQoL instruments, using social network for patient recruitment.

Development of a universal benefit-risk assessment framework and its application for regulatory agencies

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The assessment of medicines has moved from efficacy and safety to that of a benefit-risk balance and regulatory agencies and pharmaceutical companies are improving their processes in order to achieve greater consistency and transparency in decision-making. However, their efforts are largely independent and do not address the lack of consistency in decisions by different countries, albeit for the same medicine, resulting in the potential inaccessibility of important medicines. The aim of this study was the development and validation of a universal benefit-risk framework for use by regulatory authorities.

A questionnaire, specifically developed for this study, was used to evaluate the current approaches to benefit-risk assessment of medicines by14 regulatory agencies and 24 pharmaceutical companies. None of the 11 agencies (79%) and 20 companies (83%) that responded used a fully quantitative approach, but the majority used a qualitative system for benefit-risk assessment. The development of a universal benefit-risk framework for use by both regulators and industry, with the involvement of all stakeholders, was supported by the study participants.

A comparison of the existing benefit-risk assessment frameworks used by agencies and companies identified the common elements. As no major differences were observed, an 8-step universal framework was developed which incorporated the other frameworks. To support the framework in the assessment of benefits and risks, a template for documenting the benefit-risk decision together with a user manual was also developed. Four regulatory agencies conducted a retrospective pilot study to investigate the feasibility of this framework, the benefit-risk template and user manual.

Subsequently, a prospective study was conducted by TGA of Australia, Health Canada and HSA of Singapore. The agencies found the benefit-risk template was 'fit for purpose' in terms of the relevance of information supporting the benefit-risk decision, the documentation and communication and the relative importance and values of the benefits and risks. The results showed that the benefit-risk summary template was adequate to document benefits and risks, relevant summaries and conclusions for the emerging markets. The applicability and validity of the summary component of the benefit-risk template was evaluated by sixteen HSA clinical reviewers in a retrospective study. They found that the BR Summary Template was adequate to document benefits, risks, relevant summaries and conclusions. However, a revision of the BR Summary Template should include technical improvements and more details of safety information. The BR Summary Template was thought to be a useful tool for communicating benefit-risk decisions to a variety of stakeholders.

The formats of publicly available reports from major regulatory agencies were compared and found to be generally similar. When compared to the BR Template, the listing of benefits and risks, assigning of weights and values, visualisation and a more detailed, systematic standardised structure were found to be absent. This research has demonstrated that the 8-step universal framework is of value for the assessment of benefits and risks of medicines by regulatory agencies and the template was found to be useful for documenting and communicating benefit-risk decisions.

Synthetic routes to the tumour proliferation biomarker FLT and ProTide analogues for PET imaging

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Being one of the most rapidly advancing cancer imaging techniques in recent years, Positron Emission Tomography (PET) represents a standard of excellence with respect to sensitivity and resolution for the non-invasive in vivo molecular imaging of solid tumours via the detection of radiotracer molecules. Amongst these radiotracers, radiolabelled fluorinated nucleosides such as 3'-Deoxy-3'-[18F]-fluorothymidine (18F-FLT) has been widely recognized as a key, specific biomarker for tumour cellular proliferation. Current methods for the commercial production of [18F]FLT are characterized by low overall yields and time-consuming high-performance liquid chromatography (HPLC) purification. These disadvantages could be rectified by the development of a fast, efficient synthetic route to FLT that could enhance the productivity and reduce the

reaction time of the fluoridation step necessary for the synthesis of short-lived radioisotope, 18F (t1/2=110 min) installed nucleoside.

This project focussed mainly on the development of a new efficient chemical synthetic route to FLT. The synthesis and in vitro evaluation of a series of pro-nucleotide (ProTide) analogues of FLT as new potential therapeutic agents was also carried out.

Various studies regarding FLT synthesis have been carried out on the cold (non-radioactive) 19F and radioactive 18F isomer by varying and optimizing conditions for the incorporation of different protecting groups and also different fluoridation reactions by nucleophilic displacement.

Further optimization studies were made for the fluoridation step and the synthesis of [18F]FLTProTide analogues as new diagnostic PET imaging agents by variation of different chemical parameters on the phosphoramidate group was attempted.

The synthesis of 19F- FLT based ProTides as new therapeutic agents were initiated by the introduction of the phosphoramidate group at the 5'-position of the furanosyl group of thymidine under basic conditions followed by fluoridation to generate the desired analogues.

In addition to that, biological evaluation of the newly developed 19F-FLT ProTide analogues for anti-HIV 1 and anti-HIV 2 activities was undertaken on CEM cells. The results in those models indicated that the synthesized compounds were less potent than the parent nucleoside FLT. However in TK- (HIV-2) cells, the analogues retained biological activity in contrast to FLT. This suggested that the FLT ProTides bypassed the first phosphorylation step.

However, the therapeutic in vitro evaluation for anti-tumour activity on L1210, CEM and HeLa cells showed no significant activity.

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