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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 18th 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.

Rhys Thomas, Dean Routledge & Justine Jenkins
November 2020

A Rapid Review Exploring the Roles of Pharmacists in Identifying and Reducing Medication Administration Errors in Care Homes

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Background: Medicines administration errors (MAEs) in care homes cost the NHS over 96.1 million a year.[1] Several studies report the benefits of Pharmacists deprescribing and undertaking medicine reviews in care homes[2], however, the roles of Pharmacists identifying and reducing medicine administration error rates in care homes are underexplored.

Aim: to conduct a rapid review to explore the role of Pharmacists identifying and preventing MAE in care home settings.

Method: A rapid review was conducted according to methods in the World Health Organization Rapid Review: Practical Guide[3] and results were reported according to the PRISMA statement. Search for relevant literature was systematically conducted from 2005 onwards using EMBASE, Ovid EMCARE and Ovid MEDLINE and hand-searching, which evaluated the Pharmacist's role, alone or as part of a multidisciplinary team, in identifying and/or intervening to reduce MAEs. MAEs were defined as any deviation of prescriber's instructions when administering medication.[4]

Results: Out of 571 records initially retrieved, 10 papers were included in the final analysis – 8 case series (3 pre-interventions to post-intervention studies), 1 non-randomized control trial and 1 cross-sectional study. Overall, 4540 participants were included. Interventions were MDT-based, educational, or consisted of a medication chart on discharge to the care home. Identification of MAEs were via observations and were conducted by pharmacist with/without doctor. Studies demonstrated Pharmacist's identified MAEs and where pre-post interventional studies were applied, a reduction in MAEs was demonstrated.

Conclusion: Pharmacists were effective in identifying MAEs and where relevant there was a reduction of MAEs pre-post intervention. However, heterogeneity of interventions and weaker study designs require large, well designed RCT to substantiate the most effective Pharmacist intervention in reducing MAEs in Care Homes.

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Evaluation of in vitro drain biofilm models mimicking those found in a hospital setting

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A biofilm is an aggregation of microorganisms which have adhered themselves both together as well as onto a solid surface through forming an extracellular polymeric substances (EPS), contributing towards resistance. Biofilm resistance to antimicrobials, increased transferability, coupled with the vulnerable population in hospitals make biofilms a huge problem towards society. There is a need to replicate biofilm drain models to better understand their mechanisms and test effective and safe interventions against them. This study investigates the in-vitro models mimicking hospital drain biofilm.

Web of Science database was searched. Studies were included if they mimicked were undertaken within a hospital. Keywords searched for included: Biofilm, drain, model, sink, healthcare, HAI, splash, hospital. I used various combinations of these words and reviewed all the papers for appropriateness.

Limited amount of evidence is available for this topic. Searching the database gave very few papers relating to the appropriate setting of a hospital environment. Upon further screening, many were inappropriate in terms of a lacking in modelling a sink drain biofilm or not testing any interventions. Papers of merit supported an important thesis in relation to avoiding the spread of biofilms, testing splash dispersion, placement of the drain to the sink and stagnation of water. Novel approaches to combat biofilms included the introduction of microphages, an area never been explored before and needing more research.

Limitations of the available information on a wider context as well as limitations through the method choice make it hard to give strong conclusions. There are merits in the work already done, but many acknowledge their own limitations and as some are the first to investigate their area of research, more investigation is needed to make solid conclusions. More biofilm cultivation experiments need to be conducted in the appropriate settings so that eradication controls can be tested, an important issue facing healthcare.

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TM4SF1 expression in endocrine responsive and resistant breast cancer

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Oestrogen receptor positive (ER+) breast cancer (BC) is treated with endocrine therapy, however acquired resistance develops which may involve ER loss.[1] EGFR and Src associate with resistance but their targeting has limited value.[1,2] A recent microarray project at Cardiff University detected increased expression of atypical tetraspanin TM4SF1 in a Luminal A (T47D)-derived cell line with acquired faslodex resistance and ER loss (T47DFasR).[3] This project aimed to explore the relationship between TM4SF1, endocrine failure and ER loss *in vitro* and in clinical disease.

Models with acquired resistance to faslodex, 4-OH tamoxifen or oestrogen-deprivation, responsive T47D cells treated with these antihormones, and also de novo ER- cells were studied. Immunocytochemistry (ICC) with H-scoring assessed TM4SF1 protein and localisation. ER-stained coverslips and Affymetrix microarrays assessed relationships between TM4SF1 mRNA, ER and antihormone resistance. T47DFasR treated with 10^{-6}M gefitinib or saracatanib explored if TM4SF1 was EGFR or Src regulated, respectively. KMPlotter examined TM4SF1 expression in some ER+ endocrine-treated and ER- clinical BC microarray datasets.

Plasma membrane-localised TM4SF1 significantly increased in acquired Faslodex resistant models and was modestly induced in antihormone-treated T47D cells. It was not decreased by EGFR or Src inhibitors. TM4SF1 mRNA significantly increased in all acquired antihormone resistant models and related to ER loss, also increasing in ER- MDA-MB-231 cells. TM4SF1 mRNA expression significantly related to decreased overall and distant metastasis-free survival in ER+ BC and shortened relapse-free survival in ER- BC patients.

Plasma membrane TM4SF1 upregulation in T47DFasR cells and its mRNA profile in further antihormone resistant and de novo ER- models suggests TM4SF1 plays a role in acquired endocrine resistance and tumours lacking ER. Since TM4SF1 was antihormone-induced early in responsive cells, was independent from EGFR and Src, and related to poor prognosis, it might have potential as a novel therapeutic target to combat antihormone resistant BCs with ER loss.

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Is sodium zirconium cyclosilicate (Lokelma) effective in managing hyperkalaemia of chronic kidney disease in patients on haemodialysis in a clinical practice setting?

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Chronic kidney disease (CKD) can be defined as abnormal kidney function that has occurred for more than three months and has caused implications to the patients' health.[1] Hyperkalaemia occurs when serum potassium is >5.5mmol/L and can cause severe cardiovascular events if not controlled.[2] Lokelma, developed by AstraZeneca, is a novel oral potassium binding agent used in hyperkalaemia. A recent clinical trial (DIALIZE) had positive results for use of Lokelma in haemodialysis (HD) patients.[3] However, NICE cannot recommend Lokelma in this patient group due to lack of evidence of efficacy.[4] Nevertheless, we looked at this HD patient group within a clinical setting to see if results were similar to DIALIZE. We also examined patient experiences of Lokelma and how taking it compared to the current first line therapy, calcium resonium.

VitalData (patient record system used in SW Wales regional renal units) was accessed to collect data on HD patients and information about confounding factors that could affect serum potassium levels. An anonymous survey was designed and administered to the patient cohort which allowed us to investigate patient views on Lokelma.

The survey (n=13) reported 76.92% of Lokelma patients had no side effects vs 36.36% of side effects reported by calcium resonium patients. Compliance for Lokelma was significantly higher (84.62% vs 36.36%).

Prevalent HD patients (n=16) showed an overall decrease in serum potassium levels after Lokelma treatment. Prior to Lokelma, 100% of patients had K^+ greater >6mmol/L, after Lokelma, this was 68.75% had K^+ greater >6mmol/L, with the mean fall from 7.38mmol/L to 6.37mmol/L. In preventative patients (n=4), vascular access issues caused delays to dialysis so Lokelma was initiated while access issues were resolved, in these cases there was 100% avoidance of hospital admissions, with one patient experiencing a delay of six days to dialysis. Mean potassium pre dialysis was 6.0mmol/L with the next recorded pre dialysis potassium at 4.85mmol/L.

Lokelma is a valuable therapeutic option and has a place in treating and preventing hyperkalaemia in HD patients. More studies are required involving a larger cohort of patients to fully evaluate the benefits and limitations of Lokelma in routine clinical practice.

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A rapid review of falls and hospitalisations as an outcome of polypharmacy in care homes

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Polypharmacy is commonly defined as the daily use of ≥5 medicines[1] and is prevalent amongst care home residents.[2] The risk of falls and hospitalisation of care home residents is high [3,4] and the reasons for this need to be explored. A rapid review was conducted with the aim to review and critically appraise existing research on falls and hospitalisation as an outcome of polypharmacy in care homes.

MEDLINE, EMBASE and the Cochrane Library were searched from January 2000 to October 2019. English language papers were eligible for inclusion if polypharmacy was associated with a clinical outcome in care home residents (≥65 years or with a mean age of ≥70 years old), papers defined polypharmacy quantitatively (minimum of ≥3 medications) or qualitatively which could be linked to a numerical definition from included data.

Quality and risk of bias was assessed using CASP checklists and the Joanna Briggs Institute Critical Appraisal Checklists.

Of the 960 papers initially identified, seven papers were included in the review. A meta-analysis could not be completed due to heterogeneity between the studies. Overall, some association was found between polypharmacy and falls (n = 3 studies) and hospitalisation (n = 5). Associations between excessive polypharmacy (≥10 medications) and falls (odds ratio 1.30, 95% CI 0.78-2.18) and hospitalisation (odds ratio 2.56, 95% CI 1.36-5.85) were uncertain due to wide confidence intervals (CI).

Falls and hospitalisations are at least somewhat associated with polypharmacy in care homes. As a result, emphasis should be placed on the importance of medication reviews to address polypharmacy and identify residents at increased risk of falls and hospitalisation. It would be helpful to adopt a universal definition of polypharmacy as it is often described in different ways in the literatures. This would allow further studies on care home residents using a standard definition of polypharmacy.

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The incorporation of terbinafine into a biodegradable polymer (PLA and PLGA) for the use of 3D printing of microneedles

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Terbinafine is first line treatment for fungal nail infection, available in oral and topical formulations.[1] Currently, there is a gap in the market for a sustained release formulation.[2] Biodegradable polymers have previously been used as drug delivery systems. This study aims to incorporate terbinafine into biodegradable polymers Polylactic Acid (PLA) and Poly(lactic-*co*-glycolic) Acid (PLGA) and determine whether it is appropriate to produce microneedles.

PLGA, PLA and terbinafine (72%, 8% and 20% w/w respectively)[3] was formulated into two formulations, by hot melt extrusion to produce a filament, and via chloroform evaporation to produce discs. A release study was carried out over a period of 14 days. Terbinafine incorporated filaments and discs were placed in 30mLs of 25% and 50% methanol media at 37^{o}C at 140rpm in a water bath. At designated time intervals, samples were taken from the media and absorbance values were taken from UV-Visible spectrometer. Scanning electron microscopy (SEM) was carried out to determine the distribution of drug within the polymer. Mechanical properties of the filament and disc were assessed using a tablet hardness tester.

Results showed terbinafine discs released greater than 100% of the drug in 50% methanol media and 91% drug release in 25% methanol media. Comparatively, the drug incorporated filaments displayed no release of terbinafine. SEM images of terbinafine filaments and discs showed smooth images with no terbinafine crystals present on the polymer surface. Mechanical force testing showed that filaments were weaker when terbinafine was incorporated and discs displayed no strength due to its soft nature.

Filaments do not release sufficient drug and discs exhibit no mechanical strength to deliver the drug, but release drug from the polymer. These results demonstrated that neither formulations have the correct properties for the use of microneedles. Further studies need to be carried out to optimise the functioning product.

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The control of *Pseudomonas aeruginosa* in a complex biofilm

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Pseudomonas aeruginosa (*P. aeruginosa*) persists within biofilms in hospital sink drains[1,2]. Through the spread of healthcare-associated infections, drain-residing *P. aeruginosa* is contributing to antibiotic resistance and prolonged hospital stays[1,3]. We aimed to investigate the extent of *P. aeruginosa* colonisation within a complex drain biofilm and its control using chlorine-based biocides and a cleaning agent. Moreover, we assessed whether inhibitory concentrations of the biocides induced changes to the clinical susceptibility of *P. aeruginosa* towards antibiotics. Subsequently, we examined the motility of *P. aeruginosa* and deduced the speed it moves through tubing.

A complex drain biofilm model, which mimics a sink U bend, enabled the formation of multiple *P. aeruginosa*-drain biofilms in 3 sections of the U bend: front, middle and back. Total viable count determined 1) the final biofilm ratio 2) the bactericidal efficacy of the biocides and cleaning agent, and 3) motility. The European Committee on Antimicrobial Susceptibility Testing provided the basis for our antibiotic susceptibility test[4].

P. aeruginosa was found to dominate the complex biofilm. The biocides were more efficacious than the cleaning agent but did not completely eradicate the biofilm. Neither biocide altered the clinical susceptibility of *P. aeruginosa* towards the antibiotics. *P. aeruginosa* was found to be very motile and moved through tubing at a rate of 10 mm/hour.

As *P. aeruginosa* successfully colonised all sections of the U bend and dominated the complex biofilm, investigating its control in hospital drains is important. Our antibiotic susceptibility test suggests that the biocides did not change the pathogen's clinical antibiotic susceptibility. However, their bactericidal activity was arguably poor. Pre-disinfection methods should be investigated to improve their efficacy. Our findings demonstrate that *P. aeruginosa* uses its motility to move through tubing. We conclude that motility is an important factor for the transfer of *P. aeruginosa* from U bends to patients.

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Analysing Welsh Prescribing of items indicated as "Less suitable for Prescribing" to feed into the Low Priority Prescribing Project.

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There is an increased demand on the NHS.[1] In 2018-19, the number of items prescribed by GPs was the highest on record of over 80.1 million items which led to a net ingredient cost of £563.2 million.[2] It is therefore essential that prescribers prescribe the most clinically and cost-effective treatment to patients. Items listed as "less suitable for prescribing" in the BNF shouldn't be routinely prescribed as they are not the most clinically and cost-effective drugs available. This study aimed to analyse trends for items listed as "less suitable for prescribing" in the BNF to evaluate if prescribers in Wales were adhering to guidelines.

Prescribing data was collected using Comparative Analysis System for Prescribing Audit (CASPA) to establish prescribing trends for drugs listed as "less suitable for prescribing" between April 2013 and August 2019. Data was further analysed as yearly averages. Data was then compared to current guidelines and advice surrounding "less suitable for prescribing" drugs to investigate if prescribers were compliant to current guidelines.

Every drug listed as less "less suitable for prescribing" in this study decreased in prescribing over the study period except for cyanocobalamin. Cyanocobalamin increased in prescribing in every year of the study. Every

other drug decreased in prescribing with glucosamine and permethrin showing the largest decline. Every drug except for cyanocobalamin recorded their lowest quantity of prescribing in the final year of the study.

As majority of drugs in this study showed a decline in prescribing, it indicates that current guidelines and advice are being implemented by prescribers in Wales. Investigation is required to provide an explanation for when drugs don't adhere to current guidelines, especially in the case of cyanocobalamin.

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Investigating the inflammatory effects of levodopa in the 6-OHDA animal model of Parkinson's disease

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Levodopa (L-dopa) is the current mainstay treatment for Parkinson's disease, with most patient's encountering the drug at some point during their illness. Research has suggested a link between L-dopa and inflammation, which may contribute towards the pathogenesis of Parkinson's disease.[1] The mechanisms of how L-dopa may induce inflammation are unknown, though astrocytes and microglia are thought to play a role.[2] Current research is inconclusive on the inflammatory effects of L-dopa and the subsequent involvement of astrocytes and microglia, justifying further investigation in this area[3] and verification in our own lab.

30 Sprague Dawley rats were placed into 5 groups: Naïve, SHAM plus L-dopa, SHAM plus saline, 6-OHDA (6-hydroxydopamine) plus L-DOPA, and 6-OHDA plus saline. The rats were lesioned or underwent sham surgery, then were treated for six weeks with saline (1ml/kg) or L-dopa (8mg/kg s.c. with 15 mg/kg benserazide) twice daily. After treatment animals were killed, and their brain tissues prepared for immunohistochemistry targeting microglia (OX42) and astrocytes (GFAP). Stained brain sections were then analysed via optical density analysis, image subtraction and stereology to determine the differences in OX42 and GFAP between groups.

Results derived from all methods determined that there was a significant difference between the groups within the same hemisphere. However, stereology was the only method that showed a significant difference between the hemispheres of the same group. Post hoc analysis determined a significant increase in the response between the 6-OHDA L-dopa group and all other groups across all methods.

Results obtained in this study support the hypothesis that L-dopa induces inflammation. However, this inflammation was only significant when L-dopa was administered in the presence of a 6-OHDA lesion. No evidence was derived to illustrate an independent inflammatory effect from L-dopa alone, though issues with the study's methodology limit this supposition. To determine the independent inflammatory effects of L-dopa and if astrocytes and microglia play a significant role in this, further research is required.

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Antibacterial activity of thiadiazole derivatives: a rapid systematic literature review

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Antibacterial agents are the main drug treatments for bacterial infections caused by infectious bacterium. They work by disrupting the growth and reproduction of bacteria.[1] Due to antibacterial misuse, multidrug-resistance is currently one of the most alarming issues, which leads to an increase in morbidity, mortality and economic burden.[2] Thiadiazole derivatives have shown positive antimicrobial, antiinflammatory and many more

activities.[3] The main objective of this review was to justify if thiadiazole derivatives are a viable class of antibacterial agent and if further studies are needed.

The search terms “antibacterial and thiadiazole and MIC” were used for scoping publications from PubMed, SCOPUS and Web of Science to prevent missing any relevant papers in this rapid review. Only papers published in the past 10 years were included for more up to date information. Finalised published research papers were taken forward to be critically appraised based on the qualitative checklist prior to the analytical process. Due to time limitations, antitubercular activity papers were excluded.

The results suggested that thiadiazole derivatives have antibacterial activity. Addition of electron withdrawing groups have shown improvements in the antibacterial activity, due to the relatively positive charged structure, increasing the penetration through cell wall of bacteria.[4] Moreover, the studies suggested the importance of electron density around the thiadiazole ring structure, for it to chemically react with the surface of the bacterial cell wall to have antibacterial activity.

After reviewing the publications included, thiadiazole rings are a viable class of antibacterial agent as it was presented with positive antibacterial activity. Hence, more research should be done for the current tested derivatives in order to create a new antimicrobial agent with a better pharmacological profile. However, a larger scale of systematic review should be done prior to furthering medicinal research to consider its antitubercular activity.

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The environmentally friendly decontamination of bacterial spores using bacteriophages

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Bacillus anthracis is the Gram-positive, spore forming agent responsible for anthrax. *Bacillus anthracis* occurs naturally in soil in many parts of the world.[1] Current decontamination methods use toxic chemicals which make them unsuitable for environmental use.[2] *Bacillus anthracis* specific bacteriophages have been identified could be used as part of an environmentally friendly method of decontamination however, the spore form of the bacteria is resistant to bacteriophages. Once the spores are exposed to germinants, they become susceptible to the phages.[3] The aim of this study is to compare the effect of different germinant combinations on spore germination efficiency in order to find an optimal combination for use with decontamination strategies with bacteriophages.

A standard germination mixture of L-alanine, inosine and Ca^{2+} was augmented with the addition of either D-cycloserine, calcium dipicolinate (CaDPA), adenosine, or guanosine. 10^5 *Bacillus anthracis* Sterne spores were exposed to each germination mixture for different lengths of time at 37°C. Half of each sample was subject to heat-shock (water bath at 65°C for 30 minutes), the other half was not, each half was consequently serially diluted and plated to determine extent of germination.

The results were disappointing overall. Only the mixture augmented with adenosine showed any sort of statistically significant improvement over other augmented mixtures at various time points, but it was not statistically sbetter than the standard germination mixture at any time point.

Currently no mixture tested in this study proved to be optimal, further studies exploring different temperatures and shorter time points will need to be conducted for more definitive results on spore germination efficiency.

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Can a PROTAC be designed to degrade Hepatitis B viral polymerase?

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PROTAC (Proteolysis Targeting Chimera) molecules degrade disease-causing proteins through the cell's Ubiquitin-Proteasome System (UPS), which routinely degrades unneeded or damaged/misfolded proteins. PROTACs contain two molecule binding ligands attached together by a linker bond. One of these ligands targets a disease protein of interest (POI) and the other targets an E3 ligase, triggering a process called ubiquitination which leads to breakdown of the POI via the UPS. [1]

Current anti-hepatitis B (HBV) therapy are interferon-based therapies and nucleoside/nucleotide analogues that selectively target the viral polymerase reverse transcriptase (RT) domain, disrupting HBV DNA synthesis and cell cycle continuation. [2] Treatment does not cure infection and patients are on continuous life therapy.

A novel approach and the aim of this study is to design anti- HBV PROTACs. [3]

This study includes an extensive background into the HBV viral life cycle, the UPS and PROTAC technology.

Literature searches were conducted to identify a target E3 ubiquitin ligase, warhead and linkers to design six anti- HBV PROTACs. Structure-activity relationships and efficacy studies were studied from published and successful PROTACs.

These six PROTACs were input into SwissADME, an online web tool software to evaluate predictive properties of pharmacokinetics, drug-likeness and medicinal chemistry friendliness. Two PROTACs were chosen as the most likely to be successful drug candidates and their synthesis was proposed.

This study compared the von Hippel-Lindau (VHL) and cereblon (CRBN) E3 ligases; VHL was the most appropriate protein substrate target with studies of high protein target degradation and two VHL targeting PROTACs in current clinical trials. CRBN ligases pose future study as teratogenicity and toxicity risk are yet to be fully established.

Three HBV DNA polymerase inhibitors were established.

PROTACs are currently designed on a case by case basis from understanding protein and molecule interactions; designs can be potential useful leads for drug discovery.

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Research into the synthesis of the ring B constituent of Atrovirisidone B.

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Both cancer[1] and bacterial resistance[2] involve cellular changes and abnormal growth, making them extremely difficult to treat and therefore growing worldwide threats. There is a constant need for new treatments in order to tackle these issues. Natural compounds are a good potential for novel drug design as they already possess bioactivity. Depsidones are a class of structurally unique chemical compounds that have been well established. Atrovirisidone B is an example of a depsidone,[3] limited research has shown it has useful properties including antibacterial and cytotoxic activity against major human cancers such as breast, lung and prostate.[4] The aim of this study was to broaden research around the synthesis of a key constituent Atrovirisidone B.

Based on the idea that the completed Atrovirisidone B structure can be obtained from 2 constituents, with knowledge that ring A has previously been synthesised, during this study a proposed synthetic pathway was tested in attempt to synthesise the ring B structure. Four synthetic steps were tested and altered to optimise the amount of each synthetic intermediate, and keep levels of impurity to a minimum.

Three of the synthetic steps lead to the synthesis of target compound, however, further research is definitely necessary to optimise the synthesis pure compounds and eliminate impurities. The final step of the pathway was unsuccessful, there was a concern for the stability of the starting material in the suggested conditions. A compound of similar structure may be useful for future work on this particular synthetic step.

Although the ring B structure was not obtained, this study has been a good contribution to research. We have been able to gather some knowledge on what to do moving forward to optimise synthesis of the constituents of Atrovirisidone B, and so it still looks to be a good novel drug for the anti-cancer/antibacterial industry.

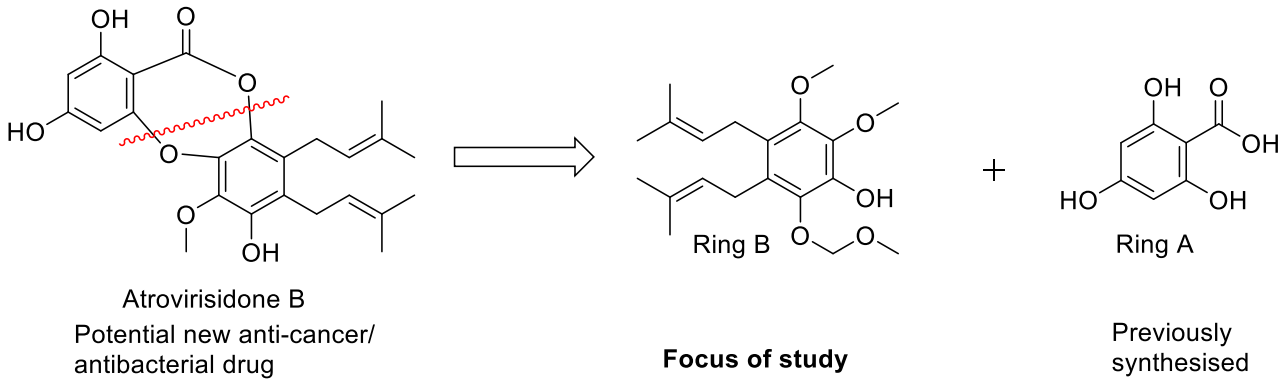

Figure 1- proposed retrosynthesis of Atrovirisidone B to give possible synthetic constituents

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Optimisation of gold coated magnetic nanorods for use in magneto-optical point of care applications

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Sepsis is a “life threatening organ dysfunction caused by dysregulated host response to infection”. Early recognition and prompt therapy can significantly improve clinical outcome.[1] C-Reactive Protein (CRP) is a reliable clinical marker for infection and its fluctuations are typically used to provide guidance on antibiotic therapy.[2] Cotton Mouton Diagnostics (CMD) have developed a magneto-optical sensing device that monitors the rotational behaviour of nanorod reporters. Rod shaped magnetic cores are coated in gold which facilitates attachment of recognition motifs such as antibodies via chemisorption. [3] A polymer is used to coat the core however it may also sterically prevent the interaction between the gold surface and the antibodies. This study aims to investigate methods that would either remove a proportion of the polymer layer or alter it in such a way that would enhance binding efficiency.

As-manufactured batches of gold-coated nanorods were subject to washes with a variety of solvents over an extended time period and the extent of dissolution was analysed using UV spectrometry. Mixed polymer systems were created using poly-acrylic acid (PAA) alongside the existing polymer to provide different chemical functionality at the rod surface. Anti-CRP antibodies were conjugated to the modified nanorods and the efficiency was assessed by performing dot blot tests, magneto-optical analysis and salt titration tests.

Most polymer was removed from the nanorod surface when isopropanol was used as the washing solvent. Although the nanorods displayed good stability post washing, the variability in terms of magneto-optical response between samples suggest that this is not a viable method for improving conjugation efficiency. Mixed polymer systems were successfully synthesised and there was evidence of effective conjugation of antibodies although assay performance was disappointing.

Further investigations that expand on this study may further enhance conjugation efficiency and produce a sensitive nanorod reporter fit for point- of- care applications.

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An Investigation into the Impact of EPMA in South West Wales Renal Unit

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Electronic Prescribing Medicines Administration (EPMA) is an ePrescribing system designed to facilitate prescribing and medication administration in hospitals and their implementation has been initiated over the last ten years.[1] It has been advocated for its ability to decrease medication errors, thereby improving patient safety.[2] Frequent problems with traditionally used paper medication charts include the charts being misplaced, illegible or incomplete.[1] EPMA has replaced the paper charts at South West Wales (SWW) Renal Unit. This project aimed to investigate the impact of EPMA upon the prescribing and administration of medications compared to paper-based drug charts previously employed; the study was conducted in one haemodialysis unit in SWW.

The research method consisted of an audit of medication charts, both paper and electronic, preceding and subsequent to EPMA implementation. Data was obtained from 78 haemodialysis patients from Carmarthen Dialysis Unit. The 'before' and 'after' data were compared to identify changes. Parameters considered were: allergy status, unrecorded medication administrations and discrepancies between the medication charts and the electronic medication record (EMR).

EPMA led to a statistically significant improvement in the recording of allergy status ($p= 0.00455$). The number of unrecorded medication administrations on EPMA was slightly higher (0.21%) than the number on the paper medication charts (0.17%), however all such instances on EPMA could be explained; there were no unintentionally missed doses. Ten discrepancies were identified between the paper charts and the EMR. EPMA has eliminated the possibility of discrepancies due to its consolidation with the EMR.

This project has added to the findings of previous research on the beneficial impacts of EPMA.[1,2] EPMA possesses several advantages over paper medication charts, ultimately leading to improvements to patient safety. Wider benefits include: improved accuracy of auditing; greater access to limited specialist staff; and liberation of staff time.

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To explore and evaluate MPharm students' perceptions of their competency to prescribe after Pre-registration

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Pharmacist independent prescribers (PIP) have brought many benefits to patients and other healthcare professionals.[1] Given NHS plans to increase number of clinical pharmacists[2] and Welsh Pharmaceutical committee plans to implement PIP within every community by 2030,[3] it is clear that the pharmacist role is evolving. The study therefore aims to explore MPharm (Master of Pharmacy) students' perceptions on their willingness to prescribe after immediately post- pre-registration.

Prior to distributing questionnaires, ethical approval was attained to ensure rights of participants were respected. First-year and fourth-year Cardiff University students participated via self-selecting sampling. An email invitation and Facebook advert message were sent to both years. Data was collected using Online Surveys and then downloaded. SPSS® was used to analysis data via descriptive and non-parametric tests.

Ninety-six students participated; 42 first years (response rate = 33.9%) and 54 fourth years (response rate = 50.5%). Study showed that under-graduate students were more likely to prescribe in scenarios that they viewed as more straightforward. Under-graduate students' views on their likelihood to prescribe was influenced by patient-centred care and working with healthcare professionals. Under-graduate students agreed that current MPharm course does not prepare students to prescribe immediately after pre-reg and changes need to be made to better prepare students in becoming independent prescribers.

Pharmacy profession is changing and moving slowly towards prescribing, however, there is a long way to go. There are many factors that influence willingness to prescribe but the main aim is to ensure prescribers prescribe within their competence. The current course is insufficient to support MPharm students to be competent to prescribe immediately post-pre-registration, it must instil core fundamental skills into under-graduate students that enable competent prescribing. Given small sample size, further research must take place to understand under-graduate students' views into their competency to prescribe.

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A Rapid Review Comparing the Efficacy of Single Enantiomer Drugs with their Racemic Counterparts

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The chiral switch, a term associated with the redevelopment of a racemic drug to its single enantiomer has been a popular approach in drug design. To attest to this, there are currently six chiral switches in the British National Formulary. Many argue that switching from the racemate allows for the halving of the dose of the drug, an increase in efficacy and the reduction of unwanted adverse effects. However, there has not been a review of the efficacy of single enantiomer drugs compared to their racemate to prove this claim. The objective of this rapid review is to assess the efficacy of enantiomerically pure drugs in comparison to their racemic counterparts.

This rapid review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) methodology. Randomised studies comparing single enantiomer to racemic drugs in efficacy were searched for in EMBASE, MEDLINE and Web of Science by one reviewer using predefined criteria. 5 from 103 study papers met the criteria and were considered for qualitative review.

The data reviewed shows that from five studies only one study (Beltran *et al.*) was able to prove statistically significant superior efficacy of the single enantiomer over racemic at pharmacologically equivalent doses. Dionne *et al.*[1] could prove no statistically significant difference between the single enantiomer and racemic post 60 minutes, and neither could McGurk *et al*[2]., Ezcurdia *et al.*[3] and Stock *et al*[4].

The information from these five studies comparing the analgesic efficacy of non-steroidal anti-inflammatory drugs (NSAID's) suggested that the single enantiomer's efficacy is not superior to the racemic. However, the methodologies of these papers did not hold up under critical review. The author has concluded that there is currently not enough significant data available to confidently make the claim that single enantiomer drugs have superior efficacy in comparison to their racemic counterparts.

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An Investigation into Analysing Welsh prescribing of items indicated as 'Less suitable for prescribing' between April 2013 to August 2019 to feed into the Low Priority Prescribing project

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In 2018-2019 NHS Wales prescribing expenditure was £0.91 billion, which is 5.9% of total Welsh Government spending.[1] Medicines are considered low priority due to poor clinical effectiveness, safety concerns or an absence of robust clinical evidence and where there are more cost-effective drugs available.[2] The aim of this study was to evaluate trends in the national prescribing of low priority medicines from the BNF in Primary Care and to compare against guideline recommendations and identify opportunities for further learning.

Comparative Analysis System for Prescribing Audit (CASPA) was used to extract and analyse quantitative monthly prescribing data on medicines classed as low priority between April 2013 and August 2019. The trends were then compared to current guidelines and literature pertinent to each medicine.

Overall, across Wales 5 of 14 selected low priority medicines had an increasing prescribing trend with peak prescribing in the number of items between April 2017 to March 2019. The remaining 9 displayed a decreasing trend and the highest number of items prescribed between April 2013 to March 2015 correlate with current guidelines. Two low priority medicines kaolin and morphine mixture and moxisylyte hydrochloride had decreasing prescribing trends compared to their first choice alternatives loperamide and nifedipine.

Increasing prescribing trends for 5 of these medicines run counter to present guidelines. Although off-license and new indications suggested by NICE evidence summaries and guidelines for two of the five medicines, clonidine hydrochloride and progesterone pessary, to some degree explain this.[3,4] Explanations for these increasing trends require further investigation in order to uncover the reasons for this lack of adherence to guidelines.

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Making health-related behaviour changes: a study of MPharm students' application of health psychology models over three years

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It is imperative for pharmacy practitioners to understand the psychology which underpins human behaviour in order to be effective in their professional role as health educators. For this reason, using '*behavioural change as a tool to support health promotion'* is included in the GPhC syllabus for pharmacy undergraduate students.[1] This study aimed to explore students' understanding and experiences of health psychology teaching via completion of a behaviour change activity.

Alongside receiving a health psychology lecture on behaviour change models, second year MPharm students at Cardiff University completed an anonymous two-week before-and-after behaviour change diary which comprised of documenting their chosen behaviour change and reflect on their experiences. Completed diaries were analysed using a mixed methodology: theoretical framework analysis was used to map barriers and facilitators to the COM-B model and the theoretical domain framework (TDF), while thematic analysis of free text comments was used to identify emergent themes.

A total of 137 diaries were submitted by students (2017/18; 73 diaries, 2018/19; 47 diaries, 2019/20; 17 diaries), of whom, 82 (60%) had mapped their behaviour change to a health psychology theory. 143 of reflective statements were mapped to more than one TDF domain, and all 14 domains were utilised. Barriers to behaviour change included shortage of time, environmental constraints and available resources, whilst facilitators included thorough prior planning. Four themes emerged from the students' overall reflections: (1) embedding into daily life; (2) influence of powerful others; (3) student motivation; and (4) patient empathy.

The engagement in this behaviour change activity over the three years varied, with fewer students taking part each year, possibly indicative of students' perception of its significance as a topic. A review of teaching on health psychology theories is therefore required to improve student engagement with this complex subject. Embedding a behaviour into daily life was key to making a successful change, and reinforcement was also perceived important. The activity provided students with an insight to the patient experience and empathy for possible barriers faced by patients when implementing a behaviour change, therefore improving how future pharmacists can provide patient support to make healthy behaviour choices.

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The stability of suxamethonium chloride in polypropylene prefilled syringes using HPLC analysis

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Effective rapid sequence intubation means less discomfort in neonates.[1] It is important to premedicate neonates with the correct dosage to ensure successful treatment. Prefilled syringes are an alternative option to allow the safe delivery of key drugs, like suxamethonium chloride for premedicating neonates.[2] Research has been conducted in the past to assess the stability of suxamethonium outside its original packaging (ampoule)[3], however, no action has been taken from pharmaceutical companies to produce suxamethonium prefilled syringes. For that reason, this project was conducted as it is considered important.

A total of 264 x 1ml test suxamethonium prefilled syringes were made for this project, each containing 10mg/ml of suxamethonium chloride in 5% glucose. For each test syringe 0.2ml was drawn up using a 1ml BD syringe from a 100mg/2ml ampoule and then diluted with 5% glucose to 1ml. No preservatives or additional reagents were added to the syringes. Four testing points were used for comparison and to assess stability, these were 0, 7, 14, 21 days at two different temperatures (room temperature (RT) and fridge(F))). The stability was assessed chemically by using a validated stability indicating HPLC analysis technique and physically by undertaking visual testing techniques, turbidity, particle count and pH measurements.

The results of this project weren't as promising as it would have been hoped. At days 7 RT and 21 F the loss percentage loss of suxamethonium was less than 10%, however, for the 21 RT more than 15% of suxamethonium was degraded, although issues with the HPLC detector meant there were questions about the reliability of the later testing ponts. There was no significant change in pH, but a slight change in turbidity. For practical purposes suxamethonium would ideally need to be stable in prefilled syringes, for a longer shelf life.

More research is needed to assess the maximum shelf life for suxamethonium prefilled syringes. A future where parenteral drugs all are manufactured and prepared in a pharmacy cleanroom setting where good manufacturing practice guidelines are more closely followed. However, this requires more research and development to ensure feasibility.

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An Investigation into the Incorporation of the Antifungal Itraconazole into Dissolvable Biocompatible Polymers (PLA/PLGA)

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Approximately 4.3% of the population suffer with a fungal nail infection (onychomycosis).[1] Onychomycosis is treated with oral antifungals but there are many implications associated with the long term use of oral antifungals. A novel sustained intradermal drug delivery technology is by the use of biodegradable polymer microneedles, two being PLGA and PLA. Thus, the aim of this project was to identify whether itraconazole can be incorporated into a PLGA-PLA polymer with a view to producing 3D-printed biodegradable polymer microneedles.

Drug incorporation was through the process of solvent casting and hot melt extrusion with scanning electron microscopy being used to confirm incorporation. Mechanical testing was carried out on the filaments and discs with and without itraconazole incorporated to determine whether the addition of itraconazole had an impact on the mechanical strength of the formulation. An *in vitro* release study was carried out over 14 days in two different release media (different concentrations of methanol were used), with samples being taken at different time points and analysed using UV-Visible spectroscopy.

SEM images demonstrated that the itraconazole had been incorporated into the polymers. The percentage drug release varied between the filaments and discs along with the medias used. Drug release was shown from the itraconazole filament and disc in the 50% media and the itraconazole disc in the 25% media. There was no significant difference in the mechanical strength of the filament with and without itraconazole incorporated. The discs lacked the mechanical strength to register a reading.

These results prove that the incorporation of itraconazole into a PLA-PLGA polymer is possible through producing solvent cast discs and hot melt extruded filaments. Although there was some release seen from the formulations further work would be needed to optimise the balance of drug release and mechanical strength to produce a candidate material for microneedles.

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Structural optimisation of a new PD-L1 small-molecule inhibitor

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Programmed cell death protein 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1), belong to a group of inhibitory immune checkpoint cell surface proteins. PD-1 is found on activated T cells, while PD-L1 is widely expressed on the surface of normal tissue and cancer cells.[1] PD-1 activation inhibits the function of T-cells protecting the human body from autoimmune diseases.[2] Abnormally high expression of PD-L1 in certain cancers leads to increased PD-1/PD-L1 interaction, inhibiting the function of T cells and the ability of the immune system to eradicate cancer cells.[3] Anti-PD-L1 and anti-PD-1 monoclonal antibodies are used to successfully treat cancers; however, their unfavourable pharmacokinetic profile is associated with toxicities and immunogenicity leading to immune-related adverse events.[4] As a result of a work previously carried out in our research group, five new small molecules were identified as potential PD-1/PD-L1 interaction inhibitors using different molecular modelling techniques and their activity confirmed in a biochemical assay.

This project aims to preform standard medicinal chemistry structural modifications on one of these molecules, AB-2476, preparing a small series of derivatives to be tested in a range enzymatic/cell-based bioassays, in order to understand which components of AB-2476 are essential for its activity.

Eight different structural derivatives of AB-2476 were designed and an appropriate synthetic pathway was developed for their preparation. A new synthetic pathway for AB-2476 was developed.

All eight structural derivatives were synthesised, purified and characterised successfully. AB-2476 was also successfully synthesised and purified developing a new synthesis pathway. Molecular docking studies were performed in order to evaluate the potential binding mode of the new molecules on PD-L1.

The newly synthesised compounds will be evaluated in different biological assays and the results will be used to structurally optimise AB-2476 in order to design new and more potent PD-1/PD-L1 interaction inhibitors.

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Do common anti-Parkinson's drugs influence neuroinflammation in the presence and absence of a stem cell transplant?

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Parkinson's disease diagnoses are expected to rise by a fifth by 2025[1] with current treatments providing symptomatic relief only. Stem cell transplantation is an up and coming treatment for Parkinson's disease[2] (PD) and in Europe clinical trials are in progress. Presently, there is no data on how ongoing medication may affect the way a transplant develops and functions. The aim of this study is to determine how anti-Parkinson's drugs can affect the inflammatory response[3] surrounding a human embryonic stem cell-derived dopaminergic (hESC) transplant. Specifically we aimed to quantify the astrocytic response through immunohistochemistry (IHC).

130 rats were unilaterally depleted of striatal dopamine via a 6-OHDA infusion into the right medial forebrain bundle. Rats were then split into groups; each receiving a different treatment out of L-dopa, ropinirole, rasagiline, citalopram and saline (control) which was continued until the animals were perfused. Each group received either a hESC or a sham graft and immunosuppression for 19 weeks pre-euthanasia. They were subjected to amphetamine rotation tests to evaluate lesion extent and graft success. IHC staining was then conducted using the anti-GFAP antibody followed by optical density (OD) measurements of the striatum and the motor cortex (MC) using ImageJ. A 2-way ANOVA and Dunnett's multiple comparison test were conducted.

Amphetamine rotation results show the hESC grafted animals displayed a significant improvement in rotations with drug treatment having no effect. In the striatum the astrocytic response in the grafted animals was not significant, however, in the MC both the hESC and sham grafted animals displayed a greater astrocytic density in the grafted hemisphere compared to the intact hemisphere.

To increase our confidence in our conclusions this study should be repeated with additions such as OX-42 staining, cell counts and nigral analysis. This study has shown that, after a longer than standard period of drug treatment, the astrocytic response was negligible suggesting that the drugs used do not affect neuroinflammation.

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Evidence to support a mechanism of action for how simvastatin induces apoptosis in human breast cancer cell lines

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Over the past few decades, epidemiological evidence has arisen for an anticancer effect of statins in different solid tumours, leading to the future possibility of repurposing statins as anticancer therapies and the

accompanying clinical and economic benefits that could arise from this. Breast cancer, and in particular Triple Negative Breast Cancer (TNBC), is a condition associated with high mortality; mainly as a consequence of the severely limited treatment options for patients with this form of the disease. This rapid review aims to identify the anticancer mechanism of action for statins in breast cancer cells and use this to support and direct future treatment research to improve patient prognosis.

A literature search was conducted across several research databases in order to find, evaluate and denote trends in papers which outlined statins possible anticancer mechanisms of action in breast cancer cell lines. Searches were assessed using PRISMA and CASP to provide quality assurance for the data arising from each search.

Results indicated that simvastatin induced apoptosis via the intrinsic pathway by decreasing phosphorylation levels in both PI3K/Akt/mTOR and Raf/MAPK/ERK signalling pathways; there was a consensus across the literature that TNBC cell lines were more sensitive to statin treatment. Additionally, data pointed to the role of improved statin drug delivery using immunoliposomes as a potential mechanism to enhance TNBC treatment.

Whilst this study and other work within the field point to a potential role for statins as anticancer drugs in breast cancers, it is clear that further in vivo research is needed alongside enhanced drug delivery approaches to better evaluate statin efficacy in tumours.

What is the optimal approach to treat anaemia using iron for patients with chronic kidney disease (Grade 3-5) who are not receiving in-centre haemodialysis? A rapid systematic review

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Iron deficiency anaemia is common in chronic kidney disease (CKD), particularly at stages 3-5. The current UK national guidelines lack specific detail on dosing iron but provide a generalized strategy for iron therapy in people not receiving haemodialysis.[1] There are slight differences in recommendations by NICE and the UK Renal Association (RA) as to the role of oral iron in ESA-treated CKD patients.[2,3] NICE recommends offering a high-dose low-frequency (HDLF) approach (IV iron doses ≥500mg given in ≤2 consecutive infusions) to ESA-treated non-dialysis patients or when oral iron is not tolerated.[3] However, the guidance on precise dosing protocols to attain and maintain adequate iron stores is not defined. This rapid review aims to establish whether the current literature offers further insight to assist clinicians in their iron treatment decisions in transplant, non-dialysis, home haemodialysis, and peritoneal dialysis patients.

Evidence-based search engines were used to systematically screen the literature for the evidence on optimal iron therapy, including safety and efficacy, in the non-in-centre population.

The search identified eighteen eligible papers, published between 1996-2019, investigating the safety and efficacy of a range of iron therapies. Only one study was identified in transplant patients and none in the home haemodialysis sub-group.

Further iron studies are needed to determine optimal iron therapy in the transplant, home-haemodialysis, and peritoneal dialysis cohorts. The literature demonstrates that the HDLF approach is safe and effective, and oral iron is suitable to consider in maintaining Hb levels after attainment is achieved by IV iron. Although the absolute optimal dose has not been established in this review, the minimum dose of 500mg used to define a HDLF protocol is suboptimal to the suggested dose in the literature, typically a benchmark dose of 1g. In ESA-treated ND people, the literature supports the national recommendations to offer IV iron to attain Hb levels.

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Could certain Amaryllidaceae alkaloids be more effective in the treatment of brain cancer than temozolomide?

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The 5-year survival rate of a brain tumour is 15%[1] resulting in over 5,000 people dying from them each year.[2] Temozolomide is currently first-line chemotherapy treatment for brain tumours[3] however due to the extremely low survival rate, there is a clear need for novel treatments. Alkaloids produced by the Amaryllidaceae family of flowering plants have been discovered to possess substantial anticancer properties towards brain tumours.[4] This aim of this project is to determine whether certain Amaryllidaceae alkaloids could be more effective in treating brain cancer than temozolomide.

A search algorithm was replicated on several online databases; PubMed, SciFinder, EMBASE and Web of Science. Inclusion criteria of Gi_{50} (growth-inhibitory) data was decided upon to choose the final number of papers. These values were then compared to values for temozolomide to determine whether Amaryllidaceae alkaloids possessed stronger anticancer activity. The PRISMA Flowchart displays that the number of papers on the Amaryllidaceae alkaloids found through searching on all four databases were narrowed down from 154 to the final 11 papers allowing a rapid systematic review to be conducted.

A quantitative analysis determined that the GI_{50} values for the alkaloids ranged from 0.029-99 μM compared to weaker values of 22.5-719 μM for temozolomide. Overall, the alkaloid that demonstrated the strongest anticancer activity was narciclasine with an GI_{50} value of 0.029 μM and the alkaloid that demonstrated the weakest anticancer activity was bulbispermine with a GI_{50} value of 99 μM.

The data within this review supported the claim that certain Amaryllidaceae alkaloids possessed superior anticancer activity towards brain cancer cell lines than temozolomide. Cardiff School of Pharmacy is currently investigating which compounds with anticancer activity are present in the juice of daffodils. Therefore, the chemical structures of promising Amaryllidaceae alkaloids within this review could aid the identification of additional alkaloids within the daffodil juice.

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The Design of SPAK and OSR1 Kinase PROTACs as Therapeutic Agents

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SPAK and OSR1 are protein kinases involved in the WNK-signalling cascade; an important pathway in the control of blood pressure. Due to the incidence of resistance, allergies and intolerance associated with current antihypertensive treatments, there is demand for novel drugs.[1] PROTACs are heterobifunctional molecules consisting of three components, with the ability to hijack the ubiquitin proteasome pathway (UPP). The UPP is a system that induces degradation of specific disease causing proteins.[2] These findings have led to a novel approach to identify, design and synthesise PROTAC molecules to be used as therapeutic antihypertensive agents by degradation of SPAK and OSR1 protein kinases.

An online literature research identified various molecular fragments that have been selected and chemically combined to form the general structure of a PROTAC molecule; the E3 ligand, linker and warhead. Using SwissADME, the physicochemical properties of six novel PROTACs formed were analysed and two PROTACs identified for potential therapeutic use. The proposed synthesis of each PROTAC was then illustrated.

VHL has been shown to be a superior inducer of targeted protein degradation in cancer cell lines and was identified as a more suitable E3 ligase target in contrast to CRBN to hijack the UPP.[3] The selection of two linkers, consisting of 19 and 10 atoms in length and compounds 13, 14 and 20 were selected as suitable warheads to complete the design of six novel PROTACs.[1, 4] Comparison of physicochemical properties resulted in the selection and illustrated proposed synthesis of two prime candidates, namely SGW002 and SGW005.

In vivo studies and mass spectrometry techniques are required to confirm the effectiveness and selectivity of SGW002 and SGW005 as therapeutic agents for hypertension.

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Evaluating adverse drug reaction (ADR) reporting from April 2017 to March 2019 at the Welsh Medicines Information Centre (WMIC)

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ADRs impact both individuals and healthcare systems and are a leading cause of hospital admissions.[1] Since 2011, pharmacy staff in medicines information (MI) have been able to report ADRs directly through MiDatabank,[2] the software used to manage enquiries. No peer-reviewed research has been conducted into reporting rates via this route. This project therefore aimed to evaluate ADR reporting rates through MiDatabank and to understand the views of MI staff about MiDatabank as a method of ADR reporting, particularly relating to barriers and facilitators.

To determine reporting rate and investigate possible factors influencing this, phase one consisted of secondary analysis of ADR related MI enquiries at WMIC from 01/04/2017 to 31/03/2019, to establish whether they were a) reportable and b) reported. Results were analysed using Microsoft Excel and SPSS. Phase two used focus groups to explore the views of MI staff, following School Ethics approval. Focus groups were audio-recorded, transcribed and thematically analysed.

In total, 61% of patient-specific ADR-related enquiries were reportable. The overall reporting rate of reportable ADRs was 34%. Of the factors investigated, status of enquirer and route of response had the greatest impact on reporting rates. Five discussion themes were identified from the focus groups: technical ADR reporting issues, knowledge of how to report, knowledge and attitudes towards ADR reporting, barriers in MI versus other areas of practice and understanding guidance.

Reporting rates were higher than expected, but significant numbers of ADRs remain unreported. Further work is required to determine whether these results are generalisable to the rest of Wales. MI staff identified a number of barriers to reporting and many of these were similar to those experienced by hospital pharmacists in general,[3,4] despite the unique working environment of MI. Recommendations from this project involve changes to training and ADR reporting software. These changes could increase ADR reporting, which will ultimately enhance patient safety.

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Design and Synthesis of Novel non-nucleoside inhibitors of Human Norovirus

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Human norovirus is the most common cause of acute gastroenteritis which has associated with significant health and economic consequence globally.[1] So far, no vaccination and therapeutic treatment are licensed to treat this infection while this raises the interest of investigating potential antiviral candidates. RNA-dependent RNA polymerase is a fundamental target in antiviral research. One of the three allosteric binding site, site B, has reported as an ideal target for de novo drug development.[2] A previous study reported two novel scaffolds, which bind to site B, obtain a promising inhibitory activity. Therefore, this project aims to modify the scaffolds to synthesise novel small molecules that have improved the drug-like properties[3].

The novel compounds were synthesized in the laboratory according to a four steps synthesis effort that has reported previously.[3] Products were purified by column chromatography or recrystallisation. Several chromatography and spectra, such as TLC, UPLC-MS and NMR were used to analyse the synthesized compounds. After that, docking studies were carried out in order to investigate the binding efforts between the new compounds and the binding pocket of RdRp by using Glide. 10 poses per each novel compound were prepared, which was then undergo visual inspection in MOE.

8 novel compounds were synthesized in the laboratory based on the optimized synthetic effort from previous study. A poor to good range of yield were obtained, which the poor yield is potentially due to poor solubility in the solvent. Docking of the new compounds revealed theoretical interactions with the RdRp site-B.

The binding efforts revealed new compounds that obtained ability to inhibit human norovirus RdRp. The inhibitory activity of the newly synthesized compound will be examined in the biological assay. Potential candidates will be evaluated the structural activity relationship and further optimized to improve the drug-like properties.

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An exploration of the views and experiences of Welsh speaking patient's on the use and availability of pharmacy services provided through the medium of Welsh.

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Communicating effectively is essential to patient-centred care and improving patient satisfaction.[1,2]

Due to most Welsh speakers having the ability of also speaking English fluently, it is often a language barrier that isn't noticed by many service providers in healthcare settings.[3] Welsh language standards and duties are expected of NHS services and independent primary care providers.[4] These include utilising bilingual advertisement and documents, establishing and respecting language preferences of patients and also raising awareness of the availability of Welsh language service provision. The aim of this study was to explore the views and experiences of Welsh speaking patient's on the use and availability of services provided through the medium of Welsh by pharmacies.

Due to the exploratory nature of the study qualitative focus groups were chosen as the data collection tool. Non-probability purposive sampling was used to recruit participants ensuring they met the study inclusion criteria; 1)Welsh speaking 2)Use of pharmacy services. Focus groups were audio recorded and transcribed verbatim. Data was thematically analysed to identify themes and sub-themes.

Four main themes were identified: Influential environmental factors, identifies how family background and location influences language choice, Welsh awareness and availability; Wellbeing, identifies sensitive and emotional factors in relation to communication; Language proficiency, identifies the language standards

accepted and expected of medical professionals by patients; and Provisional expectations, identifies the current delivery of Welsh provision, imbalance of responsibility and considerations for future improvements.

This study concluded that Welsh services by healthcare providers are not made clearly available. There is a lack of awareness of the importance of bilingual provision and the beneficial impacts of patients having their preferred language choice. Further studies are required to explore views on the Welsh service availability nationwide, evaluate the success of the active offer across Wales and future improvements to the visible awareness of Welsh provision availability.

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Exploring the Independent Prescribing Role of the Community Pharmacist

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The role of independent prescribing began in 2006 which allowed other healthcare professionals including pharmacists, as well as doctors and dentists, to prescribe medication to patients within an area of competence.[1] Independent prescribing was mostly observed in secondary care but has developed into primary care since the introduction of GP clusters in 2015. This role has recently expanded into community pharmacy with the Welsh Government proposing to introduce an independent prescriber into every community pharmacy by 2030.[2] However, there is little research surrounding their role in this setting so the aim of this project was to investigate the views of independent prescribing community pharmacists on their role and associated training.

To carry out this research a qualitative methodology was used in the form of semi-structured interviews. A purposive sampling method identified appropriate individuals.[3] Once ethical approval was gained from Cardiff School of Pharmacy and Pharmaceutical Sciences' school Ethics committee, gatekeepers were utilised to facilitate participant recruitment. Once interviews were completed they were transcribed and inductive and deductive thematic analysis was performed.[4]

Twelve interviews were conducted. The attitude towards training was positive, however, a greater emphasis on physical assessments was suggested. The pharmacists used their qualification to provide successful services within community pharmacy including a minor ailments service and addiction clinic. Nevertheless, the main barriers identified to its implementation were lack of funding, lack of support and limited access to GP records. All participants were supportive of the 2030 Vision, however, many doubted the likeliness of its success due to identified barriers.

This research identified challenges to the implementation and continuation of the role in community pharmacy. Recommendations have been provided including emphasis on hands-on skills within the MPharm degree and a standard framework for funding to be reviewed by relevant bodies.

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Testing the chemical and physical stability of folinic acid a chemotherapy adjunct in a continuous ambulatory delivery device (CADD)

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Chemotherapy is a long and complex treatment for many cancers. With advances in medicine patients are often living longer, meaning that the burden financially and socially on the NHS becomes extreme [1]. However, some of the burden can be reduced from the usage of continuous ambulatory delivery devices (CADD's), meaning chemotherapy and its adjuncts such as folinic acid can be given to patients in the comfort of their own home. There is currently little information on folinic acids stability within CADD's. Therefore, this project aims to assess folinic acids stability within a CADD during storage and in use temperatures by patients.

10 CADD cassettes were prepared containing 10mg/ml of folinic acid solution. 5 cassettes were stored at 4℃ (storage temperature) and 5 were stored at 40℃ a realistic maximum in use temperature by patients. Cassettes were sampled at day 0,3,7 and 10 and diluted to 0.5mg/ml with saline. These samples were then chemically analysed for stability via high performance liquid chromatography (HPLC). Samples were also analysed for physical stability by visual inspection, turbidity, particle count and pH measurements.

Both groups of cassettes stored at 4 and 40℃ remained above 90% of the original concentration for the entire 10-day testing period. No major increase in known degradation peaks were detected, also no new peaks were detected when comparing cassettes against a control folinic acid stored in a glass vial, indicating no incompatibilities with the container. Physical testing also indicated stability.

The results of the project show that folinic acid is stabile within the CADD cassette for a minimum of 10 days, consistent with extended stability data from Levofolic's® manufacturer Medac Pharma [2]. Thus, allowing the cassettes to be aseptically made and stored prior to dispensing to patients and given to patients to receive in the comfort of their own home.

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Evaluation of Inhaler Asthma Control, Inhaler Technique and Adherence in a Community Pharmacy setting

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339 million people are affected by asthma worldwide and it is responsible for 100 deaths per day.[1] In the last 5 years, there has been a 20% rise in deaths caused by asthma in the United Kingdom.[2] Potential causes are poor inhaler technique and adherence. The aim of this study is to investigate whether poor asthma control is caused by inadequate inhaler technique and poor adherence.

Convenience sampling was used to recruit 55 patients from 6 community pharmacies in South Wales. Participants read a Participant Information Sheet and were helped to complete the following: Patient Consent Form, Data Collection Sheet, Asthma Control Test (ACT), Test of Adherence to Inhalers (TAI) questionnaire. A Vitalograph Aerosol Inhalation Monitor (AIM) device measured inhaler technique. Mann-Whitney U or Kruskal-Wallis test was used to determine statistical differences among groups.

Major findings include 67% of patients had uncontrolled asthma. 48% of overall inhaler technique obtained a fail (Dry powder inhaler assessments scored the lowest fail percentage at 24%), indicating poor inhaler use. Metered dose inhaler (MDI) technique was significantly worse compared to the other inhalers and more MDI users shook their inhalers (38%) compared to MDI with spacer users (18%). When looking at all inhaler devices, 64% held their breath however, MDI users were more likely to hold their breath when compared to the other inhalers. 78% of patients demonstrated poor adherence. Lastly, a significant difference was found between asthma control and education.

Between poor control, inhaler technique and adherence, no significant differences were detected. However, similar studies testing similar parameters have found a correlation. [3,4] Repeated studies with larger sample sizes would be needed to find a significant difference between the three parameters.

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Correlative analysis of proteins regulating lipoprotein binding and endocytosis in cell lines tested for lipid nanoparticle mediated mRNA delivery

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Lipid nanoparticles (LNPs) have gained significant attention for their potential as vectors for intracellular messenger RNA (mRNA) delivery. mRNA utilised as a therapeutic possesses potential for curing several rare and debilitating conditions by directly targeting their genetic drivers. The delivery of bare mRNA has posed numerous difficulties because of its anionic and macromolecular nature.[1] Due to several other contributing troubles, LNPs are required to encapsulate mRNA to facilitate successful transport across the plasma membrane into cells. The mechanism of LNP uptake has been associated with low density lipoprotein receptors (LDLR) where LDLR mediated endocytosis facilitates intracellular LNP entry.[2] Recent research established that cancer cell lines HCT116, H368 and SCC9 exhibited varying expression of a protein encoded by LNP encapsulated mRNA.[3] HCT116 was deemed the best expressor, H358 a medium expressor followed by SCC9 the worst expressor.[3] This project aimed to identify the differential expression of LDLR in these cell lines to determine which were significant in LNP delivery. Consequently, there is hope for optimisation of future LNP formulation to enable optimal interaction with key receptors.

Total RNA was extracted from HCT116, H358 and SCC9 cells and used for complementary deoxyribonucleic acid synthesis (cDNA) through reverse transcription. Quantitative polymerase chain reaction (qPCR) was performed to determine the mRNA expression levels of several LDLR primarily: LDLR itself, VLDLR, ApoER2, SCARB 1, 2 and 3.

Despite HCT116 previously exhibiting the best protein expression through LNPs, it presented the lowest mRNA expression of many LDLR whereas SCC9 illustrated the greatest. This elucidated that solely LNP transport into cells may not be problematic however poor endosomal escape of mRNA may limit expression

It can be concluded that therapeutic mRNA expression is not only reliant on LDLR but is multi factorial. It can be speculated that endosomal escape of mRNA is equally important requiring further investigation.

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Molecular modelling studies on the structure and function of Nicotinamide mononucleotide adenylyl transferase 2.

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Nicotinamide mononucleotide adenylyl transferase (NMNAT) is the vital enzyme of the Nicotinamide adenine dinucleotide (NAD) biosynthetic pathway catalysing the formation of NAD through the nucleophilic attack of ATP's.[1] NMNAT exists in three human forms NMNAT1, NMNAT2, and NMNAT3, with each differing in gene sequence, catalytic properties and patterns of gene expression. NMNAT2 is the only isoenzyme whose crystal

structure has yet to be resolved.[1] NMNAT agonists have been studied for use in glaucoma gene therapy[2], with the ligand Epigallocatechin gallate(EGCG)[3], a polyphenolic constituent of green tea known to activate the enzymatic action of NMNAT2. This study aimed to locate EGCG binding pockets on a homology-based structural model of NMNAT2.

A structure-based approach was used to construct an NMNAT2 homology model. This model was refined by using molecular dynamics simulations in a solvent box to obtain a 3D structure.[1] This structure was assessed and binding sites within the structure were Site mapped using Glide. Docking processes were then used to model the interaction between EGCG and the protein NMNAT3 at the atomic level.[4] Comparative analysis was then undergone to establish effective binding pockets associated with NMNAT2.

The overall sequence identity of our homology model is 34%, with 52% positive residues and only 15% of the overall sequence missing. The results of the study also identified 7 suitable EGCG pockets within the structure of NMNAT3, that would potentially induce conformational changes upon binding. This proved the study results beneficial.

Though our results were promising we could not locate the EGCG pockets found in NMNAT3 within the NMNAT2 structure created by our homology model. Further research is required into the structure of NMNAT2 as well as a supplementary comparative analysis to detect the EGCG binding pockets within the structure of NMNAT2.

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A Rapid Review of The Testing Methods Used to Analyse two Critical Quality Attributes (Dissolution and Puncture Performance) of Coated Microneedle Delivery Systems

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Despite the clinical promise of microneedles (MNs) as a novel transdermal drug delivery system for a range of therapeutic candidates, the Critical Quality Attributes (CQAs) of the delivery system and associated standardised CQA testing methods have not been identified.[1] In order for developers to assess the safety and performance of MNs for the regulatory authorities, testing methods are needed to characterise MN CQAs. However, there are no specific standardised test methods currently available for the MN dosage form and therefore work is required to identify potentially suitable test methods. This study aims to perform a rapid review of the published literature to identify and evaluate testing methods that have been used to assess two CQAs of coated MNs for use in skin, namely dissolution and puncture performance.

A comprehensive rapid review of the published literature was carried out using the online databases OVID, Embase and Medline in order to collect information regarding the testing methods used to analyse dissolution and puncture performance of coated microneedle delivery systems. The principles of PRISMA were followed to identify and screen publications for eligibility using a designated inclusion and exclusion criteria.[2]

The rapid review identified 2379 initial publications, which were then screened for eligibility. A total of 15 publications described dissolution testing for coated MNs and 25 publications described puncture performance. From these publications, testing methods and their parameters were qualitatively evaluated. Results demonstrated that dye staining of MN created pores is the most developed and frequently used method for testing puncture performance. For dissolution testing however, publications lack detail and consistency in the testing methods and parameters used.

This study exposes the need for the development of standardised, well documented and validated test methods for dissolution and puncture performance of coated MN delivery systems in order to accelerate innovation and commercialisation of MN products.

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Viral Gene Therapy: still cursed by history?

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It could be argued that, nowhere in therapeutic development, has the promise been greater and the failures more widely-publicised than in viral gene therapy for inherited genetic conditions (VGTIGC). In the early days, VGTIGC brought hope of a cure for devastating genetic conditions, however, serious adverse events related to faults in viral vectors put these hopes to rest.[1] The objective of this study is to review descriptive data on VGTIGC clinical trials conducted worldwide from 1989-2018, to determine if VGTIGC is still being held back by its history and to predict the future of the field.

A publicly available database, 'Gene Therapy Clinical Trials Worldwide',[2] along with a second source, were used to extract the following data on the clinical trials: date of initiation, country of origin, disease targeted, gene transferred, status, phase, enrolment and sponsor.

Between 1989-2018, 281 VGTIGC clinical trials have been conducted. This number did not increase steadily over time but peaked in 2018. The USA have conducted the majority of clinical trials (45.2%) but the number of trials initiated in China is on the rise. The three main indications targeted are Adenosine Deaminase Severe Combined Immunodeficiency, Cystic Fibrosis and Chronic Granulomatous Disease, however, with no success. Only a small percentage (8%) of clinical trials have reached phase II/III or III, of these the AAV is the main vector used. Currently, 5 VGTIGC products have receive marketing authorization.

It would be unfair to say that VGTIGC is still being held back by its early setbacks. With better characterization of the viral vectors and diseases treated, the major safety issues surrounding the field are no longer such a concern.[3] Although the success rate of clinical trials are low and there are still hurdles to overcome, it seems VGTIGC might finally become a reality in the near future.[4]

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Antimycobacterial activity of Triazole derivatives: A rapid systematic literature review

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Mycobacterium Tuberculosis (Mtb) is a contagious pathogen that has had a staggering global impact and is a leading cause of mortality.[1] Triazoles are heterocyclic compounds with a broad spectrum of biological activities that has received increasing attention in biomedical research in recent years due to their versatility and the many derivatives that can be synthesised from them to produce functional motifs.[1] They have gained interest in recent years due to their potential as antimicrobial agents. Due to the development of drug-resistant TB and increasing spread of TB, the need for novel antimycobacterial agents has risen.

This rapid systematic review displays evidence in the literature of the *in vitro* antimycobacterial activity of triazole derivatives from 2009 to 2019. Three bibliographical databases were used (Scopus, Web of Science and PubMed), resulting in a total of 18 studies that were included in this review based on the eligibility criteria set and specific search terms used. The selected data was imported into EndNote X for title/abstract screening

and the articles carried through were full text screened. The data from the included articles were extracted into Word 2016 tables for comparison and analysis.

All triazole derivatives investigated were produced by chemical synthesis. A total of 34 derivatives emerged as promising antimycobacterial agents with a MIC value of 6.5 µg/mL or lower meaning 18.79% of the investigated triazoles displayed potent activity against Mtb. Only six studies calculated a CC_{50} value and gave an accurate selectivity index so not enough data on cytotoxicity was published.

The findings show triazoles and their derivatives warrant further investigation due to exhibiting potent activity against Mtb. There was a lack of information regarding cytotoxicity and the microbiological target of the triazole compounds. Further studies must be conducted to reveal their pharmacological profiles to better understand their risk factors and the pathophysiology of diseases caused by mycobacterium.

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A rapid review on the prevalence of antidepressant use and prescribing in Parkinson's Disease

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Depression is now widely recognised as one of the major non-motor symptoms (NMS) of the neurodegenerative disease Parkinson's (PD) , however depression has been underdiagnosed by General Practitioners due to a lack of recognition of the NMS presenting with PD.[1,2] The aim of this study was to produce a rapid review to determine the prevalence of antidepressant use in people with PD and to determine prescribing patterns in relation to the diagnosis of Parkinson's using a systematic review methodology.

The prevalence and use of antidepressants to treat depression as a NMS within Parkinson's was assessed by using a systematic literature search of Ovid MEDLINE (from 1990-present) to collect the studies cross linked with depression, antidepressants and PD. The titles, abstracts and full length of texts of these articles were analysed for relevance, depth of information and quality of data. After eliminating duplicates and evaluation of quality 6 articles were identified which specifically focussed on depression and antidepressant use in Parkinson's.

The results showed that with age, depression worsened when comorbid with PD. In several studies Selective Serotonin Reuptake Inhibitors (SSRIs) were found to have the highest prevalence of prescribing, but when examining prescribing factors, one study found that irrespective of the presence of Parkinson's the pharmacological treatment did not change.[3,4]

Due to little conclusive evidence towards the optimal treatment for patients suffering with depression in PD, this gives an insight into the need for more information and research into the area surrounding depression in PD. The future goals should aim to produce guidelines for the management of the condition, providing the best possible patient-centred care and overall improving patient's quality of life.

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Should nationwide prescribing incentive schemes be rolled out across Wales?

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With the increasing awareness of public health threats, such as antimicrobial resistance, health bodies are employing various strategies to manage these issues.[1] Currently, in Wales, local health bodies operate and offer prescribing incentive schemes to their regional areas as one method to improve prescribing.[2] This study

aims to explore whether Wales would benefit from a national prescribing incentive scheme in place of the local schemes currently used.

Eight semi-structured one-to-one interviews were conducted with health care professionals from medicines management teams across three health boards in Wales. The interview transcripts were thematically analysed and key opinions and trends captured. Predetermined topics of interest covering the participant's understanding of their local prescribing incentive scheme, the impact and application of the scheme and their views on the potential introduction of a national scheme, were explored.

Participants described prescribing improvements made, in terms of clinical effectiveness, cost-effectiveness and safety, as a result of their local prescribing incentive schemes. Negative views predominated in response to the proposed national prescribing incentive scheme, mainly due to the anticipated loss of ownership and specificity to individual locality needs and patient demographics. The feasibility of running a prescribing incentive scheme at a national level, that would also be representative and fair to all practices, incited scepticism. The main perceived benefit of a national scheme was the standardisation of prescribing quality across Wales.

The absence of supplementary information on the structure of the proposed national scheme limited the ability of participants to make informed comparisons to the existing local schemes. In future research provision of this information will increase the reliability of the initial findings in this study regarding the views on the proposed national scheme. A questionnaire would allow scaling of this study to cover a larger number of healthcare professional and geographical area.

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EPRS and further aminoacyl tRNA synthetases in antihormone-resistant breast cancer in vivo and in vitro

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Antihormones (AHs) block oestrogenic signals in oestrogen receptor positive (ER+) breast cancer (BC) giving initial durable responses, but often AH resistance develops[1]. Many resistance mechanisms have been proposed, including ER loss and EGFR/Src kinase upregulation, but effective treatments remain needed. The multi-synthetase complex-associated aminoacyl tRNA synthetases' (MSC-associated ARSs) canonical function is in early translation[2], but several have been implicated in cancer[3].This includes EPRS (glutamyl-prolyl-tRNA synthetase), which has been found in ER+ BC. This project aims to determine if MSC-associated ARS expression associates with AH resistance in vivo and in vitro or with ER+ clinical outcome.

An immunocytochemical assay was developed for EPRS. H-scoring quantified the impact of initial AH treatment (10^{-7}M 4-OH-tamoxifen, 10^{-7}M Faslodex or oestrogen deprivation) on EPRS expression in AH-responsive MCF7 cells. EPRS expression in acquired Faslodex-resistant cells (FASR) and its regulation by EGFR or Src pathways implicated in resistance (using 10^{-6}M gefitinib or saracatinib treatments) was also explored. Affymetrix microarrays profiled MSC-associated ARSs mRNA across a broader AH-resistant model panel, also considering ER status. KMplotter determined if mRNA expression of the MSC-associated ARSs were associated with ER+ patient outcome.

There was no significant difference in EPRS protein or mRNA expression in FASR versus MCF7 cells. AH-treatment of MCF7 cells modestly-decreased EPRS expression. FASR expression was unaffected by EGFR or SRC inhibition. However, there were significant increases in the mRNA expression of further MSC-associated ARSs in resistant models, irrespective of ER status and AH-type; these also significantly related to shortened relapse-free survival in AH-treated ER+ BC patients.

These findings suggest that altered MSC-associated ARS expression occurs in AH-resistance. Given that inhibitors are emerging to target such enzymes[4], they are worthy of continued study determining their contribution to AH response and resistance, to ascertain if they could be novel targets or biomarkers to tackle the problem of ER+ AH-resistance.

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Do statins reduce the risk of breast cancer?

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Breast cancer is the leading cancer in women in the UK.[1] A staggering 1 in 7 women in their lifetime will be diagnosed with breast cancer.[1] Subsequently, there is the constant demand and pressure to identify novel therapies to reduce risks of breast cancer incidences. Statins are well established for their role in lowering serum cholesterol levels and commonly prescribed to reduce the development of cardiovascular diseases. [2] Interestingly, epidemiological studies have investigated statins and its associations with breast cancer risk. Statins have shown to exert anti-carcinogenic effects via inhibition of the mevalonate pathway and the vital downstream products associated with cholesterol synthesis.[3] Also, there is evidence demonstrating statins interfering with cell proliferation, migration and inducing apoptosis; thus, inhibiting tumour development.[4]

A rapid review was initiated in a 6-week period undergoing a comprehensive literature search utilizing 4 online databases: Scopus, Web of Science, PubMed and EMBASE; in order to evaluate whether there was an association between statins and reduced risk of breast cancer.

Findings suggested mixed results. Some found increased breast cancer risks with increasing duration of statin use, which was also apparent in women expressing oestrogen receptor-positive tumours; whereas patients at risk of contralateral breast cancer alluded to decreased risks. Some observed lipophilic statins, especially fluvastatin, had demonstrated reduced breast cancer risks and null associations noticed with hydrophilic statins. However, null associations were also illustrated across numerous studies focusing on duration and type of statin. Overall, there appears to be no clear associations between statin use and breast cancer risk; however, analysis of specific populations yielded favourable results to certain patient groups. Therefore, further investigations are warranted focusing on type and duration of statin, to develop consistency with prior findings and give rise to the potential development of a promising novel therapy to lower the risk of breast cancer.

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Developing a rapid diagnostic test that can determine the antibiotic susceptibility of *Staphylococcus aureus*

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has remained a threat since its discovery in 1961.[1] Of the 805 cases of MRSA in England in 2018-2019, 779 had mortality outcome information with 24.5% resulting in death.[2] Current methods take 18-24 hours to determine antibiotic susceptibility, in which time inappropriate treatments may be used. Delaying effective treatment results in patients' conditions worsening or becoming deadly. This study aimed to develop a rapid diagnostic test capable of becoming a point-of-contact testing device that detects the antibiotic susceptibility of *Staphylococcus aureus*. [3] The test detects the MecA gene, which causes resistance in MRSA by altering a penicillin binding protein, called PBP2a, to lower affinity for βeta-lactam antibiotics, including oxacillin.

10 confirmed *Staphylococcus epidermidis* strains were isolated from 16 skin swab samples. 8 MRSA isolates from in-house collections were confirmed as methicillin-resistant. Phenotypic characterisation testing differentiated between the *Staphylococcus* species.[4] DNA extracted from each isolate, using a commercial kit, was screened with DNA probes designed by Cardiff University in an enzyme-linked immunosorbent assay (ELISA). The *S.epidermidis* isolates were markers of the ELISA's ability to differentiate between *S.aureus* and MRSA, and non-*S.aureus Staphylococci.*

No template controls, which contained no DNA, were incorrectly identified as *S.aureus* and MRSA by both *S.aureus* and MecA+ DNA probes in 45.5% of repeats conducted. *S.epidermidis* isolates also consistently produced stronger signals than the MRSA isolates in the MecA+ assay. This can be attributed to non-specific binding creating false-positive results.

The probes' ability to non-specifically bind and create false signals indicates that the probes require redesigning before this project can be developed further. Although the results of this study did not fulfil the objectives, the current promising research with rapid POCT devices and previous studies undertaken in Cardiff showing good results indicate that this is a definite alternative to traditional culturing and antibiotic susceptibility testing.

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Evaluating the factors that contribute to Asthma Control

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Asthma control has a significant effect on quality of life[1], yet studies suggest uncontrolled asthma is still highly prevalent.[2] With asthma prevalence expected to continue to rise[3], asthma deaths related to uncontrolled asthma may follow the same trend. This study aims to identify the factors that contribute to asthma control.

52 participants were recruited from 6 pharmacies across Wales via convenience sampling. Participants completed questionnaires including the Asthma Control Test, Test of Adherence to Inhalers and a General Information Questionnaire. Inhaler technique was identified using a Vitalograph Aerosol Inhalation Monitor (AIM) as well as visual inspections of factors not covered by the AIM.

Results in this study reflect poorly on the clinical management of asthma, most notably: 67% of the sample had uncontrolled asthma with 90% having inadequate adherence. Participants typically displayed severely deficient inhaler technique, with dry powder inhaler technique superior to metered dose inhaler (MDI) technique. The majority of participants were prescribed MDI only (73.1%) with very few using a spacer device (13.5%). GP's did not ask their patients to demonstrate their inhaler technique in the vast majority (71.4%) of cases. In contrast, nurses and pharmacists asked their patients in over 80% of cases, those who were asked to demonstrate their inhaler technique displayed significantly superior inhaler technique compared to those who were not. No statistically significant relationship was identified between adherence, inhaler technique, previous inhaler education, socioeconomics or smoking status with asthma control.

This study highlights that asthma treatment requires considerable improvement. This study enabled investigators to directly improve inhaler technique by training participants correctly, thus demonstrating the opportunity that lies within community pharmacies and may offer patients a more accessible means to improve asthma control. Further research is required to fully understanding why inadequate asthma control, adherence and inhaler technique is still so prevalent.

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Molecular Modelling Investigation on Narciclasine Potential Biological Targets

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Narciclasine is isolated from the bulb of daffodils from the Narcissus species.[1] Alkaloids from this family are thought to have lots of different pharmacological properties such as anticancer, antibacterial and antifungal [2]. In particular, narciclasine has shown to be an effective anticancer compound. It is thought to be effective against cancers by inhibiting the ribosomal eEF1A elongation factor.[3] Recently, it has been shown to be effective in treating brain cancer.

The aims of this project was, using different molecular modelling techniques, to identify a pool of biological proteins as potential narciclasine targets (as anticancer compound) and off targets.

Molecular docking and dynamic simulations were used to determine whether narciclasine could bind to the different proteins. ΔG binding energy calculations were also performed to evaluate the strength of the different narciclasine/protein complex. MOE and Maestro software was used for these proteins.

A pool of 18 potential biological targets for narciclasine were identified. According to this week, four of these had a high potential to be a target or an off-targets for narciclasine. The four identified proteins were; thymidine phosphorylase (PDB ID: 1UOU), D-amino acid oxidase (PDB ID: 2DU8), adenosine A2a receptor (PDB ID: 3PWH) and serine/threonine-protein kinase 2 (PDB ID: 4I5M). In particular, examining the modelling results obtained for known proteins thymidine phosphorylase inhibitors and narciclasine, we obtained better results for narciclasine indicating that thymidine phosphorylase could be a potential biological target for its anticancer activity. D-amino acid oxidase was found to be a potential off-target binding site for narciclasine.

The study concluded that there are different potential biological targets from narciclasine, also including some possible off-targets. Further studies, including different biological evaluation, around narciclasine and these selected proteins should be conducted in order to determine the effects/impacts that could have the use of narciclasine as an anticancer treatmeny

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What are the Effects of PINK1 Modulators on the Immune Response?

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PINK1 is a protein kinase that is responsible in mitochondrial quality control. It removes dysfunctional mitochondria through mitophagy which reduced the oxidative stress by exerting its neuroprotective properties. PINK1 mutation is involved in the pathogenesis of early-onset Parkinson's disease. Several small-molecule of PINK1 activators have been developed as a new therapeutic approach for Parkinson's disease (PD).[1] This protein kinase is important for the treatment of PD but now it is becoming more or equally important in immune response. As recent studies have discovered the role of PINK1 in regulating adaptive immunity.[2] This means that small-molecule of PINK1 modulators developed for PD will have different impacts on the immune response. Hence, this project aims to establish the role of PINK1 in immunity and predict the possible effects of PINK1 modulators on immune response.

This is a literature-based project where online databases were used to search for the relevant papers involving PINK1 and immunity. Primary research papers that comply to the inclusion and exclusion criteria were analysed and relevant data is extracted in order to support the aim of this project.

PINK1 plays a role in both innate and adaptive immune response. Loss of PINK1 leads to abnormal cytokines production and activated mitochondrial-specific antigen presentation which predispose neurons to

inflammation.[2] PINK1 upregulates the signaling pathways that trigger innate immune response upon cytokine stimulation[3] and viral infection[4].

PINK1 modulators can result in different immune response. Small-molecule PINK1 activator developed for PD can lead to immunosuppression. It may also help the body to fight off infection via enhanced innate immune response. Further research is required to expand the knowledge of PINK1 and immune response as its significance in the immune system has been revealed.

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Antibiotic activity of oxadiazole derivatives: a rapid systematic literature review

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The need for a new class of antibacterial agents is rising. Since their first discovery in the early 20th century, and the subsequent “golden era” of antibiotic discovery from 1940-1960 when antibiotics resulted in easy therapeutic treatment of common bacterial infections.[1] This era was followed by the emergence of antimicrobial resistance; a current global issue that has grown in the past decades. Antibiotic discovery, conversely, has decreased since the 1960s. The demand for a new antibiotic class is increasing, and the oxadiazole class is a potential candidate.

Oxadiazole is an azole compound that has shown antibacterial activity in previous studies. This review was designed to assess the antibacterial activity of oxadiazole derivatives through searching three databases (PubMed, Scopus and Web of Science) for literature on this within the past decade (2009-2019). Oxadiazoles with promising antibacterial activity (minimum inhibitory concentration < 4 µg/mL) were included in the study. Journal articles were included if they performed *in vitro*/ *in vivo* studies to determine the minimum inhibitory concentration.

Eighteen articles passed the criteria for the review. The data from these articles was extracted, and structure activity relationships were determined through evaluating the substitutions of the oxadiazole derivatives in these articles. The antibacterial targets of these oxadiazoles and cytotoxicity data were also evaluated. These derivatives showed broad and potent antibacterial activity against Gram-positive and Gram-negative bacteria, as well as antimycobacterial activity.

This review found that oxadiazoles show potential as antibacterial agents. The derivatives seemed to have potential activity against several biological targets within bacteria/mycobacteria and showed acceptable levels of cytotoxicity. Further studies on the mechanism of action of oxadiazole derivatives should be conducted, as well as optimisation of the derivatives in this review.

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Exploring the Independent prescribing role of the community Pharmacist

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Non-medical prescribing began with the Cumberledge report in 1986, followed by the crown report in 1989 and 1999, which ultimately led to the introduction of independent prescribing in 2006.[1] Previously, independent prescriber (IP) pharmacists were mainly present in secondary care.[2] However, recently there has been a goal set by the Welsh government to have an IP in every community pharmacy (CP) by 2030.[3] There is limited research exploring the independent prescribing role of community pharmacists therefore the aim of the project was to explore the views and experiences of CP IPs.

As the research largely revolved around pharmacists' experiences and views, qualitative research methodology was most appropriate due to its flexible nature.[4] Participants were identified via a gatekeeper and purposive sampling. Semi structured interviews were conducted and audio recorded. Ethics approval was obtained and written; informed consent given by participants. Interviews were analysed using thematic analysis.

Twelve interviews were conducted. The results showed that having IPs in community pharmacies has the potential to have a positive impact on patients, other healthcare professionals and pharmacist job satisfaction. Many barriers and facilitators to implementing the role were identified. Future reccomendations were put forward by IPs including the suggestion of having a structured model to utilise IPs the most productive way in CP, changing the way pharmacists are funded and patient education.

The barriers and facilitators found supported previous research identified in other areas such as primary and secondary care.[1,2] The research has established key areas that need improvement for implementing the service in CP more effectively. It would be useful to repeat the study when the service has been fully implemented to see the changes made. To conclude, it is clear to see from the challenges the participants have highlighted with regards to implementing the role, the 2030 goal will not be easily achieved. However, it will potentially have a positive impact on patients and others.

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A study to investigate the mechanical properties of two gelatin capsule formulations and their behaviour in a single dose dry powder inhaler

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Gelatin capsules used in single dose dry powder inhalers typically rely on water as a plasticiser. At low relative humidity (RH) the reduced moisture content of capsules can cause them to become brittle.[2,3] Formulation of a gelatin capsule with an alternative plasticiser may improve the mechanical properties of the capsule at low moisture contents and thus enable inclusion of moisture sensitive drugs for inhalation. The aim of this project is to evaluate the mechanical properties of two different gelatin capsule formulations, one traditional formulation and the other with an additional plasticiser included, at a range of RHs and to characterise their behaviour during a simulated inhalation event.

Capsules were conditioned by storage in desiccators that created a range of RHs between 0.5 and 52%. Moisture content was determined using a thermobalance, the elastic and plastic properties of each capsule was evaluated using compression tests and and the behaviour of the capsules was examined in a dry powder inhaler during a simulated inhalation event.

The gelatin capsule formulated with an additional plasticiser had less breakages following the simulated inhalation event but this had no gross effect on powder lost from the capsule. Overall, this research showed improved mechanical properties with Quali GI ED which could improve patient confidence in the product and reduce waste during the manufacturing process.

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The evolution of bacterial resistance through exposure to graduated concentrations of the biocides chlorhexidine and benzalkonium chloride

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Antimicrobial resistance (AMR) is an ever increasing threat to worldwide health. There is concern that the increased use of biocidal products, particularly for domiciliary uses, is contributing to the development of AMR.[1] Biocides used at low concentrations, for example upon dilution or resides on surfaces, produce a selective pressure for bacteria to express resistance mechanisms.[2] Research has indicated that some mechanisms of resistance used are the same to both biocides and antibiotics.[3] Therefore, this study tests the hypothesis that exposure of bacteria to gradually increasing, sub-lethal concentrations of the biocides chlorhexidine (CHX) and benzalkonium chloride (BZC) can lead to reduced susceptibility to the biocide alongside cross resistance to antibiotics.

A novel, graduated plate method was used to visualise bacterial growth over a surface, in order to replicate an in situ environment. Plates were incubated at 37°C and 70% humidity and photographed daily to observe the evolution of growth. Minimum inhibitory and bactericidal concentrations (MIC/MBC) together with antibiotic susceptibility profiles were determined at baseline and at weekly intervals post exposure to the biocides.

Post exposure susceptibility profiles were compared to baseline. A two fold increase in MIC was seen in *Escherichia coli* and *Pseudomonas aeruginosa* exposed to BZC. *E. coli* was able to grow in concentrations four times the MIC. Decreased antibiotic susceptibility was seen for all samples post exposure but none of the decreases resulted in susceptibility profiles changing from clinically sensitive to resistant.

The data suggests a possible link between exposure to low levels of biocide and reduced susceptibility to both the biocide and antibiotics. However, the results were highly variable and as such this study can only provide preliminary findings and cannot make conclusive results due to lack of data. Nevertheless, the graduated plate method has shown to be a promising new technique for exploring resistance in situ.

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Physical stability of lipid parenteral nutrition and vitamin admixtures when diluted with water for injections.

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Parenteral nutrition (PN) is required where gastrointestinal nutrition is inadequate. Intravenous lipid emulsions form a staple part of PN, with PN formulations also including vitamins A, D and E as part of the lipid emulsion, or with added vitamins B and C in solution. Lipid emulsions or vitamin preparations, may be added to commercially produced chambered PN formulations and this will result in the dilution of the lipid emulsion within the admixture which may make the emulsion less physically stable. Cernevit® is an example of a commercial vitamin product which when diluted became physically unstable. This study examines the stability of Intralipid® 10%, Vitlipid® and Solivito® when diluted. Because PN can be made for home PN use over the course of a week, it is important that the physical stability of these diluted products is maintained over this time period.

Twenty seven samples of Intralipid® 10% were made up in 100ml glass bottles. Nine were stored at room temperature (20°C), nine in a fridge (5°C) and nine in a stability chamber at 40°C. Samples were then taken on the same day, after one day and after seven days. By the same method, twenty seven additional samples of Intralipid® 10% were each diluted to one part in four and one part in ten and sampled at the same timepoints. By the same method samples were also made up, stored and tested from 10ml bottles of Vitlipid® with Solivito® added to them. Samples of Vitlipid® had Solivito® were also diluted to one part in ten and their stability assessed at the same timepoints. Average lipid globule diameters were measured with a Malvern Mastersizer® 2000 laser diffraction particle sizer at three different obscuration levels to determine the effects

of dilution on result variability. Samples were also assessed by visual inspection, light microscopy and had their pH measured at the selected time points.

The average globule diameter remained below 0.5µm and fewer than 0.05% droplets were larger than 5µm. After seven days, all samples showed a cream layer on top and a water layer at the bottom which was dispersed by simple inversion. Microscopy showed no signs of crystals or many large (>5µm) globules. For diluted Vitlipid® and Solivito® emulsions the pH dropped to about 6 after a week but samples satisfied the above stability tests. Light exposure did not affect physical stability. Fridge storage slightly increased creaming. Rased temperature storage may encourage globule sizes to increase for undiluted Vitlipid® and Solivito® emulsions.

These consistent results show that Intralipid® 10%, Vitlipid® Adult and Solivito® N had good physical stability after a week, even when diluted to one part in ten. This suggests that these products could be used for home PN without stability issues. There is some evidence that a lower obscuration factor is desirable for laser diffraction measurements to reflect the true average lipid globule diameter due to reduced multiple scattering.

Can Drug Loaded Nanotubes be Injected Directly into 3D U87 Glioblastoma Spheroids – A Feasibility Study

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The use of 3D spheroid cultures of glioblastoma multiforme (GBM) could be invaluable for the development of new drugs or therapeutic delivery systems as they are a much more representative model than the 2D monolayered cultures often used.[1] Focal delivery systems, for injection into GBM tumours or resected cavities hold the potential to deliver anticancer drugs that cannot pass the blood brain barrier (BBB) as this delivery method bypasses that system.[2] However, to date, there is no report of analysing focal delivery systems in 3D spheroid cultures. This research aimed to test the feasibility of direct injection of a drug delivery system into GBM spheroid models.

Firstly, an injection cannula was manufactured using polythene tubing inserted into a needle-shaped glass capillary at one end and a 5µL Hamilton syringe at the other. Secondly, the injection feasibility was analysed by conducting 3 experiments where spheroids were injected with varying concentrations of free doxorubicin, or a model drug delivery system (polymer nanotubes)[3] either empty or loaded with doxorubicin. In addition, I analysed whether direct injection would reduce the viability of the GBM spheroids by conducting Prestoblue® assays to distinguish the viability of the cells remaining in the model and undertook daily imaging to measure the diameter/volume of the spheroid.

It was observed when delivered directly to GBM spheroids both free doxorubicin and doxorubicin loaded nanotubes affected the size of the spheroids and decreased their viability. However, the empty nanotubes showed toxicity which was contrary to previous research into them.[3]

This research demonstrated that it was possible to create a hydraulic cannula system that allows for injection into GBM spheroids, though the technique needs refining during future work to quantify the potential benefit for use in research into the feasibility of new drugs/delivery systems to treat GBM or other forms of CNS cancers.

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Optimising Cysteamine for a More Effective Treatment of Cystinosis

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Cystinosis is a rare condition caused by a mutation in the cystinosin transporter in lysosomes; cystine cannot be transported out and so it accumulates within lysosomes, crystallises and causes cell death.[1] Cystinosis has a plethora of severe side effects including hypothyroidism, diabetes and CKD.[2] As well as a high mortality it is difficult to treat as there is currently only one treatment available, cysteamine, which has a foul odour.

It exerts a therapeutic effect by breaking the disulfide bond in cystine. While effective it causes an array of side effects and is found unpalatable by many as it contains a thiol group which gives it a foul odour; lack of compliance is the major issue with this therapy. The aim of this research is to implement ProTide technology to develop an optimised cysteamine prodrug molecule that has no odour and a more efficient delivery in-vivo.[3] This is based on previous research into phosphocysteamine which has shown success already but has low efficacy.[4]

A cysteamine salt and two phosphoroamidates were produced in separate reactions under lab conditions in a multi-step synthesis and then chemically attached to each other. Two different nucleoside analogues were attached to phosphocloridate to form two phosphorodiamidates. An acetyl group is chemically attached to the thiol group of cysteamine to mask it and then cysteamine is masked by a phosphocloridate

The desired final product was confirmed to have been synthesised but within a mixture. Masking the thiol group proved successful. Mass spectrometry also confirmed the presence of the final product but suggested a larger molecule had also been produced in greater amounts. The purity for both types of phosphorodiamidate proved to be similar in that the final product wasn't standalone after HPLC. Despite success, the final products had undesirable purity and yields and couldn't be isolated.

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An investigation looking into the analytical techniques used to analyse puncture performance and dissolution performance in the manufacture of dissolving microneedles (DMNs)

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Production of all new drug products and delivery systems follow the principles of Quality by Design (QbD), which describes the process of identifying Critical Quality Attributes (CQAs) and the standards in quality and safety they must meet.[1] This study conducts a rapid review of published literature concerning the test methods used to evaluate the CQAs, puncture performance and dissolution performance, of dissolving microneedles (DMNs), identifying patterns and frequency of use to highlight areas for further research requirements.

Ovid was used as a search engine to perform a scope search and gather a cohort of studies discussing microneedles (MNs). Truncation in sets of 'passes', with varying inclusion and exclusion criteria, produced the final dataset. Data extracted was compiled into an excel spreadsheet for both puncture and dissolution performance test methods. From the excel spreadsheet, various parameters and test sections were examined, producing smaller tables and figures to describe the methods used and further evaluate them.

Results demonstrate that puncture performance tests are more than twice as frequent than dissolution performance tests with 57 and 26 studies performing these tests, respectively. While aspects of puncture performance test parameters were generally well reported, others were not. Most dissolution studies provided

details on parameters such as solvent, agitation and temperature choice, but neglected to justify parameters used.

There is a lack of evidence-based decision making by all studies reviewed, concerning the parameters used, and/or appropriateness of apparatus used to perform each test. After reviewing product manufacturing guidelines produced by governing bodies, such as the FDA, for hypodermic needle puncture performance testing and dissolution performance testing of transdermal patches, there is an apparent necessity in pursuing research into the production of such guidelines for the manufacture and CQA testing of DMNs to guarantee continuous high quality and maintenance of product safety.[2-3]

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The use of animated material as an educational tool for renal patients: An acceptability study.

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Hyperkalaemia is a common, serious complication in patients with renal impairment.[1] Approximately 40-50% of hyperkalaemia cases are associated with chronic kidney disease (CKD).[2] Renal patients are often inundated with information from health professionals about condition management. The use of multimedia education resources has been proposed as a way of enhancing health literacy.[3] An animated patient education material was created to educate renal patients on hyperkalaemia. The aim of this study was to explore the views of renal patients on the use of the animation to inform its refinement and completion.

Qualitative research methods were chosen to collect the data. A focus group was conducted with members of a renal support charity to aid the development of the data collection tool. Twelve audio recorded one-to-one semi structured interviews were carried out with renal dialysis patients that were sampled using stratified random sampling. Interviews were transcribed verbatim and thematically analysed.

Four main themes were identified: Requirement for patient education, the utility of the animation, ways of learning and the animation impact on the patient. Patients thought health education was important and definitely needed. All patients accepted the presentation and appropriateness of the animation and agreed that learning from it was valuable.

Initial views of the dialysis patients allowed improvements to be made which included slowing the rate of the animation down and the use of signaling to help complex words to be understood better. Previous studies have shown multimedia interventions to have a positive impact on learning as reflected in this study.[3] Evidence to asses whether a clinical impact was had on the patient was limited and so further research is needed to determine this.

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Hospital Pharmacy Staff's Perceived Barriers and Facilitators to Discharge Medicines Review Referrals across two Health Boards in Wales

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For many years the transition of care of patients across different healthcare sectors has emerged as an important yet vulnerable point in healthcare systems worldwide where patient safety is threatened by the risk of miscommunication and unintended changes to medicines. To overcome the issues associated with patient transfer of care and to improve the management of medicines following discharge from a care setting, the Welsh Government introduced the Discharge Medicines Review service in 2011. An independent evaluation of the DMR service aimed to examine the benefits and cost effectiveness of the DMR service and to inform decisions relating to the continuation of the service and potential service improvements. However, despite this, there is clear underutilisation of the service, with only 0.7% of the NHS commissioned DMRs being undertaken[2].The aim of this study is to explore the perceived barriers and facilitators of the hospital pharmacy team to Discharge Medicines Review referrals (DMR) in two Health Boards in Wales.

Focus groups were conducted across two Health Boards in Wales, Cwm Taf and Betsi Cadwaladr. Hospital staff were invited to partake in this study with the help of gatekeepers identified by the Chief Pharmacists' All Wales Quality and Safety Group. Each focus group was transcribed verbatim. Data was analysed inductively and deductively. Ethical approval was obtained from Cardiff School of Pharmacy and Pharmaceutical Sciences Ethics committee and the Health Boards' Research and Development departments.

A total of six focus groups were conducted. Key themes identified included lack of awareness of the service, the lack of consistent established systems throughout all the wards in the hospital, hospital pharmacy staff's perceptions of community pharmacy, the lack of prioritisation of the referring patients, gaining consent and the role of primary care pharmacists

Different suggestions to improve the uptake of the service and increase referrals are discussed. This includes the potential for the involvement of primary care pharmacists and the need to raise awareness of the DMR service among staff and patients.

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Exploring the academic resilience and wellbeing of Cardiff Pharmacy students

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University students are reporting increasing levels of stress,[1] which is likely to impact on mental wellbeing. The ability to overcome setbacks and to continue to perform well is known as resilience.[2] There is a known link between resilience and wellbeing, yet there is a gap in the literature regarding this relationship in pharmacy students. It is vital to understand current wellbeing and resilience of pharmacy students in order for the school to support and develop these skills in their students.

Following ethics approval, a cross-sectional survey was given to pharmacy students at Cardiff University (years 1-3 on paper; year 4 online). The survey comprised the Academic Resilience Scale (ARS30) and the Warwick Edinburgh Mental Wellbeing Scale (WEMWBS) to measure resilience and wellbeing, alongside demographic questions for comparative analysis. Data was entered into SPSS v25 for analysis.

A total of 369 students (77.2% response rate) completed the questionnaire. The mean ARS30 score was 108.9. There was a significant difference between the resilience scores of different year groups ($p=0.045$). There were significant differences with year 1 scoring higher than year 2 ($p=0.05$) and year 1 scoring higher than year 3 ($p=0.009$) in the ARS30. Regarding wellbeing, the mean score from the WEMWBS was 46.3, with no statistically significant differences on the basis of demographics. Bivariate analysis showed academic resilience had a medium, positive correlation with wellbeing ($r=0.562$, $p<0.001$). Multivariable regression

analysis showed wellbeing (regression coefficient B= 0.865; p= <0.001) was significantly and independently associated with academic resilience.

The findings show that pharmacy students with high levels of academic resilience have better wellbeing, and that the level of resilience of first year students was significantly higher than that of second- and third-year students. There is room for improvement and the school can use these findings to help further develop resilience and support wellbeing in their students.

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Determining the antibacterial activity of Algerian and Welsh honey against clinically important bacterial pathogens

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Currently, we are living in an era where bacteria are developing resistance to all known antibiotics resulting in complications in treating bacterial infections, medical advances, and routine operations which is increasing mortality.[1] To prevent this problem from advancing, new antibiotics need to be developed. Evidence has shown a clear presence of unidentified antibacterial compounds in honey.[2] This research determined the antibacterial activity of different honey samples against clinically important, antibiotic-resistant bacteria thus adding knowledge to this paramount field.

Honey samples attained from Algeria (3), Wales (4) and commercial Manuka (1) were screened against clinically important bacteria *MRSA*, *E. coli* and *K. pneumoniae*. An optimised agar diffusion assay was used to determine antibacterial activity. To isolate antibacterial compounds in the honey samples solvent extraction and thin layer chromatography methods (TLC) were employed.

All the samples demonstrated antibacterial activity. Hydrogen peroxide is thought to be responsible for the antibacterial activity of most honey samples.[2] To determine this the honey samples were treated with catalase, an enzyme that breaks down hydrogen peroxide.[2] Once neutralised the antibacterial activity of the honey samples were retested. All the treated honey samples retained some level of antibacterial activity indicating the presence of non-hydrogen peroxide factors. Of the seven samples tested the three most active samples came from Wales (2 samples) and Algeria (1 sample). Solvent extraction was carried out on these samples but was unsuccessful except for the hexane extract of one of the three samples. TLC was carried out on the crude extract of this sample and spots were observed under UV light. Due to limited time and a lack of resources further investigations could not be carried out.

The antibacterial activity of the honey samples looks promising which warrants further investigations to identify and characterise the compound(s) responsible for this activity.

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An analysis on pharmacy students' views on prescribing immediately post pre-registration

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Since 2006, a pharmacist independent prescriber (PIP) may prescribe autonomously for any condition within their competence.[1] This initiative was implemented by the Department of Health to improve patients' access to medicines.[2] A pharmacist must complete a General Pharmaceutical Council (GPhC) accredited course to become eligible to apply for an annotation as PIP.[1] Stakeholders were supportive of these changes, although only 11% (6188/57225) of GPhC's registrants are PIP.[3] The Royal Pharmaceutical Society (RPS) had laid out plans for pharmacy students to become prepared for independent prescribing.[4] The aim of this study is to analyse undergraduates' willingness to prescribe at different levels of clinical complexity, to identify barriers they face, and changes that need to be made to prepare them to prescribe immediately after registration.

A questionnaire primarily consisted of closed multiple-choice questions was designed by two researchers and was approved by ethics to protect respondents and researchers alike. First and fourth year pharmacy students from Cardiff University participated via purposive sampling. Researchers conducted primary analysis of the quantitative data using Statistical Package for the Social Sciences (SPSS) and some additional comments made by respondents were grouped and summarised.

96 students responded and most were willing to prescribe at less complex scenarios. A statistical significant difference between first and fourth years was identified with fourth years finding most cases less challenging, but was not found when it came to their likeliness to prescribe. Barriers were identified, which included lack of exposure to clinical pharmacy, lack of funding and general perceptions by the public.

This study found that implementing fundamental changes to the course structure and to the pre-registration year appears to be the most viable option. Further studies are required to understand the views of other pharmacy students across the UK and to explore the barriers identified.

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Cognitive impairment and falls as a negative outcome of antidepressant use in older persons in care homes: a rapid review

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Depression in care homes has historically been under-diagnosed and undertreated, and the prevalence of antidepressants in these settings has fluctuated significantly during this time.[1] There is some evidence from past publications that suggests the use of antidepressants can result in negative outcomes such as falls and cognitive impairment in older adults and residents of care homes, but this remains under explored.[2] Research looking into the challenges of antidepressant prescribing in such environments is not common and is therefore the focus of this rapid review.

An electronic literature search was conducted using the databases PubMed®, Medline® and EMBASE®. The studies that were ultimately included in this review focussed on the negative outcomes falls and cognitive impairment. A risk of bias assessment was completed according to the Critical Appraisal Skills Programme (CASP), in order to judge the levels of bias in each of the papers. All studies that were to be included in the review were organised into a table, into which data was extracted for analysis.

Of the 661 records identified through searching, ten studies were included in the final review. These included six cohort studies, three qualitative research studies, and one randomised controlled trial (RCT). All of these studies had a significant variability in bias but were all deemed to be at low risk. Overall, eight of the possible ten studies showed a potential link between antidepressants use and the outcomes cognitive impairment and falls. However, not all studies demonstrated statistically significance.

This rapid review has demonstrated the complex nature of cognitive impairment and falls in care home residents and has not conclusively demonstrated an association with the use of antidepressants in older adults residing in care homes.

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An exploration of the opinions and experiences of Welsh speakers on the use and availability of pharmacy services provided through the medium of Welsh

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Communication skills are required by pharmacists to exchange information successfully with patients and is an essential element of quality patient care.[1] Language choice is a significant factor in person-centred care and communication as patients need to understand the information that is given to them. Wales is a bilingual nation where two official languages are acknowledged – English and Welsh.[2] Although many Welsh-speakers are able to speak English, research indicates that patients are more comfortable discussing their health in their first language.[3] Legislative changes have been made to primary care providers in Wales to improve the quality of care for Welsh-speakers.[4] The aim of the study was to explore the opinions and experiences of Welsh speakers regarding the use and availability of pharmacy services through the medium of Welsh.

Qualitative focus groups were chosen as the methodological approach. Sixteen Welsh-speakers were recruited through purposive sampling. Two researchers conducted three focus groups, which were made up of five to six participants each. Focus groups were conducted in Welsh, audio recorded and transcribed verbatim. Thematic analysis was used to identify themes and sub-themes.

Four major themes were identified: language choice in healthcare, which focused on language preference of patients when discussing health; barriers to the use of Welsh, which explored reasons as to why the Welsh language may not be spoken in a pharmacy; availability of pharmacy services through the medium of Welsh and future of the Welsh language in pharmacies.

The findings show that when available, Welsh language pharmacy services are being used and are in demand. It is apparent that patients are more comfortable communicating to healthcare professionals in their first language. Despite Welsh Government schemes to enhance Welsh-speaking services, more needs to be done to improve awareness of pharmacy services through the medium of Welsh and the availability of Welsh-speaking staff.

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Assessing the stability of methotrexate within a continuous ambulatory delivery device (CADD®) cassette.

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Methotrexate is a chemotherapy drug mainly used within regimens treating lymphomas. Cancer treatment significantly affects the NHS's budget and patients' quality of life. Hospital admissions, and the adverse effects of treatments have negative effects on physical ability, emotional state, and social functioning.1 These

services also have cost implications, estimated to be £5 billion annually.2 Due to devices such as continuous ambulatory delivery devices (CADD®), treatments can now be administered outside of the hospital setting, within an ambulatory care service. Previous studies have shown only a small number of medications to be stable in the device; this does not include methotrexate.3,4 This study aims to test the stability of methotrexate in order to allow its future use in ambulatory care programmes.

Twenty CADD® cassettes were prepared, containing 100ml of 50mg/ml methotrexate solution in 0.9% sodium chloride. Ten cassettes were placed in a 2-8°C refrigerator, and ten in a 40°C stability chamber, for 10 days. Three 0.5ml samples were taken from each cassette on days 0, 3, 7, and 10. These samples were diluted to 0.25mg/ml and analysed using a validated stability indicating high performance liquid chromatography method using UV detection. Additionally samples were subjected to physical stability tests including; visual tests, turbidity, particle counting, and pH. Finally two cassettes at each temperature were weighed to assess if any moisture loss occurred at either temperature.

At both temperatures, methotrexate in CADD® cassettes retained 90-110% of the initial concentration for 10 days. No degradation peaks were observed over the testing period. Physical stability tests showed that no changes occurred over the 10 days at either temperature and no moisture loss occurred.

At 2-8°C and 40°C, methotrexate solution in CADD® Medication Cassette Reservoirs was found to be stable for 10 days. This device is suitable for administration of methotrexate within an ambulatory care service, allowing patients to receive their treatment in a more comfortable environment.

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YAP1 and its targeting in endocrine resistant breast cancer cells

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~70% of breast cancers (BC) are oestrogen receptor positive (ER+) and treated using endocrine agents.[1] However, acquired resistance remains a clinical issue which can be associated with ER loss and increased growth factor kinase signalling (e.g. EGFR, Src) and results in relapse with poor prognosis.[2] Recent research in Cardiff University identified increases in co-activator VGLL1 and its Hippo pathway nuclear transcription factor TEAD1 in luminal A-derived acquired resistant BC cells which had lost ER.[3] However, the further important TEAD co-activator YAP1 is unexplored in this setting. This project aimed to investigate whether YAP1 is deregulated and possibly functional and growth-contributory in luminal A-derived acquired endocrine resistant cell lines. It also investigated any potential to target such signalling using verteporfin ("Visudyne"), a photosensitiser that inhibits YAP1 under dark conditions.[4]

Gene microarrays and immunocytochemistry (ICC) assessed YAP1 expression and localisation, along with ER, and TEAD1, in endocrine resistant versus responsive BC models. To examine YAP1's functionality, ICC was optimised for YAP1/TEAD's transcriptional target CYR61. Treating resistant cells with gefitinib or saracatinib (1μM) explored YAP1's regulation by EGFR and Src. Verteporfin impact (1-10 μM) on Ki67 (proliferation), YAP1 and CYR61 staining was also examined.

YAP1 mRNA, nuclear YAP1 protein, its partner TEAD1, and CYR61 expression were significantly increased in Faslodex resistant cells and (where examined) other endocrine resistant models with ER loss. Neither gefitinib nor saracatinib substantially inhibited YAP1. Despite cell death hindering evaluation, there were significant dose-dependent proliferation and possibly YAP1 and CYR61 decreases with verteporfin.

YAP1 is deregulated (perhaps independently of EGFR and Src) and with its essential nuclear partner TEAD1 is likely to be functional in acquired resistant BC cells with ER loss. While the verteporfin findings suggest YAP1/TEAD signalling is growth-contributory and that this drug might potentially treat resistance, further research is necessary to consolidate whether it specifically-targets YAP1.[4]

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A preliminary investigation into the efficacy of Eugenol as a topical antifungal preparation.

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Incontinent patients typically wear disposable diapers which can frequently lead to incontinence-associated dermatitis (IAD). This leaves patients vulnerable to secondary infections, particularly from *Candida albicans* which was isolated from more than 80% of IAD cases.[1,2] Due to the growing issue of resistance, new treatments need to be found. Eugenol is a major component of clove oil (*Syzygium aromaticum*) and has proven antifungal properties.[3] The aim of this study is to identify a suitable liquid to act as a solvent for Eugenol and to measure the impact of this solvent on the minimum inhibitory concentration (MIC) of Eugenol with a view to begin developing a topical antifungal preparation.

Agar diffusion assays and a broth dilution assay were conducted to determine the MIC of Eugenol in different solvents and a recovery study was performed to identify if Eugenol is fungicidal. Pearson's R^2 and one-way ANOVA tests were used for statistical analysis.

While some solvents had innate antifungal activity, there was no statistical significance between the choice of solvent at 50% v/v Eugenol. At 5% v/v Eugenol, the choice of solvent is statistically significant and ethanol gave the best result. In the broth diffusion assay, the sweet almond oil solutions did not show growth inhibition with higher concentrations of Eugenol as there were Eugenol partitioning issues between the oil and water phases. With the ethanol based solutions we could not confidently attribute the fungal inhibition seen at higher concentrations to just Eugenol due to a flaw in the method.

Although this project was not successful in quantifying the MIC of Eugenol in combination with different solvents, the potential of ethanol and sweet almond oil has been identified and does warrant further exploration. The main barrier to this project has been issues with the methodologies which can be overcome with some modifications.

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Exploration of the role of dopamine depletion and chronic L-DOPA administration on neuroinflammation and dyskinesias in the 6-OHDA rodent model of Parkinson's disease.

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Neuroinflammation is implicated in the pathology of Parkinson's Disease (PD).[1] L-DOPA (the first-line treatment for PD) has been surrounded by debate as to whether it perpetuates this neuroinflammation.[2] Therefore, this study aims to investigate the inflammatory response following dopaminergic denervation in a rodent model, determining whether chronic L-DOPA administration affects this response. This study also sought to identify whether there is enhanced inflammation in areas linked to generation of L-DOPA-induced dyskinesias (LID), the treatment-limiting side effect of L-DOPA.

Rats were split into 3 groups receiving either a unilateral injection of the *6-hydroxydopamine* (6-OHDA) toxin (creating an animal model of PD), a SHAM surgery (for which saline was injected in place of 6-OHDA) or no surgery. SHAM or 6-OHDA lesioned rats were then given either L-DOPA or saline treatment for 6 weeks. Abnormal involuntary movement scores were assessed weekly to determine severity of LIDs. Post-mortem immunohistochemical analysis was conducted using antibodies against glial fibrillary acidic protein (GFAP) in reactive astrocytes and CD11b (OX42) in activated microglia. This was followed by optical density (O.D), stereology and image subtraction analysis to quantify inflammation.

The 6-OHDA lesion caused a significant increase in GFAP expression, specifically in the medial and lateral regions of the lesioned striatum, suggesting that dopaminergic denervation enhances neuroinflammation, however not solely in locations linked to LIDs. While O.D showed no difference in L-DOPA treated animals compared to saline, stereology data showed increase in $GFAP^+$ cells in the striatum of the lesioned hemisphere, suggesting that L-DOPA enhances the inflammatory response. The OX42 marker revealed no significant differences between treatment interventions.

This study concludes that dopamine denervation and chronic L-DOPA administration contribute individually to the inflammatory response, analogous to previous studies.[3,4] Therefore, introduction of drug treatments into animal models will be essential to ensure efficacious translation of new therapies into the clinical environment.

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Evaluating Asthma Control by Assessing Inhaler Technique and Adherence within Community Pharmacy

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Asthma is one of the most common chronic respiratory condition in the UK and approximately 1 person dies every 8 hours.[1] Clinical efficacy of asthma medications is well established [2,3] but asthma control within asthmatic population is disappointing with 80,000 emergency hospital admissions within a year alone. [(1)] This study aims to investigate potential factors (inhaler technique and adherence) which leads to poor asthma control.

53 patients were recruited via convenience sampling from different pharmacies in South Wales. Participants were asked to sign a consent form in order to take part in this study. Asthma Control Test (ACT) and Test of the Adherence to Inhalers (TAI) questionnaires were completed by the participants. A Vitalograph Aerosol Inhalation Monitor (AIM) was used to assess their inhaler technique. AIM categorised each participants technique into Good, Sub-optimal or Fail. In order to identify any statistical significance in our results, The Kruskal Wallis and Mann-Whitney U tests were used.

Of the 53 participants 68% had uncontrolled asthma. 53% of the participants had experienced exacerbations in the past, suggesting a history of poor asthma control. Overall, inhaler technique was poor with 46% of the cohort assessed as an AIMs 'fail'. Adherence among the participants was problematic with 60% of the cohort assessed as having poor adherence. Surprisingly, our results did not show any significance of inhaler technique and adherence to asthma control.

It is clear that a larger sample in needed to identify the reason behind poor asthma control. Bigger sample size will increase the statistical power to identify any differences within our data sets. Investigating in depth the reasons behind poor inhaler technique/adherence in the future study might explain the overwhelming morbidity and mortality rates in the asthmatic population.

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Characterising and comparing the mechanical properties and performance of Quali-V®-I and Quali-V®-I Extra Dry capsules for use in dry powder inhalers

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Dry powder inhalers (DPIs) are used to deliver active pharmaceutical ingredients (APIs) into the lung. Single dose hard-shell capsule based DPIs consist of an API and a carrier excipient contained within a dry powder formulation. In clinical use, a capsule is loaded into a DPI and is then punctured upon actuation by retractable pins, or cut open by a blade inside the device, before patient inhalation of the powdered capsule contents. Hygroscopic APIs or excipients can absorb moisture from the capsule wall, which may compromise the physical and chemical stability of the powder formulation.[1] Whilst reducing the moisture content of hard-shell capsules could benefit these formulations, this may affect their mechanical and puncturing properties. [2-4] The aim of this study was to characterise the performance of a novel low moisture commercial hypromellose capsule formulation (Quali-V®-I Extra Dry), and compare this with its clinically established counterpart (Quali-V®-I).

Empty Quali-V®-I and Quali-V®-I ED capsule formulations were stored in glass desiccators for two weeks at different relative humidities (RHs) to produce capsule formulations with a range of moisture contents, including Quali-V®-I capsules at the lower limit of their specification (4.5-6.5% w/w) and Quali-V®-I ED capsules within their lower moisture content specification (2.0-3.5% w/w). A compression test was used to determine the mechanical properties of the different capsule formulations and the rotational dynamics and puncture performance of both capsule formulations were investigated in a simulated inhalation event.

The compression profiles of Quali-V®-I and Quali-V®-I ED, conditioned within their moisture specification, were reproducible and comparable in terms of their shape. There were also no significant capsule fracturing events during the test. The lower moisture content Quali-V®-I ED formulation had a slightly higher mean compression force at the elastic limit (32.05±3.00N versus 28.91±2.39N for Quali-V®-I) where permanent capsule deformation occurs. The number of rotations per second during a simulated inhalation event were comparable for both Quali-V®-I (24±2) and Quali-V®-I ED (24±2). Slight differences were observed in the presence and positioning of the flap following puncture between both formulations.

The performance of capsule formulations were comparable, with small differences in the mechanical properties unlikely to affect the clinical utility of the capsule. Future studies should investigate the performance of Quali-V®-I ED capsules at the lower end of their moisture specification and further evaluate the effect of reducing moisture content on pulmonary drug delivery.

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Evaluating the pre-clinical efficacy of local doxorubicin delivery compared to systemic administration in the treatment of breast cancer.

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The mainstay treatment of the majority of breast cancers involves systemic chemotherapy, however, it has several inherent issues. The uncontrolled drug distribution means the drugs cytotoxic action affects all cells, resulting in toxic, dose-limiting, side effects, such as cardiotoxicity with doxorubicin[1] Systemic treatment also fails to give the local control needed to prevent tumour recurrence leading to a cancer relapse and greater mortality risk.[2] Localised chemotherapy, involving drug delivery directly to the tumour,[3] is a promising avenue to overcome these challenges. This project aims to determine if several doxorubicin-based local delivery methods prove more efficacious in the treatment of breast cancer compared to systemic administration.

Using data from previous studies, six different doxorubicin-based localised treatments were compared to intravenous administration and two control groups. Tumour growth was measured through tumour-cell associated bioluminescence and at the endpoint of the study, the tumour weight and metastasis profile were determined. Cardiotoxicity was determined by the final heart weight. Using these measures, the statistical significance was analysed in comparison to the control using the relevant statistical test.

Tumour growth was reduced in all localised treatments compared to systemic administration and the control. The difference only reached statistical significance by week 6, where four localised treatments were found to be significant. Tumour burden was also diminished, with the high dose microcarriers average tumour weight only 44mg. The silk hydrogel and stabilised silk film interventions were the most successful, having statistical significance for tumour growth and tumour weight. Silk hydrogel treatment also resulted in complete tumour regression in two out of five mice. Only the high dose nanotubes proved to have a significant reduction in heart weight. However, overall local delivery failed to be more beneficial preventing metastasis than systemic.

The silk hydrogel and stabilised silk film methods were shown as promising avenues to overcome the issues of systemic chemotherapy. However, both need refinement to provide greater local disease control and improve metastasis rates.

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Climate Change: Assessing the safety climate of managed sector pharmacy in Wales

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Within the National Health Service patients are being unintentionally harmed through incidents thought to be preventable, with 91,550 patient safety incidents occurring between April 2018 and March 2019.[1] The World Health Organisation (WHO) aims to improve this, with a goal of reducing medication related harm by 50% in five years.[2] The safety culture of an organisation concerns individual and group attitudes towards an organisation's health and safety management.[3] Benchmarking data to assess the safety culture of managed sector pharmacy is crucial, so that areas for improvement can be highlighted and patient safety can be improved. The aim of this project was to assess the safety climate in managed sector pharmacy with a view to monitoring the impact of the WHO campaign.

A qualitative research strategy was used, and primary data was collected through an online questionnaire containing 45 questions. The Likert scale was used to assess six main attitudes that make up an organisation's safety climate. The results were anonymous and imported into GraphPad Prism[4] for statistical analysis using one-way ANOVA. University research ethics approval was obtained.

A total of 177 people responded to the questionnaire from 2132 invitations sent, giving a response rate of 8.15%. The most positive safety attitude was teamwork, with working conditions being highlighted as a barrier to improvements, achieving the most negative response. Dispensing assistants and workers within prison

pharmacies showed the most positive attitudes to safety when compared to other pharmacy staff and the hospital and primary care sector respectively.

The results demonstrate that safety climate in managed sector pharmacy is positive, however further research into this area due to the low response rate is needed to confirm this. The data obtained from this study can be used to assess safety climate moving forward and monitor the success of the WHO campaign when introduced in Wales.

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A questionnaire on the considerations of students in selecting Pharmacy at Cardiff University

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Pharmacy is a growing, constantly developing industry with good employment potential[1], however in recent years the number of applicants to Pharmacy degrees has been falling across all schools of pharmacy whilst the number of students accepted through the Clearing application process bee rising. This has led to concerns over whether the students being accepted are of a lower quality or commitment than those who came before.[2] This study was conducted to investigate the opinions of applicants to the MPharm degree around Pharmacy itself, but also Cardiff University so that the results could inform ongoing recruitment efforts for the School of Pharmacy and Pharmaceutical Sciences (SPPS).

A link to an anonymous questionnaire was sent out to all current MPharm students attending Cardiff SPPS via the University's email system. The questionnaire contained mainly multiple-choice questions, however some free text options were provided to account for the uniqueness of the application process to the applicant. The data gathered was qualitative and best represented graphically. A pilot study could not be run due to time constraints. Ethics approval was obtained from the SPPS ethics committee. In total 185 respondents filled in the questionnaire, 125 at the initial distribution and a further 60 following a reminder email.

Students found SPPS's prestigious reputation the biggest factor in deciding to attend, however for Pharmacy itself opinions were more divided. Career prospects were a deciding factor for Pharmacy along with a strong desire to help others. The limitations of students' knowledge of Pharmacy, with almost 50% of respondents having no relevant work experience could be a factor in falling applicant rates. Few applicants had any experience with the University outside of recruitment efforts but of the recruitment efforts they faced, the interview was significant in their decision.

Applicant loss could be combated by, raising awareness not only of the University itself but also the versatility of the degree and the introduction of the Pharmacist as more than just a label on a bottle that is so lacking in public perceptions.[3]

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Morphology and protein expression of hTERT-immortalised keratinocytes in different confluencies for producing bioink in 3D skin printer.

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Currently, human skin equivalent models (HSE) can be 3D printed using primary human keratinocytes. [1] However, employing primary human keratinocytes has its limitations, including the availability of skin donors and donor to donor variation. The use of a suitable in vitro cell line such as human TERT-immortalised (hTERT) keratinocytes could solve these limitations.[2] hTERT keratinocytes were chosen because they have demonstrated the ability to mature into full-thickness HSE in vitro models with similar properties to native skin. [2,3]

The ultimate aim is to 3D print a fully matured HSE from hTERT keratinocyte. This requires bioink of hTERT keratinocytes at different stages of their cell cycle, as keratinocytes exhibit characteristic morphology and protein expression in different layers of the skin. In this study, we aim to characterise hTERT keratinocytes when grown to different confluencies to compare them to native keratinocytes in each layer of the skin. hTERT keratinocytes are grown to 30%, 60%, 100% and 120% confluency and characterised based on their morphology and their expression of Involucrin (IVL) and Cytokeratin 5 (K5). Microscopic observations of cultures and immunoblotting to test for expression of IVL and K5 was conducted.

We have shown that morphology of hTERT keratinocytes at 30% confluency resembled cells in the stratum basale and at 60% confluency they resembled the stratum spinosum. At 100% and 120% confluency, cultures have similar morphology to the granular layer but still retained their nuclei. Our results demonstrated higher expression of K5 and IVL as confluency increased.

Presence of nuclei and high abundance of K5 in higher confluencies is concluded to be due hTERT keratinocytes' differentiation and replicative potential which is beyond the capability of normal primary keratinocytes.[4] Higher levels of IVL in higher confluencies is because hTERT keratinocytes begin to differentiate in dense populations.

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Investigate the role of ZIP7 on kinase signalling pathways

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Zinc is a trace element required for cells to be able to have normal growth and development.[1] There are two families of zinc transporter the SCL30A family and the ZIP7 family. ZIP7 resides on the endoplasmic reticulum where it transports zinc into the cytoplasm. ZIP7 becomes active once it has been phosphorylated at serine residue sites S^{275} and S^{276} by kinases.[2] ZIP7 mutants P190A and E363K are being tested to show whether they can respond to kinase activation as the healthy ZIP7 does.

Wild-type, null mutant, P190A and E363K ZIP7 transporters were made, these were transfected into MCF-7 breast cancer cells. The cells were then stimulated with exogenous zinc at 0 and 10 minutes and then lysed, when treated at 0 minutes the cells are untreated. SDS-PAGE and western blot analysis were used to assess the effect of ZIP7 protein on activation of a number of different kinases.

The results showed that the P190A and E363K mutants only partially activated the kinases. The P190A mutant ZIP7 only appeared to partially transport zinc in contrast to the E363K mutant ZIP7 which could activate more kinases.

It was hypothesised that the P190A mutant ZIP7 would be able to partially transport zinc better than the E363K mutant ZIP7 due to the changes in residues in the different mutants. This decrease in activation of downstream

kinases may help to explain clinical results observed, however, the results from the western blot densitometry data was not consistent requiring further repeats.

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Hospital Pharmacy's Perceived Barriers and Facilitators to Discharge Medicines Review Provision in Betsi Cadwaladr University Health Board and Cardiff and Vale University Health Board

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The process of transitioning patients across healthcare settings is a complicated one, which can be a threat to patient safety.[1] Discharge from secondary care in hospital to primary care is considered a world-wide problem. In 2011 the Welsh Government introduced the Discharge Medication Review (DMR) service to improve transfer of care in Wales. Part one provides reconciliation between that prescribed by their general practitioner and that which the patient has been discharged with. Part two supports the patient to adhere to their medicines. Following evaluations, the services' effectiveness was highlighted [2] but also its low uptake rate. The aim of this study was to collect the perceptions of hospital pharmacy staff on the barriers and facilitators to referring to the service.

We conducted focus groups in five hospitals across two Health Boards. Gatekeepers were nominated through which all study documentation was disseminated through them to the participants via email. A quota sample of two senior pharmacists (band 8+), two junior pharmacists (band 6-7) and two technicians was used. Ethical approval had to be obtained from Cardiff School of Pharmacy and Pharmaceutical Sciences. The focus groups were recorded and then transcribed; data was analysed using inductive and deductive approaches utilising thematic analysis.[3]

A number of themes were identified preventing hospital pharmacy staff referring patients to the DMR service. These included knowledge of the DMR service and its benefits, uniformity and usability of the IT systems and perception of community pharmacy and primary care pharmacists. The ongoing, robust communication between hospital and community pharmacy for complex patients was considered a facilitator for referrals.

The overwhelming lack of knowledge of the service meant staff were not motivated to refer patients. Greater promotion and education is needed among both healthcare professionals and patients. Further work should be undertaken to gain community pharmacy and patient perspectives.

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Exploratory Study of Nurse Second Checking During the Preparation and Administration of Medicines

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Double checking by a second nurse is an intervention used in many UK hospitals to prevent administration errors.[1] Following the withdrawal of the Nursing and Midwifery Council's guidelines in 2019 amidst a

restructuring,[2] nurses have been without a protocol to adhere to when administering medicines. Following the World Health Organisation's plans to reduce minor administration errors by 50% within five years,[3] the Welsh Government have made motions to produce an all-Wales protocol to provide nurses with a 'gold standard' to adhere to.[4] The purpose of this study is to evaluate the current system of second checking by nurses during preparation and administration of medicines, and to identify opportunities for improvement.

During this service evaluation, a descriptive qualitative design was used. Following School ethics approval and receipt of informed consent, data was collected via focus groups with medicines management nurses, non-participant ethnographic observation and semi-structured interviews with ward nurses. The sample was generated by non-probability sampling, and research was continued until thematic saturation was reached. Data was evaluated through thematic analysis.

Most nurses observed or interviewed expressed a lack of understanding regarding how to perform a thorough independent second check, and which drugs required a second check. This is largely due to the lack of a centralised protocol. This leads to nurses who are unaware how to perform an independent second check developing their own system, a 'check by collusion', presenting risks to patient safety.

This research illustrates nurses' desire for a standard policy. Several nurses expressed such a policy should be both idealistic and realistic, providing nurses with a 'gold standard' to follow, as well as being achievable. Any policy considered unattainable by the nurses is useless, therefore any prospective protocol should be co-constructed with nurses to develop a system whereby nurses can provide patient treatment with minimal safety risks.

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Photosensitiser formulation for controlling food pathogens

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Antibacterial photodynamic therapy (APDT) employs the use of photosensitisers (PSs) in the presence of visible or ultraviolet light in order to produce reactive oxygen species (ROS) such as cytotoxic singlet oxygen, which inactivates bacteria.[1] At first, it was introduced to target cancer cells [1], but currently it has the potential to be used for the disinfection of food. The aims of this study were to optimise two biocide formulations based on the PSs erythrosin B (EB) and curcumin, by modifying the pH, concentration, light exposure and by adding excipients, as well as to test the most effective formulation on a variety of common food bacteria to evaluate inhibitory activity.

Stock solutions of 1 mM EB and 1 mM of curcumin in ethanol were prepared. Test inoculums of *Staphylococcus aureus, Pseudomonas aeruginosa, Listeria monocytogenes* and *Salmonella enterica* serovar Typhimurium were prepared. A suspension test based on the BS EN 1276:2009 [2] was performed, followed by the Miles and Misra [3] method, every time a specific parameter was tested or when a formulation was evaluated against different bacterial species.

The most effective PS identified was EB. An attempt to find the optimum conditions for the EB formulation such as the concentration and pH was undertaken, however further experiments are required to accurately evaluate them. The optimum exposure time identified was 5 minutes in green light. The addition of ethylenediaminetetraacetic acid (EDTA) enhanced activity against *P. aeruginosa*. EB displayed greater activity against Gram-positive species rather than Gram-negative species.

EB is a promising PS for the disinfection of food. However, further optimisation is required prior to its future use against food pathogens, such as *S. enterica* serovar Typhimurium as its spectrum of activity is still limited.

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Antifungal Activity of Thiazole Derivatives; A Rapid Systematic Literature Review

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Owing to the fact fungal infections are an ever growing health problem throughout the world[1] the need for novel antifungal therapy is now of increased importance. With the emergence of resistance[2] to current treatment and the limited therapy options the development of novel treatment is of paramount importance. This systematic review aims to determine if research from 2009-2019 has shown thiazole derivatives as a viable future class for antifungal therapy and consequently if they warrant further research.

Four bibliographical databases were consulted; Pubmed, Web of Science, Scopus and Embase in order to find literature evidence of *in vitro* and/or *in vivo* antifungal activity of thiazole derivatives. Studies were screened for their eligibility based on inclusion and exclusion criteria. After reading and inclusion of relevant studies, they were subjected to quality assessment. Data from all the included studies was extracted and variables assessed.

A total of 15 studies were included in this review based on their eligibility criteria. This review summarises; the *in vitro* and *in vivo* antifungal properties of thiazole derivatives, the reported mechanism of action, the structural activity relationships. As well as if the derivatives display promising drug candidate properties in terms of pharmacokinetic and toxicity studies.

A total of 27.1% of the investigated thiazole compounds were shown to have promising antifungal activity based on their *in vitro* activity. A possible mechanism of action involving inhibiting the ergosterol biosynthesis pathway was investigated by a number of the papers. The thiazole ring appears to give activity by hydrophobic and electrostatic interactions with the target. Furthermore, the derivatives appeared to obey drug lead likeness rules. However, further studies need to be conducted to investigate the compounds *in vivo* activity and pharmacokinetic properties.

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Design and synthesis of novel antiviral compounds to treat Machupo Virus

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The structure of GP1 bound to the hTfR1 was exploited to perform High Throughput Virtual Screening (HTVS) using a library of approximately 3 million commercially available compounds. 28 small molecules were selected for their ability to bind the hTfR1 stopping MACV GP from binding. Compound AB-2260 was identified as blocking viral replication at low concentrations. The aim of this project is to synthesise structurally diverse derivatives of AB-2260 due to synthetic accessibility to understand which component of the molecule are essential for its activity. Combinatorial library tool in MOE[1] was used to design compounds that could be readily synthesised using chemical regents already in house. The newly designed molecules, will then be docked in the hTrF1 binding pocket and ranked per a docking score.

General mechanisms for each reaction was prepared on ChemDraw saved as a reaction file (.rxn) and used in QSAR combinatorial library tool in MOE[1] to generate new derivatives from reacting amine with an aldehyde/ketone creating a central imine bond (Schiff base) by nucleophilic addition. After merging all databases and using Glide SP and refined by Glide XP[2] docked into the binding pocket of hTfR it yielded 1741 ligands. This was then evaluated per XP docking score and visual inspection of the ability to occupy the binding site and thus 37 ligands were selected to be synthesised with a binding score range of -4.7246 to -3.063 best to worst. The best performing compounds were then synthesised, purified and structurally characterised, preparing a new series of new AB-2260 derivatives with yields ranging from 16%-48%.

Structure Activity Relationship was observed as adding a hydroxyl group to the aldehyde portion of the hydrazide and pyrrole ring hydrazide derivatives have an increased binding score and visually conform better in the binding pocket of hTfR1 when compared to AB-2260.

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An Investigation into the Prescribing of Sodium Valproate by NHS General Practitioners throughout Wales between April 2013 and August 2019.

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Sodium valproate is a teratogenic drug, meaning it can result in birth defects and malformations when used by pregnant women. Since being discovered initially as an anticonvulsant in 1967, it later emerged as a mood stabiliser in the 1980s, although the risks were still unknown. This study is aimed to assess trends in the prescribing of sodium valproate in primary care at a national level in order to determine whether the current guidelines regarding sodium valproate are being adhered to.

Comparative analysis system for prescribing audit (CASPA) was used to collect information on the prescribing practices of sodium valproate between April 2013 and August 2019. Trends in the data were assessed using Microsoft Excel and SPSS to determine whether prescribing practice is influenced by recent guidelines.

Based on defined daily dose (DDD) values, prescribing of sodium valproate decreased throughout the data period. The DDD of Epilim, which was the most frequently prescribed brand of sodium valproate, fell over the data period. However, generic sodium valproate showed an upward trend between 2013 and 2019 when compared to the alternative medications for the same seizure type. Furthermore, although sodium valproate started the data period as more highly prescribed than its alternatives, levetiracetam experienced a rapid increase and surpassed valproate as the most prescribed by the end of August 2019. Statistical analysis revealed there was no significant effect of the most recent MHRA guidelines on the prescribing of sodium valproate.

The decline in sodium valproate prescribing throughout the data period is very gradual. It is feasible that this reduction is due to the introduction of medical guidelines. However, the dangers of sodium valproate have been well documented prior to April 2013, hence it is likely that the number of patients receiving sodium valproate had decreased extensively prior to this data period.

The role of the oxidised lipids produced by 12R-lipoxygenase in epidermal cell differentiation

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12R-lipoxygenase is an enzyme discovered in the epidermis that catalyses polyunsaturated lipids such as O-linoleoyl-ω-hydroxyacyl-sphingosine into hydroperoxides.[1] The enzyme target, linoleic acid, which is attached to long chain ceramides, is oxidised and is a recognition molecule for esterases to cleave.[2] The remaining structure enters additional biochemical pathways to become an element in the cornified envelope, a layer necessary for barrier function.[3] Genetic defects induce ichthyosis, a skin disorder identified by dry scaly skin due to abnormal water loss and management with emollients is recommended due to no treatment. The absence of 12R-lipoxygenase in mice models also displayed similar symptoms, with water loss being the causative factor for impaired barrier function and highlighting the role of water retention in the epidermis.[4] The study was conducted to determine a secondary role for 12R-lipoxygenase in epidermal differentiation and allow the production of fully functioning skin at a quicker rate. An attempt to drive primary cell differentiation was performed with 12R-lipoxygenase derived lipids.

Four conditions were implemented where cells were subjected to (i) culture medium, (ii) 9S,10S,13S trihydroxy,11-E-octadecanoic acid, (iii) linoleic acid, and (iv) ethanol as the control. Cell differentiation was monitored visually via microscopic inspections (10x magnification), and western blotting allowed the analysis

of involucrin protein levels expressed in each condition, enabling assessment of progress. With published literature, it was hypothesised that the oxidised lipids would have negative effects due various to pathways. The lipids displayed a detrimental effect on cell differentiation as limited growth was observed by cells subjected to linoleic acid and 9S,10S,13S trihydroxy,11-E-octadecenoic acid in comparison to cells in cell culture medium only. No repeats were performed, and one suitable control was not used, thereby making the results of the linoleic acid controversial. A definitive conclusion is therefore difficult to reach, and further experimentation is required.

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An investigation into how Medicines Information staff report yellow cards through MIDatabank

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The Yellow Card Scheme is based within the Medicines and Health Products Regulatory Agency (MHRA) and underpins pharmacovigilance within the UK. Yellow cards (YC's) should be submitted for certain adverse drug reactions (ADRs) so that the MHRA can get a better understanding of the safety of medicines/ medical devices.[1] The aim of this research is to gain a better understanding of how Medicines Information Databank (MIDatabank) is being utilised/ not utilised in the reporting of ADRs through the submission of yellow cards. There aren't any available figures for how many reports are/ could be made through MIDatabank specifically. This would be useful information for Medicines Information (MI) centres and the MHRA as it is arguably one of the most accessible routes of yellow card reporting available to Medicines Information/ Hospital pharmacists.

A secondary data set of all ADR enquiries was collected from the financial years April17-March18 and April18-March19 via a filtered search of MIDatabank (the software used to answer are archive medicines information enquires.) This secondary data was then analysed in comparative tables and line graphs. Following School Ethics approval, focus groups with MI staff were used to understand perceptions of their role in relation to ADR reporting and their perceived barriers and facilitators to reporting. Groups were audio recorded, transcribed and thematically analysed.

In April 2017-March 2018, 110/226 enquiries were correctly categorised as ADRs; in April 2018-March 2019 there were 85/225 correctly categorised. In 2017-2018 57.3% of the ADR enquires taken were being reportable and in 2018-2019 68.2% of the ADR enquires taken were being reportable. In 2017-2018 39.6% of reportable ADRs had a yellow card sent through MIDatabank, in 2018-2019 this figure was lower again at 22.4%. The focus groups show the lack of reporting found most likely stemmed from the multiple perceived barriers such as; lack of understanding in how and when to report/ lack of time to send reports/ perceived discrepancies of the ADR reporting page. There were more perceived barriers than facilitators to reporting and many potential changes suggested to both the MIDatabank software and the training for reporting ADRs that are currently in place.

From the results there is significant underreporting of yellow cards through the MIDatabank. It has become clear that there is no single reason for this, it seems it is a culmination of different perceived barriers that stop the MI staff reporting yellow cards but there is a vast potential for improving these reporting rates with relevant changes to current systems.

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Investigating novel phosphorylation sites in zinc transporter ZIP7.

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Zinc is essential for living cells, and cellular zinc levels are controlled by two families of zinc transporters. The focus is on the SLC39A family of zinc importers, especially ZIP7, which is uniquely placed on the endoplasmic reticulum and releases zinc from stores.[1] It is known that ZIP7 requires phosphorylation on S275 and S276 in order to open the zinc channel gate and release zinc from stores[2], driving several crucial signalling pathways in cells such as AKT and MAPK.[3] However, ZIP7 is also predicted to be phosphorylated on residue S293 and T294, yet the role of these residues is currently unclear. Throughout this research, these residues will be tested to discover the role they play in the downstream signalling pathways and whether they are potentially a new target in cancer.[2,4]

Through genetic manipulation, MCF-7 cells were transfected with wild-type, S275A/S276A, S293A and T294A ZIP7 constructs. Furthermore, samples were treated with and without zinc for 10 minutes to examine the effect of mutants on the activation of known zinc signalling pathways. These samples were used to probed phospho-kinase arrays and the result allowed selection of four potential kinases for further testing by western blot.

The results of the study have identified that a number of kinases that showed increased phosphorylation when ZIP7 was stimulated. Unfortunately, some previous activation data was not able to be confirmed in this study indicating more research is required. Furthermore, activation of CREB by different ZIP7 mutants provided conflicting data which did not agree with previous data.[3]

Currently this method of western blot and phosphokinase arrays is an efficient way to detect active protein kinases are activated by ZIP7-mediated zinc release. In this study, some kinases were indicated to play a role in ZIP7 activation but more work needs to be done in order to know more about the S293 and T294 phosphorylation sites.

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Investigating the role of ZIP7 on kinase signalling pathways

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Zinc is a crucial trace element required for the normal functioning of cells.[1] Zinc homeostasis is attained through two families of zinc transporters, ZIP and ZnT, due to zinc's inability to passively diffuse through cell membranes.[2] Disruption of normal zinc levels are implicated in diseases such as immunodeficiency.[3] A member of the ZIP family, ZIP7, has been discovered to be mutated in two children with poor immunity.[4] The aim of this study was to determine whether these mutants (P190A and E363K) were defective at transporting zinc, the extent of their potentially impaired functionality and the implications this could have on downstream kinase signalling pathways mediated by ZIP7 zinc release. MCF-7 cells were cultured and transfected with recombinant wild-type ZIP7, S275A/S276A (null mutant control), P190A and E363K ZIP7 mutants before being treated with exogenous zinc. Human phospho-kinase arrays were performed and their results analysed through densitometry. A heat-map and graph of these results were generated, and four phospho-kinases were selected for further investigation through Western Blot analysis.

Phosphorylation results of a number of kinases were inconclusive due to variable Western Blot triplicate data unable to repeat the array results except for pS^{82}HSP27 which was partially activated in zinc-treated P190A transfected cells and not in the E363K-mutant transfected cells, confirming the hypothesis that P190A can still transport zinc whilst E363K cannot.

P190A is theorised to either inhibit upstream NFκB molecules involved in B-cell production or veer towards activation of downstream pS^{82}HSP27 accountable for apoptosis, whereas E363K repels zinc resulting in no stimulation of downstream kinases that grow B-cells, explaining the children's immunodeficiency. However, further research is required to confirm the roles of P190A and E363K via additional replicates of the original experiment, NFκB arrays being performed, B-cells being used as the cells for investigation, different kinases being tested, and shorter zinc treatment times used.

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Design of PROTACs targeting the HIV Reverse Transcriptase as novel treatments of HIV

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The ubiquitin-proteasome system degrades proteins by proteasomes through a series of steps. Ubiquitin and E3 ligase enzymes being the key components in this process. PROTAC approach is able to induce ubiquitination and lead to the degradation of protein by hijacking the pathway. PROTAC molecules are bifunctional molecules that have structures of both the E3 ubiquitin ligase enzyme recruiting molecules and the ligand that binds the target protein.[1] The objective of this study is to design PROTAC analogues that target HIV reverse transcriptase by using anti-HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) to degrade the disease protein and disrupt the HIV cycle. HIV is a potentially life-threatening condition that has no total cure to the disease so far.[2] Designed PROTACs will hopefully change the current status of the related drug development field.

Literature searches are conducted and relevant data was collected and analysed to help in the design and synthesis of the PROTACs. Various tools such as ChemDraw, Protein Data Bank and SwissADME are used to come up with the structures of the PROTACs.

PROTAC analogues are designed and the structures are clearly shown. Chemical properties of PROTACs are evaluated. PROTACs with good properties are chosen to be synthesized and steps of synthesis are shown clearly in the work. Results are justified and supported with findings.

Careful consideration is given to develop the PROTAC structures. Each component of the PROTACs are determined based on the findings and supported by researches. Von Hippel-Lindau (VHL) was chosen as the targeted E3 ligase enzyme over the Cereblon.[3] Two different linkers were used to connect the warheads. Binding sites of both the VHL ligand and the NNRTIs are determined by evaluating the respective co-crystal structures.

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Evaluation of a Community Pharmacy-based Asthma Care Plan

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In the UK, around 5.4 million people are currently receiving treatment for asthma.[1] Despite asthma medication's clinical effectiveness, there are 185 hospital admissions because of asthma exacerbations every day in the UK.[2] In 2018, more than 1400 adults and children died from asthma attacks.[3] Poor inhaler technique

and low-adherence contributes to poorly-controlled asthma. The current study aimed at uncontrolled asthma and its connection to incorrect inhaler technique and poor adherence.

Fifty-five patients were recruited in six different community pharmacies within South Wales via convenience sampling. Validated ACT survey was used to measure asthma control, validated TAI survey measured adherence and vitalograph AIM^{TM} device assessed patient's inhaler technique using placebo pMDI, DPI and MDI with spacers. The Kruskal-Wallis H and Mann-Whitney U tests were used to analyse statistical significance between the variables, where significance was set at $p<0.05$.

67% of the respondents reported uncontrolled asthma. 51% of the respondents indicated failed technique irrespective of inhaler type used. 62% of patients reported non-adherence. Poor asthma control was not related to poor inhaler technique or poor adherence. A significant difference between MDIs and failed technique was found ($p<0.05$). Significant difference between higher education and asthma control was found. Significant difference between patients not holding breath and MDIs was found.

Overall, asthma control, inhaler technique and adherence was relatively poor. All of these can be improved with better interventions such as; more frequent clinical follow-ups, educating patients on the importance of their disease and treatment.

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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:

The traditional and non-traditional pathways of Protein C activation

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A numerical approach to investigate adhesion between dental biomaterials and relevant bacteria

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Exploring pharmacists' views on the Sore Throat Test and Treat service via the Choose Pharmacy platform in Wales

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Bioprinting 3D skin models for biology and pathology investigation – biocompatibility of a novel bio-inks

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WHAT HAS PHAGE DISPLAY CONTRIBUTED TO THE MEDICAL WORLD?

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The Development and Manufacture of Loperamide Oral Suspensions

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Characterisation of novel microneedle electrodes for electrocardiogram measurements

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Role of Adhesion in Biofilm process of Wound healing

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Development of a long-acting contraceptive patch

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Formulation and evaluation of topical formulations for the treatment of neuropathic pain conditions

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Is Herceptin Resistance an Endocytosis Problem?

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Factor H Enhances Fibrin Clot Generation Independent of von Willebrand Factor

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Role of adhesion in the wound healing process.

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Using a numerical approach to investigate adhesion between orthopaedic biomaterials and bacteria: How do material properties influence adhesion?

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The effect of complement factor H on fibrin clot lysis

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The rapid detection of drug resistant mycobacteria

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Mycobacterium abscessus is a multidrug resistant pathogen commonly isolated from patients with cystic fibrosis. Currently, there is no rapid diagnostic tool to detect the presence of *M. abscessus*. Rapid diagnosis followed by appropriate, prompt treatment remains the best curative approach to mitigate disease burden and halt transmission. A major bottle neck in developing a rapid diagnostic assay is DNA extraction. Mycobacterial cells are very difficult to lyse, the existing methods are time consuming resulting in long turnaround time to detect the pathogen. This study employed the use of microwave energy to rapidly release nucleic acids from microorganisms and test the ability to detect the released nucleic acids in a magnetic-bead-based sandwich hybridisation assay using specific DNA probes. Based on published genome sequences, probes targeting the rpoB and erm-41 genes of *M. abscessus* and M. smegmatis were designed. In a magnetic-bead-based sandwich hybridisation assay using these specific probes, *M. abscessus* and *M. smegmatis* were distinguished from non-specific isolates within 70 mins with a lower detection limit of 1 pg/µL. The disruptive effects of microwaves on biological structures has been attributed to the local generation of heat. The contribution, if any, of non-thermal factors is yet to be determined. To study the interaction of microwaves with cell membranes, the structure which represents the major barrier to DNA release, fluorescent microscopy was employed to examine the passage of different sized fluorescent dextran particles into bacterial and yeast cells following microwave exposure. The results show a transient membrane disruption, size dependent permeabilization of dextran particles into cells. In conclusion, a prototype hybridisation assay capable of detecting *M. abscessus* and *M. smegmatis* has been developed. The application of microwaves to cells induced membrane disruption allowing internalisation of varying sizes of fluorescent dextran particles and the release of intact DNA for detection in hybridisation assay.

Medicines management in care homes

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There is an increasing demand on health and social care to provide high quality care to older adults in the UK as the population of this vulnerable group grows. These services should meet the needs of individuals who can have a range of acute and chronic conditions. The capacity for NHS services to meet these demands is limited and therefore care homes provide accommodation and health services to meet this unmet need. In the lay press, there have been concerns regarding medication management in care homes and there is evidence in the literature that this process is sub-optimal. The aim of this thesis therefore was to explore medicines management in care homes focusing on the areas of prescribing, administration and medicines waste. A retrospective analysis of anonymised medication administration records (MAR charts) and an audit of medicines waste was employed to achieve this aim. The analysis revealed that a significant number of residents (84%) were exposed to polypharmacy, potentially inappropriate medications (87%), anticholinergic burden (5% with an AEC score Ñ 5), and a significant number of administration errors (6 administration errors per resident per week). The study also demonstrated a significant volume of wasted medicines in care homes. As a consequence of these issues residents in care homes are potentially exposed to practices that may lead to harm and will likely increase the demand on health and social care resources. Careful consideration of prescribing practices is needed to reduce medicines burden and efforts should be made to embed a multidisciplinary approach to the care residents. In conclusion, further study of the clinical consequences of prescribing and medication errors in care homes should be explored as a matter of urgency and efforts should be made to maximise the therapeutic benefits of medications and reduce the cost of wasted medicines.

Controlled delivery of antimicrobial and anti-inflammatory agents from un-cemented prosthesis

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The prevalence of joint replacement procedures has increased by more than 119% in the last decade and as a result the demand for a prosthesis is very likely to increase. Uncemented prosthesis is the first-choice treatment option for patients under 68, due to its long-term and more stable fixation. The two major limitations that lead to the failure of joint replacement surgery are a prosthetic joint infection and aseptic loosening. To counter these limitations this study aimed to develop a novel composite system with dual functionality for prophylaxis from postsurgical inflammation and infection. The system is versatile safe to use in in-vitro.

Combining fusidic acid with metal ions as a potential reformulation for the treatment of bacterial keratitis

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Fusidic acid is a protein synthesis inhibitor commonly used to treat Gram-positive infections caused by pathogens such as Staphylococcus aureus. Gram-negative bacteria are intrinsically resistant due to their low permeability outer membrane and efflux pumps. UK optometrists are licenced to prescribe fusidic acid for the treatment of bacterial eye infections. However, 45 % cases of bacterial keratitis – a severe, sight-threatening corneal infection – are caused by Gram-negative organisms. As some metal ions have been found to enhance the activity and extend the spectrum of established antimicrobial drugs, this work sought to investigate the efficacy of combining metal ions with fusidic acid as a potential reformulation strategy to repurpose fusidic acid as a broad spectrum, first line treatment for bacterial keratitis. The presence of Al^{3+}, Cu^{2+} or Fe^{2+} ions was found to increase the activity of the fusidic acid sodium salt, sodium fusidate, against a selection of multi-drug resistant Gram-negative Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa isolates, without reducing anti-S. aureus efficacy. P. aeruginosa was particularly susceptible to sodium fusidate with Al^{3+}. There was no apparent link between the carriage of multi-drug resistance determinants and susceptibility to the combinations. With no evidence of spontaneous complexation, the mechanism of action against E. coli was determined to be reduced fusidate solubility enabling increased membrane access combined with the independent antimicrobial activity of metal ions. Proliferation of human corneal epithelial cells was less inhibited by Al3+, Cu2+ or Fe2+ than the Gram-negative reference strains, suggesting clinical selectivity. Unfortunately, the combinations were inactive against Gram-negatives in a novel rationalised simulated tear fluid, likely due to protein binding of both agents. However, future formulation optimisation may overcome this issue. Finally, the discovery of Al3+ and sodium fusidate activity against P. aeruginosa has prompted further research into the combined mechanism of action in this important opportunistic pathogen.

Elucidating the regulation of SPAK and OSR1 kinases by ubiquitylation

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The WNK-SPAK/OSR1 signalling pathway is a master regulator of ion homeostasis. The WNK kinases, whose mutations cause an inherited form of hypertension, activate SPAK and OSR1 kinases via phosphorylation. Upon phosphorylation by WNK kinases, SPAK and OSR1 kinases, consequently, phosphorylate an array of sodium, potassium and chloride ion co-transporters leading to either their activation or inhibition. WNK kinases phosphorylate SPAK and OSR1 kinases on their N-terminal threonine-rich region (termed the T-loop) as well as their serine-rich region (termed the S-motif). Although T-loop phosphorylation of SPAK and OSR1 kinases is known to activate these kinases, the function of their S-motif phosphorylation remains unclear. This project was aimed to unravel the function of SPAK and OSR1 S-motif phosphorylation by WNK kinases. Using peptide pull-down assays that employed SPAK and OSR1 peptide sequences derived from their S-motifs, followed by mass spectrophotometry analysis, the E3 ubiquitin ligases Cullin 4A and 4B (CUL 4A and B) were identified as novel binders of SPAK and OSR1 S-motif. Additionally, the adaptor protein DDB1, which is known to form

a complex with CUL4A/B, was also identified along with two other proteins known as WDR3 and WDR6. This binding of these proteins to SPAK and OSR1 kinases was subsequently verified using pull-down assays of overexpressed proteins in cells as well as immunoprecipitation of the endogenous proteins and followed by Western blotting. The results showed that these proteins bind SPAK and OSR1 kinases when unphosphorylated on their S-motif, while phosphorylation on these sites by WNK-kinases compromises the binding. Given that CUL4A/B E3 ubiquitin ligases ubiquitylate their protein substrates, overexpressed SPAK and OSR1 kinases, along with the proteasome inhibitor, MG132, and the neddylation inhibitor MLN4924 were used to investigate whether SPAK and OSR1 kinases are ubiquitylated by the CUL4A/B-DDB1-WDR3/6 complex. The results indicated that SPAK and OSR1 are constitutively ubiquitylated under resting conditions, whereas under osmotic stress when SPAK and OSR1 kinases are phosphorylated by WNK kinases, the ubiquitylation of these proteins is significantly reduced. Together, the data presented in this work represents the first example of an E3 ubiquitin ligase system that binds SPAK and OSR1 kinases. Critically, it provides a new molecular insight that links the CUL4A/B-mediated protein ubiquitylation to ion homeostasis and the regulation of blood pressure through SPAK and OSR1 kinases.

Assessment of Ionic Liquids for disinfection of healthcare surfaces

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Surface disinfection for the prevention of healthcare associated infections (HCAI) is well recognised. Ionic liquids (ILs) possess antimicrobial activities that could make their inclusion into disinfectant products beneficial for the control of HCAI. ILs were tested against microorganisms under conditions that affect antimicrobial activity concentration, contact time, organic soiling, and were compared to the commonly used cationic biocides benzalkonium chloride (BZC) and chlorhexidine gluconate (CHX). ILs had potent antimicrobial activity in the presence of organic soiling at a short contact time. At equivalent concentrations, BZC and CHX were not as effective at reducing viability of bacteria and the type of organism and organic soiling hindered the activity. The main factor that affected the antimicrobial activity of formulations was dilution. ILs were unable to inactivate *Bacillus subtilis* spores but were sporicidal when combined with hydrogen peroxide. Cellular targets of ILs were investigated by potassium leakage from the cell and the uptake of DNA binding dyes. Significant release of potassium from the cell and uptake of dyes into the cell suggested membrane damage was caused by ILs. The ultrastructure of bacteria was assessed by scanning electron microscopy (SEM) and atomic force microscopy (AFM). Visually, cells lost structural integrity in a dose-dependent manner. Analysis by AFM shown development of valleys in the structure of *Staphylococcus epidermidis*. *B. subtilis* spore mutants lacking protective DNA proteins and spore coat were tested against ILs to assess any interaction of the formulations with intracellular biomolecules. There was no reduction in spore numbers indicating that intracellular components are not targets. Finally, IL formulations were combined with wipe material to assess if antimicrobial activity would translate into a product. As a wet wipe the formulations reduced bacteria without transferring to subsequent surfaces and were more efficacious than commercial wipes. A spill wipe was also developed and was more effective than commercial spill wipes. Formulations were cytotoxic against skin cells in vitro. Overall, ILs displayed greater antimicrobial activity against vegetative bacteria, than BZC and CHX. The proposed mechanism of action is through membrane damage of the cell and as wipe products the ILs were more efficacious than commercial products.

Impact of commonly used antimicrobial biocides on resistance and cross-resistance in carbapenemase-producing Enterobacteriaceae.

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Infections due to multi-drug resistant organisms (MDROs) are a major concern worldwide. With very few new antibiotics on the market, infection prevention and control measures, including the use of biocides, are paramount to limit the spread of MDROs. Little is known about the impact of biocide overuse and the selective pressure they exert on adaptive mechanisms (co-selection) within bacteria. This study evaluated the effects of biocides commonly used in the UK on antibiotic susceptibility and on the mechanisms they might trigger within carbapenemase-producing Enterobacteriaceae (CPE). The minimum inhibitory concentrations (MICs)

of a wide range of antibiotics and four biocides (benzalkonium chloride, chlorhexidine digluconate [CHX], copper sulphate and silver nitrate) were determined for multi-drug resistant, carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates collected from UK hospitals. Regarding biocides, MICs were found to be much lower than in-use concentrations found in most commercial products (e.g. CHX MICs: 0.5-16 µg/mL; CHX concentration in a skin decontamination product: 40,000 µg/mL). Correlation were detected between antibiotic and biocide MICs, especially between CHX and carbapenems, cephalosporins, ciprofloxacin and tetracycline in K. pneumoniae. Exposure to CHX for 50 strains led to increased lag phase duration and changes in growth rate. Addition of efflux-pump inhibitor reduced the CHX MICs. These findings seemed to indicate the involvement of efflux in reduced susceptibility to CHX and antibiotics. Overexpression of efflux-related genes (*acrB*, extruding a wide range of antibiotics; *smvA,* for cationic compounds) was observed following exposure to sub-MIC CHX concentrations for two K. pneumoniae isolates. However, the molecular changes did not necessarily translate at the phenotypical level, with unchanged susceptibility towards CHX and several antibiotics. This work highlighted the involvement of efflux pumps following CHX exposure in CPE; while it did not result in reduced susceptibility to antimicrobials, precautions should still be taken, considering the extensive use of biocides.

The stability of new generation intravenous lipid emulsions

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Intravenous lipid emulsions (IVLE's) form a staple part of parenteral nutrition (PN). PN provides life sustaining support where gastrointestinal nutrition is inadequate due to disease or prematurity. Whilst the physical stability of IVLE's is relatively well known and quantified, chemical stability is an area where little testing has occurred. Lipids are susceptible to breakdown through free radical attack leading to lipid peroxidation, a cyclical process resulting in the production of primary and secondary toxic lipid peroxidation products. This thesis presents the development and validation of a method for measurement of peroxidation and triglyceride (TAG) breakdown occurring within two intravenous lipid emulsions. The high-performance liquid chromatography (HPLC) method developed uses in-line ultra-violet (UV) and charged aerosol detection (CAD) to monitor the six main TAGs in Intralipid® emulsion and 10 TAGs in SMOFlipid® and detects the toxic secondary peroxidation products 4-Hydroxynonenal (HNE) and Hydroxyundecenal (HUE). The assay was validated in line and employed to test the chemical stability the established lipid emulsion (Intralipid®) and a newer lipid emulsion (SMOFlipid®). Both lipids were subject to up to 84 days storage within 50 ml syringes, 250 ml PN bags and 50 ml glass vials at room and fridge temperatures. The effect of light exposure was tested using light protected and non-light protected samples of each lipid. Results within each chapter detail the extensive levels of TAG losses observed within each container and the detection of secondary peroxidation products. Fridge temperature limited TAG loss and peroxidation in all containers, however secondary peroxidation products were detected. Both SMOFlipid® and Intralipid® gave in excess of 30 % losses in TAGs over 84 days storage. HNE, HUE and a triglyceride remnant were all recorded in SMOFlipid® and Intralipid® syringes (both temperatures) and small volume PN bags at room temperature. Light protection within this study showed no significant difference vs non-light protection. The results obtained from the work within this thesis are of vital importance when considering the safety of lipid emulsions for intravenous nutrition. This work provides an initial data set on the levels of peroxidation occurring within two commercially available in-use lipid emulsions and highlights the necessity for the stability and storage limits of these emulsions to be re-assessed.

Identification of novel anti-RSV and antienterovirus inhibitors by computer-aided drug design

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Respiratory Syncytial Virus (RSV), which is the principal etiological cause of LRTIs (Low Respiratory Tract Infections) worldwide, and the virus members of the enterovirus genus, causing a wide range of diseases, ranging from enteric or respiratory infections to handfoot- and-mouth disease and acute flaccid paralysis, are associated with severe treats for public health. Currently, there are no effective small-molecule antiviral on the market for the treatment or prevention of these viral infections. In the first part of the project about RSV, the N

and F proteins were chosen as targets for the identification of new anti-RSV agents. On the RSV N protein, different computer-aided techniques were used for structure-based virtual screenings, of commercially available drug-like compounds. The two most potent hits were chosen as a starting point for further investigations. A series of analogues were synthesised and evaluated for anti-RSV activity in a virus-cell-based assay. Computer-aided techniques were also used for the rational -helix mimics, able to inhibit the protein-protein interactions between the trimeric inner coiled- -helixes of the F protein. The most promising compound and a series of analogues were synthesised and evaluated for their anti-RSV activities in a virus-cell-based assay. For the second part of the project on enterovirus, the highly conserved 2C protein among the enterovirus species was investigated. Starting from fluoxetine, which has been identified to inhibit viral replication by targeting 2C protein, and the new resolved EVA 71 2C crystal structure was used to investigate and to elucidate the binding mechanism of fluoxetine, using molecular modelling methodologies. The gained data were used to design, synthesise and evaluate new antiviral agents. Also, different molecular modelling techniques were used to perform a virtual screening in order to identify new potential inhibitors of the ATPase pocket of the 2C protein.

Caveolin-1: a mediator of Glioblastoma cell invasion and an independent negative biomarker of Glioblastoma patient survival.

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Glioblastoma multiforme (GBM) is a malignant and highly aggressive form of brain tumour, with extremely poor prognosis. One of its features is the ability of the tumour to invade through normal brain resulting in tumour relapse. Our hypothesis was that Caveolin-1 (Cav-1), a major component of the caveolae and recognized to be involved in a number of signalling pathways, has a key pro-invasive role in GBM. We pursued our hypothesis by inhibiting the expression of Cav-1 in different adult GBM cell lines using different genetic techniques (liposome shRNA, lentiviral shRNA and CRISPR). We found that Cav-1 drives clonogenicity (CHAPTER 3) and invasion in a combination of two- and three-dimensional models (CHAPTER 5). We focused our research on the invasion phenomenon and, in order to provide a robust quantification approach to study invasion in 3D spheroid assays, we developed (CHAPTER 4) a open-source semi-automated script, INSIDIA, available for all researchers in the community to use. This tool was used to quantify the impact of Cav-1 on invasive capacity. In in-vitro systems, we explored the impact of Cav-1 expression upon molecules associated with the invasion phenomenon (CHAPTER 5). We found Cav-1 to be associated with CTSB, MMP1 and UPA and receptors like UPAR and CD44, as well as AKT activation. Interrogating the “The Cancer Genome Atlas” (TCGA) database, we confirmed that Cav-1 is an independent biomarker of poor prognosis in GBM patients (CHAPTER 6). This clinical data also found association of genes that may cooperate with Cav-1, including CD44, ITGA3, VIM, CTSB, CTSL, TSP-1, TIMP1 and MT1MMP. Collectively this thesis provides strong in vitro and clinical data supporting that Cav-1 as a key molecule promoting GBM invasion, and further identifying Cav-1 as a potential drug discovery target in GBM.

Molecular mechanism of highly potent NS5A inhibitors

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Hepatitis C is responsible for causing chronic infections in over 170 million people all over the world who are at a risk of developing into liver cirrhosis and hepatocellular carcinoma, locating HCV in a major public health burden. Until recently, the standard-of care treatment consisted of Interferon-alpha and ribavirin, in addition to non-structural protein 3/4 (NS3) protease inhibitors, but due to the undesired side-effects, researchers developed more efficient therapies. Nowadays, small molecules targeting non-structural viral proteins: NS3/4 protease, NS5A D1 and NS5B polymerase activities can clear the infection in 98% of the cases. These direct acting antivirals (DAAs) are widely used, however, despite advances in recently approved potent DAAs the world-wide application of these therapies remains limited due to the expensive cost and potential drug resistance. NS5A is a nonstructural multifunctional protein. Mainly composed by an amphipatic helix, which is the major membrane anchor, Domain I, which is involved in RNA binding and assembly, and Domain II and III

which are intrinsically unfolded domains and are known to interact with host factors. DAA targeting NS5A DI, Daclatasvir (DCV), has a picomolar range activity and it is used in combination therapy to combat HCV infection. Given the enormous medical relevance of NS5A inhibitors, the aim of this study was to decipher the mode of action of Daclatasvir, together with more insights to the role of NS5A structural elements. In the present study, experiments showed that DCV can block the envelopment of viral particles. Furthermore, targeting the assembly of HCV particles, this fact serve as evidence of the dual mode of action of DCV. Furthermore, we investigated the role of very conserved Proline residues in the structure of NS5A, identifying key Proline residues which are critically involved in RNA replication, and have an impact in HCV infection. This fact, also suggests that the some of these Prolines might be essential for the DCV binding, as we prove that they have a direct role in keeping the binding site of DCV. Lastly, we set up a molecular model which includes the intracellular membrane giving the full picture of how DCV works in the context of an intracellular membrane and its important interactions. Together our data, prove the dual mode of action of DCV targeting HCV replication and assembly. And importantly, we constructed a molecular model that can be use in the future to study structure-function of developing NS5A inhibitors.

Targeting zinc signalling to prevent cell division in cancer

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Zinc is the second most abundant trace element in the human body and several disease states have been attributed to zinc dysregulation. Recent evidence has shown that zinc is a second messenger with roles in a diverse range of cellular signalling pathways. Of particular interest, is the discovery that cells require zinc to enter mitosis (cell division) and that several zinc transporter proteins have increased expression in cancer, a disease of uncontrolled cell division. Furthermore, post-translational modification has been shown to play a role in ZIP transporter activity. Understanding ZIP transporter regulation in cell division is key to revealing the mechanisms of zinc signalling in cancer. A combination of molecular and cell biological techniques have been used in this project to understand the role of ZIP transporter post-translational modification in cell division and to characterise novel anti-ZIP antibodies for their potential to stop tumour growth. This project highlighted multiple post-translational modifications to ZIP10 which helps us to understand its role in maintaining cellular zinc homeostasis. One of these modifications was phosphorylation and numerous potential ZIP10 phospho-sites were investigated and their relevance to ZIP10 function explained. In addition, novel antibodies against ZIP transporters ZIP6 and ZIP10, both of which have been implicated in several cancers, were developed and the work presented here demonstrated their ability to prevent cell division in multiple cancer cell lines. This project also provided the first indication that ZIP6- and ZIP10-mediated cell division is important for non-cancerous cells, supporting the evidence that zinc signalling mechanisms are vital to human health; a finding that is relevant to the wider field of cellular biology.

Pharmacotherapeutic interventions in Parkinson’s disease: investigating prescribing factors and health outcomes

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The current thesis is the first thorough exploration of the epidemiology and pharmacoepidemiology of Parkinson’s disease (PD) in Wales. Several factors, including age, sex, and social deprivation status, were evaluated that could contribute to specific estimates of prevalence and incidence, and also to patterns of prescribing of Parkinson’s medications in newly diagnosed People with Parkinson's disease (PwP). Furthermore, as cardiovascular episodes have been identified as a concern and potential risk factor associated with levodopa usage in PwP, cardiovascular outcomes in newly diagnosed PwP initiating levodopa therapy were estimated at population level. After conducting a thorough systematic literature review, a retrospective study of PwP in Wales, aged 40 years or older, identified from the Secure Anonymised Information Linkage (SAIL) Databank between January 2000 and December 2016 was employed. During the study, 9,142 newly diagnosed PwP who had initiated PD therapy were identified. The analysis revealed that the incidence rate of PD did not differ significantly between the year 2000 and the majority of years of the study period (in 2016, the incidence rate ratio (IRR) was 1.05 95% CI 0.93–1.18). However, the overall prevalence rate increased between 2000 and 2016 (in 2016 the prevalence rate ratio (PRR) was 1.16 95% CI 1.11–1.21). Importantly,

the incidence rate of PD was significantly lower in the most socially deprived areas compared to the least deprived areas (IRR = 0.82, 95% CI 0.77-0.87). Interestingly, social deprivation also impacted on medication, with PwP residing in the least deprived areas being 22.1% less likely to be prescribed levodopa compared to those from the most deprived areas (p-value = 0.007). From a safety perspective, although there were no statistically significant associations between levodopa monotherapy for up to one year after its initiation and increased risk of ischemic heart disease (p=0.561), other cardiovascular events (p=0.233), or all-cause mortality (p=0.334), the small sample size warrants further study with a larger population to detect clinically important differences in cardiovascular risk. Overall the findings support those of other studies which indicate that PD incidence appears stable, but its prevalence is increasing, likely to be due to an ageing population. The association with lower prevalence in areas of lower socioeconomic status similarly reflected other findings but uniquely identified a change in medication regimens. In concert, these findings are consistent with the hypothesis that individuals with lower socioeconomic status may be diagnosed later in their disease (which may be due to multiple factors), at which point the prescriber may be more likely to initiate treatment with levodopa rather than a MAO-B inhibitor. Given their accessibility, pharmacists could play a role in identify early signs and symptoms of PD in socioeconomically deprived areas but other recommendations are also made for further exploration of this area. Further research exploring this unwarranted variation in care and how it may be addressed is needed.

Photodynamic high-level disinfection for medical surfaces

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This project sought to evaluate photosensitisers as feasible alternatives to traditional biocide products for disinfecting medical surfaces. Photosensitisers produce damaging reactive oxygen species in the presence of light and may be safer than traditional disinfectants. However, their biocidal efficacy has yet to be determined using standardised methods and so comparisons with current technology are not possible. After establishing the photosensitiser toluidine blue O (TBO) as a lead compound, a biocide formulation was developed which exhibited broad spectrum bactericidal activity against a range of bacterial species. In the following chapter, the effect of photosensitiser-treatment on target cells was established and was observed to target the bacterial cytoplasmic membrane and nucleic acids. Upon testing against a broad spectrum of challenge organisms, the formulation was highly biocidal against yeasts, non-enveloped viruses and fast-growing mycobacteria and moderately effective against bacterial biofilms. However, its biocidal activity was found lacking against *Aspergillus* conidia, slow-growing mycobacteria and bacterial endospores. Further investigation determined that pigments, permeability barriers and DNA protection mechanisms confer resistance to photosensitisation. Evaluation of the scalability of photosensitiser-based disinfection determined that photosensitisers boast an exceptional ecotoxicological profile and can be produced at a price comparable to other disinfectants. Whilst photosensitisers are yet to be registered as an active substance in the European Union, they fulfil the general requirements of registration and do not contradict any exclusion criteria. Incorporating photosensitiser-based disinfection technology into complex devices such as an automated endoscope reprocessors is feasible, though would require complex design considerations which may discourage its use. Overall, these data demonstrate that photosensitiser-based biocide formulations are insufficiently effective for high-level disinfection of medical surfaces. However, their low production costs and ecotoxicological properties may make them suitable for alternative applications. The technology can be readily scaled-up the disinfection of commercial food preparation surfaces and so further investigations into alternative uses are recommended.

Novel synthetic pathways for the preparation of ProTides as potential therapeutic agents

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The phosphoroamidate (ProTide) approach is a prodrug technology aimed to circumvent metabolic bottlenecks in the activation of nucleoside-based drugs and optimise their intracellular delivery. The tremendous importance of the ProTide approach is highlighted by the approval of Sofosbuvir (Sovaldi®, HCV infections) and tenofovir alafenamide fumarate (TAF, Vemlidy®, HIV and HBV infections). A great deal of success is also

demonstrated by many other compounds adopting this technology either in clinical trials or preclinical evaluations as antiviral and anticancer agents. Given the great impact of phosphor(n)oamidate nucleoside prodrugs in the antiviral arena and beyond, the application of this technology has grown dramatically. Several procedures are present in the literature for the preparation of phosphoroamidate prodrugs of nucleosides. However, an efficient and inexpensive diastereoselective synthesis to prepare ProTides as single diastereoisomers is missing. Additionally, the phosphonoamidate cognate class, one of the most significant groups of antiviral drugs, presents many synthetic challenges. Recent literature reported the synthesis of novel acyclic nucleoside backbones including the phosphonate derivatives bearing a double bond in the aliphatic chain. However, the methodologies described for the preparation of ProTides on alkenyl acyclic nucleosides are scarce and inefficient. Beside phosphoroamidates and phosphonoamidates, many difficulties can also be encountered in the preparation of modified unnatural nucleosides and related prodrugs. One of them is the ProTide of 2'-deoxy-O6-methylguanosine to be tested for mitochondrial DNA depletion syndrome. In this context, the research discussed in this thesis is focused on addressing the synthetic problems related to unnatural nucleosides and their ProTides. This thesis aims to explore novel methodologies for the preparation of both phosphoroamidate and phosphonoamidate prodrugs of biologically relevant nucleosides in order to give easy access to novel ProTides to be evaluated for their potential therapeutic activities not only as antiviral but also in new therapeutic areas such as glycosylation disorders and lysosomal storage diseases.

Novel drug therapy for mitochondrial optic neuropathy

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Mitochondrial optic neuropathies (MON) represent an important cause of chronic visual impairment, affecting at least 1 in 10,000 individuals in the United Kingdom. Despite the efforts of recent years, the treatment options remain limited, with only a few drug candidates and therapeutic approaches, either approved or in development. Recently, Idebenone has been investigated as drug therapy in the treatment of Leber's hereditary optic neuropathy (LHON), a rare genetic MON, although evidence for the efficacy of Idebenone is limited in the literature. Cytoplasmic NAD(P)H:quinone oxidoreductase 1 (NQO1) and mitochondrial complex III were recently identified as the major enzymes involved in Idebenone activity. Based on this mode of action, computer-aided techniques were employed to identify potential Idebenone-related small molecules which are capable of interacting selectively with both enzymes. A series of quinone compounds were selected and evaluated in in vitro assays, and one of them was found to rescue the effects of LHON in cell models at a low □M concentration. Based on these observations, 50 derivatives were rationally designed and synthesised in order to enhance activity, and investigate the structure-activity relationship (SAR) and mode of action of this quinone family. Of these, 7 compounds showed improved activity compared to the original hit in the nM range, and these were further evaluated in a range of biological assays. The culmination of this study was the identification a novel naphthoquinone compound 2-((4-fluoro-3-(trifluoromethyl)phenyl)amino)-3-(methylthio)naphthalene-1,3,-dione (92) which demonstrated significantly greater potency in the ex-vivo assays, in addition to lower cytotoxicity, compared to Idebenone. Although further studies are needed to further elucidate the mechanism of action, this new compound has potential for being taken forward into pre-clinical development.

The effect of biocidal residues on resistance phenotype in *Escherichia coli*

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Antimicrobial resistance (AMR) poses a threat to worldwide health, in particular in relation to multi-drug resistant organisms. Hygienic cleaning and disinfection can contribute in the prevention of AMR. There is ample evidence to support the use of disinfectants (biocides) in the decrease of healthcare acquired infections (HCAIs). However, there is also evidence of instances where disinfectant efficacy may be impeded resulting in microbial survival and emerging resistance. Biocides are said to act as a selective pressure that encourages the acquisition of resistance traits in bacterial cells. Furthermore, selective pressure may result from the overexposure of very low concentrations of biocides over long periods of time. Some biocidal products make

claims of “residual biocidal activity” whereas efficacy is usually imparted to a much higher concentration. Some microbial populations may survive exposure to low biocide concentrations and show decreased susceptibility or resistance to a biocide or consequentially other antimicrobials. This study aims to understand differences between bacterial selection and adaptation in *Escherichia coli* following exposure to realistic residual - during use - chlorhexidine (CHX) or benzalkonium chloride (BZC) concentrations. It was hypothesised that exposure to a high sub-biocide minimum inhibitory concentration (MIC) would exert a selective pressure enabling the least susceptible bacteria to survive resulting in a permanent change of susceptibility phenotype, whereas a low sub-MIC would be conducive to reactive metabolic shifts resulting in a transient change of susceptibility phenotype. iii Baseline biocide (CHX and BZC) and antibiotic susceptibility of *E. coli* isolates was obtained using a standard micro-dilution broth protocol, and EUCAST protocol. “Residual” CHX concentration left on surface over a 168 hours period was measured by HPLC. The impact of a range of biocide concentrations (including residual CHX ones) on growth kinetics was investigated. Any changes in susceptibility profile was assessed for stability. Efflux activity and metabolic regulation during exposure to low and high sub-CHX MIC were investigated aiming to identify a link with observed changes in susceptibility phenotype. Finally, the propensity for different levels of CHX exposure to influence genetic transfer via conjugation was explored. It was demonstrated that a 0.006 ± 0.002 mg/mL is a realistic residual - during use - exposure concentration of CHX. This concentration is 99% lower than the concentration initially applied (20 mg/mL). At this residual concentration, it was possible for CHX susceptible bacteria to survive the disinfection process. Five genotypically distinct strains (UCD-CFS ECP-1L3, UCD-CFS ECP-1L4, UCD-CFS ECP-1B2, UCD-CFS ECP-13P5, UCD-CFS ECP-13P4) demonstrated survival after a 5 min but not 24 hours CHX exposure. Surviving bacteria demonstrated elevated MIC and MBC values; the highest fold change was 32-fold (MIC) and 62- fold (MBC). The elevated MIC values obtained were higher than the average concentration of CHX found on surface. Decreases in MIC or MBC values were observed after residual BZC exposure. No stable changes in MIC and MBC were observed after exposure to residual CHX or BZC, but stable changes were observed for antibiotic resistance for amoxicillin/clavulanic acid, ampicillin, cefpodoxime and cephalothin. Efflux activity was observed during exposure to low (0.00005 mg/mL) but not for high (0.002mg/mL) sub-CHX and sub-BZC MIC. It was demonstrated that changes in susceptibility coincided with changes in the ability to metabolise certain substrates including salicin, L-alanine, betain, creatanine and iv phenylethlalamine. These substances were linked to cell wall and stress signalling regulatory processes. It was surmised that E. coli was able to adapt through metabolic alterations to produce transient changes in CHX susceptibility and stable changes in antibiotic susceptibility. Furthermore, our results show that a transiently adapted population may be selected amongst less tolerant sub-populations at the established CHX-during use concentration. Overall, this work suggests that the intended application concentration of a biocide may in fact be lower than the MIC of target organisms. It is concluded that residual concentrations of biocides do have the potential to drive resistance, particularly stable cross-resistance to antibiotics, through prolonged exposure to low level during use concentrations, driving metabolic modifications of the cell envelope. The potential risk of cross-resistance warrants further investigation.

Understanding how targeting zinc transporters prevents the development of aggressive cancer

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Zinc is one of the most abundant trace elements in the human body. Cellular zinc homeostasis is primarily controlled by zinc transporters, including the ZIP family of zinc importers. Since zinc homeostasis needs to be tightly controlled, dysregulation of these zinc transporters is associated with multiple diseases including cancer. ZIP7, a zinc transporter residing on the endoplasmic reticulum membrane, was discovered to be involved in driving endocrine resistant breast cancer. Findings within this project support the hypothesis that tamoxifen-resistant breast cancer cells are driven by the increased activation of ZIP7 which, together with ZIP6, drives the invasive behaviour of this more aggressive breast cancer phenotype. This study confirmed the suitability of activated ZIP7 as a good biomarker of acquired resistance to anti-hormone treatment in breast cancer, a current clinical unmet need. Zinc is also important in cell cycle progression and, in particular, is essential for progression of cells through the G2 phase and mitosis. Our group have discovered that ZIP6 forms a heteromer with ZIP10 on the plasma membrane which influxes zinc into cells to trigger mitosis. This study demonstrated that treatment of different cancer cell lines with specific N-terminal ZIP6 or ZIP10 antibodies was able to inhibit mitosis by preventing the zinc influx necessary at this stage of the cell cycle. These agents were also shown to be effective at reducing the growth of different cancer cell lines. Using a model of ZIP6 CRISPR/Cas9 knockout cells it was discovered that ZIP6 downregulation induces upregulation of ZIP10, as a compensatory mechanism to counteract the lack of ZIP6. This study revealed novel targets for proliferative diseases such as

cancer, which is manifested by uncontrolled growth. Additionally, this project brought new insight into the regulation of ZIP6.

Computer--aided design,synthesis and evaluation of novel anti--chikungunya and anti--enterovirus compounds

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RNA viruses present a large group of viruses that contains many important human pathogens. Chikungunya virus is an Alphavirus transmitted by tiger mosquitoes, causing a febrile disease that often leads to very disabling, sometimes chronic, joint and muscular pain that can last for several weeks up to months. The Picornaviridae family including enterovirus A71, coxsackievirus B3, poliovirus, enterovirus D68 and rhinoviruses cause various different clinical symptoms and diseases like hand--foot--and--mouth disease, poliomyelitis, or the common cold. For none of these viruses direct--acting antivirals are on the market yet, stressing the need to design novel compounds that could target these viruses and that may enter into (pre--)clinical development soon. The replication cycle of RNA viruses requires specific viral proteins that replicate the viral genome and fulfil other crucial functions within the host--cell but are not packed into new viral particles. These non--structural proteins present excellent targets to inhibit the viral replication and were therefore investigated using computer--aided techniques in order to find novel antiviral compounds. Pharmacophore screening and docking were used to select molecules from large chemical libraries that were then tested in cell--based antiviral assays for their activities. Then the compounds were synthesised and improved using classic medicinal-- chemistry modifications. For chikungunya several different compounds with low micromolar activity could be identified. For the picornaviruses several inhibitors were reported, but the exact mode--of--action on their molecular target (2C protein) was unknown. Possible sites and interactions were explored using site identification tools, docking and molecular dynamics simulations. In collaboration with virologists and structural biologists this lead to the clarification of the mode--of--action of fluoxetine, which exhibits a stereoselective activity on 2C. In addition, a series of novel inhibitors with broad--spectrum activity against the described picornaviruses was developed.

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

Biological evaluation of an L-dideoxy Bicyclic Nucleoside Analogue active against measles virus

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