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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, currently being ranked first in The Guardian league table. 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 13th 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, most especially Dr Keith Brain.

Rebecca Price-Davies
July 2013

Antimicrobial activity and surface structure of silver nanoparticles coated surfaces prepared by Metal Plasma Immersion Ion Implantation and Deposition (MePIIID)

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Silver nanoparticles is shown to have effective antibacterial activity[1,2] and is used for coatings of medical devices[2]. In this project, we are investigating the antibacterial properties of five silver nanoparticles coating samples prepared by Metal Plasma Immersion Ion Implantation and Deposition (MePIIID) against Gram-negative bacterium Escherichia coli (E. coli) and Gram-positive bacterium Staphylococcus aureus (S. aureus) at two different incubation time, 5 and 24 hours. We are also measuring the surface roughness and analyzing the surface morphology of the prepared samples by observing the Atomic Force Microscope (AFM) images of each sample. The coating method used, MePIIID is a combination of plasma immersion ion implantation and deposition of metals[3,4]. The main aims of this experiment are to prove MePIIID methodology of silver nanoparticles coating preparation produce an effective antimicrobial activity, observing difference in activity against two types of bacteria at two incubation time, and observing if there is any correlation between sample surface roughness and antimicrobial activity.

The experiment involves plating of bacteria on agar plate to count the number of colonies form, in order to determine the viable count per area sample of 1cm^2. The samples are firstly incubated with dilute bacteria suspension in a 24-well plate for either 5 or 24 hours, and later undergo steps like washing and vortexing.

Lower mean viable count/cm^2 of silver-coated samples compared to control showing that there is antibacterial activity but it is considered weak and not effective activity due to a high number of surviving bacteria remaining. There is greater activity against E. coli than S. aureus and no correlation found between surface roughness and antimicrobial activity.

In conclusion, weak antibacterial activity could be due to ineffective silver coating preparation, suggesting that silver nanoparticles coating method by MePIIID as prepared in this project is less effective in producing profound antibacterial activity.

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Learning Outcomes as a tool to explore final year MPharm undergraduate students' perceptions of preparedness for pharmacy practice

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Every year almost 3000 pharmacy students graduate from the UK but it is unknown how many of these feel equipped with the necessary competencies for pharmacy practice.[1] There is limited published research around whether the degree is effective in preparing students for the workplace environment.[2] This study aims to determine the perception of final year Cardiff MPharm students' preparedness for pharmacy practice measured against curriculum assessments and GPhC learning outcomes.

School ethics approval was granted from the university research committee. Purposive sampling was used to recruit 19 participants; characteristics considered during sampling were gender, ethnicity and nationality.[3] Two focus groups and nine semi-structured interviews were conducted. Each focus group and interview was audio-taped with consent, then transcribed (*ad verbatim*) before being analysed using the code and retrieve method, producing a thematic framework. Themes identified were used to inform the development of a questionnaire.[4]

Participants identified their perceptions of preparedness using GPhC learning outcomes and assessment show cards. The findings showed participants had a high level of perceived preparedness for pharmacy practice and on whole met the GPhC and curriculum outcomes. However the extent of preparedness differed

amongst students. Those who had experience outside of university felt more prepared with respect to dispensing, over the counter (OTC) supply and working with other healthcare disciplines. Students felt assessments were useful to assess competence but thought they did not provide an accurate measurement of their actual performance as a pharmacist due to time constraints and artificial environment setting.

The Cardiff MPharm degree provides students with the knowledge for pharmacy practice but the variance in the preparedness of students needs to be reduced. This study advocates more time dedicated to OTC supply, dispensing and hospital placements. This should result in qualified pharmacists from accredited GPhC degrees starting at a higher more uniform level.

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

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Skin penetration of topical medication is an important challenge to drug delivery.[1] Polar surface area (PSA) is the sum of polar surfaces, particularly nitrogen and oxygen, including the attached hydrogen atoms.[2] This can be an important indicator how successfully a topical drug in permeates the skin. This can be assessed by investigating the relationship between topographical polar surface area (tPSA) and skin permeation (J). Depending on the results of the evaluation, it would lead to a decision whether PSA can be applied as a rule of thumb for predicting successful topical medication candidates.

Relevant literature reporting skin penetration of topical medication was obtained. The reported compounds and derivatives were drawn using chemical structure drawing software to automatically calculate tPSA values. The value was then plotted against reported J-values using Microsoft Excel to enable the generation of charts to determine the relationship, if any, between tPSA and J to test the project hypothesis.

The results were found to indicate some good R^2 values, which demonstrates the linearity of the relationship. However, the best data available included only seven compounds, which is still a low number.

Further investigation of the relationship is required. This can be achieved by calculating PSA of 3D structures, and laboratory experimentation of skin penetration. After completing the research, it was concluded that there is an inverse relationship between tPSA and skin penetration. However, more work needed as there was a limited number of compounds and lack of time supplied.

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Characterising changes in the numerical competence and confidence of students between MPharm I and MPharm II

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Diagnostic numeracy tools are valuable in testing inherent numeracy skills of incoming university students.[1] The study aims were to use a diagnostic numeracy tool to establish if the numerical competence and confidence of MPharm students at Cardiff School of Pharmacy and Pharmaceutical Sciences (CSPPS) improved after one year in higher education and to determine the factors which govern numeracy skills.

In October 2011, CSPPS MPharm I students (N=140) sat a contextualised diagnostic numeracy test and one year later (on entering MPharm II) sat exactly the same test. Statistical analyses were conducted using SPSS.

Score (p<0.001) and confidence (p<0.001) significantly increased between Year 1 (score=20.3±4.33; confidence=18.2±6.17) and Year 2 (score=22.2±3.36; confidence=21.5±4.61). Students principally educated in Malaysia had higher scores and greater confidence. This was also true for students whose highest mathematics qualification was A level compared to those without A level. Scores and confidence did not differ significantly between males and females. The most incorrectly and least confidently answered questions involved unit conversions and multi-step calculations.

Feedback after test 1 and MPharm I pharmaceutical calculations teaching may have contributed to the significant improvement in numeracy skills between the two study time points. Different countries' teaching methods[2] can impact on numeracy skills and MPharm students with A level mathematics have previously demonstrated stronger numeracy skills than those without.[3] This study supports those observations. The lack of difference between males and females does not agree with the literature[4] relating to students in other scientific disciplines. However, males made up only 24% of the study group. A limitation of the study is that students from only one School of Pharmacy were involved. Future research could see the involvement of other Schools of Pharmacy.

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Imaging and analysis of bacterial pulpal tooth infection and its effect on pulpal cells

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Streptococcus anginosus is recognised as one of the earliest colonisers involved in pulpal infection[1] which can lead to pulp necrosis and irreversible tissue damage.[2] Triclosan could potentially be an alternative treatment option to a root canal, as it has both antibacterial and anti-inflammatory properties essential for healing pulpal tissue.[3] This study aims to use confocal microscopy to obtain 3D images of how *S. anginosus* grows into pulpal tissue and to test the effects 300 µg/ml triclosan against the growth of *S. anginosus*.

S. anginosus bacteria were standardised to 10^5 cfu/ml, stained with 1% FDA solution, and resuspended into a DMEM + 10% BHI co-culture media with a 0.22 µm filter. Triclosan was dissolved in 100% DMSO before diluting with the bacterial filtrate to create a concentration of 300 µg/ml. Two ml of this suspension was then used to inoculate 2 mm thick rat tooth slices anaerobically (5% CO_2) at 37°C for 24 hours. Samples were stained with Hoechst then viewed with a confocal laser scanning microscope at X20 magnification using two different protocols.

The images produced showed *S. anginosus* growth in scattered colonies throughout pulpal tissue with co-localisation between bacterial and pulpal cells. The bacteria were present at least 100 µm into the pulpal tissue as viewed with a z-stack image. Triclosan reduced the growth of *S. anginosus* in the pulp compared to samples incubated without triclosan.

Although clear trends were observed demonstrating that triclosan reduced the growth of *S. anginosus* in pulpal tissue, it was not possible to collect enough images to conduct a statistical analysis. Despite providing a promising future for the use of triclosan as an alternative treatment to a root canal in the presence of a pulpal infection, the experiment needs repeating to produce images clear enough to be counted.

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Evaluating intra- and inter- individual variability in capsule puncture within dry powder inhalers

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Dry powder inhalers (DPI) are a commonly used form of pulmonary drug delivery. Gelatin capsules have been used in single unit dose DPI since their introduction in 1971.[1,2] However more recently hypromellose (HPMC) capsules have become available for use in DPI, with some reports claiming they have better puncturing properties than gelatin capsules.[3] There has been little research into the inter- and intra-individual variability in capsule penetration. The aim of this study is to characterise the puncture performance of HPMC and gelatin capsules when perforated by a single pin DPI, operated by a member of the public.

Following informed consent participants (n=36) were supplied with a Plastiape® monodose inhaler and instruction sheet before being handed, in random sequence, five HPMC and five gelatin size 3 capsules, which had been conditioned in desiccators over a saturated solution of calcium chloride (RH 33%). Participants were provided with a questionnaire to collect demographic data. Punctured capsules were imaged using a light microscope and the puncture area of both the cap and body was measured using Image J® software.

The punctures in HPMC capsules (cap mean 1.58 ± 0.80, body mean 1.72 ± 0.79) were smaller and less variable than gelatin capsules (cap mean 3.21 ± 1.98, body mean 2.89 ± 1.34). Puncture appearance and flap condition were also more consistent in HPMC capsules than gelatin capsules. In agreement with previous publications, gelatin capsules appeared more brittle.[3]

To conclude, the punctures created by a 2-pin inhaler in HPMC capsules appear to be more reproducible than those in gelatin capsules. Patient factors, such as age and previous inhaler experience, had no noticeable impact on the area of the puncture or the condition of the flap for both HPMC and gelatin capsules.

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A study to determine the *in vitro* activity of antimicrobial peptides against various bacteria

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The emergence of antibiotic resistant bacterial strains has caused clinicians to search for other sources of antimicrobials.[1] Antimicrobial peptides (AMPs) are polyproteins isolated from various multicellular organisms. Resistance has been noted to develop slower to AMPs than to existing antibiotics.[2,3] We determined the activity of a range of commonly derived AMPs against a panel of clinically and environmentally relevant bacteria *in vitro* to which resistance to classical antibiotics has been noted.[4] This study investigates the activity of 6 AMPs: IL-37, IL-37 Scrambled, Bee defensin-1, Melittin, Pep 14 and Pep 15 against 6 different bacteria: *Staphylococcus aureus, Escherichia coli, Mycobacterium smegmatis, M. abcessus, Paenibacillus larvae* and *Clostridium difficile.*

Serial dilutions generated 6 peptide concentrations ranging from 100, 75, 50, 25,10 and 5 (ug/ml). 1ml of a 1 in 100 dilution of overnight broth culture of each bacterium was spread across the surface of agar appropriate for each bacterium before various concentrations of each peptide were spotted in 10ul drops. An appropriate antibiotic was used as a positive control for each bacterial strain. Plates were then incubated for 24 hours at 37°C and the diameter of the resulting zones of inhibition were measured in millimetres to determine the minimum inhibitory concentrations (MICs).

Only two peptides demonstrated activity compared to the controls; melittin which was active against both *S. aureus and P. larvae (*MICs were 50ug/ml and 100ug/ml respectively), and bee defensin which was active against both *C. difficile* and *P. larvae* (5 ug/ml).

AMPs seem to be good candidates for further investigation as future antimicrobials. If introduced, this would allow for a decrease reliance on classical antibiotics. Further investigation will increase understanding of the relationship between naturally derived peptides and the microbial challenge of the natural environment from which they are isolated.

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6-chloro-penciclovir phosphate prodrugs as new anti-HIV agents

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Acyclovir has shown anti-HIV activity in patients co-infected with HSV and HIV.[1] It was discovered that acyclovir could inhibit HIV reverse transcriptase[1] due to its activation in co-infected patients by thymidine kinase.[2] ProTides of acyclovir were synthesised and found to be active against HIV, however they were found to be cytotoxic[3]. In previous work, virtual screening of nucleoside analogues was carried out modifying the nucleoside base and/or the sugar moiety,[3] among these 6-chloro-penciclovir showed a good profile and therefore was chosen for this project. Phosphate prodrugs have been synthesised to improve delivery of the drug as the monophosphate cannot be directly administered.[4]

A ProTide, a cyclic phosphoramidate and a diamidate were designed and synthesised from 6-chloro-penciclovir. A bis-protide and a bis-diamidate were also produced. Due to the presence of two hydroxyl groups, the synthesis of the mono-diamidate of 6-chloro-penciclovir was not achieved; therefore the monoacetylated 6-chloro-penciclovir was produced allowing synthesis of the diamidate. A 6-chloro-monoacetylated ProTide was also synthesised.

Enzyme tests using carboxypeptidase γ in acetone-D6 and a trizma buffer were undertaken on CF3583, CF3584 and CF3596 to understand if the prodrugs could be activated. The compounds were sent for biological testing for their ability to inhibit HIV-1 (MT-4) cells. The EC_{50}, CC_{50}, and IC_{50} of the compounds were established. The nucleoside analogue, 6-chloro-penciclovir was inactive. All prodrugs produced were found to have a degree of anti-HIV activity. However they were also found to be cytotoxic. CF3595 showed promising results with a low EC_{50} and no cytotoxicity.

Six phosphate prodrugs and two nucleoside analogues were synthesised. The aim of the project was achieved as prodrugs were synthesised to release a monophosphate drug to inhibit HIV-RT. All compounds showed activity, except the parent nucleoside. Most compounds were cytotoxic. CF3595 is currently being retested to confirm the results.

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Locating natriuretic peptide receptors in the rat myocardium

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Myocardial ischaemia-reperfusion (I-R) injury is the paradoxical injury which occurs following reperfusion of ischaemic tissues. Following myocardial infarction, 50% of final infarct size is caused by I-R injury[1] but at present, there are no effective treatments for this injury. Natriuretic peptides have been shown to reduce infarct size[2, 3] by interacting with natriuretic peptide receptors and are believed to trigger signalling pathways leading to cGMP production, a cardioprotective second messenger.[4] There is currently limited evidence to show that natriuretic peptide receptors are expressed at functional levels in the myocardium. We hypothesised that NPR-A, NPR-B and NPR-C would be present in rat ventricles and in isolated cardiomyocytes.

Samples taken from naïve left and right ventricle tissue (n=4) were analysed using Western blotting to detect the three natriuretic peptide receptors: NPR-A, NPR-B and NPR-C. Cardiomyocytes were isolated by enzymatic digestion of left ventricle samples (n=4) and also analysed for the receptors using Western blotting. Reverse transcriptase polymerase chain reaction was used to determine whether mRNA for each of the receptors was present in the isolated cardiomyocytes.

Western analysis showed that all three receptors were expressed in ventricle samples. Expression of NPR-A and NPR-B was shown to be higher in right ventricle samples than in left ventricle samples, while NPR-C was expressed more in left ventricle samples than in right ventricle samples. NPR-B and NPR-C were both expressed in isolated cardiomyocytes but results for NPR-A expression were inconclusive due to poor antibody specificity. RT-PCR results showed that transcripts for all three natriuretic peptide receptors were present in cardiomyocytes.

Confirming the presence of natriuretic peptide receptors in the myocardium means that they could be potential targets for novel therapeutic strategies to reduce myocardial I-R injury. Further investigation is needed to examine the signalling pathways that are triggered by activation of these receptors.

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A framework to support pharmacist-patient consultations through the medium of Welsh

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The Medication-Related Consultation Framework (MRCF) is a tool providing pharmacists with a patient-centered consultation structure to assist in identifying medication-related issues,[1] and has recently been translated into Welsh. Pharmacies in Wales have a duty to consider the linguistic needs of the Welsh-speaking public.[2] The study aimed to explore pharmacy students' and practitioners' views about using a framework to support pharmacist-patient consultations in Welsh.

The Welsh MRCF was distributed to ten pharmacy students and twenty practitioners from all areas of Wales. Semi-structured interviews plus one focus group were held with the participants. Written feedback forms were also used to aid in capturing feedback. Interviews were transcribed verbatim and two separate thematic analyses were carried out on the students' and pharmacists' data.

Seven pharmacy students and thirteen pharmacy practitioners were interviewed. Overall, participants, thought that the Welsh MRCF was worthwhile and highlighted the significance of the Welsh language in establishing a good therapeutic pharmacist-patient relationship. Many had difficulty understanding the formality of the language used and did not believe that the current framework would make individuals feel confident about conducting consultations in Welsh.

Pharmacy students and practitioners liked the concept of having a framework in place but the formality of the language used in the current Welsh MRCF needs simplifying so that it can be understood by all levels of Welsh-speakers. Although it could be useful to provide structure to a consultation, further work would be needed to make it 'fit for purpose'.

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Does cilengitide increase overall survival for patients with glioblastoma multiforme? A systematic review

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Glioblastoma multiforme (GBM) is a highly aggressive and vascularised brain tumour that affects mostly the elderly with median survival of around 12 months following standard therapy of surgical resection followed by radiotherapy and temozolomide.[1,2] Due to the fatality of this cancer and lack of established treatment for recurrent patients, there is need for further research to increase survival rates. A promising candidate cilengitide which is a cyclic arginine-glycine-aspartic acid peptide that antagonises integrins which play an important role in the growth of GBM.[3] The primary aim of the project was to find out whether cilengitide increases overall survival and this was done by looking at studies that compared two doses (500mg/2000mg) and also looked at patients who received standard therapy alone and those who received it with cilengitide.

Following a literature search, 77 potentially relevant articles were identified. The abstracts of these papers were analysed against inclusion/exclusion criteria. Four articles were identified against the inclusion criteria. Analysis of the papers was done by extracting individual hazard ratios and where this was not possible extracting survival curves and then generating summary statistics using Review Manager and Graphpad Prism.[4]

The data shows there is an increase in overall survival for patients taking 2000mg compared to those taking 500mg with hazard ratio of 0.42(95%CI,0.34-0.51) $p < 0.00001$. However, there was no significant increase in overall survival for patients taking 500mg cilengitide with radiotherapy and temozolomide compared to radiotherapy and temozolomide alone with hazard ratio of 0.81(95%CI,0.59-1.13) $p > 0.05$.

Cilengitide shows some benefit and a high safety profile when given at a high dose (2000mg) for patients with Glioblastoma. However clinical trials need to be conducted to assess the effect of 2000mg cilengitide with radiotherapy and temozolomide.

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The role of Wnt signalling in the pathogenesis of Alzheimer's disease

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Alzheimer's disease (AD) is an irreversible, neurodegenerative disorder that leads to severe memory loss and cognitive decline.[1] An accumulation of amyloid-β (Aβ) (cleaved from amyloid precursor protein (APP)) is thought to contribute to the pathology seen in AD.[2] The London mutation mouse model used in these experiments overexpressed APP and consequently expressed Aβ with increasing age. Canonical Wnt signalling is thought to be dysfunctional in AD with debate surrounding its exact role.[3] Most current studies suggest that pharmacologically upregulating Wnt signalling could be a viable treatment option in AD.[3] This study investigated if there were any differences in canonical Wnt signalling between young, middle-aged and old wild-type (WT) and transgenic (TG) mice.

Cortices from WT and TG mice were extracted and levels of APP and Aβ determined. Levels of Wnt proteins total β-catenin, active β-catenin and Lef present were also investigated.

Overexpression of APP was confirmed in TG mice of all ages, however, increased levels of Aβ were detected only in old TG mice. The findings in this study suggested that Wnt signalling was upregulated in young TG mice (as determined by increased levels of active β-catenin in young TG animals). At middle age there was no difference in Wnt signaling between WT and TG animals suggesting an interaction between APP and Wnt in young mice that is no longer present at middle age. Results suggested that Wnt signaling was again increased in old TG mice.

It is probable that this suggested increase in Wnt signalling in old TG mice was in response to increased levels of Aβ. This increase implies that further upregulating the Wnt pathway may not be a feasible treatment option for AD and could potentially have detrimental effects. This study is important to help ascertain the eligibility of the Wnt pathway as a future pharmacological target.

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Calcium oxalate precipitate – a risk to parenteral nutrition patients?

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Parenteral nutrition (PN) is a method of feeding via the intravenous route.[1] Throughout this research it has been the degradation product of the least stable component of PN, (vitamin C) that has been of interest. It has been theorised that the final breakdown product (oxalic acid) is able to form a practically insoluble precipitate of calcium oxalate (0.67mg/100ml water) in the presence of calcium.[2] The aim was to find out the maximum amount of vitamin C that can be present with no calcium oxalate precipitate formation.

Various concentrations of oxalic acid were added to calcium chloride until a precipitate was detected. Samples were visually inspected, turbidity and pH measurements were also recorded. Experiments were carried out at pH 5-7, 2-8°C, room temperature and 35°C. The next step was to react vitamin C with calcium chloride.

Calcium oxalate solubility increased at lower pH and higher temperatures. In the reaction between ascorbic acid (0.96mg/100ml water) and calcium chloride at room temperature a precipitate was observed after 24 hours. However, at 2-8°C no precipitate was observed for 96 hours.

These experiments were carried out under conditions to drive the reaction; in the presence of oxygen and water allowing for oxidation and hydrolysis to occur. A catalyst was also present. Under clinical conditions procedures are put in place to minimise these. The use of multi-layered bags which are impermeable to oxygen have been shown to prevent against oxidative degradation.[3,4] Providing PN is stored in these multi-layered bags the commonly used levels of ascorbic acid is safe and unlikely to cause harm to PN patients.

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Prostate cancer cell exosomes are endocytosed by fibroblast cells

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Exosomes are nanosized vesicles secreted by many cells including tumours.[1] Modified exosomes have shown potential as a mode of selective delivery to a target cell and this has led to growing clinical interest in exosomes, as possible drug delivery vehicles.[2,3] In addition, current dogma suggests cancer exosomes

deliver TGF-ß to stromal fibroblast cells, which leads to their differentiation into myofibroblasts, resulting in the establishment of tumour tissue.[4] There are however, significant gaps in our understanding of the physical interaction between cancer cell exosomes and fibroblast cells. Our aim was to develop a method of direct, fluorescent labelling of prostate cancer cell exosomes that would allow tracking of interactions with fibroblasts by confocal microscopy.

Exosomes were purified from prostate cancer cells using the sucrose cushion isolation method and labelled using the fluorophore, Alexa Fluor® 488 C_5 Maleimide. Fibroblasts were exposed to labelled exosomes and/or Dextran Alexa Fluor® 647 and/or Transferrin Alexa Fluor® 633 Conjugate at 4^{o}C or 37^{o}C. Colocalization was observed on the confocal microscope.

Labelled exosomes were taken up by lung fibroblasts and significant colocalization with Dextran occurred as well as some colocalization with Transferrin. Exosome uptake was shown to be an active process and prostate cancer cell exosomes were taken up by endocytosis. A proportion of exosomes ended up in terminal lysosomes and some colocalized with the transferrin pathway.

Although a proportion of exosomes are degraded in terminal lysosomes, some exosomes go to other cell compartments. In the future, it would be useful for us to mathematically quantify the colocalisation, to further investigate the potential of exosomes as drug delivery vehicles. In addition, knockdown of key proteins involved in endocytosis, such as AP2, clathrin and flotillin-1could help to further understand uptake mechanisms. This new information makes an exciting contribution to knowledge on the dynamics of exosomes in cancer.

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Examining the impact of video instructions on the forces used by members of the public to apply “dummy” microneedle patches

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Microneedle devices are progressing rapidly towards the clinic with micron scale devices now in clinical trial. Minimal research has been conducted to examine the potential for self-administration of microneedles. The force required to apply a microneedle is a critical feature of microneedle penetration. Some microneedle designs, e.g.hollow silicon microneedles, exhibit a 5-fold safety margin between needle insertion and fracture force.[1] This study aims to characterise the application forces used by members of the public to apply “dummy” microneedle patches after watching an instructional video, and to compare them to baseline data i.e. without an instructional video.

The ethics committee at Cardiff School of Pharmacy and Pharmaceutical Sciences approved the study. An instructional video on microneedle application was developed. Demographic information (age, gender, any medical education and any experience of using needles) was recorded for each participant (n=41). Partcipants watched the information video before applying a force to the dummy microneedle patch, located both on the forearm and deltoid of themselves and the researcher, using a hand-held force gauge. Each measurement was repeated 3 times. Comments and observations were recorded. T-tests were used to analyse significance of results.

The average force used was 20.70+/-13.8 (standard deviation) N. Results varied from 2.45N to 74.85N, a 30-fold difference. This was comparable to the baseline data (n=50, mean=18.3+/-12.4N), which captured the intuitive forces used. Men (n=24, mean=25.4+/-15.0N) applied more force than women (n=17, mean=14.5+/6.8N) (P=0.004). Self-application forces (mean=25.42+/-14.8N) were significantly greater (P=0.004) than application to another person (mean=15.42+/- 11.1N).

The study concluded that video instruction did not impact on the reproducibility of forces applied by participants. To reduce the inter-patient variability in self-application forces it will be necessary to use an applicator or manufacture microneedles that can perform safely and consistently over the recorded force range.

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Stability assessment of the new generation lipid emulsion, SMOFlipid®, in the presence of glucose and oxygen

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The use of a mixed oil lipid emulsion containing fish oils rich in omega-3 fatty acids has been sought after to replace the more traditional pure soybean emulsions in parenteral nutrition.[1] The third generation lipid emulsion, SMOFlipid®, was designed in an attempt to increase the ω-6: ω-3 ratio and improve patient outcome, however, uncertainty surrounding its potential increased oxidation risk has hindered its use in clinical nutrition support.[2] The aim of this study was to generate pharmaceutical stability data for SMOFlipid® in the presence of glucose and oxygen, using a pure soybean emulsion, Intralipid®, for comparison.

Laser diffraction (LD) and optical microscopy were carried out to measure globule size changes and related to results from visual inspection, pH and dissolved oxygen (DO) analysis. Two studies were carried out in succession, the first measuring the effect of a range of glucose concentrations (0 to 16%w/v) on emulsion stability, and the second analysing the effect of an oxygen rich environment on stability. In the latter, the hypothesis suggesting temperature affects DO levels was also investigated.[3] Half of the samples were stored at 36°C, and the remainder at 4°C with calcium ions used as an agent to accelerate destabilisation.[4]

For both emulsions, glucose alone at high concentrations managed to cause an increase in maximum globule size, which was then emphasized by the addition of calcium. Changes in pH correlated well with observed variations in the globule size changes however data from microscopy and LD did not always correlate. DO testing samples tested in the presence of oxygen, particularly stored in a cold environment, had expected increased in levels of DO. SMOFlipid® generally displayed a higher level of stability across all methods.

The comparison of these two emulsions revealed the superiority of SMOFlipid® in the presence of both glucose and oxygen. Results suggest encouragement towards more frequent use of SMOFlipid® in current parenteral nutrition formulations.

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Development of an algorithm for converting the Dermatology Life Quality Index (DLQI) into EQ-5D utility values using historical data

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The Dermatology Life Quality Index (DLQI) and EQ-5D are two instruments used to measure patient health-related quality of life (HRQoL). The DLQI is a widely used dermatology-specific measure with high internal consistency and test-retest reliability.[1] The EQ-5D on the other hand is a generic utility measure preferred by NICE for the purpose of obtaining utility values for economic analysis.[2] DLQI scores can be mapped onto EQ-5D utility values in order to obtain utilities from studies where the EQ-5D was not used. Although there is an existing mapping model created by linear regression,[3] this has several weaknesses.

The aim of the study was to construct an improved algorithm to predict EQ-5D utility values from DLQI scores. Historical data was obtained from the University Hospital of Wales (n=256). Ordinal logistic regression, which has been used for mapping on previous occasions,[4,5] was used to estimate the probability that a respondent will select any given level of response on the EQ-5D dimensions. Results were compared to predicted utilities obtained using the existing linear method.

The ordinal model predicted over 40% of cases accurately while the linear model predicted none. However, the ordinal model was associated with higher mean squared error (MSE) and mean absolute error (MAE)

than the linear model, for both internal and external validation data sets. For both models, errors in prediction decreased as utility values increased, indicating that they perform poorly in poor health states.

The findings indicate that the ordinal model is inconclusive for prediction of utility values in the data set used. The ordinal model may be useful for non-UK samples as it can be used with the country-specific EQ-5D scoring tariff. It provides more detailed information on patients' health states than the linear model. It is recommended that this approach be repeated using a larger sample size to reduce standard errors and improve the model performance.

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Characterisation of new antihormone resistant breast cancer models developed from ER+/HER2- cells

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MCF7-derived breast cancer models have revealed EGFR and HER2 cross-talk with oestrogen receptor (ER) in anti-hormone resistance,[1] however promising preclinical targeting of these pathways alongside anti-hormones is not always translated into clinic.[2,3] The aim was to begin to characterize acquired resistant cells recently derived by continuous anti-hormone treatment of a further ER+ model, EFM19, as this may help clarify why some patients do not respond to combination therapies.

A panel of continuously cultured control EFM19 (CONT), faslodex (FAS), tamoxifen (TAM) and oestrogen deprivation (SFCS, X) resistant cell lines were characterized for growth and EGFR (1μM gefitinib) or HER2 (100nM Herceptin) inhibitor impact using Coulter Counting (n=3). A further experiment examined ER blockade (Faslodex 10^{-7}M). Migration studies used Boyden Chambers (n=2) and ER expression and activity (PR, phospho-ER), EGFR and HER2 profiled using immunocytochemistry with HScoring (n=6 fields from two coverslips).

While FAS resistant growth was slower (p=0.003), SFCS, X and TAM growth was equivalent to CONT. Migration decreased substantially in FAS, SFCS and X but increased in TAM by 205%. ER was decreased in FAS (p=0.002) but increased in SFCS and X (p=0.002) and was equivalent in TAM vs. CONT. PR decreased in all resistant lines (p=0.002) but phospho-ER remained detectable and TAM, SFCS and X were Faslodex growth-sensitive. EGFR (p=0.002) and HER2 increased in all resistant cells. TAM, SFCS and X were gefitinib sensitive and SFCS and X were Herceptin sensitive.

TAM was the most aggressive model in keeping with superior clinical benefit of further anti-hormones vs. tamoxifen. All resistant models were ER dependent and second-line anti-hormone responsiveness is common clinically.[4] Despite EGFR/HER2 increases, FAS were insensitive to EGFR and HER2 blockade and TAM to HER2 blockade, mirroring disappointing trial results for such agents.[3] Continued study of these models could clarify why some patients fail on combination therapy.

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

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Motivation is the process by which individuals are driven to act in order to achieve a goal. Greater levels of motivation often lead to higher levels of academic performance.[1] The aim of this study was to explore the views of first and fourth year of the MPharm students at Cardiff University, in relation to their motivation for choosing to study pharmacy, their motivation for choosing to study pharmacy at Cardiff University and from where they derive their ongoing motivation for the MPharm degree. This could highlight ways in which motivation for the MPharm degree could be improved.

Non-probability (purposive and convenience) sampling was used to identify and recruit a variety of students. Recruitment methods included email, personal approach and workshop announcements. The study was conducted using semi-structured, one-to-one, audio-recorded. The topic guide was developed following a literature review. Transcribed interviews were analysed using content analysis.

Ten fourth year students and seven first year MPharm students at Cardiff University were recruited. Students interviewed listed various motivating factors, also identified by others.[2,3] Such factors included external influences, the nature and content of the pharmacy degree, personal drive, university lecturing staff, feedback on assessed work, career opportunities, placements and end goals. Factors that negatively affected individuals' motivation were also identified.

Implications for recruitment to the Cardiff MPharm and for students while enrolled were identified during the interviews. The impact that staff can have upon student motivation was highlighted. Findings of this study have identified opportunities for further investigation within Cardiff and more widely.

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Haptic drug design: simulating the induced fit effect

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Computer aided drug design exists is an integral part of drug discovery. Its ability to dramatically decrease time spent during initial development stages makes it a valuable tool. In spite of this, errors do exist, and can result in costly setbacks. This is partly due to failure of the technology to accurately simulate ligand/receptor interactions. This is partly because of induced fit. This is a process whereby when a ligand approaches a receptor, it modifies the structure of the active site.[1] Modern computer software generally fails to incorporate induced fit.[2] This project aims to tackle this issue, with use of novel software that is capable of protein flexibility that is able to mimic the effects of included fit. The aim of the project is to deduce whether or not this new approach is able to more accurately reflect ligand/ receptor interactions, through comparisons with crystallised structures.

Two major protein families were tested with a variety of ligands. Initially, a protein was prepared without a ligand in the active site as a template. Then using a haptic device in conjunction with the computer software, the ligand was manually placed inside the active site as accurately as possible. With the use of molecular operating environment (a popular protein manipulation software) the results could be compared to the crystal structure for accuracy.

CDK produced results that differed little from traditional automatic software, with no significant protein movement. With HIV, being a larger protein (and therefore more susceptible to induced fit), the flexible software appeared superior and was able to move pocket residues to mimic induced fit (although this was not exact and protein distortion was a problem).

The investigation deduced that haptic software, operated via computer software with protein flexibility has potential for further development, particularly when used with larger proteins.

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Evaluation and characterisation of two directly compressible paracetamol powders used in the manufacture of immediate release tablets

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Direct compression is the preferred method of tablet manufacture as it requires fewer processing steps and excipients, resulting in lower production costs.[1,2] Despite this, few drugs possess the required properties needed for the process. Pure paracetamol is widely known for its poor flow and compressibility rendering it unsuitable for use in direct compression, however many paracetamol formulations have been developed to overcome this.[3,4] The aim of this study was to manufacture tablets from two different directly compressible paracetamol powders, Compap L (CL) and Compap Coarse L (CCL), and to evaluate and compare their mechanical properties. The powders were also characterised based on their flow properties and surface morphology to observe how differences affected tablet manufacture. Addition of magnesium stearate to powders was also investigated to observe effects on tablet properties.

Tablets were produced at different compression forces and their weight, thickness, crushing strength and friability were determined. Dissolution testing was carried out according to the British Pharmacopoeia method and ANOVA was used to analyse dissolution data. SEM analysis of powders was used to examine particle size and shape. Powder flow was investigated using compressibility index, Hausner ratio and flow time measurements.

Pure PAR showed poor flow properties whilst both directly compressible powders showed improved flowability and produced suitably hard compacts. CCL showed the best flowability, resulting in lower tablet weight variation; however both formulations met uniformity of weight requirements. CL tablets displayed higher crushing strength but also a higher friability. CCL tablets showed faster dissolution and reached a higher percentage of drug dissolution at 45 minutes. Magnesium stearate delayed drug release from tablets for the first 15 minutes of the test.

These findings show that CCL powder exhibits the best properties for direct compression tableting, however both powders produce good quality tablets which comply with pharmacopoeial requirements.

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Can the Theory of Planned Behaviour (TPB) predict pharmacists' engagement with Continuing Professional Development (CPD)?

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Practising pharmacists are legally obliged to complete CPD as a condition of their registration with the Regulator.[1] The TPB, a psychological theory used in the study of health-related behaviours states that the strongest predictor of behaviour is ones' behavioural intention, which is a function of their attitude, subjective norm (SN) and perceived behavioural control (PBC).[2] This study investigates whether or not the TPB can quantify pharmacists' views and engagement with CPD.

A questionnaire based on the TPB was distributed to 300 registered pharmacists, whom were either staff or postgraduate students of Cardiff School of Pharmacy and Pharmaceutical Sciences. Based on previous qualitative findings,[3] views and engagement in CPD were measured as two separate behaviours i.e. undertaking and recording CPD. Quantitative data relating to pharmacists' views and engagement with undertaking and recording CPD were analysed using SPSS® software.

A response rate of 54.7% (146/267) resulted from two mailings. Overall, pharmacists' views i.e. attitudes (MD=11.74, t=18.02, df=119, p<0.01), SN (MD=0.78, t=6.92, df=119, p<0.01) and PBC (MD=4.97, t=13.60, df=119, p<0.01) were more positive towards undertaking than recording CPD. Pharmacists reported that they undertake CPD more frequently than they record CPD. In 2011, patterns of recording did not meet the minimum Regulatory requirement in 27.3% of cases. No correlation was seen between self-reported undertaking and recording behaviours (rho=-0.092, p>0.05). Attitude (rho=0.218, p<0.05), SN (rho=0.233, p<0.05) and intention (rho=0.830, p<0.01) were significant predictors of undertaking CPD, whereas, attitude (rho=0.268, p<0.01), SN (rho=0.184, p<0.01) and PBC (rho=0.231, p<0.05) were significant predictors of recording behaviour.

The TPB was more effective at explaining pharmacists' recording behaviour than undertaking CPD behaviour. Pharmacists' views and engagement with undertaking CPD were more favourable than recording CPD. Strategies to improve pharmacists' approaches towards recording CPD should focus on the TPB constructs with the aim of removing barriers that impede the translation of intentions to record into actual CPD recording behaviour.

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An evaluation of the current discharge advice letters used in Wales

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A discharge advice letter (DAL) containing a summary of the clinical information and changes to the patient's medication is used to transfer information to general practitioners (GPs) when patients are discharged from hospital. Currently DALs are not automatically sent to the community pharmacists (CPs). The aim of this study was to evaluate the current DALs used in hospitals across Wales, to identify whether they contain the required information, as outlined by the Royal College of Physicians (RCP)[1] and the Royal Pharmaceutical Society (RPS)[2] or any sensitive information[3] . This would allow an assessment to be made on whether DALs are appropriate for CPs to review.

Five hospitals in four Health Boards (HBs) in Wales participated in the study. Qualitative interviews (face-to-face or telephone)[4] were undertaken with participants who were considered best placed to provide information on the DALs used in each hospital (n=5). Each hospital's DAL(s) (electronic +/- paper) was assessed against the RCP[1] and RPS[2] criteria. Subsequently, in 4 hospitals, systematic sampling was used to select 50-100 DALs from a representative sample of specialities, and their contents were analysed.

The interviews uncovered that each hospital had a different system in place, although similarities were identified. No hospital fully meets the RCP[1] and RPS[2] guidance on DALs. Electronic DALs contained more of the criteria and the criteria were completed more frequently than on the paper copies. Sensitive information[3] was identified on 2% of the 286 DALs reviewed in the study.

The study has identified a number of issues with DALs currently used; this will inform the further development of a new all Wales electronic discharge system currently being piloted. Further work must be done and amendments made to ensure GPs receive all the required information and the information is also made suitable for CPs to receive.

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The effect of caveolin-1 over-expression on amyloid precursor protein metabolism in Alzheimer's disease

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β-amyloid is a cleavage product of amyloid precursor protein (APP) which forms plaques and causes neurodegenerative effects in Alzheimer's disease (AD). APP is a transmembrane protein which must be internalised to enter one of two metabolic pathways; amyloidogenic metabolism by β-secretase then γ-secretase and non-amyloidogenic metabolism by α-secretase.[1,2] Internalisation is primarily via clathrin-mediated endocytosis, entering APP into the endosomal-lysosomal system.[2] Caveolin-1, a lipid-raft protein, is over-expressed in AD brains, whilst depletion increases β-amyloid and neuronal loss.[3,4] It is hypothesised that caveolin-1 influences APP metabolism. Possible mechanisms are via caveolin-1-mediated endocytosis in caveolae and caveolin-1-driven lipid-rafts mediating inclusion/exclusion at sites of internalisation.[1,2] The role of caveolin-1 was investigated by *in vitro* over-expression and quantification of relevant protein levels.

Astrocytoma (MOG-G-UVW) cells were transfected with caveolin-1 plasmid-DNA using Turbofectin8 as the transfection reagent. Western blots established the expression levels of caveolin-1, APP, caveolin-2, flotillin, clathrin, dynamin and glyceraldehyde 3-phosphate dehydrogenase (loading control; n=4). Sandwich ELISAs quantified the expression of APP and β-amyloid$_{40}$ (n=3-4). Treatment groups were Media, transfection reagent (T.R.), or T.R. with caveolin-1 plasmid-DNA.

Western blots confirmed a 6.2±1.5 over-expression of caveolin-1. APP expression levels were significantly decreased in cav-1 cells (37.2%±8.5) by ELISA, whilst β-amyloid levels showed no significant change. Three APP isoforms were resolved; expression of the 100kDa isoform was significantly reduced in caveolin-1 over-expression cells. There was no change in expression levels of the 112kDa and 142kDa APP isoforms, caveolin-2, flotillin, clathrin or dynamin.

Decreased APP levels suggest that caveolin-1 over-expression increased APP metabolism. Since β-amyloid levels were unchanged, it is likely that activity of the non-amyloidogenic pathway was increased. Caveolin-1 overexpression appeared to differentially affect the metabolism of APP isoforms; this requires further work. The lack of significant changes in the expression of caveolin-independent endocytic proteins suggests a role for caveolin-1 in APP metabolic regulation.

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Ser^{275} is essential for ZIP7-dependent cytosolic zinc release in breast cancer cells

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The expression of zinc transporter ZIP7 (SLA39A7) is highly upregulated in poorly prognostic breast cancers[1] and is thought to mediate the release of free zinc into the cytosol from intracellular stores, leading to the activation of tyrosine kinases that promote cell proliferation through multiple pathways,[2] thus contributing to the aggressive nature of breast cancer cells.[3] Here, we investigated whether phosphorylation of evolutionarily conserved[3] Ser^{275} in ZIP7 is required for zinc-mediated activation of tyrosine kinases and the downstream phosphorylation of AKT and MAPK indicative of signalling pathway activation.

Through genetic manipulation, MCF-7 cells were transfected with ZIP7 wild-type (WT), S275A and S275D mutants and treated with exogenous zinc. The cells were probed with antibodies directed against pAKT, pMAPK and pZIP7 and results collected from densitometry images produced via the Western Blot technique.

We identified that inactivation of Ser^{275} in ZIP7 S275A mutant cells prevents activation of downstream signalling pathways that promote cell proliferation. Activation of AKT and MAPK was significantly decreased in ZIP7 S275A mutant cells compared with those in WT ZIP7 cells. We also investigated a constantly active Ser^{275} in the ZIP7 S275D mutant cells and its effect on zinc transporter function.

The present results show that Ser^{275} in ZIP7 is required for zinc-mediated activation of tyrosine kinases that promote cell proliferation. Our mutations allowed for phosphorylation of Ser^{276}, which is equally conserved among organisms[3], therefore our results suggest that phosphorylation of Ser^{275} is required first to allow phosphorylation of Ser^{276} which then allows for full activation of ZIP7, leading to zinc-mediated cellular signalling. This evidence provides us with a better understanding of how ZIP7 is regulated and contributes to zinc homeostasis. Furthermore, our findings contribute to novel research working towards the prospect of targeting ZIP7 therapeutically in anti-hormone resistant breast cancer.

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Antimicrobial Silver-based Coatings for Biomedical Applications

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Biomedical devices today are an integral part in patient healthcare, however despite their uses, biomedical devices used in vivo are susceptible to biofilm formation, this can lead to a medical-device associated infection.[1] Biofilms are increasingly becoming resistant to antibiotics.[2] Silver is a useful alternative because it has broad-spectrum antimicrobial activity including against those that are antibiotic-resistant. Silver based polymers can protect the surfaces of medical devices against the attachment of microorganisms.[3] Much research is underway on how the antimicrobial properties of nanocomposites can be improved.

The aim of this study was to show how varying the power (50-150 watts) of the oxygen plasma treated silver nanocomposites can modify its surface properties by increasing surface roughness to prevent biofilm formation. Specifically E. coli (MG1655) and S. aureus (NCIMB9518) which are commonly associated with device-associated infections were investigated. Antibacterial tests were performed using five silver-coated samples of different concentrations. Atomic force microscopy was used to study the topography of the samples. Surface roughness of the pre-incubated silver samples increased with the increase in oxygen plasma power. Samples exposed to S. aureus for 24 hours showed a decrease in roughness with increase in power, however, samples exposed to E. coli showed no such correlation.

Although some of the samples showed modest reduction in bacterial growth there was little correlation with oxygen plasma power and not one sample was consistently better than the other. The AFM images show that the topography across all samples was uneven and this could have affected the bacterial adhesion properties and hence the antimicrobial efficacy of the sample.

This study demonstrates that oxygen plasma surface treatment on silver nanocomposites has the potential to inhibit bacterial biofilm formation, but further research is required as the samples have not shown sufficient antimicrobial properties, the samples and the plasma process conditions need further development.

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Does the SK Channel protect BV-2 Cells against inflammation and oxidative stress?

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The link between neurodegeneration and neuroinflammation is growing.[1] Neuroinflammation is brought about by activated microglia, resident immune cells of the CNS, and can be neuroprotective or neurotoxic. When neurotoxic, inflammatory mediators and reactive oxygen species (ROS) are released, the latter can lead to oxidative stress, another neurodegenerative trigger.[1,2] Recent findings suggest SK channels (small conductance Ca^{2+}-activated K^+ channels) regulate Ca^{2+} homeostasis and microglia activation.[1,2,3] We investigated if SK Channel modulation provides protection to BV-2 (primary mouse microglia) cells against lipopolysaccharide-induced inflammation and H_2O_2 -induced oxidative stress.

RT-PCR and Inside-out patch clamping were carried out, the target being the SK channel. Cell proliferation assays were also carried out. On Day 1, cells were seeded in 96 well plate triplicates (10,000 cells / well, method 1) and 6 well plate duplicates (300,000 cells / well, method 2). On Day 2, the insult medium was applied. 24 hours later, both MTS Assay (method 1) and cell counting (method 2) were carried out. Statistical analysis used a one way ANOVA and suitable post hoc test.

RT-PCR showed that SK4 channel mRNA was present. Patch-clamp confirmed presence of a Ca^{2+}-sensitive K^+ channel, activated by NS309 (SK4 activator), with a conductance of 37 pS consistent with SK4 (IK). MTS with BV-2 + LPS proved problematic, hence cell counting was adopted whilst BV-2 + H_2O_2 gave credible MTS results. LPS LD_{50} 10 ng/ml; H_2O_2 LD_{50} 30 µM. SK4 activation (NS309) or blockade (TRAM-34) afforded no protection against LPS or H_2O_2. DMSO was toxic at low concentrations.

SK Channel modulation in non-neuronal cells, especially microglia cells is quite topical and represents a novel therapeutic strategy, protecting neurons, by reducing microglia activation.[1,2,3] The results here were confounded by vehicle toxicity but were compared with the little data that currently exists in the literature.

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Aripiprazole and risperidone long-acting injection: 5-year outcomes in a retrospective naturalistic follow up study

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Aripiprazole and risperidone long acting injection (RLAI) are atypical antipsychotics used to treat schizophrenia. Their safety, tolerability and efficacy have been confirmed by randomised controlled trials, but these may not reflect clinical practice.[1] Naturalistic studies have attempted to overcome this issue, however, few include aripiprazole or RLAI. The aim was to assess the clinical effectiveness, safety and tolerability of aripiprazole and risperidone long-acting injection in treating schizophrenia over the latter three years of a 5-year follow up period.

This study was conducted within the acute mental health service in Cardiff, (UK). A retrospective case note review was undertaken and previous clozapine treatment was noted as an indicator of treatment-resistance. The primary outcome measure was discontinuation of treatment; other real world outcome measures were also used.

Twenty-seven patients on aripiprazole and 28 on RLAI were included in the study. Five patients were lost to follow up. Ten patients (38.5%) from the aripiprazole group and 11(45.8%) from the RLAI group discontinued treatment, the main reasons being non-compliance and side effects, respectively.

There is a lack of previous studies that are directly comparable, due to the length of the follow up period and this substantiates the uniqueness of this study. Using comparable, analogous, intermediate time-points, results are similar to those in the CATIE study with 70% of patients discontinuing before 18 months,[2] compared to 69.5% in the present study; other outcomes also compared robustly.[2-4] Despite the limitations of this study, such as small sample size, the results suggest that both RLAI and aripiprazole are moderately

effective in treating schizophrenia in a clinical setting. The 5-year attrition rate of 16%/year for aripiprazole and 16.8%/year for RLAI combined with the relatively low re-hospitalisation rates, low numbers of co-prescribed antipsychotics and infrequent dose increases, suggests that both drugs appeared to be safe and well tolerated.

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Differential cytotoxic effects of disulfiram and disulfiram analogues on MCF-7 and MDA-MB-231 breast cancer cell lines

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Breast cancer is the most common form of cancer in the United Kingdom. Disulfiram (DSF) has been used for over half a century in the treatment of alcoholism as an inhibitor of aldehyde dehydrogenase.[1] Recent studies suggest that DSF has a selective cytotoxicity against cancer cells *in vitro*.[2] This project aims to investigate the cytotoxicity of disulfiram and structurally related novel analogues to investigate the structure activity relationship.

Experiments were conducted on MCF-7 and MDA-MB-231 breast cancer cells due to their contrasting expression of major proteins. Cytotoxicity was determined using Cell-titer blue™ (CTB) viability assay after 4, 24, 48 and 72 hour incubation. CTB is a fluorometric assay that estimates the number of viable cells via the reduction of resazurin into a fluorescent end product, resorufin.

DSF and analogues displayed a cytotoxic effect upon both cell lines especially at the higher concentration of 10-100 µM and after longer incubation. Statistically significant ($p < 0.05$) biphasic effect was seen in MCF-7 between 1-10 µM after 48 and 72 hours incubation with disulfiram. Incubation of FS-01BM for 72 hours and FS-03EB for 4 and 24 hours produced a biphasic effect in MCF-7 cell line. Both MCF-7 and MDA-MB-231 cell lines display a biphasic effect when FS-07PY was incubated for 24 hours.

Degree of cytotoxicity is dependent upon the structure of the analogue tested. Extending the side chain produced an inactive analogue. By replacing the terminal groups of DSF with a pyrrolidine ring and OH group it decreases the viability of both cell lines and produced the greatest cytotoxicity profile. The data show that all compounds have some degree of cytotoxicity especially at higher concentrations of 10-100 µM against MCF-7 and MDA-MB-231 breast cancer cell lines. Data produced evidence of biphasic effect in some analogues which is a phenomenon that requires further research.

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Optimising treatment for ER-positive/Her2-positive breast cancer

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Luminal B breast cancers have a much poorer prognosis than luminal A cancers.[1] Therefore, new treatments need to be developed so as to improve the outlook for those with luminal B tumours. The effects of endocrine (Faslodex), anti-Her2 (Herceptin) and Src inhibitor (AZD0530) agents were investigated as monotherapies and as combinations of Faslodex plus Herceptin (FH) and Faslodex plus AZD0530 (FA).

Four cell lines were used; MCF7 and T47D (luminal A) and BT474 and MDA361 (luminal B). Changes in cellular growth following treatment with single and combination agents were assessed using MTT assays.

The effects of these treatments on protein expression and activity were subsequently determined through Western blotting and immunoprobing with phospho-specific antibodies.

As a single agent, Faslodex produced the greatest cell growth inhibition overall. Herceptin was very effective at inhibiting BT474 cell growth but only minimally effective with the other cell lines. Src inhibition produced the greatest growth inhibition in MDA361 cells. Protein detection revealed that Faslodex induced Src and Herceptin induced Her2 in all cell lines except BT474. AZD0530 inhibited Src activity but had little effect on other proteins investigated. Combination treatments inhibited growth in the luminal A cells better than luminal B but only BT474 cells showed FA to be statistically better than FH. BT474 cells showed the same level of growth inhibition when treated with Herceptin and FH, suggesting that this combination treatment was not beneficial. Protein detection for the combination treatments provided little evidence as to why they were more effective growth inhibitors, suggesting that other signalling molecules not investigated in this study were involved.

The data suggests that combination treatments were more effective than single treatments at inhibiting ER-positive/Her2-positive tumour cell growth. Src shows great promise as a target for treating ER-positive/Her2-positive breast cancer and AZD0530 has the potential for clinical use.

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Exploring the views of Cardiff pharmacy undergraduate students on evaluating their Velindre Hospital placements

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For the first time, 20 final year students from Cardiff School of Pharmacy and Pharmaceutical Sciences attended a voluntary half day placement at Velindre Hospital, Cardiff. Therefore, the aim of the study was to seek students' views on the value of the experience and to find out whether and how it could be improved for future students.

The methodology for this study was qualitative due to its exploratory nature.[2] Individual and group semi structured interviews were deemed to be the most appropriate for research into students' perceptions and beliefs. School ethics approval was obtained. An initial pilot interview was conducted check that the proposed interview schedule gathered reliable and valid data effectively and efficiently.[3] Each interview was audio recorded, which allowed *'ad verbatim'* transcripts to be produced for thematic analysis.[4]

In total 13 participants were interviewed. Seven main themes were identified: placement structure, educational approach, preparedness for Velindre placement, exposure to patients, personal development, multidisciplinary team and role models. All students felt it was a valuable experience that they would recommend to other pharmacy students. Students expressed a number of positive aspects of the placement, including the approach of the staff towards them and also towards patients and that the experience highlighted career options they had not previously considered. Conversely, two possible changes in future years were to increase the duration of the placement and to provide pre-placement reading. The study revealed the main link was with the oncology module in the third year and that the placement in year 3 of the MPharm would be more useful.

The interviews were successful in identifying the views of those who took part in the voluntary placements. The findings will be disseminated to the School and to the placement supervisors at Velindre Hospital. Evaluation of any changes resulting from the study is recommended.

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An evaluation of how quality training is implemented in Welsh NHS production areas; can online learning provide a role in this area?

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Online learning has revolutionised healthcare training and is fundamental for delivering high quality training to the National Health Service (NHS) workforce.[1,2] Despite the widespread use of online learning in the NHS, its application in production staff training is limited to the Technical Specialist Education and Training (TSET) packages.[3] To date, there has been no research to indicate how existing production staff training is delivered in Wales, and whether online learning could expand its presence here. The aim was to understand how quality training is delivered to NHS production personnel in Wales, and whether extending online learning here would be of any benefit.

Using topics identified from the literature, a self-complete questionnaire was developed to gather data from the entire study population (n=154). The questionnaire and covering letter was emailed to all production personnel in Wales via an NHS administrator and production unit managers, a reminder email was sent three weeks after the initial invitation. Quantitative data were analysed using Microsoft® Excel; qualitative data were entered into a Microsoft® Word document.

Questionnaires were returned from five participants; the response rate could not be calculated. The findings indicate that current training is delivered by various personnel and by several different methods. Participants agreed that online learning could play more of a role within their training at all staff grades, providing that it is supported by alternative learning formats, and that online learning material does not repeat what is already available from the TSET packages.

This study has highlighted the need to develop online learning in the training of NHS production personnel in Wales. It has underlined that where online learning is used in production staff training; it should not exist as a lone entity, but be supported by other training approaches. Additionally, any online learning developed should extend its scope beyond that of the existing TSET packages.

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Mucoadhesive chitosan/gelatin films for the sublingual and buccal delivery of punicalagin

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Apart from the peri-oral region, herpes infections can occur throughout the buccal cavity. The aim of this project was to develop mucoadhesive films that could deliver antivirals to the sublingual and buccal regions. The drug that was used in this study was total pomegranate tannins (TPT) – a purified form of pomegranate rind extract and comprised largely of punicalagin that previously demonstrated both antiviral and anti-inflammatory activities.[1]

TPT was isolated by fractionation of the rinds of pomegranates using Amberlite XAD-16 polymeric resin as stationary phase. This was formulated into mucoadhesive films based on chitosan and gelatin[2] at 0.05, 0.2 and 0.8% w/v. Firstly, moisture absorption studies were carried out to determine the water uptake ability. Next, spontaneous release and buccal membrane permeation experiments were conducted using glass Franz Diffusion cells. Each experimental set up was run with n=3 and over a period of 12 h; the samples obtained were analyzed by HPLC.[1]

It was found that as the TPT concentration increased, the water uptake ability decreased. In both the spontaneous release study and permeation study, a maximum of approx. 2.6% of punicalagin was delivered from the films. Sublingual membrane showed significantly higher permeation in comparison to buccal membrane ($p < 0.05$).

Novel mucoadhesive films were successfully prepared, although a combination of low spontaneous release and low permeation was indicative of an over-retentive dosage form (based on extensive ion pairing and

hydrogen bonding), rather than poor permeability across the membrane alone. However, the amount of punicalagin released at 12 h was determined to be approximately the same as the IC_{50} concentration against HSV-1 for TPT according to previous studies.[1] Overall, this work has shown that these novel TPT films may have potential as a new treatment for HSV infections of the buccal mucosal membranes.

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Testing the virucidal activity of disinfectant surface wipes

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Coxsackievirus B3 (CVB3) is among many easily transmissible viruses and the prevention of spread from surfaces is crucial. Many disinfectant wipes claim to be virucidal, however there is no current standardised test for evaluating the efficacy of a wipe. This study used a three-stage protocol, already proven successful with bacteria and endospores.[1,2]

Three “virucidal” wipes (A-C) and one control wipe were tested. Stainless steel discs inoculated with CVB3 and bovine serum albumin (BSA) were dried before wiping. Wipes were rotated for 10 s at 60 rpm under 150 g pressure. Virus removal from surfaces and the transfer of viruses from wipes were subsequently measured. The efficacy of wipes was also measured with no mechanical action.

The concentration of CVB3 dried on surfaces decreased by 4.9 $\log_{10}$ before any wipe treatment, which was taken into account when analysing the wipe results. The control wipe displayed a complete reduction in CVB3 (1.6 $\log_{10}$). Wipe A showed a 1.44 and 1.07 $\log_{10}$ reduction for the removal and static tests, respectively. Wipe B demonstrated a 0.934 $\log_{10}$ reduction in the static test and a complete removal (1.6 $\log_{10}$) following wiping, while wipe C, produced a 1.55 $\log_{10}$ reduction following wiping but a 0.79 $\log_{10}$ reduction in the static test. No virus was transferred to another surface by any wipes. The $\log_{10}$ reductions, after wipe usage, were statistically significantly different to the dried CVB3 titre. Only one wipe (C) had a significant difference between its removal and static tests.

The mechanical wiping action is the most important factor in removal. The complete $\log_{10}$ reduction of CVB3 seen following use of the moist control wipe is due to its ability to absorb liquid well. Wipes can be used on additional surfaces as they prevent transfer well. The three-stage protocol proved successful with coxsackievirus so is ideal for future experiments.

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Characterisation of novel *in vitro* models derived from ER+HER2+ BT474 cells to investigate the contribution of ER, EGFR and HER2 signalling in Faslodex resistance

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Currently, the effectiveness of breast cancer treatment in oestrogen receptor (ER) positive patients is limited by the problem of antihormone resistance.[1] Resistance to the antioestrogen Faslodex is poorly understood, particularly in ER+HER2+ disease.[2] A novel panel of acquired resistant models has recently been developed by continuous antihormone culture of ER+/HER2+ BT474 cells. This project focuses on characterising resistance to Faslodex in the BT474 cells, aiming to investigate whether duration of Faslodex treatment influences resistant phenotype and if this phenotype differs from that of other antihormonal resistant states (Tamoxifen, oestrogen deprivation) with regards to growth and contribution of ER and EGFR/HER2 signalling.

Coulter counting studies were performed to determine growth of Faslodex resistant BT474 cells compared with control cells cultured for equivalent timeframes (12 or 30 months). Growth impact of HER2 (Herceptin) or EGFR blockade (Gefitinib) was also evaluated. Immunocytochemical analysis was performed to monitor levels of ER, EGFR and HER2 to further characterise resistance mechanisms of the cells.

Major findings included initial slow growth in short term Faslodex resistant cells followed by substantial growth recovery as a consequence of longer-term treatment. ER was substantially reduced in short term Faslodex resistant cells but completely lost by 30 months, contrasting increases in other antihormonal resistant states. Despite superior increases in HER2 and EGFR versus other models, there was complete loss of Herceptin effectiveness on Faslodex resistant growth although EGFR blockade remained effective.

Our findings indicate long term Faslodex resistant BT474 cells undergo significant further phenotypic reprogramming versus shorter term resistance and versus additional antihormone resistant models. EGFR remains an important mitogenic pathway for Faslodex resistant cells in contrast to the HER2 pathway.[3] These findings have clinical implications for antihormone sequencing and also for interpreting trials currently examining EGFR or HER2 blockade alongside Faslodex in ER+HER2+ patients.

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Antimicrobial Activity of Silver-coated Nanoparticle Surfaces

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Silver have been widely used in implantable device coatings to prevent bacterial growth and ward off infection. Issues such as hospital-acquired infections, which are infections associated with urinary catheters, blood lines and heart bypass are on the rise. The catheters, tubes, and drains provide entry vehicles for bacteria and other pathogens regardless of the care taken by healthcare workers and the cleanliness of the facility. Due to many infections are tied to various types of tubing used medical and surgical treatments, therefore adding silver lining on the surfaces of devices is a wise alternative. The aim of this project was to determine whether silver nanoparticles coated surfaces of silica sample demonstrate a significant antimicrobial effect against E. coli and S. aureus by using plating method.

Five silicone surfaces coated with silver nanoparticles were prepared by ion implantation, with three repeats of each sample. All samples were incubated with the Gram negative E. coli MG1655 and Gram positive S. aureus NCIMB 9518 for 5 hours and 24 hours. At the end of the contact period, the samples were removed and washed three times in 1 ml PBS solution. Surviving bacteria were removed by vortexing after the final wash. Eventually, serial dilution and plating method was carried out in order to determine the viable count of bacteria.

Generally, the result obtained demonstrates that silver-coated nanoparticle surfaces showed antimicrobial effect, yet relatively weak. The silver-coated nanoparticles surfaces antimicrobial activity was less susceptible against S. aureus compared to E. coli. Besides, antimicrobial activity was more significant over 5 hours compared to 24 hours incubation. Apart from that, the surface roughness was closely related to the antimicrobial effect of silver nanoparticles.

The antimicrobial activity shown was relatively weak due to the formation of a less than monolayer coverage, insufficient concentration of silver and the silver particles were spread far apart. Apart from that, E. coli were more susceptible to silver ions S. aureus owing to the thicker cell walls of S. aureus that protect the cell from penetration of silver ions into the cytoplasm.

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An evaluation of staff attitudes to and satisfaction with Medicines Vending Units (MVUs) at ward level in Aneurin Bevan Health Board (ABHB)

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Medicine Vending Units (MVUs) are automated storage devices, consisting of computer controlled drawers.[1] Such devices have replaced medicine cupboards on some wards in Aneurin Bevan Health Board (ABHB) in order to improve efficiency, use of space, security and wastage of medicines.[2] The aim of this research was to assess staff attitudes to and satisfaction with MVUs and the automated control of ward stock at ABHB. The objectives were to identify ABHB staff's perceived advantages and disadvantages of using MVUs, compared to the cupboard storage system, as well as identifying the facilitators and barriers that occurred during the installation of MVUs.

In phase 1, a semi-structured interview was completed with 6 health care professionals (HCPs), two Advanced Nurse Practitioners, two pharmacists and two non-medical prescribers. Each participant was recruited using convenience sampling, after receiving an invitation letter, information leaflet and consent form. The interviews were audio-recorded, transcribed verbatim and thematically analysed.[3] For phase 2, a structured interview was developed using the themes identified in phase 1. Convenience and snowball sampling was used and the structured interviews were conducted on 32 participants. Data was then descriptively analysed and tabulated.

Majority of respondents at ABHB felt medicines cupboards were disorganised and a change was needed from the system. Positive aspects of the MVUs included ease-of-use, simplicity and efficiency. Problems identified with the MVUs were location, with some machines being sited too far from the wards. Another problem was software, with the system logging certain staff out. Also some staff stated the MVU training (N=8/32) was too short. Overall HCPs were willing to accept the MVUs and change in storage practice.

Attitudes towards and satisfaction with MVUs was generally positive, as most staff (N=28/32) were willing to recommend the system to other hospitals. Further research would be to look at how other health boards view the MVU system.

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The involvement of endocytosis in normal aging compared to Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disease characterised by accumulation of beta-amyloid (Aβ) in plaques in the brain.[1] The primary risk factor for AD is aging. Aβ is cleaved from amyloid precursor protein (APP) with most of the cleavage occurring along the clathrin-mediated endocytic (CME) pathway.[2] CME is thus likely to be important in the production of Aβ. The present study investigated how the expression of CME proteins is altered by increasing age in wild-type mouse brains compared to a transgenic mouse model of amyloid pathology.

Immunohistochemistry assays were performed on 3, 9 and 18 month old C57BL6 wild-type and transgenic mice expressing the London Mutation in APP (n=1-5). Microscopy images were taken of the cortex and hippocampal dentate gyrus, CA1, CA2 and CA3. The number of labelled cells were counted and protein expression analysed by one-way ANOVA and Tukey's post-hoc tests or Student's t-test.

In wild-type mice, the number of APP- and Clathrin-labelled cells significantly increased in all areas with age. PICALM-labelled cells showed a non-significant increase with age and SORLA-labelled showed no changes in the cortex or dentate gyrus but significantly increased in CA1, CA2 and CA3 regions with age. In transgenic mice, APP and Clathrin increased with age in all brain regions except the cortex where a significant decrease in Clathrin was observed. PICALM- and SORLA-labelled cells increased with a non-significant trend in all regions with age.

As APP is predominantly internalised by CME, the general increase in APP, Clathrin and PICALM infers an age-related increase in CME in the brain. This age-related increase is also present in the transgenic mice, suggesting that the increases seen in CME proteins in normal aging are accelerated in AD. The increase in SORLA contradicts other findings on the role of SORLA in amyloid pathology[3] and needs further work.

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Characterising and optimising polymer microneedle penetration in human skin

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Microneedles (MN) are an attractive alternative to conventional injection as they cause minimal damage and pain.[1] MN performance is dependent on application parameters and MN array characteristics.[2,3] Optimising penetration performance may impact future MN design, enabling improved drug delivery. Investigation of MN application to human skin *in vivo* offers a valid insight into MN performance as animal models and human skin models are limited.[4] Optical Coherence Tomography (OCT) is a non-invasive technique allowing for real-time *in vivo* visualisation of microneedle (MN) penetration and skin behaviour.

Polymer MNs with different heights and needle spacing were applied to excised human skin samples using a materials analyser to determine array characteristics and the application speed and velocity required for optimal MN penetration. Polymer MNs were also applied to *in vivo* human skin manually and imaged by OCT for assessment of MN performance and skin behaviour.

Polymer MNs were found to penetrate the SC of *in vivo* human palm skin and *ex vivo* human breast tissue. Application velocity of 2000mm/min and a force of 80N allowed for the most successful MN penetration when arrays with 900µm MN length and 1.5mm MN pitch were applied to ex vivo human skin.

MN success depends on application velocity and force, coupled with MN height and pitch. Application velocity had a greater impact on increasing penetration than force, although both parameters appear synergistic. Increased MN height and increased pitch resulting in greater penetration performance indicated that it is a combination of each of these that leads to better MN performance and potential drug delivery. Refinement of MN dimensions and further *in vivo* OCT investigation is required to assess these parameters fully.

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Medicines reconciliation – what errors and discrepancies occur upon admission to hospital and why?

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It is common for medication errors to occur on admission to hospital.[1] Medicines reconciliation is a pharmacy service designed to ensure patients' get the medication that they were on pre-admission.[2] This study at Whitchurch Hospital aimed to identify what and why errors and discrepancies occur on admission, as well as recommend improvements to the service.

Ethics approval was obtained from the Cardiff School of Pharmacy Research Ethics Committee. A data collection tool was used to assess medicines reconciliations both prospectively and retrospectively. Differences between inpatient drug charts and GP medication were split into two groups. Errors made by the healthcare professional (HCP) or discrepancies, which were instigated by the HCP. A severity scale (Level 1-6) was used to quantify errors. Semi-structured interviews were conducted and audio recorded with written

consent, to establish the views of pharmacy staff on the medicines reconciliation service. Transcribing and thematic analysis was then carried out.

160 patients were analysed, 109 were retrospective and 51 prospective. 14 patients were excluded due to insufficient information. Errors (n=129) and discrepancies (n=46) occurred for 50% of patients and ranged from 0-10 in number. Omission was the most common type (61.7%), whilst the most frequent cause was due to HCP error (53.1%). Many of the errors were level 3 (moderate) in severity (51.5%). Seven interviews were conducted three with pharmacists and four with pharmacy technicians. Although time consuming, the benefit of the service on patient care was identified. Communication barriers between multidisciplinary teams and integration into the daily routine were also discussed.

The data collected highlighted how often errors occurred on admission due to the HCP. This is a patient safety issue as many of these errors could have caused harm. The interviews were a useful insight into participant's views on the service. Recommendations were made to improve the current service, such as an education day for junior doctors on common medication errors on admission.

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The light protective effect of lipid emulsions on retinol in Vitlipid® N Infant

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Parenteral nutrition (PN) is the administration of nutrients via the intravenous route, where oral or enteral feeding cannot be established.[1] Components of PN include glucose, lipids, amino acids, vitamins, electrolytes and trace elements. Vitamins are known to cause instability and degradation issues within PN and therefore only added shortly before infusion.[2] Vitlipid is a multivitamin preparation containing a concentrated emulsion of lipid-soluble vitamins,[3] including retinol, the most photosensitive component of PN admixtures. This study investigated the effect of lipid emulsions on the photodegradation of retinol within Vitlipid ® N Infant under different light conditions.

Clear glass bottles were prepared, containing either 50 ml Vitlipid, or 10 ml Vitlipid with 40 ml lipid emulsion (either Intralipid or SMOFlipid). A sample of each mixture was exposed to natural sunlight and cool white light. At 0h, 1h, 2h, 3h, 4h and 24h, light intensity readings were recorded and samples taken for analysis. Retinol loss was assessed through HPLC analysis.

All samples showed a similar trend in retinol photodegradation but to different extents. Both lipid emulsions greatly reduced retinol photodegradation, but no significant difference was observed between the protective effect of SMOFlipid or Intralipid as the lipid source. Retinol loss was much less under cool white light compared to sunlight. The majority of retinol loss usually occurred within the first hour.

Light intensity and wavelength had a significant effect on the photodegradation rate of retinol. Lipid emulsions reduced the extent of retinol photodegradation by approximately 10% at each time, but their protection alone is not sufficient.

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Is the molecularly imprinted polymer 'p(EGDMA-*co*-MAA)' superior to other imprinted polymer systems?

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Molecular imprinting is a concept derived from the ability of biological hosts to strongly and specifically bind a particular molecular structure. Many different methods for creating a molecularly imprinted polymer (MIP) exist, along with numerous combinations of functional monomer and cross-linker. So why then is the polymer

'p(EGDMA-*co*-MAA)' by far the most widely reported MIP? Could it simply be that it is better than other polymer systems?

An extensive literature review of papers from the past few years was carried out, searching for papers that reported the use of an equilibrium batch rebinding assay and enough data to reconstruct a binding isotherm for the MIP, allowing the Binding capacity (B_{max}) and affinity (K_d) to be determined. Raw data was normalised to a standard set of units and entered into the GraphPad software to produce the binding isotherm for each MIP.

Of the large numbers of papers reviewed, only 34 papers contained enough relevant information. From this data, the mean B_{max} and K_d values were determined for p(EGDMA-*co*-MAA) systems and other polymer systems. There was no significant difference between the means for the B_{max} and K_d (with p-values of 0.8479 and 0.8850 respectively). Following removal of binding isotherms which may produce misleading B_{max} and K_d values, the mean values were again determined, and there was no significant difference between the means (with P-values of 0.5298 and 0.2273).

A total of 28 MIPs (from 34 published papers) were initially compared, followed by the comparison of the remaining isotherms upon removal of data that may produce misleading values. Based on the results of this work, it was concluded that on the whole, the polymer system p(EGDMA-*co*-MAA) is not superior to other polymer systems.

An evaluation of Interprofessional Education (IPE) sessions in 2012/13 between medicine and pharmacy undergraduate students at Cardiff University

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IPE has been defined as when 'two or more professionals learn with, from and about each other to improve collaboration and the quality of care'.[1] IPE is a required element of both medicine and pharmacy undergraduate degrees.[2,3] IPE was introduced in 2011 between pharmacists and medics at Cardiff University. Students work together on therapeutics and prescribing cases. Three IPE sessions were conducted in 2012/2013 between 3rd year medicine students and either 3rd or 4th year pharmacists. The aim of this study was to evaluate the views of the students who participated in the IPE sessions.

An anonymous, self-completion two-part questionnaire, including 5-point Likert-scale and open-ended questions, was distributed using total population sampling at the end of each 2hr session. Quantitative data were analysed using SPSS. Kruskal-Wallis and Mann-Whitney U statistical tests were used to compare student groups. Semi-structured interviews were conducted to help explain questionnaire findings. Non-probability (purposive and convenience) sampling was used to recruit 3 participants from each student group. Interview and qualitative data from questionnaires were analysed using content analysis. Ethics approval was obtained.

A questionnaire response rate of 96.7% was achieved. Both professions were positive about the sessions. Students found IPE useful and enjoyable with medics having a significantly higher level of agreement. Over 95% found working with a student from a different profession useful. Students (≥79%) also agreed more IPE should be conducted. The most frequently stated benefit was 'working with another healthcare professional' (n=212). The organisation of the session was identified by most students as needing improvement (n=73). Several suggestions were made in relation to the organisation of the session, particularly regarding the allocation to interprofessional partners. Interviews provided additional information on negatives and improvements such as 'medics got more out of the session'.

IPE sessions were beneficial and should be continued. Suggestions for change have already been made to the Schools. Evaluating the sessions as a result of any changes is recommended.

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Comparison of the effect of speed during penetration of inhalation grade gelatin and hypromellose capsules used in dry powder inhalers

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There has been a revival in the use of Dry Powder Inhalers (DPI) based on capsules, because of their inherent simplicity of design and powder formulation. The uses for pulmonary delivery has recently expanded to the administration of more complex actives such as insulin.[1] DPI are more patient friendly as they overcome the problem of patients' poor coordination when using metered dose inhalers (MDI).[2] Previous studies have shown that moisture content of capsules has an impact on capsule puncturing.[3,4] This study was designed to test the effect of the speed of movement of DPI pins during puncturing; comparing inhalation grade gelatin and hypromellose capsules that had been pre-conditioned at different relative humidities. The objective of this study was to provide data to aid in improving DPI design.

Angular pins from a 2-pin inhaler (Plastiape, Italy) were used in a Zwick materials testing machine to puncture the capsules over a range of speeds, from 20mm/min to 420mm/min. Tests were made at 20mm/min intervals. For each test the following factors were measured, shell deformation at puncture and the force required, the circularity of the puncture hole and its visual morphology.

The increase in the speed of puncturing had no significance effect on the results of each set of capsules. However, the results for the gelatin capsule that had been stored at a lower relative humidity showed a significant difference ($P<0.05$) compared to the others for all the recorded measurements. They showed significant damage; with pieces breaking off causing large irregular shaped punctures. The increase in the force to puncture these capsules correlated with previous studies, confirming that when gelatin capsules lose moisture they become more rigid and liable to fracture.[3,4]

The study showed that HPMC capsules are a much more robust system for use in DPI with regards to puncturing as they are unaffected by moisture loss. However, more studies are needed to investigate the relationship between puncture hole size/shape and the release of powder from capsules.

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Residues S^{275} and S^{276} participate in the activation of the ZIP7 transporter in MCF-7 breast cancer cells

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Zinc is an essential trace element and a second messenger in a non-genomic signalling pathway.[1] Cytosolic zinc levels rise within minutes of exogenous zinc stimulation in breast cancer cells.[2] Zinc is released from the ER intracellular store via ZIP7 efflux transporters located on its membrane.[3] It is postulated that ZIP7 is activated following phosphorylation of serine residues, S^{275} and S^{276}, by CK2. Zinc inhibits tyrosine phosphatases which causes prolonged activation of tyrosine kinases and downstream effector molecules AKT and MAPK and subsequent cell proliferation and metastasis[4]. We hypothesised that residues S^{275} and S^{276} participate in the activation of ZIP7 in MCF-7 breast cancer cells.

Wild-type (WT), null mutant (AA) and phosphomimetic mutant (DD) ZIP7 transporters were created and transfected into MCF-7 breast cancer cells. Serine residues were mutated to evaluate their contribution to transporter activation. Cells were stimulated with exogenous zinc at 0, 2, 5, 10, 15 and 20 minutes and then lysed. 12% SDS-PAGE and western blotting analysis were used to separate proteins. To assess ZIP7 activation, pZIP7 and activated downstream pMAPK and pAKT were measured using $pZIP7^{3\text{-}1\text{-}1}$, $pMAPK^{T202/Y204}$ and $pAKT^{S473}$ antibodies. Protein activation was quantified with densitometry.

MAPK and AKT were activated downstream of ZIP7 phosphorylation in wild-type cells, where S^{275} and S^{276} were retained, proving that downstream activation was ZIP7-dependent. This response was lost in the AA mutant, suggesting that S^{275} and S^{276} participate in ZIP7activation. The activation of MAPK and AKT was examined in cells expressing DD mutant.

In conclusion, residues S^{275} and S^{276} participate in the activation of ZIP7 and downstream signalling causing proliferation and metastasis in breast cancer cells. We demonstrate a potential to target S^{275} and S^{276} with small molecule inhibitors to halt zinc signalling, at the point of zinc release, in the treatment of breast cancer.

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Honey as a source of antimicrobial phytochemicals with activity against MRSA

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Honey has been used for centuries for its medicinal properties. Research has identified the main antimicrobial components of honey; low pH, high sugar content and hydrogen peroxide.[1] However honey is a rich source of phytochemicals, some of which may become potential drug development lead compounds to combat the threat of increasing antibiotic resistance. The aim of this study was to test a range of honey samples from local bee-keepers for antimicrobial activity against methicillin-resistant *Stapphylococcus aureus* (MRSA) and identify novel honey derived antimicrobial phytochemicals which inhibit the growth of MRSA.

A range of honey samples were screened for their ability to inhibit the growth of MRSA using agar diffusion and broth based assays, the most promising honey samples were extracted with three different solvents (n-hexane, ethyl acetate and methanol). The compounds present in each extraction were separated using thin layer chromatography (TLC). The TLC plates were then over-layed with MRSA to assess whether any of the TLC bands showed antimicrobial activity.

Of the six honey samples tested, four produced zones of inhibition that were significantly greater ($p<0.05$) than those produced by the positive control (phenol 5%w/v) during the agar diffusion assay. One particular honey also retained antimicrobial activity when methylglyoxal, hydrogen peroxide and bee defensin-1 were neutralised, three known antimicrobial compounds present in honey[1], suggesting the presence of novel antimicrobial phytochemicals. Screening the TLC bands from the solvent extractions resulted in nine TLC bands showing the ability to inhibit the growth of MRSA.

This study has discovered honey derived phytochemicals that have antimicrobial activity against MRSA, with further research these compounds could now be identified and act as potential drug development leads for new antibiotics.

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Investigation towards the surface imprinting of amlodipine

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Based upon the complimentary binding sites between a template and target molecule, molecular imprinting enforces recognition for a chosen molecule onto a polymer matrix. Initial “bulk” imprinting methods are flawed; with the template dispersed throughout the polymer matrix it is difficult to remove and reintroduction of the molecule is problematic.[1] Now, more sophisticated methods isolate imprinting of the template onto the surface of the polymer allowing easy access to binding sites and quick removal of the template from such pockets[2] and hence, it was by this method that we investigated the imprinting of amlodipine.[3]

Amlodipine is a calcium channel blocker, commonly used in the treatment of angina pectoris and hypertension. It was extracted from 10mg amlodipine besylate tablets and then bound to Merrifield resin.

Such a resin was chosen as its surface functional groups could be modified resulting in a bifunctional resin. Half of the chloromethyl functional groups already existing on its surface were converted to amine groups. These amine groups allowed binding of amlodipine. The remaining chloromethyl groups were bound to iniferter, sodium diethyldithiocarbamate. Resins with a full conversion or no conversion of functional groups were used as controls.

Polymerisation studies concluded that crosslinker, ethylene glycol dimethacrylate and monomer, methacrylic acid resulted in polymer growth when exposed to UV light for 2 hours. Bound to amine groups, amlodipine was successfully immobilised on the resin via crosslinker dithiobis[succinimidyl propionate] and the ability to then remove it was investigated using a cleaving agent dithiothreitol (DTT) with analysis by HPLC. A sample of amlodipine modified resin reacted with DTT contained four times the amount of amlodipine than the same resin without DTT.

Whilst amlodipine and the iniferter were not imprinted simultaneously they were successfully immobilized onto the resin independently and together, it would be hoped they would give controlled polymerisation.[4]

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Novel thienopyrimidine derivatives as anti-HCV agents

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It was estimated that 2-3% of the world's population were chronically infected with HCV in 2012.[1] The current treatment available is non-specific with significant side effects and high susceptibility to resistance,[2] NS3 helicase is an important enzyme in HCV life cycle that is essential in viral replication,[3] thus inhibiting this enzyme may prevent the progression of the disease. This project aims to design and synthesise a series of novel thienopyrimidine derivatives that is potentially involved in the inhibition of NS3 helicase by rationally modifying the lead compound obtained from previous screening.

Several modifications of the lead compound were done and the resulting compounds were analysed through docking studies to observe their interactions in the binding pocket. The best compounds were synthesised through a five-step synthesis involving Gewald reaction, pyrimidinone ring condensation, pyrimidine ring chlorination and aromatisation, hydrazine formation and production of final compounds hydrazones and hydrazides.

The docking studies showed that the newly designed compounds interacted with the key amino acid residues within the binding pockets. Ten designed compounds were then synthesised successfully with acceptable yields. The production of the pyrido groups were complicated by its high polarity. However, different approaches of the second step of the synthesis were found and could be used for further work to improve the yield.

As a conclusion, the replacement of hydrazones linker with hydrazides revealed an improvement in the binding modes of the compounds in the pocket. The yield of the products depends on the structure and polarity of the compounds. The compounds synthesised were sent for biological tests including cell-based HCV replicon assay and mutational studies to determine their antiviral activity. If any of the compounds were more active than the lead, further modifications needed to be done to optimise the activity such as using molecular docking studies to identify alterations.

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Actions of trace amines in the isolated rat ileum and oesophagus

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β-phenylethylamine (β-PEA), tyramine and octopamine are collectively known as "trace amines"(TAs). TAs are structurally and chemically related to monoaminergic neurotrasmitters including noradrenline, dopamine and 5-hydroxytryptamine (5-HT). TAs are also abundant in our diet, such as cheese, sausage and chocolate.[1] The mechanism of their action has been traditionally accepted as the displacement of endogenous classical amines from neuronal storage vesicles into synaptic cleft. The hypothesis of this study is the responses to TAs in rat gastrointestinal tract may be mediated by an indirect action on 5-HT_{2A} receptors.

Sections (2cm) of oesophagus or ileum were allowed to equilibrate in tissue baths containing Krebs solution warmed to 37°C and aerated with 5% CO_2 in O_2. Cumulative dose-response curves (DRC) to methacholine (MCh) were constructed at the beginning of each study. Repeat DRCs to trace amines were then constructed in the absence or presence of 5-HT_{2A} receptor antagonist, ritanserin (1μm).Results were expressed as a percentage of the maximum MCh response in the tissue.

β-PEA and tyramine contracted the oesophagus at high concentrations (1-10miliM, n=6). The response to β-PEA in oesophagus was reduced by ritanserin, although this was not significantly different (Emax without and with ritanserin, 101.8±28% and 26.8±18.3% respectively). Tyramine brought about dose-dependent relaxation in the tissue initially, which were converted to a contraction in the repeat curve (n=4). Octopamine induced relaxant effect in ileum and oesophagus which were not modify by ritanserin (n=1-2). There were no significant differences in the maximum response or pD_2 between any of the groups studied.

Based on our findings, we propose that the actions of TAs are not mediated through 5-HT_{2A} receptors. The responses may be mediated by other amine receptors (eg adrenoreceptors). Other possible candidate for the responses is the newly identified trace-amine-associated receptor family (TAAR)[2]. This can be tested by using a selective TAAR 1 antagonist, EPPTB4.[3]

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Characterisation of cannabinoid responses on the isolated guinea-pig ileum

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Cannabinoid compounds (CBs), such as the synthetic agonist Win 55,212-2 have been thought to inhibit electrically evoked contractions of isolated ileum preparations by reducing excitatory enteric cholinergic transmission mediated via a prejunctional CB_1 receptor.[1] Previous studies have also suggested the involvement of other novel receptor signaling mechanisms. The aim of this study was to confirm the involvement of the CB_1 receptor in mediating the inhibitory effects of cannabinoids on the isolated ileum.

Contraction in ileum obtained from male Dunkin-Hartley guinea-pigs, was stimulated using electrical field stimulation (EFS).[2] Concentration response curves (CRC's) were constructed using Win 55,212-2 ($1x10^{-6}$ M – $3x10^{-5}$ M) in the absence or presence of: SR141716A (CB_1 selective), AM281 (CB_1 selective), AM630 (CB_2 selective) and an endothelial cannabinoid receptor antagonist, O-1918 (n=3). Vehicle controls were carried out concomitantly for agonist and antagonist studies using ethanol and DMSO. This allowed for a Students paired t-test to be utilised in determining statistical significance.

Win 55,212-2 (non-selective) and ACEA (CB_1 selective) were found to cause concentration dependent decreases in the amplitude of electrically evoked contractions to 38.4 % and 55 % of the initial EFS response respectively. This was found to be statistically insignificant ($p< 0.05$) against an ethanol vehicle control apart from at a final bath concentration of $3x10^{-5}$ M. The use of CB_1 selective antagonists, SR141716A or AM281 alone or any combination of 'AM281 (CB_1)+ AM630 (CB_2)' or 'Am281+ AM630 + O-1918 (CBe)' failed to antagonise the effects of Win 55,212-2 when tested against their respective controls ($p<0.05$).

The results strongly suggest that Win 55,212-2 is acting via non CB_1 - non CB_2 receptors to mediate this inhibitory effect on motility in the isolated ileum. Cannabinoids have been shown to interact with proteins of the endocannabinoid system and other targets, in particular the Transient Receptor Potential Vanilloid type-1 (TRPV1) channel.[3]

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The antibacterial activity of black seed oil against *Mycobacterium smegmatis* and its potential use in tuberculosis therapy

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Black seed oil (BSO) is oil extracted from *Nigella sativa* and is a natural product.[1] Natural products have been used in traditional medicine and are used increasingly in early drug discovery, as the primary sources.[2] Tuberculosis (TB) is a worldwide major health problem.[3]

BSO was tested against *M. smegmatis*, which was used as a model for *M. tuberculosis* as they share some identical genomic sequences.[4] The zone of inhibition test was used to see if BSO possessed antimycobacterial activity and synergy tests were performed to see if BSO and antibiotics had greater effects when used together.

The zone of inhibition test proved that certain BSOs do possess antibacterial activity. The synergy tests showed that BSO potentiates the antibiotic effects of ethambutol and isoniazid.

It was shown that BSO has potential to be used in combination with the antibiotics to enhance their effect. Further investigations would be required before BSO was to be approved for use in TB treatment.

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Isolation of an antimicrobial compound from Humulus lupulus

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Anti tubercular antibiotics are becoming increasingly ineffective due to the development of bacterial resistance mechanisms. Plants generate organic compounds called secondary metabolites which have been identified as key components in their defence mechanisms and have exhibited considerable activity against Mycobacterium tuberculosis, the causative agent in tuberculosis (TB) infection.[1, 2] M. tuberculosis is now one of the most significant microorganisms to have developed multi-drug resistance and extensive-drug resistance.[3] The preservative action of the Hop plant, known botanically as Humulus lupulus, has been exploited in the beer brewing industry since the Middle Ages and has been shown to exhibit anti-tuberculosis activity.[4]

Organic solvents of varying polarities were used to extract compounds from two hop variants: Magnum and Amarillo. A bioautographic assay was used to analyse extracts for their antibacterial activity against Staphylococcus aureus. Column chromatography was used to separate extracts into their substituents which were also analysed for their antibacterial activity. Analysis by NMR and mass spectrometry analysis lead to limited characterisation and confirm the potential drug-like properties of compounds extracted.

A compound from the non-polar Amarillo extract was found to exhibit the most significant antibacterial activity. Five unknown compounds were obtained from column chromatography. NMR analysis did not yield comprehendible results due to concentrations of samples being too low. Mass spectrometric analysis revealed an almost drug-like compound with molecular weight (M+H)= 589.

The success of the non-polar extract to inhibit bacterial growth could be due to its ability to penetrate the lipophilic bacterial cell wall. The compounds could not be fully characterised due to the unsuccessful NMR analysis. An almost drug-like compound that is potentially novel (its measured mass does not correspond to known hops constituents) has been isolated from the Amarillo variant of Humulus lupulus. Further investigation is necessary to assess its drug-like properties, characterise its structure and to quantitatively determine its antimicrobial activity to compare it to currently used antibiotics.

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Synthesis of an [18F]-FAU precursor for PET imaging

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PET tracers are a huge demand in today's market. [18F] tracers are usually the choice of preference due to its compromised half-life of 109.8 minutes and its low positron energy (633 KeV).[1] [18F]-FAU (2'-deoxy-2'-[18f]fluoro-1-β-d-arabinofuranosyluracil) is a pyrimidine nucleoside tracer which has a huge potential, not only as a diagnostic tool for cancer, but also in monitoring levels of thymidylate synthase enzyme.[2] The aim of this research project is to develop a precursor of [18F]-FAU for PET imaging via a five steps process using uridine as the starting material.

The first step involved protection of the 3' and 5' hydroxyl group of the nucleoside. The protecting group used was a TIPDS (tetraisopropyldisiloxane) protecting group. The second step involved the protection of the 2'-hydroxyl group using TMS (trimethylsilyl) chloride. The third step involved the N-Boc (tert-Butyloxycarbonyl) protection as well as the deprotection of TMS group on the 2' hydroxyl group. The fourth step involved the introduction of a good leaving group, which is a tosyl group at the 2' position. The final step was the removal of the TIPDS protecting group and replacing it with a THP (2-tetrahydropyranyl) group.

A clean precursor was successfully synthesised. Each reaction was monitored using TLC followed by NMR. NMR spectrum for each reaction has come clean indicating the completion of each step. The yield for each reaction varied between 47% to 88%. The precursor would be brought to the PETIC (Positron Emission Tomography Imaging Center) in Heath Hospital, Cardiff for the removal of the remaining protecting group after the radio-fluoridation with [18F] at the 2' position is placed.

The precursor synthesised has never been reported in any journal article or used for radio-fluorination before. The success of synthesising this precursor opens the window of opportunity for further research on this precursor to be carried out.

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Analysis of the kinetics of vasoconstrictor responses to amphetamines in isolated aorta

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Amphetamines and structurally related trace amines including tyramine and β-phenylethylamine (β-PEA) behave as indirectly acting sympathomimetics producing vasoconstriction causing an increase in blood pressure.[2,3] However it is more recently suggested that they are also able to cause vasoconstriction via activation of trace amine associated receptors (TAARs).[1]

Male *Sprague-Dawley* rats (150-250g) thoracic aorta was removed, endothelium-denuded and cut into ring sections (approx. 0.5cm). The aortic tissue was suspended in a 50ml organ bath containing Krebs bicarbonate buffer. KCl (60mM) was added at the beginning of each experiment and used as a reference contraction. Concentration-response curves (CRCs) were constructed in the presence (except β-PEA) and absence of α_1-adrenoceptor antagonist, prazosin (1μM). Successive concentrations of agonist in half log increments were used. Also a single dose of β-PEA (100μM) was added in the presence and absence of the "inhibitors" (1μM, Prazosin; 10μM, Pargyline; 1μM, ICI-118,551 hydrochloride; 10μM, cocaine hydrochloride). Tyramine partial agonist activity in rat aorta was investigated with β-PEA. All Contractions were expressed as a percentage of KCl maximum (% KCl) in each experiment.

All three amines produced powerful vasoconstriction in rat aorta. The α_1-adrenoceptor antagonist, prazosin, failed to inhibit amphetamine, however significantly inhibited tyramine. Tyramine was a partial agonist compared with amphetamine. The order of potency (EC_{40KCl} μM) of the vasoconstrictors is as follows: amphetamine> β-PEA>tyramine. The "inhibitors" failed to alter β-PEA, whereas tyramine significantly antagonised the β-PEA response.

Trace amines it seems are able to cause vasoconstriction of isolated rat aortic rings via a mechanism independent of α- and β-adrenoceptors, or indirect sympathomimetic stimulation. Therefore the contractile responses to trace amines are probably based on the activation of recently proposed TAARs. However it is still not established that trace amine activation of the TAAR receptors effectively cause vasoconstriction, only that there is capacity of these amines to activate them.[1,4]

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The views of Cardiff undergraduate students on the community pharmacy placement scheme

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The GPhC requires pharmacy undergraduate students to obtain practical experience during each MPharm degree course.[1] The Cardiff School of Pharmacy and Pharmaceutical sciences aims to meet these requirements through providing the community pharmacy placement scheme. As part of this scheme students undertake a community pharmacy placement experience during years one, two and three. The aim of this study is to explore the views of undergraduate students at Cardiff University on their community pharmacy placement scheme. The objectives of this study are to explore the views of the undergraduate students on the organisation of the placement, the information received beforehand and the methods of assessing the placement.

To achieve these objectives a qualitative approach was chosen due to its exploratory nature.[2] Semi-structured interviews were conducted with participants in first, second and third year of the Cardiff School of Pharmacy and Pharmaceutical Sciences and thematic analysis was used.

Ten students took part in the project which was a response rate of 2.8%. Five themes emerged from the analysis. Organisation, with university organisation and student organisation as subthemes. Student preparation with feelings and outcomes as subthemes. Preparedness of supervisor, exchange of experiences and finally methods of assessment with pharmacist supervisor marking, manual and reflective entry as subthemes.

The aims and objectives of this research project were met through the use of qualitative analysis. Overall the placement scheme is valuable to undergraduate students in line with the literature.[3] However there are a number of aspects of the scheme which participants felt could be improved e.g. more and longer placements, and better communication between the university and placement supervisor.

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Investigation into the factors affecting community pharmacists' engagement with spontaneous reporting of ADRs

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Adverse drug reactions are an important health problem in terms of morbidity, mortality and costs. In the UK 6.5% of all hospital admissions are related to ADRs, 0.15% of patients admitted to hospital die from an ADR and the projected annual cost to the NHS is £466 million.[1] The UK's spontaneous adverse drug reaction reporting scheme, called the Yellow Card Scheme is fundamental to drug safety surveillance but under-reporting is a major limitation.[2] This study aimed to investigate community pharmacists' experiences of ADR reporting and explore barriers and facilitators to reporting.

Preliminary semi-structured interviews with a purposive sample of community pharmacists were conducted and transcribed. Themes were identified to aid in the development of a confidential pilot questionnaire which was mailed to a random sample of 140 pharmacists in North East England. Resulting data was analysed using SPSS.

Twenty-five percent (n=35) of the questionnaires were returned by the closing date. Thirty-nine percent of the pharmacists had previously reported an ADR and 97% agreed that it was a pharmacists' responsibility to report an ADR. Although none of the results were statistically significant, they suggested that pharmacists who had received training were more inclined to report ADRs. Furthermore 83% of respondents agreed that reporting was a part of their professional duty. The interviews (n=7) suggested that perhaps it was more accessible for a GP to report an ADR as they have access to patient medical records.

Although the numbers were low the knowledge and attitudes of pharmacists were explored, allowing an insight into the barriers and facilitators to reporting. This revelation may be useful in terms of patient safety as attitudes and knowledge are factors that can be modified. Additional research will be undertaken to support and further explore the findings of this study.

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Characterisation of Transferrin as a targeting ligand in the blood-brain barrier

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CNS therapeutic drugs must be able to gain entry into the brain parenchyma to achieve pharmacological activity. The most sought for approach is to traverse the Blood Brain Barrier (BBB), thus avoiding risky surgically invasive methods.[1] In this study, the efficacy of transferrin as a targeting ligand, for brain drug delivery was investigated using the immortalised murine BBB b.END3 cells as an *in-vitro* model.

To characterise human Transferrin (hTf) uptake and recycling in b.END3 cells, we developed fluorescently labelled hTf protein and characterised its cellular internalisation using Fluorescence Activated Cell Sorting (FACS) and confocal microscopy. Further investigation of endocytic fate of hTf in BBB cells was characterised through co-localisation studies with fluorescently labelled lysosomal marker, dextran, using confocal microscopy. We further developed hTf - poly (acrylic acid)-chitosan nanoparticle (PAA-CS NP) conjugates and studied the effect of hTf – NP coupling upon the cellular uptake and internalisation of these NPs by b.END3 cells.

hTf cellular internalisation studies, performed using FACS and confocal microscopy, strongly suggest a very rapid active process of uptake and recycling of hTf from the BBB cell line b.END3. Furthermore, co-localisation studies give evidence that hTf can bypass lysosomal degradation when internalised in the cells.

NP uptake studies show that PAA-CS NP cannot be actively internalised in the cells even when coupled to the rapidly internalised protein hTf, NPs displayed high levels of non-specific binding to cell membranes as evidenced from studies performed at 4^{o}C. The results suggest that hTf although achieving high active cellular internalisation levels in the BBB, might not be capable of delivering large cargo (>200nm) across this

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Validity and reliability of the Family Reported Outcome Measure (FROM-16©) in urology

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The Family Reported Outcome Measure is a generic family quality of life instrument that measures the quality of life of the families of patients with chronic conditions.[1] FROM-16© comprises two domains: emotional domain (EM - 6 items) and personal and social life domain (PSL - 10 items).[2] The aim of this study was to examine the psychometric properties of FROM-16© in families of patients with urological conditions.

The study was carried out in the urology clinic at the University Hospital of Wales over a nine week period. Patients completed the SF-36 (n=125) and family members completed the FROM-16© on two separate occasions (Assessment 1, n=99; Assessment 2 n=30), 5 days apart. Internal consistency of the FROM-16© was assessed using Cronbach alpha. Test retest reliability was assessed using ICC. Convergent validity was assessed by correlating FROM-16© and SF-36 domain scores. FROM-16© scores of family members and patient perceived health status were compared using analysis of variance.

The mean age of patients (male=104, female=21) was 65 years (SD= 16.2) and the mean age of family members (male=14, female=85) was 61 years (SD=14.22). Reliability of the FROM-16© total score was high (Cronbach α= 0.892; ICC=0.915). Similarly, the domains of FROM-16© showed high reliability (EM, α=0.80; PSL, α=0.89). Correlations between the SF-36 and FROM-16© domains were weak to moderate (-0.148 to -0.469). Similarly, analysis of variance between the general health state of the patients and the FROM-16© demonstrated significant differences between patients quality of life and family quality of life (Chi-squared=13.176; p=0.01), suggesting that the patients' quality of life does not necessary reflect that of the family members.

This study indicates that the FROM-16© is both valid and reliable in families of patients with urological conditions. This provides confidence for the use of this measure in urology when developing care plan and management strategies.

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Exploring the role of c-Met in drug resistant breast cancer

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The c-Met receptor is a receptor tyrosine kinase activated exclusively by its ligand HGF.[1] Deregulation of c-Met has been implicated in both tumour progression and resistance to breast cancer therapy. Tamoxifen-resistant ('TamR') breast cancer cells show upregulation of EGFR signalling, and are sensitive to anti-EGFR therapy.[2] However, prolonged treatment results in doubly-resistant cells ('DubR'), resistant to both tamoxifen and anti-EGFR treatment. Microarray analysis of the c-Met gene shows progressive amplification during the transformation from TamR to DubR cells. Consequently, the aim of this project was to investigate the role of c-Met in resistance to anti-EGFR therapy.

Western blotting was undertaken to compare the expression/activation of c-Met and related proteins between TamR and DubR cells. The cell samples analysed had been treated with HGF, crizotinib (c-Met inhibitor) gefitinib (EGFR inhibitor) or combination treatments. Secondly, MTT assays were conducted to observe the effects of these treatments on cell growth.

Surrogate markers of c-Met increased in response to HGF in both TamR and DubR cells. A dose dependent increase in MAPK activity was observed, with normalisation indicating this response was larger in DubR cells. DubR cells showed accompanying increases in Src signalling. Interestingly, crizotinib treatment resulted in increased EGFR and MAPK signalling in TamR cells. In terms of cellular growth, HGF treatment induced no significant changes, whereas crizotinib and gefitinib were growth inhibitory in both cell lines.

Results suggest a role of c-Met in both cell lines, although this may be larger in DubR cells. In TamR cells cross talk between c-Met and EGFR was identified, whereby EGFR activity increases in response to c-Met inhibition. Similar cross talk between these two receptors has been widely reported.[3,4] The role of c-Met in cell growth isn't clear from these findings, suggesting further study on alternative end points such as migration or invasion.

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Differential expression of natriuretic peptide receptors in rat myocardium

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Ischaemia-reperfusion (I/R) injury describes the paradoxical injury from the restoration of blood flow to the myocardium, during the clinical treatment of an Acute Myocardial Infarction (AMI).[1] Natriuretic peptides (NPs) attenuate I/R injury in animal models,[2,3] although the precise signalling cascade remains unclear. Emerging evidence suggests that NP signalling does not proceed via the classical natriuretic peptide receptor (NPR)-A/particulate guanylyl cyclase pathway and appears to require the nitric oxide/soluble guanylyl cyclase component,[2-4] which could potentially be coupled to NPR-C. This study examines NPR expression, in particular NPR-C, in cardiomyocytes to assess its contribution to NP signalling in limiting I/R injury.

Western blotting was used with rabbit anti-NPR-A, anti-NPR-B and anti-NPR-C antibodies to determine the differential expression of the respective NPRs in rat crude myocardial ventricular tissue extracts (n=4) and rat left ventricular isolated cardiomyocytes (n=4). The expression of mRNA coding for the NPRs was investigated in the same population of cardiomyocytes by utilising reverse transcriptase-polymerase chain reaction (RT-PCR).

Western blot analysis revealed a band for NPR-A (~118 kDa), NPR-B (~117 kDa) and NPR-C (~64 kDa) in crude myocardium and isolated cardiomyocytes. The NPRs were expressed in the rat myocardium in the rank order: NPR-C>NPR-B>NPR-A; and, in the cardiomyocytes: NPR-B>NPR-C>NPR-A. Using RT-PCR, DNA species were detected for each target by observing the appropriate base pairs (bp): NPR-A: 172 bp; NPR-B: 234 bp; and NPR-C: 158 bp. The isolated cardiomyocytes expressed mRNA for all NPRs in the rank order: NPR-B>NPR-C>NPR-A.

The results provide the biochemical confirmation that the NPRs are expressed in cardiomyocytes. In part, this indirect observation suggests that NPR-C may couple to the signal transduction pathway in NP-mediated infarct limitation in I/R injury. Further investigation into the full signalling pathway and functional regulation of cGMP is required prior to the effective therapeutic exploitation of NPs.

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Towards an ex vivo method for monitoring changes in eicosanoids in skin: application to the investigation of anti inflammatory effect of topically applied pomegranate rind extract

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When under stress, skin will inflame. This happens due to the transient up regulation of cyclooxygenase-2 (COX-2) and 12/15 lipoxygenase[1] (LOX) in keratinocytes within the viable epidermis. These enzymes will oxidise linoleic and arachidonic acid to produce inflammatory signalling molecules, known as eicosanoids. These cause vasodilation fever and pain sensitisation. Uncontrolled inflammation can lead to autoimmunity and disease states such as psoriasis and eczema. This project concerned a novel approach to monitoring the eicosanoids found in ex vivo porcine skin following treatment with topical antiinflammatories.

LCMSMS was utilised to determine the aptness of various skin preparation methods for use in determining modulation of eicosanoid levels. By analysing levels of direct LOX and COX-2 metabolites found in full thickness and epidermal skin samples,[2] the effect of different epidermal separation techniques on 12- & 15-HETE, 9- & 13-HODE, PGE2 and PGD2 was determined using LCMSMS also. The findings were applied to the effect of pomegranate rind extract (PRE) on cutaneous eicosanoids, as PRE polyphenols have been shown to reduce COX –2 levels in porcine skin.[3]

COX-2 metabolites were significantly greater in full thickness skin tissue; however, LOX metabolites were considerably less than when compared with epidermal samples. Heat separated and frozen heat separated epidermis produced greater LOX metabolites but less COX-2 products than that of enzymatic dispase separation. Samples treated with ibuprofen[4] showed reduced eicosanoids in both LOX and COX. PGE2 levels were less in PRE treated epidermis than control.

The structure of the dermis can be used to rationalise reduced LOX metabolites in full thickness skin, and thermodynamic differences in separation technique will effect enzyme kinetics and change eicosanoid profiles. Auto oxidative species are reduced in the presence of DTPA /BHT buffer solutions. Finally, in silico modelling can be useful in rationalising components of PRE that are responsible for anti-inflammatory responses.

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End point testing of total parenteral nutrition (TPN) – an exploration into current thoughts and practices within the NHS

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Total Parenteral Nutrition (TPN) is a means of intravenously delivering nutrients to patients who cannot utilize the GI system.[1] As with any medicinal product delivered directly into the bloodstream, there are risks inherent to TPN: microbial contamination, particulate matter and compositional errors. In the past, illness and even fatalities have occurred as a result of these risks.[2] The aim of this study was to ascertain the current testing practices used by hospitals, for the quality control of TPN and whether a BP monograph for TPN is needed.

A list of 11 NHS regional QA pharmacists was provided by an NHS contact, Dr. Julian Smith, for inclusion in the study. It was decided that an email questionnaire would be the most appropriate data collection tool; it being cheap, fast and convenient to return.[3] The questionnaire was developed through literature searching and supervisor interaction. Pilot studies helped to refine the questionnaire, ensuring face and content validity. Participants were sent the questionnaire and given one week to reply, after which reminders were sent.

Initial response rate was 27.3%, though some participants were able to forward the questionnaire onto individual aseptic production unit staff, bringing total responses to 6. The majority of responses were localized to southeast England. Two participants had encountered TPN related issues, the majority of which were compositional errors. Frequency and methods of testing vary widely between participants. The major testing parameter is electrolyte composition, of which sodium and potassium are most frequently measured. Common consensus was that end point testing is not always needed; participants were equally split on the need for a BP monograph.

Frequency and methods of end point testing varied wildly between participants. Common opinions were seen, such as in process checks preferred over use of end point testing, but the study was limited by poor response rate and responder bias.

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Evaluation of pharmacist independent prescribing in Wales

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The concept of other health care professionals prescribing was introduced after the publication of the Crown Report 1999, titled 'Review of Prescribing, Supply and Administration of Medicines'.[1] Supplementary prescribing was first introduced in 2003 followed by pharmacist independent prescribing in 2006.[2,3] An evaluation of pharmacist independent prescribers (PIPs) was conducted in England in 2010 with many positive results.[4] No such evaluation on PIPs has been conducted in Wales. The aim of this study was to evaluate Pharmacist Independent Prescribing in Wales.

A piloted questionnaire, covering letter and pre-paid return envelope was mailed to registered PIPs working in Wales. After 10 days a reminder mail out was sent. After a further 10 days the data was analysed using the SPSS for Windows version 18.0.

An overall response rate of 59% (n=75/128) was achieved. Only 64% (n=48/75) of the registered PIPs were practising; of those not using the PIP qualification, 3 were working as supplementary prescribers, and 11 (15%) had never used the qualification. The majority (73%) were working in a hospital environment, with n=26/51 prescribing at ward level. Advantages indicated were increased job satisfaction, improving services to patients and improving relations with Doctors. Perceived barriers included lack of time (n=10/51) and lack of funding (n=9/51).

Only around two-thirds of PIPs are using the qualification; further exploration of the reasons for this should be included in Phase II of the study. It was unexpected that so many PIPs are prescribing at ward level and further work will identify the exact model of prescribing e.g. how their prescribing is being checked. Barriers do need to be addressed and the future work proposed is to interview prescribing leads in Health Boards to explore their prescribing strategies and issues surrounding sustainability of PIPs.

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An evaluation of the provision of monitored dosage systems to patients on clozapine

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Clozapine is an atypical antipsychotic that is uniquely effective in refractory Schizophrenia.[1] It is supplied and monitored through the hospital under strict regulations. Wrexham Maelor Hospital supplies a large proportion

of its Clozapine in a compliance aid whilst Glan Clwyd Hospital does not. The aim of this study was to explore the views and experiences of staff and patients at both hospitals with regard to the use of monitored dosage systems (MDS) for Clozapine.

This study adopted an exploratory approach[2] using both quantitative and qualitative research methods. Patients' views were explored through the administration of a face-to-face questionnaire and the views of staff were explored through one-to-one interviews. The resulting patient responses were analysed using descriptive statistics and interviews were transcribed *verbatim* and analysed thematically.

Twenty eight patients (n=28) participated, 14 of whom received a compliance aid. From the statistical analysis, it was not possible to conclude that compliance aids improved compliance in these patients. Despite this, the majority of patients using the compliance aid found it to be 'very useful'. Comparable views were identified by the six healthcare professionals interviewed. All were in favour of using the MDS service but emphasised that the aid should only be given to those who genuinely need it and to determine this, a common patient assessment tool is required throughout the Trust.

No formal evaluation of the service has been undertaken in this area and although this study did not show that the MDS service improved compliance, a recent, larger scale study has shown that compliance aids improved compliance in those with a mental illness.[3] This exploratory study has shown that the MDS service is supported by both patients and staff but further work with a larger sample size is required before the service can be optimised and expanded across the Trust.

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Is Src kinase a potential target in luminal B versus luminal A breast cancer?

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The oestrogen receptor (ER) is expressed in around 70% of breast cancers diagnosed and characterise the 'luminal' breast cancer subtype. A proportion of these tumours will also express the HER2 receptor and this has led to ER+ tumours being defined as luminal A (ER+/HER2-) and luminal B (ER+/HER2+) with the latter having a poorer prognosis and treatment outcome as compared to luminal A.[1] The objective of this study is to investigate if the non-receptor tyrosine kinase, Src, known to be involved in ER activity and growth factor receptor signalling including the HER2 receptor, represents a potential target in luminal B tumours.[2]

Changes in cell proliferation (MTT assay) and signalling pathway activation (Western blotting) in luminal A (MCF7, T47D) versus luminal B (BT474, MDA361) breast cancer cell models were determined in response to the novel Src inhibitor, AZD0530, endocrine therapy (tamoxifen) or both agents in combination.

Tamoxifen was found to induce p-Src in most of the cell lines and only works in luminal A while Herceptin was effective only in luminal B and induced p-HER2 in low t-HER2 cell lines. AZD0530 was modestly effective in all cell lines with MDA361 being the most sensitive in terms of cell growth suppression. The combination treatment of AZD0530 and tamoxifen is better than single agents in all cell lines, however is only better than the current combination treatment of Herceptin and tamoxifen only in MDA361.

Tamoxifen induced p-Src may be due to involvement of the non classical pathway involving cytoplasmic ER while P-HER2 induction is due to formation of EGFR-HER2 or HER2-HER3 dimers, and Herceptin acting as HER2 partial agonist.[3,4] In luminal A, targeting both ER and Src kinase suppresses cell growth better than the current treatment of tamoxifen alone in MCF7. In luminal B, Src inhibitor improves tamoxifen response in Herceptin insensitive MDA361 cell line.

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Development and presentation of a Computer - Assisted Learning (CAL) package on food allergy

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Recently emerging technologies have opened up possibilities for providing pharmacy education through innovative strategies[1] such as Computer Assisted Learning (CAL) as a supplement to teaching. In this project, a CAL package was developed and evaluated using an online GoogleDocs® questionnaire.

The package content is summarised below. The questionnaire consisted of 23 closed statements using a 5-point centre-weighted Likert scale with space for free text comments. The package and questionnaire were piloted leading to some minor changes.

Table 1: Contents of the CAL Package on Food Allergy.

Pharmacist's Role	Immune Mechanism
Types of Sensitivity	Symptoms
Food Allergy	Diagnosis
Most Common Allergens	Food Intolerance
Childhood allergy	Other Food Reactions
Prevalence	Treating allergy
Current Research	Immunotherapy
Food Allergens	Anaphylaxis

Of 124 questionnaires, a response rate of 22% (28) was achieved. The majority agreed with the positively and disagreed with the negatively worded statements.[2] Most agreed that the package was well presented. 72% (20) thought the package was of appropriate length with only 4 agreeing that some slides contained too much information. Ninety-six per cent responded that the content fitted the purpose and only 4% (1) thought more information was needed. All students agreed that the package benefitted them and 82% agreed that the use of CAL was effective. Regarding the statement, "The use of CAL should not replace traditional learning methods," 36% had no opinion. However, qualitative comments suggested an overall preference for the use of both methods simultaneously. Seventy-eight per cent (22) replied that they would use the package for continuing professional development, but only 29% (8) would rather complete a CAL package than attend a lecture. Again however, qualitative data suggested a preference for using both together.

The overall response rate provided a representative view of third year pharmacy students on the use of CAL. It can be concluded from the questionnaire evaluation that the package was well-received and accepted overall as a beneficial tool to supplement lectures and aid revision. This reflects the findings of previous studies[3] concluding that the purpose of CAL is not to replace lectures, but to assist in learning.

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Permeability of the renal pelvis, ureter and bladder to locally delivered terazosin

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At present, there is little knowledge about drug absorption across urothelium in renal pelvis, ureter and urinary bladder. Therefore, it is complicated to target localized therapies to treat conditions like ureteral stent related pain. The aim of this study is to investigate the relative difference of permeability across urothelium of renal pelvis, ureter and bladder using terazosin hydrochloride as a model drug.

Organs were freshly obtained from porcine models and kept in iced-cold Krebs buffer to maintain viability. Franz-diffusion type cells were used in the bladder experiment. Terazosin 100 µg/ml stock solution was directly instilled into the renal pelvis and lumen of the ureter via a cannulating pipette. Tissues were incubated at 37°C for 90 minutes. Tissues were separated from underlying tissue layer and extracted in methanol overnight. Sample extracts were analysed using HPLC-UV detector at 250 nm wavelengths.

Results showed that permeability of terazosin was the highest in renal pelvis and least in the bladder. Terazosin permeability was significantly different between bladder and ureter, and between bladder and renal pelvis. There was no significant difference between ureter and renal pelvis. Urothelium/lamina propria shows rate-limiting absorption of terazosin across bladder wall. Small amount of terazosin in medulla/cortex suggests that the drug may have permeated across muscle in renal pelvis. The amount of terazosin found bladder, renal pelvis and ureter may be sufficient to cause clinical effect.

The difference in permeability between organs may be explained by the difference in anatomical distribution of uroplakin protein[1] and thickness of urothelium[2] between bladder, ureter and renal pelvis. In conclusion, results from this experiment could improve our understanding about permeability across urothelium. Therefore, more effective local drug delivery can be developed in the future for treating ureteral stent related pain and other similar complications such as urothelial cancers.

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Does modafinil enhance cognition in healthy non-sleep deprived individuals?

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Modafinil is a novel wake-promoting Central Nervous System stimulating agent that has been licensed for excessive sleepiness associated with narcolepsy with or without cataplexy[1-3] and as adjunctive treatment of obstructive sleep apnoea or hypopnea syndrome.[1,2] There are myriad off-label uses of modafinil particularly for increasing brain performance and memory i.e. cognition enhancement. However, the empirical evidence from the literature is equivocal with a lack of data addressing the long-term use of this agent.[2] The aim of this study then was to undertake a systematic review to determine whether modafinil increases cognition in healthy, non-sleep deprived individuals.

Using a range of electronic databases four randomized placebo controlled trials were identified as meeting eligibility criteria and were analysed to determine the effect of modafanil on emerging common cognitive domains such as learning and problem solving. Data extracted from the articles was inputted into RevMan 5.2 software[4] for statistical analysis. The primary outcome was to assess the effect of modafinil, compared to placebo, on cognition.

Modafinil did not display any improvements in working memory compared to placebo in tests of reaction times (Standard mean difference (SMD) 0.09[-0.36, 0.54]; $p > 0.05$,) and error rates (SMD -1.70[-5.62, 2.23]; $p > 0.05$). However, modafinil did show limited enhancement in executive function as demonstrated by improvements in elements of the Stockings of Cambridge test particularly the ability to plan (SMD -0.55[-0.97,-0.14] $p < 0.05$) although there was no significant difference in pattern recognition tests (SMD 0.38[-0.03, 0.79]; $p > 0.05$).

Despite the wide-spread use of modafinil off-license for cognition enhancement, the number of rigorous and robust trials on its effect remains limited. However notwithstanding, these data suggest that modafinil has limited utility in cognition enhancement in non-sleep deprived individuals.

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Investigating the effects of the cell permeating peptide EY1068 on cell proliferation

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The binding of Epidermal Growth Factor (EGF) to its receptor triggers many signalling pathways, ultimately resulting in cell proliferation.[1] The peptide EY1068 has been developed to competitively inhibit docking sites on the EGF receptor, thus stopping proliferation signals. The binding sequence is attached to an octa-arginine cell penetrating peptide in order to allow access to the intracellular target. Repeating arginine chains have proven cell permeating properties.[2] This study aims to investigate the effects of EY1068 on cell proliferation.

Cell proliferation will be measured using the CellTiter-Blue assay for cell viability. This method uses the respiratory process of living cells to convert the reagent to a fluorescent compound. The intensity of fluorescence is proportional to number of viable cells.[3] HeLa and A431 cells will be incubated with EGF in the presence and absence of EY1068 to determine whether there is a reduction in cell viability, indicating the suppression of cell proliferation. Microscopy will also be used to determine proliferation with and without peptide. Cells are stained with fluorescent dyes to label the nucleus and actin of the cell.

Viability assays show that the presence of EY1068 in the growth medium tends to reduce viability. This inhibitory effect is most pronounced after 48 hours incubation. Microscopy reveals that cell division is increased at increasing concentrations of EGF. Addition of EY1068 reduces both the total number of cells and the number of cells undergoing replication.

EY1068 is thought to inhibit cell proliferation by interfering with EGF signalling. A reduction in cell viability is observed when cells are incubated with the peptide, suggesting that cell proliferation is inhibited. Images of the cell nuclei show that the proportion of dividing cells is reduced in the presence of EY1068. It can therefore be inferred that the peptide is involved in preventing cell replication.

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What types of medicines-based calculations are currently being performed in pharmacy practice settings?

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Medicines-based calculations (MBCs) are commonly used in the healthcare setting. Poor numeracy of some healthcare staff has resulted in a number of medication errors.[1,2] The aim of this project was to identify examples of MBCs that are currently used in pharmacy practice settings. These will be used to review and update existing and develop new learning, teaching and assessment materials for pharmacy students and professionals, and possibly other healthcare professionals.

Research ethics approval was obtained from Cardiff School of Pharmacy and Pharmaceutical Sciences Ethics Committee. Emails were sent to all MPharm III and MPharm IV students at Cardiff, to three pre-registration pharmacists known to the researchers and to a number of hospital and community pharmacists asking for examples of MBCs performed in practice. A number of academic staff were also approached to gather information on the teaching and assessment on MBCs. Data relevant to this study were extracted from previous interview transcripts on MBCs.[3] A literature search was performed to identify medication errors arising from calculation errors.

Responses were obtained from 56 participants (24 students, 22 pharmacists, 4 pharmacy technicians and 6 academic staff). MBCs identified in this study were categorized into eight themes, namely dosage calculations, quantity (including volume), infusion dose & rate, creatinine clearance, dilution, body surface area & weight-related, unit conversion and molarity. MBC errors that resulted in death were also identified from the literature.

The types of MBCs performed in pharmacy practice were successfully explored. Some differences between the MBCs performed in community and hospital settings were established. The findings of this study have already informed the teaching of MBCs in the MPharm course. Further work is required due to the small sample size.

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eBooks to Enhance Learning in the Pharmaceutical Sciences

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The Cardiff School of Pharmacy utilises CAL packages to supplement classroom learning. These packages are hosted on the Universities' intranet requiring students to visit a campus computer lab and do not afford flexible learning. This project seeks to identify whether the CAL content may be better channelled through interactive eBooks that provide a flexible learning environment. Given the mixed data in the educational literature[1], a meta-analysis was conducted to understand the potential benefits of technology within healthcare education. The aim of this project was to create a Cell Biology eBook; supported by the outcomes of a meta-analysis.

Meta-analysis outcomes were: knowledge and skills acquisition following technology enhanced learning (TEL). Data was extracted from the literature (n = 4 trials) and summary statistics were generated to determine the effect of TEL. A technology appraisal selected Apple's iBook Author for eBook development as it is free, has rich interactive features and a shallow learning curve.

The meta-analysis showed that TEL did not improve knowledge acquisition (Correlation and 95% CI= -0.070 [-0.145, 0.006]; P=0.071) but did improve skill acquisition (Correlation and 95% CI= -0.274 [-0.354, -0.190]; P=0.0001,). Subsequently, the content of original Cell Biology CAL package was thoroughly analysed. For the eBook, 70% of the content was retained and original interactive features were improved such as the navigation and multimedia files. Enhanced features such as PowerPoint presentation and survey widgets were also included.

Despite the mixed results for TEL described in the pedagogic literature, the meta-analysis conducted here provides evidence, at least for skills acquisition, that TEL improves student learning. These data combined with the increasing penetration of eBooks in the marketplace[2] have supported the design of a multimedia rich interactive eBook which may be utilised by the School, following testing within the student body, to enhance the quality of learning experience.

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The views of supervising pharmacists on the community pharmacy placement scheme

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Many studies have been conducted into the impact of experiential placements on university students, with most finding them to be an important aspect of many university courses.[1] Cardiff School of Pharmacy (SoP) have incorporated work placements into their curriculum and have recently developed their placement scheme further. The aim of this project was to investigate the views of supervising pharmacists on the community pharmacy placement scheme.

Firstly, the research proposal was submitted and permission was gained from Cardiff SoP Research and Ethics Committee. Non-probability convenience and purposeful sampling methods were then adopted. The

participants in this research were pharmacists listed on the placement scheme database. Semi-structured interviews were carried out and audio recorded, with consent to gain an in-depth understanding of the participant's views and opinions.[2] Once interviews were transcribed, common themes were identified via thematic analysis.

Ten participants were interviewed and audio recorded. Most interviews were conducted face to face as pharmacies were within the Cardiff area. Pharmacists mentioned that the manual was important in providing structure for the placement but suggested that its flexibility could be increased. The reflective task was seen as an effective way to assess the students on the placement scheme but some thought this may be difficult for students. Formal feedback on each student from the pharmacist was deemed to be a possible future assessment method.

Only individual interviews were used for this project. Using both qualitative and quantitative methods would increase reliability of the results. Due to the small sample size (n=10) the results gained may not be representative of the larger population. In conclusion, experiential placements are an essential part of pharmacy degree scheme and the pharmacists interviewed agree with this. Overall, pharmacists were satisfied with the scheme and thought that the placements would help prepare the students for their futures as pre-registration pharmacists.

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Adaptation and testing of the self-medication scale (SMS) for flu, coughs and colds

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Flus, coughs and colds are common minor ailments and self-medicating to these is important[1] and is encouraged by the government.[2] The self-medicating scale (SMS) was developed to measure the beliefs and behaviour in response to the symptoms of pain.[3] A previous qualitative study explored patients' self-medicating beliefs and behaviours in response to a flu, cough or cold.[4] The study aimed to adapt the original 12-item SMS to measure self-medicating beliefs and behaviours in response to the symptoms of a flu, cough or cold.

A quantitative research methodology was used following ten qualitative interviews that were thematically analysed and built upon previous data[4] to inform the questionnaire design. The final questionnaire contained sixteen SMS statements and questions to measure self-medicating behaviours. All staff and MPharm students at the Cardiff School of Pharmacy and Pharmaceutical Sciences were eligible for inclusion into the study.

Of the 328 respondents, 275 (83.8%) reported having experienced symptoms relating to flu, coughs or colds in the last six months, with 208 (63.4%) choosing to self-medicate. A blocked nose (n=216, 78.5 %) was the most common symptom. Of those who self-medicated, headaches were the most commonly self-treated symptom (n=143, 68.3%), with paracetamol being the most frequently used (n=158, 76.0%).The three scales ('Reluctance', 'Run its course' and 'Don't think twice') demonstrated good internal reliability (Cronbach's alpha = 0.78, 0.85, 0.80 respectively). Statistical differences were found between the SMS scores between demographic variables (i.e. gender, ethnicity, sub-groups) and various self-medicating behaviours (i.e. number of symptoms experienced or self-medicated for and the number of medications and non-pharmacological methods used).

In conclusion, the modified SMS for flu, cough or colds shows good internal validity and reliability and can measure patients' self-medicating beliefs and behaviours. Further research is needed in the wider general public with the potential for further modification of the SMS for other minor ailments.

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Investigation of whether serine residue 276 is fundamental for the activity of zinc transporter ZIP7

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Zinc transporters operate to tightly control cellular levels of zinc. There are two main classes, ZnT and ZIP transporters.[1] An increase in intracellular zinc has been associated with the activation of downstream signalling pathways that regulate cell growth and proliferation and an increased expression of zinc transporters, especially ZIP7, has been found in breast cancer cells.[2] The activation of ZIP7 is thought to release a zinc wave due to phosphorylation by CK2 of two serine residues S275 and S276.[3] This study looks at whether or not both S275 and S276 need to be phosphorylated order to activate ZIP7, looking specifically at the S276.

MCF7 cells were transfected with wild-type ZIP7, ZIP7 S276A and ZIP7 S276D. With S276A, the serine residue was substituted with an alanine and therefore is unable to be phosphorylated and with S276D, the residue was phosphomimetic having the same confirmation as the activated/phosphorylated serine. Cells were exposed to exogenous zinc and probed for pZIP7, pMapK and pAKT proteins via western blotting.

Results correspond with published data for wild-type[3], but the main increase of activation was seen at 10 minutes, not 5. The S276A mutant showed activation of ZIP7, MapK and AKT, suggesting importance of S275. The S276D mutant was also investigated for effect on activation of MapK and AKT compared to wild-type and S276A mutant.

Data does not truly confirm that the phosphorylation of S276 alone would be sufficient to activate ZIP7, but does suggest that one active residue present is adequate to cause minor activity. When both residues were active, the results achieved were much greater suggesting, if this mechanism was going to be a target for breast cancer, to see a greater reduction in the growth and spread of the cancer both residues must be inactivated.

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Design and synthesis of novel allosteric inhibitors against Dengue Virus

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Dengue fever is the most common mosquito-borne viral infection. Classically found in tropical and subtropical regions, prevalence of dengue fever has recently spread to America and Europe.[1] The disease characterised by influenza-like symptoms is normally mild and self-limiting. Infected individuals however may develop severe conditions namely Dengue Haemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS) which are fatal if untreated. Concern arose over the increased risk of developing DHF/DSS upon secondary infection with different serotypes of DENV.[2, 3] Yet drugs and vaccine are currently unavailable and treatment remains symptomatic.[4] NS5 RNA-dependent RNA polymerase (RdRp) is an enzyme responsible for conversion of positive-sense RNA to double-stranded RNA during viral infection.[5] Inhibiting RdRp theoretically prevents RNA replication and hence viral spread.

Previous homology modelling and virtual screening resulted in a complete 3D structure of RdRp and two lead compounds with different binding mode to RdRp. The investigated site was near the priming loop known to involve in de novo initiation of RNA synthesis.[6] Over 200 compounds structurally based on N-(3,5-dimethylphenyl)-3-ethoxy-4-fluorobenzenesulfonamide (**1**) and N^1,N^5-bis(2-carbamoylphenyl)glutaramide (**2**) were docked and analysed using Glide and MOE. Newly-designed compounds demonstrated improved docking while retaining critical interactions with key residues Trp795 and Arg737 of the priming loop.

Four compounds, two from each class, were selected for synthetic development based on docking score, orientation within the binding pocket and ease of synthesis. The chosen analogues of **1** were successfully synthesised with varying yield whereas several attempts were made to synthesise analogues of **2** yet

unsuccessful. Difficulty encountered was due to by-product formation and solubility of compounds in purifying solvents.

The study has demonstrated potential for development of effective anti-DENV drugs. Designed analogues have shown promising inhibitory activity in silico. Further work nevertheless is required including biological testing of synthesised compounds and synthetic improvement of chosen analogues.

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Does magnesium affect salbutamol-induced bronchodilator responses?

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Magnesium is known to cause relaxation of a number of smooth muscle preparations; various mechanisms for this have been proposed. The main mechanism of action of magnesium is reported to be the blockage of calcium ion influx, but other roles of magnesium are also reported.[1] IV $MgSO_4$ has been shown to be clinically effective as an adjuvant to β_2-adrenergic agonists in vivo, and has been used for years, as an emergency treatment of the most severe cases of acute asthma.[2] The aim of the study was to investigate the effect of additional $MgSO_4$ on bronchoconstrictor and bronchodilator responses.

The lungs of male Dunkin-Hartley guinea pigs, weighing 300-500g, were split into two half-lungs. Cannulating the bronchi enabled one half of the lung to be perfused with Krebs containing 1.2mM $MgSO_4$ and the other half to be perfused with Krebs containing 16.2mM $MgSO_4$. Bronchodilator drugs were added to methacholine-induced (10^{-5}M), pre-constricted lungs via serial addition; then bronchoconstrictor drugs were added to relaxed lungs via the same method.

Raising the concentration of magnesium, from 1.2mM to 16.2 mM $MgSO_4$, had no statistically significant effect on the bronchodilator or bronchoconstrictor responses in 'normal' guinea pigs. Paired, 2-tailed, Student's t tests were used to determine if there were significant differences in the data between the control group and test groups, and no significant statistical differences are considered when $P>0.05$.

Additional $MgSO_4$ did not cause any statistically significant effect on bronchodilator or bronchoconstrictor responses *in vitro*, but it has been shown to do so *in vivo*.[3] This suggests that magnesium may not augment its effects by direct actions on the airway smooth muscle. This leads to idea that $MgSO_4$ may produce its effects via different mechanisms, such as actions on the parasympathetic nervous system and inflammatory cells.[1]

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Pharmaceutical potential of two specimens of Aplysina aerophoba harvested from competitive and isolated environments

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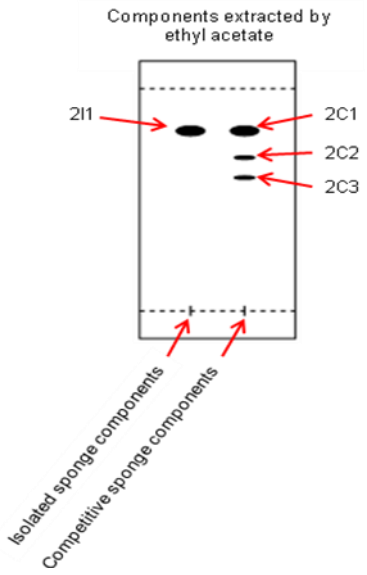
Studies have shown that numerous factors can contribute to variation of natural product biosynthesis in marine sponges,[1,2] the details accounting for such variations are not fully understood. Further research into the factors that regulate compound variation could potentially streamline the selection of organisms with a high yield of bioactive natural products. The aim of this study was to determine whether the marine sponge

Aplysina aerophoba produced different natural products when growing in competition with other sponges compared to when growing in isolation.

Crude extracts were obtained from isolated sponges and those growing in a competitive environment surrounded by other species. Dried sponge samples were extracted using hexane, ethyl acetate and methanol, then analysed by thin layer chromatography (TLC). Several compounds were isolated from the ethyl acetate extracts and further purified using preparative TLC. A bioautographic[3] technique was used to determine if any of the sponge extracts possessed antibacterial activity against Staphylococcus aureus. Isolated compounds underwent proton NMR, carbon-13 NMR and low resolution mass spectrometry (MS). High resolution MS was performed by the EPRSC National Mass Spectrometry Service Centre, Swansea University.



Only the compounds extracted using ethyl acetate demonstrated variation between the sponge samples. NMR data for 2C1 suggested this compound had between 26 and 29 hydrogen atoms. Contradictory MS data for 2C1 suggested a molecular weight of 662 as well as the molecular formulas $C_{30}H_{15}O_9N_7$ or $C_{28}H_{58}O_8N_{10}$. MS data for 2C2 and 2C3 suggested both had relatively high molecular weights (662.3 and 853.5 respectively). These compounds provided some evidence to support the hypothesis of this study as both were solely present in samples obtained from sponges growing in a competitive environment. None of the extracted components showed any conclusive antibacterial activity.

In conclusion this study showed that compound production in Aplysina aerophoba varies when the sponge is growing in a competitive versus an isolated environment. Due to time constraints the absolute identity of the isolated compounds remains uncertain.

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An evaluation of the provision of monitored dosage systems to patients on clozapine

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Clozapine is an atypical antipsychotic drug used in treatment-resistant schizophrenia.[1] Within BCUHB, clozapine dispensing differs. Wrexham supplies a large proportion in compliance aids to simplify self-administration and improve compliance.[2] Current knowledge of providing clozapine in MDS is limited. The project aims to identify reasons for clozapine non-compliance and to investigate the role of MDS by exploring patient and staff opinions.

Ethical approval from CSPPS REC was obtained. A mixed methods approach was adopted combining an exploratory semi-structured interview[3] and a structured questionnaire.[4] Purposive sampling recruited six health professionals with clozapine experience from Wrexham and Glan Clwyd hospitals including pharmacists, technicians and clinic nurses. The interviews were audio-recorded, transcribed verbatim and analysed thematically. The questionnaire was constructed around patient compliance and MDS experiences. After four weeks at each site, 28 responses were collected and input into SPSS for analysis.

A response rate of 29.2% was obtained for the questionnaire. 96.4% view taking clozapine as important. A significant negative correlation (-0.436) was found between importance and frequency in forgetting. 88.9% either never forget or forget less frequently. Main reasons for non-compliance were forgetting and side-effects. 93% of patients using a compliance aid and 50% not currently using one commented on their usefulness. Overall professionals were positive of the service and noted particular usefulness in those with a complex regimen or a history of poor compliance. Issues such as cost, equal access and hospital policies would need to be addressed. It was suggested an assessment tool should be introduced.

Patients and staff commented on the usefulness of the service in the right patients. An important feature was identifying patients' need with an assessment tool. This study of small numbers was successful in identifying issues to inform the development of the service. Further work in larger populations across the trust is needed before standardisation.

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Hydrogels containing pomegranate rind extract: active release and antimicrobial activity

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There is a current need for new topical antimicrobial products, due in part to increased microbial resistance.[1] Generally, there is a preference among patients for medicines of natural origin, and the demonstrable antimicrobial activity of the fruit of *Punica granatum L*. (pomegranate) has received much attention accordingly. Recent research has demonstrated remarkable broad spectrum anti-microbial activity of pomegranate rind extract (PRE)[2] when co-administered with potentiating agent, X.[3]

GMP-grade hydroxypropyl methylcellulose (HPMC) was sourced from two manufacturers (K100 and 90SH) and used to prepare hydrogels containing PRE and X. Firstly, these were tested for spontaneous release across a minimal-resistance membrane, followed by the analysis of punicalagin (major antimicrobial of PRE) by HPLC and X by ICPMS. The antibacterial activities of the eluates released were then used to challenge two common skin bacteria: *S. aureus* and *S. epidermidis.*

The greatest release was seen within the first hour, essential for efficacious topical formulation. The 90SH gels released more punicalagin, whereas K100 gels released larger amount of X. The most appropriate ratio (punicalagin: X) was shown by 90SH 5% w/v at 0.058: 1, although all the gels released more the initial ratio applied. The bacterial log reduction data followed the trend observed in the release ratios, as 90SH 5% gave greater than 99% kill after 2 h, followed by 90SH 2.5% with more than 90% kill. K100 2.5% and 5% showed a plateau in activity. The K100 2.5% showed the smallest zone of inhibition, concurring with the lowest release ratio, 0.016: 1M. There were differences noted between the zones of inhibition of *S. aureus* and *S. epidermidis.*

In conjunction with data obtained previously, the results obtained in this project support the further development of a hydrogel product containing PRE and X as a broad-spectrum topical antimicrobial.

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The role of GABA and nitric oxide in M_1-receptor mediated relaxation of isolated duodenum

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M_1 are a subtype of muscarinic receptor found in autonomic ganglia, glands and the cerebral cortex where they typically mediate excitatory responses.[1] They also cause relaxation in rat duodenum.[2] It is proposed that following M_1 stimulation relaxation occurs due to a number of indirect mechanisms. This study aimed to confirm the role of M_1-receptors in relaxation of duodenum and investigate the roles of GABA and nitric oxide as mediators. It is thought that following M_1 stimulation GABAergic nerves release GABA which bind $GABA_A$ receptors. This leads to chloride influx which hyperpolarises the cell.[1,2] Nitric oxide may also be released which activates guanylyl cyclase, increasing cGMP concentration. This decreases intracellular calcium, inhibiting smooth muscle contractions.[1,3]

Isolated rat duodenum was suspended in an oxygenated 50ml organ bath of Tyrode's solution at 37.5°C, under 1.5g of tension. Dose-response curves to GABA and the M_1-selective agonist McN-A-343[4] were carried out in the absence and presence of a number of drug additions: the GABA uptake inhibitor nipecotic acid, the nitric oxide synthase inhibitor L-NAME and the M_3 antagonist darifenacin.

GABA and McN-A-343 both caused relaxation in rat duodenum. Darifenacin enhanced relaxation and duration of the response of McN-A-343, especially at lower doses. Nipecotic acid significantly enhanced the response of GABA, but there were no significant differences with McN-A-343. Addition of L-NAME had no significant effect on GABA or McN-A-343.

McN-A-343 causes relaxation suggesting it is via M_1 receptors. Darifenacin enhanced McN-A-343 relaxation at lower doses suggesting McN-A-343 has contractile M_3 activity. At higher doses the larger relaxation responses mask this contraction. There is some evidence to suggest GABA may be released following M_1 stimulation. Nipecotic acid blocked GABA uptake leading to an increase in GABA available to bind $GABA_A$ receptors. There is no evidence to suggest nitric oxide is released following M_1 or $GABA_A$ stimulation.

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A study of the effects of trace amines on the contractile function of the ileum

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Trace amines are found at very low concentration in the body[1] and in the diet.[2] They are traditionally thought to cause relaxation of the gut via indirect sympathomimetic pathway.[3] Primary aim is to clarify the main effects of the trace amine on guinea-pig ileum. Secondary aim is to examine whether trace amines exert effects on other receptors directly, independent of indirect sympathomimetic activity.

Isolated guinea-pig ileum was used. Cumulative CRCs were obtained for β-PEA, tyramine, tryptamine and octopamine either in the absence or presence of ritanserin or prazosin and propranolol. Two phases of contraction, initial and secondary contractions were seen and measured separately. Non-cumulative CRCs were obtained for β-PEA and tyramine in the absence or presence of prazosin and propranolol, with dose exposure time of (30min). Initial and secondary contractions or number of spontaneous contractions were measured.

β-PEA and tryptamine caused dose-related contractions of the ileum, but tyramine contractions were not concentration-related. A 5-HT_2 receptor antagonist inhibited 5-HT contractions, but did not inhibit β-PEA or tyramine contractions. The degree of contraction was not potentiated by α_1 and β-adrenoceptors antagonists. Spontaneous contractions for β-PEA and tyramine did not increase with time but were increased by α_1 and β-adrenoceptors antagonists. Tryptamine initial contractions were inhibited by 5-HT_2 receptor antagonist and tryptamine secondary contractions were potentiated by α_1 and β-adrenoceptors antagonist. No apparent responses were elicited by octopamine.

β-PEA, tyramine and tryptamine cause contraction rather than relaxation of the guinea-pig ileum. Tryptamine exerts action mainly via the 5-HT_2 receptors. β-PEA and tyramine contractions are independent of 5-HT_2 receptors. β-PEA, tyramine and tryptamine exert opposing relaxation effect on the gut that were blocked by α_1 and β-adrenoceptors antagonists to reveal a larger contraction. The contraction is the dominant effect that masks the relaxation. Octopamine does not cause contraction of the gut.

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The effects of zeta potential and particle size of polyelectrolyte nanoparticles on their diffusion through GI mucus

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Proteins and peptides cannot be given orally due to degradation in the GI tract.[1] Nanoparticles can overcome this by protecting these drugs from harsh physiological conditions.[2] A barrier to oral nanoparticle delivery is the mucus lining covering the small intestine, in which nanoparticles can become entrapped.[3] This is due to the presence of hydrophobic and hydrophilic regions of mucus[2,3] which can interact with the nanoparticles. Cationic nanoparticles cannot diffuse through mucus due to electrostatic attraction with the negatively charged mucus. Anionic nanoparticles will be repelled by the same charge in mucus. Uncharged nanoparticles will bind the lipophilic regions in mucus through hydrophobic interactions. It is hypothesised that 'Polyelectrolyte' nanoparticles which are highly charged nanoparticles with both anionic and cationic charges, but possess a net neutral charge will achieve high diffusion rates across the mucus barrier as they would avoid electrostatic attraction and repulsion whilst being highly hydrophilic and hence avoiding hydrophobic interactions too.

Polyelectrolyte nanoparticles were produced by overnight mixing of different ratios of Chitosan and Poly (acrylic acid) (PAA) at pH6.5. The nanoparticles produced in the study were characterised by measurement of key physical attributes, namely, zeta potential and particle size. Subsequently the effects that these parameters had on diffusion of Lumogen Red® loaded nanoparticles through GI mucus were observed by confocal microscopy and the determination of diffusion coefficient through mucus.

At a ratio of 1 part PAA to 2.2 parts Chitosan the zeta potential was approximately 0mV. These particles were also the largest, due to aggregation. These neutral nanoparticles diffused through mucus at a much faster rate than either cationic or anionic nanoparticles.

PAA Chitosan nanoparticles with a high charge density, but a net neutral charge have been shown to be excellent candidates for exploitation as vehicles for protein and peptide delivery across the GI tract.

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Development and evaluation of a computer-assisted learning (CAL) package on evidence-based rationales for the management of substance abuse

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Computer Assisted Learning (CAL) is a useful supplementary teaching aid which provides interactive learning.[1] Additionally, CAL can be utilised as Continuing Professional Development (CPD) for healthcare professionals.[2] This study aimed to evaluate the potential of a CAL package on Management of Substance Abuse for teaching and CPD purposes among MPharm undergraduates and postgraduate pharmacists.

The CAL package consisted of an up-to-date and evidence-based management for alcohol abuse and opioid abuse.[3,4] Information was presented with animation, diagrams and colours to aid understanding as well as retaining students' interest. Role of pharmacists was included to make the package relevant to pharmacy practice. Quizzes and case-studies were included to test students' understanding. A questionnaire-based survey was conducted on MPharm II students to receive feedback on the CAL package presentation, content and overall impression. GoogleDocs online questionnaire was used, with a 5-point-Likert scale and a facility for comments.

Twenty-three questionnaire responses were received (19%). Overall feedback towards the CAL package was positive. Most respondents agreed that the package was well-presented (91%, n=21). Content was viewed as relevant and respondents agreed that information could be understood easily, especially with the aid of diagrams (91%, n=21). Many positive comments were received about the role of pharmacists and the case-studies. Most students would use CAL for their course (78%, n=18). Respondents confirmed that the package complemented MPharm course (74%, n=17); and would benefit their practice as a pharmacist (91%, n=21). However, use of CAL for CPD showed varied responses.

Majority believed the package was comprehensive and would benefit as a revision aid. However, several improvements were suggested: inclusion of hyperlinks, audio or video and more case studies examples. In conclusion, the package was a useful supplementary teaching aid. The value of CAL for CPD needs to be further clarified by future study on postgraduate pharmacists.

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Evaluation of FDA approved small molecule anticancer drugs in the last 5 years

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Natural products have played a vital role in the history of anticancer drugs, however the arrival of X-ray crystallography and high-throughput screening have revolutionised the field of anticancer drug discovery, allowing researchers to conduct researchers much more efficiently.[1] In this project, small molecule anticancer drugs that were approved by the FDA between 2008 and 2012 have been investigated. This project evaluated the whether if structural diversity of small molecule anticancer drugs have narrowed, along with the consensus towards target-based high-throughput screening, and whether if there is a decline in the popularity of natural products.

First, small molecule anticancer drugs that were approved by the FDA between 2008 and 2012 were isolated from the FDA website. Details of each drug such as structure, approved indication, year of the indication being approved, drug class, their mode of action and origin of discovery were obtained from various sources of information. The number of drugs approved from each origin of discovery is then compared with past literatures. The structures of the drugs are evaluated to determine whether if the structural diversity has narrowed.

Total of 45 new indications between 34 small molecule anticancer drugs were approved. After comparing these data with that of the past literature, I have found that there is a significant increase in the percentage of first time approved drugs being totally synthetic and a significant decrease in drugs that are natural products and natural product derivatives.

Despite this the number of new natural products and natural product derivatives approved each year has actually increased stating that there is no loss in popularity of natural products. It is simply the case of a significant increase in the popularity of totally synthetic drugs. The structural diversity has not narrowed judging on the wide range of structural motifs and drug modes of actions.

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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:

Production and permeation of topical gabapentin formulations across various diffusion barriers

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Design, synthesis and biological evaluation of potential anticancer drugs

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The effects of modification of 5-HT and dopamine on their biological activity

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Vitamin D and its association with cancer: selective inhibition of the CYP24A1 enzyme

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The study of the effect of temperature on the aerosol performance of nebulised salbutamol sulphate

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Comparative in vitro assessment of salbutamol sulphate metered dose inhalers: consistency of delivered dose using different priming and shaking methods

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A study of growth factor impact on signalling in the presence of a pan-erbB inhibitor in tamoxifen resistant (TAM-R) cells

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The efficacy of different wipe materials to remove bacteria from surfaces in a hospital environment

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Deducing the mechanism by which human insulin catalyses coelenterazine chemiluminescence

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Synthesis of Bcl3 inhibitors against HER2+ mammary tumours

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Design and synthesis of novel inhibitor of *Mycobacterium tuberculosis* Cytochrome P450 CYP121

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Is rectal administration an alternative route for melatonin?

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Patients and providers views on the pain or discomfort experienced by women having the insertion of an intrauterine method of contraception

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Intrauterine contraception is the most commonly used method of contraception worldwide. Pain and discomfort associated with the insertion of an intrauterine device is a known barrier to intrauterine contraception use in the West. There is no evidence that currently available analgesia and local anaesthesia are effective for pain experienced during the insertion procedure. Exploring health professionals' (providers) and women's (patients') views on pain during intrauterine device insertion will facilitate an understanding of and further research on pain experienced during intrauterine device insertion and its management.

This project aimed to determine the prevalence of and reasons for local anaesthesia use and non-use by UK health professionals during intrauterine device insertion, the pain and/or discomfort experienced by women who have the insertion of an intrauterine device, and to establish if this correlated well with pain health professionals perceived women to have experienced during their insertion procedure.

Questionnaire surveys were undertaken to determine local anaesthesia use by UK health professionals that perform intrauterine device insertions, and to collect information on the patient experience of intrauterine device insertion from both health professionals and women.

The majority of UK healthcare professionals did not routinely use local anaesthesia during intrauterine device insertions. Most women surveyed received local anaesthesia during their insertion and experienced mild pain or minimal discomfort. Health professionals had a tendency to perceive a lesser degree of pain than was actually experienced by their patients during insertions. Intrauterine device insertion may be associated with pain, even when available local anaesthesia is used. Health professionals perceive less pain than actually experienced by their patients during insertions. Healthcare professionals may better serve their patients and increase intrauterine contraception use by routinely offering local anaesthesia to women for intrauterine device insertion.

An investigation of a new compound for the treatment of adrenal insufficiency

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This was an original research study to investigate whether a modified release formulation of hydrocortisone (Chronocort®) could be used to replicate physiological cortisol release. Patients who are deficient in cortisol have to take life-long hydrocortisone replacement (the synthetic form of cortisol).

Twenty eight health male volunteers were administered either 5 mg, 10 mg, 20 mg or 30 mg modified release formulations of hydrocortisone (Chronocort®). Blood samples were taken to examine the pharmacokinetic profile. The safety and tolerability of Chronocort® was assessed and was considered to be safe and well tolerated.

The AUC demonstrated that twice daily dosing provided a similar AUC to the normative cortisol profile. A comparison of the time-segmented AUC parameter exemplifies the closeness of fit between DIURF-006 (20 mg and 10 mg) versus normative data i.e., AUC0-8: 1824.18 versus 1338.65 hr*nmol/L, AUC8-18: 3391.36 vs. 2690.81 hr*nmol/L and AUC18-24 501.53 vs. 827.32 hr*nmol/L. Hence, twice daily dosing with the modified release formulation of hydrocortisone was capable of replicating physiological cortisol release.

Pharmacovigilance and the prevention of adverse drug reaction at Guy's and St Thomas' NHS Foundation Trust: a retrospective observational study of ADRs to warfarin

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Pharmacovigilance is vital for identifying adverse drug reactions (ADRs) to medicines. The aim of this research was to raise awareness of pharmacovigilance in order to aid in the prevention of ADRs at Guy's and St Thomas' NHS Foundation Trust. This investigation involved a study of the impact of the implementation of a quality management system on pharmacovigilance reporting, to the Kings Health Partners Clinical Trials Office (KHP-CTO). Warfarin is a drug often implicated in causing ADRs. A study of warfarin-related medication incidents reported via the Datix patient safety and risk management system (from April 2007 until March 2012) was also completed. Incident data were compared against a second dataset which was collected from a cohort of patients who were prescribed warfarin.

This research produced a number of key findings: (1) the implementation of the KHP-CTO quality management system improved pharmacovigilance reporting frequency, due to increased training, awareness and improved competencies of clinical research personnel. (2) the most frequent warfarin-associated ADR was increased INR, sometimes resulting in over anticoagulation and haemorrhage. (3) The frequency of drug-drug interactions identified was limited; however two drugs were identified that may have been implicated: enoxaparin and metronidazole (an antibiotic). Enoxaparin was the root cause of two serious ADRs, including one case of retroperitoneal haemorrhage, a rare and serious ADR. The frequency of incident reporting was high; however the importance of ADR reporting via the Yellow Card Scheme should be reiterated to clinical personnel, as some suspected warfarin-related ADRs were not reported appropriately. On evaluation, medication errors accounted for 84.62% of warfarin-related ADRs as reported via Datix. (4) The warfarin prescribing and administration for inpatients requires the greatest focus for targeted quality improvement programs. (5) The Datix incident system is a valuable tool that should be developed further for pharmacovigilance purposes.

Pharmacy could assist in improving the reporting of ADRs by performing pharmacovigilance audits. Important findings could then be reported Trust-wide in order to raise awareness. Future work could compare pharmacovigilance data between NHS Trusts to assess the implementation of other quality systems. It would be interesting to investigate the relationship between concurrent warfarin and enoxaparin use and the potential for ADRs in this group. Finally, it would be important to investigate issues related to the use of recently licensed drugs: if known events to licensed drugs such as warfarin are not reported appropriately, then unknown reactions to novel drugs may also be missed.

Barriers and influences on recruitment and retention in paediatric clinical trials: a parents' perspective

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Paediatric research is necessary to ensure that the medicines given to children are safe and efficacious. The importance of research in this population has been recognised in recent EU legislation, with the inclusion of a Paediatric Investigation Plan now mandatory in all marketing authorisation applications. Parents play a key role in recruiting children to clinical trials since they have the responsibility of making the decision as to whether their child can participate. Consequently, in order to inform the design of future trials for maximisation of recruitment, it is essential to obtain the opinions of parents and guardians regarding influences on their decisions.

The study was conducted in two phases: In phase I a questionnaire was designed to assess the views and opinions of parents regarding their child's participation in research; Phase II involved distribution of the final questionnaire to parents in a single tertiary centre in the UK.

98 completed questionnaires were analysed. One of the main findings was that there is a failure to meet the expectation of parents in terms of the information they are given about research, and the opportunities to take part. Key barriers to recruitment were: unknown side effects of new treatments; additional tests that may

be uncomfortable to the child; and the child not wanting to take part. Motivating factors were benefit to the child and access to the latest treatments. Differences were identified in the opinions of subsets of the population with regard to certain barriers, for example in different ethnic and disease groups.

More needs to be done to engage with parents, as the vast majority of participants were not only happy to be contacted about relevant trials, but expected to be informed of any studies that may be appropriate for their child. Involvement of the child in the decision making process is important to families. Further investigation of the differences in the opinions of subsets of the population is needed to inform design of trials, in order to ensure that participation in clinical trials is as simple as possible for families.

Do Polish patients prefer the virtual clinical trial or the standard clinical trial where a clinic must be attended?

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75-85% of clinical trials fail to make their timelines due to insufficient patient enrolment and retention. Slow patient recruitment and poor patient retention within ongoing clinical trials is thought to be caused by limitations and inconvenience of a standard clinical trial. The virtual clinical trial introduced by Pfizer holds promise of improving patient recruitment and retention by opening up trials to a larger patient population and making trial participation more convenient.

As the virtual clinical trial is carried out is totally different to a standard trial, it would be imperative to know whether patients would like to participate in such a trial and whether they would prefer this type of trial over a standard clinical trial where a clinic must be attended.

Questionnaires (120) were sent out to five Investigators across Poland for distribution among patients that at least one time in their lives had participated in a standard clinical trial.

117 patients completed the questionnaire. The results indicated that Polish patients do not prefer virtual clinical trials over standard clinical trials as 82% of Polish patients, when given the opportunity to choose between a standard and virtual clinical trial chose the first one. Statistical analysis of the answers given by the patients showed that patients' preference for participation in a standard clinical trial over virtual clinical trial did not depend on any of the socio-demographic factors or actual use of the Internet by patients.

The results of this research study have some significant implications for the pharmaceutical industry. Firstly, virtual clinical trials might not be attractive to some patients despite their convenience. Secondly, virtual clinical trials might not resolve recruitment and retention problems and thirdly, a hybrid version of the standard clinical trial and virtual clinical trial might be the best solution towards patient recruitment and retention problems.

An investigation into a new compound for the treatment of type 2 diabetes mellitus

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This thesis reports the findings of an investigational study into a potential new oral capsule treatment for type 2 diabetes mellitus (T2DM). PSN821 is an agonist at the G protein-coupled receptor GPR119 and has shown to substantially lower glucose and cause meaningful weight loss in animal studies. The compound has so far been tested in 2 clinical trials as a suspension and has been shown to be safe and well tolerated.

The primary objective of the study was to compare the bioavailability of PSN821 administered as a suspension with two novel oral capsule formulations and assess the effect of food (high fat and if necessary a light breakfast) on bioavailability.

This was a randomised, open-label, crossover study in 18 healthy volunteers. Group 1 (9 subjects) received PSN821 capsule formulation 1 fasted and following a high fat meal, plus PSN821 suspension fasted. Group 2 (9 subjects) received PSN821 capsule formulation 2 fasted and following a high fat meal, plus suspension

fasted. Based on the interim safety and PK data collected from Periods 1 and 2, Group 2 were asked to return to receive capsule formulation 2 following a light meal. During the study 3 subjects requested early discontinuation in Group 2 and were replaced to ensure 18 completed the study. PSN821 capsule formulation 1 and 2 were found to be markedly less bioavailable than the reference suspension when administered to fasted subjects. Administration of capsule formulation 1 after a high fat meal and capsule formulation 2 after a light breakfast increased bioavailability, but both were still lower than that of the suspension. Exposure to PSN821 following administration of capsule formulation 2 after a high fat meal increased when compared to the reference suspension, although the rate of absorption was delayed and Cmax reduced.

The low bioavailability seen in the capsules following fasted administration was the likely result of slower capsule disintegration, drug dissolution and drug transit through the GI tract. The increase in bioavailability following food may be the result of a greater residence time and fluid volume, producing better disintegration and dissolution of the capsule. Additional work will need to be performed in order to develop a capsule formulation that has better bioavailability, especially if bioequivalence with the suspension is to be achieved. Additional clinical trials may be necessary to investigate this possibility.

An examination of administration of antibiotics to patients with a blood stream infection

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Blood born infections are known to have one of the worst outcomes of any infection, both clinically and financially. Prompt and effective treatment is the primary determinant in a positive outcome. Meanwhile administering medication is a fundamental nursing activity. The focus of this study was to establish how well the Trust performed against national standards in prescribing and administering anti-microbial agents in this patient group. It also assessed whether patients prescribed antibiotics (ABx) were administered it correctly and where prescriptions were not administered, was appropriate documentation completed and the relative risks evaluated between a critical care facility and an acute medical ward?

A retrospective audit of medical notes was undertaken to evaluate administration versus prescriptions of antibiotics and the documentation to explain discrepancies. All data were recorded on a database with a combination of fixed and free text data fields. Results were described in terms of percentages and relative risk.

Thirty per cent of prescriptions for ABx prescribed were not administered. There was no difference in risk across ICU or an acute medical setting. There was a significant difference in whether ABx were administered on time RR of 3.21 (95% Confidence interval: 2.989 – 3.43) between ICU and the acute medical setting, patients on ICU were three times more likely to receive their medication on time. While documentation pertaining to omissions were less likely to occur on ICU than the acute medical wards; RR 0.44 (95% Confidence interval: 0.237 – 0.882)

While rates of prescriptions administered were disappointing, they were comparable to other prospective studies. Reasons for this poor delivery of nursing care are discussed, along with the limitation of the study. While the reasons can be speculated; the issue for nurses is how to ensure that while technology is embraced to reduce these issues, nurses do not become devoid of personal contact in this most human of professions.

An educational research project to determine the level of understanding of the informed consent process from the perspective of the healthy volunteer

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The Participant Information Sheet, which forms the main part of the informed consent process has evolved into a lengthy narrative document. Designed to inform participants of trial details, it has become complex, not easily or readily understood. Much research has been documented on content and length of the participant

information sheet, but little on comprehension. The primary objective of the research was to ascertain the level of understanding of the informed consent process from a healthy volunteer perspective. Secondary objectives were: (a) To determine factors that influence people to participate in clinical trials; (b) the male : female ratio.

Method was by means of a quantitative questionnaire for clinical trial participants to complete immediately after consenting. Section 1 determined sex, age, demography, language, employment & marital status and any previous experience of consenting. These responses allowed for comparisons & correlations, answering the secondary objectives. Section 2 was designed to answer the primary objective. A healthy volunteer population was chosen based on the type of phase 1 studies being conducted in the study unit in which the researcher was employed. Questionnaires were collated, coded and complete datasets analysed. Results were in the form of visual representations, pie charts/bar graphs.

In the primary outcome measure it was established that as many participants had a high understanding as those who had a low understanding. (High 23%, Low 21%). In the secondary outcome measure it was established that - correlations between and personal circumstances and reason for participation were as follows:

1. The majority participated for financial reward.
2. The employed outnumbered the unemployed.
3. Those with previous experience of consenting for participation in a clinical trial had a poor level of understanding compared to those participating for the first time.
4. Demography was not an influencing factor and any difference between rural and urban areas were minimal.
5. More males than females participated.
6. The age range was reflected by the type of studies that were conducted.

Complete comprehension could not be established, so further research studies should be performed to determine if there are alternative options for testing comprehension.

The Impact of ICH GCP on clinical trial procedures operationally within the USA, EU and Japan

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Historically there have been differences in the regulation and law between the USA, EU and Japan on conducting clinical trials. Following the introduction of the ICH GCP Guidelines, one of the primary aims was to harmonise these three regions, but although standards of quality have been harmonised, it is still unclear whether operational procedures and efficiency within the pharmaceutical industry (sponsors as well as Contract Research Organisations) have been standardised globally.

The aim of this dissertation was to fully understand how ICH GCP has impacted clinical trial procedures within USA, EU and Japan operationally with regards to regulation and law by reviewing the following objectives;

Examining if the differences in interpretation affect the management and running of clinical trials today from a sponsor and CRO perspective;
To determine what could be done differently to aid the management and running of clinical trials today;
To explore what changes could be implemented in the future to improve operational delivery of clinical trials

The ICH GCP guidelines encompasses all aspects of clinical trials, but this dissertation will focus only on the main regulations and law that affect the initial phase of clinical trials, commonly described as “Start Up”. For the purposes of this dissertation, ‘Start Up’ was defined as the time period between protocol finalisation until the first subject has been enrolled.

Emerging countries such as Asia and India are attracting a growing number of large-scale clinical trials, as they have access to large subject populations required to run these trials. The shift to running clinical trials within these markets has increased in recent years which could lead to a drop in clinical research activities within the 3 main regions (USA, the EU and Japan). However, ICH GCP regulations have been firmly entrenched over the USA, EU and Japan for a number of years and this is reflected within the current

regulations in place. This allows for assurances from different countries that clinical trials have been performed in a robust manner and that subject safety and the data collected from these clinical trials are of a deliverable quality. This ultimately provides reassurance to the subject population and general public that the drugs that the pharmaceutical industry are bringing to market are safe and efficacious.

The socioeconomic impact of HIV/AIDS in Zimbabwe

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The Human Immunodeficiency Virus/Acquired Immuno-Deficiency Syndrome (HIV/AIDS) is the epidemic that has aggrieved many countries in Sub-Saharan Africa for over 30 years. Sub-Sahara is home to only 12% of the world's population yet, it accounts for 22.9 million of HIV-infected individuals. This thesis investigates the hypothesis that there is a negative relationship between HIV/AIDS and economic growth. This disease is nothing like other diseases, because it largely affects the healthiest and most reproductive and productive populations (individuals between the ages of 15-49). Thus, the effects on households, industries, farming, governments and the health sector can be critical and far-reaching. Consequently, such an analysis is fundamental in framing public decision-making concerning resource allocation and policy interventions and placing HIV/AIDS as a national priority.

The research makes use of secondary source of data in the form of published data from the World Bank Report (2012) and World Development Indicator (WDI) and also source data from Joint United Nations Program on HIV/AIDS (UNAIDS), (2011). Analyses are based on data from 10 southern African countries for the period 1996-2009. The study used Gross Domestic Product (GDP) per capita as a proxy for economic growth and HIV prevalence rate as the independent variable. A Spearman rank analysis was conducted to determine the nature of the correlation between the GDP per capita and HIV prevalence rate.

The analysis concluded that there is a significant correlation between HIV prevalence rate and economic growth. The correlation coefficient (0.336) is positive, denoting that there is a positive relationship between HIV prevalence and GDP per capita. The results, therefore, show an opposite relationship from the one the study hypothesised.

Acquired tamoxifen resistance and promotion of angiogenic responses in breast cancer

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In the treatment of pre-menopausal women with oestrogen positive (ER+) breast cancer, tamoxifen represents a first line of adjuvant treatment with demonstrable benefits. Despite this, resistance is frequently acquired to tamoxifen with an associated poor prognosis. Breast cancer cell models have revealed the importance of growth factor signalling networks in sustaining growth of endocrine-resistant cancers and, more recently, their ability to promote a highly migratory and invasive phenotype, together with the expression of genes with pro-angiogenic ontology. The potential of endocrine-resistant cells to elicit angiogenic responses, however, remains unknown. Real-time PCR was used to validate results from preliminary Affymetrix-based gene profiling of pro-angiogenic gene expression in endocrine-sensitive MCF7wt cells and their endocrine resistant counterparts. The expression of pro-angiogenic factors in conditioned media (CM) from these cells was assessed by ELISA. The proliferative and migratory effects of conditioned media on vascular endothelial cells (HUVEC and HECV cells), was determined by MTS cell proliferation assay, wound closure assays and Matrigel tubule formation assays. Changes in endothelial cell migration following co-culture with endocrine-resistant cells were examined using Boyden-chamber chemotaxis assays. Growth factor signalling and migration pathway activation in endothelial cells in response to CM was determined by Western blotting. TamR cells were found to express high levels of IL-8 and VEGF at an mRNA level compared with expression in MCF7wt cells. High levels of VEGF protein were also confirmed in the conditioned media from TamR cells versus their endocrine-sensitive counterparts. TamR conditioned media promoted in vivo and ex vivo endothelial cell proliferation, as well as in vitro endothelial cell migration and the formation of tubules to a greater extent than that seen in MCF7wtCM treated cells. TamR conditioned media was found to stimulate VEGFR2 phosphorylation and downstream activation of MAPK and Akt in endothelial cells compared to MCF7wt CM. Pharmacological inhibition of VEGFR2 activity in endothelial cells suppressed TamR-induced endothelial cell proliferation and VEGFR phosphorylation. Further pharmacological manipulation of Src kinase in TamR cells revealed a Src kinase dependent mechanism of VEGF production in these cells. In addition, in vivo examination of TamR xenografts illustrated higher presence of endothelial cells in these tissues than in MCF7wt xenografts. These data suggest acquired tamoxifen resistance is accompanied by development of a Src kinase-dependant pro-angiogenic phenotype which, if recapitulated in vivo, may promote tumour progression. Therapeutic targeting of Src signalling may prove beneficial in such cases.

Understanding the interactions of hydrogen peroxide with macromolecules and microbial components

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The bactericidal mechanism of hydrogen peroxide is poorly understood, with most evidence being obtained from studies involving greatly reduced concentrations aimed at investigating the effects of stress. Current theory suggests that this mechanism is based on the oxidation of protein, DNA and lipids within the cell by the production of free hydroxyl radicals through the interaction of hydrogen peroxide and intracellular iron. The mechanism of vapour phase hydrogen peroxide treatment remains unstudied, despite evidence that it may be different to the liquid phase.

This study aimed to investigate the effects of bactericidal treatments of liquid and vapour phase hydrogen peroxide on the macromolecular components of a model organism, Escherichia coli strain K12. A set of treatment conditions producing a range of reductions in colony forming units was identified, and the effects of these conditions on the protein, DNA and lipid constituents of the cells assayed.

No effect on the lipid contents and membrane integrity of treated cells was found. Liquid hydrogen peroxide was found to reduce the thiol content of cytoplasmic protein, but this was not found to be a major mechanism of bactericidal action. Extensive fragmentation of DNA was found to result by treatment with both phases, the degree of which was correlated with a reduction in colony forming unit counts. No effect on bactericidal action was found on addition of a hydroxyl radical scavenger or an inhibitor of protein synthesis, showing that

DNA damage was due to the primary action of hydrogen peroxide, and that this damage was not caused by the production of free radicals within the cell.

A modified mechanism of hydrogen peroxide bactericidal action is proposed, whereby lethality is due solely to DNA damage caused by the production of ferryl radicals by the interaction of hydrogen peroxide and iron associated with the DNA backbone.

The involvement of CaMKII in myocardial ischaemia-reperfusion injury

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CaMKII acts as a second messenger to Ca^{2+} signals within the cardiac myocyte. Cellular stresses such as ischaemia and subsequent reperfusion perturb the normal physiological oscillations of Ca^{2+} to cause an escalating concentration which damages the cell. CaMKII has been implicated as an injury signal during such cellular conditions. However, there are discrepancies as to whether CaMKII is a possible mechanism of ischaemic preconditioning as its inhibition can abrogate or improve the protective effect of preconditioning. This thesis investigated the effects of CaMKII inhibition in models of ischaemia-reperfusion (I-R) injury. It was hypothesised that CaMKII promotes irreversible injury caused by acute myocardial infarction (AMI), but would also have a beneficial role in mediating cardioprotection by ischaemic preconditioning. This work has demonstrated that: i) in an *ex vivo* rat heart model of regional I-R injury, CaMKII promoted irreversible injury but is not a feasible target for reperfusion therapy as only a pre-ischaemic intervention reduced myocardial infarction; ii) CaMKII activation was not a pre-requisite for protection with ischaemic preconditioning, although an additive protective effect of CaMKII inhibition and ischaemic preconditioning was possible; iii) models of simulated I-R or oxidative stress in the H9c2 cells did not involve CaMKII activity; iv) isolated cardiac myocytes paced at 1Hz and subjected to simulated I-R do not engage a significant amount of CaMKII activity. These studies substantiate the involvement of CaMKII during ischaemic injury and establish that it does not play a substantial role in ischaemic preconditioning. It highlights the characteristics of the kinase within *in vitro* models of I-R injury. Understanding CaMKII role in I-R may underpin the development of future therapeutic strategies for the management of AMI.

The role of viral and bacterial infections in asthma exacerbations and corticosteroid resistance

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Asthma is a chronic inflammatory disease of the airways characterised by early and late asthmatic responses (EAR & LAR) to allergen, airways hyperresponsiveness (AHR) to inhaled spasmogens, airway inflammation and airway oedema. Viral infections and lipopolysaccharide (LPS) from bacteria and environmental sources contribute to exacerbations of asthma and the development of insensitivity to corticosteroids. Complete insensitivity to oral corticosteroids is rare and most patients lie on a continuum of steroid responsiveness. This thesis aimed to examine the effect of viral infection and LPS in a guinea-pig model of asthma and determine the sensitivity to inhaled and systemic corticosteroids.

Sensitised guinea-pigs challenged with ovalbumin displayed EAR, LAR, AHR to histamine, airways inflammation and airway oedema. Inoculation of guinea-pigs with parainfluenza-3 virus alone induced AHR to histamine and airway inflammation. However this response was not consistent. Inhaled LPS alone induced an immediate bronchoconstriction, AHR, airway inflammation and oedema and goblet cell hyperplasia. LPS co-administered with ovalbumin exacerbated the allergen response by lengthening the EAR, prolonging the bronchoconstrictor response to histamine, increasing airway inflammation and oedema and goblet cell hyperplasia.

In guinea-pigs challenged with ovalbumin alone, treatment with inhaled fluticasone propionate (FP) and inhaled and systemic dexamethasone decreased the LAR, abolished AHR, airway inflammation and oedema. Responses to LPS alone were not reduced by inhaled dexamethasone or FP but partially reduced by systemic dexamethasone. Ovalbumin and LPS combined responses were insensitive to inhaled

corticosteroids, except lavage fluid protein. These responses were partially sensitive to systemic dexamethasone, with the prolonged EAR, inflammation and airway oedema all reduced.

The data in this thesis suggests that LPS inhalation exacerbates ovalbumin-induced functional and inflammatory responses rendering them insensitive to inhaled corticosteroids but partially sensitive to systemic corticosteroids. Thus, the experimental combination of ovalbumin with LPS might represent a useful preclinical model of corticosteroid-insensitive airway inflammation.

Liquid loaded microneedles for the intradermal delivery of botulinum toxin for Primary Focal Hyperhidrosis

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Primary focal hyperhidrosis (PFHH) is a medical condition characterised by over-activity of the eccrine sweat glands, primarily occurring on palmar, plantar and axillary regions. PFHH can have a significant adverse impact on a patient's quality of life. Multiple intradermal injections of a commercial formulation of botulinum toxin A (BTX A) (Botox®) is the most effective non-surgical treatment currently licensed in the UK for cases of severe PFHH. Although effective, intradermal BTX A injections are associated with considerable pain and discomfort for the patient and are time-consuming for the administering clinician. This study aims to evaluate the potential of using pocketed microneedle devices for minimally invasive intradermal delivery of BTX A, as a liquid formulation, into human skin.

Pocketed microneedles, metallic 700 µm-long needles containing a cavity within the needle shaft, were selected as an appropriate and relatively untested intradermal delivery device. Pocketed microneedle devices (PMDs) were liquid loaded by immersion into a 'Botox® like' formulation that mimicked the composition of the commercial Botox ® formulation, with the exception of BTX A, which was replaced by the model macromolecular protein β-galactosidase (~465 kDa). A water-soluble dye was also included to enable visualisation. Microneedles were assessed for loading uniformity by light microscopy and the formulation residency time was evaluated by monitoring evaporation using a digital camera. The microneedle loading capacity was determined using an established quantitative assay for β-galactosidase. Studies using excised human breast skin, maintained in organ culture, examined delivery of the model β-galactosidase from liquid loaded PMDs and the time-dependent diffusion of the protein within the dermal tissue. A more clinically representative model of BTX A, formaldehyde inactivated BTX A, i.e., botulinum toxoid, was used to determine the deposition pattern of the therapeutic within the skin. Following skin delivery the toxoid was detected by immunohistochemical staining and fluorescence imaging, following its conjugation to an appropriate fluorophore.

Immersion of the PMD into a 'Botox® like' formulation resulted in successful uptake and retention of the model protein solution. Quantitative studies indicated that nanogram quantities (~100 ng/microneedle array) of the β-galactosidase model can be loaded and retained on individual microneedles, in a liquid state. These results suggest that the loading capacity of the microneedle device is appropriate for therapeutic botulinum toxin formulations, although loading uniformity will need to be addressed. Histological analysis revealed effective delivery of the model β-galactosidase from a PMD to the epidermal and the dermal layers of the skin. Rapid and extensive diffusion of the protein within the deeper dermis was also demonstrated. Further, immunohistochemical and fluorescence studies indicated effective PMD loading and successful delivery of botulinum toxoid to the dermis of human skin. These data suggest that it should be possible for BTX A to access its therapeutic target (the eccrine sweat glands) following delivery via PMDs.

This study has demonstrated for the first time that pocketed microneedle s represent a viable, minimally invasive alternative, for the intradermal delivery of botulinum toxin A (Botox®). Future pre-clinical and clinical studies are now required to test and optimize a microneedle - based delivery system that is most suited to clinical practice.

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

Antiviral drug design, synthesis and biological evaluation for treatment of Hepatitis C virus

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Design, synthesis and biological evaluation of acyclic nucleotide prodrugs as potential antiviral agents

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Pathogenicity & a bedside real-time detection assay for clostridium difficile in the faeces of hospitalized patients

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Design, synthesis and biological evaluation of novel anti-HCV nucleosides and nucleotides: from bench to the clinical trials

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Development, characterisation and evaluation of sugar glass microneedles

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