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FOREWORD

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

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

At the Cardiff School of Pharmacy and Pharmaceutical Sciences, the combination of these strengths allows us to successfully deliver research-led learning and teaching. All of our MPharm students undertake a significant, independent Masters level research project in the final year of the four-year degree, and present and defend their research. The high 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 17th 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 our colleagues for their assistance in collating this book.

***Rebecca Price-Davies & Dean Routledge
June 2017***

Exploring the interprofessional interactions between community pharmacists and other healthcare professionals

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Interprofessional interactions (IPI) have been defined as 'a group of individuals from different disciplines or professions working and communicating with each other. In the environment of interprofessional learning, every member provides his/her knowledge, skills and attitudes to augment and support the contributions of others'.¹ Enhanced IPIs are paving the way to safer, more efficient and knowledgeable multidisciplinary healthcare teams. To develop these interactions, there needs to be effective interprofessional education (IPE) within the undergraduate pharmacy course to develop relationships between professions early on.² However, to develop effective IPE, there needs to be knowledge on what the interactions involve.

The aim was to explore the topics of interactions that community pharmacists have with other healthcare professionals through face-to-face semi-structured interviews with 15 practicing pharmacists, results were transcribed, coded and then analysed by inductive thematic analysis. From this, 5 themes emerged; problem solving, learning, stock, relationships and access to healthcare professionals.

From these findings, barriers to interactions emerged; frequent comments included the need for enhanced training between professions to form understanding of each other's roles, limitations and abilities. Additional training was suggested for the GP receptionist, who appeared to be a barrier to accessing the GP, especially if there was a lack of understanding of the pharmacists' role. Many commented that the GP receptionist often thought the pharmacists' aim was to gain more revenue, however if there was a good relationship with the receptionist then they appeared to facilitate the access to the GP.

In conclusion, pharmacists interact with other healthcare professionals frequently and about a multitude of topics however there are many barriers to overcome to improve interactions within a multidisciplinary team. The underlying foundations to successful IPI these appear to be having effective IPE sessions early within education, to enforce collaboration before healthcare professionals are working within practice, this is supported in literature, along with educating receptionists in practice and other professionals on the role of the pharmacist.

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Discovering the cellular location of STAT3 during mitosis

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Signal Transducer and Activator of Transcription 3 (STAT3) is a protein which is essential for many cellular functions including cell proliferation, differentiation and apoptosis.¹ STAT3 is found to be constitutively activated in breast cancers.² The transcriptionally active form of STAT3 activated at the Tyrosine 705 residue (pY⁷⁰⁵STAT3) has been widely studied and shown to be elevated in many cancers. Recent preliminary data has found that another form of STAT3 is present in mitotic cells. Therefore this project sought to confirm the presence of STAT3 in mitotic breast cancer cells, and to understand more about its cellular location and whether it localises with any of the tubulin subunits. α/β tubulin heterodimers are the structural components which form microtubules³ and γ -tubulin is located at the centrosomes involved in microtubule nucleation⁴.

MCF-7 breast cancer cells were probed for pS10HistoneH3 (a marker of mitosis), STAT3 and the different tubulin subunits (α, β and γ), followed by nuclear staining with DAPI. Cells were viewed using immunofluorescence microscopy, and cells at all stages of mitosis were imaged, then optimised by altering contrast and brightness.

The presence of STAT3 throughout all stages of mitosis was confirmed, and it was still present at the end of telophase, by which point pS10HistoneH3 was dephosphorylated. Similar cellular locations of STAT3 and γ -tubulin were demonstrated from the images obtained, most notably during metaphase and anaphase.

The above findings indicate that STAT3 most likely plays an important role in the division of cancer cells. This shows potential for it to be a viable target for chemotherapeutic drugs or as a marker for rapidly proliferating

cancers. More work is needed such as proximity ligation assays, in order to establish whether it binds to γ -tubulin.

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What learning needs do cluster pharmacists have when commencing their role and after one year of practice?

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In Autumn 2015, thirty-four cluster pharmacists began their roles in GP surgeries in South Wales as part of the Welsh Government's plan for a new primary care service. The plan supports the Welsh Government's vision to move services from secondary to primary care and advocates that all healthcare professionals use their clinical skills and abilities to their maximum.¹ Cluster pharmacists have the potential to optimise patient medication, reduce drug wastage and costs and ultimately transform the way that patient care is delivered in primary care.² The Wales Centre for Pharmacy Professional Education (WCPPE) was asked to develop a training programme to support these pharmacists. This project aims to explore the initial learning needs on commencement of the role and the on-going training that is required following a year of practice.

An initial literature review was conducted to inform the creation of a semi-structured interview schedule. All cluster pharmacists in South Wales (n=34) were invited to participate by email. Semi-structured interviews were conducted (n=11), recorded and then transcribed ad verbatim, before being analysed using inductive thematic analysis. Ethical approval was obtained from Cardiff School of Pharmacy and Pharmaceutical Sciences.

A response rate of 32.3% was achieved. The main findings were that pharmacists from different backgrounds (hospital or community) had different clinical learning needs on commencement of these roles but everyone felt there was a need for a mentor and training in a range of soft skills. On-going learning needs after a year in practice included formalised GP computer system training and more peer support / networking opportunities.

The recommendations made are steps towards cluster pharmacists feeling integrated within the primary care team. The WCPPE's training programme was found to be useful, especially for networking with other pharmacists. Further improvements included wanting more case-based training and differentiating aspects of the training for participants from different clinical backgrounds.

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Understanding and determining critical quality attributes for coated microneedles

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Coated microneedles (MNs) are solid micron-sized needles that are coated with a drug or vaccine.¹ They are applied to the skin surface and breach the *stratum corneum* to facilitate enhanced permeation of the drug in the epidermis and dermis, where it can act locally or enter dermal microcirculation to elicit a systemic effect.² Coated MNs are approaching clinical utility, however there are currently no standards against which MN products can be tested to allow their regulatory approval.³ The aim of this work was to define critical quality attributes (CQAs) of general coated MN products and to suggest tests to demonstrate that the quality of the product is of the necessary standard to ensure efficacy and patient safety.

A systematic literature review of 133 published papers and regulatory guidelines was conducted to inform the recommendations made in this research. An iterative process was employed by the research team, which included two experts in the MN field, who met eleven times during the six-week data collection period to

rationalise attributes and potential tests. At the end of the data collection period, a meeting was held with a pharmaceutical assessor from the MHRA to rationalise and confirm the draft table of CQAs that had been produced.

The final table contained twelve CQAs for coated MNs. These attributes included sterility, sharpness, coating uniformity, stability and dissolution. CQAs were accompanied by a rationale for their inclusion and at least one appropriate test was suggested for each.

The findings presented in this work constitute significant progress towards the establishment of specifications to allow the regulatory approval of coated MN products. The results have been ratified with a representative from the MHRA and future work should engage the international MN community more widely, including both developers and regulators, to refine the suggestions and ensure harmonisation.

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The influence of ageing and gender on oestrogen receptor expression

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Alzheimer's disease (AD) has now been named as the number one cause of death in England and Wales, along with other dementias.¹ It is a progressive neurodegenerative disease, with patients at later stages being unable to perform everyday activities. Two of the main risk factors for AD are age and gender but the reasons for this association are not yet understood.² There are no current treatments available that cure the disease³ and, with growing diagnoses and an ageing population, this poses a big problem. Changes in oestrogen receptor (ER) expression have been suggested to be involved in the development of AD, as they have been found to be neuroprotective.⁴ The aim of this study was to determine whether the expression of ERs is affected by age and/or gender, with the prediction that expression would differ with age in women.

Western blot analysis using specific antibodies for ER α and ER β was carried out on cortical brain samples from men and women aged 20 to 99.

The main findings of this study were that ER expression decreased significantly in women as they got older, whereas little fluctuation was seen in men as they aged. In addition, it was found that expression levels of ERs did not differ between young men and women, however, there was an apparent trend for a decrease in women as they got older, compared with men.

Future work could include investigations into the proteins that are involved in neuroprotection. These findings support the development of new treatments for AD involving ERs.

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Comparison of the effect of relative humidity (RH) on aerosolisation performance of hard gelatin (HG) and hydroxypropylmethylcellulose (HPMC) capsules

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The choice of capsules is important to ensure sufficient formulation protection and effective aerosolisation performance in dry powder inhalers (DPIs).¹ This study aimed to compare the aerosolisation performance of budesonide-lactose formulations emitted from a DPI using either HG or HPMC capsules under the influence of various storage relative humidity (RH).

Capsules were loaded with budesonide-lactose formulations and conditioned at 11, 33, 53, 85% RH before evaluating the moisture content of capsules. The aerosol performance of HG or HPMC capsules was measured using the dosage unit sampling apparatus (DUSA) and next generation impactor (NGI) and analysed using UV-vis spectrometry. Two-way ANOVA was performed to analyse the capsule types and the effect of RH on emitted dose (ED), fine particle dose (FPD) and fine particle fraction (FPF) parameters.

The HG capsules were shown to have higher moisture content than HPMC capsules at all %RH studied. The ED aerosolised from both capsules showed no significant difference, whereas the FPF value was found to be statistically ($p < 0.05$) different between the capsules when the storage humidity was increased from 22 to 85% RH. HPMC capsules, which showed higher FPD and FPF, demonstrated a better aerosolisation profile than HG capsules under different storage humidities.

The findings have shown that the aerosol performance of the DPI is dependent on the capsule types and storage humidity. The RH of the environment is suggested to affect the interparticulate forces between the formulation particles through moisture transfer from the environment into capsule shells and then the encapsulated formulation.² HPMC capsules, having lower moisture contents than HG capsules, are found to have improved aerosolisation profiles at all RH conditions investigated. Therefore, HPMC capsules appear to be a better capsule choice in protecting the contents of a DPI formulation, particularly when the formulation is stored at high humidity.

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The association of zinc transporter ZIP7 with lamins in MCF-7 breast adenocarcinoma cells

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Zinc is an intriguing essential element that has an indispensable role in a myriad of cellular and biological processes.¹ Belonging to the SLC39A subfamily of zinc transporters, ZIP7 co-ordinates zinc homeostasis through release of labile zinc from intracellular stores to the cytosol.⁴ Current literature has provided immunofluorescent imaging demonstrating ZIP7 localisation the endoplasmic reticulum.³ Observed in imaging is presence of a perinuclear band representing ZIP7 localisation to the outer membrane of the nuclear envelope. The primary aim of the project was to establish if ZIP7 also localised to the inner membrane of the nuclear envelope.

MCF-7 cells were cultivated and treated with antibiotics. At 80% confluence cells were transfected with recombinant wild type ZIP7. Cells were harvested, stained with primary antibodies and conjugated to fluorescently labelled secondary antibodies. Images of cells were taken on a Leica microscope using a Hammamatsu camera on Openlab software.

Co-localisation identified areas of fluorophore overlap in imaging. ZIP7 was not found to demonstrate co-localisation with nuclear pore complexes. ZIP7 antibodies appeared to co-localise with Lamin A/C and Lamin B Receptor antibodies, proteins known to reside on the inner nuclear envelope membrane.

Results suggested that ZIP7 was in close regional proximity to Lamin A/C and Lamin B Receptor inferring ZIP7 localisation to the inner membrane of the nuclear envelope. Supporting evidence from super resolution microscopy is required to reinforce this finding. ZIP7 is known to have a role within carcinogenesis² when

localised to the endoplasmic reticulum. It may be valuable to analyse nuclear located ZIP7 as it too could be implicated in breast tissue malignancy.

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Validating Optical Coherence Tomography (OCT) as a method to characterise capsule shell thickness and puncture by a dry powder inhaler (DPI)

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Two-piece hard capsules used in dry powder inhalers (DPI) are predominately made from gelatin and hypromellose.¹ The manufacturing process of hard capsules can result in slight variation of the capsule wall thickness.² Differences in thickness could potentially influence puncture by the DPI. This study aims to use optical coherence tomography (OCT) to develop a valid and reliable method to measure the thickness of a hard shell capsules for quality control purposes, using Scanning Electron microscope (SEM) as the established comparator. It also explores variability in capsule shell thickness between different capsule formulations and moisture contents. An additional aim was to investigate whether OCT can gather 3D information of puncturing event in a capsule punctured by a four pin DPI.

Gelatin and two types of hypromellose capsules were conditioned at three different relative humidities (RH: 11%, 34% and 55%). An OCT method was developed to analyse capsule thickness at two locations, the join between the two pieces of a capsule and at the centre of the dome. Capsules were observed under both SEM and OCT. Four empty capsule specimen from each different formulation and different RH were examined. Statistical differences in the thickness of capsule shells for the three capsule formulation were assessed using one-way ANOVA tests. Comparison of capsule wall thickness for OCT and SEM was evaluated using the Bland-Altman plot.

OCT provided very reproducible measurements of capsule thickness observed at both the join and dome. The study showed the type of capsule and condition has no effect on the capsules wall thickness (p-value >0.05). SEM and OCT imaging technologies produced different absolute values with the average difference of -25.88µm.

Since the two methods are inequivalent, further work is needed to determine if OCT or SEM is the most accurate tool to measure capsule wall thickness. Other imaging techniques could be used to observe capsule wall thickness or a correction factor could be applied if OCT measurements consistently under- or over-estimate capsule wall thickness. This study is the first to use OCT to characterise four pin capsule puncture by a DPI.

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Phenylalanyl-tRNA synthetase inhibitors as potential agents for the treatment of Methicillin-resistant *Staphylococcus aureus*

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Staphylococcus aureus is a common Gram-positive bacterium that is usually commensal and non-pathogenic which colonises a small percentage of the human population. However, in the case of an infection, it is capable of presenting itself as bacteraemia, bacterial endocarditis and also skin and soft tissue infections.^{1,2} However, Methicillin-resistant *Staphylococcus aureus* (MRSA) do not respond well to conventional treatments of *S.*

aureus and the increasing percentage of resistant proportions globally is concerning when coupled with the numbers of hospital-acquired infections and community-acquired MRSA infections in countries throughout the globe.^{3,4} The aim of this study was to attempt to synthesise and characterise a series of compounds that can potentially be used for the treatment of MRSA.

The design of novel compounds was first done using Molecular Operating Environment (MOE) with a homology model of phenylalanyl-tRNA synthetase (PheRS) from an unpublished PhD study as the reference protein. Computerised docking analysis was performed prior to synthesis of compounds. Synthesised compounds were then prepared and purified using recrystallisation, column chromatography and preparative-TLC. Characterisation of compounds was done with ¹H and ¹³C NMR and melting point analysis.

Docking results showed that all 3 of the designed compound were expected to have good affinity for the binding pocket and satisfy the interactions identified in the homology model. However, the final compounds contained impurities or could not be confirmed owing to the lack of characteristic signals expected for individual compounds from NMR data. However the usage of T₃P as the coupling agent was found to be optimal to produce promising yields with improved purity.

Some limitations to this study include the absence of rmsd calculations in docking results due to the lack of a crystal structure for PheRS with a bound ligand and the lack of time to explore different coupling reagents and solvent systems. Further work can be done in these areas in hopes of obtaining a pure compound with high yield for biological testing.

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Assessment of inhaler technique and implementation of an extended asthma care plan in a community pharmacy setting

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Asthmatics are offered an annual review.¹ Subsequently we see many patients with poor inhaler technique² who are unlikely to get the full benefit of their treatment due to insufficient drug deposition in the lung, going against National Institute of Clinical Excellence (NICE) guidelines.³ This reduction in the dose getting to the target could be one factor leading to high hospitalisation and mortality rates associated with asthma.⁴ This study aims to evaluate the current state of asthma in the community from a pharmacy setting.

Patients were recruited by opportunistic sampling across seven community pharmacies across South Wales. The following parameters were measured: Inhaler technique (using an aerosol inhalation monitor (AIM)), level of asthma control (using an asthma control survey (ACS) modelled on the asthma control test (ACT)) and lung function (using spirometry). Data was analysed using a Kruskal-Wallis test supported by Dunn's post hoc test in conjunction with chi-squared tests. The Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics committee granted ethical approval.

The data collected found that asthma control was very poor as only 56.5% of the sample were controlled using the ACS. Patients using meter dose inhalers (MDI) had the worst technique compared to dry powder inhalers (DPI) or MDIs used with spacers (P<0.05) and were more commonly prescribed steroids as a rescue therapy. A key finding of this data was that there are no differences in the outcome from advice provided by all healthcare professionals (HCPs), highlighting flaws within the current schemes put in place by the National Health Service (NHS).

The poor state of asthma control and inhaler technique seen coupled with ineffective schemes run by HCPs suggests a need for change in approach towards the issue. Aiming to provide better care and education to asthmatics to help them achieve adequate control of their condition.

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Evaluation of endotoxin capture materials for use in a point of care exhaled breath sensor to differentiate between viral and bacterial pneumonia in children

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Pneumonia is the single largest infectious cause of death in children worldwide. ¹ In developing countries, children are particularly susceptible to pneumonia and find it more difficult to access healthcare services, resulting in high mortality rates.^{1,2} Currently there is no simple point-of-care test available to determine the cause of pneumonia.² Endotoxin or lipopolysaccharide (LPS) is found in the cell wall of Gram-negative bacteria. Many types of Gram-negative bacteria can cause pneumonia, including *Haemophilus influenzae*; the second most common cause of bacterial pneumonia in children.¹ This project aims to find the best material to enable capture and recovery of endotoxin from exhaled breath, for use in a 3D printed prototype device, so that the cause of pneumonia can be determined.

Three types of syringe filters were screened for their ability to capture LPS. Fluorescently labelled LPS was filtered through the membranes, which were then washed with two 0.5 ml WFI washes. Fluorescent spectroscopy was used to determine level of LPS in filtrate. A nebuliser setup was used to simulate breathing into the prototype device. Various methods of endotoxin recovery were used on the filters. The Endosafe® Nexgen-PTS™ was used to quantify recovered LPS.³

Initial tests with the syringe filters at LPS concentrations of 0.01-5 µg/ml demonstrated that nylon was able to capture the greatest amount of LPS, followed by PTFE. Mixed cellulose failed to capture any LPS, with fluorescent readings being slightly higher than those observed in the 'no filter' calibration. The nylon GNWP filters were unusable, as endotoxin could not be recovered effectively using any method. The Hybond nylon blotting membrane had background endotoxin, but better recovery. Aluminium had lower capturing ability but the easiest recovery.

Nylon is the filter of choice for use in the device. The best type of nylon filter and method of recovery is yet to be confirmed.

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Numerical approach to investigate adhesion between orthopaedic biomaterials and gram negative bacteria: Influence of material roughness and surface characteristics

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In a surveillance between 2014 and 2015, 102,496 orthopaedic surgeries were conducted across 138 NHS trusts in England and on average 0.9% of these surgeries resulted in infection.¹ The majority of these infections occur in deep tissue or organ spaces with roughly 10% caused by gram negative bacteria.¹ Infections occur due to bacterial adhesion to materials and forming a layer called a biofilm. Treatment of such infections are more challenging and result in additional costs to the NHS.² The aim of this project was to study the effect of material and surface properties of orthopaedic biomaterials and bacteria and the effect of surface roughness on adhesion.

An in-house developed numerical procedure³ was used in order to collect relevant data. The procedure is based on the Johnson-Kendall-Roberts (JKR) multi-asperity adhesion model and allows the generation of adhesive force data between two interacting surfaces³. With fixed roughness adhesive force data were generated between six orthopaedic biomaterials and 5 strains of gram negative bacteria. From those results

the most and least adhesive bacteria were chosen, after that effect of surface roughness of selected materials against these two bacteria were studied

With fixed roughness, *Pseudomonas aeruginosa* AK1 was identified as the most adhesive bacteria and *E. coli* 0157K the least adhesive bacteria. The least adhesive material overall was determined to be stainless steel and increasing the material surface roughness increases the total adhesive force between bacteria and material.

Although it is seen that rougher material surfaces increase adhesion, will using smoother surfaces have an effect on the effectiveness and reliability of the prosthesis? There are also other techniques that could be used to evaluate bacterial adhesion such as the as Derjaguin and Landau, Verwey and Overbeek (DLVO) theory⁴ and ways to coat the material so roughness wouldn't be affected.

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An investigation into the prescribing of antipsychotics in care homes

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Care home residents remain some of the most frail and vulnerable members of society; most are elderly, and have multiple co-morbidities.¹ A study by Shah et al highlights that 20.92% of care home residents were prescribed an antipsychotic.² Maguire et.al suggests that elderly patients are more likely to be prescribed an antipsychotic when residing in a care home.³ The aim of this investigation was to identify the trends of antipsychotic prescribing in care homes.

EMAR data for a sample of 12 care homes in south Wales was provided and administrations were filtered to isolate data specific to the prescribing of antipsychotics. Quantitative analysis was conducted to determine the prevalence and nature of antipsychotic agents prescribed to residents, in addition to the frequency that residents were prescribed a dementia management agent. The appropriateness of the doses of antipsychotics received by residents was assessed. A Pearson's Correlation test was used to establish any correlation between the prescribing of antipsychotics and other psychotropic agents to care home residents.

Out of a total of 23 antipsychotic agents, 5 first-generation and 6 second-generation antipsychotic agents were found to be in use. Residents in the care homes were found to be nearly three-times as likely to be prescribed a second-generation over first-generation antipsychotic. A high positive correlation between the prescribing of antipsychotics and other psychotropic agents across the subject care homes, was found.

21.05% of residents in the care homes were prescribed an antipsychotic, closely mirroring that found in the Shah et.al study.³ Second generation antipsychotics were prescribed preferentially over first generation to residents, in line with BNF recommendations, to minimise adverse effects and falls. However, the prescribing of both an antipsychotic alongside a dementia management agent to residents in the care homes remained, despite the potential severe health implications and the National Strategy to reduce this.⁴

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Perceptions of Parkinson's patients on the utility of iPad based apps to collect data in a Parkinson's clinic

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Parkinson's disease (PD) has a wide range of both motor and non motor symptoms which can affect patients very differently.¹ Paper records in PD clinics can make it difficult to track changes in symptoms and disease progression, especially when patients only usually attend clinics every six months. The use of mobile technology for PD and in clinics has been studied and shown promising results.² An iPad based app has been developed for use in PD clinics.³ The app features two validated questionnaires on quality of life and non motor symptoms, and a finger tapping test to assess motor function. The aim of this study was to assess the usability of this app for people with Parkinson's and its potential for use in PD clinics using focus groups.

Six focus groups were run with participants recruited from Parkinson's UK support groups using purposive non-random sampling.⁴ Each session was audio-recorded and then transcribed verbatim. Transcripts were coded and analysed using thematic analysis, with both inductive and deductive analysis used. Ethical approval was obtained.

Three main themes were identified from results: attitudes towards technology, electronic data collection, and use of the app. Many subthemes were identified within each of these. Experience of technology varied between participants and this gave mixed responses towards the app. Concerns surrounded security and the effect the app may have on care.

The overall opinion from focus groups was that the app should continue in development. Many solutions were found to the issues identified and barriers to the apps introduction. Most participants felt that the app would be beneficial and useable, and despite concerns surrounding technology and electronic data collection, felt that the app had a future for use in clinics. Once improvements are made this app could go on to greatly improve patient care.

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Synthesis of α B-crystallin Inhibitors as potential therapy against triple-negative breast cancer

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Triple negative breast cancer (TNBC) is a subtype of breast cancer which is increasingly recognized as a disease very diverse in its clinical and biological behaviour. Treatment options for patients are problematic due to lack of targeted therapy hence the need of novel and improved therapeutics for TNBC remains as one of the highest priorities of current breast cancer research.¹ Recently, a novel strategy developed by Chen et al (2014) that target interaction between α B-crystallin and vascular endothelial growth factor served as promising new targeted therapy for TNBC.² Through virtual screening, two lead hit compounds were proposed to inhibit CRYAB-VEGF interaction. Therefore, the aim of this study was to synthesis potential inhibitors of CRYAB based on one of the two lead compound, 6-mercapto-2-(alkylthio)-7,9-dihydro-8H-purin-8-one.

The synthesis of proposed purine derivatives was first attempted via four step reactions which consist of cyclisation, S-alkylation, chlorination and thiolation. Subsequently, the synthetic route was switched to six steps reactions in order to rectify the introduction of thio-keto group instead of desired keto group in the compound. Commercially available 4,5-diamino-6-hydroxy-2-mercaptopyrimidine was used as the starting compound. Docking studies were carried out to investigate the ligands binding activities with the proposed binding pocket.

Docking studies despite preliminary showed a promising result as two of the proposed derivatives bind to the proposed binding pocket and thus, might had favourable biological activity against triple negative breast cancer

cell lines. Characterisation by ¹H-NMR and ¹³C-NMR also showed that the compounds synthesised contain several impure intermediates and the yield for final compounds was very low due to several steps involved in the synthetic process.

In conclusion, in term of new targeted therapy for TNBC treatment, CRYAB inhibitor has shown a promising potential breakthrough for treating TNBC. Growing evidence and studies to support the rationale of this newly validated target could bring a powerful impact in clinical management of this complicated disease.

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MAP Kinase and STYK1 signalling in breast cancer

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Endocrine treatment of ER+ breast cancer is limited by resistance.¹ A novel tyrosine protein kinase, STYK1, is expressed in clinical breast cancer and can drive endocrine (faslodex) resistance in vitro, while in other cancers signals through MAPK.² Thus, STYK1 acting via MAPK activation may also contribute to endocrine resistance but this remains unexplored. The aim was to determine if MAPK activity and STYK1 associate in breast cancer patient samples and in faslodex resistant (FasR) pre-clinical material.

Immunohistochemistry (IHC) was optimised for activated nuclear MAPK (pMAPK) in archival clinical breast cancer sections, FasR pellets and xenografts, using pH6 microwave retrieval. The optimised IHC was applied to a clinical breast cancer series (n=93) pre-assayed for STYK1. After H-Scoring pMAPK staining, statistical analysis explored its relationship to STYK1 and to further biological parameters available for the series.

STYK1 and nuclear pMAPK significantly correlated (p=0.013) in ER+ patients, with a weak positive trend between EGFR and pMAPK (p=0.061). In the ER- cohort, there was no association with STYK1 but significant correlations for pMAPK were shown with IGFR (p=0.046), IGF1 (p=0.026), erbB ligand HRG β (p=0.005), transcription factor FOS (p=0.008) and mTOR element p-RPS6 (p=0.039). FasR pellets and xenograft stained positive for both nuclear pMAPK and STYK1, although there was some discordance in their profile for all model and clinical samples.

This project has uncovered a novel relationship between STYK1 and nuclear MAPK activity in ER+ clinical breast cancer. However there was some discordance in all examined material including ER- tumours, suggesting that STYK1 may also act through other kinases in breast cancer.³ Additional pathways previously reported as interactive with MAPK were also prevalent in clinical breast cancers.⁴ The association found in ER+ disease and FASR material emphasises that STYK1 may contribute to emergence of endocrine resistance in part by activating MAPK.

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Critical quality attributes of biodegradable microneedles

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Microneedles (MNs) are devices consisting of a baseplate with microscopic needles attached¹, designed to breach the stratum corneum barrier of skin, to deliver drug transdermally.² MNs are currently transitioning from the laboratory to clinical trials. There are currently no regulations on their manufacture and regulators have highlighted the need for this information. The aim of this project was to identify and define critical quality

attributes (CQAs) to assist the regulatory acceptance and clinical adoption of biodegradable MNs and suggest standardised tests to demonstrate these attributes.

Online searches, through Web of Science, with combined search terms was used to identify studies focused on current MNs and similar devices and the various performance and quality tests used. There were several meetings with researchers and supervisors doing similar projects for other MNs where ideas and data were compared. A telephone conference was held with a member of the MHRA regulatory body who voiced their personal opinions on the topics raised.

Results were presented in two tables. One focused on pre-clinical development and the other focused on the end product attributes. The attributes were listed in descending order of importance to the device. The order was determined by considering how each attribute would affect the safety, efficacy or usability of the device. Each attribute was given a description of why it was critical. They were also assigned a standardised test to demonstrate them and specifications they had to meet.

Biodegradable MNs are safer and easier to produce than other MNs³. The main issues identified were the stability and sterility of the device. Challenges to overcome include GMP manufacture and protective packaging along with an appropriate expiry date. Cooperation with cosmetic companies was identified as an opportunity to enhance knowledge in the area.⁴ Identification of CQAs is essential in assisting the introduction of a regulatory framework for MN devices.

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Anti-hormone-induced Herceptin resistance in breast cancer cells in vitro

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Oestrogen receptor-positive (ER+) breast cancers are routinely treated with endocrine therapy¹ and are further subdivided into luminal A and B types according to absence or presence respectively of the ErbB receptor ErbB2. Resistance to endocrine therapy emerges in approximately 40% of all patients² but ErbB2+ breast cancers can also be treated with the ErbB2 monoclonal antibody Herceptin (trastuzumab) which may extend response to anti-hormones.² Unfortunately, 70% of patients develop Herceptin resistance within 12 months of therapy.³ Interestingly, prolonged endocrine treatment (e.g. Faslodex [fulvestrant]) can promote such Herceptin resistance in vitro but its mechanisms are unknown. This project aimed to identify any changes in ErbB2 or further receptor signalling that may underpin anti-hormone-induced Herceptin resistance in prolonged Faslodex-treated ErbB2-overexpressing breast cancer cells in vitro.

7 day triplicate preparations of Herceptin-responsive BT474 control (BT474(con)) and Herceptin-resistant BT474 Faslodex-resistant (BT474(FasR)) cells treated with or without Herceptin were studied. Western blotting was performed for ErbB2 expression and activation, downstream kinases and further growth factor receptors, quantifying by densitometry. Immunocytochemistry also analysed ErbB2 localisation in coverslip preparations. GeneSifter™ software compared ErbB receptor mRNA profiles in both sublines using pre-assembled Affymetrix microarray data.

Herceptin promoted a significant fall in ErbB2 ($p=0.026$), ErbB2 membrane downregulation, and pAKT decline ($p=0.001$) in BT474(con) but not BT474(FasR) cells. Basally, the latter line also had depleted ErbB3 expression and activation ($p=0.001$ and $p=0.001$ respectively) and decreased pAKT ($p<0.01$). Conversely higher basal ErbB4 mRNA was noted in BT474(FasR) cells ($p<0.001$). Significant increases in EGFR activation ($p=0.014$ and $p=0.027$ respectively), retained MAPK activity, and IGF-1R induction was also seen in the models with Herceptin.

Prolonged anti-hormone treatment results in failure of BT474(FasR) cells to regulate ErbB2 and a parallel shift in ErbB signalling away from ErbB3/pAKT and towards ErbB4. Such anti-hormone induced signalling changes may underpin Herceptin resistance, alongside further Herceptin-induced signalling changes.

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Perception of Parkinson's patients on the utility of iPad based apps to collect data in a Parkinson's clinic

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Parkinson's disease is a chronic, neurological condition that mainly affects the elderly population. The motor symptoms are tremor, slow movement and rigidity. Non-motor symptoms, which include depression, sleep disturbances and memory loss, are also common.¹ When attending clinic, patients complete a paper-based questionnaire regarding non-motor symptoms. This questionnaire was developed as the non-motor symptoms of Parkinson's disease are often poorly recognised and inadequately treated.² It was identified that electronic data collection could be a potential method of data capture within Parkinson's disease clinics. An iPad application was trialled and showed positive results.³ This project discovers the perception of Parkinson's patients on using an iPad application within clinic, identifying concerns and providing recommendations.

Focus group sessions were conducted at Parkinson's disease support groups across South Wales. Participants read a project information sheet and signed a consent form to become involved in the study. The sessions were conducted in a semi-structured interview approach, and later transcribed. Data analysis was conducted via a thematic approach and coding aided the identification of three themes.

Theme one discovered that many participants had negative experiences with technology, which was blamed on the symptoms of Parkinson's disease and age. Theme two found that numerous participants understood very little about technology within healthcare, but recognised its potential advantages. Theme three highlighted concerns that participants had with the iPad application, such as need for training, security and overall usability.

Many participants felt that the iPad application was a good concept, which could be beneficial to both clinicians and people with Parkinson's disease. However, it was widely expressed that considerations, such as security, confidentiality and practical issues need to be addressed. This iPad application has potential to improve data collection within clinics, and with recommendations from this study, be successfully introduced throughout Parkinson's disease clinics.

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The influence of ageing and gender on oestrogen receptor expression

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The main aim of this project is to investigate the influence of age and gender on oestrogen receptor (ER α and ER β) expression. Oestrogen has been studied for its role in neuroprotection and its ability to influence the development of neurodegenerative diseases, such as Alzheimer's disease (AD).^{1,2} There are several mechanisms by which oestrogen has been proposed to provide neuroprotection; including protecting mitochondria from amyloid beta toxicity and reducing oxidative stress.³ Age and gender are known to be risk factors for the development of AD⁴, and understanding their link to the neuroprotective actions of oestrogen may lead to improvements in preventing neurodegeneration.

Cortical brain samples were analysed from non-diseased men and women aged between 20-99 years. Western blotting was used to determine the levels of expression of ER α and ER β receptors using specific antibodies. The blots were then imaged and the results analysed with ImageJ.

As women age the expression of ER α was significantly reduced in the cortex samples, however, ER α expression was not influenced by ageing in male cortical tissue. In comparison to elderly men, elderly women had a significantly reduced ER α receptor expression. ER β expression displayed an upward trend for females as they aged but remained constant for men.

There is evidence for a link between gender and ER α expression, suggesting that this receptor plays a part in the development or prevention of neurodegeneration. The apparent increase in ER β expression with age in women also suggests that it plays a role in neuroprotection. More work is needed to understand the involvement of ERs in AD and how they could be exploited as therapeutic targets.

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Exploring pharmacists' views on the Choose Pharmacy platform within the community pharmacy setting

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The Choose Pharmacy platform is an online application delivered by the NHS Wales Informatics Service (NWIS) that enables pharmacists across Wales to electronically manage a number of enhanced services.¹ The aim is to implement Choose Pharmacy in 400 pharmacies out of the 716 in Wales.² New services have recently been added and are categorised into modules. These are: Seasonal Flu Vaccine (SFV), Emergency Medicine Supply (EMS) and Emergency Hormonal Contraception (EHC). There are seven pharmacies piloting these modules.

Qualitative research was used since this project was an exploratory study. Ethics approval was granted by Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee. Participants were recruited via email by a gatekeeper from NWIS. Participants had experience using these modules and were given a participant information sheet and a consent form. Semi-structured interviews were conducted. Interviews were audio recorded and transcribed verbatim. Thematic analysis was used to identify themes.³

Four pharmacists took part in the project. They were face-to-face interviews, conducted in the pharmacy consultation room. Five main themes were identified. These themes were information technology (IT), views of the public, workload, consultations and recommendations.

The results gathered showed two main issues with the Choose Pharmacy platform. They were issues with the software and the EHC module. The next step for NWIS is the addition of the patients' GP records which will be beneficial for pharmacists. NWIS requires approval from General Practitioners Committee Wales.⁴ A limitation to this project was the small sample size as saturation wasn't reached. As future research, the draft questionnaire produced, as a result of this project will be sent to all pharmacies that will be using the Choose Pharmacy application in the future. To conclude, it's clear to see from the study that the views of the pharmacists on the Choose Pharmacy application were positive.

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The knowledge and perceptions of pharmacy students on drugs in sport

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Many athletes and members of the public abuse medication and dietary supplements to benefit from their effects by improving sporting prowess or sustain longer training.^{1,2} Acting as doping control, pharmacists can educate those involved in competition to prevent further incidences of doping.³ Although not all pharmacists will specialise in the area of sports pharmacy, a certain level of knowledge in doping is needed on a day-to-day basis in practice. However, the level of education available in the UK on sports pharmacy in the MPharm degree is unknown. The aim of this study was to question the level of knowledge and opinions of MPharm students at Cardiff University on drugs in sport and to find out the level of education available at other pharmacy schools in the UK to determine if this is adequate for the needs of the sporting industry.

The research was mainly conducted in the form of a questionnaire, adapted from previous research in Qatar.⁴ All MPharm students at Cardiff University had the chance to participate. Additional data was obtained from individual schools of pharmacy in the UK. Ethical approval was obtained. Quantitative data was analysed using SPSS v23. Knowledge of sports pharmacy was analysed using Pearson correlation coefficient ($p < 0.01$).

A total of 196 students participated in the questionnaire out of a possible 459 students, a 42.7% response rate. Many students believed that doping was 'unfair' and 'is a form of cheating'. Significant evidence showed a positive relationship between year of study and knowledge of the prohibited statuses of cannabis, amphetamines and anabolic steroids ($p < 0.01$). Errors in knowledge were evident in laws surrounding prohibited and non-prohibited substances; insulin, anti-histamines, paracetamol, codeine and caffeine did not show a correlation between knowledge and year group. Students believed that healthcare professionals were considered the top information source to obtain information about the safe and effective use of drugs in sport. 95.41% of students believed that sports pharmacy should be on the curriculum, either as a core or elective module.

Despite the current tuition available at Cardiff University, there appears to be insufficient knowledge for students to become confident pharmacists in advising the public and athletes in the risks of abusing prescriptions medication in doping and the use of additional supplements. Students had strong opinions on the topic and many wanted to learn more. This study recommends more education of sports pharmacy on the curriculum.

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Numerical approach to investigate adhesion between orthopaedic biomaterials and gram-positive bacteria: influence of roughness and surface characteristics

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The presence of foreign materials presents a common and opportunistic source of infection in orthopaedic surgery¹. Bacteria adhere to biomaterial surfaces leading to the subsequent formation of a biofilm, which has significant clinical and economic implications.¹ With current ageing population increasing incidence of orthopaedic surgeries, there's a strong requirement to investigate other areas that may reduce the likelihood of infections.² Since adherence of bacteria is the initial stage in pathogenesis of infection, an understanding of the physical and mechanical factors affecting this can be highly beneficial in the development of novel prevention strategies.³ Therefore, the effects of Young's modulus, Poisson's ratio, and surface free energy (SFE) of biomaterials and bacteria were investigated, in addition to material roughness.

Surfaces are not truly smooth on an atomic scale; they present some degree of roughness because of rugged projections, termed asperities.⁴ These asperities provide contact points for interactions to occur between

particles - including bacteria - and surfaces.⁴ A previously-developed numerical procedure was employed, which models multi-asperity contact adhesion between two surfaces using the Johnson-Kendall-Roberts (JKR) model of contact⁴. A theoretical morphology of a biomaterial surface is recovered by generating random asperities. Then, contact and adhesive forces between two surfaces are determined by the JKR model from initialised numerical data on physical and mechanical properties.

The lowest adhesive force was observed with stainless steel and bacterial strain *Staphylococcus epidermidis* 3598. By contrast, greatest adhesive abilities were identified with biomaterial polymethyl methacrylate, and bacterial strain *Staphylococcus epidermidis* 35984. These results could be related back to their physical and mechanical properties.

Overall, effects of physical and mechanical properties have been explored, with low Young's moduli and high SFEs promoting adhesion. Effect of surface roughness was also determined, with significantly increased adhesive forces being observed when irregularities were present.

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Identifying factors that motivated pharmacy undergraduates for their third year assessments at Cardiff University

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Motivation may be described as "a desire or willingness to do something".¹ When applied to student learning, one can understand why such a concept is essential to success. Motivation has been extensively researched, with many theories developed to understand the factors that affect it.² However, research into the motivation of pharmacy students in the UK, and more widely, is lacking.³ Therefore, this investigation aimed to explore the factors that affected pharmacy student motivation at Cardiff University.

Due to the explorative nature of the investigation, a qualitative approach was taken. Development of the topic guide followed a discussion of third-year assessments. Approval was obtained from Cardiff School of Pharmacy and Pharmaceutical Sciences ethics committee. Three pilot interviews took place. Recruitment was undertaken using non-probability sampling and invitation emails were sent out. One-to-one, semi-structured interviews took place and were audio recorded with the participants written consent. The recordings were then transcribed and shared amongst the researchers. Each researcher independently analysed the transcripts using inductive thematic analysis.⁴

Thirteen interviews took place. Interviews lasted between 30 and 79 minutes. Nine themes were identified: (1) Perceived relevance to future, (2) The influence of others, (3) Contribution to degree class, (4) Performance in similar assessments, (5) The consequence of not passing, (6) Feedback as feedforward, (7) Interest in the subject material, (8) Difficulty of the subject material, and (9) 'Doing the best I can'. Suggestions to improve/enhance student motivation will be made to the school.

From the interviews conducted, it was clear that a whole host of factors influenced student motivation- no two students were the same. The study was limited as it was not known if theoretical saturation was reached. To understand pharmacy student motivation, the investigation could be implemented for the other years of the Master of Pharmacy (MPharm) degree.

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Pore forming peptides in droplet-droplet bilayers

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Studies of cellular membranes are essential as they remain the target of pharmaceuticals and are the site of disease dysfunction. A major limitation of drug delivery is enabling drugs to pass across a cellular membrane. Droplet interface bilayers (DIB) provide an artificial mimic of membranes allowing investigation of membrane-peptide interaction and suggested mechanisms for pore formation/translocation.¹ Pore forming peptides of interest included peptides which form biologically related channels and Cell Penetrating Peptides (CPPs). Aims set out in this study were to establish if different classes of pore forming peptides had similarities in their mechanism of interaction and pore formation when introduced into DIBs.

DIBs are composed of two aqueous droplets placed onto two electrodes, submerged in a lipid in oil phase. The amphiphilic nature of lipids allows for monolayer assembly at the water oil interface. Electrophysiology is combined with DIB experiments as the electrodes within droplets allows the application of a potential and measurement of ionic current through pores, thus detection of poration.²

Pore forming peptide current traces were compared against characterised traces of alpha-hemolysin fixed conductance pores, and variable conductance electropores. CTP2 resembled electroporation, whilst CTP2 D4/A had superimposed steps similar to that of the alpha-hemolysin trace. Substitution of Aspartate for an Alanine in CTP2 showed a decrease in current through pores. Both CPPs: Penetratin and a synthetic peptide, resembled electroporation with lengthened bilayer formation times. Increasing the voltage increased the electroporation effect, whilst increasing concentration led to unsuccessful bilayer formation.

CTP2 and CTP2 D4/A supports a fluctuating toroidal and stable barrel-stave pore formation respectively. A decrease in current passed through the membrane with CTP2 D4/A demonstrating the importance of Aspartate in forming pores in CTP2. In contrast, Penetratin and the synthetic peptide traces support an 'inverse micellar formation' with longer bilayer formation times. However, there is no confirmation of translocation across the membrane.³

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An evaluation of prescribing trends associated with hypnotic agents in care homes

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The majority of care home residents have two or more long term conditions¹ and as such are a vulnerable population due to polypharmacy and their susceptibility to drug harm. Approximately two-thirds of residents suffer from sleep disturbances² meaning hypnotic prescribing is high. The aim of this investigation is to identify the prevalence and type of hypnotics prescribed within care homes.

A retrospective study was conducted in South Wales in 2015 over 12 care homes. Over an eight-month period anonymised data was collected and received from an electronic medicines management system. Irrespective of this data, inclusion criteria were set to a date range of three months, looking at four different drug classes; hypnotics, antidepressants, anxiolytics and antipsychotics. Hypnotics were classified using the BNF and the type and frequency of hypnotic sorted according to our inclusion criteria in excel. SPSS was then used for further data analysis.

Overall, 10/12 care homes had residents on hypnotics and a total of six hypnotics were identified over the time period analysed. A total of 304 residents were prescribed hypnotics, with four on concurrent hypnotic therapy. A strong positive Pearson Correlation using SPSS was identified indicating that residents prescribed hypnotics are also likely to be prescribed other psychotropic agents.

The investigation showed over 80% of the care homes had residents on hypnotics, which is supported by international studies showing 50-80% of nursing homes with patients on at least one psychotropic medication.² Whilst the study showed hypnotic prescribing was high, 16% more residents were prescribed Z drugs over benzodiazepines (BZDs), supporting a study in 2016 showing a reduction in BZD prescribing over the past 20

years.³ However, future work should investigate why this prevalence is so high and whether hypnotic prescribing can be reduced by the implementation of non-pharmacological methods.

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Working towards an LPS imprinted sepsis diagnostic

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Sepsis, a syndrome of biochemical, physiological and pathological abnormalities as a result of infection is a major public health concern.¹ Successful treatment relies on early and prompt diagnosis.² Lipopolysaccharide (LPS), a major constituent of gram negative bacteria has been identified as a possible biomarker for sepsis. With the true potential of blood marker detection yet to be fully exploited, the aim was to develop an electroimpedance sensor capable of direct and sensitive detection of LPS using molecular imprinting.

Aminobenzoic acid, dopamine and pyrrole were electropolymerised on the surface of gold macro electrodes using cyclic voltammetry (CV) to deposit polymer layers. Their interaction with LPS was assessed using electrochemical impedance spectroscopy (EIS), in order to select the most appropriate monomer for imprinting. Molecular imprinting involves the polymerisation of monomers around a template molecule to form synthetic polymeric receptors. The polymer formed contains specific recognition sites complementary to the template and engages in interactions based on molecular recognition. The use of bio-recognition motifs in combination with molecular imprinting (hybrid imprinting) has been shown to produce ultra-sensitive sensing platforms, therefore both a conventional and hybrid imprinting strategy were employed.³

Out of the monomers tested poly-dopamine demonstrated the greatest interaction with LPS so was taken forward into the imprinting processes. The conventionally imprinted MIP showed increased rebinding of LPS compared to the dopamine non-imprinted polymer. To produce a hybrid imprinted system an aptamer was introduced to increase binding specificity to the imprinted pocket but demonstrated a poor response to rebinding of LPS.

Some successful imprinting was demonstrated during the conventional imprinting process, however results were largely inconclusive with mostly non-specific binding being observed. Using LPS as a template for molecular imprinting is notoriously difficult. Future studies could focus on templating Lipid-A, the endotoxin centre of LPS.

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An evaluation of the role of motivation in final year pharmacy students at Cardiff University and its impact in the assessment and feedback processes

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Motivation can be defined as “*the process whereby goal-directed activities are initiated and sustained.*”¹ Understanding the nature of motivation is important, as it can be enhanced to produce positive outcomes.² Current literature on motivation demonstrates its importance in education, due to its effect on learning behaviours.^{3,4} This study aimed to identify what factors motivate pharmacy students for their Third Year assessments and the effect this has on their learning.

Upon approval of the study by the school’s ethics committee, a qualitative approach was taken to explore students’ views. Final Year students were invited to participate in semi-structured interviews using purposive

and convenience sampling. Interview questions were developed from a topic guide that was created from the literature and through consideration of reasons behind degree of motivation by the researchers. Interviews were transcribed, following audio recording and interviewee consent. Transcripts were checked for accuracy and confidentiality, and analysed thematically.

Thirteen students were interviewed, 9 were female. Student attributes included, but were not limited to, international students, mature students, external students and future ambitions. Six major themes were identified from the transcripts namely; interest in activity, contribution of assessment to degree, relevance to future career, fear/consequence of failure, influence of others and feedback.

The study established that motivation is important in an academic environment and that it is influenced by various factors; these differ within and between students depending on the assessment, which affects their performance. There were limitations to the study, however, these can be overcome by future work. The objectives were met, as intrinsic and extrinsic factors for motivation were determined.² Suggestions for the School of Pharmacy to consider to enhance and/or maintain motivation have been made. Further research of its impact in pharmacy education may improve learning and teaching practices.

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Interplay between FAK and STAT3 in HER2+ breast cancer cells

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Breast cancer is one of the most common types of cancer in the UK ¹, with 20-30% of cases being diagnosed as HER2+.² Cross-talk between the tumour and the surrounding stromal cells is implicated in tumour progression and limitation of therapeutic response. Fibroblasts in particular have been associated with an increase in aggressive tumour cell behavior likely to favour metastasis; these observations likely arise from the ability of fibroblast cells to secrete that activate tumour cells in a pro-metastatic manner. Our aim here was to investigate whether focal adhesion kinase (FAK) is involved in fibroblast-induced breast cancer cell behaviour and whether FAK-signalling involved STAT3, a transcription factor known to be involved in the regulation of genes that control cell proliferation, migration and survival.³

Fibroblast-conditioned media ('FCM') was collected from MRC5 cells (human fibroblasts) after 3 days culture and used to stimulate the Her2+ breast cancer cell line, SkBr3. These experiments were performed in the presence or absence of the FAK inhibitor, PF271 (1 μ M). MTT and Boyden chamber assays were used to determine the effects of FCM on SkBr3 growth and migration respectively whilst Western blotting was used to investigate the activity of FAK and STAT3 in SkBr3 cells. Immunofluorescence microscopy was used to determine changes in subcellular localisation of FAK and STAT3 in response to FCM.

Whilst FCM had little effect on Her2+ breast cancer cell proliferation, it significantly increased migration of the cells. FCM also caused an increase in the phosphorylation of STAT3 (Y705 and S727) and FAK (Y397 and Y861) in SkBr3 cells; these changes were reduced in the presence of PF271.

Our data suggest that FCM promotes Her2+ breast cancer cell migration in a FAK-dependent manner and involves FAK-mediated activation of STAT3, an observation not widely reported previously. FAK may therefore represent an important target to suppress the pro-invasive characteristics of cancer cells which may be augmented in a stromal environment.

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The role of BIN1 in endocytosis and its relevance for Alzheimer's Disease

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Polymorphisms in the gene locus for bridging integrator-1 (BIN1), a protein believed to play a role in clathrin-mediated endocytosis (CME),¹ were determined to be the second largest contributing risk factor for developing Alzheimer's disease (AD).² Preliminary work showed an increase in β -CTF in cells which are a model for the blood-brain barrier (BBB), depleted of BIN1. The implications of this finding suggest that a change in BIN1 may result in a change in the endosomal and amyloidogenic processing of APP in AD. We measured the protein expression and distribution of key endocytic, amyloidogenic and lysosomal proteins to determine what effect BIN1 depletion had.

Western blotting was used to analyse protein samples from three treatment groups; a media control, a GFP siRNA control and a BIN1 targeting siRNA group of hCMEC/D3 cells, a BBB model. Immunocytochemistry was used to examine the intracellular distribution of the proteins.

Following depletion of BIN1 by siRNA, levels of CME-related proteins, clathrin, PICALM and AP2 remained unchanged. Clathrin-independent endocytic (CIE) -related proteins; caveolin 1, flotillin 1, flotillin 2, remained unchanged in cells treated with BIN1 siRNA. Caveolin 2 showed a statistically significant increase in protein expression in cells treated with BIN1 siRNA. Beta amyloid cleavage enzyme (BACE1) expression showed an increasing trend in cells treated with BIN1 targeting siRNA. The cellular distribution of EEA1 and LAMP2b appeared to change. EEA1 appeared to become less punctate and LAMP2b appeared more diffuse throughout, in cells treated with BIN1 siRNA.

The depletion of BIN1 in BBB-derived cells appears to have no effect on CME, based on protein expression. However an increase in caveolin-2 indicates a possible change in CIE. Alterations in EEA1 and LAMP2b distribution suggesting a change in endosomal and lysosomal functionality, along with an increasing trend in BACE1 expression, suggest that amyloidogenic processing of APP has increased in cells depleted of BIN1.

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Evaluation of the Cwm Taf University Health Board Domiciliary Medicines Use Review (Dom-MUR) service

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The Medicines Use Review (MUR) Service is an Advanced Service in the community pharmacy contract. It involves the pharmacist reviewing a patient's use of their medication, aiming to improve patient understanding and adherence to medication and reduce medication waste.^{1,2} Since November 2012, the Cwm Taf University Health Board (UHB) have commissioned a domiciliary MUR (Dom-MUR) service, providing housebound patients with equal access to MURs. The aim of this study was to identify the types of issues and interventions carried out by pharmacists as part of the Dom-MUR service and to explore the perceptions of these pharmacists in delivering this service.

A database of Dom-MUR entries from December 2012 to March 2014 was obtained from the UHB. Issues and outcomes arising from Dom-MURs were categorised. Data was quantitatively analysed using Microsoft Excel® and GraphPad Prism®. A pilot interview using a semi-structured interview guide was also carried out.

Data from 194 Dom-MURs was included in the database. The mean number of issues identified per patient was 1.96 (SD±1.41). The three most commonly identified issues were related to 'Patient Adherence (29%, n=110)', 'Patient Education/ Monitoring' (21%, n=79) and 'Medication Excess in Home' (12%, n=47). The mean number of outcomes per patient was 1.97 (SD±1.48). Of the outcomes, 32% (n=122) involved the pharmacist contacting the GP surgery i.e. they could not resolve these issues themselves. Issues assigned to 'Issues with Patient's Condition' were statistically less likely to be resolved by the pharmacist.

The Cwm Taf UHB Dom-MUR service has the potential to be of value. Developments within community pharmacy, such as access to patients' health records and pharmacist independent prescribing³, may benefit

this service with the potential for pharmacists to resolve more issues themselves. Interviews with pharmacists should be carried out with amendments to the interview schedule in order to further evaluate the service.

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To what extent are Welsh medium community pharmacy services being utilised?

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The Welsh Language Act of 1993¹ determines that both the Welsh and English language need to be treated on the basis of equality. The Act requires public services, including the NHS, to develop a Welsh Language Scheme.² As NHS contractors, community pharmacies are considered private sector and therefore fall outside of this requirement. In 2016 the Welsh Government collected data on what language community pharmacy services were conducted through. When community pharmacies claim payment through NECAF there are currently questions relating to whether or not the consultation was conducted through the medium of Welsh and if so, to what extent. The aim was measuring the number of services conducted in Welsh through NECAF.

A quantitative study was carried out on every Health board from April until September 2016. All seven health boards were compared to see how many Welsh consultation were requested and to what extent. Individual services were looked at within and across health boards to compare the number of Welsh language consultations requested and delivered.

From the 123,855 consultations conducted between April and September 2016, only 2% were requested for in Welsh. Aneurin Bevan Health Board (ABHB) was the health board with the lowest percentage of Welsh language consultation request at 0.06% where as Betsi Cadwaladr University Health Board (BCUHB) was the highest at 5.2%. Patients requesting a Welsh language consultation in ABHB have a 77% chance of being declined, whereas within BCUHB this is only 3%.

The low uptake of Welsh language consultations could be explained by patients' reluctance to ask for Welsh language services. Another possible reason for this could be that patients don't always know that Welsh language services are available to them. This study shows that locality is a factor in accessing Welsh language services.

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The use of an optimised cubosome formulation to enhance transdermal delivery of the ovalbumin peptide SIINFEKL

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The skin's outermost layer, the stratum corneum, limits transdermal drug delivery.¹ Microneedles have been investigated for pretreatment of the skin to increase permeability.² Cubosomes possess unique physiochemical properties³, which support the encapsulation and delivery of molecules. By using Strat-M membranes along with an optimised peptide cubosome formulation, this study aims to build on previous data generated in animal models using a synthetic membrane model more representative of human skin.

Cubosomes were formulated with TAMRA-conjugated ovalbumin peptide SIINFEKL at a range of concentrations. To determine stability of formulations, particle size and zeta potential were tested using a Zetasizer over a 96 hour storage period. Peptide entrapment was measured using a fluorescence spectrophotometer and values were analysed against a concentration calibration curve. Permeation studies using Franz diffusion cells assessed the permeation of formulations through untreated and microneedle pretreated Strat-M membranes and analysed using a fluorescence spectrophotometer.

Stability studies showed no significant difference between any concentrations at each time point, showing that peptide did not affect cubosome particle size over 96 hours at the concentrations used. There was no significant difference found between the percentage peptide entrapment or the mass of peptide found in the lipid phase in any of the formulations. Results from permeation studies showed a significant increase in peptide delivery when using 0.2mg/ml peptide cubosome formulation following microneedle pretreatment.

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Oroidin as a lead compound for novel antibiotic drug discovery

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Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites and fungi.¹ Oroidin is a bromopyrrole alkaloid which is isolated from sponges in the genus *Agelas*, which occurs in the Mediterranean sea.² Oroidin has been shown to have antimicrobial properties³. This project involved creating an analogue of oroidin to identify any antimicrobial action.

The project involved three major experiments. The first experiment looked at reacting ethyl indole-2-carboxylate with 3-phenyl-1-propylamine. In this experiment different solvents were used. The second experiment looked at reacting indole-2-carboxylic acid with 3-phenyl-1-propylamine using pyridine as the solvent and isobutyl chloroformate as the reagent. The final experiment involved protecting the indole nitrogen on the ethyl indole-2-carboxylate with di-tert-butyl dicarbonate. Following this, the resulting compound was reacted with 3-phenyl-1-propylamine.

The TLC results from the first experiment showed that the reaction did not work and therefore a compound with a better leaving group was needed. The NMR result from the second experiment showed that the indole nitrogen was reacting with the reagent isobutyl chloroformate. It was gathered that the indole nitrogen needed protecting. The NMR result from the third experiment showed that the ethyl-indole-2-carboxylate had been successfully protected by the di-tert-butyl dicarbonate. However, when this was reacted with 3-phenyl-1-propylamine the NMR result showed that the reaction had not worked due to the poor leaving group ability of the ethyl indole-2-carboxylate.

The indole nitrogen proved to be troublesome during the project, it was more nucleophilic than expected. However a method for protecting the indole nitrogen was established. It was concluded that the ethyl indole-2-carboxylate did not contain a good leaving group and therefore the nucleophilic substitution reaction did not work with 3-phenyl-1-propylamine. Further research is needed to identify compounds with better leaving groups to activate this reaction.

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Synthesis of novel CYP121 inhibitors for the treatment of *Mycobacterium tuberculosis*

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Tuberculosis (TB) remains a major problem, consistently being one of the leading causes of death due to infectious disease.¹ The emergence of resistance in tuberculosis and the lack of new medication being developed means that tuberculosis had become a major global public health issue.¹ When the genome of *Mycobacterium tuberculosis* was sequenced it was observed that it contained a high level of cytochrome P450 enzymes. CYP121 was of particular interest due to its essentiality, unique binding modes, unusual reaction

and high level of characterisation. The aim of this study was to produce a series of compounds based on azole antifungals, which are known to strongly bind to CYP121.

Molecular modelling was undertaken on a library of azole based compounds using FlexX in LeadIT and visualised using MOE 2014. FlexX was used as, unlike docking in MOE 2014, it is able to show interactions between the iron of the haem in CYP121 and the nitrogen of the imidazole ring via an interstitial water, which has been observed previously in CYP121.² However, this was not observed in the docking of these compounds.

Synthetic routes to imidazole substituted two and three benzene derivatives were devised. A 4-step synthesis starting from substituted phenylacetic acids failed to successfully isolate a final product via either of the synthesis pathways and preferentially produced elimination products in both cases.

Further work in optimising the synthesis route is required before the compounds can be screened against tuberculosis.

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Evaluation of a community pharmacy-based asthma care plan

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In the UK asthma affects 5.4 million people and the NHS spends on average 1 billion pounds a year treating and caring for people with asthma¹ Studies have shown that pharmacy-led interventions are effective in improving asthma patient outcomes, these studies are based outside of the UK² however, current UK-based studies have not measured the effect of their interventions on asthma control³ To assess asthma control and inhaler technique within a community pharmacy setting and obtain baseline measurements of lung function, asthma control and inhaler technique.

Data was collected from 145 participants, from seven community pharmacies located in South Wales, through a semi-structured interview composing of the Asthma control test⁴, spirometric testing and assessment of inhaler technique via the Vitalograph Aerosol Inhalation Monitor (AIM) machine.

43% (n=62) of the participants had uncontrolled asthma and smokers had significantly less asthma control than non-smokers (p=0.0144). Inhaler technique for metered-dose inhalers was significantly worse than inhaler technique for dry-powder inhalers (p< <0.0001) and inhaler technique training was predominantly by GP's and nurses.

Despite the advancement in medicines available to treat asthma, asthma control is poor. There are many factors that attribute to poor asthma control, mainly the prevalence of poor inhaler technique, especially for metered-dose inhalers. Smoking significantly decreases asthma control as well as other factors, such as inhaler technique training, but further research is required to understand the extent of its influence. Pharmacists as healthcare professionals have a role to play in improving asthma management. Community pharmacy asthma care plans have been successful in the past, further research is required to investigate the sustainability and implementation of a community pharmacy-based asthma care plan within the healthcare system.

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Depression and polypharmacy in Lewy body diseases

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Lewy body disease (LBD) is an umbrella term for Parkinson's disease (PD), Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB).¹ LBD has four cardinal motor symptoms and non-motor symptoms (NMS) are also prevalent, depression is the most common and is the most debilitating and influential NMS on quality of life.² Recently several studies have identified a link between polypharmacy and elevated depressive symptoms.³ Polypharmacy is the use of multiple medications and can increase a patient's chance of hospitalisation and drug-drug interactions, as LBDs are chronic conditions patients are likely to take multiple medications and thus experience polypharmacy.⁴ This study aimed to explore depression demographics and determine if high levels of polypharmacy correlate to high incidence of depression.

A retrospective study was conducted on two movement disorder clinics in South Wales between 2002 and 2016. Prevalence of LBD and depression, demographics, antidepressant use and polypharmacy were examined.

This study included 1028 patients, 65% PD, 28% PDD and 7% DLB. Prevalence of depression and antidepressant usage across all LBD was very similar. SSRIs were the most commonly used antidepressant and their proportions of use were extremely similar across all LBD. A wider diversity of antidepressants along with a higher proportion of multiple antidepressants were used in DLB. PD patients taking antidepressants were prescribed a significantly higher number of drug classes than those who were not. This pattern was not identified in PDD or DLB. Motor symptoms of depressed PD patients were more severe than non-depressed patients; this was deduced by speculating that anti-parkinsonian drug regimen correlated with disease severity.

There is a clear link between polypharmacy and antidepressant usage indicating that polypharmacy is more dependent on whether PD patients are taking antidepressants. However, this link is not replicated in PDD and DLB. Although LED is higher in PDD patients who are taking antidepressants than those not depressed there is no relationship between polypharmacy and depression.

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Evaluation of the pros and cons of drug re-positioning as a drug discovery strategy

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Drug re-positioning means using existing drugs to treat new indications.¹ There is potential of using re-positioning as a drug discovery strategy, but there are likely clinical and commercial pros and cons to this, including limited patenting opportunities.² The aim was to uncover what industry, clinicians and patient representatives perceive are pros and cons of drug re-positioning as a drug discovery strategy to reach a consensus on whether re-positioning could be a viable in this context.

A qualitative research approach was taken using a semi-structured interview schedule, with pre-determined open questions focussed on clinical and commercial aspects of re-positioning. Interviewees comprised 4 industry professionals/drug development researchers, 3 clinicians, and 2 patient representatives who were emailed re-positioning information and completed consent forms prior to interview. Interviews were recorded and transcribed, anonymising interviewees. Coding was used to collate responses under 5 themes of clinical pros, clinical cons, commercial pros, commercial cons, or no consensus of opinion. Responses for each theme were then analysed to determine sub-themes with exemplar quotes. To determine a consensus on drug re-positioning, content and number of sub-themes (and associated numbers of responses and responders) were considered for each theme.

All interviewees overall supported re-positioning from a clinical perspective, providing few negative clinically-related sub-themes for drug re-positioning. Known safety profile, patients/prescribers being happy to use re-

positioned drugs, and NHS cost savings were common positive subthemes. In contrast, only 4 interviewees were in favour overall for re-positioning from a commercial perspective, with no consensus from others. Many commercial problems of drug re-positioning were perceived, with subthemes including patenting issues, but there were also some benefits including cheaper drug development.

Overall, the consensus is that drug re-positioning would be clinically advantageous with few clinical concerns raised, but that there is no consensus on the commercial value of this strategy.

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Evaluation of a community pharmacy-based asthma care plan

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Asthma is a prevalent respiratory lung disease with an estimate of around 5.4 million people suffering from asthma in the United Kingdom alone.¹ Research indicates that around one in every three people are using their asthma inhalers incorrectly.¹ An estimate of up to 90% of asthma deaths could be prevented², highlighting that poor asthma control and patient education needs addressing, due to uncontrolled asthma possibly resulting in increased mortality rates.^{1,3} The aim of the study is to assess the quality of asthma patients' inhaler technique and asthma control.

A total of 145 asthmatic participants were recruited across seven different community pharmacies, patient recruitment was based on convenient sampling. Participants completed a biometric data questionnaire and an asthma control survey (ACS). An aerosol inhalation monitor (AIM device, Vitalograph) was used to assess inhaler technique, and a spirometer to assess lung function. Ethical and service evaluation approval was attained from the Research and Discovery Department, Aneurin Bevan University Health board.

Based on the results from the asthma control survey (ACS), 42% of participants had uncontrolled asthma. Poor asthma control was highlighted by 40.7% of participants disclosing that they had previously been admitted to hospital or taken oral steroids. Smoking also had a significant impact on reducing asthma control in comparison to non-smokers (P=0.03). Generally inhaler technique was poor. Metered dose inhalers (MDI) were associated with the worst inhaler technique, however significant improvement in technique was seen if a spacer was used. Dry powder inhalers (DPI) technique was significantly better in comparison to MDI's (P<0.01).

This study fund that participants have poor inhaler techniques and asthma control. Participants are better at using DPI and MDI with spacer, compared to MDI alone. Patient education and inhaler technique needs to be improved in patients.

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Molecular modelling studies of Notch receptors

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Notch receptors are transmembrane proteins that play a fundamental role in the cell life cycle.¹ Dysfunction of Notch receptors can give rise to a multitude of human diseases.² Notch receptor modulation is novel research area aimed to treat the diseases Notch dysfunction can cause. The aim of this project develop structures of all Notch family receptors to evaluate and understand the difference in ligand binding .Using generated 3D of Notch1-Jagged1, identify small molecules and peptides that are able potentially regulate Notch1 signalling

Homology modelling of Notch2-4 binding domain was performed with MOE using crystallised Notch1 structure. Protein-protein docking was performed using the generated structures with Jagged1 Notch ligand. Jagged1 interactions were analysed between the different Notch receptors. Using the structure of Jagged1 DSL region and bioactive peptide5, 9 small peptides were generated and docked with MOE. Peptide interactions and conformation with Notch1 were compared with the Notch1-Jagged1 model to identify a structure that may modulate Notch1. Using Glide and ROCS virtual screening techniques, 3,300,000 small compounds were screened to identify theoretically bioactive compounds. Compounds were selected based on their consensus score and visual inspection.

Protein-Protein docking of Notch1 and Jagged1 produced a model with favourable interactions with the binding regions. Two peptides showed promising resulting indicating they can theoretically modulate Notch1. A total of 117 compounds were selected from both virtual screening techniques due to their favourable interactions and conformation with Notch1. 19 of which have been purchased for future biological evaluation.

Although the work conducted is predictive, the selected compounds and peptides indicated the theoretical ability to modulate Notch1. Further experimental work needs to be undertaken to quantify the ability of the chosen structures to modulate Notch1 receptors.

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Design and synthesis of novel human Norovirus RNA-dependent RNA polymerase inhibitors

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Noroviruses are members of the Calicivirus family. They have a single stranded, positive sense RNA genome.^{1,2} Norovirus-induced gastroenteritis is estimated to affect 21 million people per annum in the United States and causing up to 200 000 deaths per year in developing countries.³ Currently there is no cure or vaccine available against this virus hence the need to develop an antiviral drug. RNA-dependent RNA polymerase was identified as the most promising target for antiviral drug development due to its crucial role in viral replication and synthesis of genomic and sub genomic RNA.^{1,4} This project aims to design and synthesise novel Norovirus RNA-dependent RNA polymerase inhibitors by structural modification of lead compound 1. Lead compound 1 was discovered following a docking-based virtual screening on the virus polymerase 4LQ3 crystal structure.

Twenty novel compounds were designed by rational modification of Lead 1. Docking studies were conducted to evaluate the predicted binding mode of these compound to the enzyme active site. Results showed interaction between the designed compounds and the enzyme amino acid residues, giving useful insights for the preparation of optimised inhibitors.

Two synthetic methods were optimised to prepare the designed compounds. First a general synthetic route with four reactions was optimised, starting with a Suzuki-Miyaura coupling, followed by a Knoevenagel condensation, and finally two type 2 nucleophilic substitution reactions. Then an alternative synthetic route involving two steps both of which are type 2 nucleophilic substitution reactions was designed and carried out. Nine novel compounds were successfully synthesised and characterised by proton and carbon NMR.

All the newly synthesised compounds will be sent for bioactivity evaluation against Norovirus RNA-dependent RNA polymerase and viral replication in cell based assays. The results will determine which compound(s) proceeds to next stage of drug development should any show promising activity against the polymerase.

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Have drug usage trends changed following the introduction of National Prescribing Indicators in Wales?

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One of the aims of All Wales Medicines Strategy Group (AWMSG) is to promote rational and cost effective prescribing, maximising patient outcomes.¹ AWMSG introduced National Prescribing Indicators (NPIs) in 2003, their purpose was to monitor prescribing and encourage practices to achieve a target based on the top 25% best performing practices² in Wales. A total of ten NPIs were analysed to investigate whether there was a change in prescribing trends following their introduction.

Data were extracted from the Comparative Analysis System Prescribing Audit (CASPA) database for each drug or drug class. CASPA provides a record of prescriptions dispensed and forwarded for pricing. An Auto Regressive Integrated Moving Average Interrupted Time Series Analysis was employed to assess whether there was statistically significant change in the dispensing trend of each of drug pre and post introduction of the NPI. Prescribing measures used included the number of defined daily doses prescribed per 1000 patients per month and proportion of drug prescribed as a percentage of a total drug group.

A statistically significant change was found for four NPIs (co-amoxiclav as a percentage of all antibacterials P=0.007, cephalosporins as a percentage of all antibacterials P=0.02, low risk NSAIDs as a percentage of total NSAIDs P=0.008, and morphine as a percentage of total strong opioids P=0.000). There was no statistically significant change in the dispensing trend of the remaining six NPIs.

Due to the retrospective, quasi-experimental³ nature of this analysis the changes observed in the dispensing trends cannot be directly linked to the introduction of the NPI. Confounding factors and competing interventions, may have exerted an influence on dispensing in addition to the NPI. Nevertheless, the temporal association between the introduction of the NPI and the changes in drug usage may indicate an influence on prescribing.

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Synthesis of novel chimeric phosphoramidate ProTides with fluorescent probes

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Nucleoside analogues (NAs) have been used clinically for the past five decades as both antiviral and anticancer agents. However, this class of drugs has limited efficacy, owing to inefficient activation, toxicity concerns and emergence of resistance. The prodrug strategy has been applied to improve the delivery of monophosphate NAs. In McGuigan's phosphoramidate ProTide approach, the negative charge of the monophosphate group is masked by an aryl motif and amino acid ester, which are cleaved off enzymatically to release the monophosphate NA in vivo. The aim of this project was to synthesise, purify and characterise four novel ProTides of the NA d4T, also known as stavudine, an approved but toxic anti-HIV agent,¹ using L-alanine esters and coumarin derivatives as masking groups. The use of a coumarin group could increase atom economy of ProTides. Coumarins with antiviral activity could work synergistically with d4T, thereby generating co-drugs with increased therapeutic efficacy. Coumarins' fluorescing ability² could be utilised for the visualisation of ProTide uptake, and to prove whether ProTides are activated in vivo.

To synthesise the ProTides, the phosphorochloridate chemistry approach was employed, as extensively reported in the 1990s.³ ProTides were purified using flash column and preparatory thin layer chromatography, and characterised and purity confirmed with nuclear magnetic resonance and mass spectrometry.

Five coumarin-containing ProTides were successfully synthesised, of which four have been isolated, with yield in the range of 7-11%. Two phosphorodiamidate compounds, which possess two amino acid ester masking groups and have been of interest recently⁴, were also isolated during the purification of ProTides.

As part of a future project, wavelength of absorbance and fluorescence of ProTides should be measured to enable visualisation of ProTide uptake and activation. All ProTides and phosphorodiamidates should be subjected to biological and toxicological testing, to determine both therapeutic activity and safety profile.

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Identification of combinations of natural products that inhibit the growth of MRSA

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It is estimated that 2% of the world's population is infected by Methicillin-resistant *Staphylococcus aureus*¹. MRSA accounts for up to 60% of hospital acquired infections². Due to the lack of new effective antimicrobials in the clinical pipeline, there is an urgent need to find alternative sources of novel antimicrobials. For centuries, plants have played a central role in the prevention and treatment of illnesses³. Therefore, using Manuka honey as a carrier matrix, extracts of tea, hops and seaweed were tested against MRSA (NCTC 11939) for their individual and combined synergistic antibacterial properties.

Initially, an agar-well diffusion assay was employed to determine the antibacterial activity of all natural products alone and in combination. This high-throughput assay allowed for the detection of antimicrobial activity. To further characterise this activity, a broth based minimum inhibitory concentration (MIC) assay was used. This assay, being more qualitative than the zone of inhibition (ZOI) assay, allowed for inhibitory specific concentrations of extracts to be identified. Finally, to identify potential synergistic activity between combinations of natural products a checkerboard assay was used.

ZOIs were measured using a digital caliper and inhibitory zones were observed by all extracts. The methanol extracts showed an increased potential, compared to the corresponding hexane extracts ($P < 0.05$). MIC of each extract was determined and were as follows: hops (0.0275% w/v), tea (0.09% w/v), seaweed (0.3% w/v) and honey (20%). The checkerboard assay identified a synergistic effect when honey was combined with either the hop extract or the tea extract. An additive effect was observed when honey was combined with seaweed.

In conclusion, it was observed that when all extracts were combined in the presence of honey there was an increased antibacterial effect, supporting the hypothesis. Thus, opening the possibility of developing honey based therapeutics capable of targeting antibiotic resistant bacteria such as MRSA.

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Investigation into the formulation factors affecting the precipitation of selenium in parenteral nutrition admixtures

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Despite several studies having been carried out in the past, selenium's stability in parenteral nutrition (PN) formulations is still not very well known. The potential to form precipitates in PN admixtures is a concern for PN manufacturers and healthcare professionals, therefore, this research project will be primarily focused on identifying any factors or components in PN formulations that could cause precipitation of selenium.

In this research project, 70 batches of PN samples were produced to test selenium's compatibility with 4 PN nutrients in different pH mediums. All batches were prepared in a laminar flow hood using aseptic techniques to minimize contamination. pH and turbidity measurements were undertaken every 24 hours across a total test

period of 3 days. Samples were also taken from these batches for visual inspection under fibre optic lighting to check whether precipitate presents.

The results indicated that both amino acid and ascorbic acid were able to cause selenium precipitation, while the former can cause precipitation across all pH environments, the latter in comparison, only caused precipitation in acidic pH conditions (pH3). It is believed that the amino acid cysteine is responsible for causing selenium precipitation, as it contains a sulfhydryl group¹ that possess strong reducing power, reducing sodium selenite to elemental selenium. Ascorbic acid on the other hand, is also a reducing agent that can reduce selenite to selenium as well.

It was also discovered that copper sulphate can prevent selenium precipitation even in the presence of amino acid and ascorbic acid across all pH environments, however due to the limited time available for this study, no further investigation could be carried out to identify the mechanism of reaction involved. Nevertheless, this finding could still be use as a starting point for any future work looking into such an issue.

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Evaluating the TEAD transcription factor in breast cancer

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In oestrogen receptor (ER) positive breast cancers, endocrine therapy is a major treatment, particularly for luminal A (ER+/HER2-) disease, but unfortunately relapse often occurs due to acquired resistance. Mechanisms of resistance are poorly-characterised, however VGLL1 is deregulated in luminal A-derived models where prolonged anti-hormones have promoted resistance and ER loss.¹ The mechanism of VGLL1 signalling is unexplored in endocrine resistance, but it is a co-activator for TEAD transcription factor which is probably present in breast cancer.^{2,3} This project aimed to evaluate TEAD in clinical breast cancer and in luminal A-derived models to establish any link with VGLL1, ER status or endocrine resistance.

An immunohistochemical (IHC) assay was optimised using pH6 pressure cook retrieval and pan-TEAD antibody to detect TEAD protein localisation. It was applied to clinical breast cancer samples (n=24) and T47D-derived models with acquired resistance to different anti-hormones, H-Scored and analysed versus ER and VGLL1 status. MRNA analysis, using microarray data, investigated individual TEAD family members in relation to clinical endocrine outcome and in resistant models versus their responsive parental T47D cells.

TEAD protein was nuclear in clinical breast tumours and in resistant and responsive models irrespective of ER or VGLL1 status. MRNA analysis in an endocrine treated luminal A breast cancer microarray dataset found increased TEAD1 associated with a shorter relapse time, and TEAD 2 to better prognosis. TEAD1 mRNA was upregulated and TEAD2 downregulated in ER- acquired resistance models.

TEAD may play a role in VGLL1 signalling in breast cancer, but could also interplay with other co-activators⁴. It likely contributes in ER+ and ER- endocrine resistance as well as responsive breast cancer. TEAD1 seems more important in endocrine resistance, whereas TEAD2 is implicated in endocrine response. Future studies should include consolidating the importance of these TEADs in a larger clinical series with outcome data.

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Evaluation of a community pharmacy-based asthma care plan

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Inhaler devices are mainly used by asthma patients to treat their medical condition. However, poor inhaler technique is still prevalent in about 94% of the asthma population.¹ Errors caused when using these devices will reduce the deposition of drugs deep in the lungs, meaning they will be less effective.²

The study evaluated patients' asthma control using an asthma control survey (ACS) based on a validated asthma control test (ACT) questionnaire. Participants' demographics were obtained. Their inhaler technique was assessed and lung function were measured using a Vitalograph AIMTM device and a Vitalograph ALPHATM spirometer respectively.^{3,4} The data collected was recorded in excel anonymously and analysed using GraphPad Prism 7. Mann-Whitney U test and Kruskal-Wallis test are used to identify any significant results obtained from the study. Results are significant if $p < 0.05$.

The results of this study indicates that a large population of the asthma patients (42%) have uncontrolled asthma as shown from their asthma control survey score. Smoking has a significant effect on patients' asthma control with 67% of smokers having uncontrolled asthma compared to non-smokers (38%). Patients using DPI also have a significantly better inhaler technique compared to those using MDI with a failure rate of only 8% for DPI users. For MDI users prescribed with a spacer, their inhaler technique is better compared to those using MDI alone. Majority of the inhaler technique were shown by nurses and GP, with only 4% being shown by pharmacists.

Poor asthma control is evident in most of the patients from the study and the main factor is poor inhaler technique. The involvement of pharmacists in advising patients on their inhaler technique is still trivial compared to nurses and GP. Their role in actively training patients should be maximized in a community pharmacy setting.

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Synthesis of deshydroxy androgen receptor antagonists for potential prostate cancer therapy

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Prostate cancer is the most common form of cancer for men in the UK and is also the second most common form of cancer for adults in the UK.¹ The androgen receptor (AR) plays a major role in promoting prostate cancer growth and has been the target of non-steroidal androgen receptor antagonists (NSAA) in the treatment of prostate cancer. Bicalutamide is advantageous over other NSAAs due to its lack of central side effects.² However, bicalutamide resistance limits its use to short term treatment of prostate cancer.^{3,4} This project aims to synthesise novel deshydroxy derivatives of bicalutamide with bulky substituents on the B ring as new AR antagonists that can potentially overcome bicalutamide resistance.

The synthesis process involves three steps. The first is the formation of an amide between 4-amino-3-(trifluoromethyl)benzotrile and methacryloyl chloride. The next step involves the Michael addition of various thiophenols onto the amide from step 1 to form sulphide derivatives. The final step oxidizes the sulphide derivatives into sulphone derivatives, the final desired compounds. A homology model of the androgen receptor in its antagonistic state was generated to predict the antagonist activity of each compound synthesised.

All sulphide and sulphone derivatives were successfully synthesised but two of the sulphides were unable to be purified. Yields of the sulphides varied from 19% to 50% yield, while the yields of the sulphones varied

largely from 19% to 95% yield. The homology model also predicts that 6 out of 8 of the synthesised compounds would have good antagonist activities.

The successfully purified compounds will be sent for in vitro testing. Overall, the synthesis was successful and the three step synthesis process is industrially practical. Hence, these compounds can potentially be commercialised in the future should any of them pass clinical trials.

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Discovering the cellular location of STAT3 during mitosis

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STAT3 is a transcription factor that is constitutively activated in many cancers and has been linked with high-grade cancers and poor prognosis¹. Activation of STAT3 occurs at the beginning of mitosis and is independent of its transcriptional activities.² As unregulated mitosis is a hallmark of cancer and an important target for therapy, the aim of this study was to investigate the cellular location of STAT3 during mitosis. Previous studies have linked STAT3 activity to the functions of the cell cytoskeleton³, therefore our hypothesis was that STAT3 co-localises with tubulin during the different stages of mitosis.

Immunofluorescence microscopy was used to detect and image cellular components of MCF-7 breast cancer cells. Cells were treated with nocodazole to increase mitotic cell number and then removed to allow cell movement through the different stages of mitosis. Cellular components, including STAT3 and tubulin, were stained with antibodies to enable images to be taken of different stages of mitosis using a microscope.

Our results demonstrated that STAT3 was present in significantly higher levels in mitotic cells compared to non-mitotic cells and was present throughout all stages of mitosis. STAT3 appeared to co-localise with γ -tubulin during the different stages of mitosis. Furthermore, both proteins appeared to co-localise at the centrosomes during metaphase.

Our study has established that STAT3 is present at the beginning of mitosis and remains activated throughout mitosis. This suggests that STAT3 may play a key role in cell division, especially by association with γ -tubulin. We support further research to evaluate whether STAT3 could be a novel biomarker or a target for cancer diagnosis and therapy.

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An investigation into the prescribing of anxiolytic agents in care homes

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Residents of care homes are elderly and often receive several medications for multiple conditions. This polypharmacy, as well as changes in pharmacokinetics and pharmacodynamics, contribute to the increased likelihood of an adverse drug event occurring.^{1,2} Anxiolytics can be particularly problematic due to their side effects. Since anxiety is said to be the most prevalent psychiatric disorder³, the aim of this project is to look at the prevalence of anxiolytic prescribing within care homes. It forms part of a wider group analysis looking at the prescribing of other psychotropic agents, including antidepressants, antipsychotics and hypnotics.

Drug administration records were collected from twelve care homes across the South Wales region. The data was filtered to extract only that relevant to anxiolytic agents within a three month period. Descriptive analysis was carried out to examine the extent and nature of anxiolytic prescribing and to quantify the amount of prescribed dosing errors. A Pearson's Correlation statistical test was also carried out to identify whether a correlation existed between the prescribing of anxiolytic agents and the prescribing of other psychotropic agents.

14.1% (43 out of 304) of care home residents within the time frame were prescribed at least one anxiolytic agent, most of which were benzodiazepines (12%). This was not including a group of serotonin-manipulating agents that could have been used for either anxiety or depression. The majority (85%) of prescriptions were prescribed at the correct dose. The Pearson's Correlation test revealed that a strong positive relationship existed between the number of distinct anxiolytic prescriptions and the number of other psychotropic agent prescriptions.

Anxiolytic prescribing was widespread among residents and benzodiazepine use appeared high despite guidance against their use due to the associated risks.⁴ More consideration should be put into the prescribing process in order to optimise prescribing of anxiolytic agents in care homes.

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Evaluation of the Triage and Treat Service in community pharmacies within Hywel Dda University Health Board

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Hywel Dda University Health Board (H DUHB) created the Triage and Treat Service after two minor injury units in west Wales closed. The service aims to treat low-level injuries in a community pharmacy. It first piloted in 2014 and is now available in 16 pharmacies across Wales.¹

Objectives:

- To identify the number and type of Triage and Treat consultations provided in community pharmacies and the treatments given;
- To assess whether patients were satisfied with the service provided;
- To explore the perception and attitudes of the pharmacy team towards the service;
- To identify any suggestions for improvements of the service from the pharmacy teams' perspective.

The evaluation was performed in three phases. Two phases (phase one: type of consultations and treatment provided; phase three: patient feedback) consisted of descriptive analysis of data collected by H DUHB. Phase two comprised of semi-structured interviews with the pharmacy members, which were thematically analysed inductively and deductively.

From April 2015 to September 2016, 228 consultations were undertaken with 84% of patients receiving treatment within the pharmacy. More residents used the service than tourists with the most common age ranging between 66 – 80 years old. Feedback from participants interviewed (n=6) and patients (n=28) were positive. Two suggestions for improvements identified from the interviews were the need for additional training and enhanced advertising of the service.

The service has achieved its aim by successfully treating the majority of patients who have suffered minor injuries. As more pharmacies are commissioned to undertake this service and as the number of patients utilising the service increases, there is potential for this service to reduce admissions to Accident and Emergency (A&E). Suggestions for improvement include further training to enhance the pharmacists' confidence when treating through the Triage and Treat service and sustained advertising possibly through digital marketing schemes.

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Defining pre-clinical studies and critical quality attributes of solid and hollow microneedle devices

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Microneedles (MN) devices have received growing interest as a novel drug delivery system. This has driven manufacturers to fabricate a range of MN systems which have now reached clinical trials.¹ However, there is currently a lack of information and understanding regarding key microneedle (MN) device attributes and the quality control testing required throughout MN device production. This project aims to determine the pre-clinical tests and critical quality attributes for two specific types of devices, hollow and solid MNs.

A literature review examined pharmacopoeias, regulatory guidelines and published journal articles to gather information on MN device attributes, tests that have been used for micron-sized needles and also specifications that existed for comparable medical devices e.g. transdermal patches. The data was used to draft two tables that describe suggested (i) pre-clinical studies (PCS) and (ii) critical quality attributes (CQA) to be tested for clinical approval. Weekly meetings with the research team assisted iterative development of CQA tables prior to a meeting with an MHRA representative that was used to finalise data.

PCS tables included the following: Perforation Testing; 'ADME' studies; Fluid flow testing; In-vitro Penetration testing; Integrity of connections (Leakage) testing. CQA tables included the following: Sterility/Endotoxin levels/Particulate matter levels; Packaging sterility; Needle axial mechanical strength; Needle shear force resistance; Base plate strength; Needle geometry; Needle bore diameter; Array size and density; Integrity of connections; Needle blockage.

The project has successfully constructed a first draft of tables which categorise PCS and CQA testing for solid and hollow MN devices. Future work will share this with manufacturers, researchers and relevant regulatory bodies including the MHRA and FDA, with the aim of producing guidance that facilitates production of safe, efficacious and easily usable SMD and HMD in the forthcoming years.

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An investigation into the prescribing trends of antidepressant drugs in care homes

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There is much evidence of polypharmacy in care homes¹ and the high prevalence of depression²; antidepressant drugs are associated with dangerous adverse drug reactions³ and are open to abuse. This study aimed to evaluate the prescribing trends of antidepressants in care homes. This study is part of a wider study into psychotropic drug prescribing in care homes, also looking at antipsychotics, anxiolytics and hypnotics.

Data generated by an electronic dispensing system used in care homes was obtained. It detailed each drug admission and was filtered for relevant data on antidepressant prescribing. All antidepressant drugs which could be prescribed were searched for. This data was then manipulated using descriptive statistics, to show the number of prescriptions of different drugs and in different care homes. Doses prescribed were individually assessed to judge appropriateness based upon BNF guidelines. A Pearson correlation was carried out to judge whether or not a correlation was present between antidepressant prescribing and prescribing of the other psychotropic drug classes in care homes.

Prescribing in the data was generally good, with the majority of prescriptions at appropriate doses and of appropriate drugs. Polypharmacy was prevalent within the data. A strong correlation was found between the level of antidepressant prescribing in a care home and the level of prescribing of the other 3 psychotropic drug classes.

Depression in care homes is common; therefore the prescribing of drugs to treat depression is important. Prescribers are choosing mainly appropriate agents at appropriate doses. The correlation between psychotropic drugs may suggest a disparity in prescribing of psychotropic drugs as a whole between care homes. This study was held back by lack of data and the small sample size.

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The role of cluster pharmacists in pharmacovigilance

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An adverse drug reaction (ADR), is “a response to a medical product which is noxious and unintended”.¹ They are a burden patients’ health and well-being and a financial burden on the NHS. To identify and therefore prevent ADRs pharmacovigilance systems have been set up.² They utilise reports from health professionals obtained via the Yellow Card Scheme however currently less than 10% of ADRs are being reported.³ Welsh Health Boards set out to improve on the safe, effective and prudent use of medicines by recruiting cluster pharmacists.⁴ This project aims to explore how pharmacovigilance and ADR reporting currently fit into the cluster pharmacist role in order to identify potential future opportunities for increasing ADR reporting.

A qualitative approach was adopted. A semi-structured interview schedule consisting of both open and closed questions was designed. Ethical and Health Board approval was obtained. Non-probability, purposive sampling techniques were used to recruit participants. The interviews were conducted face-to-face or via telephone, audio-recorded with consent, and transcribed to give a full verbatim record. Inductive and deductive analysis methods was used to identify major themes.

Nine interviews were conducted. The major themes identified were: the role of the cluster pharmacist in primary care, WCPPE training session, the Yellow Card Scheme, Information Technology, reporting and responsibility, patient contact, experiences of ADRs, targets, obstacles to reporting, increasing awareness of reporting, cluster pharmacists as Yellow Card Champions and recommendations for the future.

The objectives were met and recommendations were made on how the role of the cluster pharmacist could be developed to increase reporting, and thus improve public health and ease the burden on the NHS. This project was the first to look at how cluster pharmacists fit into pharmacovigilance and ADR, the results will be of value to Yellow Card Centre Wales in developing ongoing initiatives to increase reporting rates.

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Potential role of BIN1 in Alzheimer’s disease: links with endocytosis

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A hallmark of Alzheimer’s disease (AD) is the build-up of extracellular, β -amyloid ($A\beta$)-containing, plaques¹. $A\beta$ is produced from amyloid precursor protein (APP) cleavage via the amyloidogenic pathway². This pathway internalises cell surface APP, predominantly via clathrin-mediated endocytosis (CME), before being cleaved by BACE1 to produce β -CTF. β -CTF is subsequently cleaved, producing $A\beta$ ². BIN1 has been identified as a key susceptibility gene implicated in AD and is known to be involved in CME³. Previous unpublished experiments showed β -CTF levels were increased in response to BIN1 depletion. We therefore decided to investigate the role of BIN1 in endocytosis at the blood-brain barrier (BBB), known to be disrupted in AD, to determine if this explained the changes in β -CTF⁴.

Levels of BIN1 were depleted in hCMEC/D3 cells (a BBB model) by transfection of siRNA targeting BIN1. Western blotting was used to detect any changes in expression levels of endocytic proteins implicated in CME,

clathrin-independent endocytosis (CIE) or APP processing. Results were analysed using Student's t-test. Distribution of specific proteins were visualised using immunocytochemistry.

BIN1 expression was successfully decreased ($91.6 \pm 4.2\%$, $p < 0.01$). In response to BIN1 depletion, no significant changes in CME-related proteins were seen but there was a significant increase in caveolin-2 expression ($68.4 \pm 19.8\%$, $p < 0.05$), involved in CIE. A trend in BACE1 levels suggested an increase in expression. Alterations were seen in the localisation of the late endosomal/lysosomal proteins, RAB9 and LAMP2b.

These findings suggest BIN1 depletion does not affect CME but instead may influence CIE and the late endosomal/lysosomal pathway. Alterations to these processes and the possible increased levels of BACE1 may have been responsible for the increased levels of β -CTF seen. Overall, this suggests BIN1 has an effect on endocytosis, which may alter the processing of APP, and has helped to further our understanding of the role of BIN1 in AD.

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Pharmacovigilance and ADR reporting in the cluster pharmacist role

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Research has revealed that ADRs are a problem within healthcare. ADRs can cause serious health complications leading to the hospitalisation of many patients and have an estimated annual cost of £466m.¹ Despite their prevalence, ADRs are under-reported to systems such as the Yellow Card Scheme (YCS).² The YCS has made many developments in its reporting systems to increase the number of ADR reports it receives and improve patient safety. In 2015, the Welsh Government developed the cluster pharmacist role to integrate into multidisciplinary teams seen in the primary healthcare setting.³ The following project aims to explore how pharmacovigilance and ADR reporting fits into the cluster pharmacist role, and thus identify opportunities to improve ADR reporting rates.

A qualitative approach was adopted to explore cluster pharmacists' perceptions of ADR reporting. A semi-structured topic guide was developed. Non-probability, purposive sampling was used to recruit participants. Face-to-face or telephone interviews were conducted and transcribed ad verbatim. Thematic analysis was used to identify major themes and sub-themes. Ethical approval and approval from Health Board Research and Development Departments was obtained.

Nine interviews were conducted; six face-to-face and three telephone interviews. Themes that emerged were like those found in previous research and comparable to Inman's seven deadly sins of reporting.⁴ Barriers to reporting included lack of time and uncertainty. However, the role is facilitating reporting with some cluster pharmacists reporting ADRs on behalf of GPs. Suggestions to increase reporting included further education of healthcare professionals to increase awareness and introducing pre-populated reports to reduce time taken to report.

This exploratory study found that cluster pharmacists are ideally placed for the recognition and reporting of ADRs. Although the research was with limited participants, many important themes emerged which will be valuable for the Yellow Card Scheme to improve reporting rates via the cluster pharmacist role.

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Is a binding isotherm really a general tool for comparing molecularly imprinted polymers?

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Molecular imprinted polymers (MIPs) are a synthetic approach trying to mimic natural selective molecular interactions¹. Still relatively early in their development, MIPs continue to stimulate considerable research interest but due to the significant differences in how performance is evaluated, inter-laboratory comparison is challenging.² Previous research by Castell³ attempted to unify research to aid comparison and facilitate progression within the field. A bound analyte per MIP molecule vs absolute free isotherm was proposed [3]. However, experimental data by Eppler⁴ suggested that these isotherms are mass-dependent. Consequently, different isotherms were produced for the same polymer, hindering comparison. Therefore, the primary aim of this project was to determine if theoretical consideration of binding kinetics could help explain these conflicting results.

A two-dimensional Monte Carlo (MC) model simulated different MIP/analyte concentrations to produce isotherms. Following this, MIP re-binding experiments were performed using propranolol imprinted p-MAA-co-DVB-co-EGDMA polymers. Two different polymer mass loadings were used. Both centrifuging and filtering methods were employed to isolate the supernatant and the resulting samples were analysed by measuring UV absorbance.

The computational modelling supported the originally proposed isotherm³ as no divergence was seen between different MIP concentrations. However, experimental data did not coincide with this as there was a clear divergence seen with an increased polymer mass, supportive of Eppler.⁴ The method used to produce the supernatant affected results; the filtering method showed a higher concentration of propranolol bound compared to centrifuging.

It is unclear as to why the computational results conflict with experimental data. Perhaps the polydiversity within real MIPs will change the binding kinetics. On the other hand, there is clear evidence to suggest that the way in which MIP re-binding studies are performed affects results obtained. Further research is needed to investigate these unanswered questions to unite research and facilitate advances in this exciting technology.

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Assessment of inhaler technique and asthma control in a community pharmacy setting

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Asthma is a debilitating condition, presently affecting 5.4 million people in the UK, 314,000 in Wales.¹ A recent survey by Asthma UK, found that around a third of asthma sufferers use inhalers ineffectively.¹ This study aims to contribute to the assessment of asthma control and inhaler technique.

Seven fourth-year students collected data over 4 weeks in an allocated community pharmacy. Following consent, the data collection involved a modified ACT (named an asthma control survey (ACS)), questions about their inhalers and who had shown them inhaler technique, an AIMS test (inhaler technique) and finally a Spirometry test.

According to the ACS 43% of participants had uncontrolled asthma over the past four weeks. Participants using MDIs showed poorer inhaler technique, compared with participants using DPIs. Better inhaler technique was observed when using a spacer than using MDI alone. There were no statistical differences in the quality of inhaler technique for patients trained by a nurse, GP or pharmacist. Only a small number of participants had been shown by a pharmacist (2%). 56% of participants who smoke (n=27) had uncontrolled asthma compared to only 38% of participants who are non-smokers (n=97). 17 out of 145 participants had been

admitted to hospital this year due to their asthma. 2 of these participants had never been shown how to use their inhalers, and both of them failed the AIMS test.

The main findings were that asthma is uncontrolled in a large proportion of asthma patients and that inhaler technique is generally poor. These findings highlight the need for healthcare professionals to prioritize the education of asthma patients about their condition and its treatment to reduce the high rates of morbidity and mortality. There is potential for pharmacists to be more involved with this as they are conveniently located, with regular contact with patients.^{2,3}

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The evaluation of the Triage and Treat service in community pharmacies in the Hywel Dda University Health Board

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Two Minor Injury Units in Tenby and Pembrokeshire were closed down due to lack of funding and staff shortage.¹ This led to the establishment of the Triage and Treat service within Community Pharmacies in the area. The service aims to provide the treatment of low level injuries in pharmacies, close to the patient home, to take pressure off other local health care services. The project's aim was to evaluate the Triage and Treat service. The objectives were to identify the number of patients seen by the Triage and Treat service between April 2015 and September 2016, explore the views of the pharmacy team providing the service and to assess patient feedback.

The evaluation took place in 3 phases, a quantitative analysis of claim forms used to document patient information, qualitative analysis of interviews with pharmacy staff that ran the service and an analysis of patient feedback forms.

The results for phase 1 show that the service seems to be increasing in popularity as more patients used the service in the 6 months between March and September 2016 than in the previous 12 months. Phase 2 interviews showed that a lot of the pharmacists found running the service satisfying and beneficial to the community, but limitations were identified in training and advertising. The majority of information analysed on patient feedback forms was positive.

Triage and Treat service has shown that it relieves pressure on local healthcare services and fulfils the aim of the Royal Pharmaceutical Society to use the pharmacy teams full potential.² There is the need to address the advertising necessary to increase awareness of the service and the addition of a refresher-training course for pharmacy staff, but overall the service has been well received in the pharmacies where it is established.

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Investigating local infiltration analgesia in total knee arthroplasty

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Local Infiltration Analgesia (LIA), a minimally invasive intraoperative technique used to provide post-operative analgesia after Total knee Arthroplasty (TKA), involves infiltrating the surgical site with local anaesthetic (LA) alongside other agents.¹ It is important that patients receive sufficient analgesia postoperatively, increasing comfort, aiding earlier mobilisation and shortening recovery time.² This conforms to the Enhanced Recovery After Surgery (ERAS) programme, improving patient satisfaction and reducing costs to the NHS.³ Although commonly used, there is no ready-to-use gold standard LIA formulation. LIA has no standardised protocols for

its preparation or administration when prepared locally prior to use. Therefore calculation errors, contamination and the production of an unstable LIA mixture may occur. Attributable to this, patients are subjected to potential avoidable risks;⁴ a ready-to-use commercial product would reduce this. The aim of this project is to investigate current practices to determine the optimal LIA formulation and the potential of a commercially available, ready-to-use LIA formulation.

Current literature was reviewed investigating LIA practices. The previous questionnaire (2015/16) underwent minor modifications before ethical approval was granted. Data collection was gathered from NHS and private UK hospitals via an online questionnaire disseminated by e-mail, including an invitation letter. Participants were approached through hospital-listed contacts, ERAS conference and via the Snowballing technique.

Out of 48 responses the most common participants were orthopaedic surgeons and anaesthetists. 95.7% of respondents used LIA. Twenty formulae were reported, the most common being levobupivacaine and adrenaline (16.7%). Most LIA mixtures were prepared on site by nurses (59.1%). SPSS statistical analysis deemed the results statistically insignificant.

Professionals preparing LIA mixtures require training to ensure aseptic techniques are utilised. There is an evident gap in the market for a pre-prepared LIA mixture, however research on a larger scale is required to determine the ideal, rationalised combination of ingredients. A ready-to-use product would reduce the associated risks, ensuring patient safety.

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Synthesis of novel oroidin analogues and their antimicrobial activity

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Antimicrobial resistance is an increasing health crisis which can be prevented by expanding the number of novel antibiotics being developed.¹ One area of interest is the natural product, oroidin — a secondary metabolite of the marine sponge, *Agelas oroides*, first isolated in 1971.² The aim of this project was to synthesize novel oroidin analogues in a two-step process. The newly synthesized compounds were then tested against two gram positive (MSSA and MRSA) and two gram negative bacteria (*E.coli* and *P. aeruginosa*).

The first step in the synthesis was to produce the pyrrole-unsubstituted compounds by reacting various amines with 2-(trichloro)acetylpyrrole in DMF. The second step consisted of brominating two products, using NBS, in order to make them more oroidin-like. These compounds were tested for antimicrobial activity using the disk diffusion method. The zones of inhibition were measured and recorded.

¹H NMR and mass spectrometry data showed that 6 novel compounds were synthesised (four unsubstituted and two brominated compounds). The zones of inhibition for each compound show very small or no activity against one or more bacteria. The largest activity recorded was (7) against MRSA. However, there are several limitations which make these results less reliable.³

(5) produced the highest yield of 80% when using acetonitrile as the solvent. Therefore, a future avenue to explore would be to use CH₃CN instead of DMF for the lowest yielding reactions. Another future route would be to improve the methods of analysis so its possible to identify where exactly on the molecule the bromines lie. Because of the limitations of the antimicrobial test, it would be good to use wells diffusion to test these compounds further.⁴

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The reconstitution of the anthrax toxin pore (PA63) into droplet interface bilayers

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Membrane proteins such as the anthrax toxin pore (PA63) are challenging to study due to their inherent instability. The development of new methods is required to allow research into membrane proteins to become simpler and more cost-effective. Droplet interface bilayers (DIBs) are an in-vitro mimic of the cell membrane.¹ By demonstrating that proteins can be reconstituted into DIBs will provide a new, more efficient way to study membrane proteins. The aim of this study was to establish a method for the reconstitution of the PA63 pore into a DIB and to characterise the behaviour of the pore within the bilayer. Pore blocking agents were also investigated.

DIBs were formed by submerging two aqueous droplets on electrodes in an oil-lipid mixture. The droplets acquired a lipid monolayer and when the droplets were brought into contact a bilayer was formed.^{1,2} Membrane proteins dispersed within the droplets incorporated into the bilayer and when a potential was applied the current flowing through any pores in the bilayer could be measured.² Visual inspection of the current traces generated allowed pore insertion and pore blocking events to be identified.

Reconstitution of the PA63 pore into a DIB was achieved using a protein preparation concentration of 50%, with potassium chloride buffer in both droplets and a droplet size of 0.2µl at pH 5.5. The current increase on pore insertion was small; 0.8pA which reflected the narrow diameter of the pore channel. The amount of time the pore spent in an open state was short; on average 2.8 seconds, this was likely to be due to LF; another component of anthrax toxin which temporarily blocks the pore.³ A pore blocking agent; fluphenazine was tested but the results were inconclusive. Unexpectedly, fluphenazine appeared to interact with the bilayer in the presence of certain lipids.

This project demonstrates the reconstitution of functional PA63 into DIBs. This success should allow research into this membrane protein system to become more efficient. Further investigations into fluphenazine as a pore blocking agent are recommended.

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Bacterial adhesion between dental biomaterials and relevant gram-positive and gram-negative bacteria: influence of surface roughness and material characteristics

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In the year 2015, 10,000 dental implant procedures took place in the lower jaw of patients in the UK. ¹ A report found that 10% of patients with implants in Sweden had developed peri-implantitis², a bacterial infection that leads to loss of bone from the jaw which supports the implant. Additionally, the NHS dental survey found that 85% patients interviewed, had a dental restoration procedure carried out.³ Out of these patients, 26% had secondary decay or an unsound restoration.³

The aim of this study was to investigate which materials exhibited the least levels of bacterial adhesion and the influence of material roughness on bacterial adhesion. Elastic moduli, Poisson's Ratio and Surface Energy values was gathered for three implant materials (nickel chromium, tantalum and titanium) and two dental cements (Polymethyl Methacrylate (PMMA) and zinc phosphate). The same values were obtained for bacteria which often cause oral infections (*Actinobacillus actinomycetemcomitans*, *Veillonella parvula*, *Staphylococcus aureus*, *Streptococcus mutans* and *Streptococcus salivarius*). This data was then entered into a previously developed algorithm based on the Johnson-Kendall-Roberts (JKR) model of adhesion.⁴ This calculated the

force of adhesion of bacteria to each material. The algorithm was then altered to change the roughness of nickel chromium. This was then run against *S salivarius* and *S aureus*.

Zinc phosphate displayed the highest levels of adhesion to all bacteria. *S salivarius* was the most adhesive bacteria. PMMA was the least adhesive of all materials. When surface roughness of nickel chromium was increased, adhesive force increased significantly from 9.60 μ N to 18.87 μ N.

Zinc phosphate and PMMA were the most and least adhesive materials respectively. But one major limitation with the JKR model is the exclusion of considering non-contact forces. Further studies using the Derjaguin-Muller-Toparov model would take into account non-contact forces into adhesive force calculations.

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Measuring the interaction of a short chain polymyxin derivative with lipopolysaccharide

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Lipopolysaccharide (LPS) is a Gram-negative bacterial endotoxin that is ubiquitously associated with sepsis, a process that can cause multi organ failure and death.¹ Polymyxin antibiotics are able to bind LPS with high affinity, and are therefore useful in the treatment of Gram-negative infections², however their use has been limited by associated neuro and nephro toxicity. This toxicity is believed to be a consequence of the N-terminal acyl chain of the molecule³, and so investigations into N-terminal modifications to find a less toxic alternative are popular. The aim of this study was to evaluate the interaction of a short chain polymyxin B (scPmB) derivative with LPS, with comparison to polymyxin B (PmB).

Electrochemical impedance spectroscopy (EIS) was used to measure the interaction. To develop a stable LPS functionalised electrode, calcium was used to bridge the LPS molecules. LPS monolayers were challenged with increasing concentrations of polymyxin derivative, whilst the impedance of the system was monitored. R_{ct} values were calculated from Nyquist plots using an equivalent circuit model. Average ΔR_{ct} values were used to correlate changes in impedance against concentration.

Short chain polymyxin B interacted well with LPS, showing relatively higher changes in R_{ct} at all concentrations when compared to polymyxin B. Challenge with conventional polymyxin B resulted in breakdown of the LPS monolayer at low concentrations, which was only observed with scPmB at higher concentrations.

Degradation of the immobilised LPS monolayer will have affected interaction results, particularly for polymyxin B. When comparing the interaction results from this study this should be considered. The LPS immobilised electrode showed potential for measuring interaction but requires optimisation. ScPmB showed promising interaction with LPS, and is an exciting polymyxin derivative requiring more investigation into antibacterial activity, toxicity or use in sensing.

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Evaluation of a community pharmacy-based asthma care plan

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Asthma is an inflammatory lung disease. Its high prevalence leads to long term morbidity and preventable mortality rates.¹ Some asthma-associated mortality rates are due to poor asthma control.¹ Factors shown to facilitate poor asthma control are: low patient adherence to therapy, poor inhaler technique, a lack of education and knowledge about the long term management of the disease.² The aim of this study was to measure and assess the level of asthma control and inhaler technique within patients, together with factors that are influential to this.

A consultation using a semi-structured interview approach was carried out with each patient, consisting of: assessing the level of asthma control via an asthma control survey (ACS) and assessing inhaler technique performance via an Aerosol Inhaled Monitor (AIM) device. Quantitative data was analysed with Prism. Kruskal-Wallis and Mann-Whitney U statistical tests were used for non-parametric data.

Altogether, 145 patients were recruited. A high rate of uncontrolled asthma control was found, just under half (43%) of the study population failed the ACS. This was amplified by 42% of patients who had been either hospitalised or had received oral steroids for their asthma. Patients were more likely to use metered dose Inhalers (MDIs) incorrectly (56%) compared to only 4% who used their dry powder inhalers (DPIs) incorrectly. Inhaler technique was found to affect asthma control. Factors influencing inhaler technique were: geographical location of pharmacies and whether patients had been shown how to use their inhalers.

Using DPIs instead of MDIs could be a solution in overcoming MDI misuse, but factors such as inspiratory flow rate and cost would need to be considered.³ The difference of inhaler technique performance found in localities suggests that patients are not receiving consistent training from healthcare professionals. Asthmatic patients require more support to achieve better asthma control.

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What impact did the 'Communicating for Success' training have on pharmacy professionals' abilities to communicate more effectively in practise?

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The role of the pharmacy professional is rapidly evolving, requiring professionals to communicate in new ways, to a more diverse audience. The 'Communicating for Success' workshop was designed to improve all aspects of communication and to equip pharmacy professionals with enhanced presentation skills that would improve the quality of their communication.¹ The aim of this study was to evaluate the impact that the workshop had on pharmacy professionals' abilities to communicate more effectively in practise.

Participants who had attended this training programme were invited to participate in the study (n=23) via email. Semi-structured telephone interviews were conducted (n=8), recorded then transcribed ad verbatim. The qualitative data was analysed using deductive thematic analysis. Ethical approval was obtained from the school's research and ethics committee. A response rate of 34.8% was achieved.

Overwhelmingly, every respondent now incorporates more visual aids and less text into their presentations, as research has strongly suggested that the use of visual aids increase the audience's retention of the principal message, [2] which was arguably the key message of the training day. Another key finding was the storytelling technique; with majority of respondents now using this technique when presenting. Every respondent unanimously agreed that the workshop was highly beneficial in providing skills to make presentations more engaging, yet a few of the respondents still said that they were partially or not confident at all in presenting to an audience.

The 'Communicating for Success' workshop was useful in teaching skills that enhance the quality of communication and presentations. As more pharmacy professionals routinely deliver presentations, such as primary care pharmacists, this workshop has a unique place in pharmacy and should therefore be continued in the future.

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Welsh language use within community pharmacy services: pharmacists' perspectives

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19% of the population in Wales are Welsh speakers.¹ In 2011, the Welsh language (Wales) measure was introduced to promote the use of the Welsh language and established the role of the Welsh Commissioner.² The results of the commissioner's first inquiry showed that only 29% of fluent Welsh speakers had their last conversation with a pharmacist in Welsh.³ In response to this, new questions have been added to the National Electronic Claims and Audit Forms (NECAF) in community pharmacies to track the utilisation of Welsh within pharmacy services. Good communication with patients is a key part of a pharmacists' role as set out in the standards of conduct, ethics and performance.⁴ The aim of this study was to explore the views of pharmacists about Welsh language medium provision of community pharmacy services.

Qualitative research methods were used and ethical approval was obtained. Six semi-structured interviews were conducted. Pharmacists were sampled from the data submitted to NECAF using purposive and convenience methods. A topic guide was devised and was used in interviews following piloting. Consent was obtained from participants following distribution of a participation information sheet. Interviews were transcribed verbatim, coded manually and analysed thematically.

Four themes were identified: Pharmacists' awareness, pharmacists' willingness, technology and barriers to services. Interviewees felt confident in their ability to conduct Welsh medium service provision, but suggested that a lack of confidence could be a barrier to more Welsh language pharmacy services overall. All pharmacists interviewed agreed that further training would be beneficial. Pharmacists highlighted the benefits of Welsh language services to patients. Not one service was perceived to be easier to conduct than another through the medium of Welsh. The new questions on NECAF did not seem to encourage pharmacists to conduct services in Welsh.

Several areas for improvement were identified for future including the increased availability of resources and further training opportunities. Further evaluation of the data submitted to NECAF should be considered in future.

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Design and synthesis of novel natural product derivatives from a daffodil source

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Narciclasine activates fibres in glioblastoma multiforme cells, significantly increasing human survival in glioblastoma preclinical models.¹ BioExtractions Wales Limited provided a 5g sample of waste from galantamine production, thought to contain ~80% narciclasine. The aim was to isolate the samples' main

constituent, and from this design and semi-synthesis a novel derivative that can penetrate the blood-brain barrier (BBB) and treat glioma.

Crude sample isolation, via base extraction, revealed 46% galantamine rather than 80% narciclasine. Galantamine is a reversible acetylcholinesterase inhibitor used in the treatment of mild to moderate dementia in Alzheimer's disease. It has a low BBB penetration², and is poorly tolerated at high doses compared to other drugs in its class.³ A novel derivative was designed to optimize galantamine's characteristics, this was produced using a 2-step synthesis. First the oxidation of the secondary alcohol on galantamine to a ketone. Then reacting the ketone with O-benzyl hydroxylamine to form the novel derivative.

In step-one of synthesis manganese dioxide was unsuccessful as an oxidising agent for all equivalents and conditions. Potassium permanganate successfully oxidised galantamine to a ketone, however a higher quantity of ketone and epoxide product, than ketone product was produced. Yields 2% to <1% respectively. The second step had a 56% yield.

Diocetyl phthalate was found in step 2 of synthesis, it has the same molecular weight as the novel derivative. The novel derivative is distinguishable due to its polarity, and yield. The prevalence of Alzheimer's disease is increasing; the disease currently has no cure and the symptomatic therapies are far from flawless.⁴ A derivative of galantamine with increased BBB partitioning may aid drug delivery to the active site, thus improving tolerability. If a method with increased yield could be found for step one of synthesis this compound could be a step towards a promising lead compound.

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Exosomes: discovering new insights into their definition, characterisation, biological function and therapeutic potential

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Exosomes are a product of the endocytic pathway and can be loosely defined as 'small membrane vesicles of endocytic origin that are released into the extracellular environment on fusion of multivesicular bodies (MVB) with the plasma membrane'.¹ The structure of an exosome is 'limited by a lipid bilayer' and they are known to contain certain components² such as proteins. Since their first discovery, in the early 1980's, they have also been discovered to contain functioning messenger RNAs (mRNAs) and micro RNAs (miRNAs) and are believed to be powerful mediators of cell-to-cell communication.³ 'Exosome' is a term often used to discuss extracellular structures released by cells, but its actual meaning is often interpreted differently by different researchers.⁴ Other extracellular vesicles include microvesicles and apoptotic blebs. This study was designed to investigate how exosome research has evolved since they were first discovered, how they are isolated and characterised and discover proteins commonly enriched on exosomes.

A thorough literature search was carried out to gather information about key exosome milestones, analyse publication dates of exosome research and discover data related to exosome characterisation. As well as conducting literature searches, discussions with exosome experts were also organised to aid objectives.

Exosome research is a rapidly expanding field and the definition of exosomes has evolved with time. Cancer is the leading field in terms of exosome research which is surprising as they are present in almost all cell types and eukaryotic fluids. There are currently many isolation and characterisation methods and this potentially poses a danger to the field if impure exosomes are used in studies. It was discovered that the three most common protein families enriched on exosomes are antigen presenting proteins, tetraspanins and annexin.

This study proposes that exosomes be referred to as nanovesicles, derived from late endosomes, loaded with various cargo, that are released into the extracellular space when multivesicular bodies fuse with the plasma membrane. In order to differentiate between other extracellular vesicles, five main factors; size, shape, density, sedimentation and biogenesis, should all be considered.

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The knowledge and views of pharmacy students on drugs in sport

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Doping is considered to be the use of prohibited drugs, prohibited methods, refusal to take a drug test or attempt to interfere with doping controls to improve results.¹ A lot of medication, including over the counter medicines, contain banned substances in sport. Pharmacists should be aware of this and be able to give advice to patients who participate in sport. The main aim of this study was designed to explore the knowledge and views of pharmacy students at UK universities towards the use of drugs in sport.

A cross sectional survey was conducted through Cardiff University Pharmacy School. The questionnaire used was adapted, designed and validated to be distributed to all undergraduate students. The questions were split into four sections covering the knowledge on doping, views on healthcare professionals in sports and sports pharmacy content within the MPharm curricula. Also, twenty-nine pharmacy schools across the UK were approached to acquire information about the content regarding drugs in sports within their MPharm course.

196 responses were received across all 4 years of the course and coded appropriately to be entered in to IBM SPSS to be analysed. 90% of students supported the banning of drugs in sport. The majority of students knew the legal status of the drugs in sport but some gaps were observed when asked about the legality of the use of prescription medications insulin and codeine.² 82% of respondents thought that healthcare professionals should be the most likely used source of information for safe and effective use of drugs in sport.

Most students had a basic level of knowledge though it wasn't entirely due to the training provided at university. Playing and watching sport had a significant correlation to the knowledge. WADA encourages more education for healthcare professionals through its code which lines up with the responses from students wanting more training.³ Overall, students need more training on this subject which could be provided through their MPharm course.

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Investigations into the physical stability of lipid emulsions in multi-layered mini bags compared to plastic syringes over an extended storage period

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Parenteral nutrition (PN) lipid emulsions provide fundamental energy to neonatal patients¹ and are typically stored in 50ml plastic syringes allowing a 7-day shelf life. Following the deaths of three babies who received contaminated PN², Cardiff and Vale NHS Trust (C&V) are implementing rapid microbe testing that identifies contamination within 48 hours. To aid this implementation C&V want to store and deliver PN lipid emulsions from 50ml mini-bags that will extend the clinical shelf life and improve patient safety. The aim of this study was to generate physical stability data for two PN lipid emulsions (40ml Intralipid® or SMOFlipid® with 10ml reconstituted vitamins) in 125ml mini-bags (50ml unavailable) over 7 or 14 days at storage and administration temperatures, using 50ml syringes for comparison.

Visual inspection, pH, microscopy and laser diffraction were used to study the stability of samples on days 0, 7 and 14 (after storage at 2-8°C) and 8, 9, 15 and 16 (after storage at 35°C). Linear regression graphs with 95% confidence intervals were used to assess statistical differences in results.

Visual changes were redispersible and neither formulation or device dropped below the required pH range of 6 to 9.³ Laser diffraction results for both formulations and devices showed no globules greater than 0.34µm which is below the threshold of 5µm that defines stability.⁴ Microscopy results showed an unexpected decrease in globule size over time.

The majority of results showed no statistical differences in stability over time whilst results which indicated differences showed only marginal changes. Both formulations and devices remained physically stable at storage and administration temperatures over the time period tested. Future work on chemical stability is recommended as only physical stability was assessed. Additionally, in the interest of patient safety testing with the correct mini-bag size must happen before mini-bags use is initiated.

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Are long-term parenteral nutrition patients receiving enough selenium? A retrospective database analysis

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Parenteral nutrition (PN) provides nutrients intravenously to patients who are unable to digest or absorb sufficient nutrition.¹ Additrac[®] is the standard micronutrient preparation used in PN to provide the nine essential trace elements (TE).² Patients on long-term (LT) PN have demonstrated nutritional abnormalities, particularly the TE selenium.³ The project aim was to investigate the selenium dosing requirements for LT PN patients in correlation to patients' blood test (BT) results.

Patients on the intestinal failure clinic list at Cardiff and Vale were identified and data was collected from their PN prescriptions and BT results from January 2015 until October 2016. Each BT was matched with a prescription the patient had been receiving for at least 3 months. Matched data was separated into four main categories according to the inclusion of Additrac[®] and/or extra selenium. Selenium BT results and prescribed doses of selenium were reviewed and analysed.

As of each patients' latest prescription, 74% of patients did not receive Additrac[®]. As of each patients' latest selenium BT result, 23% were deficient. Upon further analysis, selenium BT results were deficient more frequently when Additrac[®] was included in the PN formulations than without. The dose of selenium when directly manipulated was almost twice the dose provided by Additrac[®] alone. However, the percentage of maximum dose of selenium prescribed was low in many cases.

High numbers of LT PN patients are not being prescribed Additrac[®] although the preparation is marketed to provide basal TE requirements. BT results were more frequently in range when doses were directly manipulated, suggesting clinician prescribed dosing is more efficient. Low percentage of maximum dose of selenium prescribed raises the question why the dose is not being increased particularly to those deficient, as physical stability is not the limitation.

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What are the attitudes of community pharmacists in Wales towards the provision of Welsh language resources?

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Language barriers can drastically affect a patient's ability to communicate and engage in their own health, it's therefore important that patients receive their care in their first language.¹ In 2012 the Welsh Government launched the strategic framework 'More than just words....' to improve the provision of the Welsh language in health and social care settings in Wales.² The Welsh Language Commissioner highlighted a lack of Welsh language resources in community pharmacies in her 'My Language, My Health' inquiry.³ Language barriers can be reduced through the use of bilingual resources, this has been demonstrated in previous studies concentrating on Hispanics in the USA.⁴ This study aims to investigate the attitudes of community pharmacists in Wales towards the provision of Welsh language resources.

Semi-structured interviews with a convenience sample of both Welsh speaking and non-Welsh speaking community pharmacists were conducted. Interviews were tape-recorded, transcribed verbatim, coded manually and analysed thematically.

Results from interviews (n=9) showed that there is currently a lack of Welsh language resources available in community pharmacy. Participants believed that Welsh language resources were important for the provision of the Welsh language to patients, especially in cases where the pharmacist did not speak Welsh. Participants believed that further developments in Welsh language resources were needed to further improve the provision to patients and ease future practice.

Welsh language resources are an important tool to increase patient engagement and understanding of their own health. Further development is necessary to increase resource availability and accessibility in order to improve patient care and meet the needs of Welsh-speaking patients.

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Investigating the antibacterial effect of red clover (*Trifolium pratense*) against methicillin-resistant *Staphylococcus aureus*

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The aim of this project was to determine whether red clover (*Trifolium pratense*) has antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and then isolate and identify the compounds responsible. MRSA poses a serious threat to health and it is estimated that people infected with MRSA are 64% more likely to die as a result than their counterparts with a non-resistant *Staphylococcus aureus* infection.

¹ Although research into red clover as an antibacterial against MRSA is currently limited, the utilisation of plants and other natural products in therapeutics has been successfully documented throughout history.²

Red clover flowers were tested following solvent extraction with methanol and hexane, respectively. Two commercial forms of red clover were also tested. An agar disc diffusion assay³ was employed to screen each preparation for inhibitory activity against MRSA. Separation and identification of antibacterial compounds was initiated using thin layer chromatography (TLC) and a bacterial overlay assay.⁴ Rf values of compounds responsible for antibacterial activity were noted and the antibacterial analytes identified then underwent LC-MS analysis to determine their molecular masses.

All preparations demonstrated antibacterial activity against MRSA, with the exception of commercial red clover capsules. The methanol extract of the flowers produced significantly (p<0.05) greater zones of inhibition in the

agar disc diffusion assay than the hexane extract, indicating that polar compounds are responsible for the majority of the antibacterial activity observed. Results of the LC-MS analysis indicated the presence of five principal peaks. Identification of the compounds responsible proved difficult within the timescale of this project.

Red clover extracts demonstrated inhibitory activity against MRSA and thus red clover has promise as a potential antibacterial against it. Additional studies need to be undertaken to identify the compounds responsible for the antibacterial activity and to explore the activity further.

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What impact did skills based training have on the pharmacy professionals' self-perceived behaviours in practice?

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Pharmacy professionals use leadership skills on a daily basis in practice. This does not just apply to managers or pharmacists, but to every member of the team. Effective leadership leads to better service. 'Effective governance, leadership and accountability in keeping with the size and complexity of the health service are essential for the sustainable delivery of safe, effective person-centred care.'¹ To assist with the development of leadership within pharmacy, the Wales Centre for Pharmacy Professional Education run a six-month Introduction to Leadership programme, where participants explore their strengths and weaknesses and aim to develop their leadership skills. This project aims to determine whether the leadership programme had an effect on the participants' behaviour in practice.

Data was collected previously and was retrospectively analysed. Inductive thematic analysis was used to analyse participant reflections and the online questionnaire and basic quantitative methods were used to analyse the self-ratings. Ethics approval was obtained.

86% of participants improved across the self-ratings after the programme and the online questionnaire and reflections on programme generated very positive outcomes, where participants gave various examples of how they have developed as professionals. Themes were identified including increased self-awareness, increased self-confidence, better delegation and better management skills.

The objectives of the project were met as participants showed a clear development of skills and gave examples of changes in their interaction with patients and colleagues after the programme. The findings can facilitate the development of future skills based training programmes and recommendations, such as feedback from peers on improvement of skills being included in programme results.

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Factors affecting copper and zinc precipitation in parenteral nutrition admixtures

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Parenteral nutrition (PN) is the administration of nutrients, electrolytes and fluids, intravenously to a patient. Trace elements (TE), are also required in PN formulations to avoid associated deficiencies.¹ Precipitation has been observed in PN and is a significant clinical and stability risk. TE's are being noted as being involved in precipitation, particularly copper. The aims of this study were to investigate what factors affected copper and zinc precipitation in PN formulations.

Eight separate 100ml batches, were aseptically prepared over the course of the experiment. Each batch had an overall variation regarding the TE present. Each batch was divided into 8 separate sub-batches which had variations in their components. These sub-batches contained a varying amino acid, glucose and TE component

in alternating ratios and combinations. These batches were tested for precipitation every 24 hours until 72 hours had passed. The tests comprised of three methods; visual inspection using fibre optic lights, turbidity with a Hach Turbidimeter and pH with an Orion pH meter.

The main results of this study of interest were batches 5, 6 and 7. Batches 5 and 6 (with increased copper and zinc respectively) batches showed signs of precipitation observable by visual inspection and also showed corresponding large increases in turbidity. Also batch 7 sub-batches displayed a very clear and selective pattern of precipitation observable by both visual inspection and turbidity with the increases in copper only batches clearly highlighting an interaction between cysteine i.e. Vaminolact® and copper.

Based on these results the hypothesis that the presence of Vaminolact®, compared to Aminoven 25®, would result in greater precipitation in PN was correct. These results are in accordance with previous studies indicating that cysteine-containing amino acid solutions, i.e. Vaminolact®, complexes with trace elements resulting in precipitation, and in particular copper.^{2,3}

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Perception of Parkinson's patients on the utility of iPad based apps to collect data in a Parkinson's clinic

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An iPad application has been developed for use in Parkinson's clinics to provide clinicians with additional information about their patients. Previous pilot research found that the application is easy to navigate and complete within clinic timeframes and age appears to be no barrier to using the device.¹ This project aims to gather the opinions of people with Parkinson's and their carers regarding the application in order to refine and develop it further.

Qualitative methods were deemed to be the most appropriate for this study.² Six focus groups were conducted in Parkinson's support groups across South Wales to elicit views of patients and carers about the use of the iPad application at Parkinson's clinics and identify potential developments. The focus groups were audio-recorded and transcribed. The qualitative data generated was analysed thematically by coding and linking excerpts to establish meaning. Ethics approval was obtained.

Dexterity and cognitive impairment were found to be potential issues for the patient group. Some were concerned about confidentiality of electronically-held data and the suitability of the waiting room environment to complete the application. The increased value of the application compared to paper was noted by participants and formatting alterations were suggested to improve its accessibility. The content of the application was well received but additional sections and remote access were suggested as possible features for development. Comparison to other studies in the field was not always possible due to a small literature base.

The project found generally positive views of the application but also highlighted several potential issues of practicality, especially for use in this particular patient group. Clarification of the proposed alterations is needed to ensure that the application is optimised for clinical use. Views of others who will be involved in the implementation of the application such as clinic staff should also be consulted.

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Statins and breast cancer

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Statins, typically indicated for hypercholesterolemia, may exert a novel anti-cancer effect in breast cancer¹ and clinical studies appear to support this with a retrospective study on 40,421 USA female veterans demonstrating a 51% risk reduction of breast cancer in women taking statins compared to those who didn't.² One potential mechanism for this effect is down regulation of the MAPK/ERK pathway.³ The aim of this project was to investigate whether Pravastatin can suppress growth of different types of breast cancer and how this may happen at a molecular level.

Five breast cancer cell models were used that collectively reflected the main clinical subtypes: MCF7 (ER+, 'luminal A'), BT474 (ER+/Her2+, 'luminal B'), SKBR4 (ER-/Her2+, 'Her2') and two cell lines modelling triple negative breast cancer (ER-/Her2-): MDAMB231 and MDAMB468. Initial Pravastatin dose response experiments using MTT assays were conducted to identify Pravastatin-sensitive cells for subsequent analysis (Ki67 proliferation marker expression and Western blotting). Where possible, statistical analysis was carried out using IBM SPSS Version 20.

MTT assays revealed that Pravastatin induced a significant decline in cell proliferation in MDA231 and MDA468 cells with the greatest effect in MDA231 cells; this was also reflected in the Ki67 staining. Western Blotting showed a decrease in pEGFR (Y845), tEGFR, pSTAT3 (Y705), pSRC (Y416) and tAkt but an increase in pMAPK (S202/T204) and tMAPK following three-day treatment with the statin. Little change was seen in EGFR, tEGFR, STAT3 and tAkt.

In conclusion, our data shows that Pravastatin suppresses the proliferative capacity of triple negative breast cancer, a particularly aggressive form of breast cancer, through a mechanism that may involve disruption of the MAPK/ERK signalling pathway. These data may thus suggest that repurposing of statins might represent a potential approach to the treatment of an aggressive form of breast cancer.

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The effect of triboelectric charging on drug release and deposition into the lung when an inhalation formulation is released from hard shell capsules using a dry powder inhaler

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Triboelectric charging occurs when two materials are rubbed together and can result in unsatisfactory aerodynamic performance properties of inhaled powders¹. This issue arises in transport, manufacturing and potentially during patient use.² The aim of this study is to investigate the effect of tribocharging on the lung deposition of inhalable formulations delivered via a dry powder inhaler (DPI) using two different capsule materials, hydroxypropyl methyl cellulose (HPMC) and gelatin.

A binary mixing method was used to create a drug-carrier formulation using an inhalation grade lactose and the micronised corticosteroid, budesonide. The two capsule materials were filled with either 20mg ± 5% lactose alone or the budesonide/lactose blended formulation. Half of the capsules were electrically charged using a tablet friability machine.² Capsules were loaded into an RS01 DPI, punctured and subjected to a flow rate of 60L/min for 4 seconds.³ Powder collection utilised a Next Generation Impactor (NGI) for budesonide formulation samples, or Dosage Unit Sampling Apparatus for lactose samples. The NGI plates were washed with 2 x 5mL of methanol and analysed using a UV-VIS spectrometer set at a 243nm wavelength to determine important aerosol characteristics.

Capsules filled with lactose showed tribocharging reduced the amount of powder released from gelatin capsules, although not from HPMC. The capsules filled with budesonide formulation showed no significant

differences in Emitted Dose. However, the Fine Particle Dose (FPD) and Fine Particle Fraction (FPF) results show HPMC capsules emit more fine particles than gelatin ($p=0.0028$).

HPMC capsules, whether they have undergone tribocharging or not, generate a higher FPD and FPF than gelatin capsules. This is more desirable for maximum pulmonary drug deposition.⁴ In conclusion, the powder contained within gelatin capsules is more adversely affected by tribocharging than the powder contained in HPMC capsules, therefore HPMC capsules would be the most suitable choice for DPI drug delivery.

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The role of the cluster pharmacist in pharmacovigilance

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Adverse Drug Reactions (ADRs) place a significant burden on the NHS costing around £466 million annually. Over 70% of ADRs are considered preventable.¹ ADRs are reported to the MHRA via the Yellow Card Scheme which suffers from underreporting as only 6% of ADRs are reported.² With over 40 primary care clusters within Wales currently employing a pharmacist³, cluster pharmacists are in a prime position to identify and report ADRs. This project aims to explore the perceptions and experiences of cluster pharmacists of the Yellow Card Scheme and the barriers to ADR reporting.

After obtaining ethical and Research and Development (R&D) approval, qualitative methods were used to explore the views of the cluster pharmacists in order to obtain rich, detailed data. A combination of open and closed questions were used during semi-structured interviews. The interviews were audio-recorded (with consent) and transcribed ad verbatim. They were then analysed using a combination of deductive and inductive thematic analysis.

A total of nine participants were interviewed: six face-to-face and three via the telephone. The themes were: the cluster pharmacist role, choosing to report an ADR, submitting a yellow card report, cluster pharmacists' views on the Yellow Card Scheme, the importance of education in pharmacovigilance, uncertainty over reporting an ADR, time as a hindrance to pharmacovigilance and improving communication to increase ADR reporting.

A lack of time and uncertainty over reporting ADRs have been identified as the main barriers to ADR reporting. Suggestions have been made with a view to overcoming these barriers and encouraging yellow card reporting and ultimately increasing patient safety. Suggestions included enabling ADR reporting directly from within a patient's record in GP practices and further educational interventions. The findings will be useful in developing both the Yellow Card Scheme and the cluster pharmacist role.

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Can microwaves be to increase the detection of viral RNA, as a step towards developing a rapid norovirus detector?

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Norovirus, known as the winter vomiting bug, is the most common cause of gastroenteritis in humans. Acute gastroenteritis (diarrhoea and vomiting) bears the second greatest burden of any infectious disease globally. It is increasingly a problem with an ageing population and a larger number of patients in healthcare settings.¹

There is no treatment or vaccine for norovirus, so rapid detection is key in reducing the spread and burden of disease caused by the virus. Microwave technology has been shown to be effective in increasing the amount of nucleic acid available for detection from *Clostridium difficile*, *Bacillus anthracis* and MRSA.^{2,3} It is hypothesised that this microwave technology can be applied to increase the amount of genetic material released from MS2, a norovirus substitute, as a step in developing a rapid, handheld norovirus detector. Microwaves can be pulsed at different percentage powers, called duty cycles (DC's). These microwaves are thought to disrupt membrane structures, and could be used to increase release contents from a sample. A key step in the development of this detector is determining the most effective duty cycle for the release of genetic material.

MS2 was cultured in *Escherichia coli* host, before being exposed to microwaves of varying duty cycles. Microwaved samples and a non-microwaved control were then quantified using fluorometry, a real time electrochemical Vantix assay and then examined under Scanning Electron Microscopy (SEM), to determine the RNA release after microwave treatment. Pure MS2 RNA was also exposed to microwaves to determine if microwave treatment effects RNA.

An increase in MS2 RNA recovery was seen at all duty cycles, compared to no microwave treatment. 10% duty cycle was determined to be the most effective for releasing RNA. A statistically significant reduction in particle size was seen under SEM after microwave treatment, suggesting that microwave treatment was responsible for a reduction in particle size.

This work has the potential to be clinically significant. Rapid detection is key in reducing the spread of and burden of disease caused by norovirus. This technology should be tested in faecal and vomit samples, as these are the most common samples for testing. Once verified, tests should be completed using norovirus, to confirm that this technology is clinically applicable.

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The development of a questionnaire to measure patient views on the redistribution of patient returned medication

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The Redistribution of Patient Returned Medication (ROPRM) is defined as the idea of dispensing medicines that have been previously returned by the patient and undergone the appropriate safety check requirements. Recent estimates state that across the UK, £400 million is being wasted on drug wastage.¹ Due to the current state of the NHS a funding gap of £30 billion must be closed by 2021² thus the ROPRM may be a good opportunity for making the NHS more sustainable. The aim of this project is to build and pilot a questionnaire to measure patient views on the ROPRM.

A thematic analysis was conducted from patient statements extracted from transcribed semi-structured interviews and public article discussions. From the data collected in the thematic analysis a questionnaire was then produced. The questionnaire mainly consisted of closed-questions and 5-point Likert scales in order to aid in improved response rates and allow the data to be easily quantitatively analyzed.³

From the thematic analysis 11 themes were identified and segregated within a table with their corresponding statements. The themes identified were: Waste, Packaging, Tampering, Storage, Form, Cross-Contamination, Cost, Consent, Opportunity for Fraud, Safety Check Requirements, and Educating the Public. Several drafts of the questionnaire were made and a final draft was also produced after feedback given from patients on their interpretation of the questionnaire had been received. Maximum variation sampling was used in piloting to allow the data produced from it to be more representative of the wider population.

This questionnaire is to be posted on Health Wise Wales in Spring 2017 for quantitative analysis of patient views. From patient comments, all patients seemed to agree that the cost of drug wastage is a tremendous waste however ROPRM may present too many barriers for it to be widely accepted as a potential solution.

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Discovering the cellular location of the zinc transporter ZIP7

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The zinc transporter ZIP7 (SLC39A7) is a member of the LIV-1 subfamily of zinc transporters and is currently only known to be on the endoplasmic reticulum (ER). ZIP7 mediated zinc release and ZIP7 overexpression has been associated with widespread phosphatase inhibition that is associated with aggressive forms of breast cancer.¹ Fluorescent dyes of ZIP7 show perinuclear staining which is unusual for an ER only protein. Although zinc is known to be found in abundance in the nucleus², currently no zinc transporters are known to be located in the inner nuclear membrane that is able to contribute to the nuclear pool of zinc. In this study, we aim to investigate if ZIP7 is able to access the inner nuclear membrane of MCF-7 cells.

Using fluorescent microscopy, we imaged ZIP7 alongside inner nuclear membrane proteins to discover if ZIP7 is localised in the inner nuclear membrane of MCF-7 cells.

We found evidence of association of ZIP7 and three proteins associated with the inner nuclear membrane: Lamin A/C, Lamin B and the Lamin B receptor.

These data suggests that ZIP7 has access to the inner nuclear membrane, though further studies are required to confirm it. The confirmation of the location of ZIP7 in the inner nuclear membrane will have implications for future research seeking to discover novel therapeutic strategies relevant to ZIP7's role in breast cancer.

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Evaluating the effect of moisture content on puncturing performance of gelatin capsules and inhalation grade hydroxypropyl methycellulose (HPMC) capsules used in dry powder inhalers

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Dry powder inhalers (DPIs) are designed to puncture hard shell capsule to release the drug. ¹ Gelatin capsules have been traditionally used in marketed DPI for many years² but it was reported that there have been an issues with brittleness of gelatin capsules stored in low humidity. HPMC is an alternative material that has better functional properties than gelatin when used in DPI.^{3,4} The aim of this study is to study the effect on puncture force of storing HPMC and gelatin capsules in a high humidity and comparing with those conditioned at a low and normal humidity.

A puncture testing method was used to generate force displacement curves for both HPMC capsules (Quali-V®-I) and gelatin capsules (Quali-G), which were conditioned in desiccators over saturated solutions of four different salts to modify the moisture content of the capsules. A single pin from a DPI was mounted in a material testing machine. HPMC and gelatin capsule samples were placed in a special capsule bush with the cap uppermost directly under the pin. Puncture tests were carried out and each puncture event was recorded as force displacement curve.

The results showed that the higher the moisture content, the lower the force required to puncture both gelatin and HPMC capsules. Gelatin capsules required higher puncture forces than HPMC capsules at four different humidities. Different capsule materials produced their own signature puncture profiles. Methodology which employed from previous study was proven to be robust as reproducible puncture profiles were produced in this study.⁴

In conclusion, moisture content of capsules at adverse storage conditions is the key influence of capsules physical properties (either too brittle or too soft). Puncturing performance of HPMC capsules is more stable over a range of storage conditions compared to gelatin capsules that are more affected by changes in their moisture content.

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Assessment of inhaler technique and implementation of an extended asthma care plan in a community pharmacy setting

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In the UK, respiratory diseases such as asthma are extremely common and increasing¹: one in eleven children and 1 in 12 adults is asthmatic.² Inhaled therapies are the most popular treatments for asthma sufferers. This study focuses on the impact of several factors, (age, gender, inhaler technique tuition, inhaler type, and smoking status) which are all claimed to influence inhaler technique and asthma control.

In an interviewer led consultation study, participants were asked to demonstrate their inhaler technique, using a Vitalograph AIM™ machine³, and also underwent asthma control and spirometry tests.

Participants (145) were recruited, and demonstrated a total of 201 inhaler techniques, (12 metered dose inhaler (MDI), 40 MDI plus spacer and 53 dry powder inhaler (DPI)). Results indicated that age was not a controlling factor for MDI inhaler technique. However for DPI, age appeared to have a marginal influence; younger age groups (<50 years) exhibited better technique compared to older participants (>50 years). Male participants expressed a marginally better technique compared to females for only MDIs. No difference was apparent when either gender used a DPI or a MDI plus spacer. No significant trend was observed for inhaler technique irrespective of which health care professional (nurse or GP) performed the tuition. Regarding the influence of inhaler type on inhaler technique, this study demonstrated that the use of DPIs outperformed both MDI and MDI plus spacer. However, the inclusion of a spacer to MDI significantly improved participant's inhaler technique. The influence of smoking status on asthma control indicated that the ACT score of non-smokers and ex-smoker were equivalent, whilst that for current smokers was significantly lower.

The key findings from this study is that inhaler type and smoking status are the most important influencing factors that determine good inhaler technique and asthma control.

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The best approach for WCPPE to deliver live CPD events in rural Wales

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Continuing Professional Development (CPD) ensures the ongoing competency of pharmacy professionals.¹ WCPPE (the Wales Centre for Pharmacy Professional Education) offer CPD events to pharmacists, pharmacy technicians, and pre-registration pharmacists.² 'Live' events include events like expert speaker presentations and service delivery events, as well as webinars, live streaming, and video conferences. In rural Wales (here defined as the Mid and West), attendance at these has been low.³ My research aim was to increase engagement of pharmacy professionals with them. Objectives involved discovery of preferences using a previously drafted questionnaire.

After obtaining ethical approval and piloting, the questionnaire was distributed to 575 pharmacists, pharmacy technicians and pre-registration pharmacists registered with WCPPE as living or practising in these areas. A

reminder email was distributed one week prior to the deadline. Non probability and convenience sampling was used and responses were collated using Microsoft Excel. SPSS was used to compare results by profession and health board.

The questionnaire achieved a 29% response rate. Analysis of the data and wider literature regarding the health system in Wales resulted in suggestions for WCPPE to: Pilot shorter and earlier evening events, host events in Llanelli and Builth Wells; Better communicate on how to access webinars, live streaming and video conferences (as well as the differences between them); Offer recordings for post-event and home access; Improve the design and navigation of the WCPPE website; Promote multidisciplinary, interprofessional and professionalism events through working with the government and local health boards.

WCPPE need to implement respondent preferences around event frequency duration, location, topic and delivery method to improve engagement of their pharmacy professionals.

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Oestrogen receptor downstream signalling differences between males and females with Alzheimer's Disease

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Apart from their influence in the reproductive system, recent studies document the neuroprotective effects of oestrogens from memory loss, cognitive decline and neurodegenerative diseases such as Alzheimer's disease (AD).¹ AD is characterised by the formation of insoluble amyloid- β peptide (A β) and neurofibrillary tangles (NFTs) composed phosphorylated tau.² Studies propose a link between the decline of oestrogen levels in post-menopausal women and the prevalence of AD as studies show that two-thirds of AD patients are women.³ The objective of this study was to explore the activity of protein-kinases involved in downstream oestrogen signalling in order to determine potential differences in oestrogen signalling between males and females with AD.

Western blotting was carried out to analyse the change in phosphorylation status of mitogen-activated protein kinase (MAPK), Protein Kinase B (AKT) and Glycogen synthase kinase 3 β (GSK3 β); proteins involved in oestrogen downstream signalling. Proteins were transferred onto a nitrocellulose membrane and detected using chemiluminescence. Light intensity from the chemiluminescence, relative to the amount of protein present in each sample, was quantified using image J software.

Data showed greater phosphorylation of MAPK, AKT and GSK3 β in male AD tissues relative to female AD tissues. Additionally data showed greater phosphorylation of MAPK, AKT and GSK3 β in male AD tissues relative to male Non-AD tissues. Results on the other hand showed less phosphorylation of MAPK, AKT and GSK3 β in female AD tissues relative to female Non-AD tissues.

Themes within the data suggest potential differences in oestrogen signalling between males and females. It is however premature to make any definitive claims of differences in oestrogen signalling between genders. As a result, further experiments must be performed to fully explore and understand oestrogen signalling in AD and how gender influences it's signalling.

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Investigating the sporicidal activity of blue light (401 nm) against clinical isolates of *Clostridium difficile*

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Clostridium difficile infection is the primary cause of antibiotic associated diarrhoea in the UK with each case costing the NHS an additional £4,000-£10,000.^{1,2} It has recently been reported that blue light can inactivate *C. difficile* spores³. The aims of this study were to determine the sensitivity of spores of two different strains of *C. difficile* (CD630 and R20291) which have been dried onto stainless steel discs to inactivation by blue light and to determine if the presence of organic material modelled by bovine serum albumin (BSA) influenced the sensitivity of the spores to the sporicidal activity of blue light.

Testing involved seeding spores onto a stainless steel disc then exposing them to blue light. As a control, spores were exposed to light and dark. At the time points 30, 60, 90, 120, 240 minutes a disc was attached to a 100g weight and pressed down onto a BHIS agar plate. These plates were incubated for 24 hours anaerobically and colony forming units present were counted. This was conducted for both strains both in the presence and absence of BSA.

A less than 1-log₁₀ reduction of spores was observed after 240 minutes of blue light exposure for both strains in the presence and absence of BSA. All results were not statistically different to the controls except for R20291 in the absence of BSA. A comparison of the two strains to blue light inactivation revealed a lack of difference. A comparison of the sensitivity of each strain to blue light in the presence and absence of BSA revealed that the presence of BSA inhibited spore inactivation.

These results suggest that this technology in its current configuration is ineffective against *C. difficile* spores. Further research is warranted in exploring the sporicidal activity of alternative wavelengths of blue light and optimisation of this technology.

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Invertebrate haemolymph as an untapped source of natural bioactive antimicrobial peptides to combat antimicrobial resistant (AMR) bacteria

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Antimicrobial resistance occurs when microorganisms are no longer susceptible to antimicrobials. It is estimated that by 2050, antimicrobial resistance could cost \$100 trillion globally and, deaths attributable to resistance could reach 10 million per year.¹ Therefore it is crucial to develop alternative antimicrobial treatments to prevent a global relapse into a pre-antibiotic era. In response to an immune challenge the *Manduca sexta* caterpillar releases antimicrobial peptides (AMPs) into its haemolymph (invertebrate blood stream).² Previous research has involved study of specific peptides³ whereas this study investigated the whole haemolymph extract upon challenge with a range of microorganisms. In this study we sought to determine if exposure of the caterpillar to clinically relevant organisms would stimulate the production of peptides with activity against the organisms themselves; *Clostridium difficile*, *Bacillus anthracis* SdT and Sterne, *Klebsiella pneumoniae* and *Escherichia coli*.

Groups of caterpillars were individually challenged with the above wild-type strains, and 9 naïve larvae served as the control. Their haemolymph was extracted 21 hours post-challenge and cross-tested against the panel of above bacteria in well diffusion assays (n=3). [4] A broth-microdilution assay of the active haemolymph against the affected strain (5 concentrations) was performed and absorbance recorded over 19 hours.⁴

Activity was not present in all diffusion assays with one exception; AMR resistant *K. pneumoniae*-induced haemolymph produced 2.3mm zones of inhibition (n=6) against *E. coli*. A reduction in *E. coli* growth (0 to 8 hours) was observed from results of the broth-microdilution assay. Furthermore, the growth reduction was

sustained at different cell concentrations, suggesting that haemolymph activity was not proportionally affected by the 10-fold increases in *E.coli* cells.

These results suggest that the haemolymph exhibits a bacteriostatic effect on *E. coli* and provides a basis for future investigations. The next step would be to isolate the bioactive peptide, and to determine the extent of the activity.

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Adhesive interactions between antimicrobial coatings and gram positive and gram negative bacteria: influence of surface roughness and material properties

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Healthcare associated infections (HAI) such as pneumonia are estimated to cost the NHS £1 billion a year.¹ The rise in these infections deem it necessary to investigate methods in preventing bacterial adhesion to hospital surfaces and so prevent the spread of pathogenic bacteria. This project investigates which antimicrobial coatings are most effective at preventing bacterial adhesion, biofilm formation and so spread of HAIs and whether material properties or surface roughness have an influence.

Six antimicrobial coatings were chosen; triclosan, zinc, silver, copper, polyethylene glycols (PEG) and diamond-like carbon films (DLC), to test against 3 gram positive (*S. aureus*, *S. epidermidis* and *S. salivarius*) and 3 gram negative bacteria (*E. coli*, *P. aeruginosa* and *A. baumannii*). A numerical procedure previously developed by Prokopovich, based on the Johnson-Kendall-Roberts multi-asperity adhesion model, was used to estimate adhesive forces between biomaterial-bacteria sets.² Biomaterial surface roughness was then altered to study its effect on adhesive interactions.

PEG was found to be the least adhesive biomaterial with a mean adhesive force of $4.14\text{mN} \pm 0.08$ against all bacteria. Copper was the most adhesive with a mean adhesive force of $66.96\text{mN} \pm 0.99$ against all bacteria. *A.baumannii* had low adhesion compared to the other bacteria, indicating its bacterial physico-chemical properties such as fibrillar appendages had a role. Asperity radius on the biomaterial surface was then narrowed to represent increasing surface roughness, which increased bacterial adhesion. However decreasing roughness didn't have any conclusive effect.

The most effective antimicrobial coatings use the antifouling method to prevent bacterial adhesion, therefore more work should be done investigating this mechanism.³ The representation of roughness used in this project is not a complete model of altering a rough surface. Future work should be done to see the effect changing asperity height or using an alternate adhesion model such as Derjaguin-Muller-Toporov would have on bacterial adhesion.

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Rivastigmine usage in Lewy body dementias

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Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are two different presentations of a single underlying disease process which both cause cognitive and motor impairments.¹ Dopaminergic

neuronal loss produces motor symptoms while reduced cholinergic transmission is the pivotal mechanism in cognitive dysfunction.^{1,2} Evidence suggests that cholinesterase inhibitors are an effective option for symptomatic treatment for dementia.^{2,3} The aim of this study was to explore the use and effectiveness of rivastigmine, a cholinesterase inhibitor, in PDD and DLB, as this is yet to be thoroughly investigated.⁴

A retrospective analysis was conducted using data from 'The Electronic Clinical Network Parkinson's Disease and Related Disorders Database' collected from patients attending two movement disorder clinics in South Wales. Prevalence of dementia, basic demographics and cognitive test scores were explored in relation to rivastigmine use.

This study included 364 patients, 79% PDD and 21% DLB. Both diseases were more prevalent in males. Most patients were currently taking rivastigmine with only 121 not taking a cholinesterase inhibitor. 24% of PDD patients were living in nursing homes compared to 33% in DLB. Of the patients living in their own homes, most were taking rivastigmine in both diseases, 58% and 79%. In both diseases mortality rates were lower in patients taking rivastigmine. Rivastigmine slowed cognitive deterioration in both diseases as more patients showed an increase or no change in Mini-Mental State Examination (MMSE) scores and fewer patients showed a decline if they were taking it. Patients who were taking rivastigmine also had more comments from consultants or carers that indicated an improvement in their condition.

Although patient numbers were small in some analyses, rivastigmine appeared to be linked with a reduction in cognitive decline and with improved performance of daily living activities. This may have contributed to a reduced need for residential care.

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Investigating the mechanical performance of capsules to be used in dry powder inhalers

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Gelatin (Quali-GTM) and HPMC (Quali-V® and Quali-V®-I) capsules are used in dry powder inhalers (DPIs) to deliver micronized drugs to the respiratory system. At low humidities, gelatin capsules become brittle, causing aerosolised fragments to be inhaled and irritate patients' throats when pierced.^{1,2} There are no pharmacopoeia tests designed specifically for the quality assurance of hard shell capsules for inhalation. This study aims to develop a simple compression test to assess the mechanical properties of hard shell capsules, to determine how humidity and formulation impact on capsule mechanical performance and to investigate capsule integrity during a simulated inhalation event from a DPI.

Compression tests were developed to assess the mechanical properties of Quali-GTM, Quali-V® and Quali-V®-I capsules stored at three different humidities. Capsules were compressed at a quasi-static speed, 10mm/min, with a flat metal compression plate and a force-displacement curve was generated (n=20). In a simulated inhalation event the studied capsules were pierced and rotated to predict capsule fragmentation during patient inhalation (n=10). The number of fragments generated in the event were visualised by light microscopy and manually counted and sized.

Force-displacement curves were a consistent shape for all capsule materials and at all studied humidities. Quali-GTM capsules required a statistically significant greater compression force than Quali-V® and Quali-V®-I capsules, which required compression forces of comparable magnitude. Compression forces increased for capsules stored at low humidity. In the inhalation event, Quali-V® and Quali-V®-I capsules showed minimal fragmentation. Quali-GTM capsules, however, fragmented extensively, with the degree of fragmentation increasing as humidity decreased.

Simple compression tests may be able to predict capsule integrity during inhalation and be employed as a valuable tool for quality assurance of hard shell capsules for DPIs. Further work is recommended to ascertain a definitive correlation between capsule compression forces and their inhalational integrity.

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CYP121 inhibitors as potential tuberculosis therapeutics

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Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (Mtb).¹ As TB is considered one of the deadliest diseases on the planet², a major concern is the rise in Mtb strains that are resistant to current therapies¹, therefore there is an urgent need to develop new drugs and to research novel targets within Mtb to control this disease. One such target is the cytochrome P450 enzyme, CYP121, which has shown promise as an anti-TB target. [3] The aim of this project was to design and synthesise molecules which act as CYP121 inhibitors, with the view that these molecules could then be developed into anti-TB drugs.

The molecular modelling programmes, MOE and LeadIT, were used to design potential inhibitors based on the structures of CYP121's natural substrate, dicycloyrosine, and the azole antifungals, clotrimazole and fluconazole. Docking studies were then conducted to evaluate which molecules best interacted with the haem group of CYP121, an action that is essential for inhibition to occur.³ The synthesis of these compounds was attempted in the laboratory using a four-step method comprising a Steiglich esterification, Grignard reaction, tosylate formation and nucleophilic substitution to obtain the final compound.

The docking studies revealed that the compounds where R= F or Br best interacted with the haem group. Difficulties with some reactions meant that both the synthesis method and desired final compound were amended to avoid a Grignard reaction. The revised method seemed promising at first, giving good yields (>50%). However, the final synthesis step did not yield the desired final compound.

No desired final compounds were successfully synthesised. An elimination reaction had occurred during the final synthesis step, producing an alkene as opposed to the desired imidazole. Attempts were made to refine the method to improve yields, however more work is required to generate a method that can reliably produce the desired final compound.

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Phenylalanyl-tRNA synthetase (PheRS) inhibitors as potential agents for the treatment of MRSA

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MRSA (methicillin resistant *Staphylococcus aureus*) is a multidrug resistant bacterium of growing clinical concern due to bacterial resistance to antibiotic treatments.¹ To combat this problem, new antibiotics need to be developed which have a novel mechanism of action.² An example of this, is the enzyme phenylalanyl-tRNA synthetase (PheRS). This target enzyme is vital for MRSA's survival³, and an inhibitor for this target could fulfil this need. Therefore the aim of this project is to design and synthesise a novel compound to competitively inhibit two sites, the phenylalanine and ATP sites, on the PheRS to provide a new treatment for MRSA.

A molecular modelling program was used to model the novel compounds with the PheRS enzyme. This was to determine the suitability of the compounds to bind to the active site of the PheRS. Four compounds were synthesised using a three step synthesis (a crossed aldol type reaction with Knoevenagel condensation (Doebner modification), an amide synthesis via TBTU/T₃P® coupling, and a Boc deprotection under acidic conditions). Intermediates and the final compounds were checked by TLC, ¹H NMR and ¹³C NMR to ensure the structures were correct, and purity was suitable. ¹H NMR, ¹³C NMR and melting points were used to characterise the compounds.

Three of the four compounds synthesised made it to the final compound. None of these was pure, and one was lost while attempting purification due to solubility issues. The results showed there were two stages which could be optimised, the coupling stage and the deprotection stage of the synthesis.

Alternative coupling reagents/methods and alternative deprotecting agents/conditions could be used for optimisation. The three step synthesis was not completely successful, however, with the modifications and optimisation, it is probable that pure final compounds could be achieved by this method.

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A study to explore and identify factors influencing motivation of final year Cardiff University students in relation to the assessments within the MPharm degree

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Motivation is “a reason or reasons for acting or behaving in a particular way”.¹ There is a vast amount of literature surrounding motivation, particularly in educational contexts, yet few studies focus on undergraduate pharmacy students. The Self Determination Theory describes two sources of motivation, intrinsic and extrinsic.² Motivation has been shown to positively influence academic performance therefore, understanding motivation may enable educators to facilitate positive learning behaviours.³ The aim of this study was to explore and identify factors influencing final year pharmacy students motivation, with regards to assessments within the MPharm at Cardiff School of Pharmacy and Pharmaceutical Sciences (CSPPS).

A qualitative, semi-structured approach was used. The researchers, including three final year pharmacy students and the project supervisor developed a topic guide having reviewed the relevant literature. Following ethical approval, participants were recruited via convenience and purposive sampling. Informed consent was obtained prior to participation. Three pilot interviews were undertaken although these were not included in the data analysis. One-to-one interviews were audio-recorded and transcribed verbatim. Transcripts were anonymised and analysed inductively using thematic analysis.⁴

Thirteen interviews were undertaken and seven themes were derived, namely “how the school helps the cohort prepare for assessments”, ‘impact of group assessments’, ‘influence of others’, ‘assessment contribution to the degree’, ‘fear of failure’, ‘assessment topic’ and ‘effect of feedback’.

This study found that students motivation was multifactorial. The factors vary and show overlap amongst students therefore, changing one aspect may improve motivation for some but not others. The findings have identified potential areas for improvement to maintain or enhance students motivation in assessments. As a result, a variety of recommendations have been put forward to CSPPS. Further research is needed into the motivation of MPharm students at other UK Pharmacy Schools.

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Amaryllidaceae alkaloids extraction from *Narcissus pseudonarcissus* cv. ‘Carlton’ and synthesis of novel galanthamine derivatives

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This project focuses on finding a suitable method to extract galanthamine and other Amaryllidaceae alkaloids from aerial parts of *Narcissus pseudonarcissus* cv. ‘Carlton’. Subsequent work focuses on the derivatization

of galanthamine at the hydroxyl group. Galanthamine has a low blood-to-brain ratio (<2)¹ therefore the aim of the derivative synthesis is to enhance brain penetration by increasing the lipophilicity and conjugating galanthamine with phenylalanine using the ethylamino group as a linker to make it a substrate of LAT1 for treatment of Alzheimer's disease.

Two methods were attempted for alkaloid extraction namely base extraction and non-base extraction. Saturated NaHCO₃ was used in base extraction before the solvent separation step. The organic layer was obtained, dried with a rotary evaporator and washed with diethyl ether to yield galanthamine. For non-base extraction, the crude sample was dissolved in methanol and compounds were separated via preparative TLC. All samples were analysed by ESI-MS and NMR for structure elucidation. Furthermore, the hydroxyl group was alkylated via SN₂ reaction. A series of test reactions with varying solvents and schemes were attempted to find the right conditions. ESI-MS would be the major analytical tool for compound identification.

Base-extraction was found to be the method that extracted more galanthamine (46% w/w) than non-base extraction (0.98%). Galanthamine was the major alkaloid extracted. Other alkaloids, possibly roserine, narcidine or 9-O-methylpseudodycorine², were observed on ESI-MS, albeit in low intensity. The methyl and cycloalkyl derivatives were successfully synthesised although with poor yields (12% and 18% respectively). The reactions to conjugate galanthamine with phenylalanine were not accomplished.

The base is a key substance to achieve higher yield of galanthamine.³ The method used was relatively simple too. Furthermore, this project illustrated the challenge in modifying hydroxyl group of galanthamine that possibly signify its relative inertness.⁴ However, these derivatives are novel hence further investigations are worthwhile.

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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:

Synthesis of new Bcl-3 inhibitors as potential anti-metastatic agents

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Potassium permanganate as a treatment of chronically infected wounds

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Demonstrating the presence of dry bacterial biofilms on healthcare surfaces

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Developing optical assays for application in artificial bilayers

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Efficacy of disinfectant solutions to inhibit recovery and transfer of *Staphylococcus aureus* NCIMB 9518 dry biofilms

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Demonstrating the presence of dry bacterial biofilms on healthcare surfaces

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Investigating the susceptibility of dry bacterial biofilm to disinfection

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The synthesis of novel Bcl-3 inhibitors: A potential therapy for metastatic breast cancer

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The development of novel FAK inhibitors for potential treatment of metastatic breast cancer

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Motivation of pharmacy students for academic study: a review of the literature

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Motivation has been linked to student learning and academic achievement in a wide range of educational settings. It can inform teaching practice and influence student achievement. However, there is relatively little research in this area relating to pharmacy students. The aim of this project was to undertake a review of studies relating to pharmacy students and motivation, using a systematic approach, to investigate the relationship between student motivation and educational achievement.

A search strategy was developed using a logical and iterative approach. Search terms were formed with reference to keywords in the research question. Using these terms, Web of Science, PubMed, Embase, Scopus, PsychInfo, British Education Index, and ASSIA databases were searched. The results from each database were uploaded into EndNote™ online and duplicates were removed. The articles were then screened at abstract level using the inclusion and exclusion criteria. The remaining articles were then screened at full-text level. Subject to confirmation by the project supervisor, those studies deemed appropriate were included in the review.

The database searches identified 176 potentially relevant articles. At abstract level, 136 articles were screened. Then, 25 articles were screened at full-text level. Finally, eighteen articles, comprising seventeen studies, were included in the review and were analysed and discussed.

The studies indicated that motivation influenced student learning and academic achievement. However, there was a paucity of research in this area relating to pharmacy students during a period when pharmacy practice is undergoing significant change. Four recurrent themes were identified from studies that used different contemporary theories of motivation. These were goal orientation, teacher qualities, relating teaching to pharmacy practice, and performance anxiety.

A Phase II randomized double blind placebo-controlled dose ranging pilot study, investigating the efficacy and safety of an extract of *Artemisia annua* in improving symptoms of hip and knee osteoarthritis

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The objective/aim of this study was to investigate the safety and efficacy of the dietary supplement, Arthrem (ART), on pain, stiffness and functional limitation in osteoarthritis (OA) of the hip or knee. ART contains an extract from the medicinal plant *Artemisia annua*.

In this randomized placebo controlled double blind (DB), parallel, single-centre, 12-week Phase II pilot study, a total of 42 patients were randomized to one of three treatment groups with a total of 14 in each of the following: one capsule of 150 mg *Artemisia annua* extract (ART) twice daily (BD) (ART low dose), one capsule 300 mg ART BD (ART high dose) or one placebo capsule BD administered (all capsules were taken 8 hours apart) over 12 weeks. The percent change from baseline (CfB) was used to assess any changes or reductions in pain, stiffness and functional limitation in OA of the hip or knee at week 12. In order to assess the efficacy, the Western Ontario and McMaster University Osteoarthritis Index (WOMAC©) and visual analogue scale (VAS) for pain was used. The clinical response (WOMAC© responder rate was measured by percent changes from baseline; a comparison of ART groups individually were compared statistically to the placebo group.

No statistical differences in the percent change from baseline of WOMAC© total scores, WOMAC© pain scores, WOMAC© stiffness, WOMAC© physical function scores or VAS pain scores were found between either the ART dose groups (low or high ART dose group) or placebo at week 12. The low dose ART group did appear to show improvements in pain at week 12. However, this improvement was not statistically significant for any efficacy parameter compared to placebo. The most common adverse events were gastrointestinal disorders, musculoskeletal and connective tissue disorders and infections or infestations. The aftertaste of the capsular herbal supplement was noted by one patient in the high dose ART group which led to withdrawal from the clinical trial.

Safety revealed low dose ART to be well tolerated in the 12 week study. The anti-inflammatory/analgesic benefits of *Artemisia annua* extract verified ART to have potential as a treatment in the OA arena. Treatment with ART 150 mg BD (low dose) in patients with OA of the hip or knee demonstrated reductions in pain over 12 weeks compared with baseline. However, no statistical differences between the low dose ART group and placebo were deduced in percent change from baseline at week 12. This pilot study is the first of its kind in this therapeutic area and further studies to demonstrate clinically relevant conclusions are warranted.

A single centre pilot study to identify and establish hospital staff engagement for the consent of Trust patients to be approached to register their interest in clinical trials

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This single centre pilot study was conducted to establish staff engagement in maximizing recruitment strategies for clinical trials in a local District General Hospital. This specific strategy was to obtain baseline universal consent from patients to be approached to receive research information before a specific trial commenced. This would aid in offering patients the opportunity to take part in research as per the NHS constitution (Department of Health, 2013). A qualitative research method was adopted for this study. The views and experience of hospital Trust staff members were captured using a focus group as well as semi-structured one-to-one interviews. The advantage of using these two qualitative approaches were that the participants were given the freedom to describe, explore and express their own opinion on this topic allowing the researcher to gather descriptive information and gain insight into the research topic from the participants perspective. A manual colour coding system was used to analyse the data.

Five robust themes were evident post data analysis. No particular theme was more significant to the participants and it was imperative that all themes were discussed equally. The recruited participant experiences and opinions on the topic of patients giving baseline universal consent to be approached for clinical research, was centred on the following five themes: increased awareness of clinical research,

terminology, opt out versus opt in, data protection and timeframes. A common thread across all themes identified was that further investigation of some highlighted issues would need to be addressed prior to the implementation of this recruitment strategy and that lessons could be learned from other hospitals and institutions that adopt this approach.

Overall, the results of this single centre pilot study demonstrated that the participants involved felt that approaching patients for consent to be contacted about clinical research being conducted at the hospital, was a positive thing to do. This scheme would improve patient awareness in clinical trials, establish better communications between the hospital Trust and patients potentially improving patient recruitment to hospital based clinical research trials. Finally, it would encourage future research projects to answer the questions generated from this pilot study. The researcher felt that the aim of the study, to establish Trust engagement with this topic was achieved.

Hospital pharmacy staff awareness and perceptions of adverse reaction reporting via the Yellow Card Scheme at the Royal Brompton and Harefield NHS Foundation Trust

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Adverse drug reactions (ADRs) are of great clinical importance. In Europe, it is estimated that over 5% of hospital admissions and about 197,000 deaths annually are attributed to ADRs. The cost of this is thought to be in the region of €79 billion per year. The Medicines and Healthcare products Regulatory Agency (MHRA) has responsibility for pharmacovigilance in the UK and the Yellow Card Scheme (YCS) is the cornerstone of this activity, accepting spontaneous reports of ADRs from professionals and patients. Existing evidence suggests that there is gross under-reporting of ADRs via the YCS overall, including that by hospital pharmacists. The aims of this research project were to gain an understanding of the extent of, and reasons for, under-reporting of ADRs and to identify channels for improving ADR reporting rates.

A qualitative approach was used to answer the goal-based questions of the study. Following ethics approval, focus groups and one-to-one semi-structured interviews were undertaken with pharmacy staff within the Trust. Data was also audio-recorded, transcribed verbatim and analysed via a thematic approach using a combination of deductive and inductive coding.

Nineteen participants were recruited into four focus group sessions and four one-to-one semi-structured interviews. The size of the focus groups ranged between three to five participants per session. Attitudes to reporting were found to be positive, though activity was found to be poor. Experiences of reporting were stated to be straightforward, but also onerous and time-consuming. There was seen to be lack of clarity in knowing when to report and little awareness of current developments. Barriers to reporting and perceived reasons for under-reporting were found to be poor awareness, lack of profile, time constraints, follow-up burden, uncertain association, limited access to clinical information and a perceived lack of importance. Suggestions for improvement included raising the profile of awareness, education and training, feedback and the establishment of a central coordinating point.

The extent of under-reporting is wide and a multidisciplinary culture change needs to be driven at a senior level. Real improvements to ADR reporting can only be realized if featured higher on the medication safety agenda. Finite clinical staffing capacity to support reporting means that policy and guidance will need to continually challenge the value of competing commitments and reassess priorities for improving patient safety.

A quantitative study of attitudes and awareness of clinical trials amongst health care professionals in a district hospital in order to inform future recruitment

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There are clear gains and benefits to be made to the NHS, the District Hospital and local population by engaging with clinical trials. The local population can access high quality clinical research opportunities and

gain access to new and novel treatments as a standard of care at their hospital. The establishment itself becomes a contributor to evidence based practice within the NHS via collaboration opportunities with academic institutions and the commercial sector.

A service evaluation was conducted using a web based seventeen point anonymous questionnaire designed to capture the attitudes and awareness of clinical trials in Yeovil District Hospital where it was administered. The methodology used a combined end-weighted five-point Likert scale measure to capture frequency and a selection of open questions designed to obtain current levels of attitude and awareness of clinical trials amongst staff at the District Hospital. This combination methodology enabled quantitative analysis with a qualitative outcome. Following an initial pilot study, the main questionnaire was administered and responses were received from one hundred and seventeen staff that had provided consent. The data yielded qualitative information of the various attitudes and overall, awareness of clinical trials. Themes and frequency from a multidisciplinary cohort of responders were identified.

Attitudes and awareness were clearly demonstrated and the data highlighted areas perceived as barriers to recruitment into clinical trials, matters of success and areas where further support could be beneficial. The information collated could indeed inform robust recruitment strategies for the future which has the potential to increase patient recruitment into clinical trials. Through identification, consideration and understanding of the current levels of awareness and attitudes of clinical trials amongst health care professionals in a District Hospital, it would be possible to inform future recruitment strategies by identifying areas of the unmet requirements of health care professionals to be actively involved in trials.

The delays in gaining Research and Development approval in multicentre clinical trials and whether the Health Research Authority approval will impact on these delays

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This research aimed to investigate where the longest delays occur in the R and D approval process when opening an NHS site to recruitment in a trial and what the reasons are for these delays. Along with the introduction of the HRA approval to replace R and D approval, this research study explored whether there was a belief that this implementation would have a positive impact on the current delays experienced.

Four trials were selected to take part in the data collection of key milestone metrics to opening participating sites. Two of these trials took part in the data collection for recording delay reasons. A questionnaire was designed to capture opinion on the HRA approval and whether it would positively impact on the current delays,

Overall times to open a site were excessive, ranging from a mean of 5.9 to 13.6 months per trial. The longest delay for opening a site to recruitment occurred whilst waiting for the site specific information (SSI) form to be submitted. The main reasons recorded for delays were waiting for authorisation on the SSI form, contract execution and essential documents returned from the site. The majority of responders on the questionnaire did not think that the HRA approval would have a positive effect on the current delays.

The process of obtaining R and D approval at sites is causing unnecessarily long delays for multicentre research studies. The HRA approval is a step in the right direction, creating a much needed global review. However, in order that the process is effective on the delays, the HRA must consider introducing timelines. This would bring it in line with other UK approval processes such as Research Ethics Committee favourable opinion and Medicines and Healthcare Products Regulatory Agency clinical trial approval

Do oral HMG-CoA reductase inhibitors (statins) reduce the incidence of surgical site infections (SSIs) in patients who have undergone an elective primary hip or knee arthroplasty procedure?

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Hip and knee replacement surgery is the most prevalent and successful type of surgical intervention that is performed on both the majority of the elderly and some young NHS and private patients who have experienced the debilitating symptoms of osteoarthritis (OA). The majority of OA patients find that the clinical symptoms of OA are alleviated after they have had primary hip or knee arthroplasty. However, even though a total hip or knee arthroplasty is normally a safe and effective surgical procedure, this type of surgery carries the risk of patients developing post-operative surgical site infection (SSI). SSIs can be very difficult to treat and there have not been many possible preventative treatment options available until quite recently. A potential treatment involves the use of HMG-CoA reductase inhibitors which are more commonly known as statins.

This retrospective clinical study used the Royal Orthopaedic Hospital (Birmingham) surgical site infection database which contained 202 surgically infected primary hip and knee patients and these were matched with 202 non-surgically infected primary hip and knee patients from the Royal Orthopaedic Hospital's health informatics hip and knee database using specific risk factors and propensity score matching to analyse if there was a difference in statin use. The results from the study demonstrated that the non-SSI hip and knee cohort were less likely to develop a surgical site infection because they were undergoing statin treatment (95% confidence interval, $P < 0.0001$) and that those in the SSI and non-SSI hip and knee cohort that did take a statin (52 patients and 68 patients) 58% in the SSI knee and hip cohort and 75% in the non-SSI knee and hip cohort took simvastatin at night.

This indicated that statin use was associated with a reduced incidence in the development of a surgical site infection in those patients who had undergone an elective primary hip or knee arthroplasty procedure.

Analysis of oncology clinical trial start-up and recruitment within the European Union with comparison to global metrics from 2012-2015

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The European Commission determined that between 2007 and 2011, EU clinical trial applications fell by twenty-five percent. Diverse delays (including start-up and recruitment) within studies rose to a staggering ninety percent with associated cost increases. Ultimately, this meant a decrease in innovation and reduced competition within the EU affecting patient access to new medicines, a trend that appeared to be continuing.¹ Clinical trials are becoming more complex and additional delays in start-up can add to already tight timelines resulting in an increased cost of executing such projects. Additional concerns with dropout rates and subsequent overenrolment into clinical trials to allow for this in order to ensure statistical validity adds to the financial burden.

Data in the Clinical Trials Operational Scorecard (COS) is derived from various systems: the Clinical Trials Management System (CTMS), PlanSource (resource tool), PharmaRes and the Country Clinical Operations Annual Recruitment tool. Data was captured from this scorecard (2012-15) and European data was compared with global data for study start-up and recruitment for all oncology studies run during this timeframe.

Clinical trial applications in North America and the Asia Pacific region were growing at a faster rate than Europe² in addition, to the development of the emerging markets. This suggested that Europe may be losing some of its competitive edge within the industry. Therefore, decreasing study start-up timelines and ensuring rapid recruitment rates within Europe are of vital importance to ensure that the region continues to be one of the most "desirable" environments for clinical research in order to continue to compete on the global stage. Pharmaceutical companies, as well as other drug developers are seeking to improve efficacy of process and performance in all areas. This includes study start-up and recruitment with the overall goal of speeding up clinical product development bringing medicines to patients quickly at reduced cost to the developer ultimately with general benefit to the patient.

1. NHS European Office, 2014

2. Gehring, BMJ 2013;3:2957

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

An investigation of a new compound for the treatment of Alzheimer's disease

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Prevention of ductal carcinoma in situ (DCIS): A comparison of prevention programmes in the UK and Iran

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A survey to establish the reasons for non-participation of primary care patients in commercial research studies

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Discovery of Bcl-3 inhibitors for the potential treatment of metastatic breast cancer

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In HER-2 positive metastatic breast cancer, the proto-oncogene Bcl-3 was found to be overexpressed. Bcl-3 acts as a transcriptional co-activator: it forms a ternary complex with DNA and homodimer (p50)₂ and stimulates the transcription of a different panel of genes in the metastatic progression of the breast cancer. Its exact role in endogenous tumours is still unknown. In vivo knockdown studies shown, that Bcl-3 deficiency did not affect the primary tumour, but it reduced the occurrence of metastases by 80% without any effects on the normal mammary gland function. Patients with this type of tumour have a poor prognosis, do not respond to the typical treatment or show resistance and side effects to the usual therapeutic options. Hence, there is an urgent need to find new candidate drugs. A virtual screening targeted against a newly identified Bcl-3 binding pocket allowed the identification of 10 molecules, tested in vitro cell based assays. Four molecules were active. In this thesis, different analogues of these four hit compounds were synthesised. Based on docking studies, another two scaffolds were designed. The non-cytotoxic profile of the new analogues was assessed using the cell titer blue assay. The activity of the compounds was established using the colony forming assay (CFA). To prove the Bcl-3/p50 interaction, immunoprecipitation and co-immunoprecipitation were performed. None of the compounds was cytotoxic. Some of them exhibited a promising activity in the CFA. One molecule exhibited an interesting activity profile both in vitro and in vivo and in pharmacokinetic studies and it has been forwarded into full pre-clinical development.

Computer-aided design and synthesis of novel anti-DENV nucleoside analogues

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Dengue virus (DENV) is one of the most important human pathogens among the genus flavivirus, with 3.9 billion people at risk of infection through mosquitoes, such as the widely spread 'Asian tiger' mosquitoes, and the four serotypes of DENV are endemic in over 100 countries in tropical and subtropical regions. Clinical manifestations of infection with DENV range from flu-like symptoms to the life-threatening dengue haemorrhagic fever. The dramatic increase in the incidence of the DENV infection, the rapid spread of DENV to new areas and the recent re-emergence of another member of the genus flavivirus, Zika virus (ZIKV), have highlighted the urgent need for specific antiviral therapies against infections with DENV and related viruses, which are not currently available. DENV RNA-dependent RNA polymerase (RdRp), the enzyme responsible for the synthesis of the viral genome, is one of the most attractive targets for the development of direct acting antiviral agents but its molecular mechanisms are poorly understood. Therefore, the aims of this PhD project were i) to build a model of the de novo initiation complex of DENV RdRp, of which there is currently no crystal structure available, ii) in silico design and synthesis of novel nucleoside and nucleotide analogues as potential inhibitors of DENV replication, iii) and finally to investigate the mechanism of the RNA synthesis by DENV RdRp.

Molecular modelling techniques allowed for the creation of a model of the de novo initiation complex. The application of in silico drug design approaches resulted in the identification of three families of promising adenosine analogues: ribose-modified, nucleobase-modified and acyclic adenosine analogues. Strategies for the preparation of these nucleosides were investigated and ten adenosine analogues and eight nucleotide prodrugs, which are phosphoramidate ProTides, of specific nucleosides were synthesised and sent for biological evaluation in vitro. Innovative microwave irradiation conditions for the preparation of phosphoramidate ProTides were developed and successfully applied to synthesised nucleoside analogues. Finally, the application of molecular dynamics simulation methods on different complexes of DENV RdRp provided insights on the conformational changes of DENV RdRp during the synthesis of the viral genome. These results contributed to the understanding of DENV RdRp activity and will aid the design of inhibitors of the viral replication.

Phosphorus prodrugs of S1P receptor modulators as a novel therapeutic opportunity

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The sphingosine 1-phosphate receptor modulator fingolimod / Gilenya / FTY720 has become an effective and commercially available therapeutic agent for the treatment of relapsing-remitting multiple sclerosis. Fingolimod is phosphorylated by sphingosine kinase *in vivo* to the pharmacologically active S-phospholipid phosphate. The original aim of the work was to synthesise novel phosphate delivery prodrug analogues of fingolimod and determine whether or not these novel analogues could provide an improved therapeutic profile. The principal phosphate delivery prodrug method to be investigated was phosphoramidate "ProTide" chemistry. ProTide fingolimod analogues were found to have a poor level of stability and readily degrade to unwanted cyclised structures at room temperature and when exposed to very mildly basic conditions. In order to mitigate the poor stability issues it was considered possible that forming ProTide analogues of mono-alcohol S1P receptor modulators, as opposed to diol fingolimod, would lead to greater stability. The synthesis of mono-alcohol S1P receptor modulator benzyl ether derivative analogues published by Tsuji et al was attempted and successfully achieved. Previously reported ProTide synthesis and *in vitro* testing methods were employed. Carboxypeptidase, human serum, base stability, acid stability and cell lysate processing experiments were conducted in the School of Pharmacy. Homology modelling was employed to determine S1P1 selectivity of benzyl ether derivative analogues and novel structures. ProTide benzyl ether derivative analogues were found to have a far greater level of stability than ProTide fingolimod analogues and *in vitro* processing experiments showed that they are processed to the desired pharmacologically active monophosphate. The research signifies the development of an entirely new family of potential therapeutic agents.

Design, synthesis and biological evaluation of nucleoside phosphoramidates with potential anticancer activity

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One in seven approved anticancer drugs in the UK are nucleoside analogues (NA). However, frequent development of resistances and unpredictable toxicity are crucial drawbacks of these compounds. Some of the main resistance mechanisms against NAs include limited cellular permeability and decreased initial phosphorylation of the NAs, thus limiting the concentration of active NAs inside the target cells. The ProTide approach is a pronucleotide technology that successfully overcomes these drawbacks by releasing the monophosphorylated NA into the cell and has led to multiple clinical candidate drugs.

This work was focussed on the application of the ProTide approach to novel and known anticancer NAs with the aim of improving their performance and pharmacological properties. Herein, new synthesis and optimisation of selected pyridine and purine NA with modifications in the base and / or in the sugar moieties, along with different synthetic approaches to build the prodrugs are reported.

The anticancer activity of the compounds was evaluated *via* cell viability assays, and the activation of the prodrugs and resistance to enzymatic degradation was proved *via* enzymatic assays involving Nuclear Magnetic Resonance (NMR) or spectrophotometric methods. Molecular modelling studies were performed in order to understand the interaction of the ProTides and their metabolites with the enzymes.

Finally, the family with the best *in vitro* activity results was enlarged by developing novel ProTide-related nucleoside diamidate prodrugs, which aimed to further improve their bioavailability and stability characteristics.

Resistance mechanisms during endocrine treatment in breast cancer

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Prolonged endocrine therapy is the mainstay of treatment for ER+ breast cancer patients. However, resistance develops in many patients which leads to more aggressive disease. Understanding the mechanisms of acquired resistance that emerge as a consequence of prolonged endocrine treatment remains critical. This study aimed to use gene expression profiling to discover induced mechanisms shared by a panel of MCF7-derived acquired resistant cells that underpin endocrine resistant growth. The in vitro panel represents resistance to oestrogen deprivation, tamoxifen or fulvestrant and includes long-term (3year) models to better-mimic clinical endocrine exposure. Affymetrix 1.0ST microarrays detected 572 genes induced in all resistant models versus MCF7. Over-represented ontologies, pathways and functional classification for these genes revealed induction of oxidative phosphorylation (OxPhos) and TCA cycle enzymes in the resistant models, a finding further confirmed by mass spectrometry. Increased oxygen consumption, NADH dehydrogenase and/or cytochrome C oxidase activity was detected in resistant cells, and targeting with OxPhos inhibitors Metformin or Antimycin A confirmed growth-dependency on OxPhos. Western blotting for AMPK (energy sensor) activity and its downstream anabolic targets (ACC, mTOR/P70S6K) showed Metformin reduced fatty acid and protein synthesis in growth-sensitive endocrine resistant cells. In silico analysis inferred clinical relevance since many TCA/OxPhos genes associated with earlier relapse in ER+ and/or tamoxifen treated patients. Monitoring basal glycolysis (extracellular lactate) and growth impact of 2DG or glutamine restriction demonstrated glycolysis and glutaminolysis also contribute to endocrine resistance. The microarrays furthermore revealed that metabolic kinases PCK2, ALDH18A1 and PFKFB2, and components of cell response to Zn were commonly-induced which may additionally help endocrine resistant growth. This study has revealed increased OxPhos arises as a consequence of prolonged endocrine treatment and is a key bioenergetic pathway sustaining resistance. Since resistant growth is Metformin-sensitive, such targeting of this energy pathway (alongside further antihormones or glycolysis/glutaminolysis inhibitors) could help treat resistance.

Factors influencing discharge decisions in dermatology outpatients: checklist and educational methods to support appropriate discharge

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The decision whether or not to discharge an outpatient is vital in determining outpatient clinic attendance numbers, directly affecting overall patient care efficiency. A review of the factors influencing discharge decisions revealed that there was limited evidence of these factors and a lack of understanding as to how clinicians take discharge decisions. This project's objectives were to describe the influential factors on discharge decisions from the clinicians' and patients' perspectives, to demonstrate the development and clinical evaluation of a novel "Traffic-light" design dermatology outpatient discharge information checklist to improve appropriateness and consistency in discharge decision-making. Semi-structured interviews were carried out with 40 consultant dermatologists across England. One hundred and forty-eight influences were generated and thematically analysed both manually and also using NVivo10 software. A wide array of nonclinical factors (clinician-based, patient-based, practice-based and policy-based factors) influence discharge decision-making. Observations of 64 consultations and 56 semi-structured interviews with dermatology outpatients were carried out to understand their experience concerning the decision for their discharge. Twelve of the 31 patients (39%) who were discharged, considered their discharge inappropriate. A three-round Delphi exercise with 17 dermatology consultants (100% response) was carried out to reach agreement on what a high quality discharge information checklist should contain. There was strong inter-rater reliability (ICC=0.958) and fair inter-rater agreement (Fleiss Kappa=0.269). Thirteen items were identified that formed the "Traffic-light" design checklist. Twelve (67%) dermatology clinicians who evaluated the checklist found it useful. This study has demonstrated the importance of approaching discharge decision taking in an informed, structured manner. The checklist provides the basis for making discharge decisions more systematic, auditable and transparent, improving patient safety and optimising healthcare costs. These methods are potentially useful in other clinical disciplines.

Defining the role of the actin cytoskeleton in cellular uptake of cell penetrating peptides

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The increased need for macromolecular therapeutics, such as proteins and nucleotides, to reach intracellular targets asks for more effective delivery vectors and a higher level of understanding of their mechanism of action. Cell Penetrating Peptides (CPPs) have been shown to deliver a range of macromolecules into cells either through direct plasma membrane translocation or by endocytosis. All known endocytic pathways involve cell cortex remodelling, a process shown to be regulated by reorganisation of the actin cytoskeleton. Links between actin remodelling and CPP uptake has been shown but more information is required to determine the extent of this association and how it could influence further research into improving the delivery capacity of these entities. This project, by using the CPP octaarginine (R8) investigated how actin disorganisation influences the cellular entry of this peptide when attached to a model fluorophore Alexa 488 or Enhanced Green Fluorescent Protein (EGFP). A confocal microscopy technique was initially developed, allowing for high-resolution and spatial characterization of the actin cytoskeleton at different cell depths. Analysis using this developed method was used to highlight that serum starvation has a strong influence on the capacity of R8 to cause membrane blebs and possibly macropinocytosis. Using a range of direct or indirect actin inhibitors this work also highlighted how they can rapidly cause dramatic cellular deformities beyond the level of actin or more subtly affect actin organisation. Further confocal studies revealed that choice of cell line significantly affects the effect of actin disruption on CPP entry and that this is highly dependent on the nature of the probe. This was exemplified by results showing inhibition of EGFP-R8 uptake in HeLa cells treated with cytochalasin D, latrunculin B and jasplakinolide but a dramatic increase in uptake in A431 cells when they were treated with these drugs. The regulation of actin dynamics involves various kinases including Rho-associated kinases ROCKs, and Src family kinases. The ROCK inhibitor Y27632 induced the formation of actin needles running perpendicular to the plasma membrane of A431 cells and increased EGFP-R8 internalisation. By contrast, Src inhibitor PP2 had little effect on both the actin cytoskeleton and EGFP-R8 uptake. Overall this study highlights the importance of analysing actin in detail to identify how CPPs and possibly other drug delivery vectors and formulations interact with cells to gain entry. Under defined experimental conditions R8 can modify the actin cytoskeleton and requires a functional or dysfunctional actin network to allow for maximal cellular entry.

Characterising skin immune cells to inform development of intradermal vaccines and therapeutics

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Epidermal Langerhans cells (LCs) and multiple subsets of dermal dendritic cells (dDCs) make skin a valuable route for vaccination, offering the potential for antigen-sparing immunisation. The interconnected immunological functions of dDC subsets and LCs are not fully understood however. This Thesis therefore aimed to explore the interactions of skin immune cells with viral pathogens and vaccines to inform the development of future therapeutics and intradermal vaccines. LCs and dDCs were isolated from ex vivo human skin tissue using a walkout protocol which allowed the enrichment of the migratory cells from the tissue. LCs and dDCs were infected with a lentiviral vector encoding GFP, allowing study of post-entry HIV viral restriction. The study uncovered the existence of a SAMHD1-independent antiviral factor unique to LCs. LCs and dDCs from ex vivo skin were used to examine the cross-presentation of an inactivated influenza virus-derived matrix peptide to CD8⁺ T-cells. Two CD11c⁺ subsets of dDCs were found to potently cross present the antigen. Delivery of VLPs, which lack genetic material, markedly reduced cross-presentation, suggesting that viral genetic material is vital for dDCs to activate cross-presentation pathways. Future work is required to determine if this is true of other influenza peptides or pathogens. Vaccine delivery studies performed using murine and human models found that dDCs were responsible for the greatest uptake of ovalbumin peptide antigen and LCs did not migrate out of the epidermis in the first 4 hours after inactivated influenza virus vaccine delivery respectively. Collectively, this work highlighted the importance of dDCs in antigen uptake and cross-presentation to prime cytotoxic T-cell responses. Innovative delivery methods such as microneedles offer a means of accessing the dermal compartment in a pain-free manner, though further work is required to determine the optimal combination of vaccine formulation and delivery method to harness the immunostimulatory abilities of dDCs.

Characterization and mechanisms of thiol-induced protection against myocardial infarction

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Hydrogen sulfide (H₂S) is the simplest endogenously produced thiol and has an indispensable role in cardiovascular homeostasis. It has been shown that exogenous H₂S supplementation protected the heart against myocardial ischaemia/reperfusion injury through a mechanism which is yet to be defined.

In this thesis, it was hypothesised that controlled application of thiol/H₂S donors at reperfusion would mitigate acute myocardial infarction. We sought to characterise the cardioprotection and molecular targets of three H₂S donors (mesna, GYY4137 (a slow-releasing, non-mitochondrial targeted H₂S donor) and AP39 (a mitochondria-targeting H₂S donor). This characterisation was conducted using a broad range of experimental models and techniques including anaesthetised rat model of ischaemia/reperfusion injury, Western blotting and mitochondrial studies using isolated cardiomyocyte mitochondria, namely subsarcolemmal and interfibrillar mitochondria.

Mesna did not limit infarct size when it was given pre-ischaemia or at reperfusion. GYY4137 and AP39 significantly limited infarct size when given specifically at the time of reperfusion through different mechanisms. Cardioprotection established by GYY4137 was mediated mainly by triggering of PI3K/Akt/GSK-3 β signalling at reperfusion with partial dependency on eNOS activity. Selective mitochondrial delivery of H₂S at reperfusion using AP39 had no effect on Akt, eNOS, GSK-3 β and ERK1/2. In isolated mitochondria, AP39 inhibited Ca²⁺-sensitive opening of PTP in subsarcolemmal and interfibrillar mitochondria through attenuation of mitochondrial reactive oxygen species generation.

The studies presented in this thesis provided novel mechanistic insights into cardioprotection by H₂S. These studies suggest that targeted delivery of H₂S represents a novel and effective adjunctive therapy to ameliorate the injurious effects of reperfusion which contribute to acute myocardial infarction.

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